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Review

Adhesion Molecules in Lung Diseases

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Abstract. The human body possesses highly specialized cellular defense mechanisms that, when activated pathologically, can induce a number of immunologic disorders. For a normal cellular immune response, the following conditions must be fulfilled: (1) accumulation of white blood cells, (2) their diapedesis through the vessel walls of the inflammatory area affected by an injurious agent, and (3) normal cellular effector functions in the tissue. This cascade of inflammatory processes has recently been shown to be regulated by a group of molecules that are termed adhesion molecules and consist of three subfamilies: selectins, the immunoglobulin supergene family, and integrins.

The cellular functions influenced by adhesion molecules include, among others, cytotoxic T-cell responses, CD4-dependent activation of B lymphocytes by T lymphocytes, activation of granulocytes and macrophages, phagocytosis of opsonized particles by monocytes, macrophages, and granulocytes, antigen-presenting function of macrophages, their antibody-dependent cytotoxicity, initiation of a respiratory burst by white blood cells, and activation of fibroblasts.

Studies performed in recent years have shown that pathogenetically relevant changes in the expression and function of adhesion molecules are involved in a variety of pulmonary diseases. These changes include the accumulation and activation of alveolar macrophages in smokers, experimentally induced bronchial hyperreactivity in bronchial asthma, accumulation of eosinophils in allergic rhinitis, bleomycin-induced pulmonary fibrosis, binding of viruses and bacteria to respiratory mucosa, and various mechanisms of acute damage to pulmonary parenchyma. Though their role in tumor development is still unclear, adhesion molecules are obviously involved in determining the route and organotropism of metastases. Further studies of

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the function of adhesion molecules in pulmonary diseases will contribute to our understanding of the pathomechanisms of these diseases and, through the development of specific antibodies, may provide attractive new therapeutic approaches to problems for which treatment is not yet available.

Key words: Integrins—LeuCAM—Sarcoidosis—Pulmonary fibrosis—Asthma—Corticosteroids

Introduction

Our understanding of the physiology of inflammatory processes has increased markedly over the last 10 years. This is due especially to the discovery and description of a group of molecules closely associated with the mechanisms of accumulation and activation of inflammatory cells at the site of inflammation. These cell-surface molecules were designated as adhesion molecules because of one of their first-described properties. In a multicellular organism, adhesion processes are involved in embryonal development, the organization of organ differentiation, the preservation of tissue architecture, and the ability of the organism to react to injuries, infections, and tumors [4, 124, 141]

The adhesion molecules, which are expressed by all body cells, primarily regulate cell-cell and cell-matrix interactions and ensure anchorage of the cells in the tissue [2]. In addition, these molecules also mediate signals for the growth, differentiation, and activation of cells [110]. It is the aim of this survey article to present the family of adhesion molecules in a systematic way, to describe their structural and functional properties, and to discuss their possible role in pulmonary diseases.

Gene Families of Adhesion Molecules

In a simplified classification, the adhesion molecules can be subdivided into three families which share a number of structural, functional, and genetic properties. The epithelial, endothelial, and leukocytic adhesion molecules characterized so far belong to either the immunoglobulin supergene family, the selectin gene family, or the integrin gene family [16] (Table 1).

The immunoglobulin (Ig) supergene family is characterized by one or more repetitive immunoglobulin-like domains consisting of about 100 amino acids and a central disulfide bond. This family includes the adhesion molecules ICAM-1, ICAM-2, and ICAM-3 (intercellular adhesion molecules 1, 2, and 3), VCAM-1 (vascular cell adhesion molecule 1), NCAM (neural cell adhesion molecule), and PECAM-1 (platelet endothelial cell adhesion molecule 1) [40, 49, 138]. Lymphocyte surface molecules, which play a crucial role in activation, antigen recognition, and adhesion processes, also belong to the Ig supergene family; among them are the receptors CD2 and its ligand LFA-3, parts of the CD3 complex, CD4, CD8, MHC class-I and class-II receptors, immunoglobulins,

platelet-derived growth factor (PDGF) receptor [144], and carcinoembryonic antigen (CEA) [81]. The shared structural properties, high structural constancy, and wide biological spread are regarded as evidence for evolutionary significance and the proven stability of these structures [124]. Adhesion molecules of the immunoglobulin supergene family are expressed by epithelial and endothelial cells, lymphocytes, monocytes, platelets, and granulocytes [101]. While ICAM-2, ICAM-3, and PECAM-1 are constitutional cell-surface components, ICAM-1 and VCAM-1 show stronger expression after stimulation mediated primarily by cytokines (e.g., tumor necrosis factor-alpha, interleukin-beta, interferon-gamma, interleukin-8, granulocyte-macrophage CSF) but also by endotoxins or lipopolysaccharides [93, 124, 135].

The family of selectins has an important role in margination along the vessel wall and the initially loose adhesion of leukocytes to endothelial cells in the vascular bed. Members of this family are the molecules P-selectin, E-selectin, and L-selectin, which are also called GMP-140 (granule membrane protein 140), ELAM-1 (endothelial leukocyte adhesion molecule 1), and LECCAM-1 (leukocyte endothelial cell adhesion molecule 1) [22, 61, 101, 120, 123, 124, 140]. Their ligands are carbohydrate molecules.

Integrins mediate adhesion to other cells and to components of the extracellular matrix. They consist of two noncovalently bound, structurally different peptide chains (alpha-, beta-heterodimers) [16, 70, 111, 110, 124]. Table 2 lists the most important integrins according to their function [3]. Six different beta-chains have been identified so far and these can combine with a large number of alpha-chains to form the corresponding receptors [16]. The extent of integrin expression differs widely from one cell type to another. Cultured cells express 2 to 10 different types of integrins. Some of these are cell-type-specific, e.g., gpIIb/IIIa (megakaryocytes and platelets) and the CD11/CD18 group, which is expressed only by leukocytes [110].

