

3. Adhesion molecules and receptors

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Adhesion molecules are necessary for leukocyte trafficking and differentiation. They serve to initiate cell-cell interactions under conditions of shear, and they sustain the cell-cell and cell-matrix interactions needed for cellular locomotion. They also can serve directly as signaling molecules activating pathways critical to cell functions, and they can act as accessory molecules maintaining cellular contacts necessary for signaling through other receptors. Given their critical role in the emigration of leukocytes into sites of inflammation, genetic mutations that thwart adhesion molecule expression or function can produce profound disruptions in host defense. Adhesion molecules might serve as therapeutic targets for inflammatory diseases. (J Allergy Clin Immunol 2008;121:S375-9.)

Key words: *Integrins, selectins, immunoglobulin superfamily, leukocytes, adhesion, shear stress, intercellular adhesion molecule, junctional adhesion molecule*

The major adhesion molecule families involved in leukocyte trafficking, activation, and differentiation include the integrins, selectins, and immunoglobulin superfamily members (Table I).

INTEGRINS

Integrins¹⁻³ are noncovalently linked $\alpha\beta$ heterodimers. Each subunit has a large extracellular domain, a single transmembrane domain, and a short cytoplasmic domain (20-70 residues). In vertebrates there are 18 α subunits and 8 β subunits combining to form 24 integrins with diverse ligand and recognition specificity, including cell-surface and extracellular matrix molecules. Some subunits occur only in a single integrin, whereas others occur in multiple integrins; for example, $\beta 1$ occurs in 12 integrins, and αV occurs in 5. The specific $\alpha\beta$ pairs influence coupling to components of the cytoskeleton and downstream signaling pathways, and subfamilies of integrins are grouped according to the identity of their β subunits. Four of the β subunits are expressed on leukocytes (ie, $\beta 1$, $\beta 2$, $\beta 3$, and $\beta 7$; Table I), with $\beta 2$ and $\beta 7$ expression limited to leukocytes, and $\beta 1$ expression occurring on most of the body's cell types.

The N-terminal portions of the α and β subunit together form a globular head containing the ligand-binding region. It is connected to the cell membrane by a stalk approximately 170 Å in length. The adhesiveness of integrins is regulated through a process termed *inside-out signaling*. Stimuli from cell receptors

Abbreviations used

ADAM: A metalloproteinase and disintegrin
HEV: High endothelial venule
ICAM: Intercellular adhesion molecule
JAM: Junctional adhesion molecule
LAD: Leukocyte adhesion deficiency
PSGL-1: P-selectin glycoprotein ligand 1
SCR: Short consensus repeat
sLeX: Sialyl Lewis X
VCAM: Vascular cell adhesion molecule
VLA: Very late antigen

(eg, for antigens, chemokines, and cytokines) activate pathways that act on the cytoplasmic portions of integrins, altering their affinity for ligands or influencing their clustering on the cell surface, thus altering their avidity. In addition, ligand binding transduces signals from the extracellular integrin domains to downstream cytoplasmic pathways, a process termed *outside-in signaling*. These adhesive dynamics of leukocyte integrins are necessary for normal cell migration and immune function.

