Adhesion Molecules - Potential Targets of New Anti-Inflammatory Therapies

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Introduction

Cell-to-cell and cell-to-matrix adhesive interactions play central roles in a number of essential physiologic processes. These include the establishment of cellular morphology, the processes of cellular differentiation and migration during embryologic development and organogenesis, as well as various aspects of host defense and tissue repair such as thrombosis, wound healing, immune surveillance and tumor metastasis. During all of these processes, cell-to-cell and cell-to-matrix interactions are mediated by a variety of integral membrane molecules, many of which belong to three major families: 1) the immunoglobulin superfamily; 2) the selectins; and 3) the integrins. The expression and functional activity of these various molecules, therefore, are critical determinants of many of the integrated functions of multicellular organisms.

During inflammation and immune surveillance, adhesion molecules play an especially critical role by mediating localization of inflammatory cells and their functional activation. This review will briefly detail the molecules involved in cell-to-cell and cell-to-matrix interactions and highlight their potential as targets of new anti-inflammatory and immunoregulatory therapies.

Integrins

Molecules that "integrate" or connect one cell with another or with its extracellular matrix

1. One of 21 currently identified heterodimeric glycoproteins composed of one of 15 known α chains non-covalently bound to one of 8 known β chains.

2. Most integrins are expressed on a wide variety of cells and most cells express several integrins.

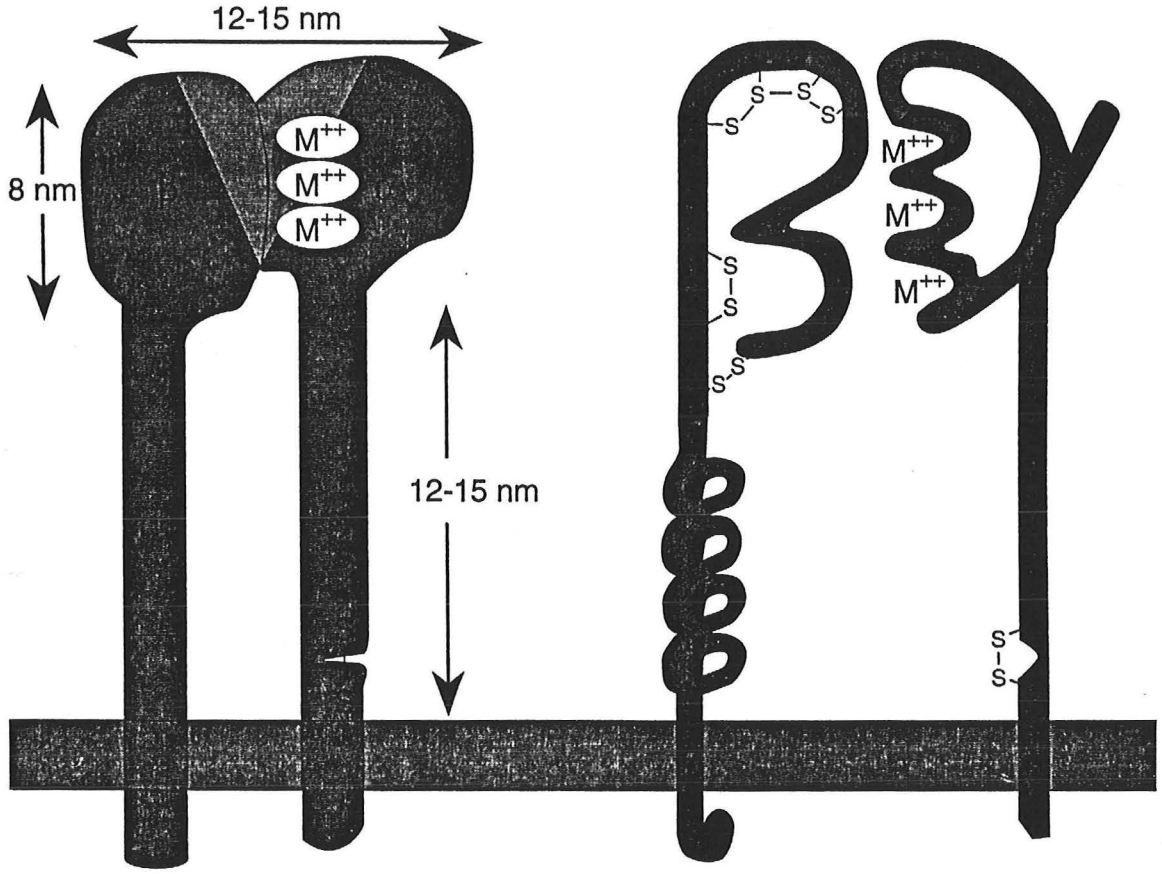
3. Binding activity is regulated by divalent cations.

4. Integrins are expressed but inactive on resting cells, requiring cellular activation for induction of binding activity.

5. Integrins may bind one or more ligands, including:
   a. extracellular matrix proteins
   b. plasma proteins
   c. cell surface molecules

6. Families of integrins
   a. β_1 - Very Late Activation antigens (VLAs).
   b. β_2 - Leukocyte Cell Adhesion Molecules (LeuCams).
   c. β_3 - Cytoadhesins.
   d. Other.