The β_1-subfamily includes the VLA (very late activation antigen) receptors, while the subfamily that shares the β_2-shain determined on chromosome 21 comprises the LeuCAM receptors (CD11/CD18) [4]. The β_3-subfamily consists of the two cytoadhesins, vitronectin receptor and thrombocyte-glycoprotein IIbIIIa (gpIIbIIIa) [58, 59, 76, 110].

The extracellular domain of the integrins contains cysteine-rich repeats within the β-chain, i.e., repetitive regions with disulfide bonds that ensure a rigid tertiary structure [74] as well as a disulfide bond that stabilizes the large loop of the N-terminal region of the extracellular domain [4]. The extracellular domain of the alpha-chain also contains disulfide bonds, which stabilize the secondary structure, and its large loop, which leans toward the β-chain, includes regions binding to calcium and other divalent cations [4, 63] (Fig. 1).

Little is known about the transmembranous region, but it is the intracellular domain of these receptors that is of interest. The latter contains regions that can bind to actin filaments of the cytoskeleton by means of the cytoskeleton proteins talin, vinculin, or alpha-actinine [77, 82], and are involved in motor phenomena that are important for transmigration and processing of signals between receptor molecules and intracellular second messenger substances.

Table 1. *Adhesion molecules*

Family name	Name of member	Distribution	Ligands
Immunoglobulin-Supergene family	ICAM-1	endothelial cells, leukocytes incl. different lymphocytes, macrophages, fibroblasts, epithelial cells, keratinocytes, melanoma cells	LFA-1 Mac-1
	ICAM-2	endothelial cells, T and B lymphocytes, monocytes, follicular dendritic cells	LFA-1
	ICAM-3	T lymphocytes, monocytes, macrophages	?
	VCAM-1	endothelial cells	VLA-4
	NCAM (CD56)	natural killer cells, T lymphocyes, fibroblasts in wounds	NCAM, heparan sulfate (?)
	PECAM-1 (CD31)	platelets, some white blood cells, endothelial cells	homophylic
Integrin-superfamily β_1-Integrins (very late activation antigen VLA (CD29))	VLA-1 (CD49a)	lymphocytes, fibroblasts, basement membranes	laminin, collagen
	VLA-2 (CD49b)	T lymphocytes, platelets, fibroblasts, endothelial cells, epithelial cells	collagen, laminin
	VLA-3 (CD49c)	epithelial cells, fibroblasts	fibronectin, laminin, (collagen?)
	VLA-4 (CD49d)	most leukocytes (eosinophils, not PMN), neural crest, fibroblasts	fibronectin, VCAM-1
	VLA-5 (CD49e)	T lymphocytes, fibroblasts, epithelial cells, endothelial cells, platelets	fibronectin
	VLA-6 (CD49f)	T lymphocytes, platelets	laminin

β_2-Integrins (LFA-1, CD18-group)	LFA-1 (CD11a/CD18)	most leukocytes	ICAM-1 (CD54), ICAM-2 (mainly on endothelial cells)
	Mac-1, (CD11b/CD18), Mo-1, CR3	macrophages, monocytes, granulocytes	ICAM-1 (CD54) (mainly on endothelial cells) C3bi, fibrinogen, factor X, LPS
	p150,95 (CD11c/CD18), CR4	macrophages, monocytes, granulocytes, platelets	ICAM-1, (C3bi?), ?
β_3-Integrins (Cytoadhesins)	Platelet glycoprotein IIbIIIa (CD41/61)	platelets	after activation: fibrinogen, fibronectin, vitronectin, von Willebrand factor
	vitronectin receptor (CD51)	most mesenchymal cells	vitronectin, fibrinogen, von Willebrand factor, thrombospondin
Selectin family (LECCAM)			
	L-selectin (MEL-14, (LAM-1, LECCAM-1)	most leukocytes	vascular addressins, e.g., GlyCAM-1 + ?
	E-selectin (ELAM-1)	endothelial cells, PMN	Sialyl-Lewis X
	P-selectin (PADGEM/GMP-140, CD62)	a) platelets (α-Granula), b) endothelial cells (Weibel-Palade bodies)	Lewis X, unknown receptors
Cadherin family	E-cadherin, Uvomorulin (epithelial cadherin)	epithelial cells	homophylic
	N-cadherin (Neural cadherin)	neural tissue, muscle	"
	P-cadherin (Placental cadherin)	placenta, epithelial tissue, transitionally	"
	LCAM (liver cell adhesion molecule)	in other tissues ?	"
Unclassified adhesion molecules	CD44 (Hermes Antigen, pgp-1, ECMRIII)		hyaluronic acid, matrix proteins
	Sialyl-Lewis X (sialylated CD15)	white blood cells	E-selectin

LFA-1, lymphocyte function-associated antigen 1; VCAM-1, vascular cell adhesion molecule; VLA, very late antigen; LAM-1, leukocyte adhesion molecule 1; ELAM-1, endothelial leukocyte adhesion molecule 1; PADGEM, platelet activation-dependent granule-external membrane protein; GMP-140, granule membrane protein 140 (140 kDa molecular mass); ICAM, intercellular adhesion molecule; LCAM, liver cell adhesion molecule; for other abbreviations see text

Table 2. Simplified classification of integrins based on binding characteristics [3]

	Subunit	Ligands
Integrins that function as cell–cell-adhesion molecules	α_L/β_2 (LFA-1)	ICAM-1, -2
	α_M/β_2 (Mac-1)	ICAM-1, C3bi
	α_Z/β_2 (gp 150,95)	?
	α_4/β_1	VCAM-1
Integrins that bind primarily to basement membrane proteins	α_1/β_1	Laminin/collagen
	α_2/β_1	Collagen/laminin
	α_3/β_1	Laminin/collagen/fibronectin
	α_6/β_1	Laminin
	α_6/β_4	Laminin
Integrins that bind primarily to matrix proteins of inflammation, wound healing,and development	α_4/β_1	Fibronectin (CSII site)
	α_5/β_1	Fibronectin (RGD site)
	α_V/β_1	Fibronectin
	α_V/β_3	Vitronectin, fibrinogen, thrombospondin, von Willebrand's factor
	α_V/β_5	Vitronectin

A special feature of β_2-integrins is that the affinity of the receptor can be enhanced transiently by intracytosolic signals [139] through an Mg^{2+}-dependent change in the conformation of the receptor structure on the cell exterior [7] after phosphorylation of intracellular parts [136]. Only after this change in their conformation are integrins able to bind to their ligands ICAM-1, ICAM-2, or ICAM-3 with high affinity [23, 43]. This phenomenon plays an important role in the adhesion cascade of leukocytes because their interaction must be transient and they must be able to detach again from their temporary binding site.

