

Chapter 15

Personalized Management of Pulmonary Disorders

Introduction

There are a large number of pulmonary disorders some of which present challenges in management. Role of genetic ancestry in lung function is under investigation. There is still limited information on pharmacogenomics and pharmacogenetics of pulmonary therapeutics. Personalized approaches to some pulmonary diseases will be described briefly as examples in this chapter.

Role of Genetic Ancestry in Lung Function

A study shows that incorporating measures of individual genetic ancestry into normative equations of lung function in persons who identify themselves as African Americans may provide more accurate predictions than formulas based on self-reported ancestry alone (Kumar et al. 2010). The same argument may apply to other ancestrally defined groups; further studies in this area are necessary. Further studies are also needed to determine whether estimates informed by genetic ancestry are associated with health outcomes. The authors noted that environmental factors such as premature birth, prenatal nutrition, and socioeconomic status may also play an important role in the association between lung function and ancestry. It remains to be seen whether differences associated with race or ethnic group in the response to medications that control asthma are more tightly associated with estimates of ancestry. Although measures of individual genetic ancestry may foster the development of personalized medicine, large clinical trials and cohort studies that include assessments of genetic ancestry are needed to determine whether measures of ancestry are more useful clinically than a reliance on self-identified race.

Biomarkers of Pulmonary Disorders

Some of the biomarkers of pulmonary disorders in general are similar to those found in involvement of other organs. Biomarkers of pulmonary disorders with exception of lung cancer are listed in Table 15.1.

Table 15.1 Biomarkers of pulmonary diseases

Biomarkers	Sample	Applications
Alpha 1-antitrypsin/AAT gene polymorphism	Blood: finger prick	Detection of AAT deficiency predisposing to emphysema
Angiogenic growth factor overexpression	Bronchoalveolar lavage fluid	Overexpression of VEGF and PIGF are biomarkers of chronic obstructive pulmonary disease (COPD)
Brain natriuretic peptide (BNP)	Plasma	Detection of pulmonary hypertension in patients with chronic lung disease
Calprotectin	Sputum and serum	Track changes in lung inflammation during an exacerbation of cystic fibrosis
CF-specific serum proteomic signature	Plasma	Cystic fibrosis (CF)
Chromagranin A (CgA)	Serum	A neuroendocrine activity biomarker that is increased in male smokers with impaired lung function
Copeptin, the precursor of vasopressin	Serum	A prognostic biomarker for poor prognosis in exacerbation of COPD requiring hospitalization
C-reactive protein (CRP)	Serum	Elevated in acute exacerbation of COPD
H ₂ O ₂	Exhaled breath condensate	Measurement of oxidative stress in pulmonary diseases
F2-isoprostanes		
Malondialdehyde		
4-hydroxy-2-nonenal		
Antioxidants		
IgE level	Serum	The dose of omalizumab is that required is to reduce circulating free IgE levels to less than 10 IU per milliliter
Inflammation	Blood	WBC count, CRP and VCAM-1 relate to poorer lung function in the elderly
Nitric oxide (NO)	Exhaled breath	Inflammatory lung disorders, e.g., asthma Rhinosinusitis
	Urine	Higher levels of urinary NO are strongly associated with improved survival in acute respiratory distress syndrome
Osteoprotegerin (OPG)	Serum	Increased specifically in COPD
Serum amyloid A (SAA)	Serum	Exacerbation of COPD by respiratory tract infections.
Surfactant proteins: A (SP-A)	Tracheal aspirates	Interstitial lung disease
	Bronchoalveolar lavage	Acute respiratory distress syndrome
D (SP-D)	Pleural effusions	Radiation pneumonitis

Biomarkers of Inflammation and Lung Function in the Elderly

Low lung function is associated with increased morbidity and mortality. It is therefore of interest to identify biomarkers that are associated with impaired lung function. Lung function (FEV1 and FVC) and a panel of 15 inflammatory biomarkers (including cytokines, chemokines, adhesion molecules, CRP and WBC count) from blood samples were analyzed subjects aged 70 years (Kuhlmann et al. 2013). WBC count, CRP and VCAM-1 were found to relate to poorer lung function. A dose-related association was found for the combination WBC count and CRP towards FEV1 and WBC and VCAM-1 towards FVC. This indicates that combination of two biomarkers yielded more information than assessing them one by one when analyzing the association between systemic inflammation and lung function.