STRUCTURAL FEATURES OF INTEGRINS



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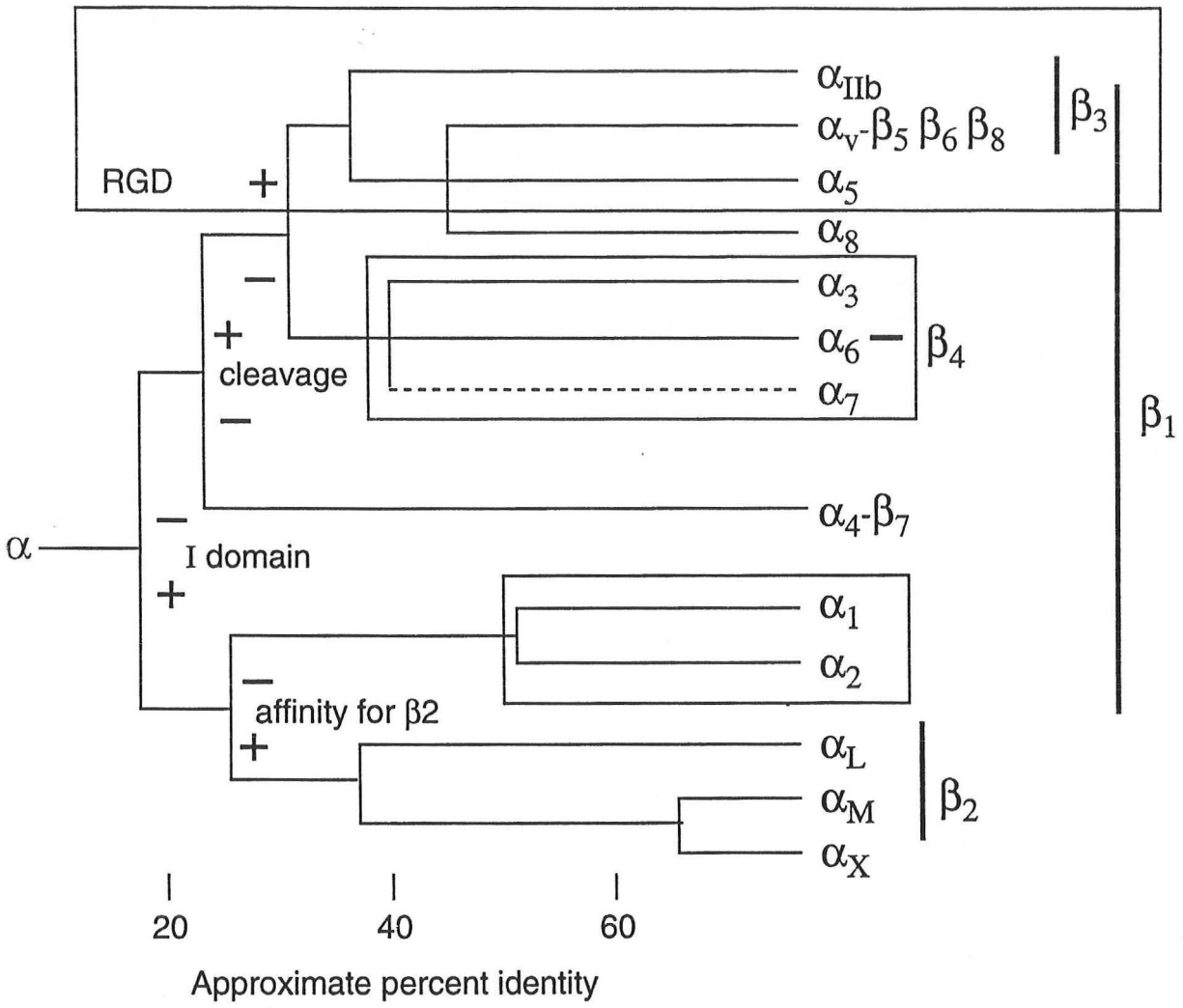
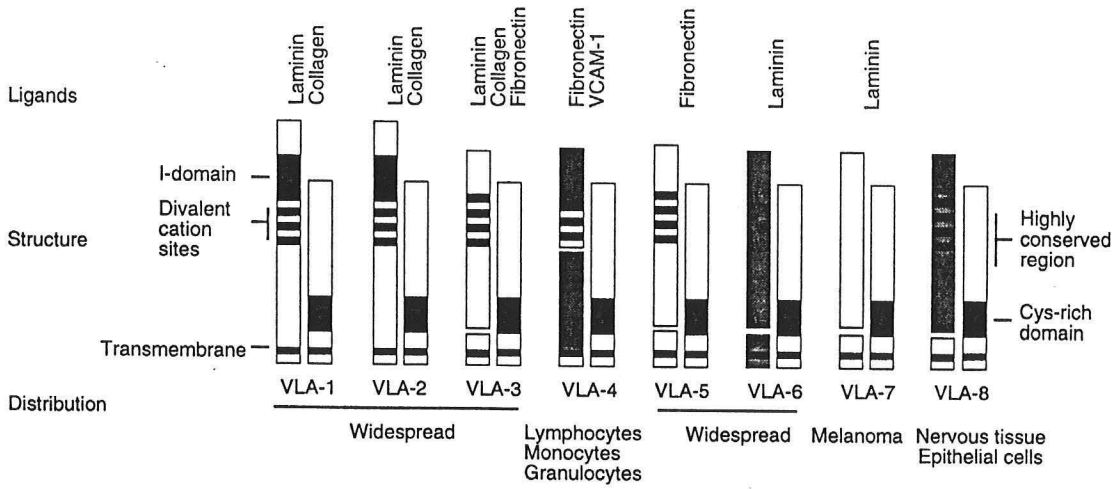
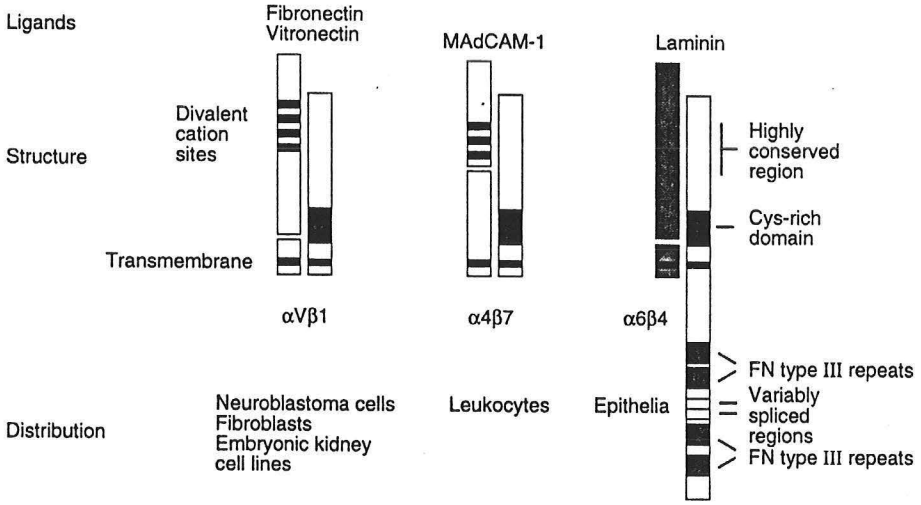
STRUCTURAL FEATURES OF INTEGRINS