β_2-integrins are constitutional molecules expressed by all leukocytes. The β_2-integrins CD11b/CD18 and CD11c/CD18 are stored in the granules of neutrophils and monocytes and can be released to the cell surface within minutes. Upon stimulation, the expression of CD11a/CD18 remains unchanged on neutrophils and shows only a slight increase on monocytes [74]. Resting memory T cells express significantly more adhesion molecules than native T cells; the number of CD11a/CD18 receptors on the surface of native cells is 50,000–60,000 as opposed to over 300,000 on memory cells and natural killer cells [103]. Probably more important than quantitative receptor density, due to increased recruitment of molecules to the cell surface, is the above-described higher affinity of the receptors in the sense of an activation or functional upregulation of adhesions molecules [27, 148].

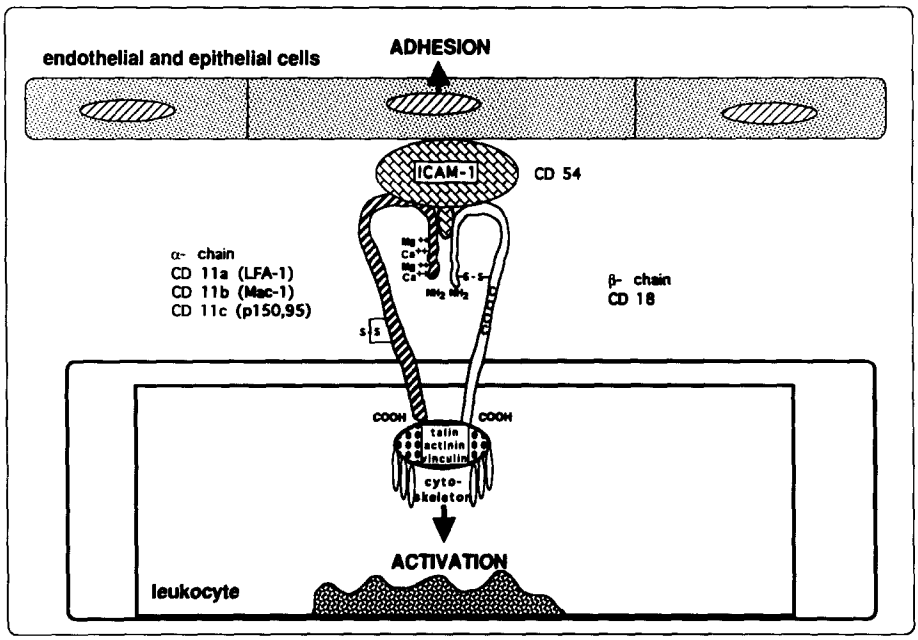

Fig. 1. Schematic view of the heterodimeric leukocyte cell adhesion molecule (β_2-integrin), interacting with the intercellular adhesion molecule-1 (ICAM-1), the most important inducible counterpart on endothelial cells. β_2-integrins are expressed in thousands on the leukocyte surface. The affinity of the β_2-integrin is dependent on conformational changes. Adhesion parallels activation of the cell. For further explanation see text.

Leukocyte Adhesion and Migration

Subtle regulatory mechanisms recruit and activate the white blood cells required for the defense reaction and attract them to the site of injury. Endothelial cells, whose surfaces are enlarged by furrowing [120], have a fundamental regulatory role due to their strategic position and omnipresence at the interface between blood or lymph and tissue. This role has been demonstrated not only for inflammatory and immunologic processes but also for the regulation of vascular tone, hemostasis, and fibrinolysis, as well as for cell growth and differentiation [53, 87, 120, 144].

In accordance with the concentration gradient of chemotactic substances, leukocytes can adhere to endothelial cells at the nearest vessel wall and transmigrate through the basement membrane between the endothelial cells to reach the effector site in the tissue matrix [100, 131, 135]. The specific expression of proteoglycans on different endothelial cells is assumed to codetermine the type of cytokines bound on the cell surface, and this probably is an additional regulatory component [84].

In the systemic circulation, leukocyte passage into the tissue occurs in the postcapillary venules, where the flow rate of the blood is lowest and is even

