Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Chapter

18

Molecular Basis of Pulmonary Disease

Carol F. Farver . Dani S. Zander

INTRODUCTION

Pulmonary pathology includes a large spectrum of both neoplastic and non-neoplastic diseases that affect the lung. Many of these are a result of the unusual relationship of the lung with the outside world. Every breath that a human takes brings the outside world into the body in the form of infectious agents, organic and inorganic particles, and noxious agents of all types. Although the lung has many defense mechanisms to protect itself from these insults, these are not infallible and so lung pathology arises. Damage to the lung is particularly important given the role of the lung in the survival of the organism. Any impairment of lung function has widespread effects throughout the body, since all organs depend on the lungs for the oxygen they need. Pulmonary pathology catalogs the changes in the lung tissues and the mechanisms through which these occur. What follows is a review of lung pathology and the current state of knowledge about the pathogenesis of each disease. We believe that a clear understanding of both morphology and mechanism is required for the development of new therapies and preventive measures.

NEOPLASTIC LUNG AND PLEURAL DISEASES

Lung cancer is a major cause of morbidity and mortality throughout the world. The most recent estimates available from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute are that in 2007 over 213,000 people in the United States were diagnosed with cancer of the lung and bronchus, and over 160,000 will have died due to this disease [1]. However, in the past decade incidence and mortality rates have begun to move in a more positive direction, particularly in men. Overall, men show a decline in lung cancer incidence, while in women, although lung cancer rates grew from 1975 through 1998, they stabilized from 1998 through 2004 [2]. Similarly, cancer death rates due to lung cancer have declined for men and have slowed for women. Although, for women, lung cancer death rates have increased since 1975, the rate of increase has slowed to 0.2% annually from 1995 to 2004 [2]. These trends parallel changes in the prevalence of tobacco smoking, the most important risk factor for development of lung cancer.

Given the tremendous societal and individual impacts of this disease, it is not surprising that the molecular biology of lung cancer is a major focus of investigation. Elucidation of the molecular pathogenesis of these neoplasms has progressed significantly, offering insights into new, targeted therapies, and predictors of prognosis and therapeutic responsiveness. Recognition of precursor lesions for some types of lung cancers has been facilitated by our expanded understanding of early molecular changes involved in carcinogenesis.

The *World Health Organization* (WHO) classification scheme is the most widely used system for classification of these neoplasms (Table 18.1) [3]. Although there are numerous histologic types and subtypes of lung cancers, most of the common malignant epithelial tumors can be grouped into the categories of nonsmall cell lung cancers (NSCLCs) and small cell carcinomas (SCLCs). NSCLCs include adenocarcinomas (ACs), squamous cell carcinomas (SqCCs), large cell carcinomas, adenosquamous carcinomas, and sarcomatoid carcinomas. SCLCs include cases of pure and combined small cell carcinoma. Common pulmonary symptoms associated with these tumors include cough, shortness of breath, chest pain or tightness, and hemoptysis (coughing up blood). Since some tumors cause airway obstruction, they predispose to pneumonia, which can be an important clue to the existence of a tumor in some patients. Constitutional symptoms can include fever, weight loss, and malaise. Some neoplasms will declare themselves with symptoms related

Table 18.1 World Health Organization Histological Classification of Tumors of the Lung

Malignant Epithelial Tumors

- Squamous cell carcinoma
  - Papillary
  - Clear cell
  - Small cell
  - Basaloid
- Small cell carcinoma
  - Combined small cell carcinoma
- Adenocarcinoma
  - Adenocarcinoma, mixed subtype
  - Acinar adenocarcinoma
  - Papillary adenocarcinoma
  - Bronchioloalveolar carcinoma
    - Nonmucinous
    - Mucinous
    - Mixed or indeterminate
  - Solid adenocarcinoma with mucin production
    - Fetal adenocarcinoma
    - Mucinous ("colloid") carcinoma
    - Mucinous cystadenocarcinoma
    - Signet ring adenocarcinoma
    - Clear cell adenocarcinoma
- Large cell carcinoma
  - Large cell neuroendocrine carcinoma
    - Combined large cell neuroendocrine carcinoma
  - Basaloid carcinoma
  - Lymphoepithelioma-like carcinoma
  - Clear cell carcinoma
  - Large cell carcinoma with rhabdoid phenotype
- Adenosquamous carcinoma
- Sarcomatoid carcinoma
  - Pleomorphic carcinoma
  - Spindle cell carcinoma
  - Giant cell carcinoma
  - Carcinosarcoma
  - Pulmonary blastoma
- Carcinoid tumor
  - Typical carcinoid
  - Atypical carcinoid
- Salivary gland tumors
  - Mucoepidermoid carcinoma
  - Adenoid cystic carcinoma
  - Epithelial-myoepithelial carcinoma
- Preinvasive lesions
  - Squamous carcinoma *in situ*
  - Atypical adenomatous hyperplasia
  - Diffuse idiopathic pulmonary neuroendocrine hyperplasia

Mesenchymal Tumors

- Epithelioid hemangioendothelioma
- Angiosarcoma
- Pleuropulmonary blastoma
- Chondroma
- Congenital peribronchial myofibroblastic tumor
- Diffuse pulmonary lymphangiomatosis
- Inflammatory myofibroblastic tumor
- Lymphangioleiomyomatosis
- Synovial sarcoma
  - Monophasic
  - Biphasic
- Pulmonary artery sarcoma
- Pulmonary vein sarcoma

Benign Epithelial Tumors

- Papillomas
  - Squamous cell papilloma
    - Exophytic
    - Inverted
  - Glandular papilloma
  - Mixed squamous cell and glandular papilloma
- Adenomas
  - Alveolar adenoma
  - Papillary adenoma
  - Adenomas of salivary-gland type
    - Mucous gland adenoma
    - Pleomorphic adenoma
    - Others
  - Mucinous cystadenoma

Lymphoproliferative Tumors

- Marginal zone B-cell lymphoma of the MALT type
- Diffuse large B-cell lymphoma
- Lymphomatoid granulomatosis
- Langerhans cell histiocytosis

Miscellaneous Tumors

- Hamartoma
- Sclerosing hemangioma
- Clear cell tumor
- Germ cell tumors
  - Teratoma, mature
  - Immature
  - Other germ cell tumors
- Intrapulmonary thymoma
- Melanoma

Metastatic Tumors

Reprinted with kind permission from Travis, W. D., Brambilla, E., Müller-Hermelink, H. K., and Harris, C. C. (2004). *Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart.* IARC Press, Lyon [290].

to local invasion of adjacent structures such as chest wall, nerves, superior vena cava, esophagus, or heart. SCLCs are known for early and widespread metastasis and are therefore particularly prone to being discovered through presentations as metastases in distant sites. Some tumors are discovered due to pathophysiologic changes triggered by the release of soluble substances from tumor cells. Endocrine syndromes due to elaboration of hormones are well recognized, and include Cushing syndrome, syndrome of inappropriate antidiuretic hormone, hypercalcemia, carcinoid syndrome, gynecomastia, and others. Hypercoagulability commonly occurs with lung cancers, leading to manifestations of venous thrombosis, nonbacterial thrombotic endocarditis, and disseminated intravascular coagulation. Hematologic changes can include anemia, granulocytosis, eosinophilia, and other abnormalities. Other paraneoplastic syndromes such as clubbing of the fingers, myasthenic syndromes, dermatomyositis/polymyositis, and transverse myelitis are noted in subsets of patients.

When lung cancer is suspected, evaluation of the patient includes a thorough clinical, radiologic, and laboratory assessment, with collection of tissue or cytology samples to establish a pathologic diagnosis of malignancy and to classify the tumor type. Fiberoptic bronchoscopy is often performed to collect samples for diagnosis. Sample types can include transbronchial and endobronchial biopsies, bronchial brushings, bronchial washings, bronchoalveolar lavage samples, and transbronchial needle aspirates. Submission of sputum samples for cytologic

examination can provide a diagnosis in some cases, particularly for centrally located tumors such as SqCC and SCLC. Tumors arising in a peripheral location can also be sampled, in many cases, by fine needle aspiration or core needle biopsy performed under radiologic guidance. If a pleural effusion is present in combination with a lung parenchymal tumor, analysis of the pleural fluid cytology often allows one to establish a diagnosis. Pleural biopsy, mediastinoscopy with biopsy, and wedge biopsy can also be performed, depending on the clinical and radiologic findings. For tumors with apparent distant metastasis, biopsy of the metastasis focus can both establish a pathologic diagnosis and determine the stage of the tumor.

The prognosis of lung cancers is closely related to tumor stage. For NSCLCs, the *American Joint Commission on Cancer* TNM staging system is widely used (Table 18.2) [4], and for SCLCs, disease is classified as limited (restricted to one hemithorax) or extensive. Overall, for lung cancers, the 5-year survival is 13.4% for men and 17.9% for women [5]. An important factor leading to this relatively poor survival is the late stage at which many lung cancers are diagnosed. Information from the SEER database, from 1996–2003, indicates that 16%, 35%, 42%, and 7% of patients were diagnosed with localized, regional, distant, or unstaged disease, respectively [5]. The corresponding 5-year survival rates are 49.0%, 15.3%, 2.8%, and 8.7%, and 10-year survival rates are 37.8%, 10.3%, 1.6%, and 5.1% [5].

For patients with NSCLCs, treatment depends on stage and comorbid conditions [6]. Surgical resection is the preferred approach to treatment of localized NSCLCs, provided there is no medical contraindication to operative intervention. Lobectomy or more extensive resection (depending on tumor extent) is usually recommended rather than lesser surgeries, unless other comorbid conditions preclude these procedures.

Table 18.2 American Joint Commission on Cancer Lung Cancer Staging

Primary Tumor (T)

TX	Primary tumor cannot be assessed, or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor $\leq$ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus
T2	Tumor with any of the following features of size or extent: $>$ 3 cm in greatest dimension, involves main bronchus $\geq$ 2 cm distal to the carina, invades visceral pleura, associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T3	Tumor of any size that directly invades the chest wall, diaphragm, mediastinal pleura, parietal pericardium; or lies $<$ 2 cm distal to the carina but without involvement of the carina; or is associated with atelectasis or obstructive pneumonitis of the entire lung
T4	Tumor of any size that invades the mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or has separate tumor nodule(s) in same lobe; or is associated with a malignant pleural effusion.

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, including intrapulmonary nodes involved by direct extension of the primary tumor
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s).

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis; includes separate tumor nodule(s) in a different lobe.

TNM Stage Groupings

Occult	T0	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	Any T	N3	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

Based on Greene, F. L., Page, D. L., Fleming, I. D., Fritz, A., Balch, C. M., Haller, D. G., and Morrow, M. (2002). *AJCC Cancer Staging Manual*. Springer, New York [4].

Intraoperative mediastinal lymph node sampling or dissection is also recommended for accurate pathologic staging and determination of therapy. Subsets of patients also benefit from chemotherapy and radiotherapy. For more advanced NSCLC and for SCLC, chemotherapy and radiotherapy are the primary treatment modalities [6]. Rare patients with limited-stage SCLCs can be considered for surgical resection with curative intent.

Common Molecular Genetic Changes in Lung Cancers

Development of lung cancer occurs with multiple, complex, stepwise genetic and epigenetic changes involving allelic losses, chromosomal instability and imbalance, mutations in tumor suppressor genes (TSGs) and dominant oncogenes, epigenetic gene silencing through promoter hypermethylation, and aberrant expression of genes participating in control of cell proliferation and apoptosis [7]. There are similarities as well as type-specific differences in the molecular alterations between NSCLCs and SCLCs, and between SqCCs and ACs [8–10]. Oncogenes that play a part in the pathogenesis of lung cancer include *MYC, K-RAS* (predominantly ACs), *Cyclin D1, BCL2*, and *ERBB* family genes such as EGFR (epidermal growth factor receptor) (predominantly ACs) and HER2/neu (predominantly ACs) [11,12]. Also, lung cancers often display abnormalities involving TSGs including *TP53, RB, p16^{INK4a}*, and new candidate TSGs on the short arm of chromosome 3 *(DUTT1, FHIT, RASFF1A, FUS-1, BAP-1)* [11,13]. As research advances, these lists continue to grow, and as knowledge has expanded about the roles of these genes in carcinogenesis and tumor behavior, new targeted therapeutic agents have been designed to treat this disease (Figure 18.1 and Table 18.3) [14]. Many other agents are under investigation.

In cancers, chromosomal regions harboring TSGs and oncogenes are often deleted or amplified. Allele loss involving loci in 3p14–23 is a consistent feature of lung cancer pathogenesis [15,16]. Wistuba et al. reported allelic losses of 3p, often multiple and discontinuous, in 96% of the lung cancers studied and in 78% of the precursor lesions [15]. Larger segments of allelic loss were noted in most SCLCs (91%) and SqCCs (95%) than in ACs (71%) and preneoplastic/preinvasive lesions [15]. There was allelic loss in the 600-kb 3p21.3 deletion region in 77% of the lung cancers; 70% of the normal or reneoplastic/preinvasive lesions associated with lung cancers; and 49% of the normal, mildly abnormal, or preneoplastic/preinvasive lesions found in smokers without lung cancer, but no loss was seen in the samples from people who had never smoked [15]. 8p21–23 deletions are also frequent and early events in the pathogenesis of lung

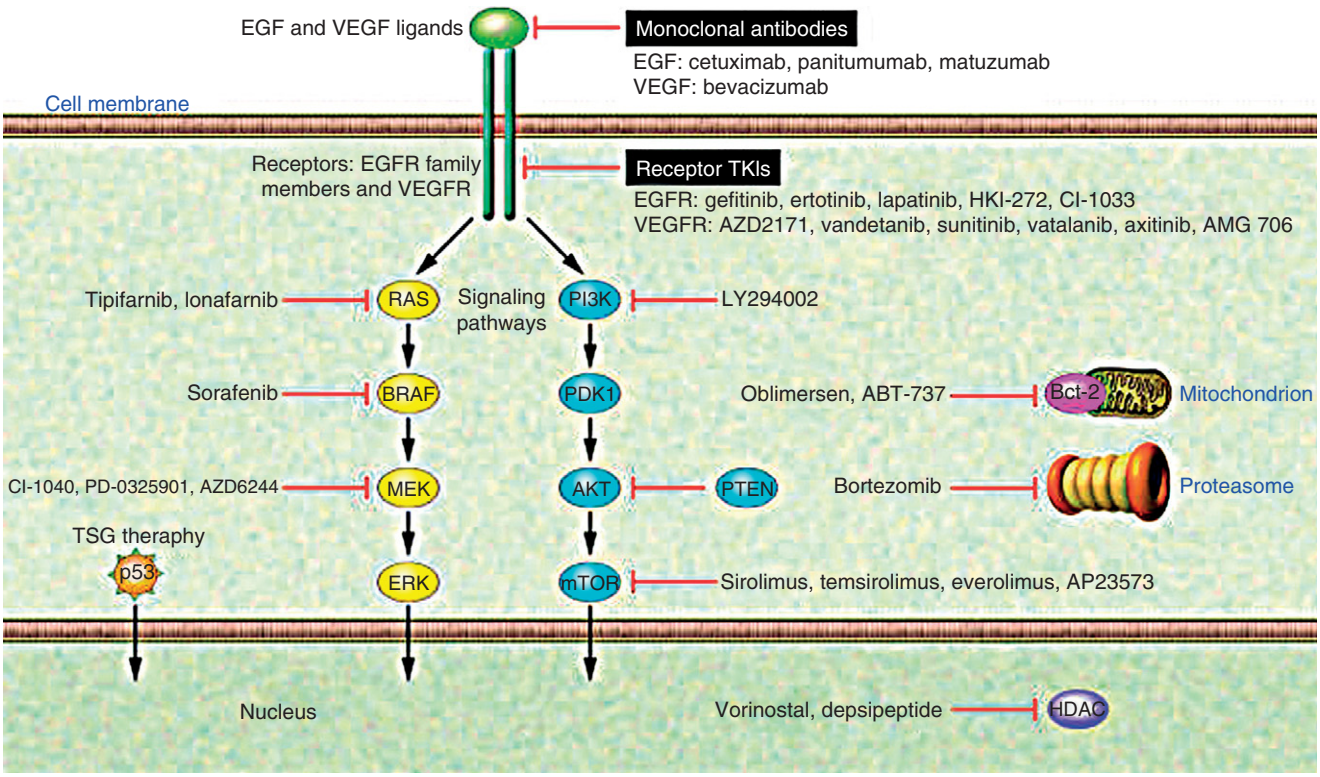

Figure 18.1 Targeted therapies are focused on key oncogenic pathways in lung cancer. These agents are designed to interfere with lung cancer cell proliferation, inhibition of apoptosis, angiogenesis, and invasion. EGFR = epidermal growth factor receptor; VEGFR = vascular endothelial growth factor receptor; TKIs = receptor tyrosine kinase inhibitors; TSG = tumor suppressor gene; PR = proteasome; PDK1 = pyruvate dehydrogenase kinase isoenzyme 1; PTEN = phosphatase and tensin homolog. Reprinted with kind permission from Sun, S., Schiller, J. H., Spinola, M., and Minna, J. D. (2007). New molecularly targeted therapies for lung cancer. *J Clin Invest* **117**, 2740–2750 [14].

Table 18.3 Selected Targeted Agents in Clinical Development for Lung Cancer Treatment

Target	Drug	Trade Name	Stage of Development in Lung Cancer
EGFR pathway inhibitors			
EGFR	Gefitinib	Iressa	Approved for advanced NSCLC
EGFR	Erlotinib	Tarceva	Approved for advanced NSCLC
EGFR	Cetuximab	Erbitux	Phase II/III
EGFR	Matuzumab		Phase I
EGFR	Panitumumab	Vectibix	Phase II
EGFR, HER2	Lapatinib	Tykerb	Phase II
EGFR, HER2	HKI-272		Phase II
EGFR, HER2, ERB4	CI-1033		Phase II
VEGF/VEGFR pathway inhibitors			
VEGF-A	Bevacizumab	Avastin	Approved for advanced NSCLC
VEGFR-2, EGFR	ZD6474; Vandetanib	Zactima	Phase II/III
VEGFR-1–3	AZD2171	Recentin	Phase II/III
VEGFR-1–3, PDGFR, c-KIT, FLT-3	SU11248; Sunitinib	Sutent	Phase II
VEGFR-1–3, PDGFR-β, c-KIT, c-fms	PTK787; Vatalanib		Phase II
VEGFR-1–3, PDGFR, c-KIT	AG-013736; Axitinib	Champix	Phase II
VEGFR-1–3, PDGFR, c-KIT	AMG 706		Phase I
Ras/Raf/MEK pathway inhibitors			
Ras	Tipifarnib (FTI)	Zarnestra	Phase III
Ras	Lonafarnib (FTI)	Sarasar	Phase III
Raf-1, VEGFR-2 and -3, PDGFR, c-KIT	BAY 43–9006; Sorafenib	Nexavar	Phase II
MEK	CI-1040		Phase II
MEK	PD-0325901		Phase I/II
MEK	AZD6244		Phase I
PI3K/Akt/PTEN pathway inhibitors			
PI3K	LY294002		Phase I
mTOR	Rapamycin; Sirolimus	Rapamune	Phase I
mTOR	CCI-779; Temsirolimus		Phase I/II
mTOR	RAD001; Everolimus		Phase I/II
mTOR	AP23573		Phase I
Tumor suppressor gene therapies			
p53	p53 retrovirus		Phase I
p53	p53 adenovirus (Ad5CMV-p53)	Advexin	Phase I
FUS1	FUS1 nanoparticle		Phase I
Proteasome inhibitors			
Proteasomes	Bortezomib	Velcade	Phase II
HDAC inhibitors			
HDAC	SAHA; Vorinostat	Zolinza	Phase II
HDAC	Depsipeptide		Phase I
Telomerase inhibitors			
Telomerase	GRN163L		Phase I

Reprinted with kind permission from Sun, S., Schiller, J. H., Spinola, M., and Minna, J. D. (2007). New molecularly targeted therapies for lung cancer. *J Clin Invest* **117,** 2740–2750 [14].

carcinomas [17], and other common alterations include LOH at 13q, 17q, 18q, and 22p [16].

Allelic losses that are more frequent in SqCCs than ACs include deletions at 17p13 (*TP53*), 13q14 (*RB*), 9p21 ($p16^{INK4a}$), 8p21–23, and several regions of 3p [11,15,17,18]. A recent study utilizing a bacterial artificial chromosome array to perform high-resolution whole genome profiling of SqCC and AC cell lines showed that regions of frequent amplification shared by both types of tumors included 5p; chromosome 7, 8q, 11q13, 19q, and 20q; and common regions of deletion included 3p, 4q, 9p, 10p, 10q; chromosome 18; and chromosome 21 [10]. However, ACs appeared to have higher frequencies of deletion of chromosome 6; 8p, 9q, 15q; and chromosome 16 than SqCCs, and possess small regions of amplification on chromosomes 12 and 14 not seen in SqCCs. Chromosome arms 2q and 13q were frequently deleted in AC but amplified in SqCC cell lines. Both types of tumors showed deletion of chromosome arm 17p, but it was more frequent in the SqCC cell lines, while amplification of chromosome 17p was more frequent in ACs. Amplification of chromosome 3q was common to both types of tumors but showed frequent alteration at 3q23–3q26 in the SqCC lines and at 3q22 in the AC lines.

Inactivation of recessive oncogenes is believed to occur through a two-stage process. It has been suggested that the first allelic inactivation occurs, often via a point mutation, and the second allele is later inactivated by a chromosomal deletion, translocation or other alteration such as methylation of the gene promoter region [19]. Inactivating mutations in the TSG *TP53*, which encodes the p53 protein, are the most frequent mutations in lung cancers. These mutations are found in up to 50% of NSCLCs and over 70% of SCLCs, and are largely attributable to direct DNA damage from cigarette smoke carcinogens [20]. *TP53* mutational patterns show a prevalence of G to T transversions in 30% of smokers' lung cancers versus only 12% of lung cancers in nonsmokers [20]. p53 protein is a transcription factor and a key regulator of cell cycle progression; cellular signals induced by DNA damage, oncogene expression, or other stimuli trigger p53-dependent responses including initiating cell cycle arrest, apoptosis, differentiation, and DNA repair [21]. Loss of p53 function in tumor cells can result in inappropriate progression through the dysregulated cell cycle checkpoints and permits the inappropriate survival of genetically damaged cells [22].

The $p16^{INK4a}$-cyclin D1–CDK4–Rb pathway, which plays a central role in controlling the G1 to S phase transition of the cell cycle, is another important tumor suppressor pathway that is often disrupted in lung cancers. It interfaces with the p53 pathway through $p14^{ARF}$ and $p21^{Waf/Cip1}$. Thirty percent to 70% of NSCLCs contain mutations of $p16^{INK4a}$, including homozygous deletion or point mutations and epigenetic alterations, leading to $p16^{INK4a}$ inactivation [22]. Almost 90% of SCLCs and smaller numbers of NSCLCs, on the other hand, display loss of Rb expression [23], and mutational mechanisms usually responsible include deletion, nonsense mutations, and splicing abnormalities that lead to truncated Rb protein [22]. $p16^{INK4a}$ leads to hypophosphorylation of the Rb protein, which causes arrest of cells in the G1 phase. The active, hypophosphorylated form of Rb regulates other cellular proteins including the transcription factors E2F1, E2F2, and E2F3, which are essential for progression through the G1/S phase transition. Loss of $p16^{INK4a}$ protein or increased complexes of cyclin D-CDK4–6 or cyclin E-CDK2 lead to hyperphosphorylation of Rb with resultant evasion of cell cycle arrest and progression into S phase [21,23]. Cell cycle progression is inhibited by $p21^{Waf/Cip1}$ through its inhibition of the cyclin complexes. The 10%–30% of NSCLCs lacking detectable alterations in $p16^{INK4a}$ and Rb may have abnormalities of cyclin D1 and CDK4, which cause inactivation of the Rb pathway [22]. Figure 18.2 provides an overview of the p53 and retinoblastoma (Rb) pathways, showing the complex interactions between the components [21].

Epigenetic alterations (hypermethylation of the 5′ CpG island) of TSGs are also frequent occurrences during pulmonary carcinogenesis, and methylation profiles of NSCLCs show relationships to smoke exposure, histologic type, and geography. Methylation rates of $p16^{INK4a}$ and *APC* and the mean methylation index (MI) (a reflection of the overall methylation status) in current or former smokers were significantly higher than in never smokers; the mean MI of tumors was highest in current smokers; methylation rates of *APC, CDH13,* and *RARbeta* were significantly higher in ACs than in SqCCs; methylation rates of *MGMT* and *GSTP1* in cases from the United States and Australia significantly exceeded those from Japanese and Taiwanese cases; and no significant gender-related differences in methylation patterns were found [24].

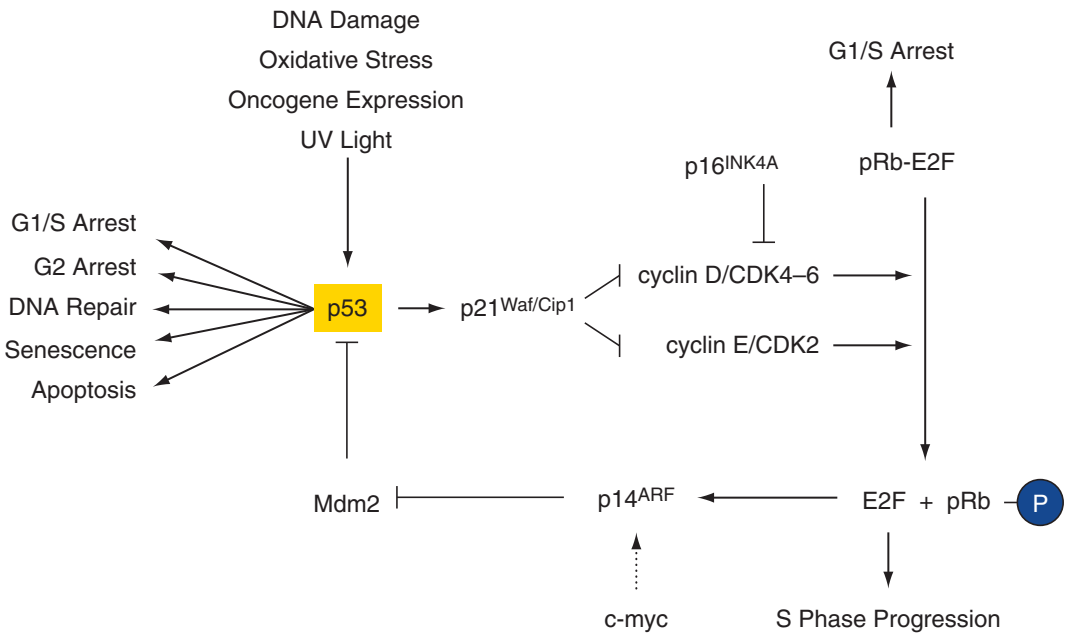

Figure 18.2 The p53 and retinoblastoma (Rb) pathways. A phosphate residue on Rb protein is indicated with a blue P. UV = ultraviolet. Reprinted with kind permission of Springer Science+Business Media, from Stelter, A. A. and Xie, J. (2008). Molecular oncogenesis of lung cancer. In *Molecular Pathology of Lung Diseases* (Zander, D. S., Popper, H. H., Jagirdar, J., Haque, A. K., Cagle, P. T., and Barrios, R., eds.), pp. 169–175, Springer, New York, NY [21].

Proto-oncogene activation and growth factor signaling are important in pulmonary carcinogenesis. The tyrosine kinase epidermal growth factor receptor *(EGFR)* is frequently mutated in NSCLCs, particularly in ACs, and the mutational status is important in determining response to tyrosine kinase inhibitors. A related pathway, the phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway, is frequently deregulated in pulmonary carcinogenesis. As reviewed by Marinov et al., this pathway has been reported to mediate the effects of several tyrosine kinase receptors, including EGFR, c-Met, c-Kit, and IGF-IR, on proliferation and survival in NSCLC and SCLC [25]. Clinical trials are ongoing, investigating the efficacy of the mTOR inhibitor rapamycin and its analogues on lung cancer [26]. HER2/neu is another related receptor tyrosine kinase that is upregulated in approximately 20%–30% of NSCLCs [27,28], but unlike the situation with HER2/neu-positive breast cancers, treatment with anti-HER2/neu antibody (trastuzumab) does not seem to yield comparable benefits for NSCLC when used alone or in combination with chemotherapy [28,29]. Point mutations of RAS family proto-oncogenes (most often at *K-RAS* codons 12, 13, or 61) are detected in 20%–30% of lung ACs and 15%–50% of all NSCLCs [22]. Although farnesyl transferase inhibitors prevent Ras signaling, these agents have not shown significant activity as single-agent therapy in untreated NSCLC or relapsed SCLC [30]. MYC family genes *(MYC, MYCN,* and *MYCL),* which play roles in cell cycle regulation, proliferation, and DNA synthesis, are more frequently activated in SCLCs than in NSCLCs, either by gene amplification or by transcriptional dysregulation [22].

Vascular endothelial growth factor (VEGF) is a homodimeric glycoprotein that is overexpressed in many lung cancers and directly stimulates endothelial cell proliferation, promotes endothelial cell survival in newly formed vessels, and induces proteases involved in the degradation of the extracellular matrix needed for endothelial cell migration [31]. Its angiogenic effects are mediated by three receptors: VEGFR-1, VEGFR-2, and VEGFR-3; ligand binding leads to tyrosine kinase activation and activation of the signaling pathways required for angiogenesis [31]. Monoclonal antibodies to VEGF (bevacizumab) and tyrosine kinase inhibitors to VEGFRs have been developed and show promise for treatment of NSCLC. A phase III trial of bevacizumab showed significantly improved overall and progression-free survival when this agent was used in combination with standard first-line chemotherapy in patients with advanced NSCLC, and several small-molecule VEGFR tyrosine kinase inhibitors have yielded favorable results in phase I and II trials in NSCLC [32].

MicroRNAs are a recently discovered class of nonprotein-coding, endogenous, small RNAs which regulate gene expression by translational repression, mRNA cleavage, and mRNA decay initiated by miRNA-guided rapid deadenylation [33]. Some microRNAs such as *let-7* have been suggested to play roles in carcinogenesis by functioning as oncogenes or tumor suppressors, negatively regulating TSGs and/or genes that control cell differentiation or apoptosis [33]. Investigations of the therapeutic potential of microRNAs are also under way.

Adenocarcinoma and Its Precursors

Clinical and Pathologic Features

In the 2004 version of the WHO classification scheme, AC is defined as "a malignant epithelial tumour with glandular differentiation or mucin production, showing acinar, papillary, bronchioloalveolar or solid with mucin growth patterns or a mixture of these patterns" [34]. AC has become the most frequent histologic type of lung cancer in parts of the world. It occurs primarily in smokers, but represents the most common type of lung cancer in people who have never smoked and in women. A small subset of these tumors arise in patients with localized scars or diffuse fibrosing lung diseases such as asbestosis and interstitial pneumonia associated with scleroderma [35]. These neoplasms usually arise in the periphery of the lung, and are more likely to invade the pleura and chest wall than other histologic types of lung cancers. Radiologic studies can show one or more nodules, ground-glass opacities, or mixed solid and ground-glass lesions. On gross examination, the neoplasms are often solitary gray-white nodules or masses, sometimes with necrosis or cavitation, which pucker the overlying pleura. Mucin-producing tumors can have a glistening, gelatinous appearance. Other presentations include a pattern of consolidation resembling pneumonia (usually bronchioloalveolar carcinoma) (Figure 18.3), multiple nodules, diffuse interstitial widening due to lymphangitic spread, endobronchial lesions with submucosal infiltration, and diffuse visceral pleural infiltration and thickening resembling mesothelioma.

Common histologic patterns displayed by ACs include acinar (Figure 18.4), papillary, bronchioloalveolar (Figure 18.5, Figure 18.6), and solid arrangements, and

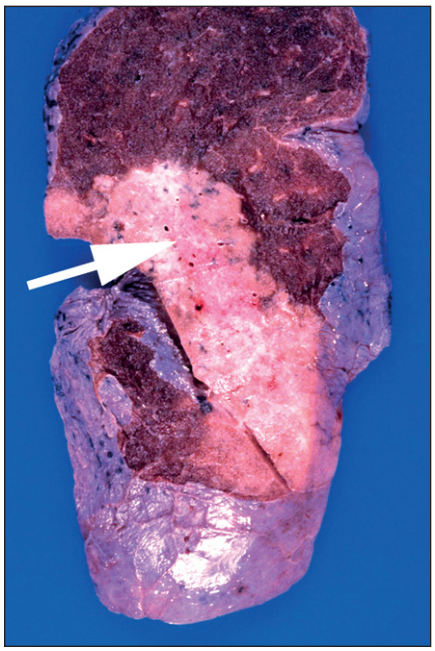

Figure 18.3 Bronchioloalveolar carcinoma. The tan tumor (arrow) replaces a large portion of the normal lung parenchyma.

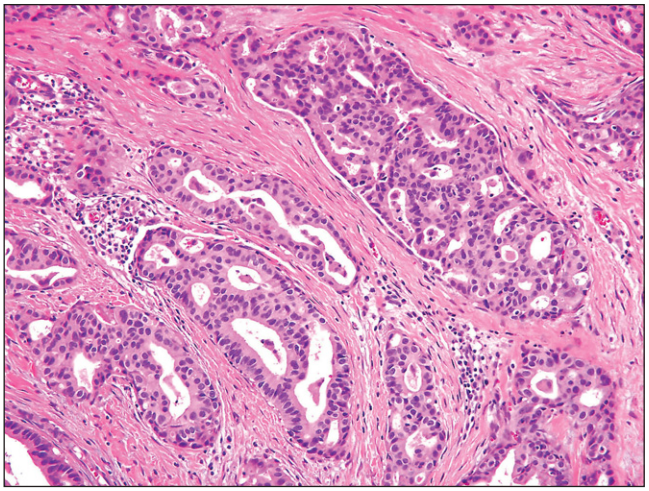

Figure 18.4 Adenocarcinoma with acinar pattern. The tumor consists of abnormal glands, some showing cribriform architecture, in a desmoplastic stromal background. The desmoplastic stroma has a dense collagenized appearance and reflects the presence of invasion. The abnormal glandular structures are lined by columnar tumor cells with abundant cytoplasm and mildly pleomorphic nuclei.

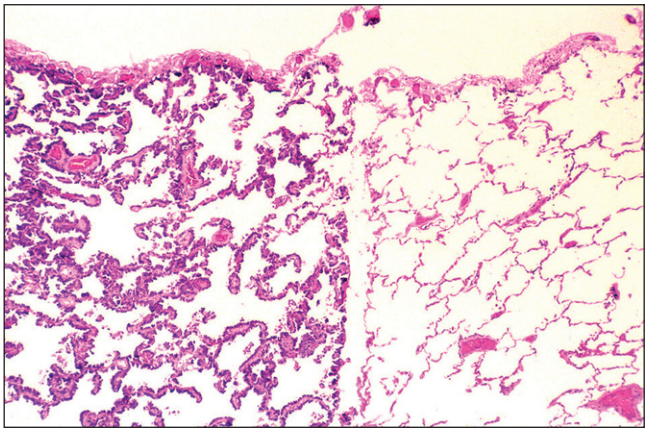

Figure 18.5 Adenocarcinoma with bronchioloalveolar pattern (left) compared with normal lung (right). Bronchioloalveolar carcinoma displays a lepidic growth pattern, in which tumor cells extend along alveolar septa, maintaining the alveolar architecture of the lung. This is illustrated by comparing the section of the figure on the left with that on the right. Notice that although open alveoli are present on both sides, the alveolar septa in the left portion are lined by tumor cells and have a thickened appearance, in contrast to the alveoli on the right, which have thin septa lined by flat pneumocytes.

mixtures of these patterns are very frequent. Less common histologic subtypes include fetal AC, mucinous (colloid) AC, mucinous cystadenocarcinoma, signet ring AC, and clear cell AC [34]. ACs usually exhibit differentiation toward Clara cells or type II pneumocytes or, less often, goblet cells. They manifest a range of differentiation extending from very well-differentiated tumors with

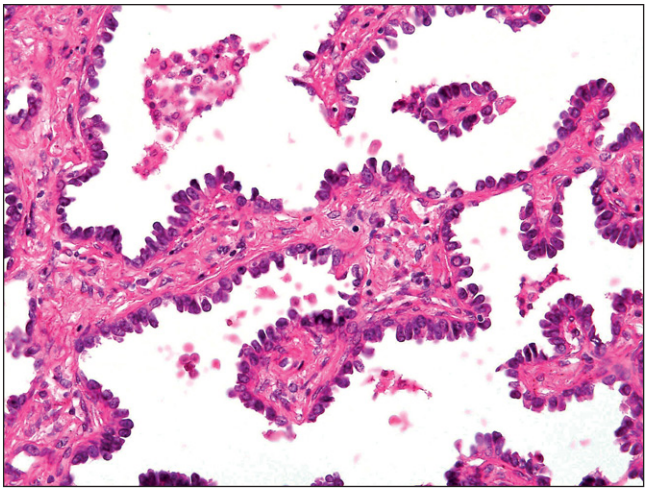

Figure 18.6 Adenocarcinoma with bronchioloalveolar pattern. Columnar tumor cells with a hobnail appearance line thickened alveolar septa. The tumor cells have enlarged, hyperchromatic nuclei. They remain on the surface of the alveolar septa and do not invade the lung tissue. This pattern is considered to represent an *in situ* lesion.

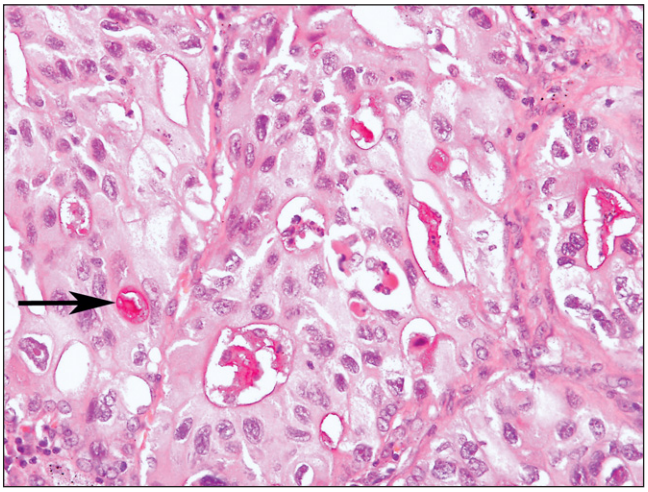

Figure 18.7 Adenocarcinoma (mucicarmine stain). Intracytoplasmic (arrow) and luminal mucin stains dark pink. The production of mucin indicates glandular differentiation.

extensive gland formation and little cytoatypia, to poorly differentiated, solid tumors that cannot be categorized as ACs unless one orders a mucin stain (Figure 18.7). However, most examples include readily identifiable glands. Invasiveness is reflected by the presence of neoplastic glands that infiltrate through stroma or pleura, stimulating a fibroblastic (desmoplastic) response (Figure 18.4), or by cells in the lumens of blood vessels or lymphatics.

In recent years, atypical adenomatous hyperplasia (AAH) has been recognized as a precursor lesion for peripheral pulmonary ACs. This lesion is defined as "a localized proliferation of mild to moderately atypical cells lining involved alveoli and, sometimes, respiratory bronchioles, resulting in focal lesions in peripheral

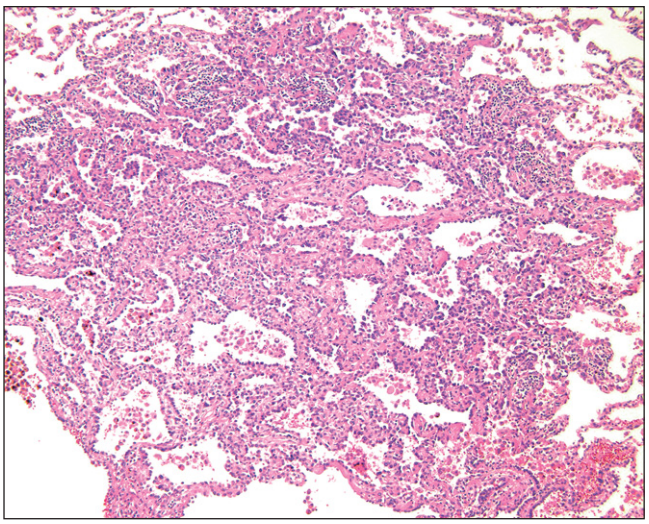

Figure 18.8 Atypical adenomatous hyperplasia. This lesion, which has been defined as a precursor lesion for peripheral pulmonary adenocarcinomas, consists of a well-circumscribed nodule measuring several millimeters in diameter, in which alveolar septa are lined by mildly moderate atypical cells.

alveolated lung, usually less than 5 mm in diameter and generally in the absence of underlying interstitial inflammation and fibrosis" (Figure 18.8) [36]. AAH exists on a histologic continuum with bronchioloalveolar carcinoma (BAC), which is defined as an *in situ* (noninvasive) form of AC, in which the neoplastic cells grow along alveolar septa (lepidic growth) without invasion of stroma or vasculature (Figure 18.5, Figure 18.6) [34]. Most BACs exceed 1 cm in diameter and consist of cells with greater degrees of cytoatypia than AAH. Although AAH is found in approximately 3% of patients without lung cancer at autopsy [37], it has been reported in 9%–21% of lung resection specimens with all types of primary lung cancer and 16%–35% of lung resection specimens with AC [36]. The progenitor cell for BAC and AAH is believed to be an epithelial cell located at the junction between the terminal bronchiole and alveolus, termed the bronchioalveolar stem cell [38].

Molecular Pathogenesis

A recently published large-scale study of primary lung ACs, using dense single nucleotide polymorphism arrays, described 57 significantly recurrent copy-number alterations in these tumors (Table 18.4) [12]. Twenty-six of 39 autosomal chromosome arms showed consistent large-scale copy-number gain or loss, and 31 recurrent focal events, including 24 amplifications and 7 homozygous deletions, were found.