THE VLA INTEGRIN FAMILY



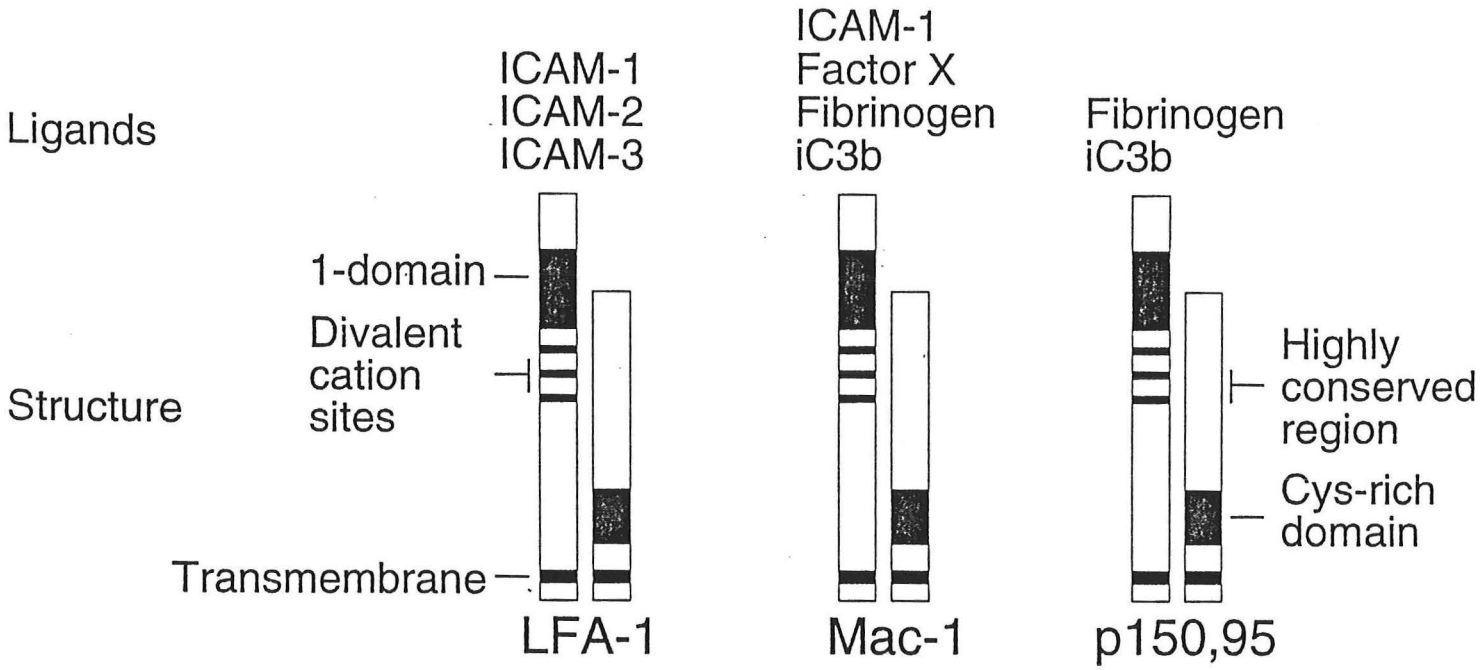


Leukocyte Specific Integrins

-β2 Integrins, LeuCams-

Receptor	Ligand/Counter-receptor	Expression	Regulation
LFA-1 (CD11a/CD18, $\alpha L\beta_2$)	ICAM-1 ICAM-2 ICAM-3	Leukocytes	Binding activity increased by divalent cations, cellular activation
Mac-1 (CD11b/CD18, CR3, αMβ2)	ICAM-1 Fibrinogen Factor X iC3b	Myeloid cells Large granular lymphocytes Some T cells B cell leukemias	Rapid redistribution to surface from granules with stimulation
P150/95 (CD11c/CD18, αXβ2)	Fibrinogen, iC3b	Myeloid cells Large granular lymphocytes Some B cells	Increased by TNFα

LEUKOCYTE SPECIFIC (β2) INTEGRINS



Leukocyte Adhesion Deficiency - I
(LAD-I)