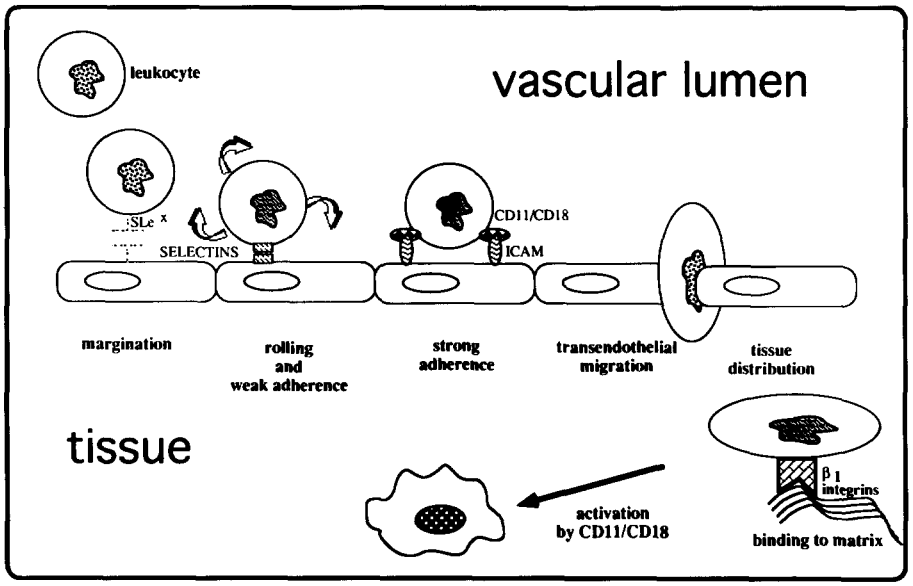

Fig. 2. Adhesion cascade: In postcapillary venules, the area of slowest flow rate of the circulatory system, shear forces between activated endothelial cells and/or activated leukocytes provoke a slowing-down and rolling of leukocytes by the weak and temporary adherence mediated by selectins. Strong adherence is mediated by the transient activation of β_2-integrins that interact with inducible intercellular adhesion molecules on endothelial cells. Adhesion, transendothelial migration, and locomotion through extracellular matrix are chiefly directed by cytokines and their concentration gradients. Abbreviations: SLeX, Sialyl Lewis X; ICAM, Intercellular Adhesion Molecule. For further explanation see text.

further reduced by the dilatation of vessels in the presence of inflammation [120]. The adhesion cascade, in which all three of the above families of adhesion molecules are involved, can be subdivided into three steps (Fig. 2). In the first step, the selectins induce rolling of the leukocyte; it touches the vessel wall under flow conditions and is slowed down by the combined effect of transient binding and shearing forces, and thus rolls along the endothelial cells [56, 64]. The second step, firm attachment of the leukocyte to endothelial cells, is induced by the transient activation of the β_2-integrins on the leukocyte. This is followed by transmigration of the leukocyte through the basement membrane between the endothelial cells into interstitial tissue [148], which is associated with a change in the shape of the cell (polarization of the neutrophils, formation of pseudopods, or a local increase in the density of receptors for CD11b/CD18 on lymphocytes [74, 79, 84, 104]. The further course of cell migration is dominated by adhesion to the extracellular matrix, e.g., to the glycoproteins fibronectin and vitronectin.

There are five possible mechanisms by which the recruitment of inflammatory cells can be increased: a change in the number or affinity of leukocytic

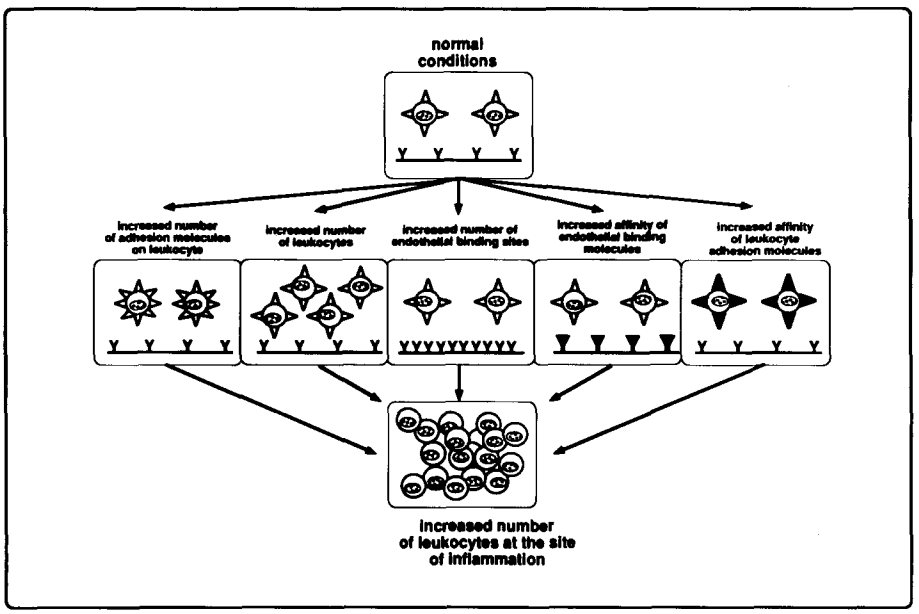

Fig. 3. The five possibilities for the recruitment of leukocytes to inflammatory sites. For further explanation see text.

molecules, increased supply in the circulation, and an increase in the number or affinity of endothelial ligands on capillary endothelial cells (Fig. 3).

Special Status of the Lung

The lung is the only organ in which all white blood cells pass the capillary network [88]. Only little is known about the regulation of neutrophil transit through pulmonary microcirculation, but it is clearly different from that of systemic circulation. In the pulmonary circulation, leukocytes enter the tissue only in the capillary bed [85]. Intravascular pressure in the pulmonary circulation is markedly lower than in the systemic circulation, and the flow is pulsatile rather than constant. The pulmonary capillary bed is the most important store of intravascular neutrophilic granulocytes [85, 88]. There is presumably a dynamic equilibrium between the circulating and the non-circulating neutrophil pool in the pulmonary capillaries. This factor may play an important role in the development of adult respiratory distress syndrome (ARDS) in cases of shock associated with reduced blood flow [42, 85, 132].

Videomicroscopic studies suggest that the neutrophils are sequestered exclusively in the pulmonary capillaries; margination or rolling has been observed neither in the arterioles nor in the venules. In vitro studies have demonstrated that there is a clear correlation between the reduced deformability of neutrophils

upon activation and their sequestration in the pulmonary capillaries [85, 135, 144]. Though CD11/18 seems not to be required for the sequestration of normal neutrophils in the normal vascular bed of the lungs, it mediates neutrophil migration in case of inflammation [27, 41, 145].

The recruitment processes in the pulmonary circulation described here for neutrophils are similar for monocytes, to which we will return later.