Although some of the alterations involved regions known to harbor a proto-oncogene or TSG, these genes remain to be identified in some of the other regions affected. Amplification of chromosome 14q13.3 was the most common event noted, found in 12% of samples. This region includes *NKX2–1*, which encodes a lineage-specific transcription factor (thyroid transcription factor-1 [TTF-1]) that activates transcription of target genes including the surfactant proteins, and may be an important proto-oncogene involved in a significant fraction of lung ACs. Immunohistochemical staining for TTF-1 can be performed to detect expression of this factor in most lung adenocarcinomas, aiding in the determination of the lung as the site of origin of the tumor (Figure 18.9). Additional work using small interfering RNA (siRNA)-mediated knockdown of this gene in lung cancer cell lines with amplification led to reductions in tumor cell proliferation, through both decreased cell cycle progression and increased apoptosis, suggesting that gene amplification and overexpression contribute to lung cancer cell proliferation rates and survival [39].

EGFR and *K-RAS* mutations are mutually exclusive mutational events in AC of the lung, which suggests the existence of two independent oncogenic pathways [40,41]. EGFR is a receptor tyrosine kinase whose activation by ligand binding leads to activation of cell signaling pathways such as Ras/mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-kinase, which in turn propagates signals for proliferation, blocking of apoptosis, differentiation, motility, invasion, and adhesion [21]. Tumor-acquired mutations in the tyrosine kinase domain of EGFR, often associated with gene amplification, have been found in approximately 5%–10% of NSCLCs in the United States, and are associated with AC histology, never-smoker status, East Asian ethnicity, and female gender [14,40,42]. *EGFR* mutations are frequently in-frame deletions in exon 19, single missense mutations in exon 21, or in-frame duplications/insertions in exon 20, and occasional missense mutations and double mutations can also be detected [40,43]. *EGFR* mutation has an inverse correlation with methylation of the $p16^{INK4a}$ gene and SPARC (secreted protein acidic and rich in cysteine), an extracellular Ca2+-binding glycoprotein associated with the regulation of cell adhesion and growth [41]. *EGFR* status is an important predictor of response to EGFR kinase inhibitors: patients with *EGFR* mutations are most likely to have a significant response to EGFR tyrosine kinase inhibitor therapy, and EGFR amplification and protein overexpression have been reported to correlate with survival after EGFR tyrosine kinase inhibitor therapy [14,44]. K-Ras is a member of the Ras family of proteins, which function as signal transducers between cell membrane-based growth factor signaling and the MAPK pathways [21]. *K-RAS* mutations are associated with smoking, male gender, and poorly differentiated tumors [43]. *HER2* (also known as *EGFR2* or *ERBB2*), a member of the EGFR family of receptor tyrosine kinases, is mutated in less than 2% of NSCLC, and does not occur in tumors with *EGFR* or *K-RAS* mutation [45]. The *HER2* mutations are in-frame insertions in exon 20 and are significantly more frequent in ACs (2.8%), never smokers (3.2%), Asian ethnicity (3.9%), and women (3.6%), similar to *EGFR* mutations [45].

Alterations in DNA methylation appear to be important epigenetic changes in cancer, contributing to chromosomal instability through global hypomethylation, and aberrant gene expression through alterations in the methylation levels at promoter CpG islands [46].

Table 18.4 Top Focal Regions of Amplification and Deletion

Cytoband*	q Value	Peak Region (Mb)*	Max/Min Inferred Copy No.	Number of Genes* #	Known Proto-Oncogene/Tumor Suppressor Gene in Region*^	New Candidate(s)
Amplifications						
14q13.3	2.26×10^{-29}	35.61–36.09	13.7	2	–	*NKX2–1, MBIP*
12q15	1.78×10^{-15}	67.48–68.02	9.7	3	*MDM2*	–
8q24.21	9.06×10^{-13}	129.18–129.34	10.3	0	*MYC@*	–
7p11.2	9.97×10^{-11}	54.65–55.52	8.7	3	*EGFR*	–
8q21.13	1.13×10^{-7}	80.66–82.55	10.4	8	–	–
12q14.1	1.29×10^{-7}	56.23–56.54	10.4	15	*CDK4*	–
12p12.1	2.83×10^{-7}	24.99–25.78	10.4	6	*KRAS*	–
19q12	1.60×10^{-6}	34.79–35.42	6.7	5	*CCNE1*	–
17q12	2.34×10^{-5}	34.80–35.18	16.1	12	*ERBB2*	–
11q13.3	5.17×10^{-5}	68.52–69.36	6.5	9	*CCND1*	–
5p15.33	0.000279	0.75–1.62	4.2	10	*TERT*	–
22q11.21	0.001461	19.06–20.13	6.6	15	–	–
5p15.31	0.007472	8.88–10.51	5.6	7	–	–
1q21.2	0.028766	143.48–149.41	4.6	86	*ARNT*	–
20q13.32	0.0445	55.52–56.30	4.4	6	–	–
5p14.3	0.064673	19.72–23.09	3.8	2	–	–
6p21.1	0.078061	43.76–44.12	7.7	2	–	*VEGFA*
Deletions						–
9p21.3	3.35×10^{-13}	21.80–22.19	0.7	3	*CDKN2A/ CDKN2B*	–
9p23	0.001149	9.41–10.40	0.4	1	–	*PTPRD*‖
5q11.2	0.005202	58.40–59.06	0.6	1	–	*PDE4D*
7q11.22	0.025552	69.50–69.62	0.7	1	–	*AUTS2*
10q23.31	0.065006	89.67–89.95	0.5	1	*PTEN*	–

*Based on hg17 human genome assembly.
#Ref Seq genes only.
^Known tumor suppressor genes and proto-oncogenes defined as found in either COSMIC30, CGP Census31, or other evidence; if there is more than one known proto-oncogene in the region, only one is listed (priority for listing is, in order: known lung adenocarcinoma mutation; known lung cancer mutation; other known mutation (by COSMIC frequency); listing in CGP Census).
@*MYC* is near, but not within, the peak region.
‖Single gene deletions previously seen, this study provides new mutations as well.
Reprinted with kind permission from Weir, B. A., et al (2007). Characterizing the cancer genome in lung adenocarcinoma. Nature 450, 893–898 [12].

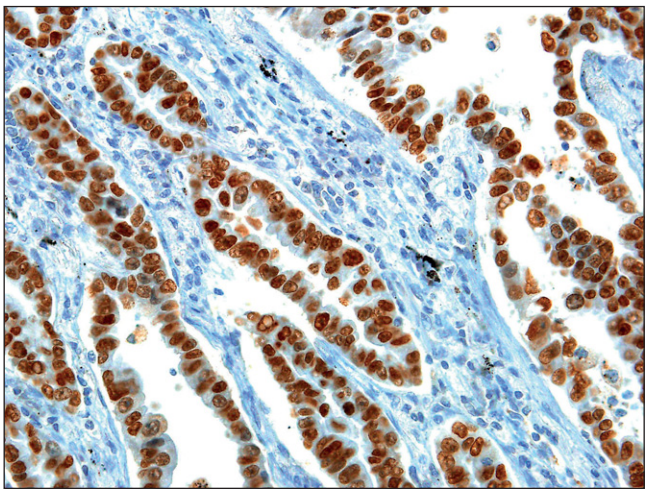

Figure 18.9 Adenocarcinoma (immunohistochemical stain for thyroid transcription factor-1 [TTF-1]). The brown-stained nuclei are positive for TTF-1. TTF-1 is expressed in the majority of pulmonary adenocarcinomas and small cell carcinomas, as well as in the thyroid.

Epigenetic differences exist between *EGFR*-mediated and *K-RAS*-mediated tumorigenesis, and may interact with the genetic changes. A recent study showed that the probability of having *EGFR* mutation was significantly lower among those with $p16^{INK4a}$ and *CDH13* methylation than in those without, and the methylation index was significantly lower in *EGFR* mutant cases than in wild-type. In contrast, *K-RAS* mutation was significantly higher in $p16^{INK4a}$ methylated cases than in unmethylated cases, and the methylation index was higher in *K-RAS* mutant cases than in wild-type [47].

Squamous Cell Carcinoma and Its Precursors

Clinical and Pathologic Features

SqCC is defined as "a malignant epithelial tumour showing keratinization and/or intercellular bridges that arises from bronchial epithelium," in the WHO classification scheme [48]. It is a common histologic type of NSCLC that is closely linked to cigarette smoking. In most patients, this tumor arises in a mainstem, lobar, or segmental bronchus, producing a central mass on imaging

studies. Many of these tumors have an endobronchial component that can cause airway obstruction, leading to postobstructive pneumonia, atelectasis, or bronchiectasis. Not infrequently, it is the pneumonia that prompts evaluation of the patient and leads to discovery of the tumor. Less often, SqCCs develop in the periphery of the lung.

Gross examination reveals a tan or gray mass that usually arises in a large bronchus and often includes an endobronchial component (Figure 18.10, Figure 18.11). Partial or complete airway obstruction can be associated with changes of pneumonia, bronchitis, abscess, bronchiectasis, or atelectasis. Necrosis and cavitation are very common in these tumors. Involvement of hilar lymph nodes by tan-gray tumor can be visible in some resected specimens. Microscopically, the key features of this tumor are its keratinization, sometimes with formation of keratin pearls, and intercellular bridges (Figure 18.12). As is true of ACs, the degree of differentiation of this tumor varies from very well differentiated cases, in which there are abundant keratinization and intercellular bridges and little cytoatypia, to very poorly differentiated cases, in which keratinization and intercellular bridges can be quite inconspicuous and the tumor consists of sheets of large atypical cells with marked cytoatypia and frequent mitoses. However, most cases fall more toward the middle of the spectrum. Invasiveness is reflected by the presence of irregular nests and sheets of cells that infiltrate through tissues, stimulating a fibroblastic response, or by cells inside vascular or lymphatic spaces.

Invasive SqCCs are often accompanied by SqCC *in situ* and dysplasia, their precursor lesions. These lesions arise in the bronchi and may be contiguous with the invasive tumor or exist as one or more separate foci. These precursor lesions can also be observed without coexisting invasive carcinoma. Like SqCC, tobacco smoking is the main predisposing factor for SqCC *in situ* and dysplasia. Unlike invasive SqCC, however, these lesions are not invasive—they do not extend through the basement membrane of the bronchial epithelium. Grossly, they may be invisible or appear as flat, tan or red discolorations of the bronchial mucosa, or tan wart-like excrescences. Microscopically, these lesions encompass a

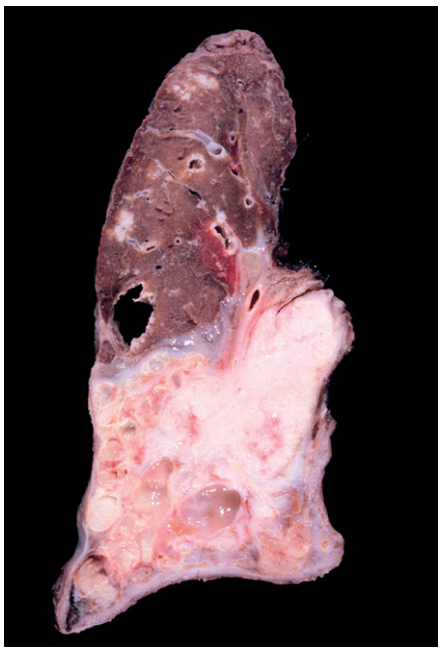

Figure 18.10 Invasive squamous cell carcinoma with postobstructive pneumonia and abscesses. This tan tumor lies in the central (perihilar) area of the lung and replaces the normal lung tissue. Distal to the tumor, the lung has extensive cystic changes reflecting abscesses and bronchiectasis, as well as a background of tan consolidation representing pneumonia.

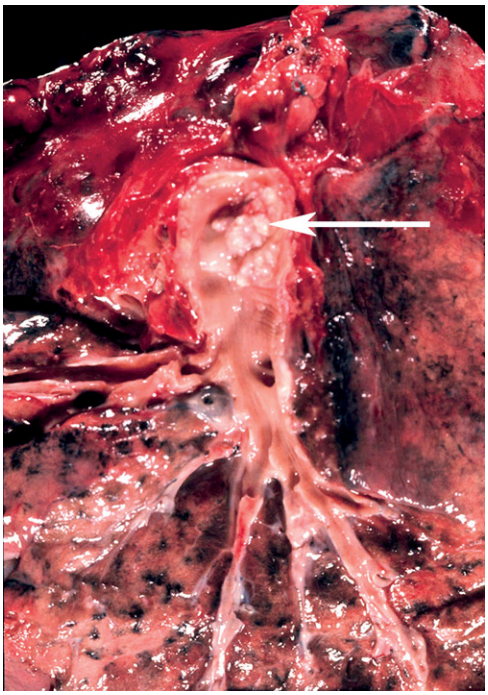

Figure 18.11 Squamous cell carcinoma. The tumor has an endobronchial component (arrow) that partially obstructs the airway lumen and has a warty appearance.

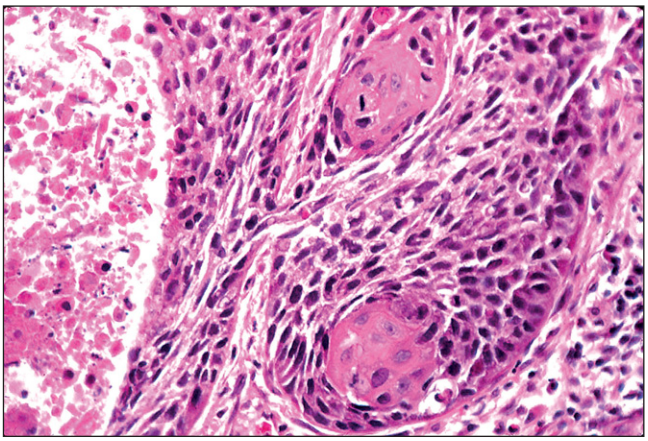

Figure 18.12 Invasive squamous cell carcinoma. This tumor consists of cells with hyperchromatic, pleomorphic nuclei and eosinophilic cytoplasm. Two keratin pearls are present (center) and a portion of the tumor is necrotic (left).

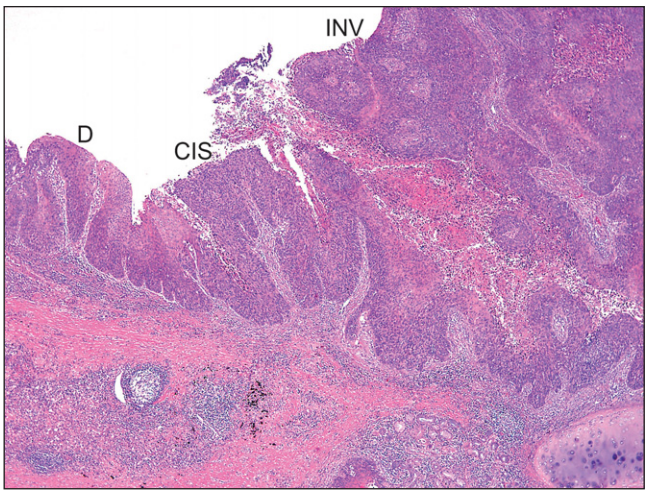

Figure 18.13 Dysplasia, squamous cell carcinoma *in situ*, and invasive squamous cell carcinoma. The dysplastic squamous epithelium (D) demonstrates increased thickness of the basal layer with mild squamous atypia. The atypia is full thickness in the area of carcinoma *in situ* (CIS), and in this area the entire epithelium consists of similar appearing cells with increased nuclear:cytoplasmic ratios. Invasion (INV) into the underlying bronchial tissues is present as well.

range of squamous changes that include alterations in the thickness of the bronchial epithelium, the maturational progress of squamous differentiation, cell size, and nuclear characteristics (Figure 18.13, Figure 18.14) [11,49]. As dysplasia increases from mild to moderate to severe, the epithelium thickens, and maturation is increasingly impaired. The basilar zone expands with epithelial cell crowding, the intermediate zone shrinks, and there is reduced flattening of the superficial squamous cells. Cell size, pleomorphism, and anisocytosis usually increase, and there is coarsening of the chromatin and appearance of nucleoli, nuclear angulations, and folding. In carcinoma *in situ*, although the epithelium may or may not be thickened and the cell size may be small, medium, or large, there is minimal or no maturation from the base to the superficial aspect, and the atypical nuclear features are present throughout the entire thickness of the epithelium. Mitoses appear in the lower third (mild or moderate dysplasia), lower two-thirds (severe dysplasia), or throughout the full thickness of the epithelium (carcinoma *in situ*).

Basal cells in the bronchial epithelium are believed to represent the progenitor cells for invasive SqCC, and the sequence of events leading to SqCC is believed to include basal cell hyperplasia, squamous metaplasia, squamous dysplasia, carcinoma *in situ*, and invasive SqCC (Figure 18.14) [11,49–51]. Regression of lesions preceding invasive SqCC can occur, particularly the earlier lesions [52]. However, severe dysplasia and carcinoma *in situ* are associated with a significantly increased probability of developing invasive SqCC in patients followed over time with surveillance bronchoscopy [53].

Molecular Pathogenesis

Wistuba and colleagues evaluated SqCCs and precursor lesions for loss of heterozygosity (LOH) at 10 chromosomal regions (3p12, 3p14.2, 3p14.1–21.3, 3p21, 3p22–24, 3p25, 5q22, 9p21, 13q14 *RB*, and 17p13 *TP53*)

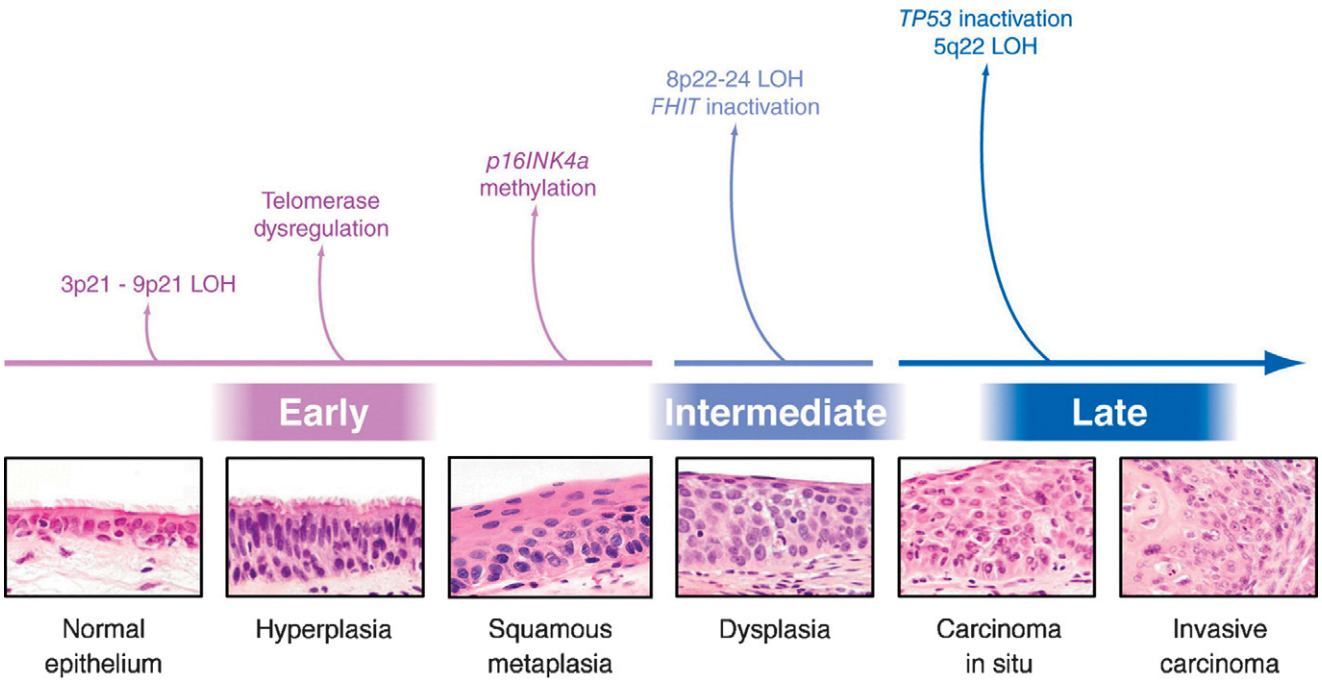

Figure 18.14 Histologic and molecular changes in the development of pulmonary squamous cell carcinoma. These changes occur in a stepwise fashion, beginning in histologically normal epithelium. LOH = loss of heterozygosity. Reprinted with kind permission from Wistuba, II and Gazdar, A. F. (2006). Lung cancer preneoplasia. *Annu Rev Pathol* **1**, 331–348 [11].

frequently deleted in lung cancer and found multiple, sequentially occurring allele-specific molecular changes in separate, apparently clonally independent foci, early in the pathogenesis of SqCCs of the lung, suggesting a field cancerization effect [11,18]. They observed clones of cells with allelic loss at one or more regions in 31% percent of histologically normal epithelium and 42% of specimens with hyperplasia or metaplasia; increasing frequency of LOH within clones with increasing histopathologic lesional severity; the most frequent and earliest regions of allelic loss at 3p21, 3p22–24, 3p25, and 9p21; increasing size of the 3p deletions with progressive histologic changes; and *TP53* allelic loss in many histologically advanced lesions (dysplasia and CIS) [18]. An overview of the sequential molecular events leading to invasive SqCC is shown in Figure 18.14 [11].

Large Cell Carcinoma

Clinical and Pathologic Features

Large cell carcinoma is an undifferentiated NSCLC without light microscopic evidence of squamous or glandular differentiation, although squamous or glandular features may be detectable by ultrastructural examination (Figure 18.15) [54]. Histologic subtypes of large cell carcinoma include large cell neuroendocrine carcinoma (LCNEC), combined LCNEC, basaloid carcinoma, lymphoepithelioma-like carcinoma, clear cell carcinoma, and large cell carcinoma with rhabdoid phenotype [54]. Clinical signs and symptoms resemble those of other types of NSCLC. Most tumors develop as peripheral lung masses, except for basaloid carcinomas, which usually form centrally located masses. Histologically, large cell carcinomas consist of sheets and nests of large cells with vesicular nuclei, prominent nucleoli, and moderate or abundant amounts of cytoplasm. LCNECs demonstrate neuroendocrine architectural features and immunohistochemical or ultrastructural evidence of neuroendocrine differentiation. Basaloid carcinomas display nests of small, monomorphic, rounded or fusiform tumor cells with little cytoplasm, numerous mitoses, comedo-type necrosis, and hyaline or mucoid stromal degeneration. Clear cell carcinoma consists of large tumor cells with clear cytoplasm. Precursor lesions are not currently recognized for any of the subtypes of large cell carcinoma. However, basaloid carcinoma is associated with squamous dysplasia in about one-third of cases [54].

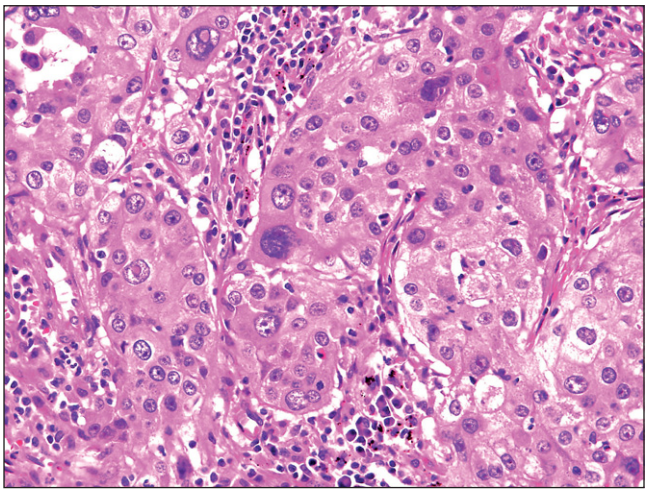

Figure 18.15 Large cell carcinoma. This poorly differentiated tumor displays large cell size with marked nuclear pleomorphism, large nucleoli, nuclear inclusions, and abundant eosinophilic cytoplasm. Evidence of squamous or glandular differentiation is not observed. The intervening stroma is inflamed.

Molecular Pathogenesis

Large cell carcinomas are poorly differentiated carcinomas that can demonstrate features of AC (most frequent), SqCC, or neuroendocrine differentiation when examined by immunohistochemistry, electron microscopy, or molecular methods [55].

These tumors often demonstrate losses of 1p, 1q, 3p, 6q, 7q, and 17p, and gains of 5q and 7p, more closely resembling ACs than other histologic types of lung cancer [56]. Common molecular abnormalities include *TP53* mutation, *C-MYC* amplification, and *p16* promoter hypermethylation, while *K-RAS* mutation is less common [55]. *EGFR* tyrosine kinase domain mutation is not characteristic of large cell carcinomas, and *EGFRvIII* (deletion mutations in the extracellular domain of *EGFR*) is uncommon [57,58].

Neuroendocrine Neoplasms and Their Precursors

Clinical and Pathologic Features

The major categories of pulmonary neuroendocrine (NE) neoplasms include small cell carcinoma (SCLC), large cell neuroendocrine carcinoma (LCNEC), typical carcinoid, and atypical carcinoid. SCLC and LCNEC are high-grade carcinomas, typical carcinoid is a low-grade malignant neoplasm, and atypical carcinoid occupies an intermediate position in the spectrum of biologic aggressiveness. In one large series, the 5-year and 10-year survival rates for typical carcinoid were 87% and 87%, 56% and 35% for atypical carcinoid, 27% and 9% for LCNEC, and 9% and 5% for SCLC, respectively [59]. By light microscopy, these tumors display NE architectural features including organoid nesting, a trabecular arrangement, rosette formation, and palisading. These patterns are more prominent in carcinoids than in LCNECs and may or may not be visible in individual SCLCs. Typical carcinoids contain fewer than 2 mitoses per 2 mm^2 (10 HPF) and lack necrosis (Figure 18.16), while atypical carcinoids show 2–10 mitoses per 2 mm^2 (10 HPF) or necrosis, which is often punctate [60]. SCLC consists of small, undifferentiated tumor cells with scant cytoplasm and finely granular chromatin and absent or inconspicuous nucleoli (Figure 18.17). Nuclear molding is characteristic, necrosis is common, and the mitotic rate is typically high, with a mean of over 60 mitoses per 2 mm^2 [61]. Combined

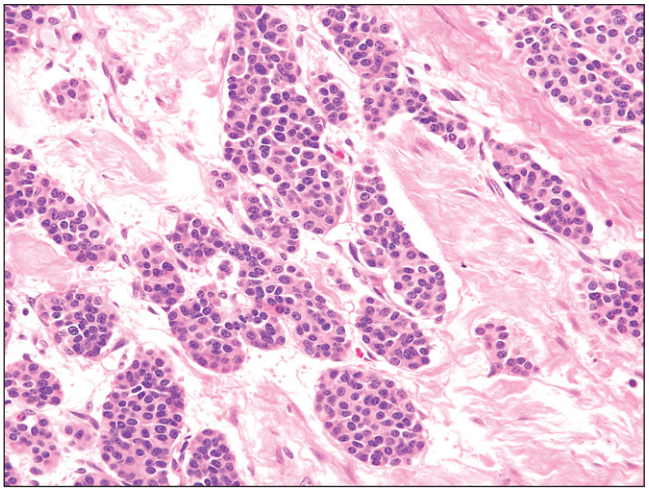

Figure 18.16 Typical carcinoid. This tumor consists of nests of uniform tumor cells with round or ovoid nuclei, fine chromatin, and little nuclear cytoatypia. A moderate amount of cytoplasm is present. No necrosis or mitoses are observed. The stromal background is hyalinized.

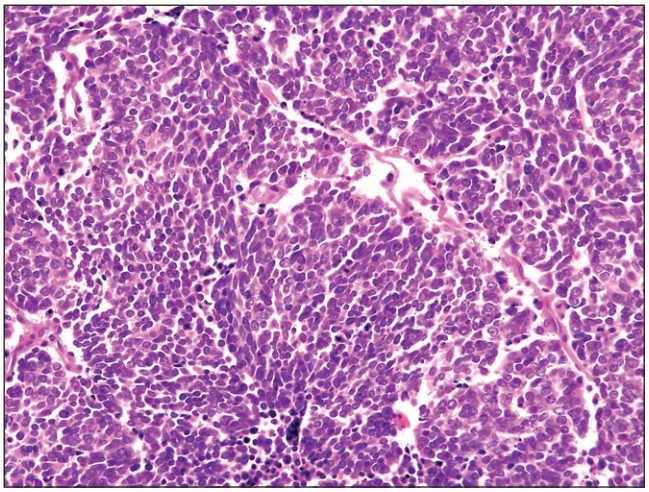

Figure 18.17 Small cell carcinoma. Small cell carcinomas typically display sheets of small tumor cells with scant cytoplasm and nuclei demonstrating fine chromatin. Numerous mitoses and apoptotic cells are characteristic.

SCLCs include an SCLC component accompanied by one or more histologic types of NSCLC. LCNECs consist of large tumor cells resembling those of large cell carcinoma, with NE architectural patterns, necrosis, a high mitotic rate (median of 70 per 2 mm^2), and NE differentiation reflected in immunohistochemical staining for one or more NE markers (chromogranin A, synaptophysin, leu-7 [CD57] or N-CAM [neural cell adhesion molecule, or CD56]) or the presence of neurosecretory granules on ultrastructural examination (Figure 18.18) [60].

Differences also exist in the characteristics of patients with carcinoids, as compared to patients with SCLC and LCNEC. Patients with carcinoids are typically younger and less likely to smoke than those with SCLCs and

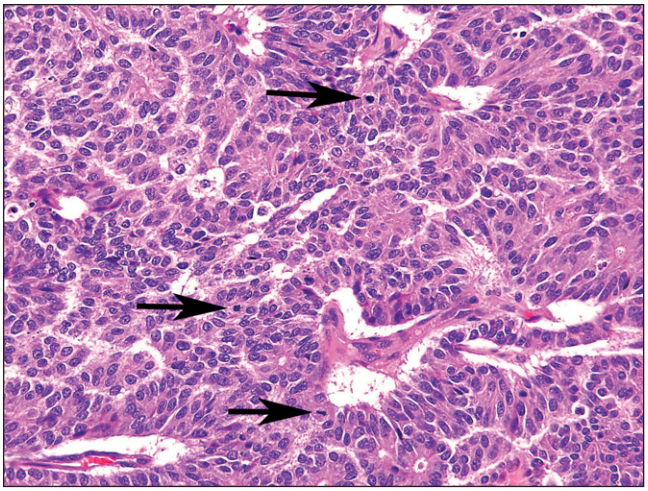

Figure 18.18 Large cell neuroendocrine carcinoma. The tumor forms rosettes, a feature that is commonly observed in low-grade neuroendocrine tumors. Although necrosis is not present, mitoses are numerous (several indicated by arrows) and exceed 10 mitoses per 2 mm^2, justifying classification as a large cell neuroendocrine carcinoma.

LCNECs, the vast majority of whom have a current or previous history of tobacco smoking [62,63]. Rare patients with carcinoids have the multiple endocrine neoplasia 1 (MEN1) syndrome, an association that is not seen with SCLCs and LCNECs. In addition, an association with diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) has been noted for carcinoids but not for SCLCs and LCNECs, leading to classification of DIPNECH as a preinvasive lesion in the most recent version of the WHO classification scheme [64]. DIPNECH is a diffuse proliferation of single cells, small nodules (NE bodies), and linear proliferations of pulmonary NE cells that may reside in the bronchial and/or bronchiolar epithelia (Figure 18.19), and may be accompanied by extraluminal proliferations

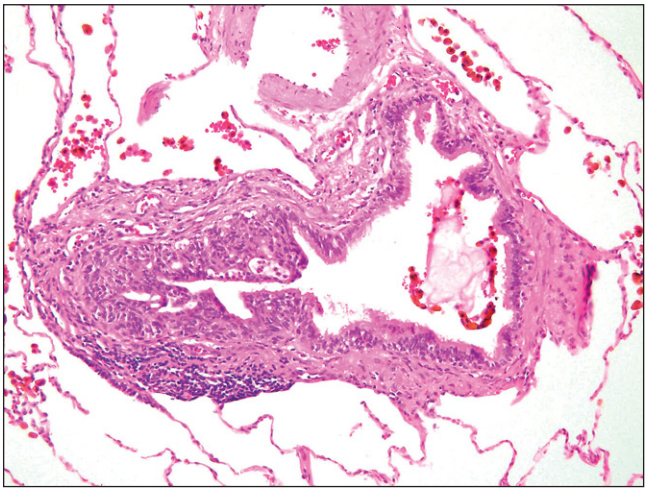

Figure 18.19 Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. A proliferation of neuroendocrine cells expands the epithelium of the left half of this bronchiole.

(tumorlets and carcinoids) [64]. However, morphologically identifiable precursor lesions for SCLC and LCNEC have not been established.

Molecular Pathogenesis

Molecular markers of pulmonary NE tumors include chromogranin A, synaptophysin (Figure 18.20), and N-CAM (CD56). These markers are expressed by all categories of NE tumors, with higher frequencies observed in the carcinoids and atypical carcinoids than in small cell and large cell neuroendocrine carcinomas. Gastrin-releasing peptide, calcitonin, other peptide hormones, the insulinoma-associated 1 *(INSM1)* promotor and the human achaete-scute homolog-1 *(hASH1)* gene have also been reported as overexpressed by these tumors [65,66]. Thyroid transcription factor-1 (TTF-1) is expressed by 80%–90% of SCLCs, 30%–50% of LCNECs, and 0%–70% of carcinoids [67–70].

SCLCs are aneuploid tumors with high frequencies of deletions on chromosomes 3p (including *ROBO1/DUTT1* [3p12.13], *FHIT* [3p14.2], *RASSF1* [3p21.3], *β-catenin* [3p21.3], *Fus1* [3p21.3], *SEMA3B* [3p21.3], *SEMA3F* [3p21.3], *VHL* [3p24.6], and *RARβ* [3p24.6]), 4q (including the proapoptotic gene *MAPK10* [4q21]), 5q, 10q (including the proapoptotic gene *TNFRSF6* [10q23]), 13q (location of the *Rb* gene), and 17p (*TP53*), and gains on 3q, 5p, 6p, 8q, 17q, 19q, and 20q [71–76]. More than 90% of SCLCs and SqCCs demonstrate large, often discontinuous segments of allelic loss on chromosome 3p, in areas encompassing multiple candidate tumor suppressor genes, including some of those listed previously [15,75]. Atypical carcinoids show a higher frequency of LOH at 3p, 13q, 9p21, and 17p than typical carcinoids, but not as high as the high-grade NE tumors [77]. Some typical and atypical carcinoids possess mutations of the *multiple endocrine neoplasia 1* (*MEN1)* gene on chromosome 11q13 or LOH at this locus [78], while these abnormalities occur with lower frequencies in SCLCs and LCNECs, supporting separate pathways of tumorigenesis [79]. *MEN1* encodes for the nuclear protein menin, which is believed to play several roles in tumorigenesis by linking transcription factor function to histone-modification pathways, in part through interacting with the activator-protein-1 family transcription factor JunD, modifying it from an oncoprotein into a tumor suppressor protein [80]. Oncogenes frequently amplified in SCLCs include *MYC* (8q24), *MYCN* (2p24), and *MYCL1* (1p34), and additional amplified genes that represent candidate oncogenes include the antiapoptotic genes *TNFRSF4* (1p36), *DAD1* (14q11), *BCL2L1* (20q11), and *BCL2L2* (14q11) [76]. The Myc proteins are transcription factors that are important in cell cycle regulation, proliferation, and DNA synthesis, and can induce $p14^{ARF}$, leading to apoptosis through p53 if cellular conditions do not favor proliferation [21].

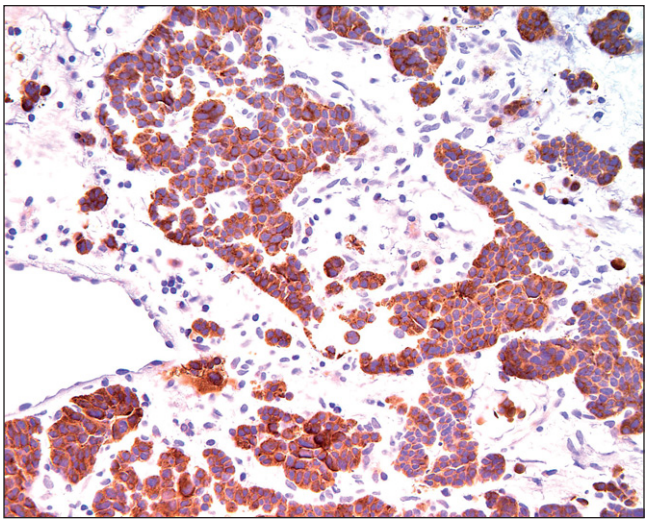

Figure 18.20 Carcinoid (immunohistochemical stain for synaptophysin). The brown-stained cytoplasm contains synaptophysin, a marker of neuroendocrine differentiation.

TSGs are inactivated in the majority of SCLCs. Eighty percent to 90% of SCLCs demonstrate *TP53* mutations, as compared to more than 50% of NSCLCs, fewer atypical carcinoids, and virtually no typically carcinoids [74,81]. Most of the *TP53* mutations in SCLCs are missense point mutations that result in a stabilized p53 mutant protein which can be easily detected by immunohistochemistry [71]. p53 protein overexpression occurs frequently in high-grade NE carcinomas, but is unusual in typical carcinoids and intermediate in atypical carcinoids [82,83]. Dysregulation of p53 produces downstream effects on Bcl-2 and Bax. Antiapoptotic Bcl-2 predominates over proapoptotic Bax in the high-grade NE carcinomas, while the reverse is true for carcinoids [82]. LCNECs resemble SCLCs in their high rates of *TP53* mutation and predominance of Bcl-2 expression over Bax expression [84].

Alterations compromising the $p16^{INK4a}$/cyclin D1/Rb pathway of G1 arrest are consistent in high-grade pulmonary NE carcinomas (92%), primarily through loss of Rb protein, but are less frequent in atypical carcinoids (59%) and are uncommon in typical carcinoids [23]. Mutations in the *RB1* gene exist in many SCLCs, with associated loss of function of the gene product [71,74,85]. In another study, 89% of the NE carcinomas (excluding carcinoids) versus 13% of the non-NE carcinomas exhibited LOH and loss of Rb-protein expression [86]. The hypophosphorylated form of Rb protein functions as a cell cycle regulator for G1 arrest; cyclin D1 overexpression and $P16^{INK4a}$ loss produce persistent hyperphosphorylation of Rb with consequent evasion of cell cycle arrest [23]. Recent data also suggest that in SCLCs, overexpression of *MDM2* (a transcriptional target of p53) or $p14^{ARF}$ loss leads to evasion of cell cycle arrest through the p53 and Rb pathway (Figure 18.2) [71].

The transcription factor E2F-1 appears to play a role in cellular proliferation by activating genes required for S phase entry. E2F-1 product is overexpressed in 92% of SCLCs and 50% of LCNECs, and is significantly associated with a high Ki67 index and Bcl-2:Bax ratio >1 [87]. A mediator of the proteasomal degradation of E2F-1, the S phase kinase-associated protein 2 (Skp2) F-box protein accumulates in high-grade NE carcinomas (86%), and its overexpression has been associated with advanced stage and nodal metastasis in pulmonary NE tumors [88]. In the high-grade NE tumors, Skp2 appears

to interact with E2F-1 and stimulate its transcriptional activity toward the cyclin E promoter [87,88].

Telomeres play an important role in the protection of chromosomes against degradation. Telomerases, the enzymes that synthesize telomeric DNA strands, serve to counterbalance losses of DNA during cell divisions. High telomerase activity has been noted in over 80% of SCLCs and LCNECs [89–91] versus 14% or fewer typical carcinoids [91,92]. Expression of human telomerase mRNA component (hTERC) and human telomerase reverse transcriptase (hTERT) mRNA were reported, respectively, in 58% and 74% of typical carcinoids; and in 100% and 100% of atypical carcinoids, LCNECs and SCLCs, and telomere length alterations in LCNECs and SCLCs were greater than in typical carcinoids [92].

Aberrant methylation of cytosine-guanine (CpG) islands in promoter regions of malignant cells is an important mechanism for silencing of TSGs (epigenetic inactivation). Methylation of DNA involves the transfer of a methyl group, by a DNA methyltransferase, to the cytosine of a CpG dinucleotide [93]. *RASSF1A* is a potential TSG that undergoes epigenetic inactivation in virtually all SCLCs and a majority of NSCLCs through hypermethylation of its promoter region [94,95]. NE tumors have lower frequencies of methylation of *p16, APC,* and *CDH13* (H-cadherin) than NSCLCs [95]. SCLCs have higher frequencies of methylation of *RASSF1A, CDH1* (E-cadherin), and *RARβ* than carcinoids [95]. Promoter methylation of *CASP8*, which encodes the apoptosis-inducing cysteine protease caspase 8, was also found in 35% of SCLCs, 18% of carcinoids, and no NSCLCs, suggesting that *CASP8* may function as a TSG in NE lung tumors [96].

Although histologically defined precursors for SCLC are lacking, a higher incidence of genetic abnormalities is found in the normal or hyperplasic airway epithelium of patients with SCLC than NSCLC [97]. By extension, it has been suggested that SCLC may arise directly from histologically normal or mildly abnormal epithelium, rather than evolving through a sequence of recognizable histologic intermediary changes [11]. Relatively little is known about molecular abnormalities in precursors of carcinoids. Although carcinoids have been viewed as arising from tumorlets, 11q13 *(int-2)* allelic imbalance is significantly more common in carcinoids (73%) than in tumorlets (9%), and may represent an early event in carcinoid tumor formation [98]. The *int-2* gene lies in close proximity to *MEN1*, a tumor suppressor gene frequently mutated in NE tumors [98]. The molecular pathology of DIPNECH remains to be elucidated.

Mesenchymal Neoplasms

Mesenchymal neoplasms included in the WHO classification scheme (Table 18.1) encompass a spectrum of malignant and benign proliferations that show differentiation along multiple lineages. Overall, these tumors are much less common in the lung than are epithelial neoplasms. Information about molecular pathogenesis has emerged for some of the mesenchymal neoplasms. Pulmonary inflammatory myofibroblastic tumor (IMT) is a lesion composed of myofibroblastic cells, collagen, and inflammatory cells that primarily occurs in individuals less than 40 years of age, and is the most common endobronchial mesenchymal lesion in childhood (Figure 18.21) [99]. Synovial sarcoma is usually a soft tissue malignancy, but uncommonly arises in the pleura or the lung and often takes an aggressive course [100]. Pulmonary hamartomas are benign neoplasms consisting of mixtures of cartilage, fat, connective tissue, and smooth muscle, which present as coin lesions on chest radiographs and are excised in order to rule out a malignancy (Figure 18.22).