1. Genetic - Defect in the expression of the β2 subunit (CD18) of the integrins

2. Physiologic - Defects in neutrophil and monocyte function:

   Chemotaxis
   Aggregation
   Phagocytosis
   Endothelial cell and iC3b binding

3. Clinical - Recurrent bacterial infections

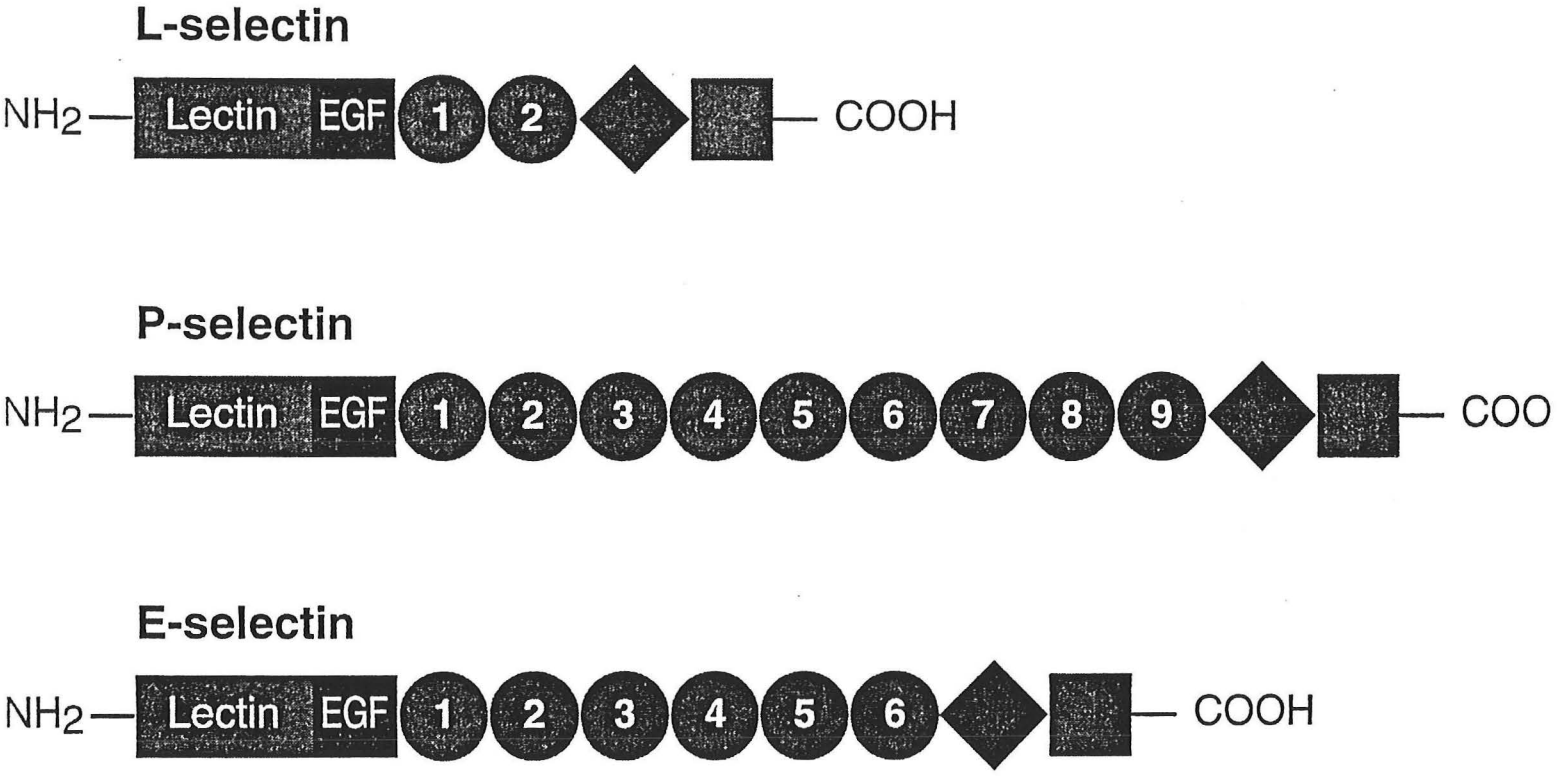
   Persistent neutrophilia

   Poor leukocyte mobilization

   Impaired wound healing

   Delayed umbilical cord separation

THE SELECTINS



Selectins

Selective cellular expression and Lectin binding domain

1. A family of heavily glycosylated adhesion proteins containing an amino terminal domain homologous to a calcium-dependent (c-type) lectin, an epidermal growth factor domain and multiple complement regulatory domains each containing 6 cysteinyl residues.

2. Selectins are encoded by a cluster of genes on the long arm of chromosome 1.

3. Ligands
   a. Oligosaccharides related to sialyl-Lewis x on leukocytes (sLe^x) and sialyl Lewis a (sLe^a) on malignant cells.
   b. Phosphorylated mono and polysaccharides.
   c. Sulfated polysacchrades.

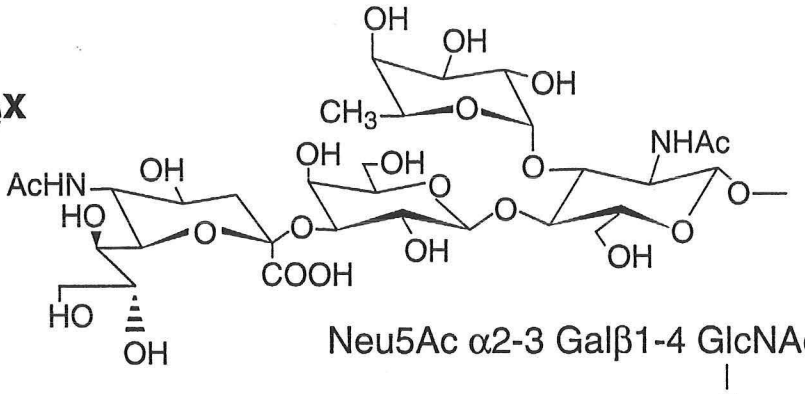
4. Promote initial contact of leukocytes with the endothelium and rolling under conditions of fluid shear stress.