Nine of the α subunits (αL , αM , αX , αD , αE , $\alpha 1$, $\alpha 2$, $\alpha 10$, and $\alpha 11$) contain a domain of about 200 amino acids (the inserted or I domain, also referred to as the von Willebrand factor type A domain). It is the major or exclusive ligand-binding site in these integrins. Divalent cations are necessary for ligand binding, and the residues coordinating metal binding are referred to as the *metal ion-dependent adhesion site*. The remaining α subunits are non- αI , and ligand binding involves specific regions of the N-terminal portions of both α and β subunits. The ligand-binding characteristics of integrins have been extensively studied, and clusters of integrin-ligand combinations reflecting a structural basis for the molecular interactions are beginning to emerge.² Two clusters have considerable experimental support. The Arg-Gly-Asp (RGD)-binding integrins recognize ligands containing an Leu-Asp-Val (RGD) tripeptide active site. This group includes the 5 αV integrins ($\alpha V\beta 1$, $\alpha V\beta 3$, $\alpha V\beta 5$, $\alpha V\beta 6$, and $\alpha V\beta 8$), 2 $\beta 1$ integrins ($\alpha 5\beta 1$, $\alpha 8\beta 1$), and $\alpha IIb\beta 3$. The Leu-Asp-Val (LDV)-binding integrins bind ligands with an acidic motif related to LDV. These include $\alpha 4\beta 1$, $\alpha 4\beta 7$, $\alpha 9\beta 1$, $\alpha E\beta 7$, and the $\beta 2$ integrins. Integrins can also be loosely grouped by ligand class,⁴ although some integrins have a diverse binding capacity. The basal extracellular matrix molecules that are dominant ligands for integrins (eg, many $\beta 1$ integrins) include collagen, laminin, thrombospondin, and tenascin. In addition, cryptic sites in extracellular matrix recognized by integrins can be exposed by proteases during tissue remodeling or inflammation. Molecules of provisional matrix during healing include fibronectin, fibrinogen, thrombospondin, and von Willebrand factor. Cell-surface ligands for integrins include members of the immunoglobulin superfamily (eg, intercellular adhesion molecule [ICAM] 1). The complexity is far from resolved, though, as discussed in the brief review by Humphries et al.²

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TABLE I. Major adhesion molecules important to leukocyte trafficking and differentiation

Adhesion molecule	Distribution	Binding partner
A1 β 1, VLA-1, CD49a/CD29	T cells, B cells, monocytes	Collagen
α 2 β 1, VLA-2, CD49b/CD29	T cells, B cells, monocytes	Collagen
A4 β 1, VLA-4, CD49d/CD29	Lymphocytes, monocytes, eosinophils, neutrophils	VCAM-1, fibronectin, JAM-B
α 5 β 1, VLA-5, CD49e/CD29	T cells, monocytes, neutrophils	Fibronectin
α 6 β 1, VLA-6, CD49f/CD29	T cells, monocytes, neutrophils	Laminin
α 9 β 1	Neutrophils	VCAM-1, tenascin, osteopontin
α L β 2, LFA-1, CD11a/CD18	Lymphocytes, NK cells, monocyte/macrophages, neutrophils, dendritic cells, eosinophils	ICAM-1, ICAM-2, ICAM-3, ICAM-5, JAM-A
α M β 2, Mac-1, CR3, CD11b/CD18	Neutrophils, monocytes, macrophages, NK cells, eosinophils, some T cells	ICAM-1, iC3b, fibrinogen, heparin, JAM-C, and many others
α X β 2, CR4, CD11c/CD18	Monocytes, macrophages, NK cells, dendritic cells, neutrophils	iC3b, ICAM-2, VCAM-1, fibrinogen
α D β 2, CD11d/CD18	Monocytes, macrophages, eosinophils, neutrophils	ICAM-3, VCAM-1
α IIb β 3	Platelets	Fibrinogen
α V β 3	Neutrophils	Vitronectin, CD31, fibronectin, tenascin
α 4 β 7, LPAM-1	Lymphocytes, monocytes, NK cells	MAdCAM-1, fibronectin
L-selectin, CD62L	Lymphocytes, neutrophils, eosinophils, monocytes	PSGL-1 and sialyl 6-sulfo Lewis X-bearing glycoproteins (sLeX)
E-selectin, CD62E	Endothelial cells	CD44, sLeX-bearing glycoproteins, PSGL-1
P-selectin, CD62P	Platelets, endothelial cells	PSGL-1 and sLeX-bearing Glycoproteins
ICAM-1, CD54	Endothelial cells, most leukocytes, fibroblasts	α L β 2, α M β 2
ICAM-2	Endothelial cells	α L β 2, α M β 2, α X β 2
ICAM-3	Most leukocytes	α D β 2, α L β 2, α D β 2
ICAM-4	Erythrocytes	α L β 2, α M β 2, α X β 2, α V β 3, α IIb β 3, α 4 β 1
ICAM-5	Central nervous system	α L β 2
JAM-A, F11R, JAM1	Endothelium, epithelium, platelets, neutrophils, lymphocytes, monocytes	α L β 2, JAM-A
JAM-B, JAM2	Endothelium	α 4 β 1, JAM-C
JAM-C, JAM3	Endothelium	α M β 2, JAM-B
VCAM-1, CD106	Endothelium, epithelium, fibroblasts, smooth muscle cells	α 4 β 1, α 9 β 1, α X β 2, α D β 2

VLA, Very late antigen; LFA, lymphocyte function antigen; NK, natural killer; LPAM, lymphocyte Peyer's patch adhesion molecule; MAdCAM, mucosal addressin cell adhesion molecule.