Adhesion Molecules in Pulmonary Diseases

In the following, we present some of the results obtained in studies investigating the role of adhesion molecules in pulmonary diseases. We will focus on those disorders in which leukocyte integrins (LeuCAM) appear to play an important pathogenetic role: pulmonary diseases caused by smoking, bronchial asthma, pulmonary infections, acute and chronic damage to the lung parenchyma, and malignancies.

Smoking-Related Lung Diseases

Inhalation smoking can lead to the development of pulmonary obstruction, which begins in the small airways and later extends to the large bronchi when smoking is continued [96, 128]. Smoking also causes pulmonary emphysema, with destruction of the architecture of the alveolocapillary units [34]. These changes are the result of inflammatory processes, since smoking is associated with the accumulation of inflammatory cells in the lung. This accumulation is regulated by adhesion molecules. While there are many studies in the literature on the pathogenetic role of neutrophils in inhaling smokers [26, 28, 44, 69, 86, 126], little is known about the contribution of alveolar macrophages.

The pool of alveolar macrophages is two to three times larger in smokers than in nonsmokers [18, 144]. The expression density of the receptors CD11/CD18 varies on human alveolar macrophages from nonsmokers [19, 66, 114]. The alveolar macrophages of nonsmokers show a relative decrease in CD11a expression and a relative increase in CD11c and CD11b expression compared to peripheral blood monocytes, which is similar to the expression described for other resting tissue macrophages [51]. Since a quantitative difference in the mRNA coding for these molecules was not found, the regulatory mechanisms can be assumed to be posttranslational [5].

There are no uniform data in the literature on the effect of inhalation smoking on the expression of LeuCAM molecules on human alveolar macrophages. Some investigators have reported an increased expression of adhesion molecules as well as changes in their expression pattern [19, 114]. It was found that inhalation smoking leads to a relative increase in CD11b expression and a decrease in CD11a expression, which results in an expression pattern indicative of a higher activation level of alveolar macrophages. Possible explanations for the increased expression are a higher influx of monocytes into the lungs or changes in the expression or affinity of the receptors induced by proinflamma-

tory stimuli. Another study, using a different method, only demonstrated an increase in the absolute number of CD11/CD18-positive alveolar macrophages in smokers [66], while the relative expression was reduced compared to nonsmokers.

Interestingly, the expression of CD11/CD18 receptors has different effects on the functional repertoire of alveolar macrophages in smokers and nonsmokers. It was shown, for instance, that the adhesive propensity of alveolar macrophages on ICAM-1-expressing endothelial cells is markedly higher in smokers than in nonsmokers and that this is at least partly due to the binding of CD11/CD18 to ICAM-1 [114]. Since receptor-ligand binding of β_2-integrins leads to an activation of the cell, which is reflected in an increase in intracellular free calcium and a higher translocation rate of protein kinase C [136], altered adhesive propensity may be important in the activation of alveolar macrophages. As for neutrophils [99], there is obviously also a close relationship between the induction of a respiratory burst and adhesion molecules on human alveolar macrophages. The increased spontaneous production of superoxide anions by smoker as opposed to nonsmoker alveolar macrophages [20, 65] can be markedly reduced by blocking the β-chain of the CD11/CD18 receptors [114].

Adhesion Molecules and Allergic Reactions of the Respiratory Tract

It has been demonstrated in a primate model in 1990 that the intravenous administration of an antibody directed against ICAM-1, the ligand of CD11/CD18 receptors, can prevent the development of experimentally induced bronchial hyperreactivity [142]. In asthma, this effect depends on the LFA-1/ICAM-1-mediated adhesion of eosinophils to the endothelial cells in the pulmonary vessels [13, 23, 31]. Stimulation with proinflammatory stimuli such as tumor necrosis factor alpha (TNF-α), γ-interferon, and interleukin-1β was found to enhance the expression of ICAM-1 on bronchial mucosa and vascular endothelial cells in bronchial vessels [142]. However, the effect of an anti-ICAM-1 antibody on the accumulation of inflammatory cells was seen in this primate model only when recently sensitized animals were used.

Proinflammatory cytokines such as interleukin-1 or TNF-α have also been shown to markedly enhance the expression of ICAM-1 on human epithelial cells of the trachea [133]. This enhancement is associated with an increased adhesion of human neutrophilic granulocytes, which can be reduced by the administration of antibodies directed against both CD11/CD18 and ICAM-1. But there are also studies that did not find a difference in the expression of ICAM-1 and ELAM-1 in bronchial mucosa of clinically stable asthmatics and control subjects [92].

Following segmental bronchial antigen expression, there is an increase in the expression of CD11b on alveolar granulocytes [52], which is accompanied by an intra-alveolar increase in lymphocytes, neutrophils, and eosinophils in the involved segments of the bronchial tree. Severity of asthma correlates with the number of eosinophils in the bronchial mucosa [25]. It is important, in

connection with the increased number of eosinophils in the bronchial mucosa of patients with asthma, that the transendothelial migration of eosinophilic cells through human endothelial cells appears to be dependent on the expression of CD11/CD18 on eosinophilic granulocytes and of ICAM-1 on endothelial cells [45].

The markedly increased expression of ICAM-1 seen in allergic patients was also demonstrated on mucosal cells of the nasal mucosa in allergic rhinitis [91]. The latter is also associated with an increase in the number of CD11a-positive leukocytes in the nasal mucosa.

Of particular interest for the pathogenesis of asthma is the interaction between CD11/CD18 receptor expression and platelet-activating factor (PAF), a proadhesive phospholipid that is released by eosinophilic granulocytes and endothelial cells [75, 147, 148]. It has been shown that the permeability of the intestinal mucosa following stimulation of the tissue with PAF can be markedly reduced by administration of anti-CD11/CD18 antibodies. This effect is probably due to granulocyte depletion of the mucosa induced by administration of the anti-LeuCAM antibodies [75]. The fact that the migration of eosinophilic cells through endothelial cells can be blocked by selective PAF antagonists such as WEB-2086 [29] suggests that PAF stimulates or costimulates the expression of these molecules, or that PAF influences the affinity of the receptors by means of an intracellular regulatory mechanism [147, 148].