Biomarkers of Oxidative Stress in Lung Diseases

Oxidative stress is the hallmark of various chronic inflammatory lung diseases. Increased concentrations of ROS in the lungs of such patients are reflected by elevated concentrations of oxidative stress markers in the breath, airways, lung tissue and blood. Traditionally, the measurement of these biomarkers has involved invasive procedures to procure the samples or to examine the affected compartments, to the patient's discomfort. Non-invasive approaches to measure oxidative stress have been investigated. The collection of exhaled breath condensate (EBC) is a non-invasive sampling method for real-time analysis and evaluation of oxidative stress biomarkers in the lower respiratory tract airways. The biomarkers of oxidative stress such as H₂O₂, F₂-isoprostanes, malondialdehyde, 4-hydroxy-2-nonenal, antioxidants, glutathione and nitrosative stress such as nitrate/nitrite and nitrosated species can be measured in EBC. Oxidative stress biomarkers also have been measured for various antioxidants in disease prognosis. EBC is currently used as a research and diagnostic tool in free radical research, yielding information on redox disturbance and the degree and type of inflammation in the lung. It is expected that EBC can be exploited to detect specific levels of biomarkers and monitor disease severity in response to treatment.

Biomarkers of Community-Acquired Pneumonia

Community-acquired pneumonia (CAP) is one of the most common reasons for emergency department. Despite its prevalence, there are many challenges to proper diagnosis and management of pneumonia. There is no accurate and timely gold standard to differentiate bacterial from viral disease, and there are limitations in precise risk stratification of patients to ensure appropriate site-of-care decisions. Clinical risk scores such as pneumonia severity index (PSI) and CURB-65 (confusion, urea, respiratory rate, blood pressure, age >65 years), and blood biomarkers

of different physiopathological pathways are used in predicting long-term survival in patients with CAP. In a prospective study, patients admitted with CAP were followed for 6 years and Cox regression models as well as area under the receiver operating characteristics curve (AUC) were used to investigate associations between initial risk assessment and all-cause mortality (Alan et al. 2014). Initial PSI and CURB-65 scores both had excellent long-term prognostic accuracy, with a step-wise increase in mortality per risk class. The addition of inflammatory (pro-adrenomedullin) and cardiac (pro-atrial natriuretic peptide) blood biomarkers measured upon hospital admission further improved the prognostic capabilities of the PSI.

BNP as a Biomarker of Chronic Pulmonary Disease

Circulating BNP levels were evaluated as a parameter for the presence and severity of pulmonary hypertension (PH) in patients with follow-up of ~1 y, significant pulmonary hypertension (mean pulmonary artery pressure >35 mmHg) was diagnosed in more than one-fourth of patients and led to decreased exercise tolerance and life expectancy. Elevated BNP concentrations identified significant pulmonary hypertension with a sensitivity of 0.85 and specificity of 0.88 and predicted mortality. Moreover, BNP served as a risk factor of death independent of lung functional impairment or hypoxemia. It is concluded that plasma BNP facilitates noninvasive detection of significant PH with high accuracy and can be used as a screening test for the presence of PH. In addition, BNP enables an assessment of the relevance of PH and could serve as a useful prognostic parameter in chronic lung disease.

Plasma Biomarkers Related to Inflammation

Plasma biomarkers related to inflammation –IL-8 and enhanced neutrophil recruitment to the lung (ICAM-1)– are independently associated with increased mortality in patients with acute lung injury (ALI). Higher levels of IL-8 and ICAM-1 independently predicted death (McClintock et al. 2008). In addition, lower levels of the coagulation marker protein C were independently associated with an increased risk of death. The association of lower protein C levels with non-survivors continues to support the role for disordered coagulation in ALI/ARDS. These associations exist despite consistent use of lung protective ventilation and persist even when controlling for clinical factors that also impact upon outcomes. The two biomarkers with an independent association with mortality, IL-8 and ICAM-1, need to be studied further for their potential value in stratifying patients in clinical trials.

Urinary NO as Biomarker

Acute respiratory distress syndrome (ARDS) is the rapid onset of respiratory failure—the inability to adequately oxygenate the blood—that often occurs in the critically ill. ALI precedes ARDS as severe respiratory illnesses progress. Both conditions can be life-threatening. In a large-scale, multicenter trial of patients with

ARDS or ALI, higher levels of nitric oxide (NO) in urine were strongly associated with improved survival, more ventilator-free days, and decreased rates of organ failure (McClintock et al. 2007). The authors speculated that NO has a beneficial effect on ALI since it scavenges oxygen free radicals that are generated during oxidative stress. Since NO increases microcirculation, it helps to better perfuse tissue beds in the lungs. The investigators offered an alternative hypothesis to explain their findings: NO created inside the body may have a beneficial effect on organs other than the lung during ALI. It might help prevent further tissue damage by improving oxygen and nutrient delivery to the tissues, while helping to decrease the amount of toxic oxygen species. The authors also speculated that NO might have antibacterial effects that could be important in infectious conditions that predispose patients to ALI.