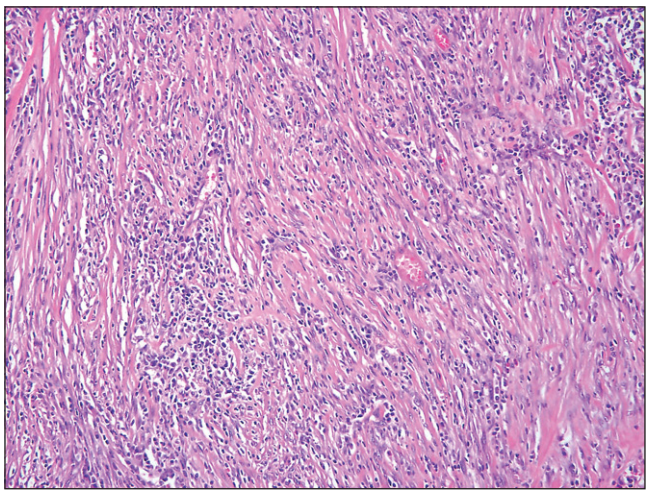

Figure 18.21 Inflammatory myofibroblastic tumor. The tumor consists of a proliferation of cytologically bland spindle cells in a background of collagen, with abundant lymphocytes and plasma cells.

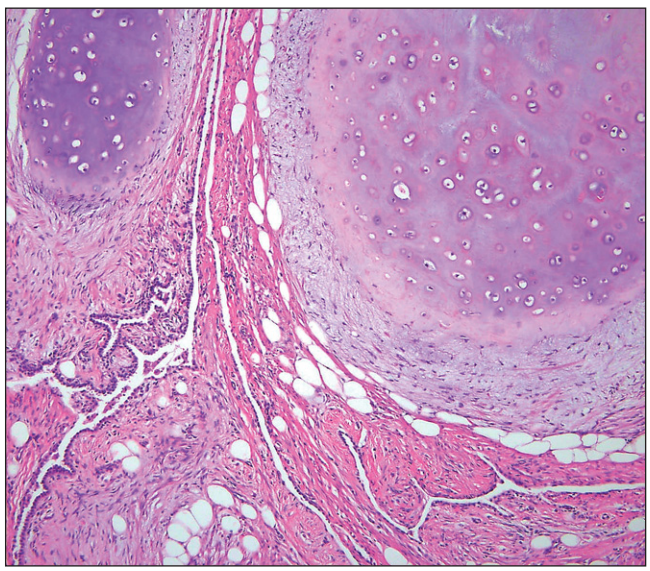

Figure 18.22 Hamartoma. A hamartoma typically includes the components of mature cartilage, adipose tissue, and myxoid or fibrous tissue, all of which are shown here.

Molecular Pathogenesis

Many IMTs demonstrate clonal abnormalities with rearrangements of chromosome 2p23 and the anaplastic lymphoma kinase *(ALK)* gene [101]. The rearrangements involve fusion of tropomyosin (TPM) N-terminal coiled–coil domains to the ALK C-terminal kinase domain, producing two ALK fusion genes, *TPM4–ALK* and *TPM3–ALK*, which encode oncoproteins with constitutive kinase activity [102]. Like their soft tissue counterparts, more than 90% of pulmonary and pleural synovial sarcomas demonstrate a chromosomal translocation t(X;18) *(SYT-SSX)* [103,104]. Detection of this translocation can be very helpful for confirming the diagnosis of synovial sarcoma in this unusual location. Most pulmonary hamartomas show abnormalities of chromosomal bands 6p21, 12q14–15, or other regions [105], corresponding to mutations of high-mobility group (HMG) proteins, a family of nonhistone chromatin-associated proteins that serve an important role in regulating chromatin architecture and gene expression [106].

Pleural Malignant Mesothelioma

Clinical and Pathologic Features

Malignant mesothelioma (MM) is an uncommon, aggressive tumor arising from mesothelial cells on serosal surfaces, primarily the pleura and peritoneum, and less often the pericardium or tunica vaginalis. The most important risk factor for MM is exposure to the subset of asbestos fibers known as amphiboles (crocidolite and amosite) [107]. The incidence of this tumor in the United States peaked in the early to mid-1990s, and appears to be declining, likely related to decreases in the use of amphiboles since their peak period of importation in the 1960s [107]. These tumors are characterized by long latency periods between asbestos exposure and clinical presentation of the tumor, with a mean of 30–40 years [108]. Radiation, a nonasbestos fiber known as erionite, and potentially other processes associated with pleural scarring have also been implicated in the causation of smaller numbers of cases of malignant mesothelioma [108], and a role for Simian virus 40 (SV40) in the genesis of this tumor has been suggested by some, but remains controversial [109,110].

Pleural MM most commonly arises in males over the age of 60. Presenting features typically include a hemorrhagic pleural effusion associated with shortness of breath and chest wall pain. Weight loss and malaise are common. By the time the tumor is discovered, patients usually have extensive involvement of the pleural surfaces. With progression, the tumor typically invades the lung, chest wall, and diaphragm. Lymph node metastasis can cause superior vena caval obstruction, and cardiac tamponade, subcutaneous nodules, and contralateral lung involvement can also occur. From the time of diagnosis, the median survival is 12 months [110]. Treatment may include surgery, chemotherapy, radiotherapy, immunotherapy, or other treatments, often in combination [110]. The intent of surgery is usually palliative. Whether extrapleural pneumonectomy with chemotherapy and radiotherapy can lead to cure is unclear [111]. New agents are currently under investigation for their potential to improve the life expectancy and quality of life in patients with this aggressive malignancy.

Gross pathologic features of MM include pleural nodules which grow and coalesce to fill the pleural cavity and form a thick rind around the lung. A firm tan appearance is common, and occasionally the tumor can have a gelatinous consistency (Figure 18.23). Extension along the interlobar fissures and invasion into the adjacent lung, diaphragm, and chest wall are characteristic. Further spread can occur into the pericardial cavity and around other mediastinal structures, and distant metastases can also develop.

Histologically, MM manifests a wide variety of histologic patterns. The major histologic categories include epithelioid mesothelioma, sarcomatoid mesothelioma, desmoplastic mesothelioma, and biphasic mesothelioma [108]. Epithelioid mesothelioma consists of round, ovoid, or polygonal cells with eosinophilic cytoplasm and nuclei that are usually round with little cytoatypia (Figure 18.24). These cells most often form sheets, tubulopapillary structures, or gland-like arrangements, and some tumors can have a myxoid appearance due to production of large amounts of hyaluronate. Sarcomatoid mesothelioma is composed of malignant-appearing spindle cells occasionally accompanied by mature sarcomatous components (osteosarcoma, chondrosarcoma, others). Desmoplastic mesothelioma can be a diagnostic challenge due to its frequently bland appearance and resemblance to organizing pleuritis. It consists of variably atypical spindle cells in a dense collagenous matrix (Figure 18.25). Helpful features for separating

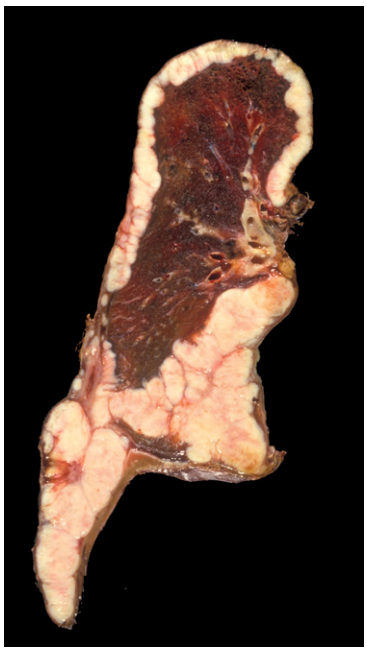

Figure 18.23 Malignant mesothelioma. The tan/white tumor involves the entire pleura surrounding and compressing the underlying parenchyma, which appears congested but relatively unremarkable.

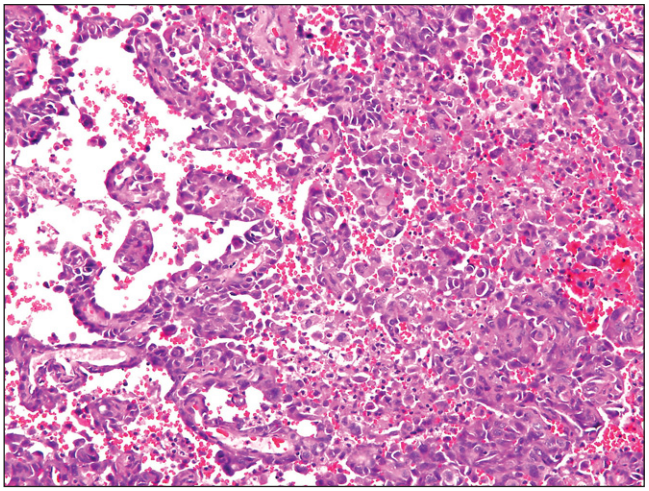

Figure 18.24 Malignant mesothelioma, epithelioid. This neoplasm consists of sheets of polygonal cells with pleomorphic nuclei and also forms some papillary structures (left).

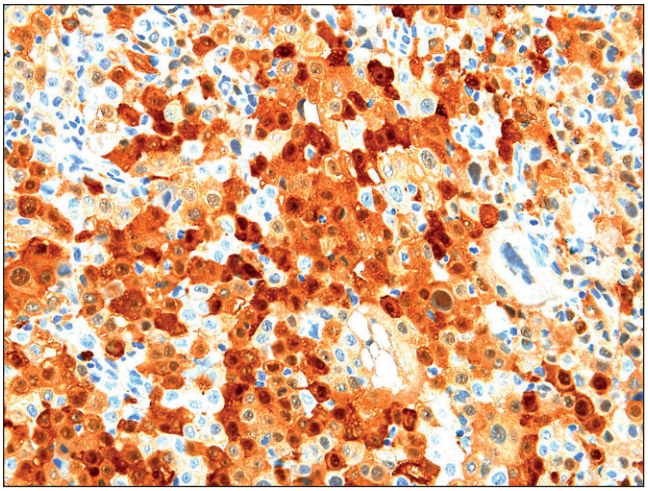

Figure 18.26 Malignant mesothelioma (immunohistochemical stain for calretinin). The tumor demonstrates cytoplasmic and nuclear staining (brown) for calretinin, which is expressed by many epithelioid malignant mesotheliomas.

this tumor from organizing pleuritis include invasion of chest wall muscle or adipose tissue and necrosis. Biphasic mesotheliomas include both epithelioid and sarcomatoid elements, each comprising at least 10% of the tumor [108].

Pathologic diagnosis of MM has been greatly assisted by the expanded availability of antibodies for use in immunohistochemistry [112]. Mesothelial differentiation can be supported by immunoreactivity with cytokeratin 5/6, calretinin (Figure 18.26), HBME-1, D2–40, and other antibodies. Histologic distinction of epithelioid mesotheliomas from metastatic ACs is a common need in practice, and a panel approach using calretinin and cytokeratin 5/6, with other antibodies reactive with ACs (CEA, MOC-31, Ber-EP4, leu M1, B72.3, and others) will usually be successful. Electron microscopy can also be helpful in difficult cases by demonstrating long thin microvilli in many MMs with an epithelioid component. Pan-cytokeratin staining is helpful for supporting a diagnosis of sarcomatoid or desmoplastic MM as opposed to sarcoma, since most (but not all) sarcomas will not stain for pan-cytokeratin. Other mesothelial and mesenchymal markers can also be useful for assisting in the differentiation of MM from histologically similar sarcomas.

Precursor lesions for MM have not been clearly defined from a histologic standpoint, although it is likely that an *in situ* stage exists [108]. The term atypical mesothelial hyperplasia has been recommended for surface (noninvasive) proliferations of mesothelial cells of uncertain malignant potential [108].

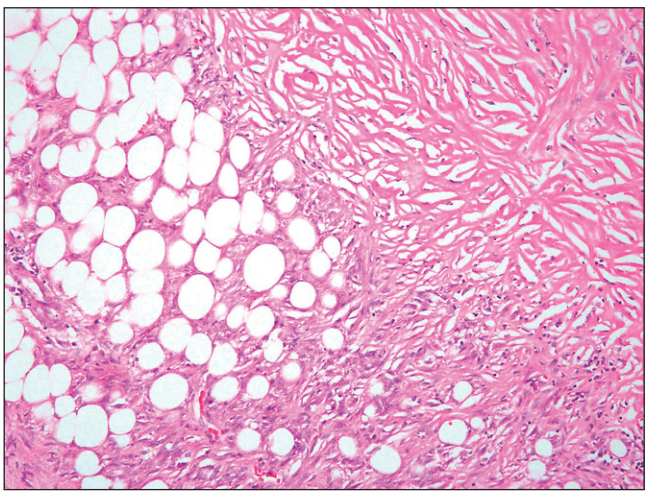

Figure 18.25 Malignant mesothelioma, desmoplastic. Abundant dense collagen is characteristic of this tumor, and is shown in the upper right. Tumor cells are spindle shaped and relatively cytologically bland. The slit-like spaces observed in the dense collagen are another frequent feature. The tumor infiltrates adipose tissue, which is helpful in confirming that the tumor is a mesothelioma, as opposed to organizing pleuritis.

Molecular Pathogenesis

Exposure to asbestos fibers is believed to trigger the pathobiological changes leading to the majority of MMs. Currently, it is believed that asbestos may act as an initiator (genetically) and promoter (epigenetically) in the development of MMs [113]. The degree to which tumorigenesis results from direct interactions of the fibers with the mesothelial cells, or through other mechanisms involving oxidative stress (or both), is unresolved [113,114]. Multiple chromosomal alterations are often noted in MMs, and inactivation of TSGs plays an important part in the pathogenesis of MM [113]. A variety of genetic abnormalities have been reported including deletions of 1p21–22, 3p21, 4p, 4q, 6q, 9p21, 13q13–14, 14q, and proximal 15q, monosomy 22, and gains of 1q, 5p, 7p, 8q22–24, and 15q22–

25 [108,115]. The most common genetic abnormality in MM is a deletion in 9p21 encompassing the *CDKN2A* locus encoding the tumor suppressors $p16^{INK4a}$ and $p14^{ARF}$, which participate in the p53 and Rb pathways and inhibit cell cycle progression (Figure 18.2) [113,116]. Recent studies have shown that SV40 large T antigen (present in some MMs) inactivates the TSG products Rb and p53, raising the possibility that asbestos and SV40 could act as co-carcinogens in MM and suggesting that perturbations of Rb- and p53-dependent growth-regulatory pathways may be involved in the pathogenesis of MM [115]. Other common findings include inactivating mutations with allelic loss in the TSG neurofibromin 2 (*NF2),* found at chromosome 22q12 [117], and inactivation of *CDKN2A/p14ARF* and *GPC3* (another TSG) by promoter methylation [108]. Loss of *CDKN2A/p14ARF* also results in MDM2-mediated inactivation of p53 [116]. However, in MMs, unlike many other epithelial tumors, mutations in the *TP53, RB,* and *RAS* genes are rare [118].

The Wnt signal transduction pathway is also abnormally activated in MMs and appears to play a role in pathogenesis [119]. Activation of the pathway leads to accumulation of β-catenin in the cytoplasm and its translocation to the nucleus. Interactions with TCF/LEF transcription factors promote expression of multiple genes including c-*myc* and C*yclin D*. The mechanism of activation does not appear to involve mutations in the *β-catenin* gene, but may instead involve more upstream components of the pathway, such as the disheveled proteins [119]. Recent evidence also suggests that the phosphatidylinositol 3-kinase (PI3–K/AKT) pathway is frequently activated in MMs, and that inhibition of this pathway can increase sensitivity to a chemotherapeutic agent [120]. The *Wilms' tumor gene (WT1)* is also expressed in most MMs, but its role in the pathogenesis of MM is unclear [114]. Finally, EGFR signaling in MMs has recently become a focus of greater attention, and there are some data showing that the EGFR is an early cell membrane target of asbestos fibers and is linked to activation of the MAPK cascade [113]. Unfortunately, a Phase II clinical trial of gefitinib treatment in patients with MMs did not show effectiveness, despite *EGFR* overexpression in over 97% of cases [121]. Another study found that common *EGFR* mutations conferring sensitivity to gefitinib are not prevalent in human malignant mesothelioma [122]. Further investigation continues into new, potentially efficacious agents for the treatment of MM.

NON-NEOPLASTIC LUNG DISEASE

Non-neoplastic pulmonary pathology comprises inflammatory and fibrosing diseases of the conducting airways, alveoli, vessels, and lymphoid tissue. This pathology may be localized or diffuse, may either have an obvious etiology or be idiopathic, and may cause injury that is reparable or irreparable. Most importantly, an understanding of non-neoplastic lung pathology plays a vital role in the clinical management of these diseases. This section covers the major types of obstructive and interstitial diseases, the vascular lesions, the pneumonias, the occupational diseases, the major histiocytic conditions, and the most common developmental anomalies. This list does not include all of the non-neoplastic diseases that can affect the lung, but it represents those that are responsible for the majority of illness. Also, the conditions highlighted within each of these categories are those about which we best understand the molecular biology of the disease mechanisms.

OBSTRUCTIVE LUNG DISEASES

Obstructive lung diseases are characterized by a reduction in airflow due to airway narrowing. This airflow reduction occurs, in general, by two basic mechanisms: (i) inflammation and injury of the airway, resulting in obstruction by mucous and cellular debris within and around the airway lumen; and (ii) destruction of the elastin fibers of the alveolar walls, causing loss of elastic recoil and subsequent premature collapse of the airway during the expiratory phase of respiration. There are four major obstructive lung diseases: asthma, emphysema, chronic bronchitis, and bronchiectasis.

Asthma

Clinical and Pathologic Features

Asthma is a chronic inflammatory disease of the airways that affects more than 150 million people worldwide. The prevalence of disabling asthma has increased over 200% since 1969, ranging from as low as 1% in rural Ethiopia to over 20% among children in parts of Central and South America [123]. In the United States, asthma affects approximately 8%–10% of the population and is the leading cause of hospitalization among children less than 15 years of age [123]. Clinically, the disease is defined as a generalized obstruction of airflow with a reversibility that can occur spontaneously or with therapy. It is characterized by recurrent wheezing, cough, or shortness of breath resulting from airway hyperactivity and mucus hypersecretion. The hyperresponsiveness is a result of acute bronchospasm and can be elicited for diagnostic purposes using histamine or methacholine challenges. The key feature of these symptoms is that they are variable—worse at night or in the early morning, and in some people worse after exercise. It has previously been assumed that these symptoms are separated by intervals of normal physiology. However, evidence is now accumulating that asthma can cause progressive lung impairment due to chronic morphologic changes in the airways. The treatment strategies for this complex disease are myriad. In atopic individuals, allergen avoidance should be the primary therapy. For example, in children, reducing exposure to house dust mites early in life decreases sensitization and the incidence of disease. For those who do develop the disease, avoidance of allergens later in life improves symptom control. Established treatments for asthma flairs include inhaled corticosteroids, and short-acting and long-

acting β2-adrenoceptor agonists. Phosphodiesterase (PDE) inhibitors such as theophylline have been used for decades to treat asthmatic bronchoconstriction, but both cardiac and central nervous systems side effects have limited their use. Newer PDE inhibitors without side effects include non-xanthine drugs such as rofumilast.

The pathologic changes to the airways in asthma are very similar to those seen in chronic bronchitis. They consist of a thickened basement membrane with epithelial desquamation, goblet cell hyperplasia, and subepithelial elastin deposition. In the wall of the airway, smooth muscle hypertrophy and submucosal gland hyperplasia are also present (Figure 18.27). In acute asthma exacerbations, a transmural chronic inflammatory infiltrate with variable amounts of eosinophilia may be present, resulting in epithelial injury and desquamation that can become quite pronounced. One sees clumps of degenerating epithelial cells mixed with mucin in the lumen airway. These aggregates of degenerating cells are referred to as Creola bodies and can be seen in expectorated mucin from these patients. Also present in these sputum samples are Charcot-Leyden crystals, rhomboid-shaped structures that represent breakdown products from eosinophil cytoplasmic granules (Figure 18.28). The changes seen in the walls of these airways represent long-term airway remodeling caused by prolonged inflammation. This remodeling may play a role in the pathophysiology of asthma. The amount of airway remodeling is highly variable from patient to patient, but remodeling has been found even in patients with mild asthma. Currently, the effect of the treatment on this chronic pathology is unclear [124].

Molecular Pathogenesis

The pathogenesis of asthma is complex, and most likely involves both genetic and environmental components. Most experts now see it as a disease in which an insult initiates a series of events in a genetically susceptible host. No single gene accounts for the familial component of this disease. Genetic analysis of these patients reveals a prevalence of specific HLA alleles, polymorphisms of *FcεRiB, IL-4,* and *CD14* [125,126]. Asthma can be classified using a number of different schema. Most commonly, asthma is divided into two categories: atopic (allergic) and nonatopic (nonallergic). Atopic asthma results from an allergic sensitization usually early in life and has its onset in early childhood. Nonatopic asthma is late-onset and, though the immunopathology has not been as well studied, probably has similar mechanisms to atopic asthma. Although this nosology is convenient for purposes of understanding the mechanisms of the disease, most patients manifest a combination of these two categories with overlapping symptoms.

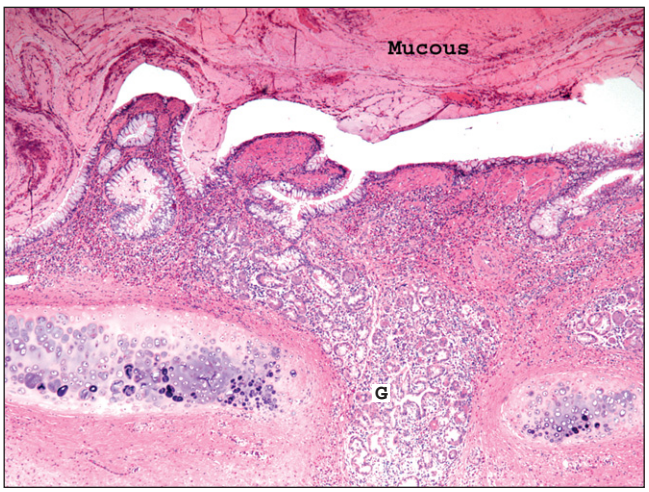

Figure 18.27 Asthma. The bronchial wall from a patient with asthma shows marked inflammation with eosinophils, mucosal goblet cell hyperplasia (G), and an increase in the smooth muscle.

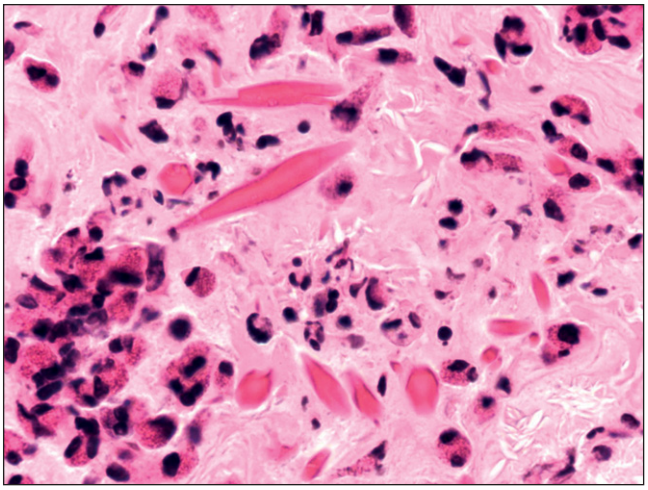

Figure 18.28 Asthma. Charcot-Leyden crystals are rhomboid-shaped structures within a mucous plug from an airway of an asthmatic patient. In addition, there are abundant eosinophils. These crystals are made of breakdown products of eosinophils, including major basic protein.

Th0 pathogenetic mechanisms of both types encompass a variety of cells and their products. These include airway epithelium, smooth muscle cells, fibroblasts, mast cells, eosinophils, and T-cells. The asthma response includes two phases: an early response comprising an acute bronchospastic event within 15–30 minutes after exposure, and a late response that peaks approximately 4–6 hours and that can have prolonged effects. If one wants to understand this complex response, it is best to divide it into three components: (i) a type 1 hypersensitivity response, (ii) acute and chronic inflammation, and (iii) bronchial hyperactivity.

Type 1 Hypersensitivity In general, human asthma is associated with a predominance of Type 2 helper cells with a CD4+ phenotype. These Th2-type cells result from the uptake and processing of viral, allergen, and environmental triggers that initiate the episode. The processing includes the presentation of these triggers by the airway dendritic cells to naive T-cells (Th0), resulting in their differentiation into populations of Th1 and Th2. The Th2 differentiation is a result of IL-10 release by the dendritic cells, and the Th2 cells then

further propagate the inflammatory reaction in two ways. First, they release a variety of cytokines such as IL-4, IL-5, and IL-13 that mediate a wide variety of responses. IL-4 and IL-13 stimulate B-cells and plasma cells to produce IgE, which, in turn, stimulates mast cell maturation and the release of multiple mediators, including histamine and leukotrienes. Second, these Th2 cells secrete IL-5 that, together with IL-4, also stimulates mast cells to secrete histamine, tryptase, chymase, and the cysteinyl leukotrienes causing the bronchoconstrictor response that occurs rapidly after the exposure to the allergen. IL-5 from these lymphocytes also recruits eosinophils to the airways and stimulates the release of the contents of their granules, including eosinophil cationic protein (ECP), major basic protein (MBP), eosinophil peroxidase, and eosinophil-derived neurotoxin. These compounds not only induce the bronchial wall hyperactivity but are also responsible for the increased vascular permeability that produces the transmural edema in the airways.

The cells can differentiate into Th1 cells as a result of IL-12 produced by dendritic cells. These Th1 cells produce interferon-gamma (IFN-γ), IL-2, and lymphotoxin, which play a role in macrophage activation in delayed-type hypersensitivity reactions as seen in diseases such as rheumatoid arthritis and tuberculosis [123]. These Th1 cells are predominantly responsible for defense against intracellular organisms and are more prominent in normal airways and in airways of patients with emphysema than in asthmatics. However, in severe forms of asthma, Th1 cells are recruited and have the capacity to secrete tumor necrosis factor (TNF)-α and IFN-γ, which may lead to the tissue-damaging immune response one sees in these airways (Figure 18.29) [127,128].

Acute and Chronic Inflammation The role of acute and chronic inflammatory cells, including eosinophils, mast cells, macrophages, and lymphocytes, in asthma is evident in the abundance of these cells in airways, sputum, and bronchoalveolar samples from patients with this disease. The number of eosinophils in the airways correlates with the severity of asthma and the amount of bronchial hyperresponsiveness. Proteins released by these cells including ECP, MCP, and eosinophil-derived neurotoxin cause at least some of the epithelial damage seen in the active form of asthma. Neutrophils are prominent in the more acute exacerbations of asthma and are probably recruited to these airways by IL-8, a potent neutrophil chemoattractant released by airway epithelial cells [123]. These cells also release proteases, reactive oxygen species (ROS), and other proinflammatory mediators that, in addition to the epithelial damage, also contribute to the airway destruction and remodeling that occurs in the more chronic forms of this disease. The susceptibility of the epithelium in asthma to this oxidant injury may be increased due to decreased antioxidants such as superoxide dismutase in these lungs [129]. Finally, mast cells are activated to release an abundance of mediators through the binding of IgE to FcεRI, high-affinity receptors on their surface. Allergens bind to IgE molecules and induce a cross-linking of these molecules, leading to activation of the mast cell and release of a number of mediators, most notably histamine, tryptase, and various leukotrienes, including leukotriene D_4 (LTD_4), and interact with the smooth muscle to induce contraction and the acute bronchospastic response [130].

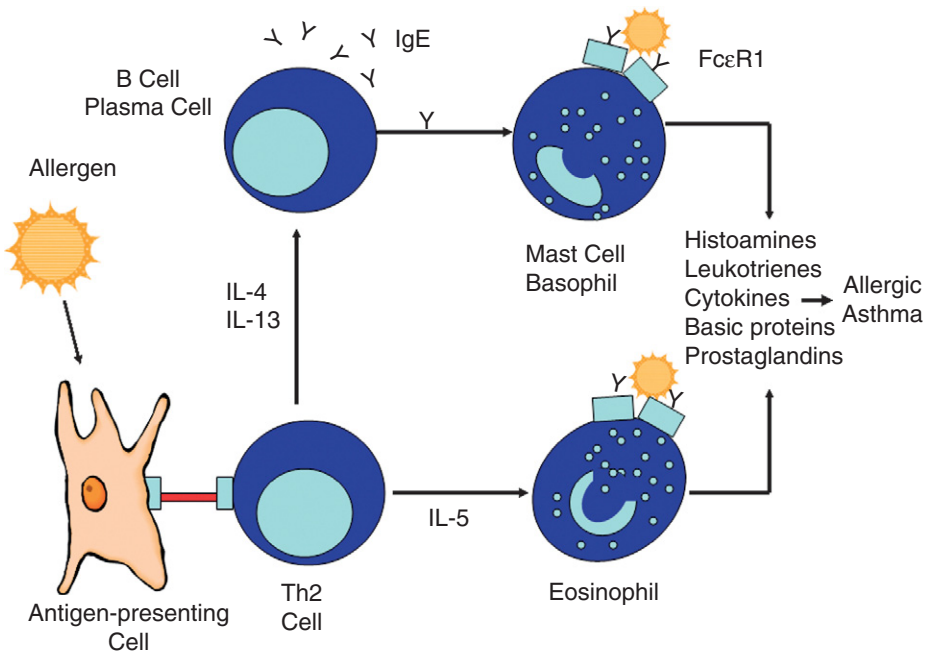

Figure 18.29 Inflammation in asthma. Inflammatory cascade in allergic asthma involves presentation of the allergen by an antigen-presenting cell to Th2 cells. This causes a release of multiple cytokines that lead to the recruitment of eosinophils, macrophages, and basophils [adapted from 128].

Bronchial Hyperactivity The cornerstone of asthma is the hyperactive response of the airway smooth muscle. The mechanism by which this occurs combines neural pathways and inflammatory pathways. As stated, the inflammatory component of this response comes predominantly from the mast cells. The major neural pathway involved is the nonadrenergic noncholinergic (NANC) system. Although cholinergic pathways are responsible for maintaining the airway smooth muscle tone, it is the NANC system that releases bronchoactive tachykinins (substance P and neurokinin A) that bind to NK2 receptors on the smooth muscle and cause the constriction that characterizes the acute asthmatic response [123].

In addition to these acute mechanisms, the airway also undergoes structural alterations to its formed elements. In the mucosa, these changes include goblet cell hyperplasia and basement membrane thickening. Within the submucosa and airway wall, increased deposition of collagen and elastic fibers results in fibrosis and elastosis, and both the smooth muscle cells and the submucosal glands undergo hypertrophy and hyperplasia. These irreversible changes are a consequence of chronic inflammatory insults on the airways through mechanisms that include release of fibrosing mediators such TGFβ and mitogenic mediators such as epidermal and fibroblast growth factors (EGF, FGF). The exact mechanisms by which this occurs are not clearly defined, but the similarity of these factors with those involved in branching morphogenesis of the developing lung has led to a focus on the effect of inflammation on the interaction of the epithelium with the underlying mesenchymal cells [128].

Chronic Obstructive Lung Disease (COPD) – Emphysema/Chronic Bronchitis

Clinical and Pathologic Features

The term chronic obstructive pulmonary disease (COPD) applies to emphysema, chronic bronchitis, and bronchiectasis, those diseases in which airflow limitation is usually progressive, but, unlike asthma, not fully reversible [131]. The prevalence of COPD worldwide is estimated at 9%–10% in adults over the age of 40 [132]. Though there are different forms of COPD with different etiologies, the clinical manifestations of the most common forms of the disease are the same. These include a progressive decline in lung function, usually measured as decreased forced expiratory flow in 1 second (FEV1), a chronic cough, and dyspnea. Emphysema and chronic bronchitis are the most common diseases of COPD and are the result of cigarette smoking. As such, they usually exist together in most smokers. Chronic bronchitis is defined clinically as a persistent cough with sputum production for at least 3 months in at least 2 consecutive years without any other identifiable cause. Patients with chronic bronchitis typically have copious sputum with a prominent cough, more commonly get infections, and typically experience hypercapnia and severe hypoxemia, giving rise to the clinical moniker blue bloater. Emphysema is the destruction and permanent enlargement of the air spaces distal to the terminal bronchioles without obvious fibrosis [133]. These patients have only a slight cough, while the overinflation of the lungs is severe, inspiring the term pink puffers.

The pathologic features of COPD are best understood if one considers the whole of COPD as a spectrum of pathology that consists of emphysematous tissue destruction, airway inflammation, remodeling, and obstruction [134]. The lungs of patients with COPD usually contain all of these features, but in varying proportions. The pathologic features of chronic bronchitis include mucosal pathology that consists of epithelial inflammation, injury, and regenerative epithelial changes of squamous and goblet cell metaplasia. In addition, the submucosa shows changes of remodeling with smooth muscle hypertrophy and submucosal gland hyperplasia. These changes are responsible for the copious secretions characteristic of this clinical disease, although studies have reported no consistent relationship between these pathologic features of the large airways and the airflow obstruction [135].

The pathology definition of emphysema is an abnormal, permanent enlargement of the airspaces distal to the terminal bronchioles accompanied by destruction of the alveolar walls without fibrosis [133]. The four major pathologic patterns of emphysema are defined by the location of this destruction. These include centriacinar, panacinar, paraseptal, and irregular emphysema. The first two of these are responsible for the overwhelming majority of the clinical disease. Centriacinar emphysema (sometimes referred to as centrilobular) represents 95% of the cases and is a result of destruction of alveoli at the proximal and central areas of the pulmonary acinus, including the respiratory bronchioles (Figure 18.30). It predominantly affects the upper lobes

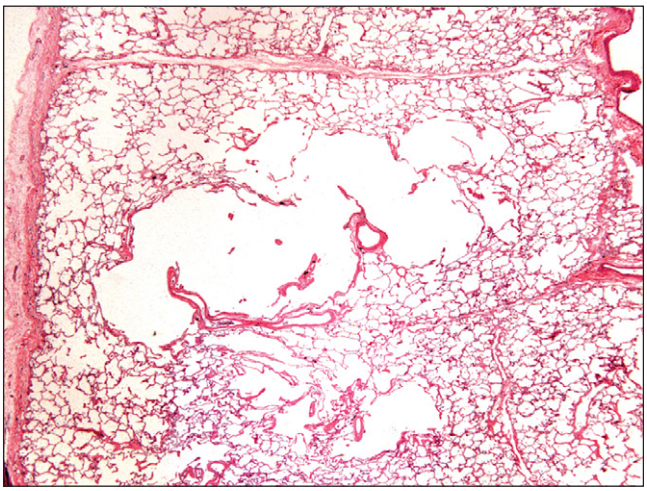

Figure 18.30 Centrilobular emphysema. Tissue destruction in central area of the pulmonary lobule is demonstrated in this lung with a mild centrilobular emphysema. The pattern of tissue destruction is in the area surrounding the small airway where pigmented macrophages release proteases in response to the cigarette smoke.

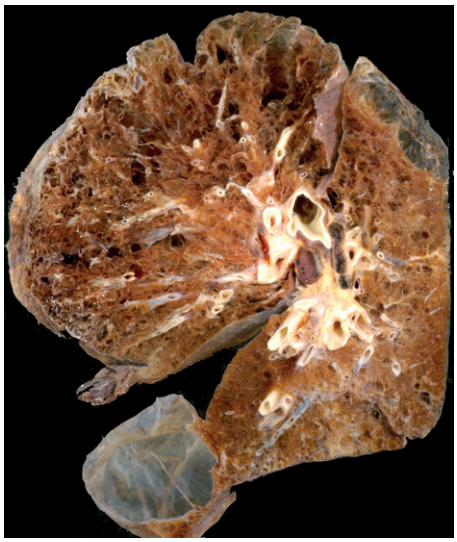

Figure 18.31 Centrilobular emphysema. This sagittal cut section of a lung contains severe centrilobular emphysema with significant tissue destruction in the upper lobe and bulla forming in the upper and lower lobes.

(Figure 18.31). Panacinar emphysema, usually associated with α1-antitrypsin (αAT) deficiency, results in a destruction of the entire pulmonary acinus from the proximal respiratory bronchioles to the distal area of the acinus, and affects predominantly the lower lobes (Figure 18.32). The remaining two types of emphysema, paraseptal and irregular, are rarely associated with clinical disease. In paraseptal emphysema, the damage is to the distal acinus, the area that abuts the pleura at the margins of the lobules. Damage in this area may cause spontaneous pneumothoraces, typically in young, thin men [136]. Irregular emphysema is tissue destruction and alveolar enlargement that occurs adjacent to scarring, secondary to the enhanced inflammation in the area. Though this is a common finding in a scarred lung, it is of little if any clinical significance to the patient.

Though the emphysema in these lungs plays the dominant role in causing the obstruction, small airway pathology is also present. Respiratory bronchiolitis refers to the inflammatory changes found in the distal airways of smokers. These consist of pigmented macrophages filling the lumen and the peribronchiolar airspaces and mild chronic inflammation and fibrosis around the bronchioles (Figure 18.33). The pigment in these macrophages represents the inhaled particulate matter of the cigarette smoke that has been phagocytized by these cells. The macrophages in turn release proteases, which destroy the elastic fibers in the surrounding area, resulting in the loss of elastic recoil and the obstructive symptoms.

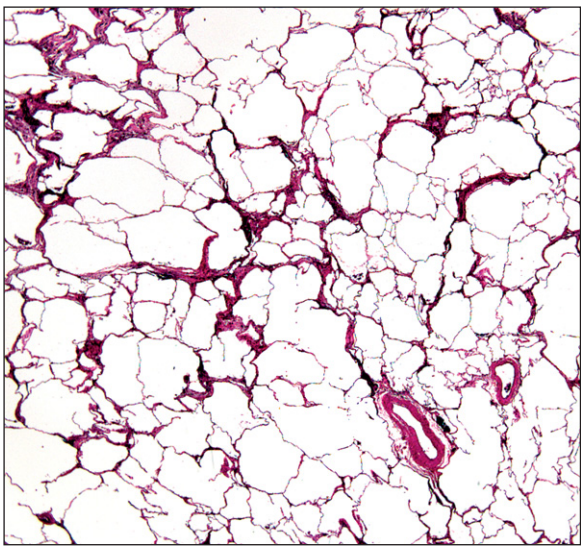

Figure 18.32 Panacinar emphysema. Tissue destruction in panacinar emphysema occurs throughout the lobule, producing a diffuse loss of alveolar walls unlike that of centrilobular emphysema with more irregular holes in the tissue.

Molecular Pathogenesis

In general, COPD is a result of inflammation of the large airways that produces the airway remodeling characteristic of chronic bronchitis as well as inflammation of the smaller airways that results in the destruction of the adjacent tissue and consequent emphysema. The predominant inflammatory cells involved in this process are the alveolar macrophages, neutrophils, and lymphocytes. The main theories of the pathogenesis of COPD support the interaction of airway inflammation with two main systems in the lung: the protease–antiprotease system and the oxidant–antioxidant system. These systems help to protect the lung from the many irritants that enter the lung via the large pulmonary surface area that interfaces with the environment.

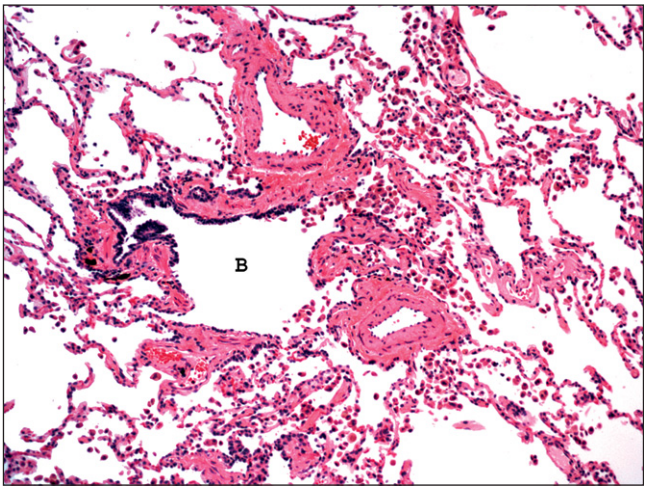

Figure 18.33 Respiratory bronchiolitis. Present in the lumen of the small bronchiole (B) and extending into the surrounding alveolar spaces are pigmented macrophages in a lung from a smoker. The pigment in these macrophages represents particulates from the cigarette smoke and stimulates the release of the proteases that are responsible for the tissue destruction in centrilobular emphysema.

In the protease–antiprotease system, proteases are produced by a number of cells, including epithelial cells and inflammatory cells that degrade the underlying lung matrix. The most important proteases in the lung are the neutrophil elastases, part of the serine protease family, and the metalloproteinases (MMPs) produced predominantly by macrophages. These proteases can be secreted in response to invasion by environmental irritants, most notably infectious agents such as bacteria. In this setting, their role is to enzymatically degrade the organism. However, proteases can also be secreted by both inflammatory and epithelial cells in a normal lung to repair and maintain the underlying lung matrix proteins [137]. To protect the lung from unwanted destruction by these enzymes, the liver secretes antiproteases that circulate in the bloodstream to the lung and inhibit the action of the proteases. In addition, macrophages that secrete MMPs also secrete tissue inhibitors of metalloproteinases (TIMPs). A delicate balance of proteases and antiproteases is needed to maintain the integrity of the lung structure. An imbalance that results in a relative excess of proteases (either by overproduction of proteases or underproduction of their inhibitors) leads to tissue destruction and the formation of emphysema.

This imbalance occurs in different ways in the two major types of emphysema: centriacinar and panacinar. In centriacinar emphysema, caused primarily by cigarette smoking, there is an overproduction of proteases primarily due to the stimulatory effect of chemicals within the smoke on the neutrophils and macrophages. Though the exact mechanism is not completely understood, most studies support that nicotine from the cigarette smoke acts as a chemoattractant, and ROS also contained in the smoke, stimulate an increased release of neutrophil elastases and MMPs from activated macrophages, leading to the destruction of the elastin in the alveolar spaces [137]. This inflammatory cell activation may come about through the activation of the transcription factor NFκB that leads to TNFα production [132]. In addition, the elastin peptides themselves may attract additional inflammatory cells to further increase the protease secretion and exacerbate the matrix destruction [137].