SELECTINS

The selectin family⁵⁻⁷ consists of 3 members of C-type lectins that bind glycoproteins and glycolipids bearing sialyl Lewis X (sLeX) in a calcium-dependent manner. The lectin domain is adjacent to a domain homologous to epidermal growth factor, a variable number of short consensus repeats (SCRs; a motif found in many complement regulatory proteins), a single transmembrane domain, and a C-terminal cytoplasmic domain. The size difference among the selectins largely reflects the number of SCRs: L-selectin has 2 SCRs, E-selectin has 6 SCRs, and P-selectin has alternatively spliced forms of 8 and 9 SCRs. This is a highly conserved gene family, with more than 60% amino acid identity in the lectin and epidermal growth factor domains.

P-selectin is stored in granules of endothelial cells (Weibel-Palade bodies) and in α granules of platelets. It is mobilized rapidly after cell activation (eg, histamine stimulation of endothelial cell or thrombin stimulation of platelets). E-selectin is expressed by cytokine-stimulated (eg, TNF- α and IL-1 β) endothelial cells. L-selectin is constitutively expressed on all leukocytes, and surface levels are modulated by metalloprotease-dependent shedding of the extracellular domain.

The dominant ligands for L-selectin are P-selectin glycoprotein ligand 1 (PSGL-1), a sialomucin expressed on most leukocytes, and glycoproteins found on high endothelial venules (HEVs) of Peyer's patches and HEVs of peripheral lymph nodes. PSGL-1 binding allows initiation of leukocyte aggregation, and binding to HEV might initiate the transmigration necessary for lymphocyte homing. The dominant ligand for P-selectin expressed on platelets or endothelial cells is PSGL-1. This ligand is critical for tethering and rolling of leukocytes on endothelial cells or surface-bound platelets displaying P-selectin. E-selectin recognizes a number of glycoproteins decorated with sLeX-related carbohydrates, including PSGL-1.

PSGL-1 is a disulfide-bonded homodimer with two 120-kd subunits containing functional sialylated O-glycans. It is modified with α 2,3-linked sialic acid and α 1,3-linked fucose. It is also sulfated on 1 or more of 3 tyrosine residues on the N-terminal region, a site that includes at least 1 tyrosine sulfate and at least 1 sialylated and fucosylated core-2 O-glycan. L-selectin and P-selectin recognize the region containing sulfated tyrosines. In contrast, E-selectin recognizes the sialylated and fucosylated core-2 O-glycans. PSGL-1 is found predominately

on the tips of microvillus-like projections from the leukocyte surface.

IMMUNOGLOBULIN SUPERFAMILY

ICAM family

The 5 members of this subfamily⁸⁻¹² share sequence homology of 30% to 50%. They are type I transmembrane glycoproteins composed of from 2 to 9 immunoglobulin superfamily domains, a hydrophobic transmembrane region, and a short cytoplasmic domain. ICAM-1 (CD54) has 5 extracellular immunoglobulin domains and is constitutively expressed on venular endothelium and some leukocytes. After stimulation with inflammatory cytokines (eg, TNF- α), most of the body's cell types can express ICAM-1. On the cell surface, ICAM-1 resides as a Y-shaped homodimer resulting from noncovalent interaction at domain 4. This structure exposes binding sites on D1 for α L β 2 (lymphocyte function antigen 1 and CD11a/CD18) and D3 for α M β 2 (Mac-1 and CD11b/CD18). ICAM-2 (CD102) has 2 extracellular immunoglobulin domains and exists as a monomer on the cell surface. It is constitutively expressed on platelets and on endothelial cells, where it is concentrated on the apical surface near intercellular junctions. Unlike ICAM-1, it is not upregulated by inflammatory cytokines. ICAM-3 (CD50) is most closely related to ICAM-1, having 5 extracellular domains, but its distribution is mostly limited to leukocytes. ICAM-5 is also closely related to ICAM-1, contains 9 extracellular immunoglobulin domains, and is expressed prominently in the central nervous system. ICAM-4 (CD242, Landsteiner-Wiener blood group) has 2 extracellular immunoglobulin domains, and its expression is restricted to erythrocytes. Studies with blood-derived human macrophages reveal its importance in erythrophagocytosis, and in mice erythroblastic islands in the bone marrow are dependent on α V/ICAM-4 interactions.

