

Integration of Cells into Tissues

Why cells integrate to form tissues?

Cells integrate to form tissues for a reason; they need to perform specific functions, and if more than one cells are performing a same common function, they try to combine in order to do so more effectively. Imagine it like this: suppose there are 50 nerve cells in the body, all of which are separately trying to transmit impulses. Now there is one huge impulse that needs to be transmitted to a specific region, say a neuromuscular junction. If every cell tries to take that impulse down all by itself, it won't succeed, and the impulse won't be transmitted. But if all of these cells integrate into a nervous tissue, then not only will the impulse be transmitted easily, but the function of your body will also be performed with more ease.

The coordinated functioning of many types of cells within tissues, as well as of multiple specialized tissues, permits the organism as a whole to move, metabolize, reproduce, and carry out other essential activities. Despite the diversity of animal cell forms and functions, they can be grouped relatively easily in only five classes:

- a. **Epithelial tissue**
- b. **Connective tissue**
- c. **Muscular tissue**
- d. **Nervous cells**
- e. **Blood**

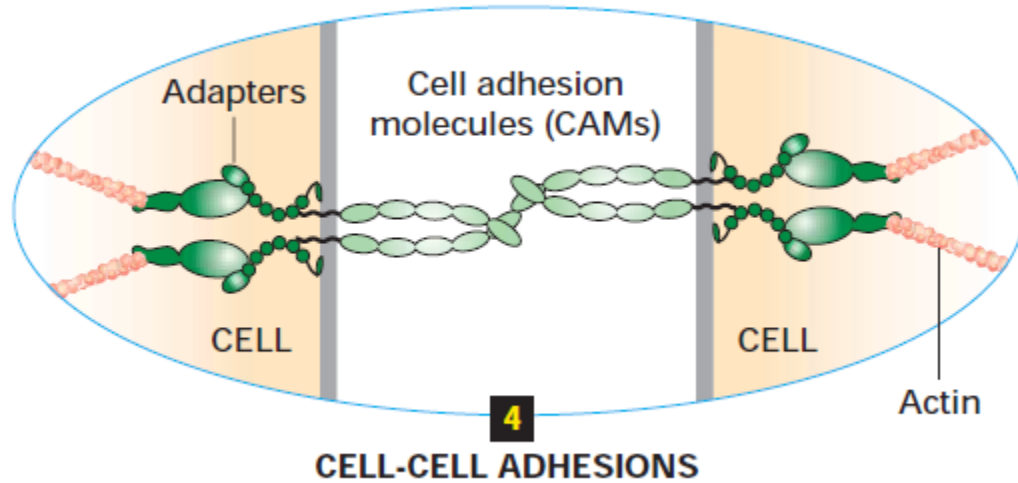
Now, without any further painstaking ado, we will move on to the main part: how cells integrate with one another to form tissues.

Cells can adhere to each other by two ways:

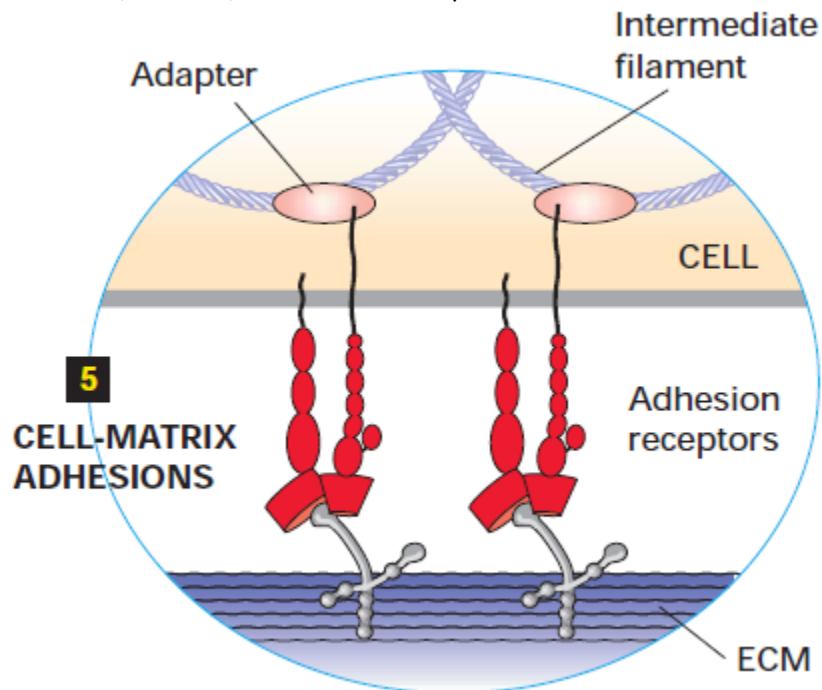
1. **Direct adhesions (also called cell-cell adhesions):** This interaction is done with the aid of special integral membrane proteins (Connect to Cell Membrane Structure in physiology) which are called **Cell-adhesion molecules (CAMs)**. Think of these like connecting fibers: there are two cells; each cell has one of these fibers, as the cells come closer the fibers bind to one another. CAMs function on the same principle but not in the same way. We will get back to them after

Integration of Cells into Tissues

some time.