Unlike centriacinar emphysema, panacinar emphysema is most commonly caused by a genetic deficiency of antiproteases, usually due to alpha-1 anti-trypsin (αAT) deficiency, a condition that affects approximately 60,000 people in the United States [138]. αAT deficiency is due to a defect in the gene that encodes the protein αAT, a glycoprotein produced by hepatocytes and the main inhibitor of neutrophil elastase. The affected gene is the *SERPINA1* gene (formerly known as P1), located on the long arm of chromosome 14 (14q31–32.3). The genetic mutations that occur have been categorized into four groups: base substitution, in-frame deletions, frame-shift mutations, and exon deletions. These mutations usually result in misfolding, polymerization, and retention of the aberrant protein within the hepatocytes, leading to decreased circulating levels. αAT deficiency is an autosomal codominant disease with over 100 allelic variants, of which the M alleles (M1–M6) are the most common; these alleles produce normal serum levels of a less-active protein [139]. Individuals who manifest the lung disease are usually homozygous for the alleles Z or S (ZZ and SS phenotype) or heterozygous for the 2 M alleles (MZ, or SZ phenotype) [139]. An αAT concentration in plasma of less than 40% of normal confers a risk for emphysema [140]. In individuals with the ZZ genotype, the activity of αAT is approximately one-fifth of normal [141].

The second system in the lung involved in the pathogenesis of emphysema is the oxidant–antioxidant system. As in the protease system, the lung is protected from oxidative stress in the form of ROS by antioxidants produced by cells in the lung. ROS in the lung include oxygen ions, free radicals, and peroxides. The major antioxidants in the airways are enzymes including catalase, superoxide dismutase (SOD), glutathione peroxidase, glutathione S-transferase, xanthine oxidase, and thioredoxin, as well as nonenzymatic antioxidants including glutathione, ascorbate, urate, and bilirubin [142]. The balance of oxidants and antioxidants in the lung prevents damage by ROS. However, cigarette smoke increases the production of ROS by neutrophils, eosinophils, macrophages, and epithelial cells [143]. Evidence that damage to the lung epithelium and matrix is a direct result of ROS includes the presence of exhaled H_2O_2 and 8-isoprostane, decreased plasma antioxidants, and increased plasma and tissue levels of oxidized proteins, including various lipid peroxidation products. In addition to this direct effect, ROS may also induce a proinflammatory response that recruits more inflammatory cells to the lung. In animal models, cigarette smoke induces the expression of proinflammatory cytokines such as IL-6, IL-8, TNFα, and IL-1 from macrophages, epithelial cells, and fibroblasts, perhaps through activation of the transcription factor NFκB [144,145] (Figure 18.34). Finally, there is some evidence that cigarette smoke further disturbs the oxidant–antioxidant balance in the lung by depleting antioxidants such as ascorbate and glutathione [132].

Bronchiectasis

Clinical and Pathologic Features

Bronchiectasis represents the permanent remodeling and dilatation of the large airways of the lung most commonly due to chronic inflammation and recurrent pneumonia. These infections usually occur because airway secretions and entrapped organisms cannot be effectively cleared. This pathology dictates the clinical features of the disease, which include chronic cough with copious secretions and a history of recurrent pneumonia. The five major causes of bronchiectasis are infection, obstruction, impaired mucociliary defenses, impaired systemic immune defenses, and congenital. These may produce either a localized or diffuse form of the disease. Localized bronchiectasis is usually due to obstruction of airways by mass lesions or scars from previous injury or infection. Diffuse bronchiectasis can result from defects in systemic

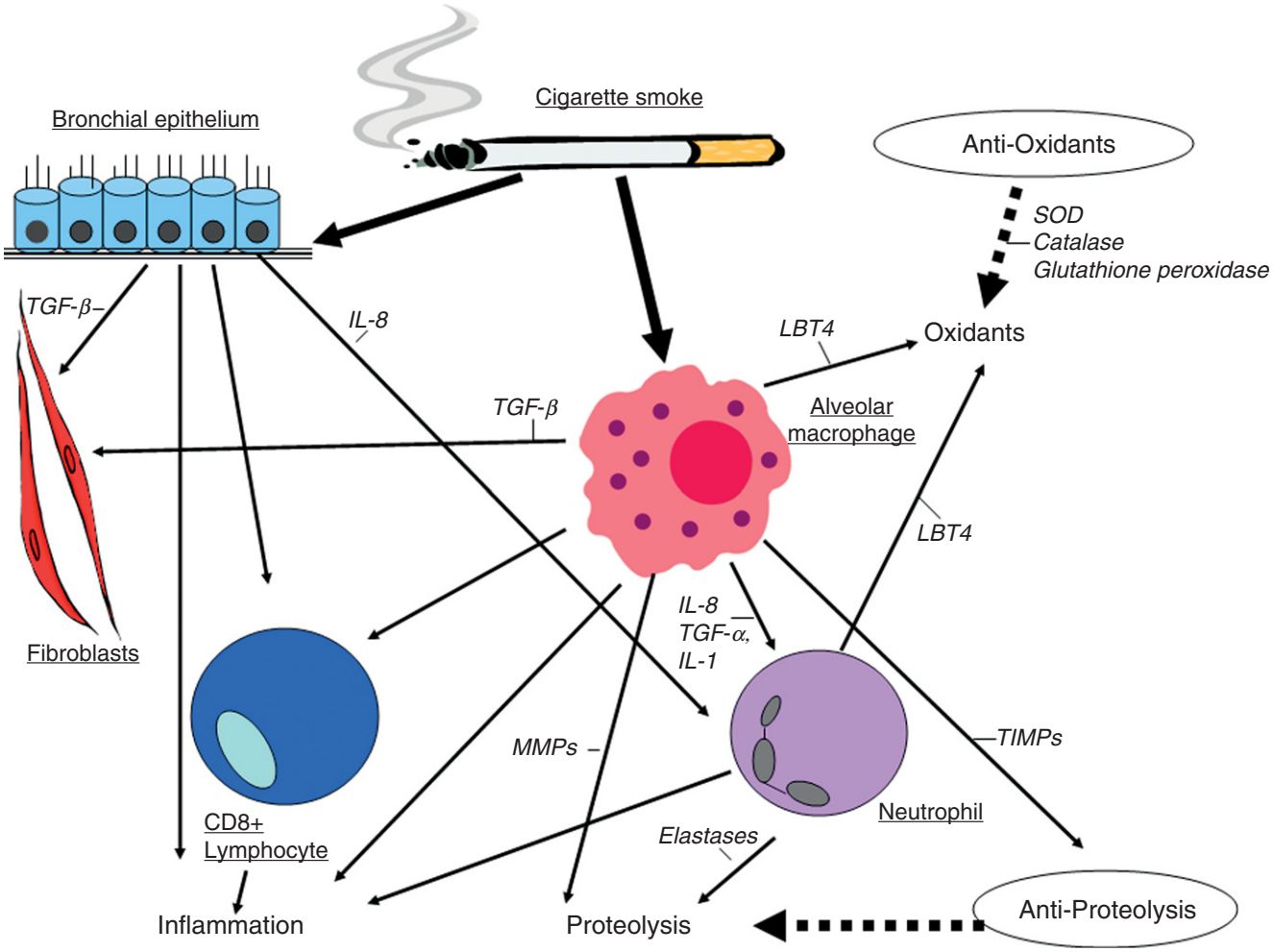

Figure 18.34 Pathogenesis of chronic obstructive pulmonary disease. Inflammatory cells including alveolar macrophages, lymphocytes, and neutrophils are involved in generating inflammation, proteolysis, and oxidative stress in chronic obstructive pulmonary disease caused by cigarette smoke. Antioxidants and antiproteases help to inhibit these effects. Profibrotic mediators stimulate fibroblasts and myofibroblasts to repair and remodel the lung after this injury [adapted from 145].

immune defenses in which either innate or adaptive immunity may be impaired. Diseases due to the former include chronic granulomatous disease (CGD), and diseases due to the latter include agammaglobulinemia/hypogammaglobulinemia and severe combined immune deficiencies. Defects in the mucociliary defense mechanism that is responsible for physically clearing organisms from the lung may also cause diffuse bronchiectasis. These include ciliary dyskinesias that result in cilia with aberrant ultrastructure and cystic fibrosis (CF). Congenital forms of bronchiectasis are rare but do exist. The most common include Mounier-Kuhn's syndrome and Williams-Campbell syndrome, the former causing enlargement of the trachea and major bronchi due to loss of bronchial cartilage, and the latter causing diffuse bronchiectasis of the major airways probably due to a genetic defect in the connective tissue [146,147].

The pathology of bronchiectasis is most dramatically seen at the gross level. One can see dilated airways containing copious amounts of infected secretions and mucous plugs localized either to a segment of the lung or diffusely involving the entire lung as in cystic fibrosis (Figure 18.35). Microscopic features include chronic inflammatory changes similar to those of chronic bronchitis but with ulceration of the mucosa and submucosa leading to destruction of the smooth muscle, and elastic in the airway wall and the characteristic dilatation and fibrosis. These enlarged airways contain mucous plugs comprising mucin and abundant degenerating inflammatory cells, a result of infections that establish themselves in these airways following the loss of the mucociliary defense mechanism. Bacteria may be found in these plugs, most notably *P. aeruginosa.*

Molecular Pathogenesis

The pathogenetic mechanism of bronchiectasis is complex and depends on the underlying etiology. In general, the initial damage to the bronchial epithelium is

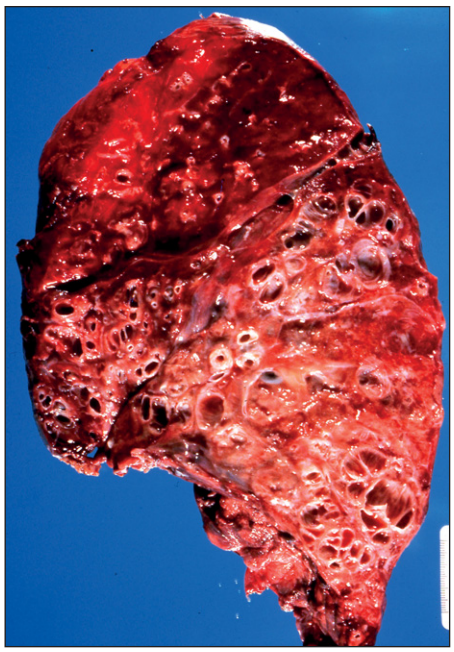

Figure 18.35 Cystic fibrosis. This sagittal cut section of a lung from a patient with cystic fibrosis demonstrates a diffuse bronchiectasis illustrated by enlarged, cyst-like airways. This is the typical pathology for cystic fibrosis. The remainder of the lung contains some red areas of congestion.

due to aberrant mucin (cystic fibrosis), dysfunctional cilia (ciliary dyskinesias), and ineffective immune surveillance (defects in innate and antibody-mediated immunity), leading to a cycle of tissue injury, repair, and remodeling that ultimately destroys the normal airway. The initial event in this cycle usually involves dysfunction of the mucociliary mechanism that inhibits the expulsion from the lungs of organisms and other foreign substances that invade the airways. This may be due to defects in the cilia or the mucin. Ciliary defects are found in primary ciliary dyskinesia, a genetically heterogeneous disorder, usually inherited as an autosomal recessive trait that produces immotile cilia with clinical manifestations in the lungs, sinuses, middle ear, male fertility, and organ lateralization [148]. Over 250 proteins make up the axoneme of the cilia, but mutations in 2 genes, *DNAI1* and *DNAH5*, which encode for proteins in the outer dynein arms, most frequently cause this disorder [149]. In CF the main defect affects the mucin. In patients with this autosomal recessive condition, there is a low volume of airway surface liquid (ASL) causing sticky mucin that inhibits normal ciliary motion and effective mucociliary clearance of organisms. This is due to a defect in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, located on chromosome 7 that encodes a cAMP-activated channel which regulates the flow of chloride ions in and out of cells and intracellular vacuoles, helping to maintain the osmolality of the mucin. This protein is present predominantly on the apical membrane of the airway epithelial cells, though it is also involved in considerable subapical, intracellular trafficking and recycling during the course of its maturation within these cells. This genetic disease manifests in multiple other organs that depend on chloride ion transport to maintain normal secretions, including the pancreas, intestine, liver, reproductive organs, and sweat glands [150].

The genetic mutations in CF influence the CFTR trafficking in the distal compartments of the protein secretary pathway, and various genetic mutations produce different clinical phenotypes of the disease. Over 1600 mutations of the *CFTR* gene have been found. However, only four of these mutations occur at a frequency of greater than 1%. These mutations are grouped into five classes according to their functional deficit: Group I, CFTR is not synthesized; Group II, CFTR is inadequately processed; Group III, CFTR is not regulated; Group IV, CFTR shows abnormal conductance; Group V, CFTR has partially defective production or processing. Approximately 70% of CF patients are in Group II and have the same mutation, F508Δ CFTR, a deletion of phenylalanine at codon 508 [154]. In these patients, most of the CFTR protein is misfolded and undergoes premature degradation within the endoplasmic reticulum, though a small amount of the CFTR protein is present on the apical membrane and does function normally. CF patients may have a combination of genetic mutations from any of the five groups. However, those patients with the most severe disease involving both the lungs and pancreas usually carry at least two mutations from Group I, II, or III [151].

Systemic immune deficiencies cause bronchiectasis through the establishment of persistent infection and inflammation. There are four major categories of immune deficiencies. The first category consists of a number of genetic diseases that cause either agammaglobulinemia or hypogammaglobulinemia. These include X-linked agammaglobulinemia (XLA) and common variable immunodeficiency (CVI). XLA is caused by a mutation of the Bruton's tyrosine kinase (BTK) gene that results in the virtual absence of all immunoglobulin isotypes and of circulating B lymphocytes. In CVI there is a marked reduction in IgG and IgA and/or IgM, associated with defective antibody response to protein and polysaccharide antigens. As expected, both of these diseases increase susceptibility to infections from encapsulated bacteria. The second category of immune deficiency is hyper-IgE syndrome, a disease with markedly elevated serum IgE levels that is characterized by recurrent staphylococcal infections. The third category is chronic granulomatous disease (CGD), a genetically heterogeneous group of disorders that have a defective phagocytic respiratory burst and superoxide production, inhibiting the ability to kill *Staphylococcus* spp. and fungi such as *Aspergillus* spp. Finally, severe combined immune deficiency (SCID) comprises a group of disorders with abnormal T- cell development and B-cell and/or natural killer cell maturation and function, predisposing these patients to *Pneumocystis jiroveci* and viral infections [152].

After the initial insult, the subsequent steps in the development of bronchiectasis include destruction of the epithelial cells and bronchial wall connective tissue matrix by the proteases and ROS secreted by the neutrophils.

This proinflammatory milieu is produced by multiple factors. First, infections can persist in these lungs due to defective host immune systems and mechanisms certain organisms have developed to evade these immune defenses. For example, *Pseudomonas aeruginosa*, changes from a nonmucoid to a mucoid variant and also releases virulence factors to protect against phagocytosis [153]. Second, in the case of cystic fibrosis, neutrophils are directly recruited by proinflammatory cytokines, such as interleukin-8 (IL-8), released from the bronchial epithelial cells as a result of the defective CGFT protein [154]. Finally, the necrotic cellular debris and other breakdown products act as chemoattractants that recruit more inflammatory cells to the airway wall, further exacerbating the damage.

The final phase of the repair and remodeling begins when macrophages invade and recruit fibroblasts that secrete collagen, leading to the fibrosis seen in the pathology. However, in the absence of effective airway clearance mechanisms, these ectatic airways remain a reservoir of infection that continues the cycle of inflammation and tissue destruction.

INTERSTITIAL LUNG DISEASES

Idiopathic Interstitial Pneumonias – Usual Interstitial Pneumonia

Clinical and Pathology Features

The idiopathic interstitial pneumonias (IIPs) comprise a group of diffuse infiltrative pulmonary diseases with a similar clinical presentation characterized by dyspnea, restrictive physiology, and bilateral interstitial infiltrates on chest radiography [155]. Pathologically, these diseases have characteristic patterns of tissue injury with chronic inflammation and varying amounts of fibrosis. By recognizing these patterns, a pathologist can classify each of these entities and predict prognosis. However, the pathologist cannot establish the etiology, since these pathologic patterns can be seen in multiple clinical settings.

The pathologic classification of these diseases, originally defined by Liebow and Carrington in 1969 [156], has undergone important revisions over the past 35 years with the latest revision by the *American Thoracic Society/European Respiratory Society* in 2003 [157]. The best known and most prevalent entity of the IIPs is idiopathic pulmonary fibrosis (IPF), which is known pathologically as usual interstitial pneumonia (UIP). UIP is a histologic pattern characterized by patchy areas of chronic lymphocytic inflammation with organizing and collagenous type fibrosis. These patients usually present with gradually increasing shortness of breath and a nonproductive cough after having had symptoms for many months or even years. Imaging studies usually reveal bilateral, basilar disease with a reticular pattern [155]. Therapy begins with corticosteroids, advancing to more cytotoxic drugs such as methotrexate and cytoxan, but most current therapies are not effective in stopping the progression of the disease. The current estimates are that 20/100,000 males and 13/100,000 females have the disease, most of whom progress to respiratory failure and death within 5 years [158].

The pathology is characterized by a leading edge of chronic inflammation with fibroblastic foci that begin in different areas of the lung at different times. These processes produce a variegated pattern of fibrosis, usually referred to as a temporally heterogenous pattern of injury [159]. Because it occurs predominantly in the periphery of the lung involving the subpleura and interlobular septae, the gross picture is one of more advanced peripheral and basilar disease (Figure 18.36). The progression from inflammation to fibrosis includes interstitial widening, epithelial injury and sloughing, fibroblastic infiltration, and organizing fibrosis within the characteristic fibroblastic foci. Deposition of collagen by fibroblasts occurs in the latter stages of repair. The presence of the abundant collagen produces stiff lungs that are unable to clear the airway secretions, leading to recurrent inflammation of the bronchiolar epithelium with eventual fibrosis and breakdown of the airway structure. This remodeling produces mucous-filled ectatic spaces giving rise to the gross picture of honeycomb spaces, which is seen in the advanced pathology (Figure 18.36) [160].

Molecular Pathogenesis

Theories of the pathogenesis of IPF have evolved over the past decade. Early theories favored a primary inflammatory process, while current theories favor the concept that the fibrosis of the lung proceeds independently of inflammatory events and develops from aberrant epithelial and epithelial-mesenchymal responses to injury to the alveolar epithelial cells (AECs) [161]. The AECs consist of two populations: the type 1 pneumocytes and the type 2 pneumocytes. In normal lungs, type 1 pneumocytes line 95% of the alveolar wall, and type 2 pneumocytes line the remaining 5%. However, in lung injury, the type 1 cells, which are exquisitely fragile, undergo cell death, and the type 2 pneumocytes serve as progenitor cells to regenerate the alveolar epithelium [162]. Though some studies have suggested that repopulation of the type 2 cells depends on circulating stem cells, this concept remains to be fully proven. According to current concepts, the injury and/or apoptosis of the AECs initiates a cascade of cellular events that produce the scarring in these lungs. Studies of AECs in lungs from patients with IPF have shown ultrastructural evidence of cell injury and apoptosis as well as expression of proapoptotic proteins. Further, inhibition of this apoptosis by blocking a variety of proapoptotic mechanisms such the Fas-Fas ligand pathway, angiotensin, and TNFα production, and caspase activation can stop the progression of this fibrosis [163].

The result of the AEC injury is the migration, proliferation, and activation of the fibroblasts and myofibroblasts that leads to the formation of the characteristic fibroblastic foci of the UIP pathology and the deposition and accumulation of collagen and elastic fibers in the alveoli (Figure 18.37). This unique pathology

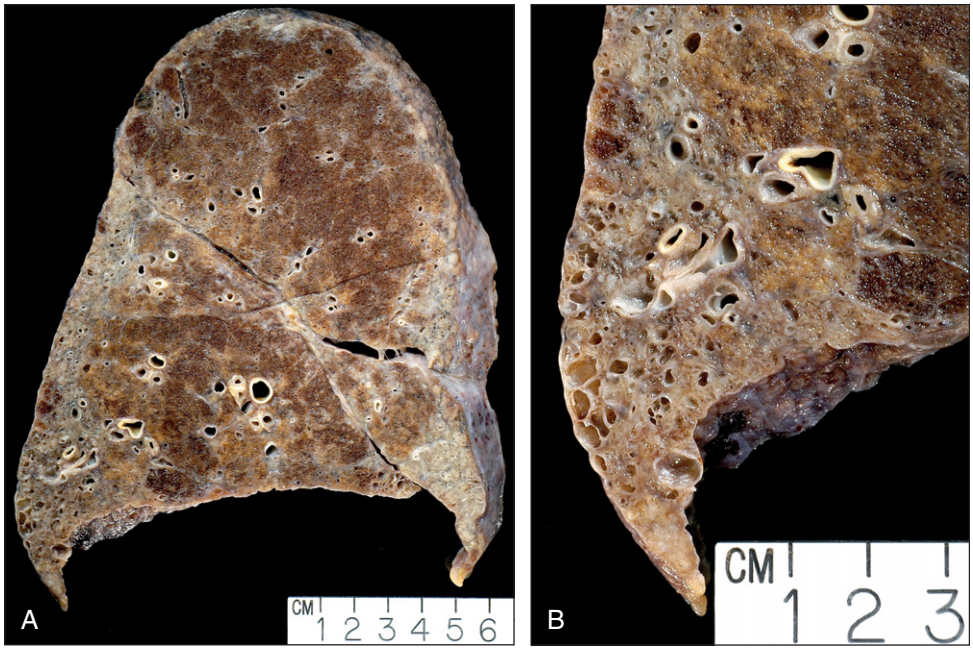

Figure 18.36 Usual interstitial pneumonia. A sagittal cut of a lung involved by usual interstitial pneumonia reveals the peripheral and basilar predominance of the dense, white fibrosis (A). A higher power view of the left lower lobe highlights the remodeled honeycomb spaces in the area of the lung with the endstage disease (B).

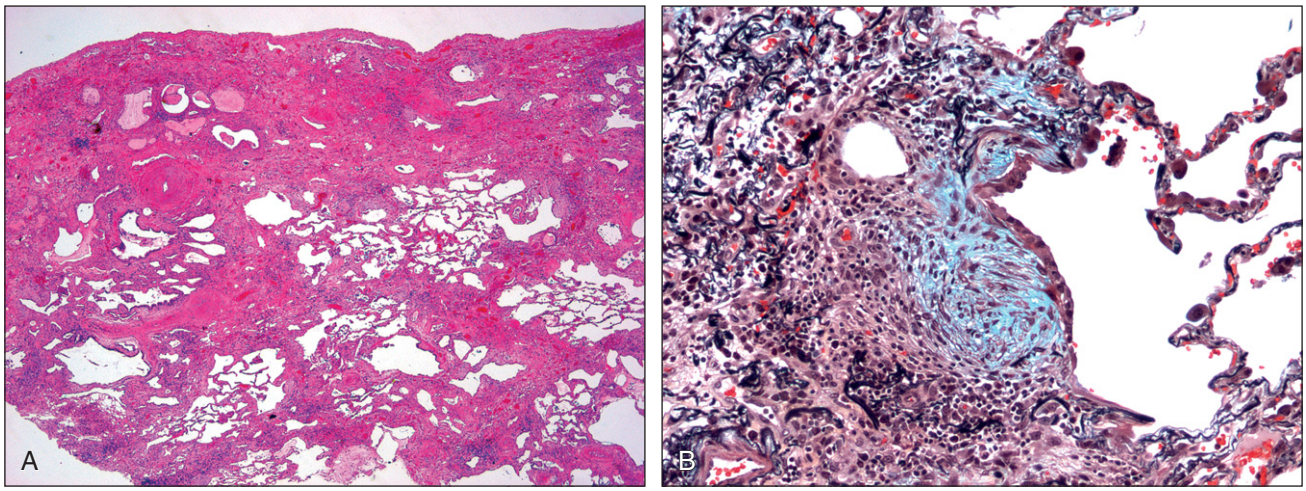

Figure 18.37 Usual interstitial pneumonia. The microscopic features of UIP lungs are characterized by inflammation and fibrosis that demonstrate the temporally heterogenous pattern of pathologic injury with normal, inflamed, and fibrotic areas of the lung, all seen at a single lower power view. (A) The leading edge of inflammation is represented by deposition of new collagen in fibroblastic foci. These consist of fibroblasts surrounded by collagen containing mucopolysaccharides highlighted in blue by this connective tissue stain (B).

may be a result of the increased production of profibrotic factors such as transforming growth factor-α (TGFα) and TGFβ, fibroblastic growth factor-2, insulin-like growth factor-1, and platelet-derived growth factor. An alternative pathway might involve overproduction of inhibitors of matrix degradation such as TIMPs (tissue inhibitors of matrix production) [164]. In support of the former mechanism, fibroblasts isolated from the lungs of IPF patients exhibit a profibrotic secretory phenotype [165].

Multiple factors, such as environmental particulates, drug or chemical exposures, and viruses may trigger the initial epithelial injury, but genetic factors also play a role. Approximately 2%–20% of patients with IPF have a family history of the disease with an inheritance pattern of autosomal dominance with variable penetrance. Two genetic mutations have been implicated in this familial form of IPF. One large kindred has been reported with a mutation in the gene encoding surfactant protein C, and six probands have been

reported with heterozygous mutations in genes *hTERT* or *hTR*, encoding telomerase reverse transcriptase and telomerase RNA, respectively, resulting in mutant telomerase and short telomeres [166].

Diffuse Alveolar Damage

Clinical and Pathology Features

Adult respiratory distress syndrome (ARDS) represents a constellation of clinical, radiologic, and physiologic features in patients with acute respiratory failure that can occur after a variety of insults. ARDS is defined by clinical criteria that include a rapid onset of severe hypoxemia that is refractory to oxygen therapy, the presence of abnormal chest radiographs with evidence of bilateral alveolar filling and collapse, increased pulmonary artery occlusion pressure, and a resistance to improved oxygenation regardless of mechanical ventilation therapy [167]. Treatment of ARDS includes eliminating the underlying cause, protective ventilation strategies that improve oxygenation, and supportive treatment that may include administration of corticosteroids.

The pathology of ARDS is diffuse alveolar damage (DAD), whose histologic picture is one of inflammation and fibrosis that diffusely involves all of the structures of the alveolus and is similar throughout the affected areas of the lung [168]. DAD is divided into three major phases that follow each other chronologically after the original insult. These are exudative, proliferative, and fibrotic DAD. The initial injury primarily involves the epithelium of the alveolar wall and the endothelium in the capillary, causing the destruction and sloughing of the type 1 pneumocytes into the alveolar space and a breakdown of the tight junctions of the endothelium. In combination, these two events result in the loss of the epithelial-endothelial barrier of the alveolus and leakage of plasma from the capillary into the alveolar space. This flooding of the airspace with fluid markedly decreases oxygen exchange and causes the hypoxia that these patients experience. In addition, acute inflammatory changes of the endothelium also cause thrombi to form in vessels, adding to a decreased amount of blood circulating through the lung and further compromising gas exchange. As air is brought into the alveoli, the positive pressure within the alveolar space forces the plasma against the alveolar wall, producing a membranous morphology referred to as hyalin membranes characteristic of the first phase of DAD, referred to as exudative DAD (Figure 18.38).

This initial injury is followed by a sequence of events that represent the lung's efforts to repair itself. First, type 2 pneumocytes undergo hyperplasia and re-epithelialize the alveolar wall after the loss of the type 1 cells. This re-establishes the epithelial barrier and, because these cells secrete surfactant, results in increased surfactant production, which lowers the surface tension of the alveolus and inhibits its collapse. Because of the increased numbers of type 2 pneumocytes, this is known as the proliferative phase of DAD (Figure 18.38). In the final phase of DAD, fibrotic DAD, fibroblasts migrate in from the adjacent interstitium to the alveolar space and produce organizing and irreversible fibrosis within both the alveolar space and the interstitium. In addition to this mechanism, fibrosis may also occur in those areas where alveolar walls collapse when surfactant is decreased during the initial insult. The histopathologic picture during this fibrotic phase is one of thickened alveolar septa, intra-alveolar granulation tissue, microcyst formation, and areas of irregular alveolar scarring. In rare cases, these microcysts progress to large cysts, an adult equivalent of bronchopulmonary dysplasia.

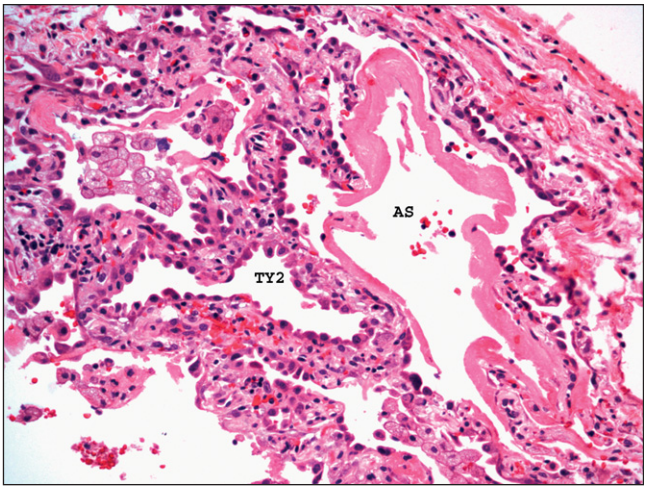

Figure 18.38 Diffuse alveolar damage. This microscopic image reveals both the exudative (right side) and proliferative (left side) phases of diffuse alveolar damage. The eosinophilic hyaline membranes outline the alveolar space (AS), and Type 2 pneumocytes are present on the surface of the adjacent alveolar walls (TY2).

Molecular Pathogenesis

The cellular events of DAD are complex and incompletely understood. In general, the disease can be broken down into two phases. In the first, a large influx of neutrophils and plasma enter the alveolar space. The role the neutrophils play in the initial cellular injury and death is unclear, but it is known that they are necessary for this injury to occur. In addition, clinical studies have shown that within the peripheral blood and bronchoalveolar lavages (BAL) of these patients, neutrophils are present along with a myriad of proinflammatory cytokines, such as IL-8, IL-1, and TGFα, all of which are capable of recruiting them to the lung. Also present in these fluids are mediators that recruit fibroblasts such as TGFβ. All of these mediators are probably the result of upregulation of NFκB, a proinflammatory transcription factor, in alveolar macrophages. The adherence of neutrophils to the capillary endothelium in the lung occurs through adhesion molecules such as selectin, integrin, and immunoglobulins. Neutrophil adherence and subsequent transmigration through the endothelium of the lung capillaries may cause some endothelial damage. However, most speculate that ROS and reactive nitrogen

species (RNS) secreted by the neutrophils modulate the majority of this injury [169]. This is supported by the finding that patients with ARDS have products of oxidative damage such as hydrogen peroxide (H_2O_2) in the exhaled breath and myeloperoxidase and oxidized αAT in the BAL.

The cell injury and death of the type 1 pneumocytes most likely occurs via two mechanisms: lipopolysaccharide (LPS)-induced caspase-dependent apoptosis and hyperoxia-induced cell death through apoptosis and non-apoptotic mechanisms [170]. In the former, LPS, an immunogenic component of the outer membrane of gram-negative bacteria, may trigger innate immune and inflammatory responses via toll-like receptors that bind Fas-associated death domain protein and caspase-9, leading to epithelial cell death. In hyperoxia-induced cell death, hyperoxia may induce the expression of angiopoietin 2 (Ang2) in lung epithelial cells. Ang2 is an angiogenic growth factor that can activate caspase pathways and lead to apoptotic cell death [170]. Cell death in ARDS is not limited to these mechanisms, and further study of many of pathways by which this can occur is needed.

Lymphangioleiomyomatosis

Clinical and Pathologic Features

Lymphangioleiomyomatosis (LAM) is a rare systemic disease of women, usually in their reproductive years (average age of 35 years), that is characterized by a proliferation of abnormal smooth muscle cells giving rise to cysts in the lungs, abnormalities in the lymphatics, and abdominal tumors, most notably in the kidneys. In addition to sporadic cases (denoted as S-LAM), LAM also affects 30% of women with tuberous sclerosis (denoted as TSC-LAM), a genetic disorder with variable penetrance associated with seizures, brain tumors, and cognitive impairment [171,172]. Global estimates indicate that TSC-LAM may be as much as 5-fold to 10-fold more prevalent than S-LAM, though at least some suggest that TSC-LAM may have a milder clinical course than S-LAM [172]. Clinically, LAM patients usually present with increasing shortness of breath on exertion, obstructive symptoms, spontaneous pneumothoraces, and chylous effusions or with abdominal masses consisting of either angiomyolipomas and/or lymphangiomyomas. Chest imaging studies characteristically reveal hyperinflation with flattened diaphragms and thin-walled cystic changes. Mortality at 10 years from the onset of symptoms is 10%–20% [173].

LAM appears as small, thin-walled cysts (0.5–5.0 cm) randomly throughout both lungs [174] (Figure 18.39). Microscopically, LAM lungs contain a diffuse infiltration of smooth muscle cells, predominantly around lymphatics, veins, and venules. Most notably, one finds smooth muscle cells in the subpleural with hemosiderin-laden macrophages in the adjacent field, and the macrophages are also seen on bronchoalveolar lavage specimens from these patients. The hemosiderin pigment in these lungs is thought to be secondary to microhemorrhages from the obstruction of the veins

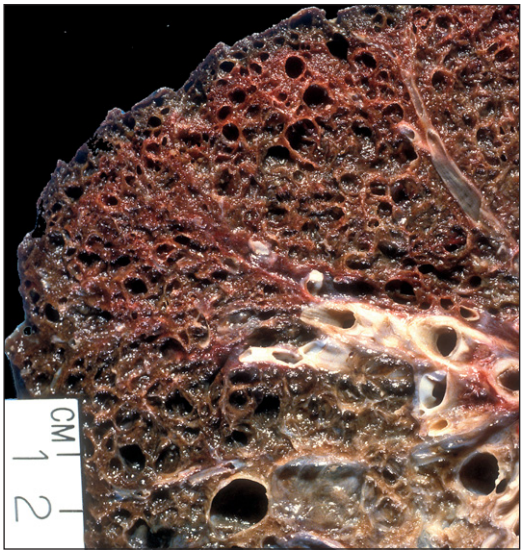

Figure 18.39 Lymphangioleiomyomatosis. The sagittal section of an upper lobe from an explanted lung from a patient with LAM demonstrates cystic features of the red/brown lung parenchyma that are characteristic of this disease.

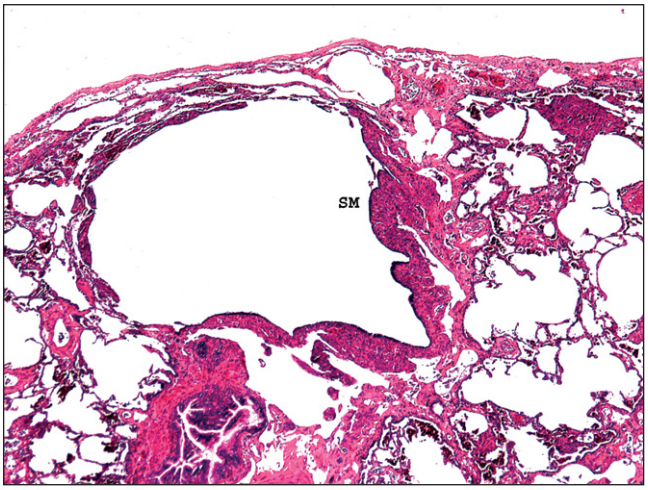

Figure 18.40 Lymphangioleiomyomatosis. The microscopic view of the LAM lung reveals cysts lined by spindled smooth muscle cells (SM). Scattered macrophages surrounding these cysts contain brown hemosiderin pigment.

(Figure 18.40) [175]. The smooth muscle cells in LAM react to antibodies to HMB-45, a premelanosomal protein. Other melanosome-like structures are also found in LAM cells, suggesting that these cells have characteristics of both smooth muscle and melanosomes [176].

Molecular Pathogenesis

The lesional cells in LAM are smooth muscle-like with both spindled and epithelioid morphology [177]. These cells are the same in both S-LAM and TSC-LAM

and are a clonal population although they lack other features of malignancy [178]. Molecular studies reveal that the abnormal LAM cell proliferation is caused by mutations in one of two genes linked to tuberous sclerosis: tuberous sclerosis complex 1 or 2 (*TSC1* or *TSC2*). These two genes control cell growth and differentiation through the Akt/mammalian target of rapamycin (mTOR) signaling pathway [172]. In this pathway, a growth factor receptor (such as insulin or PDGF receptors) becomes phosphorylated when an appropriate ligand binds, resulting in activation of downstream effectors and ultimately Akt. The gene products of *TSC1* and *TSC2* are hamartin and tuberin, which act as dimers to maintain Rheb (a member of the Ras family) in a GDP-loaded state via statins, acting as a break to the Akt/mTOR pathway, thereby retarding protein synthesis and cell growth. In LAM cells, loss-of-function mutations in these two genes remove this inhibition, leading to enhanced Rheb activation, mTOR activation (with raptor), and subsequent phosphorylation of downstream molecules which result in uncontrolled cell growth, angiogenesis, and damage to the lung tissue (Figure 18.41) [179].

The abnormal proliferation of LAM cells is thought to damage the lung through overproduction of matrix metalloproteinases (MMPs), which degrade the connective tissue of the lung architecture, destroy the alveolar integrity, and result in cyst formation with air trapping [179]. These destructive capabilities of the LAM cells are enhanced by their secretion of the angiogenic factor VEGF-C, which is thought to cause the proliferation of lymphatic channels throughout the lung [179].

Sarcoidosis

Clinical and Pathologic Features

Sarcoidosis is a multisystemic disease that involves the lung in over 90% of the cases [180]. It is most common in the 20–40-year age group and among females. In the United States, African Americans are more commonly affected than Caucasians [181]. The clinical picture of sarcoidosis is variable, but most patients present with systemic symptoms including fatigue, weight loss, and fever. The most common finding on chest imaging studies is bilateral hilar lymph node enlargement and reticular, reticulonodular, and focal alveolar opacities within the lung parenchyma [182].

Pulmonary sarcoidosis is characterized by granulomas which consist of activated histiocytes, called epithelioid histiocytes that form nodules ranging in size from 15–20 microns (Figure 18.42) [183]. Unlike infectious granulomas that usually contain areas of central necrosis, the granulomas in pulmonary sarcoidosis are predominantly non-necrotizing [184]. Also, the granulomas in sarcoidosis follow a distribution along the lymphatics, which includes the area in the subpleural, along the interlobular septae and around the bronchovascular area containing the bronchiole and branch of the pulmonary artery (Figure 18.42). The granulomas occur much more commonly in the upper lobes, leading to the predominant upper lobe fibrosis and bronchiectasis that can be seen in long-standing sarcoidosis [185].

Molecular Pathogenesis

Despite over 50 years of research on sarcoidosis, the etiology remains unknown. Most agree that the disease is probably a result of environmental triggers acting on a genetically susceptible host [186,187]. A genetic basis of sarcoidosis has been suggested by studies that demonstrate familial clustering and racial variation [188,189]. Further, complex inheritance patterns for the disease suggest that more than one gene may be involved [190]. Several genes of the major histocompatibility complex (MHC) region of the genome have been implicated. Most are clustered on the short arm of chromosome 6 that encompasses the human leukocyte antigen (HLA) domain. The HLA class I MHC molecules associated with sarcoidosis are the *HLA-B7* and *HLA-B8* class I alleles [191,192]. HLA Class II molecules implicated in susceptibility include the *HLA-DR* alleles [193,194]. Genes other than MHC genes thought to regulate the susceptibility to sarcoidosis include those for chemokines such as macrophage inflammatory protein-1α and RANTES (*CCR5* and *CCR3*) [195,196].

Environmental factors that have been implicated are those that are aerosolized. Therefore, these environmental agents have a mode of entry into the lungs and can cause granulomas in the lung, similar to sarcoidosis. These factors can be divided into two major categories, which include infectious and noninfectious agents. The mycobacteria have been the most extensively studied organisms. However, their role in this disease remains controversial due to the difficulty in identifying them by either culture or histochemical stains in sarcoid tissue. Recently, molecular techniques have been able to demonstrate mycobacterial nucleic acid in sarcoid tissue [197,198]. However, even studies using this technology have not produced consistent results, and the role of these organisms in the disease requires further study.

The immune response in sarcoidosis has two major features: (i) the initial event leading to granuloma formation and (ii) the progression of this granulomatous response to either resolution or fibrosis [199]. The formation of the granulomas, triggered by activation of T-cells and antigen-presenting dendritic histiocytes, results in a release of proinflammatory cytokines and chemokines, and recruitment, activation, and proliferation of mononuclear cells, predominantly T-cells. These activated T-cells are predominantly CD4-expressing T-helper (Th) cells, which release IFN-γ and IL-2. Alveolar macrophages at the site release TNFα, IL-12, IL-16, and other growth factors. This results in the granuloma formation and alveolitis, the characteristic morphologic features of the disease [200].

