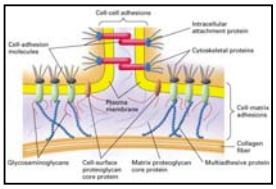
Cellular adhesion

Physical connections between cells

- Cells in multicellular organisms are in contact with each other and extracellular matrix
- Cell connections involve multiple ligands and cell adhesion receptors



Forming the connections between cells

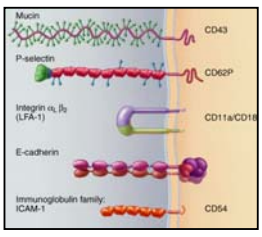
- **Cell adhesion receptors** enable cells to recognize and bind molecules on other cells or in the extracellular matrix
  - Ligands can be other cell adhesion receptors (receptor-receptor contact) or extracellular matrix molecules
- Make cells stick to other cells or extracellular matrix
- Cell adhesion receptors also activate intracellular signaling pathways (primarily for cell death/survival but also secretion etc.)

Forming the connections between cells

- The interaction between cell adhesion receptors and their ligands are relatively weak
  - A lot of weak interactions make a strong bond
- Cell adhesion are too weak to support permanent contact between cells
- Following adhesion connections have to be stabilized by cytoskeleton to form cell junctions

Principal classes of cell-adhesion receptors

- Cadherins
- Ig-family of cell adhesion molecules
- Integrins
- Selectins
- Others such as
  - Mucins
  - Connexins



Cell adhesion receptors

Can form

- Homophilic (or homotypic) adhesions – between same type of molecules
  - Cadherin - cadherin
- Heterophilic (or heterotypic) adhesions – between different type of molecules
  - Selectins - mucins

Interactions of cell adhesion receptors

- Integrins are the only one that mediate cell – extracellular matrix adhesion
- Other types mediate cell-cell adhesion
- Cadherins and Ig-superfamily CAMs form primarily homophilic connections
- Mucins, selectins and integrins heterophilic connections
- Many cells use several different cell adhesion receptors to mediate cell-cell adhesions

Cells can regulate their adhesion by

- Selective expression of cell adhesion receptors
- Regulating surface density
- Receptor clustering
- State of receptor activation

Cadherins

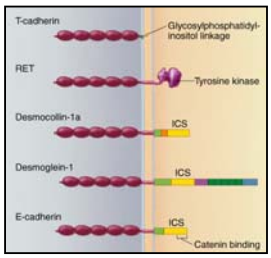
- Mediate Ca^{2+} - dependent homophilic cell-cell adhesion
  - Used in organ formation
- Primarily link epithelial and muscle cells to their neighbors
  - Form desmosomes and adherens junctions
- Play critical role during development (cell sorting)

Cadherins

- Do not interact with extracellular matrix
- Interaction with the same type of cadherins is favored over interactions with other cadherins (organ formation)

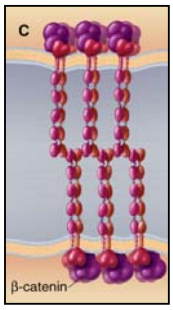
Cadherins

- Integral membrane glycoproteins
- Single transmembrane region
  - Except T cadherin that is GPI anchored



Cadherins

- Form parallel homodimers
- Extracellular N-terminus with multiple CAD domains and Ca^{2+} binding sites
- C-terminal cytoplasmic domains interact with the cytoskeleton through cytoplasmic adapter proteins catenins



Physiological roles of cadherins

- Very specific tissue distribution
- E-cadherins hold epithelial cells together (adherens junctions and desmosomes)
- N-cadherins expressed in nervous system are responsible for the specificity of neuronal connections
- Protocadherins participate in synapse formation

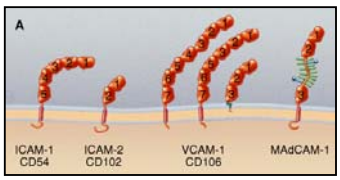
Molecule	Predominant Cellular Distribution
E-cadherin	Preimplantation embryos, non-neural epithelial tissue
P-cadherin	Trophoblast
N-cadherin	Nervous system, lens, cardiac and skeletal muscle

"Contact inhibition"

- Inhibition of cell growth and motility when epithelial cells come in contact with each other
- Suppresses spread of cancer cells derived from somatic mutations
- Loss of cadherins is implicated in tumor metastasis

