Adhesion molecules and inflammation: Introduction

Web sites worth visiting.

♦ “Inflammation: The Leukocyte Adhesion Cascade”
This is an excellent web site and well worth visiting. It includes a lot of information that is directly relevant to the lecture.
http://bme.virginia.edu/ley/index.html

♦ Extra information on cell adhesion molecules: quite a good summary on cadherins, selectins and an overview of integrin adhesion.
http://www.cytochemistry.net/Cell-biology/adhesion_molecules.htm

and open the on-line version of “Molecular Biology of the Cell” and look at chapter 19 - key “cell-cell adhesion” into the search box will get you there.

♦ Nueromuscular Adhesion molecules. This site also has overviews of the main adhesion molecule families with links to further information.
http://neuromuscular.wustl.edu/lab/adhesion.htm

♦ Cell Adhesion under fluid flow. This site contains real life pictures and videos of cell involved in adhesion to blood vessel walls. Give an idea of firm adhesion and rolling.
http://www.ent.ohiou.edu/~adhesion/
Adhesion molecules and inflammation: Introduction

Inflammation is a disease where cell adhesion plays a critical role.

Cell adhesion is the way cells talk to each other.

It is important for:

- tissue formation during morphogenesis
- cell migration
- regulation of: cell proliferation, gene expression and cell death (apoptosis)

A large number of cell surface and extracellular matrix (ECM) molecules contribute to cell adhesion.

Complexes of adhesion molecules, signalling molecules & cytoskeletal components.

Stable Adhesion: Multiple binding events frequently involving different adhesion molecules binding their receptors (ligands).

Specificity: achieved by different combinations of adhesion molecules.

Cell-cell adhesion: very stable ↓ long lasting (cells in tissues)

↓

very transient ↓ cells interacting with blood vessel walls
There are many different families of adhesion molecules:
- vary in molecular structure, and
- perform different tasks.

Cell-cell adhesion is the result of multiple, different adhesion molecule-ligand binding events

⇒ Co-operation between different adhesion molecules.

Considerable redundancy → adhesion is a fundamental process essential for many physiological processes.

Not all adhesion molecules are consistently expressed on cell surfaces

Expression varies according to:
- differentiation state of the cell,
- stage of cell cycle,
- cytokine activation of cell, or
- cell activation caused by signals arising from other adhesion molecules having bound their ligands.
Integrins: Involved in cell-extracellular matrix adhesion and cell-cell adhesion.

- Structure: heterodimer consisting of two transmembrane glycoprotein subunits (α and β), which are non-covalently bound.

- Functional integrins always have: one α subunit and one β subunit.

- Both subunits contribute to ligand binding.

- About 18 α subunits and 8 β subunits have been identified, giving ~24 unique integrins.

→ A large number of possible specificities.

- Ligand binding is divalent cation dependent (Ca ++, Mg ++ and Mn ++)

- Common ligands are: the ECM proteins fibronectin, vitronectin, collagen and laminin (recognised by multiple integrins) or members of the Ig superfamily.

Figure from “Molecular Biology of the Cell” Alberts et al., 2002
Adhesion molecules & inflammation: Integrins

Different types of integrins.


Integrins connect the actin cytoskeleton to extracellular matrix proteins outside the cell.

The clustering of integrins - formation of focal adhesions.

Signals generated at focal adhesions help to regulate cell division, growth and survival, as well as being important for cell migration.

Above Figure from "Molecular Biology of the Cell" Alberts et al., 2002
**Adhesion molecules & inflammation: Ig-super family**

Ig-superfamily of adhesion molecules: includes around 70 members. All possess one or more Ig-like domain.

- Ig-like domains are β-sheets stabilised by di-sulphide bonding.
- Ig domains are resistant to proteases and are adaptable for the presentation of recognition domains.
- They recognise both homophilic and heterophilic ligands.

Fig (B) NCAM recognising another NCAM molecules on a different cell (homophilic ligand).

- Integrins are frequently heterophilic ligands for Ig-superfamily members e.g. ICAM binds to β2-integrins on blood cells;
- \( \text{Ca}^{++} \) dependence for ligand binding is variable.

Figure from “Molecular Biology of the Cell” Alberts *et al.*, 2002
The Selectins: There are three selectins

- E-selectin, found exclusively on endothelia
- L-selectin, found on all circulating leukocytes except activated T-lymphocytes
- P-selectin, found in secretory granules of platelets and endothelial cells.