The second phase of this immunologic response that leads to either resolution of the disease or persistence of the granulomas and fibrosis is less well characterized. Ongoing granuloma formation and inflammation may be a result of the persistent presence of antigens, the excessive synthesis of chemotactic factors, or the

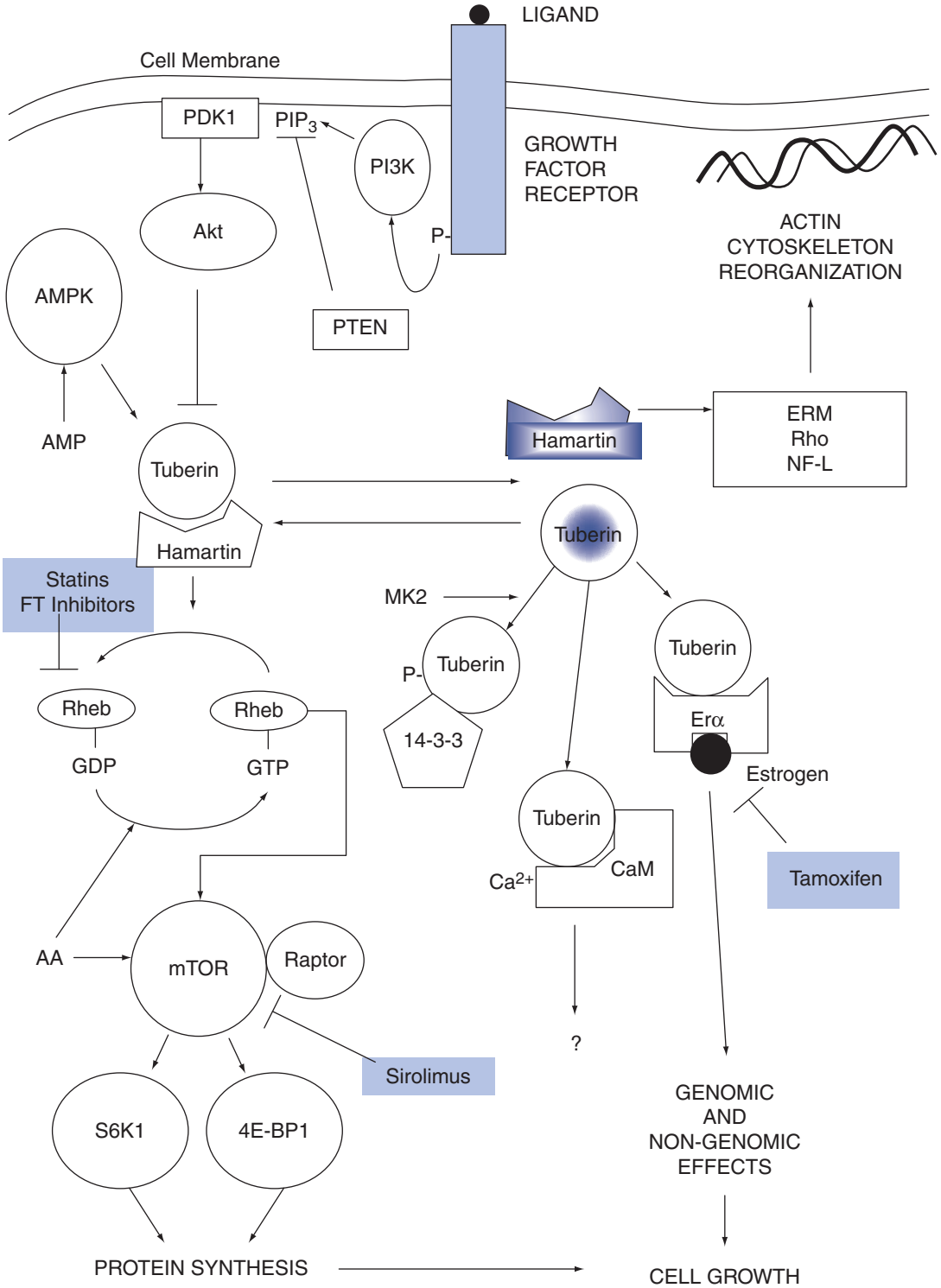

Figure 18.41 **Signal transduction pathways involving the TSC1 and TSC2 gene products, hamartin and tuberin.** *Arrowheads* indicate activating or facilitating influences*; flat-headed lines* indicate inhibitory influences. The harmartin-tuberin dimer maintains Rheb in a GDP-loaded state, thereby preventing activation of mTOR, which requires activated Rheb-GTP. Growth and energy signals tend to inhibit this function of the hamartin-tuberin complex, permitting mTOR activation. The sites of action of several drugs with therapeutic potential in LAM are indicated in gray-shaded boxes. AA, amino acids; FT, farnesyltransferase. (Reprinted with kind permission from Juvet, SC, McCormack FC, Kwiatkowski DJ, Downey GP. (2007). Molecular pathogenesis of lymphangioleiomyomatosis: lesson learned from orphans. *Am J Respir Cell Mol Biol*, 398–408 [179]).

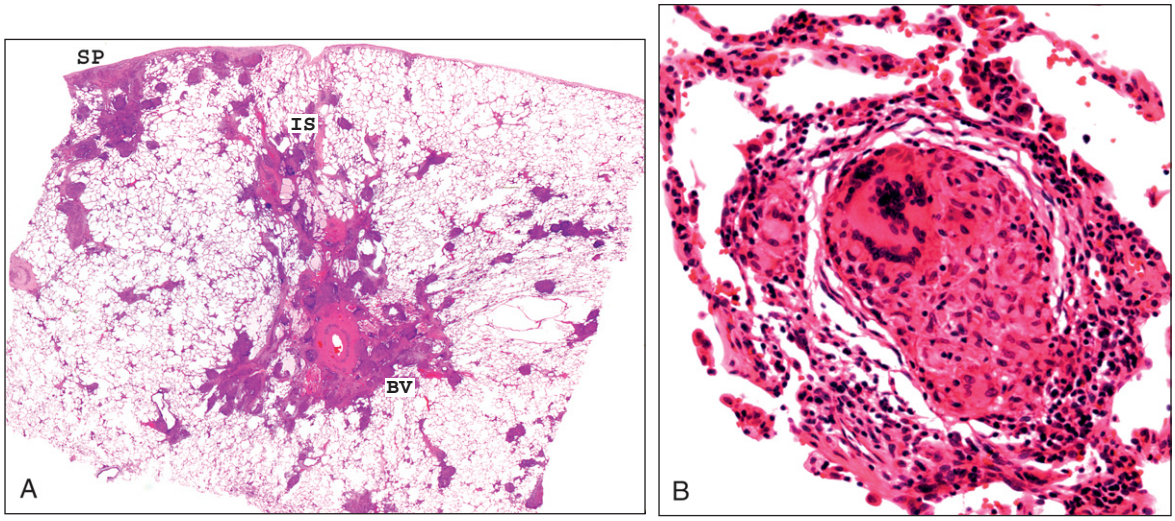

Figure 18.42 Sarcoidosis. (A) The distribution of granulomas in sarcoidosis follows the lymphatics in the lung, which includes within the subpleural (SP), along the interlobular septae (IS), and around the bronchovascular areas (BV). (B) The granulomas are composed of activated "epithelioid" histiocytes, usually containing multinucleated giant cells and surrounded by a rim of T-lymphocytes.

persistence of the mononuclear cells within the granulomas. Importantly, the role of the T-cells in these granulomas is to secrete cytokines that attract, stimulate, and ultimately deactivate the fibroblasts that are responsible for the fibrosis that is seen in the chronic disease. The balance between the profibrotic mediators such as TGFβ, insulin-like growth factor-I, platelet-derived growth factor (PDGF), and the antifibrotic mediators, such as IFN-γ, probably dictates the natural history of sarcoidosis in the lung [201]. Genes involved in macrophage-derived cytokines, chemokines, and mediators of fibrosis are all possible candidates for the underlying genetic cause of this complicated disease.

Pulmonary Alveolar Proteinosis

Clinical and Pathologic Features

Pulmonary alveolar proteinosis (PAP) is a rare disease of the lungs characterized by accumulation of surfactant in the alveolar spaces. The names alveolar proteinosis, lipoproteinosis, or perhaps most accurately phospholipoproteinosis, apply equally to this entity. PAP takes three forms clinically: (i) congenital (2%), (ii) secondary (5%–10%), and (iii) idiopathic or primary (88%–93%) [202–204]. PAP arises in previously healthy adults with the median age at diagnosis of approximately 40 years and a male-to-female ratio of 2.7:1. The clinical presentation is variable and usually includes an insidious onset of slowly progressive dyspnea, a dry cough, and other symptoms of respiratory distress, including fatigue and clubbing. However, almost one-third of patients are asymptomatic and are found clinically by abnormal chest X-rays [205,206]. The secondary form of PAP can be found in patients with environmental exposures, including fine silica, aluminum, titanium dioxide, and kaolin dust [206]. Also, secondary PAP may be found in patients with malignancies, most commonly hematologic malignancies such as myelogenous leukemia [207,208].

Chest imaging studies in both the idiopathic and secondary forms most commonly show fine, diffuse, feathery nodular infiltrates, centered in the hilar areas, sparing the peripheral regions [206]. On chest computerized tomographs, the infiltrates may have a geometric-type shape, sometimes referred to as crazy paving [209].

The most prominent microscopic feature of both idiopathic and secondary PAP is the filling of the alveoli with finely granular period acid-Schiff-positive diastase-resistant (PASD) acellular material (Figure 18.43). The

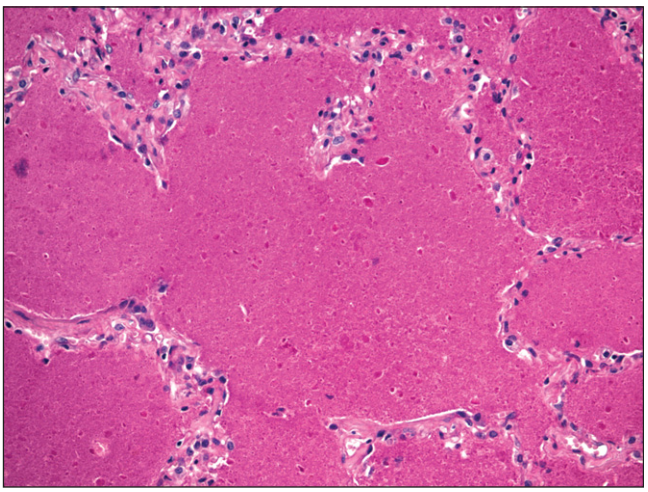

Figure 18.43 Pulmonary alveolar proteinosis. The microscopic features of this disease reveal a Periodic acid-Schiff positive surfactant-like substance filling the alveoli that otherwise show only a minimum of inflammatory changes.

material consists of phospholipids (90%); surfactant proteins A, B, C, and D (10%); and carbohydrate (<1%) [210]. Alveolar macrophages (AMs) with prominent foamy cytoplasm are commonly seen, while alveolar septa are remarkably normal in appearance. In some alveolar spaces there are denser, more solid clumps of PAS-D-positive material. Definitive pathologic differences between the idiopathic and secondary forms of PAP have not been well documented [211,212].

Molecular Pathogenesis

The etiologies of the two adult forms of PAP have been well studied with the most known about the idiopathic variant. Theories of the pathogenesis of this form have focused on the abnormal accumulation of the surfactant-like material within the alveolar spaces. Since the regulation of surfactant levels in the alveoli depends on appropriate synthesis, recycling, and catabolism, the two opposing hypotheses have included overproduction versus decreased degradation of this material.

In normal hosts, surfactant is essential to maintaining the low surface tension needed for proper alveolar inflation and gas exchange. The critical role of maintaining the proper composition and amount of surfactant in the alveoli is performed by two cell types: type 2 pneumocytes and alveolar macrophages [213]. The type 2 pneumocytes synthesize surfactant in the endoplasmic reticulum and Golgi, and store it as lamellar bodies [213], which are then delivered to and fuse with the apical plasma membrane, secreting the surfactant into the airways [214]. Catabolism of surfactant is carried out by type 2 pneumocytes and AMs. In PAP, most evidence suggests that the clearance of surfactant by the AM is decreased [203,215].

The first clue as to the underlying mechanism for this defect in AM function came in 1994 when studies revealed that knockout mice deficient in granulocyte-macrophage colony-stimulating factor (GM-CSF) develop lung lesions similar to those in patients with PAP [216]. This rather serendipitous finding prompted explorations centered on the AM and the effect diminished GM-CSF might have on its cellular functions. Subsequent studies from humans with PAP revealed an autoimmune mechanism by which a circulating neutralizing antibody to GM-CSF blocked its binding to the GM-CSF receptor, depressing the effect of GM-CSF on the AMs [217–219]. Neutralizing antibodies to GM-CSF have most often been identified in the idiopathic variant of PAP. However, recently these antibodies have also been reported in patients with secondary PAP [220].

Genes that control many functions in the AM are controlled by signaling pathways initiated by GM-CSF binding to the AM. One pathway is mediated through a transcription factor PU.1 that controls genes involved in surfactant degradation, among other bactericidal functions [221,222]. Another transcription factor, peroxisome-proliferator-activated receptor γ (PPARγ), is also part of a pathway activated by GM-CSF. PPARγ controls the expression of genes involved in intracellular lipid metabolism. AMs from patients with PAP have a deficiency of this transcription factor, which is correctable by GM-CSF therapy [223]. Overall, the lack of GM-CSF-initiated signaling in AMs from patients with PAP leads to inhibition of both PPARγ and PU.1 pathways. This results in decreased surfactant catabolism, intracellular lipid metabolism, and the accumulation of surfactant in the alveoli (Figure 18.44).

PULMONARY VASCULAR DISEASES

Pulmonary Hypertension

Clinical and Pathologic Features

Pulmonary hypertension consists of a group of distinct diseases whose pathology is characterized by abnormal destruction, repair, remodeling, and proliferation of all compartments of the pulmonary vascular tree, including arteries, arterioles, capillaries, and veins. The classification of these diseases has undergone a number of revisions. The most recent revision (in 2003) groups these diseases based on both their pathologic and clinical characteristics [224]. There are five major disease categories in the current classification system: (i) pulmonary arterial hypertension (PAH); (ii) pulmonary hypertension with left heart disease; (iii) pulmonary hypertension associated with lung disease and/or hypoxemia; (iv) pulmonary hypertension due to chronic thrombotic and/or embolic disease; and (v) miscellaneous causes, including sarcoidosis, histiocytosis X, and lymphangioleiomyomatosis. The clinical course of most patients with pulmonary hypertension begins with exertional dyspnea, and progresses through chest pain, syncope, increased mean pulmonary artery pressures and, eventually, right heart failure. The rate of this clinical progression varies among patients, from a few months to many years [225]. Treatment of these diseases focuses on blocking the mediators involved in the pathogenesis of the diseases. However, current therapies rarely prevent progression of the disease, and lung transplantation provides the only hope for long-term survival.

The major group of this classification, PAH, can be subdivided into familial PAH, idiopathic PAH, PAH associated with other conditions (such as connective tissue diseases, HIV, congenital heart disease), and PAH secondary to drugs and toxins (such as anorexigens, cocaine, and amphetamines). In these diseases, the primary pathology is localized predominantly in the small pulmonary arteries and arterioles. However, two other diseases in this group, pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis, involve predominantly other components of the pulmonary vasculature, the veins, and the capillaries, respectively. The pathologic changes seen in the pulmonary vessels of these patients primarily reflect injury to and repair of the endothelium. Early pathologic changes include medial hypertrophy and intimal fibrosis that narrows and obliterates the vessel lumen. These are followed by remodeling and revascularization, producing a proliferation of abnormal endothelial-lined spaces. These structures are known as plexogenic lesions and are the pathognomonic feature of PAH (Figure 18.45). In the

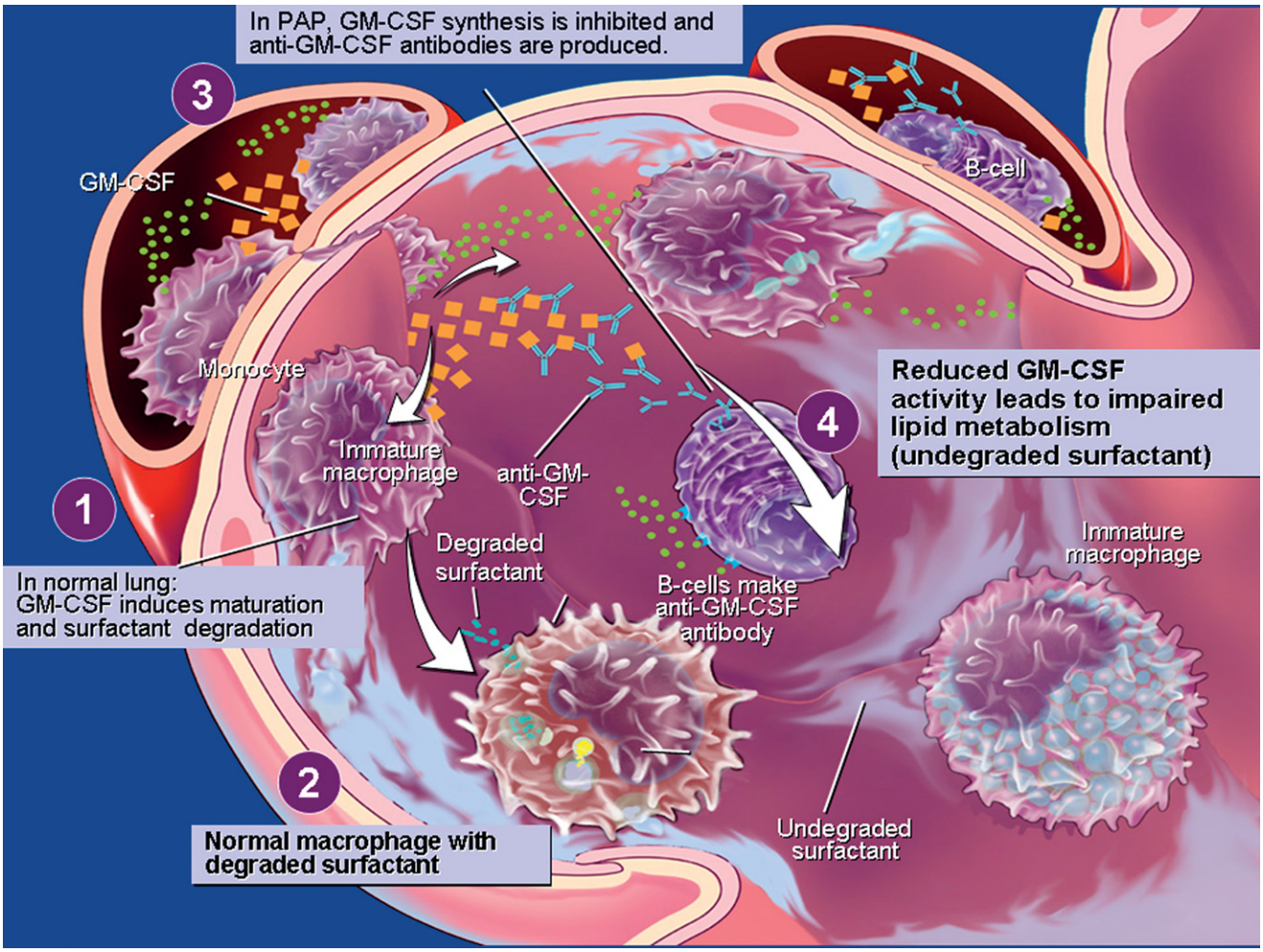

Figure 18.44 **Pulmonary alveolar proteinosis.** In alveoli of patients with PAP, anti-GM-CSF antibodies produced by B-cells block binding of the GM-CSF to alveolar macrophages (AM), which leads to impaired lipid metabolism and undegraded surfactants.

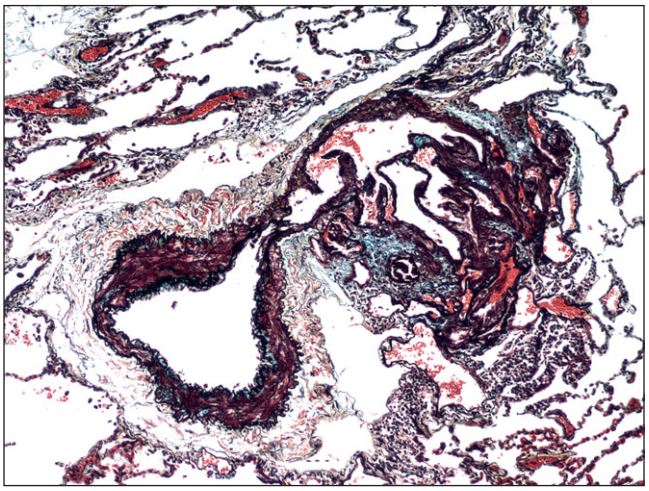

Figure 18.45 **Pulmonary hypertension.** A plexogenic lesion in a lung from a patient with idiopathic pulmonary hypertension reveals slit-like spaces (upper right corner) emerging from a pulmonary artery. These remodeling vascular spaces represent the irreversible damage done to these vessels in this disease.

most severe pathologic lesions, these abnormal vascular structures become dilated or angiomatoid-like and may develop features of a necrotizing vasculitis with transmural inflammation and fibrinoid necrosis.

Molecular Pathogenesis

Though the exact pathogenetic mechanism of PAH remains unknown, research over the past 10 years has begun to offer some clues. The familial form of PAH, with a 2:1 female-to-male prevalence, has an autosomal dominance inheritance pattern with low penetrance. The genetic basis for this has been found to be germline mutations in the gene encoding the bone morphogenetic protein receptor type 2 (*BMPR2*). These mutations account for approximately 60%–70% of familial PAH and 10%–25% of patients with sporadic PAH [233]. Approximately 140 *BMPR2* mutations have been identified in familial PAH, each resulting in a loss of receptor function, either through alteration in transcription of the gene through missense, nonsense, or frameshift alterations in the codon or by RNA spicing mistakes [226].

The mechanism by which a single mutation to the *BMPR2* gene induces vascular smooth muscle proliferation and decreased apoptosis that is not completely understood, but it most likely involves defects in the BMPR2 signaling pathway. BMPR2 is a receptor for a family cytokines (BMPs) that are members of the TGFβ superfamily of proteins that play a role in the growth and regulation of many cells, including those of the pulmonary vasculature. In the vascular smooth muscle cells of the lung, TGFβ signaling causes a proliferation of smooth muscle in pulmonary arterioles, while BMPR2 signaling causes an inhibition of the proliferation of these cells, favoring an apoptotic environment. The BMPR2 signaling occurs through an activation of a receptor complex (BMPR1 and BMPR2) that leads to phosphorylation and activation of a number cytoplasmic mediators, most notably the Smad proteins (Mothers against decapentaplegic). These Smad proteins, especially the Smad 1, Smad 5, and Smad 8 complex with Smad 4, translocate to the nucleus where they target gene transcription that induces an antiproliferative effect in the cell. In familial PAH, the *BMRPR2* gene mutation may lead to insufficient protein product and subsequent decreased protein function, in this case decreased BMPR2 receptor function, decreased Smad protein activation, and decreased antiproliferative effects in the vascular smooth muscle cells. The imbalance between the proproliferative effects of the TGFβs and the antiproliferative effects of the BMPs results in the formation of the vascular lesions of PAH (Figure 18.46) [227,228].

Despite these advances, questions regarding the pathogenesis of PAH remain. Most notably, why do only 10%–20% of patients with the mutation develop clinical disease? Some speculate that genes confer susceptibility but a second hit is required to develop the clinical disease, such as modifier genes or environmental triggers, perhaps drugs or viral infections [227,229]. In addition, though *BMPR2* mutations have been found in both the familial and the idiopathic form of

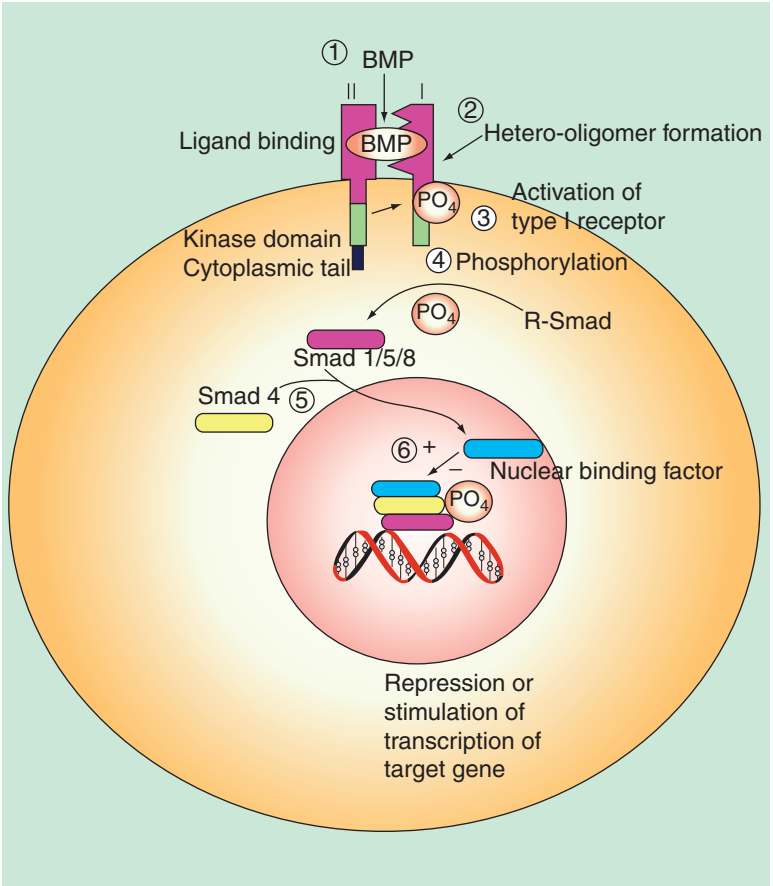

Figure 18.46 **Bone-morphogenetic-protein signaling pathway.** 1 and 2: BMPR1 and BMPR2 are present on most cell surfaces as homodimers or hetero-oligomers. With ligand (bone morphogenetic proteins; BMP) binding, a complex of ligand, two type I receptors, and two type II receptors is formed. 3: After ligand, two type I receptors and two type II receptors phosphorylate the type I receptor in its juxtamembrane domain. 4: The activated type I receptor then phosphorylates a receptor-regulated Smad (R-Smad); thus, the type I receptors determine the specificity of the signal. 5: Once activated by phosphorylation, the R-Smads interact with the common mediator Smad 4 to form hetero-oligomers that are translocated to the nucleus. 6: In the nucleus, the Smad complex interacts with transcription factors and binds to DNA to induce or suppress transcription of target genes. (Reprinted with kind permission from Runo JR and Loyd JE. (2003). Primary pulmonary hypertension. *Lancet* **316**:1533–1544 [228]).

PAH, they are present in only 30% of all PAH patients, suggesting that further research is needed to uncover additional etiologic agents.

Pulmonary Vasculitides

Pulmonary vasculitides present as diffuse pulmonary hemorrhage and are usually caused by one of three major pulmonary vasculitis syndromes: Wegener's granulomatosis, Churg-Strauss syndrome, and microscopic polyangiitis. All three diseases have similar clinical presentations and considerable overlap in their pathologic features as small vessel systemic vasculitides that affect the lung as well as other organs, most notably the kidney.

Clinical and Pathologic Features

Wegener's granulomatosis (WG) is an unusual disease that affects the upper and lower respiratory tract and the kidneys. It usually presents between 40 and 60 years of age and is slightly more common in men than women. The clinical presentation depends on the affected organ, but when the lung is involved, hemoptysis is the major presenting symptom. Chest imaging studies may show a variety of patterns, most commonly bilateral ground glass opacities with masses, usually in the lower lobes that may cavitate. Immunologic testing of peripheral blood or end organ tissue can be helpful in revealing characteristic immunofluorescent staining patterns for antineutrophilic cytoplasmic antibody (ANCA), an antibody that targets two substances: proteinase 3 (PR3) and myeloperoxidase (MPO). When present in either the blood or the tissue, the pattern of immunofluorescent staining can be cytoplasmic (cANCA) or perinuclear (pANCA). The former pattern is more commonly seen in Wegener's granulomatosis, and the latter is more commonly seen in microscopic polyangiitis and Churg-Strauss syndrome (CSS).

CSS is a systemic disorder defined by the presence of asthma, peripheral blood eosinophilia, and systemic vasculitis. Similar to WG, it usually presents between 40 and 60 years of age, and a clinical diagnosis requires a history of asthma, a peripheral blood eosinophilia, neuropathy, an abnormal chest imaging study, and sinusitis. Other organs involved include the heart, the central nervous system, kidneys (though less commonly than WG), gastrointestinal tract, and skin. Chest imaging usually shows patchy, multifocal infiltrates; masses and cavitation are rare. Laboratory tests reveal positive pANCA tests in 70% of patients.

Microscopic polyangiitis (MPA) is similar to both WG and CSS in that it is a systemic vasculitis that involves the lung and usually presents in the fourth or fifth decade of life. The clinical onset is usually sudden with fever, weight loss, myalgias, and arthralgias. The kidney is the main organ involved, and MPA is the most common cause of pulmonary-renal syndrome. Lung involvement occurs in approximately 50% of the patients, and skin and upper respiratory tract are other common sites. Similar to WG and CSS, ANCA testing is helpful with positive pANCA in 80% of patients. Chest imaging usually shows bilateral infiltrates without masses, similar to CSS. Treatment for all three diseases is immunosuppression with glucocorticoids or cyclophosphamide, and all three usually respond well, although WG has a greater relapse rate after treatment than either CSS or MPA [230].

The pathology of WG, CSS, and MPA have overlapping features of an acute and chronic vasculitis that involves medium- and small-sized vessels in the lung. The inflammatory cell infiltrate that destroys the blood vessels is both lymphocytic and neutrophilic, and areas of fibrinoid necrosis are seen. However, in WG, there are characteristic areas of microabscesses that lead to masses of geographic necrosis with basophilia. Scattered multinucleated giant cells are present, but no well-formed granulomas are seen. This helps to distinguish it from other vasculitides and infection (Figure 18.47). Similarly, the pathology of CSS has distinguishing features, with the early pathology characterized by an eosinophilic pneumonia with areas of loosely formed granulomas with central necrosis containing degenerating eosinophils (Figure 18.48). The infiltrate is predominantly eosinophils, but neutrophils, lymphocytes, and plasma cells are also present. Capillaritis can be seen in WG, CSG, and MPA, and all three have hemosiderin deposition present, both within alveolar macrophages and deposited in the connective tissue of the interstitium and the vessel walls.

Molecular Pathogenesis

The pathogenesis of these three pulmonary hemorrhage syndromes is similar to the mechanisms of these diseases in the kidney. In general, these diseases in the lung and the kidney represent immune-mediated

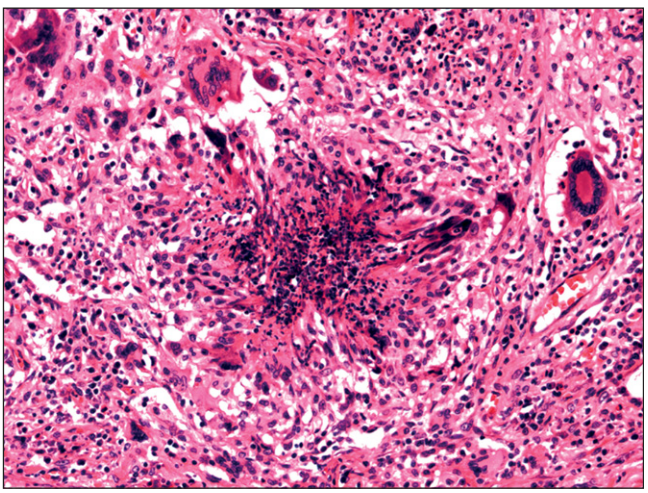

Figure 18.47 Wegener's granulomatosis. The inflammation in lungs involved by Wegener's granulomatosis includes neutrophilic microabscesses in a stellate pattern. Giant cells are commonly seen in the surrounding areas. These lesions are thought to be the early form of the larger areas of geographic necrosis that produces the mass-like nodules found in these lungs.

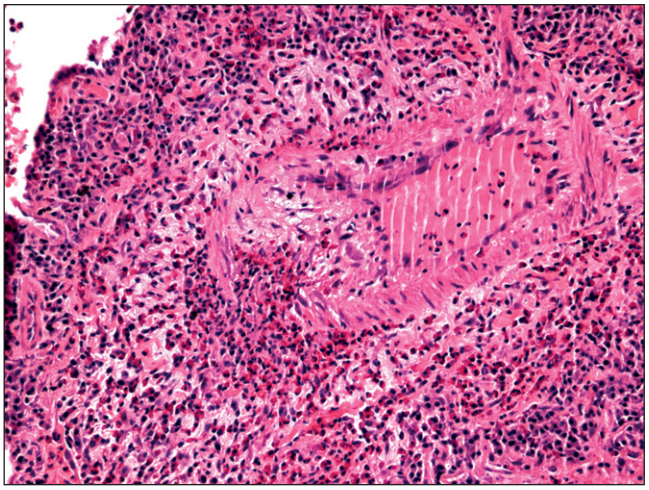

Figure 18.48 Churg-Strauss Syndrome. An eosinophilic infiltrate invades the wall of a medium-sized artery in this lung from a patient with CSS. The surrounding lung also contains a dense infiltrate of eosinophils, lymphocytes, and plasma cells.

necrotizing vasculitides that have few or no immune deposits in the vessels but exhibit the presence of ANCA autoantibodies to myeloperoxidase (MPO) and proteinase 3 (PR3), the components of primary granules of neutrophils. MPA and CSS are primarily diseases of MPO antibodies, and WG is primarily a disease of PR3 antibodies. The mechanism by which the ANCAs are induced is not known but may be part of an autoimmune response to environmental exposures early in life. These autoantibodies then inflict damage on the vessels through a mechanism that is not yet completely understood. One theory suggests that circulating ANCAs bind to PR3 and MPO on the surface of neutrophils and initiate a respiratory burst, degranulation, and apoptosis. ROS and proteases are released and inflict endothelial and tissue damage on the adjacent vessel. The ANCA binding may also induce the release of proinflammatory cytokines and chemokines such as IL-1 and TNFα that further contribute to the vascular inflammation. The second theory postulates that circulating immune complexes of excess ANCA antigen (MPO or PR3) and ANCA autoantibodies attach to the vascular endothelium and activate complement that results in the chemotaxis and adhesion of inflammatory cells, causing these cells to undergo a respiratory burst and, as in the first theory, release of ROS and proteases that cause the vascular endothelial damage. In both theories, it is important to remember that MPO and PR3 are also present in monocytes and that ANCA autoantibodies may be involved with monocytes in similar ways to release inflammatory mediators [231].

PULMONARY INFECTIONS

Infectious diseases of the lung are a common cause of pulmonary disease given the constant exposure of the lungs to the environment. Various organisms are capable of causing these infections, including common viruses and bacteria, as well as more uncommon fungi, parasites, and protozoa. The diagnosis of the specific etiologic agent can be challenging given that most have similar clinical features and many are difficult to identify in the lung tissue. This brief overview of the defense mechanisms the lung uses to protect itself will serve to introduce the pathology of these lung infections.

Overview of Pathogenesis of Lower Respiratory Tract Infections

Anatomic Defenses

The lung has multiple anatomic mechanisms by which it defends itself against invasion by various pathogens. First, the upper nasal cavities and respiratory tract serve as anatomic barriers to inhaled organisms. The ciliated epithelium and torturous cavities of the sinuses screen large organisms (typically larger than 10 microns). For those particles that venture further down the respiratory tract, the cough reflex that the upper trachea elicits serves to expel them up and out. Second, the mucociliary tree of the upper respiratory tract captures organisms that evade these two mechanisms. The bronchial epithelium contains cilia of up to 20 microns in length that extend into the air surface liquid (ASL). The ASL is a bilayer of 50–100 microns in thickness consisting of a low-viscosity or watery lower layer that is covered by a high-viscosity or gel upper layer secreted by adjacent goblet cells. This sticky upper layer serves to trap organisms, and the coordinated beating of the cilia moves these entrapped invaders up this mucociliary escalator to the larynx, where they can be expectorated.

Soluble Mediators

Present in the secretions of the large airways and within the surfactant lining the alveolar walls are soluble mediators secreted by various cells. These mediators include lysozyme and lactoferrin, which lyse bacteria and inhibit their growth; the defensins and cathelicidins, small peptides both with microbicidal properties; and surfactant proteins A and D at the alveolar level, which bind to microorganism and enhance phagocytosis and also have direct bactericidal activity [232].

Cells of Innate Immunity

The major cells of the innate immune response of the lung are the alveolar macrophages (AM) and the polymorphonuclear leukocytes (PMN). Neutrophils phagocytize and destroy bacteria such as S. *aureus,* *S. pneumoniae,* and *H. influenzae* through a respiratory burst that generates NADPH oxidase-dependent ROS. In some instances, AMs may ingest but not kill an organism. This occurs with such organisms as *Mycobacterium* spp., *Nocardia* spp., and *Legionella* spp. Because of the ability of these organisms to continue to replicate within

the AM, cell-mediated immunity is required for their complete elimination. Patients with defects in NADPH oxidase are especially prone to respiratory infections by such organisms as *S. aureus, Nocardia* spp. and *Aspergillus* spp.

Bronchial epithelial cells are important in innate immunity through secretion of cytokines and molecules including IL-1, IL-5, IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor (GM-CSF). These molecules attract macrophages as well as neutrophils and other inflammatory cells to the area to enhance the inflammatory response to the organism [233]. Bronchial epithelial cells also serve an important role in recognizing pathogens through pattern-recognition receptors (PRRs).

Natural killer (NK) cells are involved in the innate immune response with surface receptors that recognize cells infected with viruses such as RSV, influenza, parainfluenza, and rhinovirus. The NK cells release IFN-γ, which recruit other immune cells to add to the antiviral response.

Dendritic cells are tissue histiocytes positioned around the airways and lymphatics in the lung that recognize pathogens and their antigens and trigger the proliferation and amplification of antigen-specific T-cells. This immune response bridges the innate immune response to the adaptive immune responses and is especially important in fungal infections. This mechanism is mediated through toll-like receptors (TLRs) that are able to distinguish pathogens from self-components by triggering cytokine production through NFκB and AP-1 and expressing co-stimulatory molecules necessary for this T-cell activation [234].

Adaptive Immunity

For those organisms that evade the basic, innate immunity of the lung, there are adaptive immune mechanisms that encompass both humoral and cellular immune mechanisms. Humoral immunity is an important defense against encapsulated bacteria, most notably *S. pneumoniae*, and for other pyogenic bacteria such as *H. influenzae,* and *Staphylococci* spp., and resolution of these infections requires the production of IgG antibodies to the organisms. Cellular immunity is especially important against such respiratory viral infections as influenza, RSV, CMV, varicella, and also against opportunistic infections. These viruses induce a CD4+ and CD8+ T-cell response that clears the lung of these viruses within 8–10 days post infection.

Granulomas

Granulomas are a common inflammatory response to both pathogens and foreign material. The most notable granulomatous infections in the lung are due to mycobacteria and fungal organisms. Activation of CD4+ T-cells by these organisms leads to proliferation and differentiation of these CD4+ T-cells into T-helper-1 cells. The release of IFN-γ by the Th-1 cells activates lung macrophages to form epithelioid macrophages that have an increased ability to kill the microorganisms and express surface molecules that promote cell-to-cell fusion into giant cells. In addition, activation of these macrophages results in the release of numerous cytokines including IFN-γ and TNFα. In patients who are deficient in CD4+ T-cells or IFN-γ, granuloma formation is very poor, altering the pathologic picture of these infections. This effect is most obvious in the nontuberculous mycobacterial infections, which have numerous patterns of injury depending on the immune status of their host.

Clinical Overview

Pneumonias can be broadly categorized into one of five major clinicopathologic categories, including (i) community-acquired pneumonias (acute and atypical), (ii) nosocomial pneumonias, (iii) aspiration pneumonias and lung abscess, (iv) chronic pneumonias, and (v) pneumonias in immunocompromised hosts. Each type presents with a characteristic clinical pattern and may be caused by any of several pathogens so that treatment is many times empiric.

The first category comprises community-acquired pneumonias (CAP). These represent the majority of the lung infections that receive medical treatment, usually on an outpatient basis, with low (<1%) mortality. Patients hospitalized for these infections typically have other comorbidities. The responsible organisms include respiratory syncytial virus (RSV); rhinovirus, parainfluenza, and influenza virus; bacteria, including *Mycoplasma pneumoniae* and rickettsia; and most notably *Chlamydia pneumonia.* Chlamydia causes what is termed atypical pneumonia with a clinical course characterized by a progressive onset of fever without chills, a dry cough, and chest imaging that reveals focal infiltrates. Acute or typical CAP presents abruptly with high fever, chills, productive cough, and radiographs with lobar or segmental consolidation. The most common pathogens are *Streptococcus pneumoniae, Haemophilus influenza, Staphylococcus aureus,* and *Moraxella catarrhalis.*

The second category, nosocomial pneumonias, consists of infections acquired within the hospital or from healthcare associated facilities. These infections are usually found in patients with predisposing risk factors and are a major source of morbidity and mortality, with some studies reporting a mortality range of 20%–50%. The most common risk factors include respiratory ventilation, artificial airways, nasogastric tubes, supine positioning, and medications that alter gastric emptying. The responsible organisms include *Klebsiella* spp., *Legionella* spp., *Staphylococcus aureus*, and *Pseudomonas aeruginosa.*

The third category includes aspiration pneumonias and lung abscesses. These infections occur in the setting of patients with aberrant swallow or gag reflexes that allow gastric or oral contents into the airways. The organisms where necrosis and cavity formation occurs include *S. aureus, K. pneumoniae*, the anaerobic oral flora, and mycobacteria. Clinically, these infections may have an acute course with fever and dyspnea or a more insidious course, many times with patients first

presenting with lung cavities, empyemas, or necrotizing pneumonias.

The fourth category, chronic pneumonias, includes indolent infections that cause a localized mass-like lesion in an otherwise healthy host. *Nocardia* and *Actinomyces* spp. are the most common pathogens, but mycobacteria and fungi may also cause these pneumonias. The fifth category includes pneumonias that occur in the setting of an immunocompromised patient. These include a number of organisms that otherwise would not act as pathogens such as the viruses CMV and HSV, the fungi Aspergillosis and Pneumocystis pneumonia, and the bacterium *Mycobacterium avium* complex.

Clinical and Pathologic Features

Bacteria

Streptococcus pneumoniae *Streptococcus pneumoniae*, a gram-positive diplococcus also known as pneumococcus or *Diplococcus pneumonia*, is a common cause of bacterial pneumonia in infants and elderly patients, alcoholics, diabetics, and patients with immunosuppression. This pneumonia usually presents abruptly with chills, a cough with rust-colored sputum and pleuritis, with high fevers, tachycardia, and tachypnea. The characteristic gross pathology is a lobar pneumonia that progresses from a red acute phase to a gray organizing phase. A fibrinous pleuritis is common, which eventually organizes to entrap the lung parenchyma in a fibrous capsule [235]. The microscopic examination reveals abundant fibrin, neutrophils, and extravasated red blood cells within the alveolar space and congested capillaries.

Hemophilus influenzae *Hemophilus influenzae* is a gram-negative bacillus that inhabits the upper respiratory tract and can cause otitis media, epiglottitis, and meningitis, and usually enters the lung through aspiration or hematogenous spread. Six serotypes are defined based on their capsular antigens, with Type B the most common cause of pneumonias. This type of pneumonia is most commonly found in children or in the elderly with underlying chronic lung disease such as emphysema, cystic fibrosis, bronchiectasis, in patients with HIV infection, or in alcoholics. This bacterial pneumonia is usually preceded by a viral or mycoplasma infection that damages the mucociliary elements in the airways and allows for colonization by *H. influenzae*. The symptoms include fever; a productive, purulent cough; and myalgias. The incidence of this pneumonia as a common community-acquired pneumonia in children is quite low due to the advent of effective vaccines. However, it is increasing in incidence as a nosocomial infection [236]. Like pneumococcal pneumonia, the pathology of *H. influenzae* pneumonia is in a lobar distribution with a neutrophilic-rich infiltrate and a pleural effusion. Necrosis and empyema may occur but are uncommon.