Vascular cell adhesion molecule 1

Vascular cell adhesion molecule (VCAM) 1 (CD106) is a transmembrane protein with 6 or 7 extracellular immunoglobulin domains, a single transmembrane domain, and a short cytoplasmic domain.^{13,14} Like ICAM-1, it serves as a ligand for some integrins, functions as a signaling molecule, and is expressed on a variety of vascular and nonvascular cells in response to inflammatory cytokines (eg, TNF- α).

Junctional adhesion molecules

Members of this group of immunoglobulin superfamily molecules most clearly related to leukocyte trafficking are junctional adhesion molecule (JAM) A (R11R, JAM1), JAM-B (JAM2), and JAM-C (JAM3).¹⁵ They are type I transmembrane proteins with 2 extracellular immunoglobulin domains, a single transmembrane domain, and a short cytoplasmic tail. There are dimerization motifs on the N-terminal domain (D1) predicting homodimerization at the cell surface. The cytoplasmic domain has a presynaptic density protein 95/disk-large/ZO-1 (PDZ)-binding motif facilitating interactions with tight junctional proteins (eg, zona occludins-1) and phosphorylation sites that appear to target JAMs to intercellular junctions. JAMs are widely expressed on epithelium and endothelium and contribute to the formation and integrity of tight junctions. In addition, they are expressed on leukocytes and platelets and function as adhesion molecules involved in cell trafficking.

FUNCTIONAL INTERACTIONS OF ADHESION MOLECULES RELEVANT TO LEUKOCYTE TRAFFICKING

Leukocyte rolling

Migration of leukocytes from blood into tissue requires coordinated sequential interactions of numerous adhesion molecules. The simplest generic model posits that selectins initiate interactions of leukocytes with endothelial cells. Selectin binding takes place under dynamic conditions, where shear forces exerted by flowing blood act on leukocytes and platelets as they interact with each other and with endothelial cells. Selectin binding requires a threshold level of shear for leukocytes to tether to ligands, a phenomenon referred to as "catch bonds."⁵ As force on the selectin-ligand bond increases, the off rate increases less for selectin-ligand bonds than for most receptor-ligand bonds (eg, integrins and antibodies). Small forces prolong the lifetime of selectin-ligand bonds, but force beyond a threshold shortens the lifetime. This enables leukocytes to roll along the endothelial surface at velocities of 100 to 1000 times slower than the mean blood flow velocity. Rolling is sustained as new bonds are formed downstream balanced by dissociation of bonds upstream. L-selectin is constitutively expressed on leukocytes and is critical to rolling adhesion of lymphocytes on HEV glycoproteins in lymphoid tissues. Rolling adhesions at sites of inflammation are primarily dependent on changes in endothelial cells or platelets. Acute stimulation of endothelial cells by agents such as histamine induces rapid translocation of prestored P-selectin from Weibel-Palade bodies to the apical surface, allowing interactions with PSGL-1 on leukocytes. Inflammatory cytokines (eg, TNF- α) induce new synthesis of E-selectin by endothelium, allowing interactions with sLeX and related moieties on leukocyte surface glycoproteins. Thus the combination of venular level shear forces and endothelial cell activation bring leukocytes into contacts with endothelium that might facilitate stable integrin-dependent adhesion and subsequent transmigration at sites of inflammation.