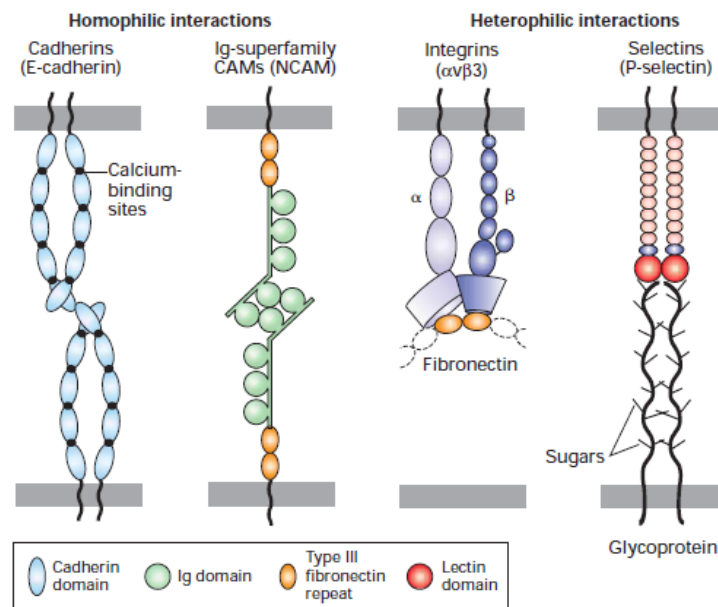
2. **Cell-Matrix Adhesions:** Remember the Extracellular matrix (ECM), the complex meshwork of proteins and polysaccharides secreted by cells? Cells have specific membrane proteins called **adhesion receptors** on the plasma membrane. These adhesion receptors (ARs) bind to the ECM. Now you might be wondering what this has to do with the integration of cells into tissues. We will get to that later on, but first, some basic concepts.



Integration of Cells into Tissues

The different types of Interactions:

- **Remember, remember** one thing. There are specific proteins that can function **both as CAMs and ERs**. These are, for instance, Integrins that bind to adhesive proteins in the ECM like fibronectin. So when we describe the families of CAMs we will also be describing families of ERs as well.
- **Homophilic Interactions:** When the CAMs on one cell, which belong to a specific family, like E-Cadherins, bind directly to exactly the same type of CAMs on the other cell, the interaction that results is called a homophilic interaction.
- **Heterophilic Interactions:** When the CAMs on one cell binds to a different class of CAMs on adjacent cells, the interactions are called heterophilic interactions.



- **Homotypic Interactions:** Up till now, we've been discussing interactions between different types of CAMs. Remember that CAM's mediate, through their intracellular domains, interactions between cells. If the cells which are interacting are of the same type, then this kind of interaction is called homotypic.
- **Heterotypic Interactions:** If the cells which interact by mediation of CAMs are of different types, this interaction is called heterotypic.
- So you see, cell-cell interactions can be:
 - Homotypic, homophilic**
 - Homotypic, heterophilic**
 - Heterotypic, homophilic**
 - Heterotypic, heterophilic**

A Brief Discussion of CAM families:

CAMs and ERs belong to a few main classes, which have been categorized as four major families (see the figure above): These are:

Integration of Cells into Tissues

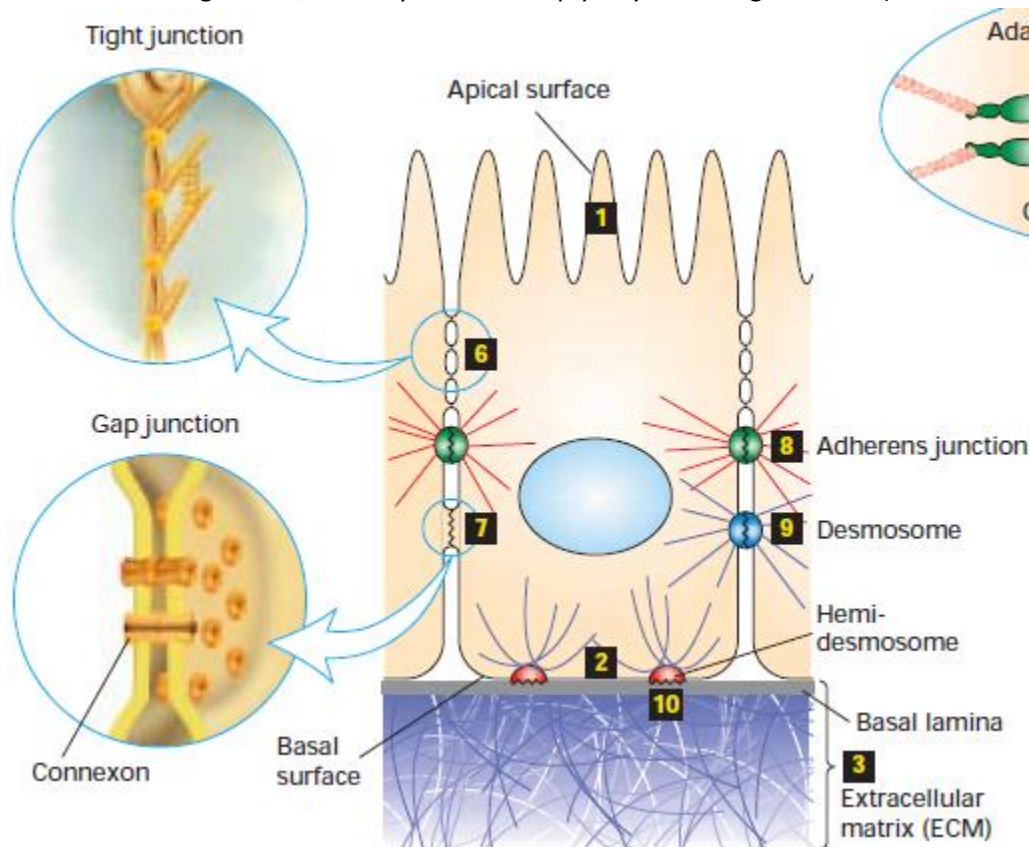
1. **Cadherins:** They are dimeric and most commonly form homophilic interactions.
2. **Immunoglobulins (Ig superfamily):** They can form both homophilic and heterophilic linkages.
3. **Integrins:** These heterodimeric proteins function as CAMs or ERs that bind to the large adhesive ECM proteins (such as fibronectins).
4. **Selectins:** They are dimeric, and have a special “lectin” domain. These domains bind to special sugar structures of glycoproteins and glycolipids in adjacent cells.

CAMs, as can be seen in the figure above, are mosaics of multiple, distinct domains. If these domains recur in the same molecule many times, they are called repeats. Some of these “repeat” domains confer binding specificity to a particular protein.

Where do CAMs occur?

CAMs:

- a. May be broadly distributed along the regions of plasma membrane that bind with other cells.
- b. May be clustered in some discrete patches called as **cell junctions** (which might be **gap junctions, adherens junctions, desmosomes or hemidesmosomes**. I can explain them here, but that would be digression, and so you must simply rely on the figure below):



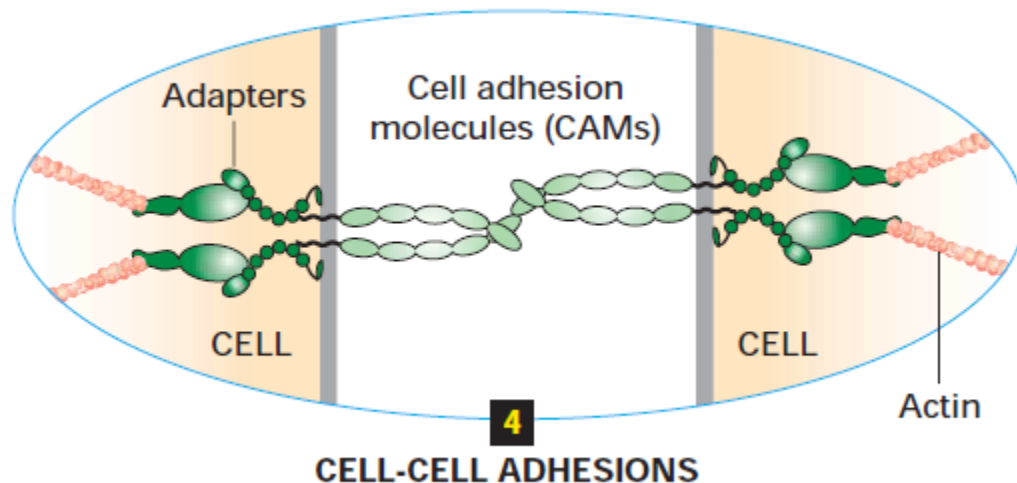
Physical Nature of Cell Adhesions:

They can be:

Integration of Cells into Tissues

1. Tight and long lasting, like the **adhesions between nerve cells**.
2. Weak and transient, like the **temporary adhesions between leukocytes** as they travel along a blood vessel to the site of infection.