Selectins

Selectin	Other Names	Expression	Induction	Ligands	Function
L-Selectin	mLHR, Leu8, TQ-1, $gp90^{Mel}$ LAM-1, Lecam-1, Leccam-1	Lymphocytes Monocytes Neutrophils Eosinophils	Constitutive, shed following cellular activation	Lymphocytes-PNAd (Vascular Addressin); Neutrophils, monocytes-E&P selectin, GlyCAM-1	1. Lymphocyte homing to lymph node 2. Adhesion of neutrophils and monocytes at sites of inflammation
P-Selectin	PADGEM GMP-140 CD62	Platelets Endothelial Cells	From storage granules by thrombin, histamine, C, H_20_2 (minutes) New synthesis by cytokines (hours)	L-selectin: neutrophils, monocytes	Binding of activated platelets and endothelium to neutrophils, monocytes
E-Selectin	ELAM-1	Endothelial Cells	New synthesis by cytokines (hours)	L-selectin: neutrophils, monocytes CLA: memory T cells	Adhesion of neutrophils, monocytes, a subpopulation of memory T cells, eosinophils and basophils to cytokine - activated endothelium

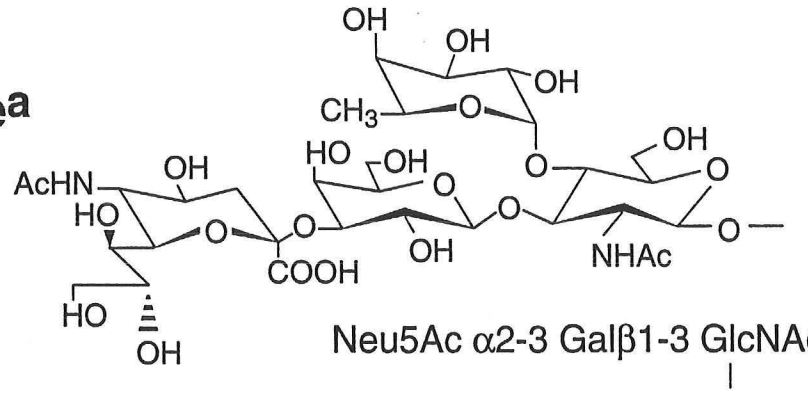
OLIGOSACCHARIDE LIGANDS OF THE SELECTINS

sLe^x



Neu5Ac α2-3 Galβ1-4 GlcNAc —
|
Fucα1-3

sLe^a



Neu5Ac α2-3 Galβ1-3 GlcNAc —
|
Fucα1-4

Leukocyte Adhesion Deficiency - II
(LAD-II)

Genetic - Genetic defect in fucose metabolism leading to deficient production of sialyl - Lewis x (sLe^x)

Physiologic - 1. Defect in the adhesion of neutrophils to E-selectin and P-selectin