Transition from rolling to firm adhesion

Rolling leukocytes can arrest on the apical surface of endothelial cells,^{3,16} a process that depends on shear stress and inside-out signaling changes in integrin affinity and avidity. Both L-selectin and PSGL-1 on the leukocyte surface can activate signaling pathways as a result of interactions with endothelial selectins or ligands. However, the dominant signaling comes from chemokine receptors on the leukocyte surface interacting with secreted chemokines (eg, CXCL8) bound to endothelial surface proteoglycans (eg, heparan sulfate) or chemokines that are themselves transmembrane molecules (eg, CX3CL1). Inactive integrins are folded with the globular head near the membrane, whereas inside-out signaling results in conformational changes that extend the globular head with its binding site to a distance above the membrane about 4- to 5-fold that of the inactive state. These changes are not fixed but are in equilibrium, with intermediate affinity states involving not only extension but also rearrangements of the headpiece that influence affinity. Ligand binding and low forces pulling on the bonds appear to stabilize the bound conformation. Thus the combination of leukocyte activation through inside-out signaling and venular level shear forces facilitate leukocyte integrin binding to ligands on endothelial cells. Additional strengthening of adhesion involves integrin linkage to cytoskeletal elements and recruitment of additional integrins to the binding sites.

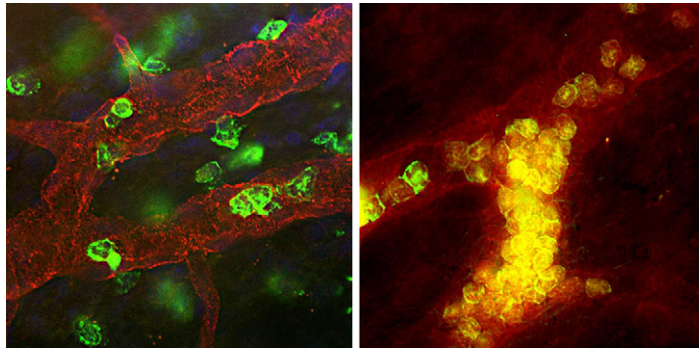


FIG 1. Vessels in the limbus of the cornea with inflammation induced by central corneal epithelial abrasion. The *left panel* shows vessels (postcapillary venules) in a wild-type mouse with transigrated neutrophils outside the vessels (neutrophils are *green*; vessels are *red*) 3 hours after initiating inflammation. The *right panel* shows vessels in a CD18 knockout mouse. Neutrophils are unable to migrate out of the vessels at this time and accumulate within vessels at the inflammatory site.

Transendothelial migration

After arrest, leukocytes have been observed in animal models to crawl along the luminal surface of endothelium to arrive at a point of transendothelial migration. Passage through the endothelium requires active participation of both the leukocytes and the endothelial cells. The route of transmigration can either be paracellular (ie, through intercellular junctions) or transcellular (ie, through the endothelial cell body). Route determination is poorly understood, but it is clear that integrins, especially $\beta 2$ integrins and $\alpha 4$ integrins, on the leukocytes are involved depending on the leukocyte subset. A number of endothelial adhesion molecules (mostly of the immunoglobulin superfamily) are involved as binding sites, as well as signaling molecules. These include E-selectin, VCAM-1, and ICAM-1 on the apical surface and CD31 (platelet endothelial cell adhesion molecule-1), CD99, JAM-A, and ICAM-2 at the interendothelial junctions. Leukocyte locomotion depends on these adhesion molecules, as well as chemokines released by endothelial or extravascular cells. Leukocyte trafficking is determined in general by adhesion molecules and chemokines, with their combinations reflecting leukocyte and endothelial heterogeneity. These factors determine tissue specificity and inflammatory stimulus specificity.

Platelets and leukocyte trafficking

Activated platelets can adhere to endothelial cells, denuded vessels walls, and leukocytes.¹⁷⁻¹⁹ Mobilization of P-selectin from platelet α -granules allows tethering under shear conditions to PSGL-1 on leukocytes. Leukocyte activation might follow as a result of signaling through PSGL-1 or platelet-derived chemokines, and firm adhesion of the platelet to the leukocyte involves leukocyte integrins (eg, $\alpha M\beta 2$ binding to platelet glycoprotein 1b α). Circulating platelet/leukocyte aggregates are readily seen in human subjects, and selective platelet depletion in animal models has demonstrated their importance to neutrophil, eosinophil, and lymphocyte accumulation in acute inflammatory sites in several locations (eg, lung, retina, and intestines).

