Cells to Tissues

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From one cell to ensembles of cells.

Multicellular organisms require individual cells to work together in functional groups. This means cells must stick to each other and communicate with each other to coordinate their activities.
• Adhesion between cells
• Signaling between neighboring cells
• Cell adhesion to extracellular matrix
Cell to Cell Adhesion
Interactions between neighboring cells and between cells and ECM hold tissues together. Adhering junctions, Desmosomes, Gap junctions, and Integrins are complexes that mediate cell adhesion. Adhering junctions are found in most tissues and cells. Desmosomes are found primarily in cells subject to stress (e.g., cells of the skin). Gap junctions allow communication between neighboring cells. Integrins allow cell to attach to the extracellular matrix which is a set of fibers and carbohydrates outside the cell. The complexes that mediate cell adhesion all interact with components of the cytoskeleton. In addition, the proteins in the cell membrane that interact with proteins in adjacent cells or the extracellular matrix are clustered to strengthen their interactions. In addition, to provide sites of adhesion, both adhering junctions and integrins participate in signaling pathways.
Cadherins are the adhesion molecule of adhering junctions and desmosomes. Most cadherins are single transmembrane proteins that contain multiple copies of an extracellular cadherin domains. Interaction between cadherins in adjacent cells occurs through most N-terminal cadherin domain. Cadherins localize to periphery of cells and between neighboring cells and cluster where cells form initial attachments.
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Cadherins are a large family of proteins. All have a cadherin domain with variable number of repeats. Most pass membrane once but some span the membrane multiple times. There are several tissue-specific types of cadherins:

- E-cadherin -> epithelia.
- N-cadherin -> neural tissue.
- VE-cadherin -> endothelial cells.

Each of these cadherins interact homotypically, so that E-cadherins only bind other E-cadherins. The homotypic interaction between cadherins allows cells of different types to segregate.
Cells can be sorted by types and expression level of cadherins.

This cartoon shows experimental evidence of how expression of different cadherins can separate cells. Cells expressing either E or N cadherin were mixed in culture. After a period of time, the cells segregate from each other and cluster in groups in which all cells express the same cadherin. A similar effect is seen when cells that express different amounts of the same type of cadherin are mixed. In this case, the cells that express higher amounts of cadherin cluster in the center whereas the cells expressing lower levels of cadherin remain on the outside.
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Changes in expression of cadherins leads to development of different tissues.

The differential expression of cadherins is important for separating different tissues during development. The neural tube that will develop into the spinal cord and other nervous tissue separates from the ectoderm which will give rise to the epithelia. Cells destined to become neural tube express N-cadherin to dissociate from ectoderm and start to cluster together.
Cadherin interactions are dependent on calcium.

Interaction between cadherins calcium sensitive. In the absence of calcium, cadherin domains folded over preventing interaction. Calcium causes cadherin domains to extend lengthening cadherin molecule.
Clustering of cadherins increases strength of interactions between cells.

Interactions between individual cadherins is weak. The strength of adhering junctions and desmosomes comes from clustering of cadherins in common domain. Similar to velcro.
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Links to cytoskeleton cluster cadherins in desmosomes and adhering junctions.

Most proteins in the cell membrane diffuse rapidly due to thermal energy and become evenly distributed around the cell. These electron micrographs show cadherins clustered in domains in desmosomes and adhering junctions. In both cases the cadherins are attachment to the underlying cytoskeleton. Disrupting the cytoskeleton or the linkage to the cytoskeleton causes cadherins to diffuse apart and weaken adhering junction or desmosome.
Catenins link cadherins to actin filaments in adhering junctions.

The cadherins in adhering junctions are linked to actin filaments. They don’t bind directly to actin but are linked through set of proteins, including alpha and beta catenins which bind the cytoplasmic domain of cadherins.
In desmosomes, cadherins are linked to intermediate filaments.

Cadherins in desmosomes linked via a set of proteins to intermediate filaments via set or proteins. Linkage to intermediate filaments means that desmosomes are involved in generating mechanical strength between cells.
Signaling between neighboring cells
Cell contacts regulate cell division and coordinate activities between cells.

Cell to cell contacts not only play a critical role in holding cells together in a tissue but intercellular connections also function as means of communication between cells. Cells in common tissues coordinate many of their activities (cell division, metabolism, morphology) and the intercellular connections mediate this coordination. For example, many cells will divide in culture dishes until they make contact with another cell. The cell connections cause both cells to exit from the cell cycle and remain quiescent.
Beta-catenin in adhering junctions is a transcription factor activated by Wnt signaling.

Beta-catenin links cadherins to actin but it also functions as transcription activator that can trigger cell proliferation. Cells contain two pool of beta-catenin. One is bound to cadherin that can’t activate transcription because it’s tied up at adherins junctions. The other is free in the cytosol and potentially able to enter the nucleus to activate gene transcription. In many differentiated or quiescent cells, the cytosolic pool of beta-catenin is kept low by a complex of proteins that phosphorylates beta-catenin, marking it for degradation.