Personalized Therapy of Asthma

Asthma affects 5–7 % of the population of North America and may affect more than 150 million persons worldwide. Airway hyperresponsiveness (AHR) is the main feature of asthma and is defined as an increase in the ease and degree of airway narrowing in response to bronchoconstrictor stimuli. It is a chronic inflammatory disease but there is no clear definition of the disease and no single symptom, physical finding or laboratory test is diagnostic of this condition. The disease is manifested as variable airflow obstruction and recurrent bouts of respiratory symptoms. Allergens and viral infections induce an increased sensitivity. Little is known about the mechanisms that determine asthma development and severity and why some individuals have mild symptoms and require medication only when symptomatic whereas others have continuous symptoms despite high doses of several medications (refractory asthma). Asthma is often triggered by an allergic response and the environmental factors play an important role in manifestations of the disease. Although there is a significant hereditary component, genetic studies have been difficult to perform and results have been difficult to interpret. Only a few therapeutic agents based on novel mechanisms of action have been developed over the past two decades. Asthma is a complex disease with marked heterogeneity in the clinical course and in the response to treatment. Variability in the type of airway inflammation may underlie this heterogeneity. Despite treatment with inhaled glucocorticoids, many patients continue to have uncontrolled asthma that requires more intensive therapy. Approximately one in three patients with asthma who use inhaled glucocorticoids may not benefit from this therapy. Biomarkers and some of the other methods for guiding therapy of asthma are described here.

Biomarkers of Asthma

Although the aim of management of patients with asthma is to control their symptoms and prevent exacerbations and morbidity of the disease, optimal management may require assessment and monitoring of biomarkers, i.e., objective measures of lung dysfunction and inflammation.

Biomarker for Rhinovirus-Induced Asthma Exacerbation

Clinical observations suggest that rhinovirus infection induces a specific inflammatory response in predisposed individuals that results in worsened asthmatic symptoms and increased airway inflammation. A study has shown that IFN- γ -induced protein (IP)-10 is specifically released in acute virus-induced asthma, and can be measured in the serum to predict a viral trigger of acute exacerbations (Wark et al. 2007). Primary bronchial epithelial cell models of rhinovirus infection were used to identify mediators of rhinovirus infection and responded to infection with rhinovirus-16 by releasing high levels of IP-10, RANTES, and IL-16, as well as smaller amounts of IL-8 and TNF- α . IP-10, perhaps in combination with TNF- α , might be a useful clinical marker to identify rhinovirus and other virus-induced acute asthma. Additional findings suggest that IP-10 or CXCR3 (an IP-10 receptor that is highly expressed in activated T cells) might have a role in worsening of airflow obstruction and airway inflammation, and may therefore be potential therapeutic targets.

Biomarkers for Predicting Response to Corticosteroid Therapy

International guidelines on the management of asthma support the early introduction of corticosteroids to control symptoms and to improve lung function by reducing airway inflammation. However, not all individuals respond to corticosteroids to the same extent and it would be desirable to be able to predict the response to corticosteroid treatment. Several biomarkers have been assessed following treatment with corticosteroids including measures of lung function, peripheral blood and sputum indices of inflammation, exhaled gases and breath condensates. The most widely examined measures in predicting a response to corticosteroids are airway hyperresponsiveness, exhaled NO (eNO) and induced sputum. Of these, sputum eosinophilia has been demonstrated to be the best predictor of a short-term response to corticosteroids. More importantly, directing treatment at normalizing the sputum eosinophil count can substantially reduce severe exacerbations. The widespread utilization of sputum induction is hampered because the procedure is relatively labor intensive. The measurement of eNO is simpler, but incorporating the assessment of NO in an asthma management strategy has not led to a reduction in exacerbation rates. The challenge now is to either simplify the measurement of a sputum eosinophilia or to identify another inflammatory marker with a similar efficacy as the sputum eosinophil count in predicting both the short- and long-term responses to corticosteroids.

Cytokines as Biomarkers of Asthma Severity

Severe asthma is characterized by elevated levels of proinflammatory cytokines and neutrophilic inflammation in the airways. Blood cytokines, biomarkers of systemic inflammation, may be a feature of increased inflammation in severe asthma. One study found that IL-8 and TNF- α levels were higher in severe asthmatics than in

mild-moderate asthmatics or in controls and, in conjunction with augmented circulating neutrophils, suggest the involvement of neutrophil-derived cytokine pattern (Silvestri et al. 2006). Furthermore, in patients with severe asthma, TNF- α level was positively correlated with both eNO and circulating neutrophil counts. Cytokine levels were elevated even though the patients were on high-dose inhaled steroids. This finding might reflect the inability of these drugs to significantly suppress production of this cytokine by airway cellular sources including epithelial cells and inflammatory cells. In patients with severe asthma there may be an imbalance between IL-8 production and the blocking capacity of IL-8 autoantibodies. The findings of this study may be clinically relevant and suggest that drugs that block TNF- α release or activity might represent a new treatment option in severe asthma.