Now, let us recall a figure we saw earlier:



Here you can see specific **adapter proteins** facing the cytosol of the cell. These multifunctional adapter proteins are actually “**linkers**”. They directly or indirectly connect/bind CAM to the cytoskeleton (see the actin microfilaments?). They **also “recruit” specific intracellular molecules** to function in signaling pathways that control gene expression and protein activity (didn’t I tell you they were multifunctional?).

Connectivity Leads to Communication

The CAMs that link the cells together are also connected to cytoskeletal and signaling pathways. As a result, we can say that the surrounding of a cell influence its function. This is called an **outside-in effect**.

Likewise, the cellular shape and function also effect the outer environment of the cell. This is called an **inside-out effect**.

Thus connectivity and communication inside a cell are linked.

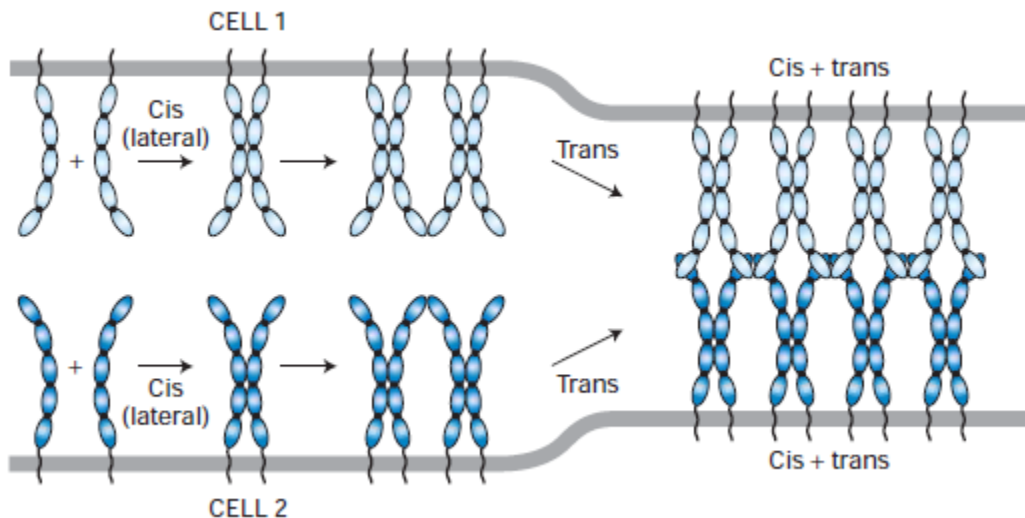
How Cell-Cell Adhesions arise?

This is simply explained, but not simply understood. Imagine the CAMs as vertical rods. Two of these rods join together side by side (laterally) to form a dimer. Now this dimer again connects laterally to another dimer to form an oligomer. This process goes on to form (by lateral bonding only) to form a large oligomer and even hexamers. Now this process (again, it is strictly laterally binding) is a **cis interaction**.

Integration of Cells into Tissues

Now suppose you have two series of rods. You put one series on top of the other. In the case of our CAM oligomers, we bind the oligomers on one cell to same or different CAM oligomers to an **adjacent cell**. This is what forms a **trans interaction**.

This can be best visualized by a figure:



Role of Extracellular Matrix in Adhesion and Other Functions:

We have already discussed the ECM in relation to adhesion. For a bigger picture let's go into some more fancy details that I'm sure you will abhor right now. Take it easy. This is life.

Okie dokie, so all of us know that there is a family of CAMs known as **integrins**. These integrins, you will recall, are heterodimeric structures that bind to the fibronectin, the multiadhesive protein in the ECM. In fact, many cells which have integrins bind in the same fashion to the ECM, and this common interaction with the ECM binds cells together. This I believe is all about it. That's all folks!

Components of ECM

Three abundant ECM components are usually seen:

1. **Proteoglycans**
2. **Collagen**
3. **Soluble Multiadhesive Matrix Proteins (simply remember good old fibronectin).**

If you want to know, you can simply remember that there are two basic forms of ECM:

1. **Basement Membrane** (you might have studied everything about it. Still.) It is ECM between epithelial and stromal layers of cells.
2. **Interstitial Matrix:** It is the ECM that forms a 3D lattice around cells.