Staphylococcus aureus Staphylococcal pneumonia is caused by *Staphylococcus aureus*, gram-positive cocci that usually spread to the lung through the blood from other infected sites, most often the skin. Though a common community pathogen, it is found twice as frequently in pneumonias in hospitalized patients. It often attacks the elderly and patients with CF and arises as a co-infection with influenza viral pneumonia. The clinical course is characterized by high fevers, chills, a cough with purulent bloody sputum, and rapidly progressing dyspnea. The gross pathology commonly reveals an acute bronchopneumonia pattern (Figure 18.49) that may evolve into a necrotizing cavity with congested red/purple lungs and airways that contain a bloody fluid and thick mucoid secretions. The histologic pattern is characterized by a bronchopneumonia that spreads distally from the small airways into to the alveolar spaces (Figure 18.50) to form abscesses that connect with the pleural surface and may result in empyemas. The treatment of this organism has become increasingly problematic due to antibiotic-resistant strains, most notably methicillin-resistant *S. aureus*.

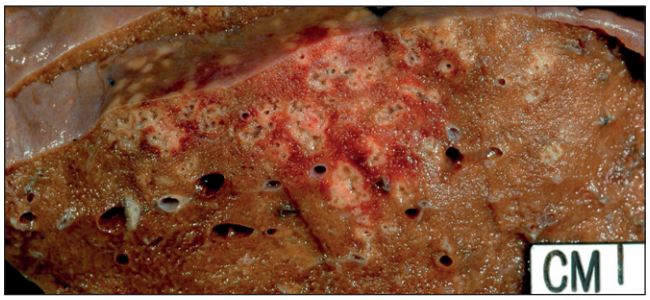

Figure 18.49 Bronchopneumonia. The cut surface of an upper lobe of lung reveals scattered tan nodules surrounded by red erythema, features of an early acute bronchopneumonia. The tan areas represent the earliest inflammation surrounding the small airways seen in Figure 18.50.

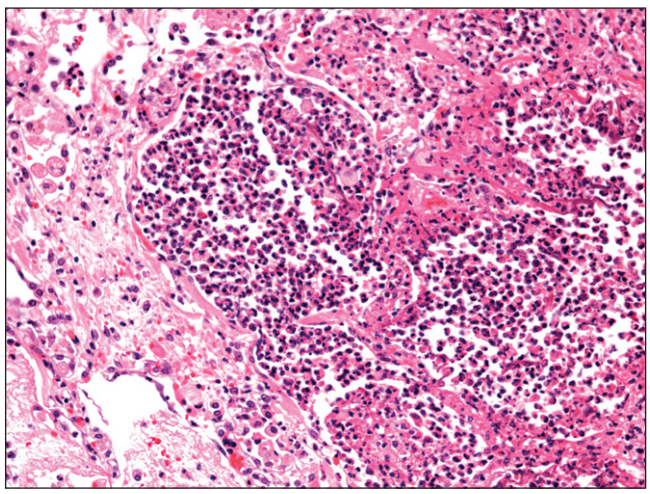

Figure 18.50 Acute bronchopneumonia. A microscopic picture of an acute bronchopneumonia caused by *S. aureus* reveals an abundant infiltrate of neutrophils filling a small bronchiole and extending into the adjacent alveoli.

Legionella pneumophila *Legionella* are gram-negative bacilli found predominantly in aquatic habitats such as lakes, rivers, and ponds. Standing pools of water from humidifiers and other water outlets may be other sources. Approximately 50% of air conditioners contain these bacilli. Though 15 serogroups of *Legionella* have been identified, 3 cause the overwhelming majority of human pneumonia. The clinical disease takes two forms: (i) Legionnaires' disease, named after the outbreak of pneumonia at the 1976 American Legion convention in Philadelphia; and (ii) Pontiac fever, a self-limiting flu-like disease with nonspecific symptoms. *Legionella* pneumonia presents as a severe infection of the lung with chills and rigors with a nonproductive cough. It can progress rapidly to systemic symptoms of nausea, vomiting, and diarrhea and can lead to renal failure and death without immediate antibiotic therapy. The infected lungs are remarkably red and congested and appear to be distended with fluid. The microscopic picture reveals fibrinopurulent exudates that fill the alveolar space mixed with a necrotic, cellular infiltrate of degenerating neutrophils and monocytes (Figure 18.51). Hyaline membranes may form in the periphery of the lesions, and pleural effusions consisting of fibrinoserous exudates are common.

Pseudomonas aeruginosa *Pseudomonas aeruginosa* is a gram-negative bacillus that is found throughout the environment and in 50% of the airways of hospitalized patients. It usually enters the body through a disruption of the epithelial surface by cuts, burns, or therapeutic devices such as mechanical ventilators or intravascular catheters. Pneumonias caused by this organism are usually found in intensive care units of hospitals and burn units, in patients with underlying chronic lung diseases including cystic fibrosis, emphysema, and in patients with prolonged hospitalization. The pathology is necrosis with a bronchopneumonia pattern that usually consists of an area of congestion and hemorrhage that is surrounded by a halo of tan/white consolidation (Figure 18.52). A necrotizing vasculitis with abundant organisms in vessel walls can be seen, and cavitation is common (Figure 18.53). In treated lungs, healed cavities or pneumatoceles may appear as smooth-walled fibrous cysts.

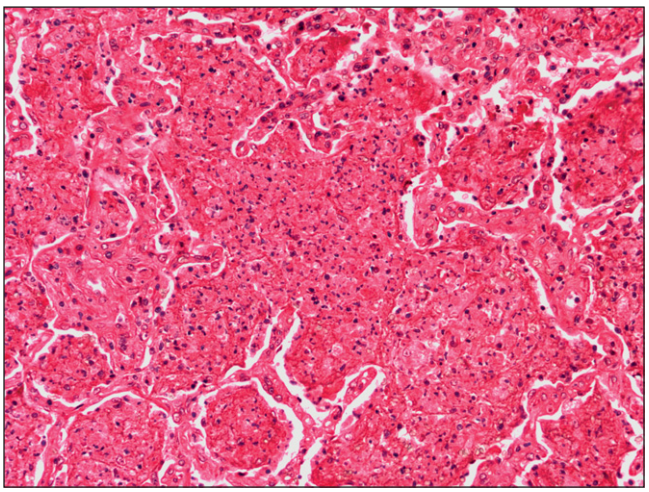

Figure 18.51 ***Legionella pneumonia.*** An eosinophilic exudate containing neutrophilic and histiocyte debris involves the alveolar of a lung infected by *L. pneumoniae.*

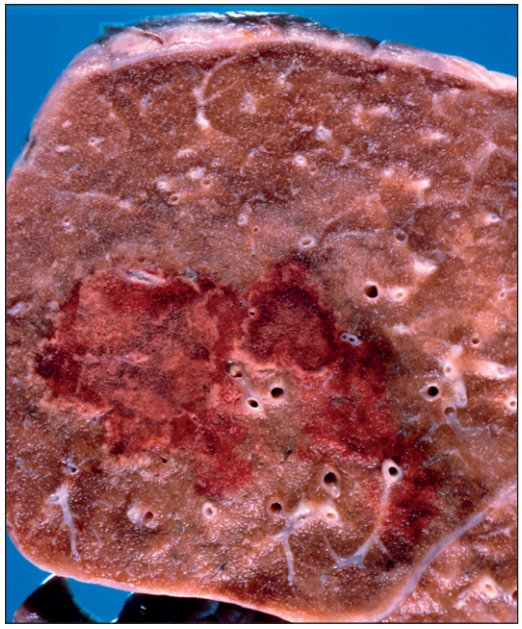

Figure 18.52 ***Pseudomonas aeruginosa.*** The cut surface of this upper lobe of a lung reveals an erythematous patch surrounded by a tan rim, characteristic of an acute pneumonia caused by *P. aeruginosa.* As this infection progresses, it can cavitate and result in abscesses and pneumatoceles that are commonly seen in this pneumonia.

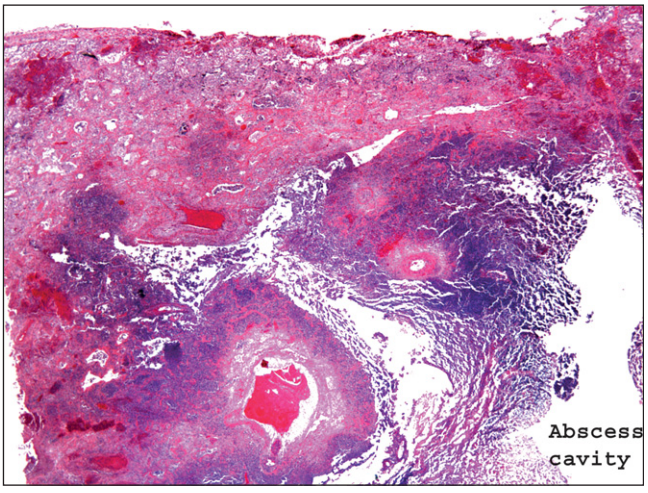

Figure 18.53 ***Pseudomonas aeruginosa.*** A microscopic picture of a more advanced acute infection from *P. aeruginosa* with abscess formation. The blue areas adjacent to the cavity contain neutrophilic debris surrounding large vessels within the lung. The cavity formation in this infection usually results from an ischemic necrosis secondary to a vasculitis caused by the organisms invading into these adjacent vessels.

Other Gram-Negative Bacilli Gram-negative bacilli such as *Klebsiella pneumoniae, Acinetobacter*, and various *Enterobacteriaceae* spp. are common nosocomial pathogens. Similar to *P. aeruginosa*, these pathogens colonize the oropharynx and are usually introduced into the lung by inhalation or aspiration of oral contents. The most notable of these is Friedlander's pneumonia caused by *K. pneumoniae*, the most common cause of gram-negative bacterial pneumonia. This typically occurs in men over 40 years of age, usually in the setting of alcoholism, diabetes mellitus, or chronic lung disease. These patients produce large amounts of thick, bloody sputum, a product of the viscous mucopolysaccharide capsule of the organism, and present with severe systemic symptoms of hypotension and generalized weakness. The pathology of these pneumonias is similar to Pseudomonas pneumonia with marked cavitation and abundant organisms on microscopic examination.

Nocardia spp. Nocardiosis of the lung is caused by *Nocardia asteroides*, a gram-positive rod found in the soil or organic matter. This infection is most common in immunocompromised adult patients and can be seen in the setting of pulmonary alveolar proteinosis, chronic lung diseases, and mycobacterial and other granulomatous diseases that affect the lung. Its clinical course is indolent and usually begins 1–2 weeks before the patient presents for medical therapy. Cough is common, often with thick, purulent sputum. In the immunocompromised setting, fever, chills, dyspnea, and hemoptysis are common, and weight loss may occur as the disease progresses. The pathology is remarkable for suppurative abscess formation with multiple cavities filled with green, thick pus. The inflammatory infiltrate consists of neutrophils, macrophages, and abundant necrotic debris with epithelioid histiocytes and giant cells within the wall of the cavity (Figure 18.54). Empyema and pleura involvement occur in the majority of cases.

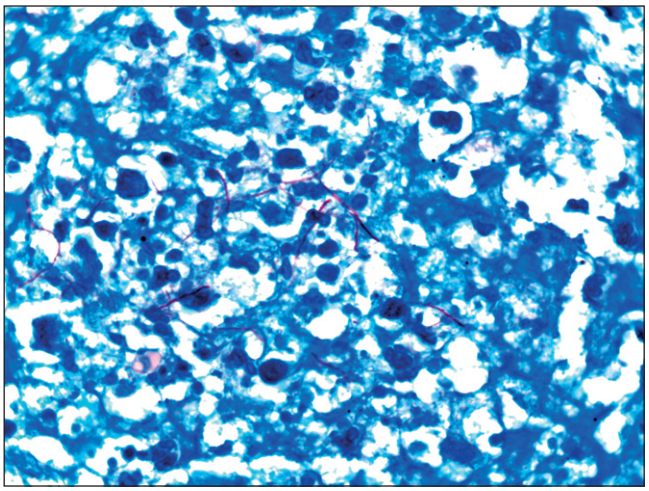

Figure 18.54 ***Nocardia.*** A Fite stain reveals branching filamentous organisms within an abscess caused by *N. asteroides*.

Mycoplasma and Rickettsia Pneumonias *Mycoplasma pneumoniae* pneumonia is among the most common infections of the lower respiratory tract and usually occurs in small epidemics in closed populations. It often presents with atypical features of a progressive onset, fever without chills, a dry cough, diffuse crackles on physical examination, and chest imaging studies that reveal patchy interstitial infiltrates. The pathologic features are a result of the attachment of the organisms to the bronchiolar epithelium where they cause epithelial injury and ulcerations through secretion of peroxide [237]. In cases of severe infection, diffuse alveolar damage may be present.

Chlamydial Pneumonia *Chlamydia* spp. causes pneumonia in a variety of clinical settings. *Chlamydia trachomatis* is an infection found predominantly in the postnatal period, *Chlamydia psittaci* is the result of direct transmission from infected birds, including parakeets, parrots, and pigeons. *Chlamydia pneumoniae* is the most common of the three and is a frequent cause of community-acquired pneumonia. It typically causes a very mild or asymptomatic infection with fever, sore throat, and nonproductive cough. The course of this infection may be severe in the elderly. Chest imaging studies show alveolar infiltrates, and pleural effusions are present in the majority of cases. The pathology has not been well defined since the infection is usually self-limited. However, in experimental animal models there is a neutrophilic response in the early stages, and an interstitial, peribronchiolar, and perivascular infiltrate of lymphocytes, macrophages, and plasma cells in the latter stages of the infection.

Mycobacteria

Mycobacteria, a major cause of lung infections, are nonmotile, aerobic, catalase-producing, acid-fast bacilli. Clinically significant lung infections can be caused by *M. tuberculosis* and by a group of nontuberculous mycobacteria (NTM). The latter group consists of over 100 species, of which three cause the overwhelming majority of pulmonary disease. These are *M. avium-intracellulare* (*M. avium* complex), *M. kansasii*, and *M. fortuitum-chelonae*. Throughout history, tuberculosis (infection with *M. tuberculosis*) was the major disease caused by these organisms and was responsible for worldwide morbidity and mortality. However, over the past two decades lung diseases caused by NTM have become much more common and now represent the majority of the pulmonary mycobacterial disease.

Mycobacterium Tuberculosis Pulmonary tuberculosis is spread by interpersonal contact through aerosolized droplets. Once in the alveoli, the bacteria cause a cell-mediated inflammatory response that is capable of inducing granuloma formation and necrosis. As in all infections, the extent of the disease is a function of the host's immune response. The most susceptible

patients are those with certain conditions that include immunosuppression, diabetes, malignancy, renal failure, among others. Clinically, an infected patient has a productive cough, fever, and weight loss, and may develop hemoptysis as the cavitation progresses and erodes into the pulmonary vessels. Extensive involvement of the lung can produce significant dyspnea and pleuritic chest pain.

The pathology of tuberculosis is primarily that of granuloma formation and acute pneumonia. The granulomas are predominantly necrotizing, and the pneumonia usually contains abundant fibrin and neutrophils that fill the alveolar spaces. The gross lesions are referred to as caseous or cheese-like, because of the amount of necrosis present. This caseous material can extend into airways and is commonly coughed up during the active disease. In chronic forms of the disease, the area can undergo fibrosis and involute into a firm, hard scar. There are three major clinicopathologic variants of the disease: (i) primary tuberculosis, (ii) postprimary or reactivation tuberculosis, and (iii) progressive fibrocavitary disease.

Primary tuberculosis. In this form of the disease, the initial site of infection can be anywhere in the lung, but is usually in the lower lobe or anterior segment of the upper lobe, the areas that receive the most ventilation. The lesion usually consists of a dense consolidation with acute pneumonia and necrotizing granulomas. Cavitation may occur, especially in the setting of immunocompromised hosts. From these foci, the organisms may spread through the lymphatics to elsewhere in the lung, the hilar lymph nodes, and the bloodstream, and lay dormant for long periods of time. The combination of the primary site of infection and the involved hilar lymph nodes is known as a Ghon complex [238].

Postprimary tuberculosis. This form of tuberculosis represents reactivation of old, scarred primary lesions long after the initial insult. The lesion can occur anywhere in the lung where the bacteria from the primary lesion have spread, but is usually apical. It consists of a focus or organizing pneumonia and fibrosis with central caseation. In an active lesion, the typical parenchymal pattern is an acute pneumonia with cavitation that expands to include the surrounding lung with aggregates of granulomas. The controversy surrounding this lesion arises as some evidence suggests that these lesions represent exogenous reinfection. The pathology of reactivation or reinfection may be indistinguishable, although reactivation tuberculosis may appear to arise out of a fibrotic, calcified chronic lesion [239].

Progressive fibrocavitary disease. This form of the disease may arise out of either primary or postprimary tuberculosis. However, the latter is the more common scenario. The cavities that develop in this form of the disease begin as a slowly progressive, necrotizing pneumonia with abundant granulomas (Figure 18.55). The active disease may spread through the airways, causing ulceration, necrosis, and fibrosis of the surrounding bronchi and bronchioles. The extension of the disease in this way depends on the host, and patients with depressed immune systems can have large areas of the lung involved with massive pulmonary necrosis. Usually, a fibrous capsule develops in the area of the cavitation, although inspissated necrotic material into the adjacent airways remains a continuous source of inflammation that can lead to reinfection and ongoing scarring [240].

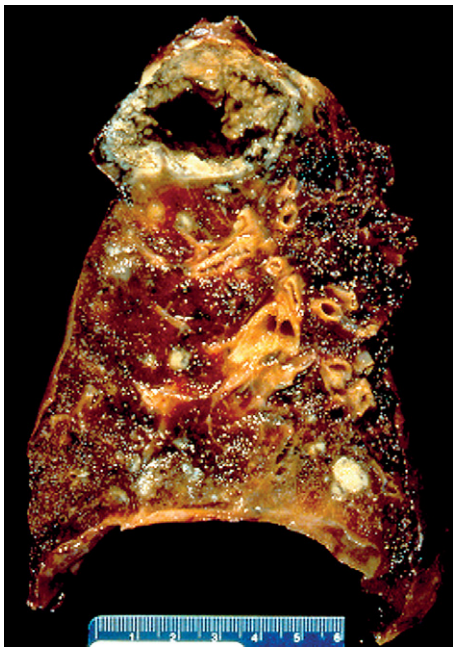

Figure 18.55 Pulmonary tuberculosis. This sagittal cut section of lung reveals a remarkable necrotic cavity in the upper lobe of progressive fibrocavitary disease. Within the right lower lobe, there is a tan white nodule, representing infection that has spread through the airways to distal parts of the lung.

Nontuberculous Mycobacteria The nontuberculous mycobacteria (NTM) are ubiquitous inhabitants of our environment, isolated from soil, fresh and brackish water, house dust, birds, animals, and food, and are increasingly important in causing pulmonary disease. There are currently more than 100 NTM species known. Those organisms thought to be pathogenic to the lung include the following: *M. avium* complex, *M. kansasii*, *M. xenopi*, *M. scrofulaceum*, *M. szulgai*, *M. simiae*, *M. fortuitum-chelonei*, and *M. malmonense*. Of these, *M. avium-intracellular*, *M. kansasii*, and *M. fortuitum-chelonei* account for the overwhelming majority of the pulmonary disease caused by NTM. *M. avium* and *M. intracellulare* are usually lumped together as *Mycobacterium avium* complex (MAC) simply because most laboratories are not equipped to distinguish between the two organisms. The clinical presentation of these lung infections can vary from minimally symptomatic small lesions discovered by routine radiography to sudden hemoptysis from advanced disease with severe cavitation (Table 18.5). The two most characteristic lesions are those of diffuse infiltrates in an immunocompromised patient, seen most commonly in the HIV-positive population and an

Table 18.5 Clinical and Pathologic Features of Nontuberculous Mycobacterial Respiratory Infections

Clinical Features	Pathology Features	Organisms
Asymptomatic nodule	Hyalinized, calcified nodule	*M. avium* complex
Immunocompromised	Diffuse, histiocytic infiltrate	*M. avium* complex
Elderly male with chronic lung disease	Apical cavitary pneumonia	*M. avium* complex
Indolent chronic small airway disease in women	Chronic bronchitis and bronchiolitis	*M. avium* complex
Hypersensitivity pneumonitis ('Hot tub lung')	Interstitial pneumonitis with loosely formed granulomas	*M. avium* complex

indolent inflammation of small airways, usually in the right middle lung causing bronchiolectasis, found in middle-aged women.

Viruses Most pulmonary infections are due to viruses from four major groups: influenza, parainfluenza, respiratory syncytial virus (RSV), and adenovirus (Table 18.6) [241]. The clinical presentations of these infections have some common features, including insidious onset, nonproductive cough, fever, and chest pain. Chest imaging studies usually reveal bilateral, multifocal infiltrates, most without evidence of cavitation or pleural involvement. These infections are mild, self-limiting, and require no more than supportive therapy except in immunocompromised hosts, where the clinical course can be much more serious. Also, immunocompromised patients are susceptible to other viruses such as herpesvirus and cytomegalovirus pneumonias, which are not common pathogens in normal hosts [242]. Since the 1980s, a subset of pulmonary viral infections has emerged with a much more aggressive clinical course, most notably SARS, coronavirus, and Hantavirus. These viruses present with systemic symptoms of headache, myalgias, and weakness followed by a deteriorating clinical course with respiratory distress, shock and, in over 50% of the cases, death [243,244]. Therapy for most respiratory viral infections is supportive, although antivirals are available for some viruses, mostly used in the setting of immunocompromised patients. Ribavirin, a guanosine analogue, is the main antiviral used for RSV; M2 inhibitors or adamantanes (amantadine and rimantadine) are used against influenza A and neuraminidase inhibitors (oseltamivir and zanamivir) are used against both influenza A and B [245]. Cytomegalovirus is treated with ganciclovir, foscarnet, or cidofovir, while herpesvirus is treated with acyclovir [241].

The pathologic patterns of injury for most viruses are similar, making morphologic distinctions among them difficult. However, some characteristic patterns emerge, most notably in those viruses that cause cytopathic changes. Influenza, adenovirus, SARS, coronavirus, and Hantavirus all cause an acute lung injury pattern with diffuse alveolar damage, and in the case of the latter two viruses, evidence of hemorrhage and edema. Influenza and adenovirus will also cause a necrotizing bronchiolitis due to their preferential infection of bronchial epithelial cells. Finally, some viral infections can be distinguished by their characteristic cytopathic inclusions. Adenovirus can be identified by characteristic smudge cells that present in advanced stages of the disease and represent adenovirus particles in the nucleus of an infected cell (Figure 18.56). Cytomegalovirus has both nuclear owl's eye inclusions, as well as cytoplasmic inclusions (Figure 18.57). Herpesvirus has glassy intranuclear inclusions and can also have multinucleation (Figure 18.58).

Table 18.6 Common Respiratory Viral Pathogens

Virus	Family	Genome	Respiratory Infection
Influenza A,B	Orthomyxoviridae	Single-stranded RNA	Pneumonia, Pharyngitis, Laryngitis
Parainfluenza 1,2,3	Paramyxoviridae	Single-stranded RNA	Pneumonia, Pharyngitis, Laryngitis
Adenovirus 1,2,3,4,5,7	Adenoviridae	Double-stranded DNA	Pneumonia, Pharyngitis, Laryngitis
Respiratory Syncytial Virus A,B	Paramyxoviridae	Single-stranded RNA	Sinusitis, Pneumonia
CMV	Herpesviridae	Double-stranded DNA	Laryngitis, Pneumonia
HSV	Herpesviridae	Double-stranded DNA	Pharyngitis, Pneumonia
Hantavirus	Bunyaviridae	Single-stranded RNA	Pneumonia
SARS virus	Coronaviridae	Single-stranded RNA	Pneumonia

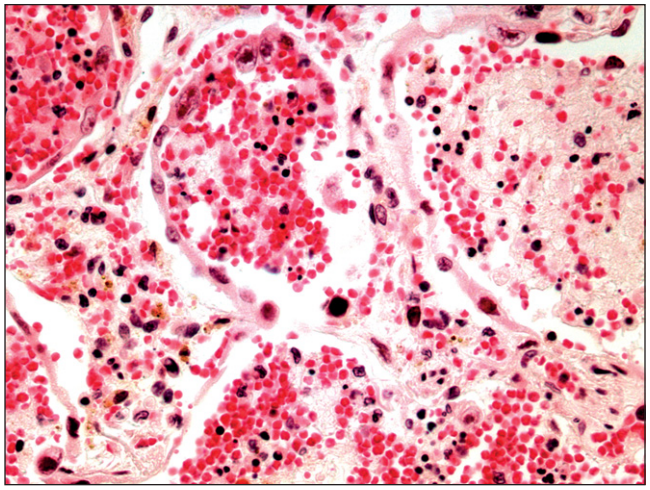

Figure 18.56 Adenovirus. The microscopic features of a severe adenovirus infection in this immunocompromised patient are that of a necrotizing pneumonia with cellular debris within the alveolar space. The viral inclusions are present within the dark nucleus in the center of the field. These cells are called smudge cells due to the obscuring of the nuclear features by these viral inclusions.

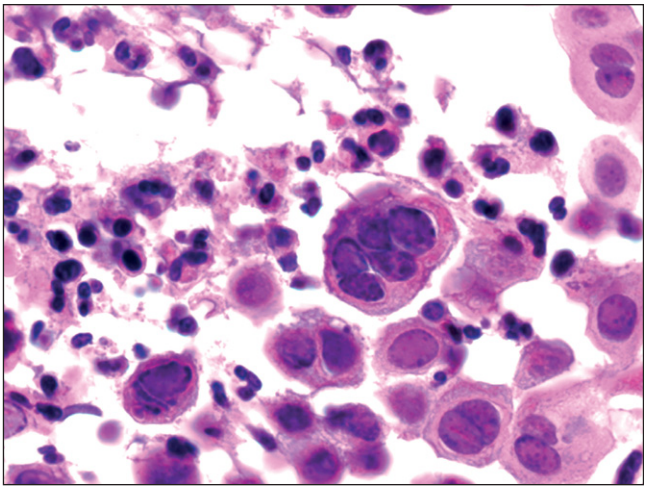

Figure 18.58 Herpesvirus. This microscopic photo is from a lung of an immunocompromised patient with a herpetic simplex pneumonia. In the center of the field is a multinucleated cell representing the cytopathic features of an HSV infection in the lung. These viral inclusions can be found in single cells or syncytia and represent Cowdry A herpetic nuclear inclusions.

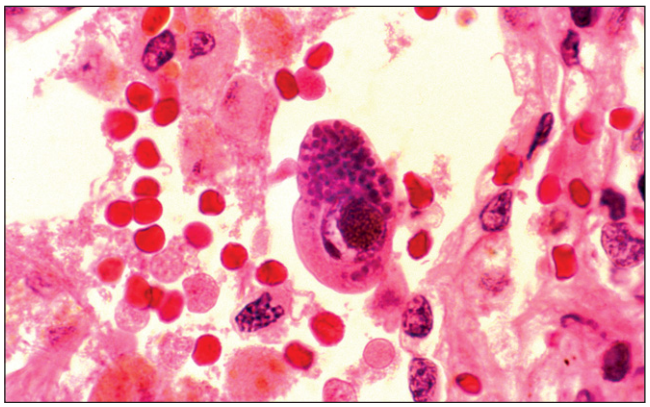

Figure 18.57 Cytomegalovirus. This alveolar macrophage illustrates the microscopic features of a cell infected by the CMV virus. The three features of these cells include (i) cytomegaly, (ii) basophilic cytoplasmic inclusions, and (iii) nuclear amphophilic inclusions.

Fungus

Fungi are larger and more complex than bacteria, and their patterns of injury in the lung are different and in general more destructive. These pathogens are common in our environment and enter the lungs through inhalation. Though many fungi are capable of causing pulmonary disease, most only inhabit the lung as colonizers. Those of most concern for causing clinical disease include the endemic fungi of North America—*Histoplasma capsulatum, Blastomyces dermatitidis,* and *Coccidioides immitis*—and two fungi that are commonly seen in immunocompromised hosts—*Aspergillus fumigatus* and *Pneumocystis jiroveci.*

Histoplasma capsulatum *Histoplasma capsulatum* is a dimorphic fungus most prevalent in the middle portion of the United States from the Great Lakes to Tennessee. The fungus is present in soil that has been contaminated with guano and other debris by nesting birds, most commonly blackbirds and chickens, and by bats. The organism lives in the environment as spores or conidia and germinates to form hyphae. These structures divide to create the yeast forms, which, when inhaled, induce granuloma formation in the lung. Approximately 75% of people have skin tests that are positive for exposure to *H. capsulatum,* but most exposures do not cause clinical disease. Disease typically occurs in people exposed to large amounts of organisms, such as construction workers who move large volumes of dirt or spelunkers who venture into bat-ridden caves. The acute disease has flu-like symptoms which are self-limiting. Healed disease may leave behind calcified granulomas in the lung that appear as buckshot on chest imaging studies. The most chronic forms of this disease may slowly progress, giving rise to cavitating and fibrous lesions. In the immunocompromised host, disseminating histoplasmosis can be seen, although reactivation is uncommon [246].

The pathology reveals characteristic necrotizing granulomas distributed around the airways (Figure 18.59), which contain silver-positive yeast forms of 2–4 microns. These granulomas may resolve into scarred nodules, which can calcify and produce the characteristic chest

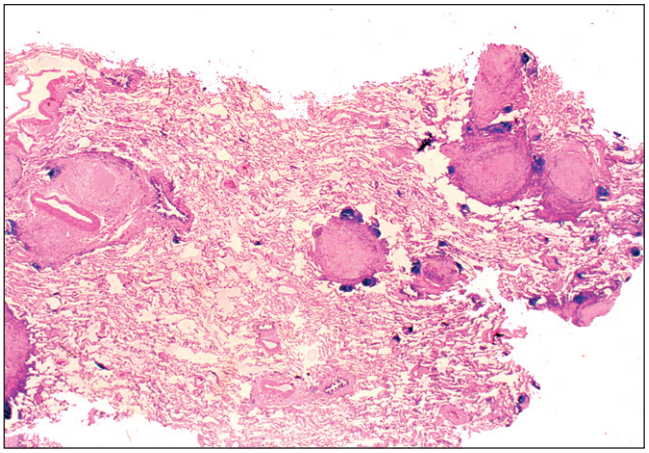

Figure 18.59 Histoplasmosis. Necrotizing granulomas centered on the airways within this lung are the characteristic feature of acute histoplasmosis. Within the center of these granulomas, one can find yeast form of *H. capsulatum.*

images. Cavities may form in the apices with progression of the disease, and the disseminated form of the disease has an abundance of organisms both within macrophages in the lung and throughout many organs in the body.

Blastomyces dermatitidis *Blastomyces dermatitidis* is also endemic to the middle United States, including the Ohio and Mississippi River valleys. It is found in wooded terrain, usually during the wet seasons, putting campers and outdoorsmen at risk. The clinical disease takes two forms, cutaneous and systemic, the latter beginning in the lungs through inhalation. The acute pulmonary infection takes a nonspecific form with fever, malaise, and chest pain. Imaging studies may show either infiltrates or a mass-like infiltrate. Thus, *Blastomyces* infection may mimic other diseases, and the diagnosis may be delayed. Some patients go on to chronic disease with cavitation or progressive pulmonary blastomycosis, which manifests as acute respiratory distress syndrome, cavitary lesions, and a poor prognosis [247].

The pathology of *Blastomyces* infection is similar to histoplasmosis with necrotizing granulomas. However, the lesions are larger, showing more neutrophilic necrosis. The organisms are also larger (8–15 microns), with prominent broad-based budding, and are apparent on routine hematoxylin and eosin staining (Figure 18.60).

Coccidioides immitis *Coccidioides immitis* is found in the semi-arid desert climate of the southwestern United States. The organisms are inhaled as spores, causing an acute disease characterized by fever, chills, chest pain, dyspnea, and hemoptysis. Chest imaging studies typically show consolidation and cavitation, and hilar lymphadenopathy is common. Reactivation and dissemination are possible in patients with previous infection, whether or not they are immunocompromised patients [248].

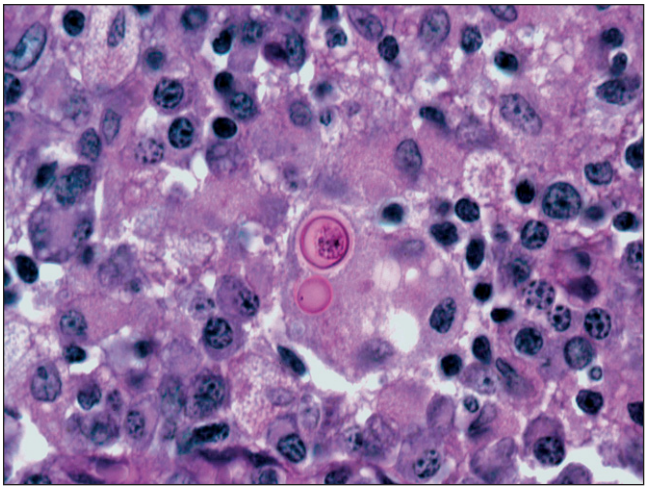

Figure 18.60 Blastomycosis. *Blastomyces dermatitidis* is a yeast form found within necrotizing granulomas and characterized by broad-based, single budding with a refractile cell wall that can be seen on the Periodic-acid Schiff stain.

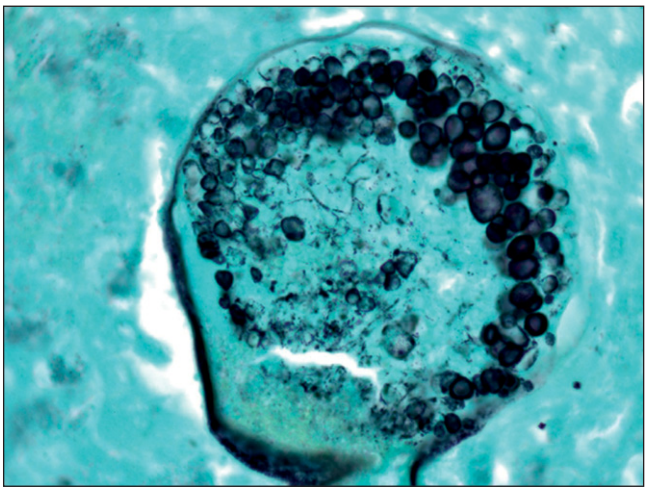

Figure 18.61 Coccidioidomycosis. *Coccidioides immitis* can be found in lungs as a large spherule containing endospores using a Grocott methenamine silver stain. These spherules can rupture and endopores can spill into the surrounding lung where they mature into new spherules.

The pathology of pulmonary coccidioidomycosis is neutrophilic, suppurative, and granulomatous. The organisms appear as large spherules containing endospores, visible on silver stains. The spherules are 30–100 microns in diameter and the endospores that are released into the surrounding tissue proceed to mature into new spherules (Figure 18.61). As in histoplasmosis, cavitating lesions may have hyphal forms that begin to germinate.

Aspergillus Fumigatus Aspergilli are asexual mycelial fungi that are ubiquitous in the environment as airborne aspergillus spores. They are weak pathogens

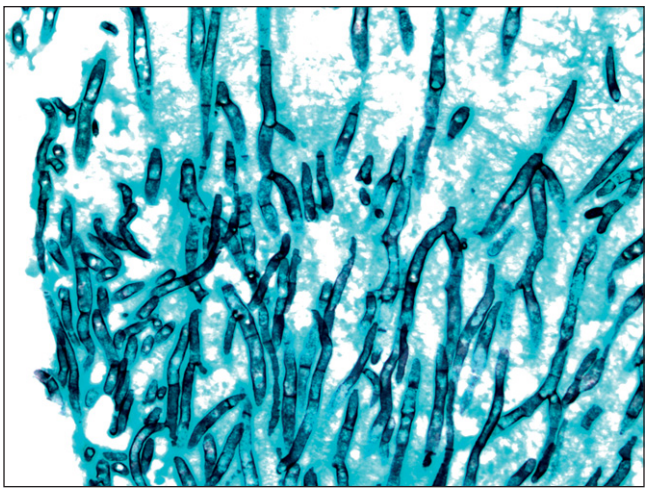

Figure 18.62 Aspergillosis. *Aspergillus fumigatus* grows within necrotizing cavities of the lung as branching septated fungal hyphae, as seen on this Grocott methenamine silver stain.

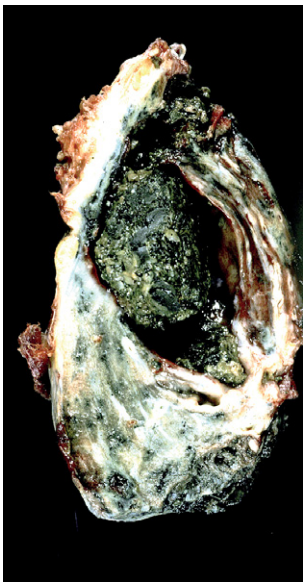

Figure 18.63 Aspergilloma. Fungal hyphae from *Aspergillus fumigatus* can colonize chronically inflamed lungs with cavities and may grow to form fungal balls with a dark, green color that are treated by surgical resection, as seen in this case of a lobectomy specimen.

that produce invasive infections predominantly in immunocompromised hosts or in those with significant chronic lung diseases. In tissue, aspergilli form septate hyphae, 3–6 microns in diameter, with characteristic acute-angle, dichotomous branching (Figure 18.62). These organisms affect the lung in three major ways: (i) saprophytic growth in bronchi or pre-existent cavities; (ii) as an allergic or hypersensitivity reaction, predominantly in asthmatics; and (iii) invasive aspergillosis in immunocompromised hosts [249,250]. As a saprophyte, aspergillus produces surface growths or minute masses of hyphae, usually in bronchiectatic cavities, emphysematous bullae, or scars from previous lung diseases such as tuberculosis or sarcoidosis. The pathology is usually that of a fibrous-walled cavity containing degenerating hyphae (Figure 18.63). In this setting, hyphae do not invade into the lung tissue, but surface erosion of a vascularized cavity may cause hemoptysis. Aspergillus causes an immunologic response resulting in mucoid impaction or eosinophilic pneumonia in asthmatics, an entity known as allergic bronchopulmonary aspergillosis (ABPA). Pathologically, one sees mucoid plugs and superficial erosions of the airways with histiocytic inflammation, with only rare hyphal fragments present. The final form of the disease, invasive pulmonary aspergillosis, is found in severely immunocompromised, neutropenic patients. The hyphae, which disseminate through the blood, invade the blood vessels causing thrombosis, hemorrhage, and infarction to form typical targetoid lesions. This form of the disease has a poor prognosis despite aggressive antifungal therapy.

Pneumocystis Jiroveci The taxonomy of *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) has changed over the past decade. Previously thought to be a protozoan based on the histological characteristics of its trophozoite and cyst life forms, it has recently been placed in the fungal kingdom after ribosomal RNA was found to have sequences compatible with the ascomycetous fungi [251]. The inability to culture *Pneumocystis jiroveci* has slowed the understanding of this organism. Animal models have helped in defining the antigenic and genotypic differences among the various *Pneumocystis* organisms, which has led to the proposal for species-specific strains, with *P. jiroveci* found in human infections [252]. The molecular methods used for the typing these species examine a number of gene loci. Most importantly, sequence analysis of the thymidylate synthase (TS) and superoxide dismutase (SODA) gene loci, the EPSP synthase domain of the multifunctional arom gene, and the mitochondrial small subunit ribosomal RNA (mtSSU rRNA) locus have been used to distinguish the various *Pneumocystis* species that infect different mammalian hosts [253].

Clinically, *P. jiroveci* causes disease predominantly in the immunocompromised setting. *Pneumocystis* pneumonia (PCP) has been found during recent times most commonly in the AIDS population, but prior to this epidemic, it was found in malnourished infants and other severely immunocompromised hosts. Because this organism has not been cultured, the diagnosis of PCP continues to be challenging. The clinical characteristics are nonspecific and vary with the patient's immune status. In the HIV population, patients typically develop a subacute onset of progressive dyspnea, a nonproductive cough, malaise, and a low-grade fever. In the non-HIV population, the presentation is more acute, with fulminant respiratory failure associated with cough and fever, and usually requiring mechanical ventilation [254]. Chest imaging studies typically show bilateral, symmetric, fine reticular interstitial infiltrates involving the perihilar area, which spread to involve the entire lung.

Treatment is usually with trimethoprim/sulfamethoxazole and intravenous pentamidine. Survival is 50%–95% even in severely immunocompromised patients.

The life cycle of *P. jiroveci* consists of three stages: trophozoite, cyst, and sporozoite. The trophozoite form, which adheres to the type 1 epithelium, replicates and enlarges through three precyst stages before maturing into a cyst form that is found in the alveolar space. Sporozoites develop within immature cysts through meiosis and mitosis. The mature cyst contains eight haploid sporozoites. The rupture of the cyst wall releases sporozoites into the surrounding environment where they mature into trophozoites.

The pathology of the infection is predominantly due to the interaction of the organism with the epithelium. The attachment of the organism to the lung epithelium is via glycoprotein A present on the surface of the organism. The binding of the organism to the type 1 cell occurs via surface receptors on the type 1 cell that include macrophage mannose receptors. These interact with glycoprotein A and activate pathways in the organism that induce genes encoding for pathways that induce mating and proliferation responses, and for the formation of pheromone receptors, transcription factors, and heterotrimeric G-protein subunits [263]. In addition to these genetic effects, the cyst wall contains chitins, polymers, and other substances, in particular, 1,3-glucan, that maintain its integrity and induce the inflammatory response of the host. The 1,3-glucan in the wall of the organism stimulates the release by the macrophages of reactive oxidant species and the generation of potent proinflammatory cytokines, such as TNFα, which bind to the organism and exert a toxic effect. Once inside the macrophage, the organism is incorporated into the phagolysosome and degraded. TNFα also directly recruits other inflammatory cells including neutrophils, lymphocytes, and circulating monocytes, and induces the release of IL-8 and IFN-γ that recruit and activate inflammatory cells [255]. In aggregate, the recruitment of these inflammatory cells and the mediators they release is responsible for the damage to the lung epithelium and endothelium that is seen in this disease [255].