Immunoglobulin family of cell adhesion receptors

- Hundreds of different receptors
- Homophilic interactions
- Single transmembrane segment
- Antibody like folds on the extracellular domain



Immunoglobulin family of cell adhesion receptors

- Mediate primarily homophilic cell-cell adhesion but also some heterophilic
- Adhesion is Ca^{2+} - independent
- Activate intracellular signaling pathways

Immunoglobulin family of cell adhesion receptors

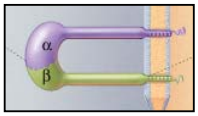
- Play critical role during morphogenesis and differentiation of muscle, glial and nerve cells
- In neurons promote the formation of myelin
- In vascular endothelial cells leukocyte adhesion and extravasation

Integrins

- Cell adhesion receptors responsible for the cell-extracellular matrix adhesion
  - $\alpha_L\beta_2$ mediates cell-cell interactions
- Also important signal transduction receptors for regulation of cell growth
- Present in membranes of all cells except erythrocytes

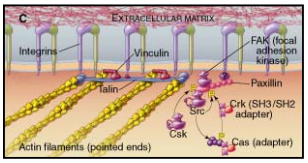
Integrins

- Heterodimers of α and β subunits (both transmembrane)
  - 18 types of α and 8 types of β subunits
  - From different combinations
  - Ligand binding site is composed from both subunits



Integrins

- Intracellular domains interact with variety of signaling and structural proteins
  - Talin and vinculin (adapter proteins) to form focal adhesions
  - Link to actin to form stress fibers
  - Paxillin (adapter proteins) to activate FAK (focal adhesion kinase)



Interactions of integrins

- Mediate weak cell-matrix and cell-cell interactions
- Multiple weak interactions allow for firm adhesion
- Strength of adhesion is modulated by changes in the activity and number of integrins

Physiological role of integrins

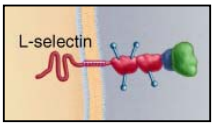
- Form hemidesmosomes and focal adhesions
- Involved in morphogenesis and cell migration
- Binding of matrix ligands to integrins modifies
  - Cell adhesion
  - Cell locomotion
  - Gene expression

Physiological role of integrins

- Bind epithelial and muscle cells to laminin in the basal lamina
- Allow platelets to stick to exposed collagen in a damaged blood vessel
- Allow fibroblasts and white blood cells to adhere to fibronectin and collagen as they move

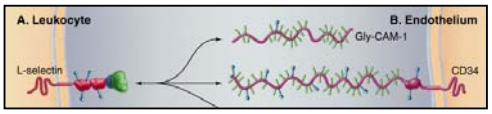
Selectins

- Lectins (proteins that bind to carbohydrates)
- Lectin domain is localized at the end of extracellular domain
  - Binding is Ca2+ dependent



Selectins

- Involved in heterophilic cell-cell interactions
- Natural ligands are carbohydrate groups on mucin-like glycoproteins



Selectins

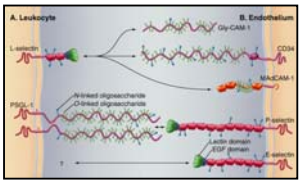
- Specific for leukocyte-endothelium interactions
- Participate in leukocyte rolling and adhesion
- Each type of selectin binds to specific oligosaccharide sequence
  - P-selectin binds to sialyl Lewis-x-antigen – sequence present on leukocytes

Regulation of selectins

- Regulated by local conditions such as inflammation
- Endothelial cells express E selectins only when stimulated by inflammatory mediators

Other adhesion receptors - mucins

- Cell surface glycoproteins with negative charge
- Interact with selectins
  - Complementary on the other cell type



Leukocyte extravasation

- Movement of blood cells (mostly leukocytes) into tissue
- Requires activation of endothelium (by conditions such as infection or inflammation)
- Initiated by successive formation and breakage of cell-cell contacts between leukocytes and endothelium

Leukocyte extravasation

- Endothelium is activated by inflammatory conditions
- Inflamed endothelial cells start to express P-selectin on their surface
  - Selectins are stored in vesicles
- Passing leukocytes adhere weakly to the endothelium (leukocyte rolling)

Leukocyte extravasation

- β2 containing integrins on the surface of leukocytes become activated by chemotactic factors
- Activated integrins bind to Ig CAMs on the surface of endothelium
- Once a leukocyte has adhered to the endothelium it translocates into the tissue

Leukocyte extravasation