The wnt signaling pathway protects beta-catenin from degradation, allowing it to accumulate in the cytosol, enter the nucleus and activate gene expression.
In differentiated cells, beta-catenin is kept in the cytosol by adhesion junctions.

In differentiated cells, the adhering junctions occupy most of the beta–catenin and the rest is degraded. Thus, there is very little free beta–catenin to activate transcription.
Loss of cell adhesion releases beta-catenin which enters the nucleus to activate transcription.

Events that disrupt cell adhesion will release beta-catenin from the adhering junctions. The increased concentration of beta-catenin in the cytosol will allow some beta-catenin to enter the nucleus.
Beta-catenin activates genes that change morphology and behavior of cell.

Beta-catenin activates genes that trigger cell division and decrease expression of genes that encode proteins involved in cell adhesion.
Mitotic cells loosen adhesion to surrounding cells.

The inverse relationship between cell adhesion and cell division can be seen in the epithelial crypts of the small intestine where cells divide to replace old cells. Cells undergoing mitosis appear to move out of the line of columnar epithelial cells. The change in cell adhesion is usually required for normal cells to divide.
Neighboring cells communicate directly through gap junctions.

Cells also communicate directly through gap junctions. Gap junctions are a collection of protein pores in the cell membrane that interconnect adjacent cells. Note in the electron micrograph that the outer leaflets of the two cell membranes appear fused at the gap junction. Looking at a gap junction end on reveals thousands of small pores.
Gap junctions allow diffusion of small molecules between neighboring cells.

The individual pores of gap junctions are size restrictive: molecules smaller than 1000 Da can freely diffuse through pores. That includes ions and most metabolites. Cells with large gap junctions have cytoplasm with common ionic composition and share metabolites and nutrients. Gap junctions allow cells to relay signals mediated by ions (e.g. calcium) or small secondary messengers. Thus, a signaling event in one cell can spread to neighboring cells, allowing cells in a common tissue to coordinate their activities.
Connexins are proteins that make up the pores in gap junctions. 6 connexins assemble in the cell membrane of one cell to form a pore that interacts with a complex of 6 connexins in neighboring cells to form a continuous channel between the two cells. Connexins are a large family of proteins some of which have been associated with diseases (e.g. connexin 26 and deafness).
Calcium causes connexin pores to shrink and prevent loss of material in damaged cells.

One problem of connecting the cytoplasm of cells is that damage to the cell membrane of one cell could affect adjacent cells. As ions and small metabolites leak out of the damaged cells, the same components could be lost in adjacent cells through gap junctions. For this reason, connexins undergo a conformational change in the presence of high concentrations of calcium. In high calcium, the pore formed by connexins closes to restrict the diffusion of material between cells.
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Cell adhesion to the extracellular matrix
Extracellular matrix contains protein fibers, proteoglycans and hyaluronon.

The extracellular matrix comprises a set of fibrous proteins (i.e. collagen), proteoglycans (proteins with sugars) and other molecules. The extracellular matrix provides mechanical strength as it can resist tensions and compression. It also regulates the availability of metabolites and signaling molecules by controlling their diffusion. Cells change their behavior based on the composition and mechanical properties of the extracellular matrix.
Extracellular matrix provides a common framework to support a group of cells.

ECM provides a common substratum for cells in one functional group to adhere to. Attachment provides mechanical strength to cells, coordinates cell behavior.
Integrins are cell surface receptors that link fibers of the extracellular matrix to the cytoskeleton.

Integrins mediate attachment of cells to the extracellular matrix. Integrins are single transmembrane proteins that form heterodimers: one alpha subunit and one beta subunit. Our genome encodes 18 alpha subunits and 8 beta subunits which can combine to form 24 different pairs. Different types of cells express different integrins. Integrins bind fibronectin and laminin in the extracellular matrix. Integrins are linked to the cytoskeleton. In most cells, integrins are linked to actin filaments.
Integrins cluster into focal adhesions that function as signaling platforms.

Integrins cluster into large macromolecular assemblies called focal adhesions each focal adhesion contains many integrins and is linked to actin filaments. Focal adhesion also function as signaling platforms. Focal adhesions appear to sense external mechanical forces and allow cells to measure the mechanical properties of the extracellular matrix.
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Integrins in cells under mechanical stress link ECM to intermediate filaments.

In cells under mechanical strain, integrins are linked to intermediate filaments in structures called hemidesmosomes.
Stiffness of ECM regulates cell survival and proliferation.

The composition and mechanical properties of the extracellular matrix affects cell behavior. If the ECM is too soft, cells can’t generate tension on their focal adhesions and can’t spread out. Instead, the cells remain round and don’t grow or divide and may undergo apoptosis. As the ECM strengthens, cells begin to spread and for stronger associations with ECM. These cells are capable of division and occasionally motility.
Take home points...

• Cadherins are receptors that link cells together at adhering junctions and desmosomes.

• Neighboring cells communicate via cadherins and gap junctions

• The extracellular matrix provides structural and metabolic support to cells

• Cells interact with components of the extracellular matrix via integrins