Exhaled NO as a Biomarker of Asthma

Airway hyperresponsiveness is the main feature of asthma and is defined as an increase in the ease and degree of airway narrowing in response to bronchoconstrictor stimuli. Inflammation plays a central role in the pathogenesis of asthma and much of it can be attributed to helper T cell type 2 cytokine activation, the degree of which strongly correlates to disease severity. One of the inflammatory mediators in asthma is NO. The eNO level is elevated in asthma, and can predict asthma exacerbation. It may be clinically more useful to compare exhaled NO values with a subject's previous values than to compare them with a population based normal range.

Cough variant asthma (CVA) and atopic cough both present with bronchodilator-resistant non-productive cough but may be differentiated from and other causes of chronic non-productive cough by measuring exhaled NO. Exhaled NO levels in patients with atopic cough are significantly lower than those in patients with CVA and bronchial asthma (Fujimura et al. 2008). There are no significant difference in the exhaled NO levels between patients with CVA and bronchial asthma.

A UK study findings show that it is feasible to measure bronchial flux NO concentration (j NO) and alveolar NO concentration (C_{alv}) in 70 % of children, with C_{alv} levels potentially reflecting alveolar inflammation in asthma (Paraskakis et al. 2006). C_{alv} and j NO were measured from the fractional exhaled NO (FeNO₅₀) at multiple exhalation flow rates in asthmatic children. Although FeNO₅₀ and j NO give essentially the same information, C_{alv} is higher in asthmatic children than in normal children. This study also highlights the relationship between poor control of asthma and C_{alv} (a biomarker of alveolar inflammation) but further work is needed to confirm the relevance of this. Researchers at the University of Pittsburgh, Pennsylvania, have developed a novel nanosensor that can detect a possible asthma attack before it begins. The minute sensor can be fitted into a hand-held device, and when a person blows into the device, it measures the NO content of their breath. Use of this device would provide asthma sufferers with a simple and cost effective way to monitor their asthma inflammation.

An explanation for increased levels of exhaled NO is nonenzymatic generation of NO from nitrite due to airway acidification in asthmatics. Reduced arginine

availability may also contribute to lung injury by promoting formation of cytotoxic radicals such as peroxynitrite. As arginine levels decline, nitric oxide synthase (NOS) itself can begin to generate superoxide in lieu of NO, thereby favoring NO consumption via the generation of peroxynitrite that could induce lung injury. This reduction in bioavailability of NO via formation of species such as peroxynitrite could be further amplified by the rapid loss of SOD activity during the asthmatic response.

Plasma arginase activity declines significantly with treatment and improvement of symptoms. Additional studies are needed to determine whether measurements of plasma arginase activity will provide a useful biomarker for underlying metabolic disorder and efficacy of treatment for this disease. The arginase activity present in serum probably does not accurately reflect whole body arginase activity or that compartmentalized in the lungs, since the arginases are intracellular enzymes. Because arginase is induced in monocytes in response to helper T cell type 2 cytokines, it is speculated that these cells are one likely source of the elevated arginase in serum, consistent with the localization of arginase expression within macrophages in the lungs.

Although exhaled NO is a clinically useful biomarker of eosinophilic airway inflammation in asthma, significant validation and investigation are required before exhaled breath condensate could be utilized for making decisions in clinical practice (Simpson and Wark 2008).

Endothelin-1 in Exhaled Breath as Biomarker of Asthma

Endothelins are proinflammatory, profibrotic, broncho- and vasoconstrictive peptides, which play an important role in the development of airway inflammation and remodeling in asthma. A study has evaluated the endothelin-1 (ET-1) levels in exhaled breath condensate (EBC) of asthmatics with different degree in asthma severity (Zietkowski et al. 2008). ET-1 concentrations in EBC of all asthmatic patients were significantly higher than in healthy volunteers. ET-1 levels were significantly higher in patients with unstable asthma than in the two groups with stable disease. Thus, measurements of ET-1 in EBC may provide another useful diagnostic tool for detecting and monitoring inflammation in patients with asthma. The release of ET-1 from bronchial epithelium through the influence of many inflammatory cells essential in asthma and interactions with other cytokines, may play an important role in increase of airway inflammation, which is observed after postexercise bronchoconstriction in asthmatic patients.