Soluble adhesion molecules²⁰⁻²²

Most of the adhesion molecules listed in Table I can be detected in plasma, often the result of ectodomain shedding, a

phenomenon that might regulate leukocyte recruitment.²⁰ The proteases ("sheddas") involved vary with the specific adhesion molecules, ranging from granular enzymes (eg, neutrophil elastase) to surface enzymes (eg, a metalloproteinase and disintegrin [ADAM] 17 and ADAM-10). Ectodomain shedding has been used to evaluate the extent of blood leukocyte activation. For example, L-selectin is rapidly and extensively shed from the neutrophil surface after activation, which is evident in states of systemic inflammation. Also, the levels of soluble adhesion molecules in serum have been assessed in chronic inflammatory states; ICAM-1 has been the most extensively studied in this regard.²¹

Adhesion molecule deficiencies

At least 3 distinct syndromes of leukocyte adhesion deficiency have been defined. Leukocyte adhesion deficiency (LAD) I results from the mutations in the CD18 ($\beta 2$ integrin) gene (ITGB2) that prevent expression of the protein or severely reduce expression. Because all members of this family are heterodimers, absence of β subunit thwarts expression of α subunits, thereby preventing all $\beta 2$ integrin functions. These patients exhibit profound susceptibility to infections as a result of deficient phagocytosis and emigration of leukocytes into sites of infection.^{23,24} Mice with a targeted deletion of CD18 demonstrate the profound reduction in leukocyte emigration (Fig 1). LAD II results from mutations in guanosine diphosphate-fucose transporter gene (SLC35C1) that result in profoundly reduced fucosylation of glycostructures (eg, sLeX) that serve as ligands for selectins.^{25,26} This markedly reduces leukocyte tethering on endothelium at sites of inflammation. These patients exhibit increased susceptibility to infection. LAD III is yet to be defined at the molecular level and might represent several variants of the LAD I syndrome. These patients can have normal levels of leukocyte integrins, but functions appear to be deficient as a result of failed inside-out signaling. Increases in integrin affinity or avidity fail to occur, thus limiting integrin functions. Unlike the LAD I syndrome, $\beta 1$ and $\beta 3$ integrins are also affected, and platelet functions are reduced.^{27,28}

Therapeutic targeting of adhesion molecules

Rational approaches to targeting adhesion molecules and reducing inflammation in reperfusion syndromes, allergy, and

autoimmune syndromes have yielded some success. A dominant approach with integrins and their ligands has been the development of humanized mAbs (eg, efalizumab, approved for psoriasis²⁹). More recently, efforts to develop small molecule inhibitors have focused on integrins. Selectin inhibitors have largely been glycomimetics blocking binding of selectin to their glycoprotein ligands. Although the conceptual basis for these approaches is adequately documented in animal models, translation to human disease has proved difficult. This is an extensive area of investigation covered in recent reviews.²⁹⁻³²

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Learning objectives: "Adhesion molecules and receptors"

1. To learn about the major adhesion molecules involved in leukocyte activation and mobility.
 2. To gain an understanding of the major steps in the sequence of adhesive interactions that lead to leukocyte emigration at sites of inflammation.
 3. To learn about the major focus in evaluating or targeting adhesion molecules in human diseases.
-

CME items

Question 1. What are the major integrin families on leukocytes?

- A. $\beta 2$, $\beta 3$, and CD106
- B. $\beta 2$, $\beta 1$, and $\beta 3$
- C. CD18, CD49, and CD29
- D. intercellular adhesion molecule 4 and junctional adhesion molecule B

Question 2. Which of the following is not an important step for leukocyte integrin functions?

- A. an increase in affinity as a result of inside-out signaling
- B. outside-in signaling
- C. binding to carbohydrate ligands
- D. chemokine binding to G-coupled receptors

Question 3. Leukocyte adhesion deficiency III results from —

- A. mutations in the guanosine diphosphate-fucose transporter gene.
- B. mutation in the *CD18* gene.
- C. failure of chemokine signaling to induce affinity changes in surface integrins.
- D. failure of protease cleavage of adhesion molecules.

Question 4. Soluble adhesion molecules found in plasma may be indicative of all of the following except —

- A. splice variants producing soluble proteins.
- B. systemic inflammation.
- C. sheddases cleaving cell surface proteins.
- D. ectodomain preservation.