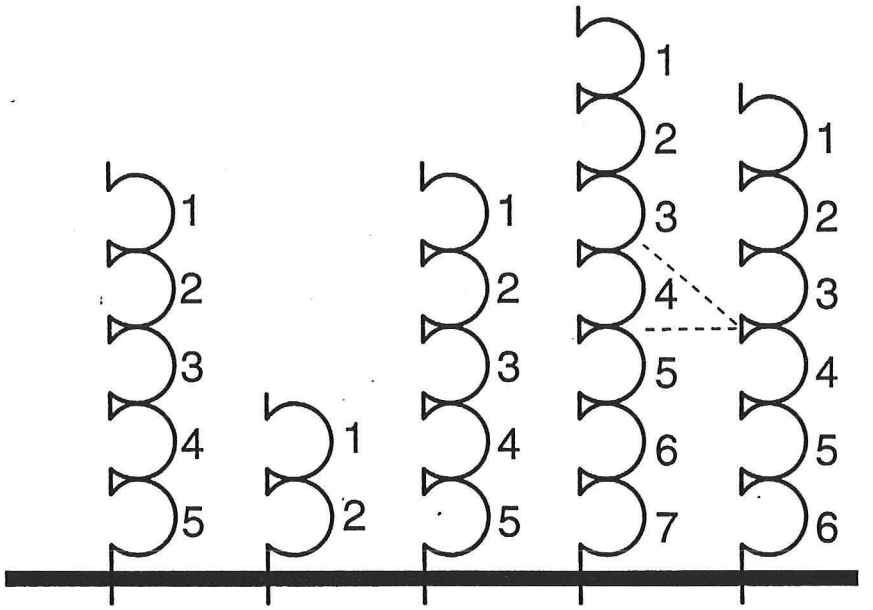
Clinical - 1. Neutrophilia

2. Recurrent bacteria infections

Immunoglobulin Superfamily Adhesive Molecules

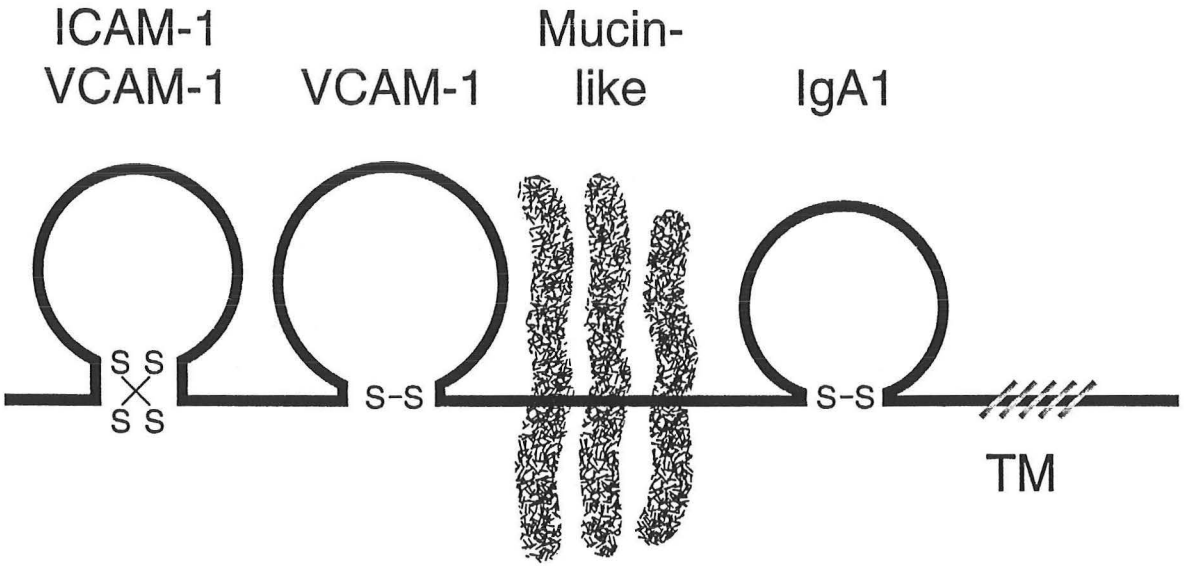
Molecule	Other Names	Expression	Regulation	Ligands/Counter-receptors
ICAM-1	CD54	Endothelial cells, fibroblasts, hepatocytes epithelial cells, leukocytes	Increased by cytokines (TNFα, IL1, IFN-γ)	LFA-1 (CD11a/CD18) Mac-1 (CD11b/CD18) Leukosialin (CD43) Fibrinogen Rhinovirus Plasmodium falciparum infected erythrocytes
ICAM-2	-	Endothelial cells, leukocytes	Constitutive	LFA-1 (CD11a/CD18)
ICAM-3	CDw50	Leukocytes	?	LFA-1 (CD11a/CD18) ? others
VCAM-1	-	Endothelial cells, fibroblasts, leukocytes	Induced by cytokines (IL-1,TNFα, IL-4)	VLA-4 (CD49d/CD29) α4β7 Plasmodium falciparum infected erythrocytes
LFA-3	CD58	Endothelial cells, leukocytes, epithelial cells	?	CD2
PECAM-1	CD31	Endothelial cells, platelets, leukocytes, smooth muscle cells	?	?
MAdCAM-1	-	Endothelial cells of mucosal tissue	?	α4β7

IMMUNOGLOBULIN SUPERFAMILY ADHESIVE MOLECULES



Major Counterreceptor	LFA-1 Mac-1	LFA-1	LFA-1	VLA-4	VLA-4

THE STRUCTURE OF MAdCAM-1



Adhesion Molecules Uniquely Expressed by Leukocytes

Integrins

VLA-4
LFA-1, Mac-1, p150/95

Selectins

L-selectin

Immunoglobulin Superfamily

ICAM-3

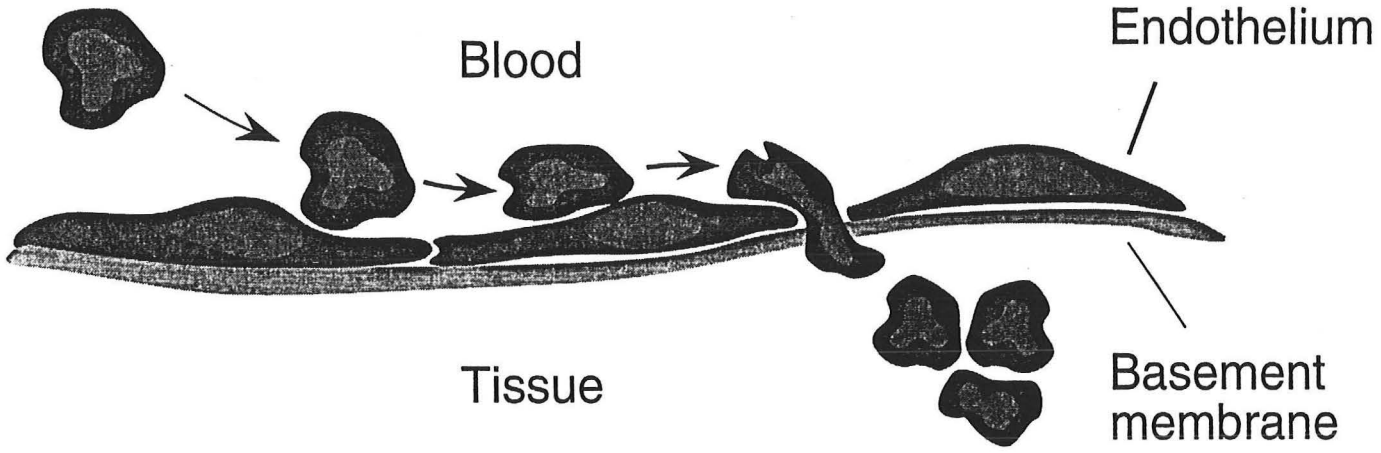
Functions of Leukocyte Adhesion Molecules

1. Cellular trafficking -

   recirculation and recruitment

2. Intercellular and cell-to-matrix interactions that regulate cell function

LEUKOCYTE BINDING AND MIGRATION INTO TISSUE



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Entry of Leukocytes into Inflammatory Sites

-The Adhesion Cascade-

Leukocyte adhesion to endothelial cells involves multiple receptor-ligand interactions. These occur both simultaneously and sequentially and serve to induce and strengthen interactions.