Glucocorticoids and Adhesion Molecules

The effect of glucocorticoids in inflammatory processes is probably due mainly to their antiinflammatory action such as reduction of cytokines and lipid mediators [56, 121, 122]. It is controversial whether glucocorticoids can reduce the in vitro expression of ICAM-1 on endothelial cells and bronchial epithelial cells [53, 137]. Glucocorticoids suppress the production and release of granulocytes from the bone marrow, as well as leukocyte activation and their adhesion-molecule-mediated passage through the vessel wall [32, 53, 55, 95]. The inhibition of cytokines probably also reduces the survival time of eosinophils in the lung, which is assumed to play a role in allergic diseases [56].

Adhesion Molecules and Pulmonary Infections

The biological significance of adhesion molecules in the defense against infection is impressively demonstrated by cases with hereditary "leukocyte adhesion deficiency" (LAD), of which more than 50 cases have been described in the literature [9, 10, 11, 24, 37, 39, 63]. LAD is inherited as an autosomal recessive disorder assumed to be caused by a point mutation within the gene region coding for CD18 on chromosome 21 in band q22.3 [17, 74]. This genetic disorder is associated with a defective production of the beta-chain of LeuCAM receptors, resulting in a low number or absence of normal receptors on the cell surface [15].

Patients with LAD develop severe bacterial infections of the body surfaces, especially of the skin, in the oral and urogenital area, the intestine, and the respiratory tract. The fact that LAD, unlike neutropenia, can also be associated with defective wound healing, i.e., the formation of peculiar, paper-thin or dysplastic scars and characteristic peridontal defects, indicates that the CD11/CD18 integrins have an important biological role in the formation and repair of connective tissue, a function that, under normal conditions, is assumed to be fulfilled by the influx of monocytes and other inflammatory tissue reactions [119, 124]. Infected tissue shows dense infiltrates of eosinophils, lymphocytes, plasma cells, and some macrophages, but is totally devoid of neutrophils and monocytes. These histologic features suggest adhesion mechanisms that are independent from CD11/CD18. VCAM-1 and the corresponding integrin, VLA-4, which are important in accumulation of eosinophils in allergic and parasitic disease, are supposed to compensate for the lacking CD11/CD18 adhesion molecules [11, 50, 57, 135]. Blood granulocyte counts are fivefold to twentyfold the normal count; in case of infection, the number rises up to 100,000/liter [9, 50]. Adhesion-dependent cellular functions such as chemotaxis and aggregation are disturbed in proportion to the extent of receptor deficiency. Phagocytosis of iC3b-opsonized particles, which is another function of Mac-1 (CD11b/CD18), does not occur due to the absence of the CR3 receptor, and there is no induction of a respiratory burst [99]. Lymphocyte function is preserved, probably because of a possible compensation by lymphocyte receptors [14].

The genetic defect has been successfully repaired in vitro by transfection of the granulocytic stem cell with a CD18-encoding sequence [62]. After successful transfection, the cells express functionally normal CD11a/CD18 molecules and show a restitution of their functional properties.

So far only two patients have been described who lack the carbohydrate ligand Sialyl-Lewisx as a binding site for E-selectin. The clinical picture is nearly identical to that of the above-described LAD [47], which suggests that selectins and integrins are indispensible for leukocyte function in common biological processes.

Adhesion molecules are also involved in other infectious diseases of the respiratory tract, since they are ligands for viral and bacterial pathogens. This is by no means accidental, since various similarities have been described to exist between cell–cell adhesion and cell–virus, cell–bacterium, or cell–protozoan adhesion [124]. Recent studies have demonstrated the N-terminal region of the ligand ICAM-1 to be a high-affinity receptor for rhinoviruses [54, 125]. Bordetella pertussis also binds to the CD11b/CD18 receptor of bronchial ciliated cells and macrophages by means of a bacterial adhesion that contains the RGD sequence of the LeuCAM receptor binding domain consisting of the three amino acids Arg, Gly, and Asp [109, 113].

Consideration of adhesion molecules also sheds light on the pathophysiologic relationship between respiratory viral infections and compromised cellular defense. The infection of mononuclear cells with respiratory syncytial virus (RSV) reduces CD11a and ICAM-1 expression by these cells [112]. However, the effects of viral infection on the expression of adhesion molecules are dependent on the type of virus used in the experiments. It has recently been shown

that the infection of human epithelial tracheal cells with parainfluenza 2 virus markedly enhances the expression of ICAM-1 on these cells, which appears to be functionally significant, since the affected cells were able to bind more neutrophils [134].

Chronic bacterial inflammatory diseases of the lungs are associated with an increased influx of mononuclear cells into the bronchial system. Monocytes from patients with bronchiectasis adhere more readily to surfaces coated with fibronectin, and their adhesion can be further increased by stimulation with lipopolysaccharides or proinflammatory cytokines [102]. Preincubation with an antibody directed against CD18 reduces the adhesion of monocytes from these patients by more than 50%. But the adhesion mechanism mediated by CD11/CD18 is not the only one, since a synthetic peptide containing the RGDS sequence instead of RGD was also shown to reduce the enhanced adhesion of these monocytes [102].

Adhesion Molecules in Models of Acute and Chronic Lung Injury

Antibodies directed against CD11/CD18 or ICAM-1 antigens can influence or even prevent experimentally-induced parenchymal damage of the lung. It was shown in guinea pigs that the intrapulmonary infusion of neutrophilic granulocytes and opsonized zymosan induces the development of pulmonary edema, which can be considerably reduced after in vitro treatment of the neutrophils with an antibody to CD18 [73]. In vitro experiments with endothelial cells have shown that this effect of anti-CD18 is based on a markedly reduced adhesive propensity of neutrophils and a markedly lower albumin permeability of the endothelial layer following incubation of the neutrophils with anti-CD18.