All are structurally closely related having, at their N-termini a carbohydrate recognition (C-type lectin) domain and variable numbers of repeats related to complement regulatory proteins.

Their ligands are carbohydrates presented on glycoproteins, their ligands are,

- E-selectin: sialylated Lewis X (SLe\textsuperscript{X}) & SLe\textsuperscript{a}
- P- & L-selectin: SLe\textsuperscript{X}, SLe\textsuperscript{a} & sulfated polysaccharides.
- The way these carbohydrates are presented on the glycoprotein helps to regulate selectin binding.

Figure from “Molecular Biology of the Cell” Alberts et al., 2002.
Hyaladherins: These are the hyaluronan (HA) binding proteins of the extracellular matrix & cell surface.

In contrast to the other families of adhesion molecules we have studied this family is not united by the molecular structure of its members but by the ligand a series of structurally different proteins bind.
CD44 is the best known of this family.

CD44 has multiple isoforms achieved by the alternative splicing of 10 variant exons. It is widely distributed but some isoforms appear only on certain cell types.

Not all CD44 variants bind HA.

CD44H is a HA binding isoform that is expressed by leukocytes and may be involved in the migration of leukocytes through the connective tissues to sites of inflammation.

HA is a high molecular weight carbohydrate and is a major component of cartilage and other soft connective tissues.

Cadherins: Large family of cell surface proteins that mediate homophilic Ca\(^{++}\)-dependent cell-cell adhesion.

- The classical cadherins, e.g. E-, P-, L-cadherins occur in the epithelial, neuronal placental and liver tissues respectively.
- They have a critical role in morphogenesis. In the adult cadherins are responsible for the tight cell-cell associations within tissues.
- They are intimately associated with the cytoskeleton, interacting via other proteins with both microfilaments and intermediate filaments.
- Cells express multiple cadherins- specificity of adhesion is due to the different combinations of cadherins expressed.

Figure from “Molecular Biology of the Cell” Alberts et al., 2002.
Cadherins are important for stable adhesion. Figure above shows the formation of a cadherin zipper and the interaction of the cytoplasmic tail of cadherin with $\beta$-catenin which binds $\alpha$-catenin and actin cytoskeleton.
Adhesion molecules: Summary

Very stable cell-cell interactions $\downarrow$ Cadherin-cadherin mediated

Interactions that allow cell movement $\downarrow$ Integrins/Ig-SF members binding their ligands

Very transient cell-cell interactions $\downarrow$ Mediated by selectins binding their ligands

The migration of leukocytes in response to inflammation illustrates how all these different molecular interactions can co-operate to perform very complex processes.

Upon tissue damage leukocytes (white blood cells) are recruited from the blood to sites of injury. It is a multi-step process that happens in sequence to many of the leukocytes that become attached to blood vessel walls.

All steps must be completed for a leukocyte to enter site of inflammation.
Leukocyte migration is controlled by the interactions that occur between the leukocyte and the vascular endothelia. Different adhesion molecules are involved at each stage.

“Inflammation: The Leukocyte Adhesion Cascade”

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Adhesion molecules & inflammation

• Initially leukocytes leave the main blood flow and come into close contact with the vessel wall - enhanced by changes in blood flow at site of injury.

Rolling: Once captured the leukocytes “roll” on the vessel wall. Rolling is mediated by E- and P-selectins expressed by the endothelial cells interacting with their carbohydrate ligands on the leukocyte. Very fast on and off rates of adhesion.

• Rolling molecules are located on the tip of micro-villi on leukocytes.

Firm Adhesion: Activation of endothelia causes up-regulation of adhesion molecule expression by endothelia. Inflammatory cytokines cause the activation.

• Adhesion molecules of the Ig-superfamily (ICAM-1 & -2, VCAM-1) most important - these bind integrin molecules (CD11b/CD18 and VLA-4) on the leukocytes.
Adhesion molecules & inflammation

**Transmigation:** Precise role of many of the molecules involved is not clear.

- The Ig-superfamily member PECAM-1 on is very important and it probably engages in homotypic adhesion: PECAM-1 on endothelial cell binds other PECAM-1 molecules on the leukocyte surface.

- VE-cadherin is important for vascular permeability. Endothelia are held together by VE-cadherins interacting with each other and with the cytoskeleton. Adhesion of leukocytes to endothelia disrupts cell junctions \( \uparrow \) permeability to cells and fluids.

http://bme.virginia.edu/ley/index.html