1. Random collisions of moving leukocytes with the endothelium to establish tenuous, unstable interactions.

2. Delivery of triggering signals that activate adhesion molecules that permit more stable interactions.

3. Establishment of strong adhesion to the endothelium.

4. Subsequent transendothelial migration into surrounding tissue.

Initial Interactions Between Leukocytes and the Endothelium

1. Interactions occur primarily in post-capillary venule where blood flow normally is the slowest. Vasodilation at the inflammatory site additionally slows blood flow.

2. Initial interactions are mediated by selectins.

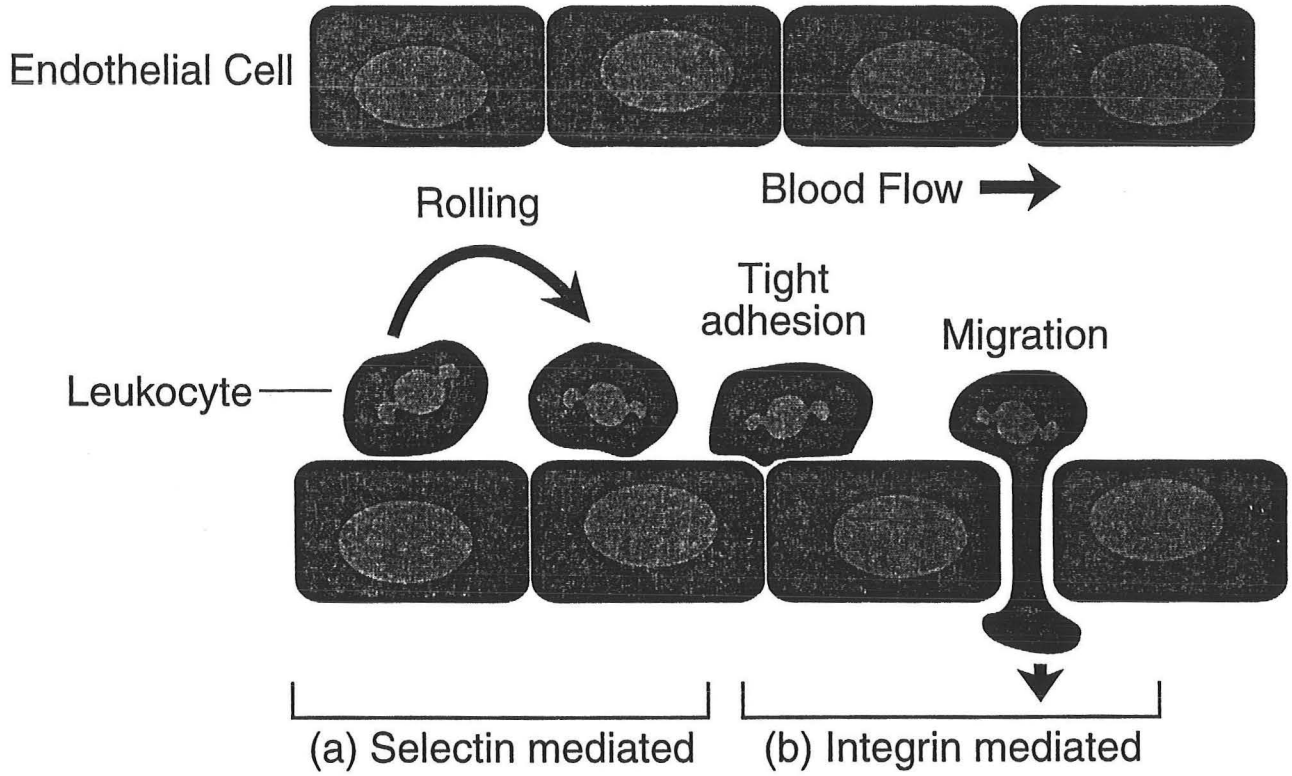
   a. The majority of leukocytes in the circulation are resting LFA-1, Mac-1, VLA-4-inactive.

   b. β_2 integrins do not bind well to ligands under conditions of physiologic shear force, although VLA-4 can mediate some binding at physiologic levels of shear.

   c. Selectins are constitutively active on leukocytes and can mediate binding under conditions of flow.

3. Initial selectin mediated interactions induce integrin activation that mediates strong adhesion.

LEUKOCYTE BINDING AND MIGRATION INTO TISSUE



Determinants of Binding of Leukocytes to Endothelium

1. Blood flow.
2. Capacity of interaction molecules to mediate binding.
3. Expression and activity of adhesion molecules.

Steps in Interaction of Leukocytes with the Endothelium

1. Reversible adhesion

   Selectin mediated "rolling".