The effect of antibodies directed against CD11/CD18 and anti-ICAM-1 on oxygen-induced pulmonary toxicity was studied in the mouse [143]. After hyperoxia for 48 h, the alveolar structures of the animals showed a markedly increased expression of ICAM-1. The injection of an anti-ICAM-1 antibody significantly reduced neutrophil infiltration of the pulmonary parenchyma and the number of neutrophils in bronchoalveolar lavage and improved the pulmonary function of the mice.

An antibody directed against the CD11b epitope appears to be able to reduce the toxic effect of intravenously administered TNF-α in dogs [46]. Although the mortality within the first 10 days after intravenous injection of a high dose of TNF-α did not differ, analysis of mortality within the first 30 h revealed a clear advantage for those dogs that had received an intravenous injection of an anti-CD11b antibody.

In another animal model, it was shown that the administration of IgA complexes induces parenchymal damage in the lung of rats, which is assumed to result from a pronounced increase in the production of oxygen radicals by alveolar macrophages [97]. These experiments also demonstrated that the intravenous administration of an anti-CD18 antibody but not of anti-CD11 nearly normalized the increased permeability of intrapulmonary vessels and markedly

reduced the number of alveolar macrophages in bronchoalveolar lavage (BAL). Similar results were obtained in rats after intravenous administration of a snake venom. In these experiments, both anti-CD11b and anti-CD18 antibodies significantly reduced the extent of acute parenchymal damage of the lung [98].

Studies in different animals and investigations in humans have elucidated the role of adhesion molecules in chronic inflammatory processes. It was shown that the administration of anti-CD11a or anti-CD11c antibodies almost completely prevents pulmonary fibrosis inducible by the intratracheal application of bleomycin [107]. For anti-CD11a, this effect was seen even when the antibody was administered 3 weeks after bleomycin application. The accumulation of platelets and alveolar macrophages was markedly lower in the antibody-treated animals. These two mechanisms might be responsible for the reduced locoregional release of platelet-derived growth factor (PDGF) and the ensuing decrease in fibroblast activation [118]. It remains open whether this therapeutic effect can also be achieved in man, since platelets in humans, unlike those in rodents, do not express leukocyte integrins.

Sarcoidosis

In sarcoidosis, the total number of alveolar macrophages correlates with the number of CD11/CD18-positive macrophages [115]. This correlation is probably due to a compartment effect of pulmonary macrophages, since a parallel increase in CD11/CD18-positive peripheral monocytes is not seen in these patients. In another study investigating monocytes by laser flow cytometry, sarcoidosis patients had fairly similar proportions of CD11/CD18-positive monocytes, but a markedly higher expression density of the epitopes on these cells [117], which might be explained by methodologic differences.

The data on the expression of individual epitopes on alveolar macrophages are contradictory. While some investigators reported an increased expression of CD11/CD18 [115], others found an increase only for CD11a, CD11b, and CD54 (ICAM-1) [89], or for CD11b and CD54 [127]. There is also one study in which the expression of CD11/CD18 was not found to be different in patients with sarcoidosis [67].

The increased expression of CD11/CD18 epitopes on the alveolar macrophages of patients with sarcoidosis is likewise accompanied by changes in alveolar cell function. It has been shown that the C3bi-mediated phagocytosis of agarose beads is dependent on CD11b [105]. The enhanced respiratory burst of the alveolar macrophages seen in sarcoidosis also depends on the expression of CD11/CD18 epitopes [115]. Since the interaction of alveolar macrophages and T cells appears to be an important pathomechanism of sarcoidosis, the expression of CD11/CD18 receptors on alveolar macrophages should also play an important role in this disorder [38]. In the case of accumulation of alveolar macrophages, there might be a marked increase in the locoregional secretion of lymphotactic cytokines and lymphocyte-activating substances from alveolar macrophages, which in turn might be responsible for the accumulation of lym-

phocytes in the alveolar space. The expression of ICAM-1 and LFA-1 on antigen-presenting alveolar macrophages is also required for the binding of specific T-cell clones (CD4-positive T cells) [8, 71, 83].

Idiopathic Pulmonary Fibrosis

Only few data are available on the behavior of alveolar macrophages and their expression of CD11/CD18 epitopes in patients with idiopathic pulmonary fibrosis [67, 115]. A correlation between the number of alveolar macrophages and the expression of CD11/CD18 epitopes has been described [115], and these receptors also appear to be involved in the enhanced respiratory burst of alveolar macrophages [115]. A contribution of CD11/CD18- and ICAM-1-positive alveolar macrophages to the pathogenesis of idiopathic pulmonary fibrosis is possible, since these receptors play an important role in the chemotaxis and activation of neutrophilic granulocytes [21, 35].

Tumors and Adhesion Molecules

While neoplastic processes, now regarded as multi-step disorders, are characterized by a loss of growth control, malignant transformation additionally involves invasive and metastatic capacity [6]. Depending on the cell type, differentiation and adhesion are coregulated by 2–10 different adhesion molecules [111]. A transient loss of cell–cell and cell–matrix adhesion, and rearrangement of cell–cell and cell–matrix contact is also required for the incorporation of the daughter cells into the tissue in normal cell division [6].

Binding to the basement membrane and to extracellular matrix proteins is mediated primarily by the integrins of the β_1 and β_4 groups [68], and by cadherines. The latter regulate extracellular cell–cell binding and, via the cytoplasmic protein catenin, the stable connections between the cytoskeleton and adjacent cells as well [82]. They are found in the zonula adherens and are involved in the formation and stabilization of cell binding [3, 82].

