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*

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

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

INTEGRINS

Integrins[1-3] are noncovalently linked αβ 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 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, β1 occurs in 12 integrins, and αV occurs in 5. The specific αβ 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, β1, β2, β3, and β7; Table I), with β2 and β7 expression limited to leukocytes, and β1 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 (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, α1, α2, α10, and α11) 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 (αVβ1, αVβ3, αVβ5, αVβ6, and αVβ8), 2 β1 integrins (α5β1, α8β1), and αIIbβ3. The Leu-Asp-Val (LDV)-binding integrins bind ligands with an acidic motif related to LDV. These include α4β1, α4β7, α9β1, αEβ7, and the β2 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 β1 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
A1β1, VLA-1, CD49a/CD29	T cells, B cells, monocytes	Collagen
α2β1, VLA-2, CD49b/CD29	T cells, B cells, monocytes	Collagen
A4β1, VLA-4, CD49d/CD29	Lymphocytes, monocytes, eosinophils, neutrophils	VCAM-1, fibronectin, JAM-B
α5β1, VLA-5, CD49e/CD29	T cells, monocytes, neutrophils	Fibronectin
α6β1, VLA-6, CD49f/CD29	T cells, monocytes, neutrophils	Laminin
α9β1	Neutrophils	VCAM-1, tenascin, osteopontin
αLβ2, LFA-1, CD11a/CD18	Lymphocytes, NK cells, monocyte/macrophages, neutrophils, dendritic cells, eosinophils	ICAM-1, ICAM-2, ICAM-3, ICAM-5, JAM-A
αMβ2, Mac-1, CR3, CD11b/CD18	Neutrophils, monocytes, macrophages, NK cells, eosinophils, some T cells	ICAM-1, iC3b, fibrinogen, heparin, JAM-C, and many others
αXβ2, CR4, CD11c/CD18	Monocytes, macrophages, NK cells, dendritic cells, neutrophils	iC3b, ICAM-2, VCAM-1, fibrinogen
αDβ2, CD11d/CD18	Monocytes, macrophages, eosinophils, neutrophils	ICAM-3, VCAM-1
αIIbβ3	Platelets	Fibrinogen
αVβ3	Neutrophils	Vitronectin, CD31, fibronectin, tenascin
α4β7, 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	αLβ2, αMβ2
ICAM-2	Endothelial cells	αLβ2, αMβ2, αXβ2
ICAM-3	Most leukocytes	αDβ2, αLβ2, αDβ2
ICAM-4	Erythrocytes	αLβ2, αMβ2, αXβ2, αVβ3, αIIbβ3, α4β1
ICAM-5	Central nervous system	αLβ2
JAM-A, F11R, JAM1	Endothelium, epithelium, platelets, neutrophils, lymphocytes, monocytes	αLβ2, JAM-A
JAM-B, JAM2	Endothelium	α4β1, JAM-C
JAM-C, JAM3	Endothelium	αMβ2, JAM-B
VCAM-1, CD106	Endothelium, epithelium, fibroblasts, smooth muscle cells	α4β1, α9β1, αXβ2, αDβ2

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 family[5-7] 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-1β) 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 α2,3-linked sialic acid and α1,3-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