IgE as a Biomarker to Guide Dosing of Omalizumab for Asthma

IgE plays a central role in the pathophysiology of asthma. The two essential phases in this pathophysiology are sensitization to allergen and clinical expression of symptoms on reexposure to the sensitizing allergen. Omalizumab (Xolair, Genentech) is a recombinant humanized IgG1 monoclonal anti-IgE antibody that

binds to circulating IgE, regardless of allergen specificity, forming small, biologically inert IgE–anti-IgE complexes without activating the complement cascade. An 89–99 % reduction in free serum IgE (i.e., IgE not bound to omalizumab) occurs soon after the administration of omalizumab, and low levels persist throughout treatment with appropriate doses. A total serum IgE level should be measured in all patients who are being considered for treatment with omalizumab, because the dose of omalizumab is determined on the basis of the IgE level and body weight (Strunk and Bloomberg 2006). The dose is based on the estimated amount of the drug that is required to reduce circulating free IgE levels to less than 10 IU per milliliter.

Genotyping in Asthma

Several clinical trials have highlighted the effects of genotype on response to asthma therapy. Various publications have described the potential of using genotyping as a tool to develop individualized patient treatment regimens for asthma to improve results and limit adverse effects of certain therapies (Lugogo et al. 2007). Increased AHR to bradykinin induced by allergen exposure is due to impaired production of nitric oxide (NO), which is associated with downregulation of eNOS and upregulation of iNOS within the airway epithelium. Polymorphisms of the eNOS gene may be associated with the development of asthma but may not affect the severity of the disease. Recently, a naturally occurring gene mutation has been identified encoding a member of enzymes that appear to be important in the innate immune response and is present in 5–10 % of the normal population. The mutation is a 24 base pair duplication that leads to undetectable mRNA expression in macrophages and a lack of enzyme activity. This role of this mutation has been studied in host immunity to parasitic infections. An assay for the mutation will be useful to gauge an individual's risk for developing asthma and an asthmatic's risk for developing severe asthma. With the rapid progress in the identification of genes involved in various ethnic populations combined with the availability in future of well-targeted drugs, it will be possible to prescribe appropriate medicines for the genetic make-up of an individual.

Collaborative, retrospective, observational health outcomes studies that combine pharmacy, medical claims and genotyping data for participating managed care patients with asthma are focusing on assessing the impact of common genetic variations on clinical outcomes and health care resource utilization for patients using drugs commonly employed for the management of asthma. The results of such studies may provide data indicating whether physicians should consider alternative regimens to improve management of asthma patients with genetic variations. Genotyping of individuals at high risk of developing asthma will enable asthma risk stratification for therapeutic measures to be implemented. In addition, genotyping can be used in clinical trials to assure the comparability of experimental and control populations. Finally, such a genetic asthma test will allow physicians to tailor therapy for asthmatics; aggressive treatment for individuals at risk for severe disease and minimal treatment (avoiding the risk of medication side effects) for those at low risk.

A study that used the clinical data and DNA resources from patients enrolled in the Childhood Asthma Management Program identified a variant in the glucocorticoid-induced transcript 1 gene (GLCCI1), rs37972, associated with a decrease in forced expiratory volume in 1 s (FEV1) in response to treatment with inhaled glucocorticoids (Tantisira et al. 2011). To offer additional reassurance that they had identified a causative SNP, the investigators provided data from isolated cell systems containing the pharmacogenetically identified SNP to show that the presence of these sequence variants was associated with biologic changes that would be consistent with a decreased response to these agents. Approximately 16 % of the population will be homozygous for the genotype responsible for the more limited response to inhaled glucocorticoids. For personalization of treatment of asthma to become a reality, the next step should be to conduct clinical trials in which patients are stratified according to their biologic signatures to determine whether knowledge of this information leads to better clinical outcomes (Drazen 2011).

Genetic Polymorphism and Response to β_2 -Adrenergic Agonists

Inhalation of salbutamol, a β_2 -adrenergic agonist that has a bronchodilator effect in asthma, aids the flow of air to the lungs. β_2 -adrenergic receptor gene contains 13 SNP and an analysis of all the possible inter-individual variations has shown that four common differences predict how people respond to salbutamol. This drug works very well in those with one pattern of DNA in a gene that helps to relax muscles in a person's lungs, not at all in those with another, and moderately in the other two groups. However, the issue of whether regular use of an inhaled β_2 -adrenergic agonist worsens airflow and clinical outcomes in asthma is controversial. Retrospective studies have suggested that adverse effects occur in patients with a genetic polymorphism that results in homozygosity for arginine (Arg/Arg), rather than glycine (Gly/Gly), at amino acid residue 16 of the β_2 -adrenergic receptor. A genotype-stratified, randomized, placebo-controlled cross-over trial found that over time the study participants' responses to daily doses of inhaled albuterol differed depending on which form of a specific gene they had inherited (Israel et al. 2004). While a few weeks of regular use of albuterol improved overall asthma control in individuals with one form of the gene, stopping the drug eventually improved asthma control in those with another form of the gene. Genotype at the 16th amino acid residue of the β_2 -adrenergic receptor affected the long-term response to albuterol use. It was recommended that bronchodilator treatments avoiding albuterol may be appropriate for patients with the Arg/Arg genotype.