The pathology of PCP has typical and atypical variants. Typically, the lung contains a dense interstitial plasma cell pneumonia that expands alveolar walls. The epithelium consists predominantly of Type 2 pneumocytes, and the alveolar spaces contain an eosinophilic, frothy exudate, which contains fine, hemoxylin-stained dots that represent a thickening in the cyst wall (Figure 18.64). In this form of the disease, the organisms are abundant and the diagnosis can usually be made by bronchoalveolar lavage. Atypical pathologic variants include a necrotizing variant that has a pattern similar to the typical form with exudative alveolar infiltrates, but which undergoes necrosis and cavity formation. These cavities heal into fibrous-walled cysts, similar in gross appearance to those found in pseudomonas pneumonia. A third variant has well-formed granulomas involving the airways, a pattern common to histoplasmosis and tuberculosis. In this form, the organisms are rare and very difficult to find, even with tissue organismal stains. In general, the pathologic pattern of injury depends on the host's immune status, with the typical pathology found in severely immunocompromised hosts as the AIDS population and the atypical forms found in hosts with immune systems that are less compromised.

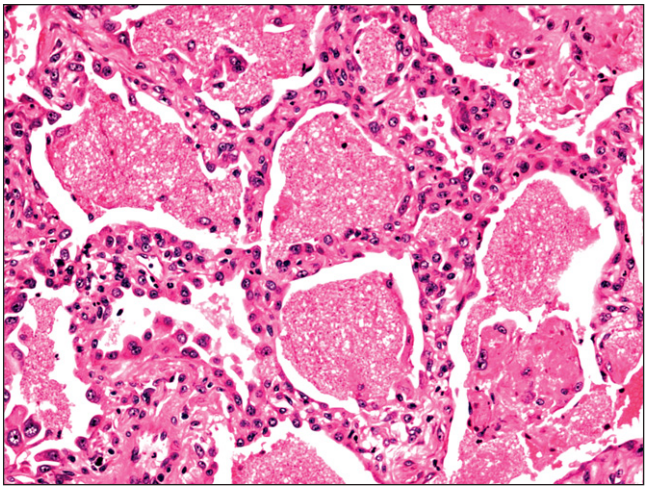

Figure 18.64 ***Pneumocystic jiroveci*** **pneumonia.** The microscopic features of this pneumonia are characterized by a foamy, eosinophilic infiltrate that fills the alveolar space. Upon close inspection, fine blue dots can be seen that represent the thickening in the cyst walls of the organism.

PULMONARY HISTIOCYTIC DISEASES

Pulmonary Langerhans cell histiocytosis (PLCH) and Erdheim-Chester disease are histiocytic diseases that primarily affect the lung. Other histiocytic diseases may affect the lung, such as Niemann-Pick disease, Gaucher disease, Hermansky-Pudlak and Rosai-Dorfman disease, but these are not considered primarily lung histiocytic diseases.

Pulmonary Langerhans' Cell Histiocytosis

Clinical and Pathologic Features

Pulmonary Langerhans' cell histiocytosis (PLCH) is a disease of the dendritic histiocytes of the lung referred to as Langerhans' cells (LCs). This disease is part of a group of diseases that are characterized by a proliferation of Langerhans cells in organs throughout the body that range from a malignant systemic disease as is seen in children [256] to the pulmonary variant that is seen in adolescents and adults. PLCH is usually the result of inflammatory or neoplastic stimuli in lungs of smokers or in lungs involved by certain neoplasms [257].

Chest radiographs from patients with PLCH usually reveal bilateral nodules, predominantly in the upper lobes, which are worrisome for metastatic disease. Treatment involves smoking cessation and steroid therapy. Typically, the disease undergoes spontaneous regression. Approximately 15%–20% of patients will progress to irreversible end-stage fibrosis [258].

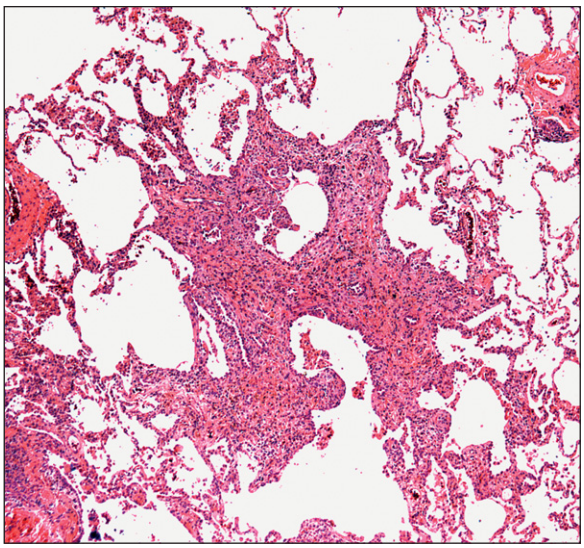

Figure 18.65 Pulmonary langerhans cell histiocytosis. This stellate-shaped scar represents the microscopic features of long-standing PLCH. These lung scars are characteristically found in the upper lung zones and represent chronic injury to the small airways.

The pathology of PLCH consists of airway-based lesions with a proliferation of LCs. The early cellular lesions contain a mixture of cells including Langerhans' cells, lymphocytes, plasma cells, and eosinophils (Figure 18.65). Though it was previously referred to as eosinophilic granuloma, eosinophils are not the major cell type present, and the lesion is, at best, a loosely formed granuloma. Immunohistochemistry reveals the LCs to be diffusely, strongly immunoreactive to S-100 protein and CD1a. Ultrastructural analysis reveals intracytoplasmic organelles called Birbeck granules, a normal constituent of Langerhans' cells, in greater numbers in PLCH [259].

Molecular Pathogenesis

The pathogenetic mechanisms of PLCH focus on defects in the homeostasis of dendritic cells (DCs) in the lungs of smokers and the role tobacco smoke may play in stimulating the proliferation of these cells [260]. Some studies suggest that stimulation of alveolar macrophages by chemicals in smoke results in secretion of such cytokines as GM-CSF, TGFβ, and TNFα [261]. In transgenic mice, accumulation of DCs around airways may be a result of excess GM-CSF [262]. Other theories suggest that cigarette smoke stimulates the secretion of bombesin-like peptide by the neuroendocrine cells in the bronchiolar epithelium and leads to a similar stimulation of alveolar macrophages and a cytokine milieu that promotes the proinflammatory proliferative changes [262].

Not all smokers get PLCH, leading to the suggestion that only smokers with an underlying genetic susceptibility will develop the disease. Studies have established that in some cases the LCs in PLCH are clonal, suggesting that cellular abnormalities must play some part in the pathogenesis of the diseases [263]. To support this, studies have shown genetic mutations and allelic loss of tumor suppressor genes in smokers with PLCH [264].

The mechanisms by which this proliferation of LCs leads to the destruction of the bronchiolar epithelium and the other observed pathology are unclear. LCs in normal lungs have little ability to interact with T-cells or act as effective antigen-presenting cells, but the LCs of PLCH have a mature immunophenotype, expressing B7-1 and B7-2, the co-stimulatory molecules needed for lymphostimulatory activity [265]. Whether this more mature immune phenotype leads to an unregulated immune response and destruction of the bronchial epithelial cells is not known. However, some studies have shown that bronchiolar epithelial cells may induce the expression of this mature phenotype by secreting cytokines in response to environmental stimulants such as cigarette smoke or viral infections, or by the development of hyperplastic or dysplastic lesions that express new foreign antigens [265].

Erdheim-Chester Disease

Clinical and Pathologic Features

Erdheim-Chester disease (ECD) is a systemic non-Langerhans' cell histiocytosis of adults that most commonly involves the long bones. Involvement of other organs, including the lung, has been reported. Lung involvement occurs in approximately 20%–35% of the cases, and the patients usually present with cough, dyspnea, rhonchi, and pleuritic pain. Radiographically, the lungs reveal infiltrates in a lymphatic distribution, predominantly upper lobe, with prominent interstitial septal markings that can mimic sarcoidosis [266–272].

Pulmonary involvement by ECD may have an unfavorable prognosis, and the fibrosis that ensues is one of the most frequently reported causes of death [266,273]. The treatment of ECD is variable with corticosteroids, chemotherapy, surgical resection, and radiation therapy reported [273].

Non-Langerhans' cell histiocytes of dendritic cell phenotype are the main cells present in this disease. This infiltrate contains foamy histiocytes with scattered giant cells, a scant number of lymphocytes or plasma cells, and some fibroblasts. The histiocytes express CD68 (macrophage antigen) and factor XIIIa (dendritic cell antigen), but express S-100 protein weakly or not at all, and do not express CD1a. Ultrastructural analysis reveals phagolysosomes, but no Birbeck granules are present [273]. This infiltrate that involves the lung is usually present in the pleura and subpleura, within the interlobular septa and around the bronchovascular structures. The remainder of the lung parenchyma is unremarkable, though fibrosis and paracicatricial emphysema can appear in the late stages of the disease [266].

Molecular Pathogenesis

The etiology of ECD is not known, but this rare disease has been established as primarily a macrophage disorder [274]. These histiocytes have abundant phagolysosomes and express the antigen CD1a and are consistent with a phagocytic cell, most likely closely related to alveolar macrophages. The peripheral monocytosis and the proinflammatory cytokine profile that is found in these patients might suggest that the histiocytic infiltrate is a result of systemic monocytic activation and invasion of circulating monocytes into the tissues throughout the body [275]. Recently, an ECD patient was successfully treated by an agent toxic to monocytes, supporting the theory that these cells play a part in the disease [275]. Alternatively, end organ cytokine production by local inflammatory cells resulting in proliferation and differentiation of resident immature histiocyte populations may produce a similar picture. Another interesting observation is that Erdheim-Chester has been reported to occur in patients with Langerhans' cell histiocytosis [276], which may suggest that this is a disease where macrophages transition between two different phenotypes along the differentiation spectrum of tissue dendritic cells [276]. Whether this is a benign or malignant proliferation has not been established. Of 5 patients studied, clonality has been demonstrated in 3 by polymerase-chain reaction [277].

PULMONARY OCCUPATIONAL DISEASES

Environmental exposures are a major cause of lung disease and can cause a wide spectrum of both acute and chronic pathology. Many organic and inorganic materials can cause lung damage, and because of their similar patterns of injury and long latent periods, it can be difficult to isolate the exact offending agent without a thorough clinical history. The two occupational lung diseases presented here—asbestosis and silicosis—represent pneumoconiosis, which are defined as diseases which result in diffuse parenchymal lung injury due to inhaled inorganic material. Both have many pathologic patterns of injury that depend on the amount and length of time of exposure, and both can also cause neoplastic diseases of the lung.

Asbestosis

Clinical and Pathologic Features

Asbestos fibers are naturally occurring silicates that are commonly used in construction materials such as cement and insulation and in many textiles. They can be separated into two groups based on their mineralogic characteristics. Serpentine fibers, named as such because they are long and curly, include chrysotile asbestos. Amphibole fibers, more straight and rodlike, include predominantly amosite and crocidolite asbestos. In the United States most of the asbestos is chrysotile. The amphiboles are more pathogenic and are responsible for most of the neoplastic and non-neoplastic pulmonary diseases associated with asbestos exposure.

By definition, asbestosis is bilateral diffuse interstitial fibrosis of the lungs that can be attributed to asbestos exposure. The disease, which mostly affects textile and construction workers, is usually the result of direct exposure over 15–20 years. The latency to clinical disease is inversely proportional to the level of exposure. The symptoms are a gradual onset of shortness of breath, a cough with dry rales at the bases on inspiration, and digital clubbing. In the early disease, the chest x-ray shows basilar disease that begins predominantly as thickening of the subpleural, but progresses as infiltrates and fibrosis that involve the middle zone, eventually leading to thickening of the airways and traction bronchiectasis. The apex of the lung is usually spared. The clinical findings are nonspecific and have considerable overlap with UIP, so the diagnosis is usually made only when a history of significant exposure is discovered.

The gross picture includes a bilateral lower lobe gray/tan fibrosis with honeycomb changes in late disease. Microscopically, asbestosis can cause many patterns of injury in the lung, but the most common is collagenous deposition in the areas of the lymphatics where the fibers are in the highest concentration. These areas include the subpleural, interlobular septae, and around the bronchovascular areas that contain a bronchiole and a branch of the pulmonary artery. Hyalinized pleural plaques are a common manifestation of asbestos exposure but are not specific for asbestos and can be found in the absence of pulmonary parenchymal disease. Eventually, the fibrosis involves the alveoli beyond the bronchioles and causes distortion of the lung architecture to form remodeled, dilated airspaces similar to those seen in UIP. Distinguishing this fibrosis from other forms of fibrosing lung disease can be difficult, but the presence of ferruginous bodies, asbestos fibers coated by iron, proteins, and a mucopolysaccharide coat are indicative of significant asbestos exposures and support this diagnosis (Figure 18.66) [278].

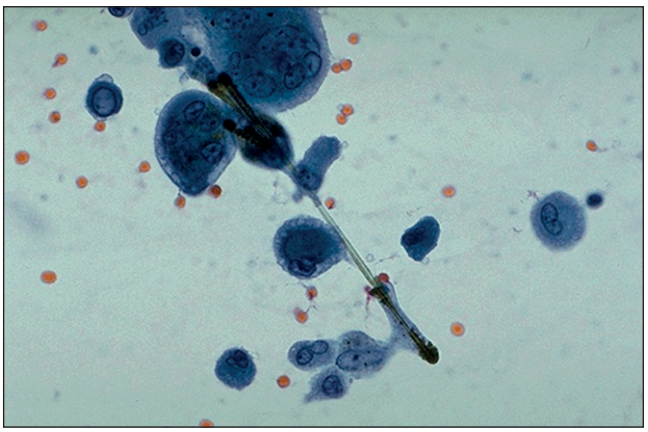

Figure 18.66 Asbestosis. This cytopathologic preparation from a bronchoalveolar lavage specimen illustrates an asbestos fiber coated by an iron-protein-mucopolysaccharide substance and appears as a golden brown, beaded structure known as a ferruginous body.

Silicosis

Clinical and Pathologic Features

Silicosis results from chronic, high-dose exposure to crystalline silica, which consists of silicon and oxygen with trace amounts of other elements, usually iron. The most common silica is quartz, which is present in large amounts in such rocks as granite, shale, and sandstone and is among the more fibrogenic of all silica types. Thus, occupations most at risk for silicosis include sandblasting, quarrying, stone dressing, and foundry work where exposure to quartz is high. The disease takes three major clinical and pathologic forms that have different clinical characteristics.

Simple or nodule silicosis is marked by the presence of fine nodules $\leq$1 cm, on chest imaging studies, usually in the upper lobes. Patients with this condition are typically asymptomatic, with normal respiratory physiology. The pathology in these lungs reveals discrete, hard nodules that have a green/gray color, centered either on the small airways or in the subpleura. Microscopically, these nodules have an early stellate shape that eventually transforms to a more whorled appearance with dust-laden macrophages scattered throughout it. Polarized light examination reveals weakly birefringent material.

Complicated pneumoconiosis represents similar pathologic findings only with larger and more circumscribed nodules, which coalesce into a large upper lobe mass, a condition known as progressive, massive fibrosis (Figure 18.67). These patients are symptomatic with a productive cough and mixed pulmonary function tests with a reduced diffusing capacity as the fibrosis increases. Diffuse interstitial fibrosis may occur; however, unlike asbestosis, this pattern is found in pneumoconiosis. When complicated pneumoconiosis is found with rheumatoid nodules in the setting of a patient with rheumatoid arthritis, this is known as Caplan's syndrome.

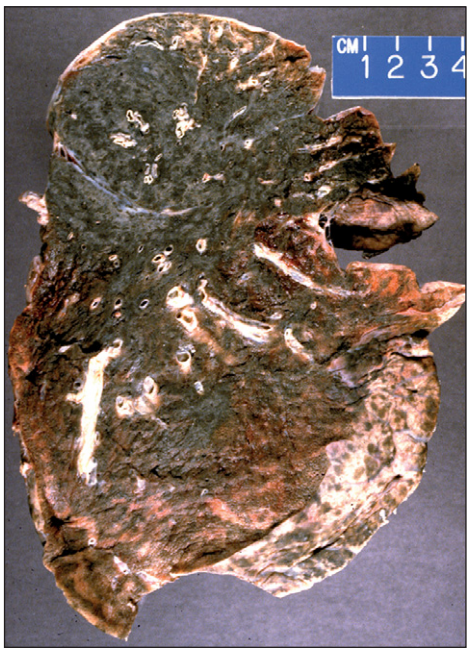

Figure 18.67 Complicated pneumoconiosis/ progressive massive fibrosis. This sagittal cut section of lung reveals a large gray/black mass that extends from the apex to include the majority of the lung. The patient had a long history as a coal mine worker, and the microscopic sections revealed abundant anthracotic pigment and scarring in this area.

Molecular Pathogenesis

The pathogenesis of both asbestosis and silicosis depends upon inflammation and fibrosis caused by the inhaled fibers. In humans, the amount of fiber needed to cause fibrosis varies from person to person. This may be related to a difference in fiber deposition based on the size of the lungs or to the efficacy with which the lung clears these fibers [256]. Some studies have also suggested that fiber length determines the amount of pathology. However, this association has not been confirmed in humans for either asbestosis or silicosis. In both diseases, it is known that other factors increase the risk of developing disease. For example, smokers exhibit worse disease than nonsmokers with similar exposures to asbestosis. The mechanism for this effect is unclear, although speculation centers on the inhibition of fiber clearance in smokers. Also, it is known that smoking enhances the uptake of fibers by pulmonary epithelial cells and in this way may increase the fibrogenic and inflammatory cytokine production by these cells.

The cellular mechanisms by which both asbestos and silica fibers induce the inflammation and fibrosis are mediated predominantly through alveolar macrophages. In the case of silica, it is known that the uptake of these fibers into the alveolar macrophages is by way of a scavenger receptor expressed on the surface of the cell known as MARCO (macrophage receptor with a collagenous structure). Once inside the cells, the fibers activate the release of ROS that can lead to cellular and molecular damage through a number of pathways. First, ROS can directly cause lipid peroxidation, membrane damage, and DNA damage. Second, silica-induced free radicals can trigger phosphorylation of cellular proliferation pathways through mitogen-activated protein kinases (MAPKs), extracellular signal regulated kinases (ERKs), and p38. These pathways are also involved in the proliferation of fibroblasts in asbestosis and of mesothelial and epithelial cells in the neoplastic diseases associated with the inhalation of these fibers [279]. In addition, these fibers can activate proinflammatory pathways controlled by such transcription factors as nuclear NFκB and activator protein 1 (AP-1). These pathways result in the activation of the early response genes *c-fos* and *c-Jun* and the release of proinflammatory cytokines such as IL-1 as well as fibrogenic factors such TNFα [280].

TNFα plays a prominent role in both diseases, and its regulation has been studied in animal models exposed to silica. It is now known that a transcription factor labeled nuclear factor of activated T-cells (NFAT) plays a key role in the regulation of TNFα.

Binding sites for NFAT have been found in the promoter region of the *TNFα* gene. The mediation of silica-induced *TNFα* transcription is probably via O_2- but not H_2O_2 [280,281].

DEVELOPMENTAL ABNORMALITIES

Tracheal/Bronchial Atresias and Sequestrations

Clinical and Pathologic Features

Atresia of the lung represents a premature closure of the airway at any level of the bronchial tree including the lobar, segmental, or subsegmental airways. Clinically, these children usually present between 10 and 20 years of age for symptoms of dyspnea, wheezing, recurrent pneumonias, or for incidental findings on a chest imaging study. These lesions are more common in the proximal segmental bronchi, right more often than left. When atresia is associated with anomalies of the vascular supply to the affected airway, the lesion represents a separate, aberrant segment of lung known as a sequestration, either intralobar or extralobar type.

The pathology of bronchial atresias and sequestrations represents sequelae of chronic inflammation due to the accumulation of secretions in these blind-end airways. These features consist of cystically dilated airways with mucus and parenchymal fibrosis with honeycomb changes. In intralobar sequestrations (ILS), the anomalous vessel is a muscular artery that enters through the pleura from an aortic source, usually from the thoracic area. ILS are separate, isolated areas of lung invested with the normal visceral pleura without bronchial or arterial connections (Figure 18.68). Extralobar sequestrations (ELS) are pyramid-shaped accessory pieces of lung that have their own pleura with an artery from the lung but without airway connections.

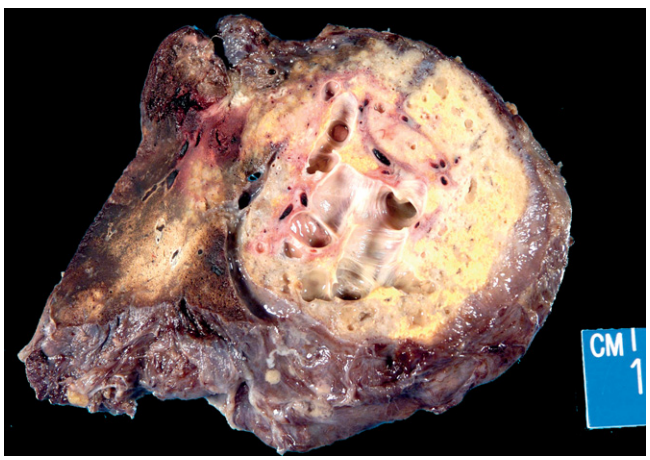

Figure 18.68 Intralobar sequestration. The tan and white mass involving this left lower lobectomy specimen represents chronic pneumonia and fibrosis in the sequestered area of the lung. The dilated airways are features of an endstage fibrosis that is commonly found in this entity.

Congenital Pulmonary Cystic Diseases

Clinical and Pathologic Features

The category of congenital pulmonary cystic diseases represents the majority of congenital pulmonary disease and includes foregut cysts and cystic adenomatoid malformations. Foregut cysts include bronchogenic, esophageal, and thymic cysts that form from defects in the foregut branching. Clinically, these cysts are usually incidental findings on chest imaging studies, but they can present with complications due to infection or hemorrhage.

Pathologic features of these cysts include subtle differences that are usually only apparent after microscopic examination. Grossly, these cysts usually arise proximally either within the mediastinum (over 50%) or in the proximal regions of the lungs, right more commonly than left, along the esophagus, and rarely within the lung parenchyma or below the diaphragm [282]. Microscopically, each cyst contains a simple cuboidal or columnar epithelium, ciliated or nonciliated, that may undergo squamous metaplasia. Distinguishing among the three types of cysts requires the presence of other elements. Bronchogenic cysts have submucosal glands and/or hyaline cartilage within their walls, and thymic cysts may contain residual thymus.

Congenital cystic adenomatoid malformations (CCAM), now more commonly referred to as congenital pulmonary airway malformations (CPAM), are segments of lung with immature airways and alveolar parenchyma. These are usually classified by their predominant cyst size into types 0–4. Type 1 cysts, which contain a main large cyst of up to 10 cm, are the most common. These cysts are distinguished from foregut cysts upon the recognition in the CPAM of immature alveolar duct-like structures connecting to the surrounding lung parenchyma. This type of CPAM is also notable, as it is known to undergo malignant transformation, usually to mucinous bronchioloalveolar cell adenocarcinomas.

Molecular Pathogenesis

These anomalies arise due to defects during the various stages of development and are best considered within these developmental stages. The embryonic stage occurs within the first 3–7 weeks of life when the ventral wall of the foregut separates into the trachea and esophagus and branches to form the left and right lungs. The splanchnic mesenchyme that surrounds this foregut forms the vascular and connective tissues of the lungs. Defects in this phase result in complete lack of lung development known as pulmonary agenesis and incomplete separation of the trachea and esophagus, causing tracheal-esophageal atresias and fistulas. The pseudoglandular stage, between weeks 7–17 of development, is a time of rapid development of the conducting airways including the bronchi and bronchioles and the expansion of the peripheral lung into the acinar buds. The mesenchymal tissue

that surrounds these buds begins to thin, becomes vascularized, and forms the cartilage that surrounds the more proximal branching airways. During the canalicular (week 17–24), saccular (weeks 24–38), and alveolar (weeks 36 to maturity) stages of development, the acinar buds continue to expand, and the mesenchyme surrounding this continues to thin. During the canalicular stage, the pulmonary vascular bed begins to organize, the distance between the blood in the vascular spaces and the air in the alveoli narrows, and the respiratory epithelium begins to form. The gas exchange unit of the alveolus becomes functional during the saccular stage with further differentiation of the respiratory epithelium to include Clara cells, ciliated and nonciliated cells, and type 2 cells with the first production of surfactant occurring during this period. This gas exchange unit continues to mature during the alveolar stage with the growth and septation of the alveoli. This process continues postnatally through 6–8 years of age.

The different types of CPAMs arise at different stages of development. CPAMs 0, 1, and 2 are a result of defects during the early embryonic and pseudoglandular stages of development, producing pathology with features of primitive alveolar buds and immature and abnormal airway cartilage structures. CPAMs 3 and 4 result from abnormal formation of the more distal airways and pulmonary parenchyma during the canalicular, saccular, and alveolar phases, causing pathology with immature alveolar, or alveolar simplification with enlarged alveoli [283].

Various genetic defects in the pathways that control lung morphogenesis have been associated with these congenital lung diseases. Two major transcription factors are responsible for the normal branching morphogenesis. The first, thyroid transcription factor-1 (TTF-1), is a member of the Nkx2.1 family of hemeodomain-containing transcription factors. This factor plays a role in the lung epithelial-specific gene expression and proper lung bud development in the embryonic stage, as well as in the maturation of the respiratory epithelium. The second major factor is somatic hedgehog (SHH)/Gli, expressed by endodermally derived cells and required for branching morphogenesis. The development of the lung bud from the foregut endoderm depends on the appropriate expression of these lung-specific genes at the correct time in development. In the presence of genetic defects, aberrant lung development may occur. For example, mutations of various types in the *SHH/Gli* gene have been found to cause tracheoesophageal fistulas, anomalous pulmonary vasculature, and aberrant airway branching. Also, deletions in the *TTF-1* gene are associated with tracheoesophageal fistulas and a variety of forms of lung dysgenesis [284]. Finally, factors present in the surrounding mesenchyme play a role in inducing the proper development of the pulmonary endoderm. A prominent mesenchymal factor in this process is fibroblast growth factor (FGF), which modulates both the proximal and distal lung branching morphogenesis. Deletions in this gene may cause lung agenesis and tracheal malformations [284].

Surfactant Dysfunction Disorders

Clinical and Pathologic Features

Surfactant dysfunction disorders represent a heterogenous group of inherited disorders of surfactant metabolism, found predominantly in infants and children. Pulmonary surfactant includes both phospholipids and surfactant proteins, designated surfactant proteins A, B, C, and D (SP-A, SP-B, SP-C, SP-D), synthesized and secreted by type 2 cells beginning in the canalicular stage of lung development. Damage to type 2 cells during this time period can lead to acquired surfactant deficiencies. However, more commonly these deficiencies are the result of genetic defects of the surfactant proteins themselves.

The major diseases are caused by genetic defects in the surfactant protein B (*SFTPB*, chromosome 2p12-p11.2); surfactant protein C (*SFTPC*, chromosome 8p21); and adenosine triphosphate (APT)-binding cassette transporter subfamily A member 3 (*ABCA3*, chromosome 16p13.3). Defects in *SFTPB* and *ABCA3* have an autosomal recessive inheritance pattern, and defects in *SFTPC* have an autosomal dominant pattern. SP-B deficiency is the most common. It presents at birth with a rapidly progressive respiratory failure and chest imaging studies showing diffuse ground glass infiltrates. The gross pathology in these lungs consists of heavy, red, and congested parenchyma with microscopic features that range from a PAP-like pattern to a chronic pneumonitis of infancy (CPI) pattern. In SP-B deficiency, the PAP pattern predominates with a histologic picture of cuboidal alveolar epithelium and eosinophilic PAS-positive material within the alveolar spaces that appears with disease progression. In the late stages of the disease, the alveolar wall thickens with a chronic inflammatory infiltrate and fibroblasts. This alveolar proteinosis-type pattern of injury can be confirmed with immunohistochemical studies that establish the absence of SP-B within this surfactant-like material. Diseases due to *ABCA3* or *SFTPC* deficiency may present within a week of birth or years later; the former has a poor prognosis, but the latter has a more variable prognosis with some patients surviving into adulthood. Indeed, SP-C mutations have also been recognized in some families as a cause of interstitial pneumonia and pulmonary fibrosis in adults [285]. The pathology of SP-C deficiency has more CPI features and less proteinosis. In contrast, *ABCA* deficiency can have either PAP or CPI features, with the former present early in the disease and the latter present in more chronically affected lungs [286].

Molecular Pathogenesis

The SP-B gene (*SFTPB*) is approximately 10 kb in length and is located on chromosome 2. There are over 30 recessive loss-of-function mutations associated with the *SFTPB* gene. However, the most common mutation is a GAA substitution for C in codon 121, found in about 70% of the cases. The lack of SP-B leads to an abnormal proportion of phosphatidylglycerol and an accumulation of a

pro-SP-C peptide, leading to the alveolar proteinosis-like pathology.

SP-C protein deficiency is due to a defect in the *SFTPC* gene localized to human chromosome 8. There are approximately 35 dominantly expressed mutations in *SFTPC* that result in acute and chronic lung disease. Approximately 55% of them arise spontaneously, and the remainder are inherited. The most common mutation is a threonine substitution for isoleucine in codon 73 (I73T), found in 25% of the cases, including both sporadic and inherited disease [287]. This mutation leads to a misfolding of the SP-C protein, which inhibits its progression through the intracellular secretory pathway, usually within the Golgi apparatus or the endoplasmic reticulum [288]. The absence of SP-C within the alveolar space causes severe lung disease in mouse models. Infants with documented mutated proSP-C protein, the larger primary translation product from which SP-C is proteolytically cleaved, can have respiratory distress syndrome (RDS) or CPI. In older individuals, pathologic patterns observed in the lungs with these mutations include nonspecific interstitial pneumonitis (NSIP) and UIP. In this affected adult population, the pathology and age of disease presentation vary even within familial cohorts, suggesting the involvement of a second hit, perhaps an environmental factor [289].

The ABCA3 protein is a member of the family of ATP-dependent transporters, which includes the CFTR, and is expressed in epithelial cells. Mutation in this gene results in severe respiratory failure that is refractory to surfactant replacement. The cellular basis for the lack of surfactant in patients with this genetic mutation is not known. The presence of abnormal lamellar bodies within the type 2 cells by ultrastructural analysis suggests a disruption in the normal surfactant synthesis and packaging in this disease. There is some evidence that this gene contains promoters that share elements consistent with their activation by the transcription factors TTF-1 and Foxa7, and deletions in either or both of these genes may play a role in this disease [289].

REFERENCES

1. http://seer.cancer.gov/csr/1975_2004/results_single/sect_01_table.01.pdf.
2. Espey DK, Wu XC, Swan J, et al. Annual report to the nation on the status of cancer, 1975–2004, featuring cancer in American Indians and Alaska Natives. *Cancer.* 2007;110:2119–2152.
3. Travis WD, Brambilla E, Müller-Hermelink HK, et al. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. Lyon: IARC Press; 2004.
4. Greene FL, Page DL, Fleming ID, et al. *AJCC Cancer Staging Manual.* New York: Springer; 2002.
5. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 17 Regs Limited-Use, Nov 2006 Sub (1973–2004 varying), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2007, based on the November 2006 submission.
6. Alberts WM. Diagnosis and management of lung cancer executive summary: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest.* 2007;132:1S–19S.
7. Wistuba II. Genetics of preneoplasia: Lessons from lung cancer. *Curr Mol Med.* 2007;7:3–14.
8. Virmani AK, Fong KM, Kodagoda D, et al. Allelotyping demonstrates common and distinct patterns of chromosomal loss in human lung cancer types. *Genes Chromosomes Cancer.* 1998;21:308–319.
9. Girard L, Zochbauer-Muller S, Virmani AK, et al. Genome-wide allelotyping of lung cancer identifies new regions of allelic loss, differences between small cell lung cancer and non-small cell lung cancer, and loci clustering. *Cancer Res.* 2000; 60:4894–4906.
10. Garnis C, Lockwood WW, Vucic E, et al. High resolution analysis of non-small cell lung cancer cell lines by whole genome tiling path array CGH. *Int J Cancer.* 2006;118:1556–1564.
11. Wistuba II, Gazdar AF. Lung cancer preneoplasia. *Annu Rev Pathol.* 2006;1:331–348.
12. Weir BA, Woo MS, Getz G, et al. Characterizing the cancer genome in lung adenocarcinoma. *Nature.* 2007;450:893–898.
13. Minna JD, Roth JA, Gazdar AF. Focus on lung cancer. *Cancer Cell.* 2002;1:49–52.
14. Sun S, Schiller JH, Spinola M, et al. New molecularly targeted therapies for lung cancer. *J Clin Invest.* 2007;117:2740–2750.
15. Wistuba II, Behrens C, Virmani AK, et al. High resolution chromosome 3p allelotyping of human lung cancer and preneoplastic/preinvasive bronchial epithelium reveals multiple, discontinuous sites of 3p allele loss and three regions of frequent breakpoints. *Cancer Res.* 2000;60:1949–1960.
16. Gazdar A, Franklin WA, Brambilla E, et al. Genetic and molecular alterations. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC, eds. *Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart.* Lyon: IARC Press; 2004:21–25.
17. Wistuba II, Behrens C, Virmani AK, et al. Allelic losses at chromosome 8p21–23 are early and frequent events in the pathogenesis of lung cancer. *Cancer Res.* 1999;59:1973–1979.
18. Wistuba II, Behrens C, Milchgrub S, et al. Sequential molecular abnormalities are involved in the multistage development of squamous cell lung carcinoma. *Oncogene.* 1999;18:643–650.
19. Knudson Jr AG. Hereditary cancers disclose a class of cancer genes. *Cancer.* 1989;63:1888–1891.
20. Pfeifer GP, Denissenko MF, Olivier M, et al. Tobacco smoke carcinogens, DNA damage and p53 mutations in smoking-associated cancers. *Oncogene.* 2002;21: 7435–7451.
21. Stelter AA, Xie J. Molecular oncogenesis of lung cancer. In: Zander DS, Popper HH, Jagirdar J, Haque AK, Cagle PT, Barrios R, eds. *Molecular Pathology of Lung Diseases.* New York, NY: Springer; 2008:169–175.
22. Sekido Y, Fong KM, Minna JD. Molecular genetics of lung cancer. *Annu Rev Med.* 2003;54:73–87.
23. Beasley MB, Lantuejoul S, Abbondanzo S, et al. The P16/cyclin D1/Rb pathway in neuroendocrine tumors of the lung. *Hum Pathol.* 2003;34:136–142.
24. Toyooka S, Maruyama R, Toyooka KO, et al. Smoke exposure, histologic type and geography-related differences in the methylation profiles of non-small cell lung cancer. *Int J Cancer.* 2003;103:153–160.
25. Marinov M, Fischer B, Arcaro A. Targeting mTOR signaling in lung cancer. *Crit Rev Oncol Hematol.* 2007;63:172–182.
26. Gridelli C, Maione P, Rossi A. The potential role of mTOR inhibitors in non-small cell lung cancer. *Oncologist.* 2008;13:139–147.
27. Scheurle D, Jahanzeb M, Aronsohn RS, et al. HER-2/neu expression in archival non-small cell lung carcinomas using FDA-approved Hercep test. *Anticancer Res.* 2000; 20:2091–2096.
28. Hirsch FR, Scagliotti GV, Langer CJ, et al. Epidermal growth factor family of receptors in preneoplasia and lung cancer: Perspectives for targeted therapies. *Lung Cancer.* 2003;41(Suppl 1): S29–42.
29. Clamon G, Herndon J, Kern J, et al. Lack of trastuzumab activity in nonsmall cell lung carcinoma with overexpression of erb-B2: 39810: A phase II trial of Cancer and Leukemia Group B. *Cancer.* 2005;103:1670–1675.
30. Johnson BE, Heymach JV. Farnesyl transferase inhibitors for patients with lung cancer. *Clin Cancer Res.* 2004;10:4254s–4257s.
31. Sun S, Schiller JH. Angiogenesis inhibitors in the treatment of lung cancer. *Crit Rev Oncol Hematol.* 2007;62:93–104.
32. Gutierrez M, Giaccone G. Antiangiogenic therapy in nonsmall cell lung cancer. *Curr Opin Oncol.* 2008;20:176–182.
33. Zhang B, Pan X, Cobb GP, et al. microRNAs as oncogenes and tumor suppressors. *Dev Biol.* 2007;302:1–12.

34. Colby TV, Noguchi M, Henschke C, et al. Adenocarcinoma. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC, eds. *Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart*. Lyon: IARC Press; 2004:35–44.
35. Yang Y, Fujita J, Tokuda M, et al. Lung cancer associated with several connective tissue diseases: With a review of literature. *Rheumatol Int*. 2001;21:106–111.
36. Kerr KM, Fraire AE, Pugatch B, et al. Atypical adenomatous hyperplasia. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC, eds. *Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart*. Lyon: IARC Press; 2004:73–75.
37. Yokose T, Doi M, Tanno K, et al. Atypical adenomatous hyperplasia of the lung in autopsy cases. *Lung Cancer*. 2001; 33:155–161.
38. Kim CF, Jackson EL, Woolfenden AE, et al. Identification of bronchioalveolar stem cells in normal lung and lung cancer. *Cell*. 2005;121:823–835.
39. Kwei KA, Kim YH, Girard L, et al. Genomic profiling identifies TITF1 as a lineage-specific oncogene amplified in lung cancer. *Oncogene*. 2008;27:3635–3640.
40. Shigematsu H, Lin L, Takahashi T, et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. *J Natl Cancer Inst*. 2005;97:339–346.
41. Suzuki M, Shigematsu H, Iizasa T, et al. Exclusive mutation in epidermal growth factor receptor gene, HER-2, and KRAS, and synchronous methylation of nonsmall cell lung cancer. *Cancer*. 2006;106:2200–2207.
42. Shigematsu H, Gazdar AF. Somatic mutations of epidermal growth factor receptor signaling pathway in lung cancers. *Int J Cancer*. 2006;118:257–262.
43. Tam IY, Chung LP, Suen WS, et al. Distinct epidermal growth factor receptor and KRAS mutation patterns in non-small cell lung cancer patients with different tobacco exposure and clinicopathologic features. *Clin Cancer Res*. 2006;12:1647–1653.
44. Hirsch FR, Varella-Garcia M, Cappuzzo F, et al. Combination of EGFR gene copy number and protein expression predicts outcome for advanced non-small-cell lung cancer patients treated with gefitinib. *Ann Oncol*. 2007;18:752–760.
45. Shigematsu H, Takahashi T, Nomura M, et al. Somatic mutations of the HER2 kinase domain in lung adenocarcinomas. *Cancer Res*. 2005;65:1642–1646.
46. Kerr KM, Galler JS, Hagen JA, et al. The role of DNA methylation in the development and progression of lung adenocarcinoma. *Dis Markers*. 2007;23:5–30.
47. Toyooka S, Tokumo M, Shigematsu H, et al. Mutational and epigenetic evidence for independent pathways for lung adenocarcinomas arising in smokers and never smokers. *Cancer Res*. 2006; 66:1371–1375.
48. Hammar SP, Brambilla C, Pugatch B, et al. Squamous cell carcinoma. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC, eds. *Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart*. Lyon: IARC Press; 2004:26–30.
49. Franklin WA, wistuba II, Geisinger K, et al. Squamous dysplasia and carcinoma in situ. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC, eds. *Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart*. Lyon: IARC Press; 2004:68–72.
50. Giangreco A, Groot KR, Janes SM. Lung cancer and lung stem cells: Strange bedfellows? *Am J Respir Crit Care Med*. 2007;175: 547–553.
51. Bota S, Auliac JB, Paris C, et al. Follow-up of bronchial precancerous lesions and carcinoma in situ using fluorescence endoscopy. *Am J Respir Crit Care Med*. 2001;164:1688–1693.
52. Breuer RH, Pasic A, Smit EF, et al. The natural course of preneoplastic lesions in bronchial epithelium. *Clin Cancer Res*. 2005; 11:537–543.
53. George PJ, Banerjee AK, Read CA, et al. Surveillance for the detection of early lung cancer in patients with bronchial dysplasia. *Thorax*. 2007;62:43–50.
54. Brambilla E, Pugatch B, Geisinger K, et al. Large cell carcinoma. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC, eds. *Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart*. Lyon: IARC Press; 2004:45–50.
55. Eleazar JA, Borczuk AC. Molecular pathology of large cell carcinoma and its precursors. In: Zander DS, Popper HH, Jagirdar J, Haque AK, Cagle PT, Barrios R, eds. *Molecular Pathology of Lung Diseases*. New York: Springer; 2008:279–292.
56. Johansson M, Dietrich C, Mandahl N, et al. Karyotypic characterization of bronchial large cell carcinomas. *Int J Cancer*. 1994; 57:463–467.
57. Ohtsuka K, Ohnishi H, Fujiwara M, et al. Abnormalities of epidermal growth factor receptor in lung squamous-cell carcinomas, adenosquamous carcinomas, and large-cell carcinomas: Tyrosine kinase domain mutations are not rare in tumors with an adenocarcinoma component. *Cancer*. 2007; 109:741–750.
58. Marchetti A, Martella C, Felicioni L, et al. EGFR mutations in non-small-cell lung cancer: Analysis of a large series of cases and development of a rapid and sensitive method for diagnostic screening with potential implications on pharmacologic treatment. *J Clin Oncol*. 2005;23:857–865.
59. Travis WD, Rush W, Flieder DB, et al. Survival analysis of 200 pulmonary neuroendocrine tumors with clarification of criteria for atypical carcinoid and its separation from typical carcinoid. *Am J Surg Pathol*. 1998;22:934–944.
60. Travis WD. The concept of pulmonary neuroendocrine tumours. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC, eds. *Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart*. Lyon: IARC Press; 2004:19–20.
61. Travis WD, Nicholson S, Hirsch FR, et al. Small cell carcinoma. In: Travis WD, Brambilla E, Müller-Hermelink HK and Harris CC, eds. *Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart*. Lyon: IARC Press; 2004: 31–34.
62. Fink G, Krelbaum T, Yellin A, et al. Pulmonary carcinoid: Presentation, diagnosis, and outcome in 142 cases in Israel and review of 640 cases from the literature. *Chest*. 2001;119: 1647–1651.
63. Skuladottir H, Hirsch FR, Hansen HH, et al. Pulmonary neuroendocrine tumors: Incidence and prognosis of histological subtypes. A population-based study in Denmark. *Lung Cancer*. 2002;37:127–135.
64. Gosney JR, Travis WD. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC, eds. *Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart*. Lyon: IARC Press; 2004: 76–77.
65. Pedersen N, Pedersen MW, Lan MS, et al. The insulinoma-associated 1: A novel promoter for targeted cancer gene therapy for small-cell lung cancer. *Cancer Gene Ther*. 2006;13:375–384.
66. Jiang SX, Kameya T, Asamura H, et al. hASH1 expression is closely correlated with endocrine phenotype and differentiation extent in pulmonary neuroendocrine tumors. *Mod Pathol*. 2004; 17:222–229.
67. Du EZ, Goldstraw P, Zacharias J, et al. TTF-1 expression is specific for lung primary in typical and atypical carcinoids: TTF-1-positive carcinoids are predominantly in peripheral location. *Hum Pathol*. 2004;35:825–831.
68. Saqi A, Alexis D, Remotti F, et al. Usefulness of CDX2 and TTF-1 in differentiating gastrointestinal from pulmonary carcinoids. *Am J Clin Pathol*. 2005;123:394–404.
69. Sturm N, Rossi G, Lantuejoul S, et al. Expression of thyroid transcription factor-1 in the spectrum of neuroendocrine cell lung proliferations with special interest in carcinoids. *Hum Pathol*. 2002;33:175–182.
70. Cai YC, Banner B, Glickman J, et al. Cytokeratin 7 and 20 and thyroid transcription factor 1 can help distinguish pulmonary from gastrointestinal carcinoid and pancreatic endocrine tumors. *Hum Pathol*. 2001;32:1087–1093.
71. Brambilla E. Small cell carcinoma. In: Zander DS, Popper HH, Jagirdar J, Haque AK, Cagle PT, Barrios R, eds. *Molecular Pathology of Lung Diseases*. New York: Springer; 2008: 293–300.
72. Balsara BR, Testa JR. Chromosomal imbalances in human lung cancer. *Oncogene*. 2002;21:6877–6883.
73. Petersen I, Langreck H, Wolf G, et al. Small-cell lung cancer is characterized by a high incidence of deletions on chromosomes 3p, 4q, 5q, 10q, 13q and 17p. *Br J Cancer*. 1997;75:79–86.
74. Righi L, Volante M, Rapa I, et al. Neuro-endocrine tumours of the lung. A review of relevant pathological and molecular data. *Virchows Arch*. 2007;451(Suppl 1):S51–59.

