Adhesion molecules

The adhesion of cells to one another and to the extracellular matrix is crucial to **embryonic development**, **maintenance of tissue architecture**, **the inflammatory response**, **tumor metastasis**, and **wound healing**.

Over the last decade much progress has been made towards determining the specific cell surface receptors that mediate these adhesive interactions. More recently, investigators have begun to address the role of adhesion molecules in airway inflammation, and acute and chronic lung injury.

Families of cell adhesion molecules

The known cell adhesion molecules can be grouped into distinct families on the basis of their molecular structure: **cadherins**, **selectins**, **integrins**, and members of the **immunoglobulin superfamily**.

Some of the adhesion molecules important in the inflammatory response are listed in Table 2.

Cadherins

They are a family of calcium dependent adhesion molecules found both within and outside the nervous system. In humans at least 11 different cadherins have now been identified.

Function:

They mediate **homotypic cell-cell adhesion**, although heterotypic binding between different cadherins molecules is possible. They thus act as both **receptor** and **ligand**.

Family Molecule	Distribution	Counter Receptor(s)
Integrin		
LFA-1	All leukocytes	ICAM-1, ICAM-2
Mac-1	Neutrophils, Monocytes, some Lymphocytes	ICAM-1, Fibrinogen
VLA-4	Eosinophils, Lymphocytes, Monocytes	VCAM-1
Immunoglobulin Superfamily		
LFA-2	All T-Lymphocytes	LFA-3
LFA-3	Wide spread	LFA-2 (CD2)
ICAM-1	Endothelial and Epithelial cells, Eosinophils, other cells	LFA-1, Mac-1
ICAM-2	Endothelial and other cells	LFA-1
VCAM-1	Endothelial cells	VLA-4
PECAM-1	Endothelial cells, Platelets, some Leukocytes	PECAM-1, Glycosaminoglycans
Selectins		
E-Selectin	Endothelial cells	Sialyl Lewis x, Sialyl Lewis a, L-Selectin
P-Selectin	Endothelial cells, Platelets	Sialyl Lewis x, L-Selectin
L-Selectin	Lymphocytes, Neutrophils, Eosinophils	E- and P-Selectin

Table 2: Adhesion molecules involved in inflammation.

Selectins

The selectins are a group of transmembrane glycoproteins.

Function:

There is strong evidence that E-, P- and L-Selectin are involved in the **inflammatory response** and therefore represent novel therapeutic targets. They function in cell-cell interactions and appear crucial for the initial binding of leukocytes to endothelial cells in inflammatory responses.

Integrins

The integrins are a family of transmembrane glycoproteins that function in both cell-cell and cell-substratum adhesions. Structurally, they are highly disulfide-linked, noncovalently associated heterodimers consisting of α and β subunits. Originally, thought to consist of three subfamilies with a common β subunit capable of associating with a specific group of α subunit. It is now clear that certain α subunit can associate with more than one β subunit.

Function:

They function as the **major receptors for extracellular matrix** and as **cell-cell adhesion molecules**. They play an important role in numerous biological processes such as **platelet aggregation**, **inflammation**, **immune function**, **wound healing**, **tumor metastasis** and **tissue migration during embryogenesis**.

Immunoglobulin superfamily

This family of adhesion molecules characterized structurally by repeated immunoglobulin-like domains in the extracellular portion of the molecule.

Function:

The roles of the family members are **multivarious**, but are linked by the common theme of controlling cell behavior. Such control is exerted by molecules acting as **signal transducing receptors** or as **intracellular adhesion molecules** or, as becoming increasingly apparent, as both. With few exceptions, they can all be found as cell surface molecule, although soluble isoforms also exist for a number of family members.

Adhesion molecules in normal lung structure

In order for the pulmonary epithelium and endothelium to form and maintain functional permeability barriers, there must be firm adhesion to the extracellular matrix and tight contact between adjacent cells. Molecules in the **integrin** family are the most important for the **cell-matrix adhesion**, with some contribution from other **proteins** and **proteoglycans**. For **cell-cell adhesion**, the **cadherins** and **integrins** interact with **cytoplasmic proteins** to form the structures that characterize epithelial and endothelial junctions.

Adhesion molecules in pulmonary inflammation

The development of an inflammatory response requires that the resident cells of a given tissue communicate with circulating effector cells. This communication can occur through the production of soluble mediators (**cytokines and chemoattractants**) and/or through cell-cell adhesion. *In vivo* there are complex interactions between soluble mediators and adhesion molecules: the soluble mediator can alter the expression of adhesion molecules, and cell adhesion can result in the elaboration of soluble mediators.

Leukocytes flowing in a vessel lumen must first adhere to an endothelial cell, then migrate between adjacent endothelial cells, and finally move through the extracellular matrix to perform effector functions in a given tissue. An evolving paradigm to explain the molecular mechanisms involved in this process has been termed the "**leukocyte-endothelial cell adhesion cascade**". Cytokines, cell adhesion molecules and chemoattractants are expressed in a programmed and interactive manner to create a specific inflammatory response.

Leukocyte Function Associated molecule-1 (LFA-1 or CD11a/CD18)

It is a member of the **integrins** family.

Cellular distribution:

Lymphocytes, **neutrophils**, **monocytes** and **macrophages**.

Function:

It has a key role in **mediating leukocyte adhesion to endothelium during inflammatory responses through binding to ICAM-1**. It is also involved in most immune phenomena involving T lymphocytes such as adhesion of cytotoxic T cells to their target cells, mixed lymphocytes' reactions and T cell-dependent antibody response. It is also involved in homotypic leukocyte interactions between B and T cell.

Ligands:

ICAM-1, ICAM-2 and ICAM-3.

Intercellular Adhesion Molecule-1 (ICAM-1 or CD54)

It is a member of the **immunoglobulin superfamily** family.

Cellular distribution:

It is basally expressed in significant amounts on a limited number of cell types, including **monocytes** and **endothelial cells**. It is widely inducible, or upregulated, on many cells including **B** and **T lymphocytes**, **thymocytes**, **dendritic cells**, **endothelial cells**, **fibroblasts**, **keratinocytes**, **chondrocytes** and **epithelial cells**.

Function:

It is important in **mediating immune and inflammatory responses**. Also, it mediates the **adhesion of T cells with antigen-presenting cells** or **target cells** and is **involved in T cell/T cell and T cell/B cell interactions**. Binding of ICAM-1 has a **co-stimulatory effect on T cell activation**. It is important in the adhesion of monocytes, lymphocytes and neutrophils to activated endothelium. Expression of ICAM-1 has been implicated in tumor metastasis.

Ligands:

LFA-1 and Mac-1. The receptor/ligand is calcium dependent.

Alternative forms:

Soluble forms detected in sera.