Lebrikizumab for Personalized Treatment of Asthma

Lebrikizumab (Roche) is an injectable humanized MAb designed to block IL-13, which contributes to key features of asthma. Lebrikizumab improves lung function in adult asthma patients who are unable to control their disease on inhaled corticosteroids.

IL-13 induces bronchial epithelial cells to secrete periostin, a matricellular protein. Increased levels of periostin, a biomarker of asthma, can be measured in the blood. In the MILLY phase II trial, patients with high pretreatment periostin levels had greater improvement in lung function when treated with lebrikizumab, compared to patients with low periostin levels (Corren et al. 2011). The primary endpoint of the trial showed that at week 12, lebrikizumab-treated patients had a 5.5 % greater increase in lung function from the baseline compared to placebo. Lebrikizumab-treated patients in the high-periostin subgroup experienced an 8.2 % relative increase from baseline forced expiratory volume in 1 s (FEV1), compared with placebo. In the low-periostin subgroup, those patients on the drug experienced a 1.6 % relative increase in FEV1, compared with placebo. These results support further investigation of lebrikizumab as a personalized medicine for patients who suffer from moderate to severe uncontrolled asthma periostin enables selection of patients who will benefit most from the drug.

Personalized Therapy of Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD), which comprises emphysema and chronic bronchitis, is a major public health problem. COPD is defined as low ratio of forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) after an inhaled bronchodilator. The grade, or severity, of COPD is based on level of impairment in FEV1 as a percentage of the predicted value, which reflects a decrease in the volume of air forcibly exhaled from the lungs during the beginning of exhalation. COPD affects >16 million Americans and it is the only disease among the top 10 causes of death with a rising mortality rate in the US. It is predicted to be the third largest cause of death by 2020 and has already reached worldwide epidemic proportions. The natural history of this disease is generally characterized by continued decline in lung function, which is highly variable.

Biomarkers of COPD

There has been increasing interest in using pulmonary biomarkers to understand and monitor the inflammation in the respiratory tract of patients with COPD. Bronchial biopsies and bronchoalveolar lavage provide valuable information about inflammatory cells and mediators, but these procedures are invasive, so that repeated measurements are limited. Sputum provides considerable information about the inflammatory process, including mediators and proteinases in COPD, but samples usually represent proximal airways and may not reflect inflammatory processes in distal bronchi. Analysis of exhaled breath is a noninvasive procedure so that repeated measurements are possible, but the variability is high for some assays. There is relatively little information about how any of these biomarkers relate to other clinical outcomes, such as progression of the disease, severity of disease,

clinical subtypes or response to therapy. More information is also needed about the variability in these measurements. In the future pulmonary biomarkers may be useful in predicting disease progression, indicating disease instability and in predicting response to current therapies and novel therapies, many of which are now in development.

Measurements of C-reactive protein (CRP), a biomarker of inflammation, provide incremental prognostic information beyond that achieved by traditional biomarkers in patients with mild to moderate COPD, and may enable more accurate detection of patients at a high risk of mortality (Man et al. 2006). Lung function decline was significantly related to CRP levels, with an average predicted change in FEV1 of -0.93% in the highest and 0.43% in the lowest quintile. However, respiratory causes of mortality were not significantly related to CRP levels.

Alpha1-Antitrypsin Gene Polymorphisms Predisposing to Emphysema

Alpha1-antitrypsin (AAT) is a plasma glycoprotein that inhibits neutrophil elastase, and individuals who inherit altered AAT genes resulting in deficiency of the protein are at high risk for COPD and liver cirrhosis. This deficiency can be detected by serum protein pattern studies. In the past, testing for the deficiency has been done retrospectively in patients with COPD or liver disease, but the introduction of a home-administered finger-stick blood spot test for AAT genotype enables affected families to construct pedigrees to enable them to identify children who are at risk for developing COPD in later life and should avoid exposure to dust and smoke.

Biomarkers of Lung Failure in COPD

Lung failure, also termed “lung attack”, is the most common organ failure seen in the intensive care unit. Lung attacks, which affect individuals with COPD are among the leading cause of visits to emergency rooms among chronic disease sufferers. Other causes are neuromuscular impairment, pulmonary edema, pneumonia, and vascular diseases such as acute or chronic pulmonary embolism. When a patient is admitted into the hospital with a severe lung failure, it usually takes >3 months to get to 80% of his or her baseline health. If the patient’s health is poor to start with, the new attack can be devastating or even fatal. A test that could more accurately present a patient’s disease could make it easier to predict and treat COPD progression to lung failure. There is need for a test that could be performed in any clinical lab and could be used far more widely than the current lung function tests, which are performed in certain centers by specially trained personnel.