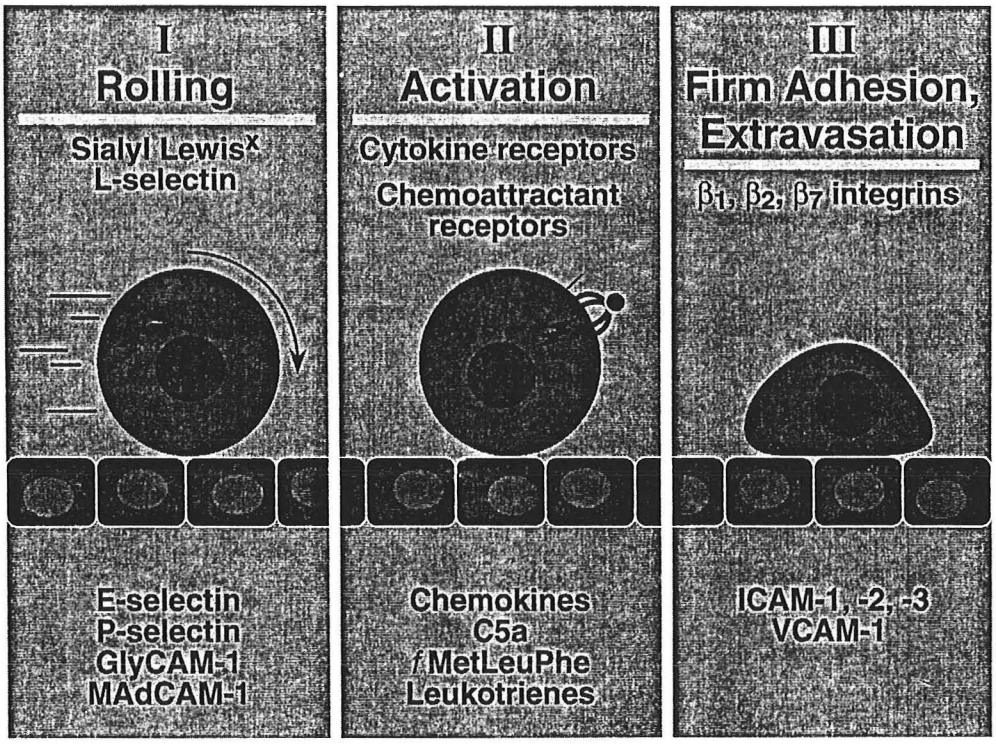
2. Leukocyte activation

   Activation of integrin function by lectin mediated interactions, chemokines and other inflammatory mediators.

3. Activation dependent binding

   Mediated by integrins.

STEPS IN LEUKOCYTE ADHESION



Adhesion Molecules are Targets of New Anti-Inflammatory Therapies

1. Entry of leukocytes into tissue is mediated by adhesion molecules.

2. In situations in which tissue pathology is mediated by the entry of leukocytes into tissue and their functional activation, blocking the function of adhesion molecules might be anticipated to block the inflammatory response.

Therapeutic Effects of Monoclonal Antibodies to Adhesion Molecules

1. E-selectin
    a. Inhibit neutrophil influx and chronic airway obstruction in models of asthma.
2. P-selectin
    a. Reduce reperfusion injury.
    b. Reduce complement mediated lung injury.
3. L-selectin
    a. Blocks cytokine induced cutaneous inflammation.
    b. Blocks DTH responses.
    c. Blocks neutrophil accumulation in experimental peritonitis.
4. CD18/ICAM-1
    a. Blocks tissue damage in several models of inflammation
        1. reperfusion injury
        2. shock
        3. acute immune complex and complement mediated lung injury
        4. experimental asthma
        5. adjuvant arthritis, antigen-induced arthritis
        6. allograft rejection - heart, kidney
        7. models of hepatic injury
        8. burn injury
5. VLA-4
    a. Partially inhibit lymphocyte migration into sites of DTH in skin and joints.
    b. Prevents development of EAE in the rat.

Use of Monoclonal Antibodies to ICAM-1 in Patients with Rheumatoid Arthritis

Rheumatoid arthritis is a chronic disease characterized by continued infiltration of the synovial tissue and synovial fluid by a variety of inflammatory cells. The inflammatory cells entering the synovium account for the signs and symptoms of the disease.

Animal models of arthritis, including adjuvant arthritis and antigen-induced arthritis are effectively prevented and/or treated by monoclonal antibodies to ICAM-1 and the beta chain of the leukocyte integrins, respectively.

BIRR1

1. Murine IgG2a anti-ICAM-1 (CD54)

2. Binds to domain 2 of ICAM-1 and blocks interactions with LFA-1 (CD11a/CD18) and Mac-1 (CD11b/CD18)

3. Has been used to prevent delayed graft function in high risk renal allograft recipients

Anti-ICAM-1 Treatment of Rheumatoid Arthritis

-Treatment Protocols-

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5 day regimens

60/20/20/20/20 mg	n=2
120/40/40/40/40 mg	n=10
240/80/80/80/80 mg	n=1

1 or 2 day regimens

120/120 or 120/0 mg	n=6
240/80 or 240/0 mg	n=2

Anti-ICAM-1 Treatment of Rheumatoid Arthritis

Patient Demographics

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17 women, 4 men

Age: 49.3 ± 2.8 years

Disease duration: 18.4 ± 2.1 years

Previous DMARDs: 4.4 ± 0.3

Response of Patients with Severe Rheumatoid

Arthritis to Treatment with BIRR1

Treatment Regimen	Number of Patients	Response	Days 8	15	29	60	90
5 day	13	Marked	4	3	4	2	0
		Moderate	5	3	3	6	2
1-2 day	8	Marked	0	1	1	0	0
		Moderate	3	0	0	1	1

Response defined by Paulus criteria

Adverse Events During anti-ICAM mAB Therapy

Nausea	-	8 patients
Fever	-	7 patients
Headache	-	6 patients
Dizziness	-	2 patients
Pruritus	-	2 patients
Urticaria	-	1 patient
None	-	9 patients

Conclusion

Administration of monoclonal antibodies to ICAM-1 to patients with rheumatoid arthritis

- blocks the entry of lymphocytes into inflammatory sites
- diminishes signs and symptoms of inflammation

Conclusion

Emerging knowledge of the role of specific adhesion molecules in cell-to-cell and cell-to-matrix interactions involved in the entry of inflammatory cells into tissues and their local activation has provided a series of potential targets for new anti-inflammatory therapies. Effective treatment of inflammatory disease in experimental animals with monoclonal antibodies has provided evidence of the validity of this concept. Additional detailed knowledge of the protein-protein or protein-carbohydrate interactions that mediate binding of adhesion molecules to their ligands and counterreceptors should yield new and highly specific approaches to treat inflammatory conditions.

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