The role of adhesion molecules in the development of tumors may be complex. On one hand, upregulation can affect the growth, differentiation, and proliferation of cells and thus directly promote or induce tumor genesis [4, 116]. On the other hand, downregulation can reduce cell binding and thus facilitate metastasis formation, which depends on the loss of normal cell–cell and cell–matrix adhesion [3, 108, 129]. In addition, adhesion molecules are also involved in the pathomechanisms of hematogenic and lymphogenic metastatic spread (Fig. 4). The mechanisms involved in hematogenic spread are cell–cell and cell–matrix interactions with endothelial cells, and the capacity for transendothelial migration with diapedesis into the interstitial stroma through the basement membrane [30, 80], while the adhesion molecules of the CD44 family seem to be involved in lymphogenic spread [130]. Macrophages and T and B lymphocytes transiently express molecules of the CD44 family to achieve tolerance in the lymph nodes and lymphatic tracts. Tumor cells possibly express variants of the CD44 molecule and thus evade the lymphatic immune defense,

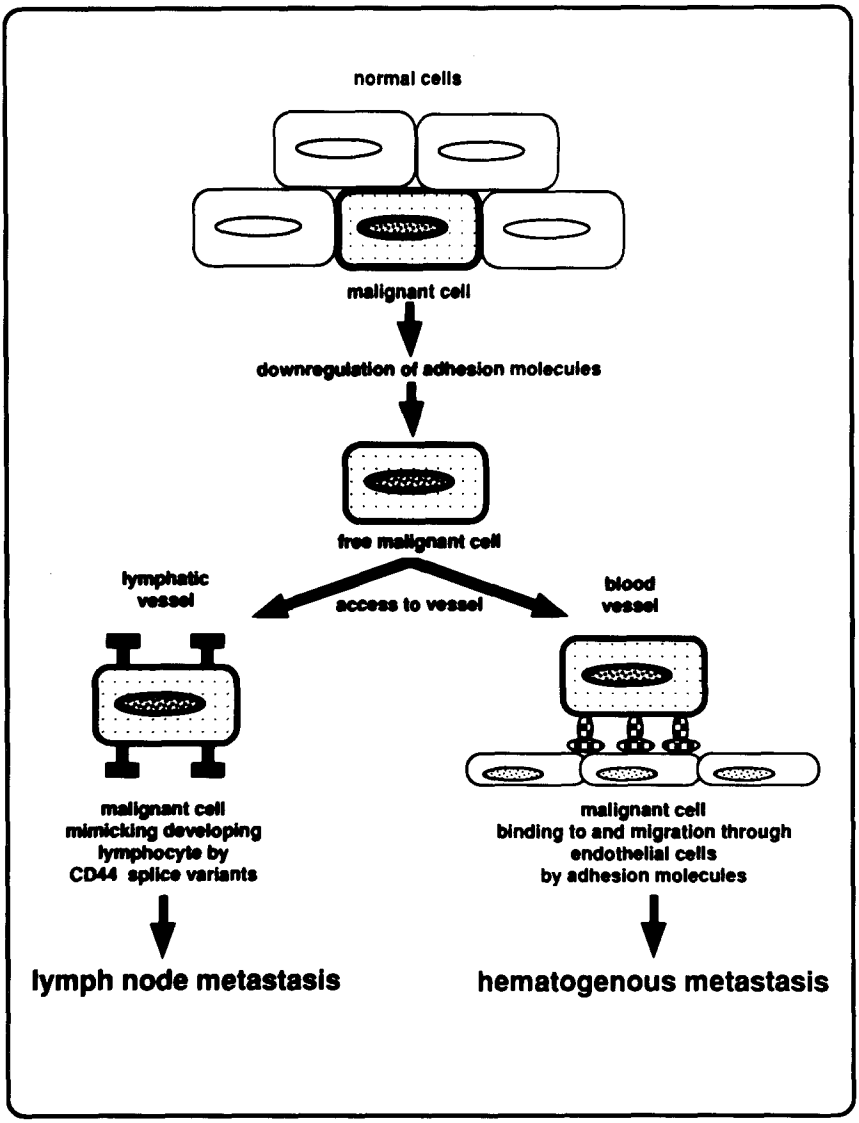

Fig. 4. Hypothetic role of adhesion molecules in malignancy. Lymphatic spread may be associated with exprimation of splice variants of the adhesion molecule CD44, possibly mimicking a lymphocyte in lymphatic tissue, or by important regulatory mechanisms, e.g., specific activation processes, associated with its expression on the cell surface. In hematogenous spread, which is often tissue-specific, specific "vascular addressins" might regulate adhesion of neoplastic cells, and therefore tissue-specific metastatic spread. For further explanation see text.

while they are recognized as developing cells in the lymph nodes [12, 72]. On the other hand, they might interact with adhesion processes, as a modulation of CD2 and LFA-1 by antibodies to CD44 has been found [60]. The organotropism of metastatic spread is presumably determined by organ-specific endothelial adhesion molecules, termed "vascular addressins" [1, 3, 146].

Since different lung tumor cell lines show a wide variation in the expression of integrins, it has not yet been possible to establish any characteristic patterns or to arrive at any clear conclusions as to the pathophysiological processes involved [36, 90]. Small-cell lung cancer is characterized by very early metastatic spread. Interestingly, preliminary studies of five cell cultures have shown that these tumors weakly express the alpha-chains aL and aM (CD11a and CD11b) of the β_2-integrins, whereas aX (CD11c) could not be demonstrated. Northern blot analysis did not identify mRNA for the expression of β_2-integrins but did for β_1-integrins [48]. The β_4-integrins, on the other hand, are expressed by non-small-cell carcinomas but not by small-cell carcinomas [33]. It has also been observed that all small-cell bronchial carcinomas express neural cell adhesion molecule (NCAM), which is expressed by only 20% of the non-small-cell carcinomas. The latter are associated with a markedly poorer prognosis compared to tumors that do not express NCAM [94].

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