In 2012, Canada’s Prevention of Organ Failure (PROOF) Center of Excellence in Vancouver received funding from Genome British Columbia to develop a biomarker-based test for determining a COPD patient’s risk for having a lung attack. Genes and protein biomarker sets that have been discovered at PROOF Center could have the ability to predict COPD-caused lung attacks and need to be validated.

Chromogranin A as Biomarker of COPD in Smokers

A study has revealed that serum levels of the neuroendocrine activity biomarker chromogranin A (CgA) are increased in male smokers with impaired lung function, and are associated with both respiratory symptoms and the degree of airway obstruction (Sorhaug et al. 2006). The subgroup of airway epithelial cells belonging to the diffuse neuroendocrine system, termed pulmonary neuroendocrine cells, may represent a putative regulatory function of CgA as a prohormone. They are considered to control growth and development of the fetal lung and regulation of ventilation and circulation, but may also have a role in the pathogenesis of smoking-induced airway disease. The findings indicate that neuroendocrine activation may be important in smoking-related airway inflammation and remodeling, and raise the possibility that CgA could be of predictive value as a biomarker of prognosis in smoking-associated diseases.

Gene Expression Studies of Lung Tissue in COPD

Gene expression analysis using microarrays showed that cigarette smoke induces significant changes in oxidant defense responses in persons who develop COPD (Pierrou et al. 2007). Microarray analysis has demonstrated downregulation of NOTCH pathway-related genes associated with smoking and COPD (Tilley et al. 2009). Whole-genome gene expression is a useful method for studying the molecular changes underlying COPD as well as the heterogeneity among patients with COPD.

Further studies have revealed a 98-gene expression signature of COPD and lung function impairment that reflects disease-associated changes in small airway and lung tissues. Transcriptomic approaches to study the lung tissues in COPD will further improve the knowledge of molecular mechanisms underlying this heterogeneous disease and identify molecular subtypes of disease that have similar clinical manifestations (Steiling et al. 2013).

Gene Expression Profile in Peripheral Blood of Patients with COPD

Genome-wide expression profiling of peripheral blood samples from subjects with significant airflow obstruction was performed to find non-invasive gene expression biomarkers for COPD (Bhattacharya et al. 2011). Correlation of gene expression with lung function measurements identified a set of 86 genes. A total of 16 biomarkers showed evidence of significant correlation with quantitative traits and differential expression between cases and controls. Further comparison of these peripheral gene expression biomarkers with those previously identified from lung tissue of the same cohort revealed that two genes, RP9 and NAPE-PLD, were decreased in COPD cases compared to controls in both lung tissue and blood. These results contribute to our understanding of gene expression changes in the peripheral blood of patients with COPD and may provide insight into potential mechanisms involved in the disease.

Increased Expression of PIGF as a Biomarker of COPD

Decreased expression of vascular endothelial growth factor (VEGF) and its receptor has been implicated in the pathogenesis of COPD. Levels of placenta growth factor (PIGF), another angiogenic factor, are increased in the serum and bronchoalveolar lavage (BAL) fluid of patients with COPD and are inversely correlated with FEV1 (Cheng et al. 2008). Serum levels of PIGF in patients with COPD were more than double those in smokers and nonsmokers without COPD. These findings suggest that bronchial epithelial cells can express PIGF, which may contribute to the pathogenesis of COPD. Both PIGF and VEGF expression levels were increased in cultured bronchial epithelial cells exposed to pro-inflammatory cytokines such as TNF α and IL-8. Although the mechanisms underlying the observed detrimental effects of PIGF remain to be clarified, persistent PIGF expression might have adverse effects on lung parenchyma by down-regulating angiogenesis.

Prognosis of COPD

The BODE index (including body-mass index, airflow obstruction, dyspnea, and exercise capacity) was an important contribution to the prognostic assessment of patients with COPD. However, the BODE index is rarely used in primary care settings where most patient treatment options are managed, because exercise capacity cannot be easily measured in the usual physician's office. The BODE index has been updated to improve its calibration, and a simplified ADO (including age, dyspnea, and airflow obstruction) index was developed for use in primary-care settings (Puhan et al. 2009). Both the updated BODE and ADO indices accurately predicted 3-year mortality and could lend support to the prognostic assessment of patients with COPD in specialized and primary-care settings, e.g. to predict a patient's risk of dying from COPD. Such assessment enhances the targeting of treatments to individual patients.