75. Zabarovsky ER, Lerman MI, Minna JD. Tumor suppressor genes on chromosome 3p involved in the pathogenesis of lung and other cancers. *Oncogene.* 2002;21:6915–6935.
76. Kim YH, Girard L, Giacomini CP, et al. Combined microarray analysis of small cell lung cancer reveals altered apoptotic balance and distinct expression signatures of MYC family gene amplification. *Oncogene.* 2006;25:130–138.
77. Onuki N, Wistuba II, Travis WD, et al. Genetic changes in the spectrum of neuroendocrine lung tumors. *Cancer.* 1999;85: 600–607.
78. Debelenko LV, Brambilla E, Agarwal SK, et al. Identification of MEN1 gene mutations in sporadic carcinoid tumors of the lung. *Hum Mol Genet.* 1997;6:2285–2290.
79. Debelenko LV, Swalwell JI, Kelley MJ, et al. MEN1 gene mutation analysis of high-grade neuroendocrine lung carcinoma. *Genes Chromosomes Cancer.* 2000;28:58–65.
80. Dreijerink KM, Hoppener JW, Timmers HM, et al. Mechanisms of disease: Multiple endocrine neoplasia type 1-relation to chromatin modifications and transcription regulation. *Nat Clin Pract Endocrinol Metab.* 2006;2:562–570.
81. Wistuba II, Gazdar AF, Minna JD. Molecular genetics of small cell lung carcinoma. *Semin Oncol.* 2001;28:3–13.
82. Brambilla E, Negoescu A, Gazzeri S, et al. Apoptosis-related factors p53, Bcl2, and Bax in neuroendocrine lung tumors. *Am J Pathol.* 1996;149:1941–1952.
83. Przygodzki RM, Finkelstein SD, Langer JC, et al. Analysis of p53, K-ras-2, and C-raf-1 in pulmonary neuroendocrine tumors. Correlation with histological subtype and clinical outcome. *Am J Pathol.* 1996;148:1531–1541.
84. Brambilla E. Neuroendocrine carcinomas and precursors. In: Zander DS, Popper HH, Jagirdar J, Haque AK, Cagle PT and Barrios R, eds. *Molecular Pathology of Lung Diseases.* New York: Springer; 2008:301–306.
85. Kaye FJ. RB and cyclin dependent kinase pathways: Defining a distinction between RB and p16 loss in lung cancer. *Oncogene.* 2002;21:6908–6914.
86. Gouyer V, Gazzeri S, Brambilla E, et al. Loss of heterozygosity at the RB locus correlates with loss of RB protein in primary malignant neuro-endocrine lung carcinomas. *Int J Cancer.* 1994; 58:818–824.
87. Eymin B, Gazzeri S, Brambilla C, et al. Distinct pattern of E2F1 expression in human lung tumours: E2F1 is upregulated in small cell lung carcinoma. *Oncogene.* 2001;20:1678–1687.
88. Salon C, Merdzhanova G, Brambilla C, et al. E2F-1, Skp2 and cyclin E oncoproteins are upregulated and directly correlated in high-grade neuroendocrine lung tumors. *Oncogene.* 2007;26:6927–6936.
89. Hiyama K, Hiyama E, Ishioka S, et al. Telomerase activity in small-cell and non-small-cell lung cancers. *J Natl Cancer Inst.* 1995;87:895–902.
90. Lantuejoul S, Soria JC, Moro-Sibilot D, et al. Differential expression of telomerase reverse transcriptase (hTERT) in lung tumours. *Br J Cancer.* 2004;90:1222–1229.
91. Zaffaroni N, Villa R, Pastorino U, et al. Lack of telomerase activity in lung carcinoids is dependent on human telomerase reverse transcriptase transcription and alternative splicing and is associated with long telomeres. *Clin Cancer Res.* 2005;11:2832–2839.
92. Nishio Y, Nakanishi K, Ozeki Y, et al. Telomere length, telomerase activity, and expressions of human telomerase mRNA component (hTERC) and human telomerase reverse transcriptase (hTERT) mRNA in pulmonary neuroendocrine tumors. *Jpn J Clin Oncol.* 2007;37:16–22.
93. Leotlela PD, Jauch A, Holtgreve-Grez H, et al. Genetics of neuroendocrine and carcinoid tumours. *Endocr Relat Cancer.* 2003;10:437–450.
94. Burbee DG, Forgacs E, Zochbauer-Muller S, et al. Epigenetic inactivation of RASSF1A in lung and breast cancers and malignant phenotype suppression. *J Natl Cancer Inst.* 2001;93:691–699.
95. Toyooka S, Toyooka KO, Maruyama R, et al. DNA methylation profiles of lung tumors. *Mol Cancer Ther.* 2001;1:61–67.
96. Shivapurkar N, Toyooka S, Eby MT, et al. Differential inactivation of caspase-8 in lung cancers. *Cancer Biol Ther.* 2002;1: 65–69.
97. Wistuba II, Berry J, Behrens C, et al. Molecular changes in the bronchial epithelium of patients with small cell lung cancer. *Clin Cancer Res.* 2000;6:2604–2610.
98. Finkelstein SD, Hasegawa T, Colby T, et al. 11q13 allelic imbalance discriminates pulmonary carcinoids from tumorlets. A microdissection-based genotyping approach useful in clinical practice. *Am J Pathol.* 1999;155:633–640.
99. Yousem SA, Tazelaar HD, Manabe T, et al. Inflammatory myofibroblastic tumour. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC, eds. *Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart.* Lyon: IARC Press; 2004:105–106.
100. Travis WD, Churg A, Aubry MC, et al. Mesenchymal tumours. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC, eds. *Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart.* Lyon: IARC Press; 2004:141–142.
101. Coffin CM, Patel A, Perkins S, et al. ALK1 and p80 expression and chromosomal rearrangements involving 2p23 in inflammatory myofibroblastic tumor. *Mod Pathol.* 2001;14:569–576.
102. Lawrence B, Perez-Atayde A, Hibbard MK, et al. TPM3–ALK and TPM4–ALK oncogenes in inflammatory myofibroblastic tumors. *Am J Pathol.* 2000;157:377–384.
103. Begueret H, Galateau-Salle F, Guillou L, et al. Primary intrathoracic synovial sarcoma: A clinicopathologic study of 40 t(X;18)-positive cases from the French Sarcoma Group and the Mesopath Group. *Am J Surg Pathol.* 2005;29:339–346.
104. Hartel PH, Fanburg-Smith JC, Frazier AA, et al. Primary pulmonary and mediastinal synovial sarcoma: A clinicopathologic study of 60 cases and comparison with five prior series. *Mod Pathol.* 2007;20:760–769.
105. Kazmierczak B, Meyer-Bolte K, Tran KH, et al. A high frequency of tumors with rearrangements of genes of the HMGI(Y) family in a series of 191 pulmonary chondroid hamartomas. *Genes Chromosomes Cancer.* 1999;26:125–133.
106. Hess JL. Chromosomal translocations in benign tumors: The HMGI proteins. *Am J Clin Pathol.* 1998;109:251–261.
107. Weill H, Hughes JM, Churg AM. Changing trends in US mesothelioma incidence. *Occup Environ Med.* 2004;61:438–441.
108. Churg A, Roggli V, Galateau-Salle F, et al. Mesothelioma. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC, eds. *Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart.* Lyon: IARC Press; 2004:128–136.
109. Rizzo P, Bocchetta M, Powers A, et al. SV40 and the pathogenesis of mesothelioma. *Semin Cancer Biol.* 2001;11:63–71.
110. Robinson BW, Lake RA. Advances in malignant mesothelioma. *N Engl J Med.* 2005;353:1591–1603.
111. Maziak DE, Gagliardi A, Haynes AE, et al. Surgical management of malignant pleural mesothelioma: A systematic review and evidence summary. *Lung Cancer.* 2005;48: 157–169.
112. Marchevsky AM. Application of immunohistochemistry to the diagnosis of malignant mesothelioma. *Arch Pathol Lab Med.* 2008;132:397–401.
113. Ramos-Nino ME, Testa JR, Altomare DA, et al. Cellular and molecular parameters of mesothelioma. *J Cell Biochem.* 2006; 98:723–734.
114. Galateau-Salle F, Vignaud JM. Diffuse malignant mesothelioma: Genetic pathways and mechanisms of oncogenesis of asbestos and other agents that cause mesotheliomas. In: Zander DS, Popper HH, Jagirdar J, Haque AK, Cagle PT, Barrios R, eds. *Molecular Pathology of Lung Diseases.* New York: Springer; 2008: 347–357.
115. Murthy SS, Testa JR. Asbestos, chromosomal deletions, and tumor suppressor gene alterations in human malignant mesothelioma. *J Cell Physiol.* 1999;180:150–157.
116. Musti M, Kettunen E, Dragonieri S, et al. Cytogenetic and molecular genetic changes in malignant mesothelioma. *Cancer Genet Cytogenet.* 2006;170:9–15.
117. Sekido Y, Pass HI, Bader S, et al. Neurofibromatosis type 2 (NF2) gene is somatically mutated in mesothelioma but not in lung cancer. *Cancer Res.* 1995;55:1227–1231.
118. Toyooka S, Kishimoto T, Date H. Advances in the molecular biology of malignant mesothelioma. *Acta Med Okayama.* 2008;62:1–7.
119. Lee AY, Raz DJ, He B, et al. Update on the molecular biology of malignant mesothelioma. *Cancer.* 2007;109:1454–1461.

120. Ramos-Nino ME, Vianale G, Sabo-Attwood T, et al. Human mesothelioma cells exhibit tumor cell-specific differences in phosphatidylinositol 3-kinase/AKT activity that predict the efficacy of Onconase. *Mol Cancer Ther.* 2005;4:835–842.
121. Govindan R, Kratzke RA, Herndon 2nd JE, et al. Gefitinib in patients with malignant mesothelioma: A phase II study by the Cancer and Leukemia Group B. *Clin Cancer Res.* 2005;11: 2300–2304.
122. Cortese JF, Gowda AL, Wali A, et al. Common EGFR mutations conferring sensitivity to gefitinib in lung adenocarcinoma are not prevalent in human malignant mesothelioma. *Int J Cancer.* 2006;118:521–522.
123. Elias JA, Lee CG, Zheng T, et al. New insights into the pathogenesis of asthma. *J Clin Invest.* 2003;111:291–297.
124. Trigg CJ, Manolitsas ND, Wang J, et al. Placebo-controlled immunopathologic study of four months of inhaled corticosteroids in asthma. *Am J Respir Crit Care Med.* 1994;150:17–22.
125. Tantisira KG, Weiss ST. The pharmacogenetics of asthma: An update. *Curr Opin Mol Ther.* 2005;7:209–217.
126. Israel E. Genetics and the variability of treatment response in asthma. *J Allergy Clin Immunol.* 2005;115:S532–538.
127. Barnes PJ. Immunology of asthma and chronic obstructive pulmonary disease. *Nature Rev Immunol.* 2008;8:183–192.
128. Holgate ST. Pathogensis of asthma. *Clin Exp Allergy.* 2008; 38:872–897.
129. Comhair SA, Xu W, Ghosh S, et al. Superoxide dismutase inactivation in pathophysiology of asthmatic airway remodeling and reactivity. *Am J Pathol.* 2005;166:663–674.
130. Bradding P, Walls AF, Holgate ST. The role of the mast cell in the pathophysiology of asthma. *J Allergy Clin Immunol.* 2006; 117:1277–1284.
131. GOLD. Global Initiative for Chronic Obstructive Lung Disease (GOLD): Global strategy for the diagnosis MOCOPD. NHLBI/WHO Workshop Report. 2003.
132. Churg A, Cosio M, Wright JL. Mechanisms of cigarette smoke-induced COPD: Insights from animal models. *Am J Physiol Lung Cell Mol Physiol.* 2008;294:L612–631.
133. Snider G, Klinerman J, Thurlbeck WM. The definition of emphysema: Report of the National Heart, Lung and Blood Institute Division of Lung Diseases Workshop. *Am Rev Respir Dis.* 1985; 132:182–185.
134. Kim V, Rogers TJ, Criner GJ. Frontiers in emphysema research. *Semin Thorac Cardiovasc Surg.* 2007;19:135–141.
135. Wright JL, Churg A. Advances in the pathology of COPD. *Histopath.* 2006;10:1–9.
136. Thurlbeck WM. Pathology of chronic airflow obstruction. *Chest.* 1990;97:6s–10s.
137. Taraseviciene-Stewart L, Voelkel NF. Molecular pathogenesis of emphysema. *J Clin Invest.* 2008;118:394–402.
138. Lieberman J, Winter B, Sastre A. Alpha 1-antitrypsin Pi-types in 965 COPD patients. *Chest.* 1986;89:370–373.
139. Kohnlein T, Welte T. Alpha-1-antitrypsin deficiency: Pathogenesis, clinical presentation, diagnosis, and treatment. *Am J Med.* 2008;121:3–9.
140. Mulgrew AT, Taggart CC, McElvaney NG. Alpha-1-antitrypsin deficiency: Current concepts. *Lung.* 2007;185:191–201.
141. Ogushi F, Fells GA, Hubbard RC, et al. Z-type alpha 1-antitrypsin is less competent than M1-type alpha 1-antitrypsin as an inhibitor of neutrophil elastase. *J Clin Invest.* 1987;80:1366–1374.
142. Barnes PJ. Mediators of chronic obstructive pulmonary disease. *Pharmacol Rev.* 2004;52:515–548.
143. MacNee W. Oxidative stress and lung inflammation in airways disease. *Eur J Pharmacol.* 2001;429:195–207.
144. Rahman I, Adcock IM. Oxidative stress and redox regulation of lung inflammation of COPD. *Eur Respir J.* 2006;28:219–242.
145. Seifart C, Plagens A. Genetics of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis.* 2007;2:541–550.
146. Mitchell RE, Bury RG. Congenital bronchiectasis due to deficiency of bronchial cartilage (Williams-Campbell syndrome): A case report. *J Pediatr.* 1975;87:230–234.
147. Van Schoor J, Joos G, Pauwels R. Tracheobronchomegaly—The Mounier-Kuhn syndrome: Report of two cases and review of the literature. *Eur Respir J.* 1991;4:1303–1306.
148. Afzelius BA. A human syndrome caused by immotile cilia. *Science.* 1976;193:317–319.
149. Morillas HN, Zariwala M, Knowles MR. Genetic causes of bronchiectasis: Primary ciliary dyskinesia. *Respiration.* 2007;74: 252–263.
150. Davies JC, Alton EWF, Bush A. Cystic fibrosis. *BMJ.* 2007;335: 1255–1259.
151. Riordan JR, Rommens JM, Kerem B, et al. Identification of the cystic fibrosis gene: Cloning and characterization of complementary DNA. *Science.* 1989; 245:1066–1073.
152. Notarangelo LD, Plebani A, Mazzolari E, et al. Genetic causes of bronchiectasis: Primary immune deficiencies and the lung. *Respiration.* 2007;74:264–275.
153. Davies JC, Rubin BK. Emerging and unusual gram-negative infections in cystic fibrosis. *Semin Respir Crit Care Med.* 2007; 28:312–321.
154. Bonfield TL, Konstan MW, Berger M. Altered respiratory epithelial cell cytokine production in cystic fibrosis. *J Allergy Clin Immunol.* 1999;104:72–78.
155. Johkoh T. Imaging of idiopathic interstitial pneumonias. *Clin in Chest Medicine.* 2008;29:133–147.
156. Liebow AA, Carrington CB. The interstitial pneumonias. In: Simon M, Potchen EJ, LeMay M, eds. *Frontiers of Pulmonary Radiology.* New York: Grune & Stratton; 1969:102–141.
157. American Thoracic Society/European Respiratory Society. International multidisciplinary consensus classification of the idiopathic interstitial pneumonias: The Joint Statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS Board of Directors, June 2001, and by The ERS Executive Committee, June 2001. *Am J Respir Crit Care Med.* 2002;165:277–304.
158. Lawson WE, Loyd JE. The genetic approach in pulmonary fibrosis. *Proc Am Thorac Soc.* 2006;3:345–349.
159. Katzenstein AL, Myers JL. Idiopathic pulmonary fibrosis: Clinical relevance of pathologic classification. *Am J Respir Crit Care Med.* 1998;157:1301–1315.
160. Farver CF. Pathology of advanced interstitial diseases: Pulmonary fibrosis, sarcoidosis, histiocytosis X, autoimmune pulmonary disease, lymphangioleiomyomatosis. In: Maurer JR, ed. *Non-Neoplastic Advanced Lung Disease* in: *Lung Biology in Health and Disease.* New York: Marcel Dekker, Inc.; 2003:29–58. Chapter 2.
161. Maher TM, Wells AU, Laurent GJ. Idiopathic pulmonary fibrosis: Multiple causes and multiple mechanisms? *Eur Respir J.* 2007;30:835–839.
162. Selman M, Pardo A. Role of epithelial cells in idiopathic pulmonary fibrosis. *Proc Am Thorac Soc.* 2006;3:364–372.
163. Noble PW, Homer RJ. Idiopathic pulmonary fibrosis: New insights into pathogenesis. *Clin Chest Med.* 2004;25:749–758.
164. Chilosi M, Poletti V, Zamò A, et al. Aberrant Wnt/beta-catenin pathway activation in idiopathic pulmonary fibrosis. *Am J Pathol.* 2003;162:1495–1502.
165. Ramos C, Montana M. Fibroblasts from idiopathic pulmonary fibrosis and normal lungs differ. *Am J Resp Cell Mol Biol.* 2001; 24:591–599.
166. Armanios MY, Chen JJ, Cogan JD, et al. Telomerase mutations in families with idiopathic pulmonary fibrosis. *N Engl J Med.* 2007;356:1317–1326.
167. Anderson WR, Thielen K. Correlative study of adult respiratory distress syndrome by light, scanning, and transmission electron microscopy. *Ultrastruct Pathol.* 1992;16:615–628.
168. Tomashefski Jr JF. Pulmonary pathology of the adult respiratory distress syndrome. *Clin Chest Med.* 1990;11:593–619.
169. Tasaka S, Amaya F, Hashimoto S, et al. Roles of oxidants and redox signaling in the pathogenesis of acute respiratory distress syndrome. *Antioxid Redox Signal.* 2008;10:739–753.
170. Tang PS, Mura M, Seth R, et al. Acute lung injury and cell death: How many ways can cells die? *Am J Physiol Lung Cell Mol Physiol.* 2008;294:L632–641.
171. Taylor JR, Ryu J, Colby TV, et al. Lymphangioleiomyomatosis: Clinical course in 32 patients. *N Engl J Med.* 1990;323:1254–1260.
172. McCormack FX. Lymphangioleiomyomatosis: A clinical update. *Chest.* 2008;133:507–516.

173. Johnson SR, Whale CI, Hubbard RB, et al. Survival. *Thorax.* 2004;59:800–803.
174. Muller NL, Chiles C, Kullnig P. Pulmonary lymphangiomyomatosis: Correlation of CT with radiographic and functional findings. *Radiology.* 1990;175:335–339.
175. Steagall WK, Taveira-DaSilva AM, Moss J. Clinical and molecular insights into lymphangioleiomyomatosis. *Sarc Vasc Dif Lung Dis.* 2005;22:S49–S66.
176. Matsumoto Y, Horiba K, Usaki J, et al. Markers of cell proliferation and expression of melanosomal antigen in lymphangioleiomyomatosis. *Am J Respir Cell Mol Biol.* 1999;21:327–336.
177. Krymskaya VP. Smooth muscle-like cells in pulmonary lymphangioleiomyomatosis. *Proc Am Thorac Soc.* 2008;5:119–126.
178. Cornog JL Jr, Enter line HT. Lymphangiomyoma, a benign lesion of chyliferous lymphatics synonymous with lymphangiopericytoma. *Cancer* 1966;19:1909–1930.
179. Juvet SC, McCormack FX, Kwiatkowski DJ, et al. Molecular pathogenesis of lymphangioleiomyomatosis: Lessons learned from orphans. *Am J Respir Cell Mol Biol.* 2007;36:398–408.
180. Thomas PD, Hunninghake GW. Current concepts of the pathogenesis of sarcoidosis. *Am Rev Respir Dis.* 1987;135:747–760.
181. DeRemee RA. Sarcoidoisis. *Mayo Clin Proc.* 1995;70:177–181.
182. Chiles C, Putnam CE. Pulmonary sarcoidosis. *Semin Respir Med.* 1992;13:345–357.
183. Uehlinger ES. The morbid anatomy of sarcoidosis. *Am Rev Respir Dis.* 1961;84:6–13.
184. Ricker W. Sarcoidosis: A clinicopathologic review of three hundred cases, including twenty-two autospies. *Am J Clin Pathol.* 1949;19:725–749.
185. Sheffield EA. Pathology of sarcoidosis. *Clin Chest Med.* 1997;18:741–754.
186. Reich JM. What is sarcoidosis? *Chest.* 2003;124:367–371.
187. Culver DA, Newman LS, Kavuru MS. Gene-environment interactions in sarcoidosis: Challenge and opportunity. *Clin Dermatol.* 2007;25:267–275.
188. Rybicki BA, Maliarik MJ, Major M, et al. Epidemiology, demographics and genetics of sarcoidosis. *Semin Respir Infect.* 1998;13:166–173.
189. Rybicki BA, Iannuzzi MC, Frederick MM, et al. Familial aggregation of sarcoidosis. A case-control etiologic study of sarcoidosis (ACCESS). *Am J Respir Crit Care Med.* 2001;164:2085–2091.
190. Moller DR, Chen ES. Genetic basis of remitting sarcoidosis: Triumph of the trimolecular complex? *Am J Respir Cell Mol Biol.* 2002;27(4):391–395.
191. McIntyre JA, McKee KT, Loadholt CB, et al. Increased HLA-B7 antigen frequency in South Carolina blacks in association with sarcoidosis. *Transplant Proc.* 1977;9(suppl 1):173–176.
192. Grunewald J, Eklung A, Olerup O. Human leukocyte antigen class I alleles and the disease course in sarcoidosis patients. *Am J Respir Crit Care Med.* 2004;169(6):696–702.
193. Ina Y, Takad K, Yamamoto M, et al. HLA and sarcoidosis in the Japanese. *Chest.* 1989;95(6):1257–1261.
194. Kunikane H, Abe S, Yamaguchi E, et al. Analysis of restriction fragment length polymorphism for the HLA-DR gene in Japanese. *Thorax.* 1994;49(6):573–576.
195. Schurmann M, Lympany PA, Reichet P, et al. Familial sarcoidosis is linked to the major. *Am J Respir Crit Care Med.* 2000;162:861–864.
196. Schurmann M, Reichel P, Muller-Myhsok B, et al. Results from a genome-wide search for predisposing genes in sarcoidosis. *Am J Respir Crit Care Med.* 2001;164:840–846.
197. Bocart D, Lecossier D, De Lassence A, et al. A search for mycobacterial DNA in granulomatous tissues from patients with sarcoidosis using the polymerase chain reaction. *Am Rev Respir Dis.* 1992;145:1142–1148.
198. Drake WP, Pei Z, Pride DT, et al. Molecular analysis of sarcoidosis and control tissues for Mycobacteria DNA. *Emerg Infect Dis.* 2002;8:1328–1335.
199. Baughman RP, Lynch JP. Difficult treatment issues in sarcoidosis. *J Intern Med.* 2003;253:41–45.
200. Baughman RP, Lower EE, du Bois RM. Sarcoidosis. *Lancet.* 2003;361:1111–1118.
201. Moller DR. Pulmonary fibrosis of sarcoidosis. New approaches, old ideas. *Am J Respir Cell Mol Biol.* 2003;29:S37–41.
202. Presneill JJ, Nakata K, Inoue Y, et al. Pulmonary alveolar proteinosis. *Clin Chest Med.* 2004;25:593–613.
203. Trapnell BC, Whitsett JA, Nakata K. Pulmonary alveolar proteinosis. *N Engl J Med.* 2003;349:2527–2539.
204. Tazawa R, Hamano E, Arai T, et al. Granulocyte-macrophage colony-stimulating factor and lung immunity in pulmonary alveolar proteinosis. *Am J Respir Crit Care Med.* 2005;171:1142–1149.
205. Prakash UB, Barham SS, Carpenter HA, et al. Pulmonary alveolar phospholipoproteinosis: Experience with 34 cases and a review. *Mayo Clin Proc.* 1987;62:499–518.
206. Mazzone PJ, Jane Thomassen M, Kavuru MS. Pulmonary alveolar proteinosis: Recent advances. *Semin Respir Crit Care Med.* 2002;23:115–126.
207. Lakshminarayan S, Schwarz MI, Stanford RE. Unsuspected pulmonary alveolar proteinosis complicating acute myelogenous leukemia. *Chest.* 1976;69:433–435.
208. Bedrossian CW. Alveolar proteinosis as a consequence of immunosuppression. A hypothesis based on clinical and pathologic observations. *Human Pathol.* 1980;11:527–534.
209. Johkoh T, Itoh H, Müller NL, et al. Crazy-paving appearance at thin-section CT: spectrum of disease and pathologic findings. *Radiology.* 1999;211:155–160.
210. Brasch F, Birzele J, Ochs M, et al. Surfactant proteins in pulmonary alveolar proteinosis in adults. *Eur Respir J.* 2004;24:426–435.
211. Singh G, Katyal SL, Bedrossian CW, et al. Pulmonary alveolar proteinosis. Staining for surfactant apoprotein in alveolar proteinosis and in conditions simulating it. *Chest.* 1983;83:82–86.
212. Singh G, Katyal SL. Surfactant apoprotein in nonmalignant pulmonary disorders. *Am J Pathol.* 1980;101:51–61.
213. Ikegami M. Surfactant catabolism. *Respirology.* 2006;11:S24–27.
214. Andreeva AV, Kutuzov MA, Voyno-Yasenetskaya TA. Regulation of surfactant secretion in alveolar type II cells. *Am J Physiol Lung Cell Mol Physiol.* 2007;293:L259–271.
215. Trapnell BC, Whitsett JA. Gm-CSF regulates pulmonary surfactant homeostasis and alveolar macrophage-mediated innate host defense. *Annu Rev Physiol.* 2002;64:775–802.
216. Stanley E, Lieschke GJ, Grail D, et al. Granulocyte/macrophage colony-stimulating factor-deficient mice show no major perturbation of hematopoiesis but develop a characteristic pulmonary pathology. *Proc Natl Acad Sci USA.* 1994;91:5592–5596.
217. Thomassen MJ, Yi T, Raychaudhuri B, et al. Pulmonary alveolar proteinosis is a disease of decreased availability of GM-CSF rather than an intrinsic cellular defect. *Clin Immunol.* 2000;95:85–92.
218. Bonfield TL, Russell D, Burgess S, et al. Autoantibodies against granulocyte-macrophage colony-stimulating factors are diagnostic for pulmonary alveolar proteinosis. *Am J Respir Cell Mol Biol.* 2002;27:481–486.
219. Kitamura T, Tanaka N, Watanabe J, et al. Idiopathic pulmonary alveolar proteinosis as an autoimmune disease with neutralizing antibody against granulocyte/macrophage colony-stimulating factor. *J Exp Med.* 1999;190:875–880.
220. Inoue Y, Trapnell BC, Tazawa R, et al. Characteristics of a large cohort of patients with autoimmune pulmonary alveolar proteinosis in Japan. *Am J Respir Crit Care Med.* 2008;177:752–762.
221. Bonfield TL, Raychaudhuri B, Malur A, et al. Pu.1 regulation of human alveolar macrophage differentiation requires granulocyte-macrophage colony-stimulating factor. *Am J Physiol Lung Cell Mol Physiol.* 2003;285:L1132–L1136.
222. Shibata Y, Berclaz PY, Chroneos ZC, et al. GM-CSF regulates alveolar macrophage differentiation and innate immunity in the lung through pu.1. *Immunity.* 2001;15:557–567.
223. Bonfield TL, Farver CF, Barna BP, et al. Peroxisome proliferator-activated receptor-gamma is deficient in alveolar macrophages from patients with alveolar proteinosis. *Am J Respir Cell Mol Biol.* 2008;29:677–682.
224. Simonneau G, Galie N, Rubin HL, et al. Clinical classification of pulmonary hypertension. *J Am Coll Cardiol.* 2004;43(Suppl 1):5S–12S.
225. Chin KM, Rubin LH. *J Am Coll Cardiol.* 2008;51:1527–1538.
226. Newman JH, Phillips JA, Loyd JE. Narrative review: The enigma of pulmonary art. *Ann Intern Med.* 2008;148:278–283.
227. Austin ED, Loyd JE. Genetics and mediators in pulmonary arterial hypertension. *Clin Chest Med.* 2007;28:43–57.

228. Runo JR, Loyd JE. Primary pulmonary hypertension. *Lancet.* 2003;361:1533–1544.
229. Humbert M. Update in pulmonary arterial hypertension 2007. *Am J Respir Crit Care Med.* 2008;177:574–579.
230. Churg A. Recent advances in the diagnosis of Churg-Strauss syndrome. *Mod Pathol.* 2001;14:1284–1293.
231. Jennette JC, Falk RJ. New insight into the pathogenesis of vasculitis associated with antineutrophil cytoplasmic autoantibodies. *Curr Opin Rheumatol.* 2008;20:55–60.
232. Ganz T. Defensins: Antimicrobial peptides of innate immunity. *Nat Rev Immunol.* 2003;3:710–720.
233. Bals R, Hiemstra PS. Innate immunity in the lung: How epithelial cells fight against respiratory pathogens. *Eur Respir J.* 2004;23:33.
234. Blasi F, Tarsia P, Aliberti S. Strategic targets of essential host-pathogen interactions. *Respiration.* 2005;72:9–25.
235. Winn WC Jr, Chandler FW. Bacterial infections. In: Dail DH, Hammar SP, eds. *Pulmonary Pathology.* 2nd ed. New York: Springer-Verlag; 1994:255–330.
236. Peltola H. Worldwide Haemophilus influenzae type B disease at the beginning of the 21st century: Global analysis of the disease burden 25 years after the use of the polysaccharide vaccine and a decade after the advent of conjugates. *Clin Microbiol Rev.* 2000;13:302–317.
237. Waites KB, Talkington DF. Mycoplasma pneumoniae and its role as a human pathogen. *Clin Microbiol Rev.* 2004;17:697–728.
238. Stead WW, Kerby GR, Schlueter DP, et al. The clinical spectrum of primary tuberculosis in adults. Confusion with reinfection in the pathogenesis of chronic tuberulosis. *Ann Intern Med.* 1968;68:731–745.
239. van Rie A, Warren R, Richardson M, et al. Exogenous reinfection as a cause of recurrent tuberculosis after curative treatment. *N Engl J Med.* 1999;341:1171–1179.
240. Auerbach O. The natural history of the tuberculous pulmonary lesion. *Med Clin North Am.* 1959;43:239–251.
241. Rabbat A, Huchon GJ. Nonbacterial pneumonia. In: Albert RK, Spiro SG, Jett JR, eds. *Clinical Respiratory Medicine.* 3rd ed. Philadelphia: Mosby Elsevier; 2008:351–364.
242. Stewart S. Pulmonary infections in transplantation pathology. *Arch Pathol Lab Med.* 2007;131:1219–1231.
243. Zaki SR, Khan AS, Goodman RS, et al. Retrospective diagnosis of hanta-virus pulmonary syndrome. *Arch Pathol Lab Med.* 1996;120:134–139.
244. Chong PY, Chui P, Ling AE, et al. Analysis of deaths during the severe acute respiratory syndrome (SARS) epidemic in Singapore: Challenges in determining a SARS diagnosis. *Arch Pathol Lab Med.* 2004;128:195–204.
245. Lee I, Barton TD. Viral respiratory tract infections in transplant patinets. *Drugs.* 2007;67:1411–1427.
246. Bradsher RW. Histoplasmosis and blastomycosis. *Clin Inf Dis.* 1996;22:S102.
247. Davies SF, Sarosi GA. Epidemiological and clinical featues of pulmonary blastomycosis. *Semin Res Inf.* 1997;12:206–218.
248. Stevens DA. Current concepts: Coccidioidomycosis. *N Engl J Med.* 1995;332:1007–1082.
249. Watts JC, Chandler FW. Aspergillosis. In: Connor DH, Chandler FW, et al. eds. *Pathology of Infectious Diseases.* Stamford, CT: Appleton and Lange; 1997:033–941.
250. Yousem S. The histologic spectrum of necrotizing forms of pulmonary aspergillosis. *Hum Pathol.* 1997;28:650–656.
251. Edman JC, Kovacs JA, Masur H, et al. Ribosomal RNA sequence shows *Pneumocystis carinii* to be a member of the fungi. *Nature.* 1988;334:519–522.
252. Stringer JR, Beard CF, Miller RF, et al. A new name (*Pneumocystis jiroveci*) for pneumocystis from humans. *Emerg Infect Dis.* 2002;8:891–896.
253. Beard CB, Roux P, Gilles Nevez, et al. Strain typing methods and molecular epidemiology of *Pneumocystis* pneumonia. *Emerg Infectious Diseases.* 2004;10:1729–1735.
254. Krajicek J, Limper AH, Thomas CF. Advances in the biology, pathogenesis and identification of *Pneumocystis* pneumonia. *Curr Opin Pulm Med.* 2008;14:228–234.
256. Thomas CF Jr., Limper AH. *Pneumocystis* pneumonia. *N Engl J Med.* 2004;350:2487–2498.
256. Mossman BT, Churg A. Mechanisms in the pathogenesis of asbestosis and silicosis. *Am J Respir Crit Care Med.* 1998; 157:1666–1680.
257. Tazi A. Cells of the dendritic cell lineage in human lung carcinomas and pulmonary histiocytosis S. In: Lipscomb M, Russell S, eds. *Lung Macrophages and Dendritic Cells in Health and Disease.* New York: Marcel Dekker; 1997:725–757.
258. Vassallo R, Limper AH. Pulmonary Langerhans' cell histiocytosis. *Semin Respir Crit Care Med.* 2002;23:93–101.
259. Tazi A, Bonay M, Grandsaigne M, et al. Surface phenotype of Langerhans cells and lymphocytes in granulomatous lesions from patients with pulmonary histiocytosis X. *Am Rev Respir Dis.* 1993;147:1531–1536.
260. Vermaelen K, Pauwels R. Pulmonary dendritic cells. *Am J Respir Crit Care Med.* 2005;172:530–551.
261. Annels NE, Da Costa CE, Prins FA, et al. Aberrant chemokine receptor expression and chemokine production by Langerhans cells underlies the pathogenesis of Langerhans cell histiocytosis. *J Exp Med.* 2003;197:1385–1390.
262. Wang J, Snider DP, Hewlett BR, et al. Transgenic expression of granulocyte-macrophage colony-stimulating factor induces the differentiation and activation of a novel dendritic cell population in the lung. *Blood.* 2000;95:2337–2345.
263. Yousem SA, Colby TV, Chen YY, et al. Pulmonary Langerhans cell histiocytosis: Molecular analysis of clonality. *Am J Surg Pathol.* 2001;25:630–636.
264. Dacic S, Trusky C, Baggker A, et al. Genotypic analysis of pulmonary Langerhans cell histiocytosis. *Human Pathol.* 2003;34: 1345–1349.
265. Tazi A, Soler P, Hance AJ. Adult pulmonary Langerhans cell histiocytosis. *Thorax.* 2000;55:405–416.
266. Egan AJ, Boardman LA, Tazelaar HD, et al. Erdheim-Chester disease: Clinical, radiologic, and histopathologic findings in five patients with interstitial lung disease. *Am J Surg Pathol.* 1999;23:17–26.
267. Veyssier-Belot C, Cacoub P, Caparros-Lefebvre D, et al. Erdheim-Chester disease. Clinical and radiologic characteristics of 59 cases. *Medicine (Baltimore).* 1996;75:157–169.
268. Kambouchner M, Colby TV, Domenge C, et al. Erdheim-Chester disease with prominent pulmonary involvement associated with eosinophilic granuloma of mandibular bone. *Histopathology.* 1997;30:353–358.
269. Madroszyk A, Wallaert B, Rémy M, et al. Diffuse interstitial pneumonia revealing Erdheim-Chester's disease. *Rev Mal Respir.* 1994;11:304–307.
270. Murray D, Marshall M, England E, et al. Erdheim-Chester disease. *Clin Radiol.* 2001;56:481–484.
271. Shamburek RD, Brewer Jr HB, Gochuico BR. Erdheim-Chester disease: A rare multisystem histiocytic disorder associated with interstitial lung disease. *Am J Med Sci.* 2001; 321:66–75.
272. Rao RN, Chang CC, Uysal N, et al. Fulminant multisystem non-Langerhans cell histiocytic proliferation with hemophagocytosis: A variant form of Erdheim-Chester disease. *Arch Pathol Lab Med.* 2005;129:e39–43.
273. Rush WL, Andriko JA, Galateau-Salle F, et al. Pulmonary pathology of Erdheim-Chester disease. *Mod Pathol.* 2000;1397:747–754.
274. Devouassoux G, Lantuejoul S, Chatelain P, et al. Erdheim-Chester disease: A primary macrophage cell disorder. *Am J Respir Crit Care Med.* 1998;157:650–653.
275. Myra C, Sloper L, Tighe PJ, et al. Treatment of Erdheim-Chester disease with cladribine: A rational approach. *Br J Ophthalmol.* 2004;88:844–847.
276. Wittenberg KH, Swensen SJ, Myers JL. Pulmonary involvement with Erdheim-Chester disease: Radiographic and CT findings. *Am J Roentgenol.* 2000;174:1327–1331.
277. Chetritt J, Paradis V, Dargere D, et al. Chester-Erdheim disease: A neoplastic disorder. *Hum Pathol.* 1999;30:1093–1096.
278. Craighead JE, Abraham JL, Churg A, et al. The pathology of asbestos-associated disease of the lung and pleural cavities: Diagnostic critera. *Arch Pathol Lab Invest.* 1982;106:544–595.

279. Robledo R, Mossman B. Cellular and molecular mechanisms of asbestos-induced fibrosis. *J Cell Physiol.* 1999;180:158–166.
280. Ke Q, Li J, Ding J, et al. Essential role of ROS-mediated NFAT activation in TNF-alpha induction by crystalline silica exposure. *Am J Physiol Lung Cell Mol Physiol.* 2006;291:L257–264.
281. Tsai EY, Yie J, Thanos D, et al. Cell-type-specific regulation of the human tumor necrosis factor alpha gene in B cells and T cells by NFATp and ATF-2/JUN. *Mol Cell Biol.* 1996;16: 5232–5244.
282. Aktogu S, Yuncu G, Halilcolar H, et al. Bronchogenic cysts: Clinicopathological presentation and treatment. *Eur Respir J.* 1996;9:2017–2021.
283. Stocker JT, Husain AN. Cystic lesions of the lung in children: Classification and controversies. In: Timens W, Popper HH, eds. *Pathology of the Lung.* Sheffield, UK: European Respiratory Society Journals Ltd; 2007:1–20. European Respiratory Monograph 39; Chapter 1.
284. Maeda Y, Dave V, Whisett JA. Transcriptional control of lung morphogenesis. *Physiol Rev.* 2007;87:219–244.
285. Chibbar R, Shih F, Baga M, et al. Nonspecific interstitial pneumonia and usual interstitial pneumonia with mutation in surfactant protein C in familial pulmonary fibrosis. *Mod Pathol.* 2004;17:973–980.
286. Bullard JE, Wert SE, Whitsett JA, et al. ABCA3 mutations associated with pediatric interstitial lung disease. *Am J Respir Crit Care Med.* 2005;172:1026–1031.
287. Comeron HS, Somaschini M, Carrera P, et al. A common mutation in the surfactant protein C gene associated with lung disease. *J Pediatr.* 2005;146:370–375.
288. Hamvas A, Cole FS, Nogee L. Genetic disorders of surfactant proteins. *Neonatology.* 2007;91:311–371.
289. Whitsett JA, Wert SE, Xu Y. Genetic disorders of surfactant homeostasis. *Biol Neonate.* 2005;87:283–287.
290. Travis WD, Brambilla E, Müller-Hermelink HK, et al. *Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart.* Lyon: IARC Press; 2004.