Management of COPD

Comprehensive management of COPD includes proper assessment, monitoring of disease, reduction of risk factors, the management of stable COPD, as well as the prevention and management of exacerbations. Guidelines from the Global Initiative for Chronic Obstructive Lung Disease address each of these aspects of COPD management in detail and provide evidence-based recommendations for patients and health-care professionals (Gold 2009). Reduction of risk factors emphasizes the importance of smoking cessation and control of environmental indoor and outdoor pollutants. The management of COPD must be individualized.

An improved understanding of the pathomechanism of COPD can be leveraged to develop targeted therapies and ultimately personalize treatment of COPD based on each patient's specific molecular subphenotype. Comparisons between gene expression patterns of various diseases have been used to identify disease-specific pathway dysregulation that can be targeted with pathway-directed medications. This may enable repositioning of established drugs for other diseases for treatment of COPD in addition to discovery of new drugs targeted to pathways affected in COPD.

Personalized Management of Interstitial Lung Disease

Interstitial lung disease (ILD) is defined as restrictive lung function impairment with radiographic signs of ILD. Idiopathic pulmonary fibrosis (IPF) is the most common and lethal form of the interstitial lung disease. There are currently no effective or approved drugs available to treat it. Diagnosis is by exclusion of other lung diseases and the only definite diagnosis is by lung biopsy but it carries some morbidity and mortality. Lung transplant is the only treatment option but it is available for only a small fraction of IPF patients. Emerging concepts of pathogenesis include the role of cellular senescence, oxidative stress, endoplasmic reticulum stress, microRNAs, and mechanotransduction. Novel variants in TOLLIP and SPPL2C are associated with IPF susceptibility and one novel variant of TOLLIP, rs5743890, is also associated with mortality (Noth et al. 2013). These associations and the reduced expression of TOLLIP in patients with IPF who carry TOLLIP SNPs emphasize the importance of this gene in the disease.

Biomarkers of Interstitial Lung Disease

Pulmonary Surfactant Proteins as Biomarkers for Lung Diseases

Pulmonary surfactant, a complex of lipids and proteins, functions to keep alveoli from collapsing at expiration. Surfactant proteins A (SP-A) and D (SP-D) belong to the collectin family and play pivotal roles in the innate immunity of the lung. Pulmonary collectins directly bind with broad specificities to a variety of microorganism and possess antimicrobial effects. These proteins also exhibit both inflammatory and antiinflammatory functions. The collectins enhance phagocytosis of microbes by macrophages through opsonic and/or non-opsonic activities. The proteins stimulate cell surface expression of phagocytic receptors including scavenger receptor A and mannose receptor. Since the expression of SP-A and SP-D is abundant and restricted within the lung, the proteins are now clinically used as biomarkers for lung diseases. The levels of SP-A and SP-D in bronchoalveolar lavage fluids,

amniotic fluids, tracheal aspirates and pleural effusions reflect alterations in alveolar compartments and epithelium, and lung maturity. The determination of SP-A and SP-D in sera is a noninvasive and useful tool for understanding some pathological changes of the lung in the diseases, including pulmonary fibrosis, collagen vascular diseases complicated with interstitial lung disease, pulmonary alveolar proteinosis, acute respiratory distress syndrome and radiation pneumonitis (Takahashi et al. 2006).

Serum KL-6 as Biomarker of Interstitial Lung Disease

KL-6, a mucinous high-molecular weight glycoprotein, is expressed on type II pneumocytes and is a potential biomarker of ILD. Retrospective, cross-sectional analysis of Caucasian patients with polymyositis (PM) or dermatomyositis (DM) and ILD showed elevated serum levels of KL-6 compared to patients without ILD (Fathi et al. 2012). At a cut-off level of 549 U/ml, the sensitivity and specificity for diagnosis of ILD was 83 % and 100 %, respectively. The level of serum KL-6 may serve as measure of ILD in patients with PM/DM, and is a promising biomarker for use in clinical practice to assess response to treatment.

Developing Personalized Therapies for Interstitial Lung Disease

There is a need for therapeutic approaches that target molecular pathways to modulate aberrant processes and promote tissue homeostasis in the lung. The diversity of biological and clinical phenotypes of IPF requires a personalized medicine approach for diagnosis and treatment of this disorder (Ding et al. 2011). However, the complex tasks of making a definite diagnosis of a specific form of interstitial lung disease and formulating a patient-centered, personalized management plan in an attempt to achieve remission or stabilization of the disease process poses a challenge to clinicians (Meyer 2014). Suggestions that have been made to personalize and improve therapy of IPF are (Herazo-Maya and Kaminski 2012):

- To identify biomarkers specific to IPF to improve the diagnosis and reduce the need for costly and sometimes dangerous interventions, as well as identify patients who may respond to specific therapeutic modalities.
- To develop novel antifibrotic agents that can be tested in well-designed, randomized, and “personalized” clinical trials.

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