Functions of ECM: I'll just list them here:

Integration of Cells into Tissues

- a. Provides strength in tendon, tooth or bone
- b. Provides cushioning in cartilage
- c. Provides adhesion in most tissues.

Details about ECM Components:

They are not really that much important or whatever, but you must know about them to get the bigger picture:

1. **Proteoglycans:** These have a polypeptide “backbone” to which are attached quite a lot of polysaccharide side chains. 95% of proteoglycans are polysaccharides, and unless you are a nudnik, you must have realized by now that they resemble carbohydrates more in their properties. Another way of saying what I’ve said is that proteoglycans are heavily glycosylated proteins. This isn’t very snazzy though.

The point of attachment of [GAGs \(glycosaminoglycans\)](#) to the polypeptide is a Serine (an Amino Acid) residue (That portion of an amino acid that is present in a peptide or a polypeptide). Serine is a hydrophilic AA, and unless you are very much interested in its polarity without charged side chains, I think it’s time to move on.

So what are **the functions of proteoglycans?** They help to trap and store growth factors in the ECM. They form the ground substance in the extracellular matrix of connective tissue and serve as lubricants and support elements.

Protein components of these proteoglycans are made in the ribosomes; polysaccharides are added in ER and modification follows in the Golgi complex.

What is the difference between a glycoprotein and a proteoglycan?

Well, proteoglycans, simply put, have a lot more carbohydrate (95%) than proteins. In glycoproteins, the protein portion is more and the carb portion is less (only 4%).

2. **Collagen Fibers:** They are the most abundant proteins in the ECM and make up tendons and cartilage. They have quite a lot of forms, and provide structural support. Defects in the collagen-encoding gene can lead to conditions such as **epidermolysis bullosa** (connect to basement membrane disorders). They are very much important, but you don’t need to remember all their types and blah blah etc.
3. **Multiadhesive Matrix Proteins:** Now this is some fancy stuff. You might remember the **lamina basalis** from basement membrane. You might also remember that it is made by **laminins** (proteins). These laminins in actual are multiadhesive matrix proteins found in the ECM (of which the basal lamina is a part).

Integration of Cells into Tissues

There are other matrix proteins like **fibronectin**. These connect to CAMs like integrins (remember?) and play an important role in cell-matrix adhesions. **Fun fact:** it is also called LETS protein (Large external transformation sensitive protein). It also plays a role in differentiation, growth and migration. **One important thing:** When a wound on your body gushes blood, it is the fibronectin that binds to the platelets and helps in blood clotting. So much for one protein!

So what are the Major Functions of the ECM?

You might be wondering: hey, we've already done this! But again, details must be added for the bigger picture.

ECM plays two fundamental roles we'll describe here:

1. **Cell Signaling**
2. **Intracellular Communication**

How does it perform these functions?

Well, we all basically know about fibronectin. The attachment of fibronectin to the extracellular domain (i.e. transmembrane integrins) initiates intracellular signaling pathways as well as association with the cellular cytoskeleton. The question arises: **why this happens?**

Well, this intracellular communication influences cell survival, gene transcription, cytoskeletal organization, cell motility, and cell proliferation, etc. So you see the inside out and the outside in communications we were talking about earlier really depend on a lot of interconnected pathways, in which ECM plays an important role.

ECM also plays a role in cell signaling. Now this is a bit complex (I myself had to read a journal to understand it). It isn't really important, so I won't explain it. Simply remember that ECM provides space (or spatial context, if you want it that way) for ligands (An atom, a group of atoms, or a molecule that binds to a macromolecule). It plays a role in transmission of growth factor signals. Integrins and proteoglycans are the major ECM adhesion receptors which cooperate in signaling events, determining the signaling outcomes, and thus the cell fate. There is a lot more to it that I won't explain. If you really want to understand it, follow this [link](#).

You have already read (if you haven't do it now) that integrins bind cells to ECM. In this way, integrins play an important role in transferring vital information to the cell "biomachinery" of the state of the ECM. This signaling has been found to control vital functions.

[It must be absolutely clear at this stage that cell adhesion is not a simple signaling event determined by binding of integrin to its ligand, but instead a complex interplay between the biochemical signals of integrins and structural changes associated with cell spreading. The University of Pennsylvania's Chen Lab is investigating how cell shape changes effect at the molecular level.]

Intracellular Communication: An overview

If you possess a copy of the book "Guyton's Physiology", skip a lot of pages to pp. 881, and you will see a lot of fancy names like autocrines, paracrines, cytokines etc. Now all of these play a role in intracellular communication, but you are not supposed to learn all of them. In fact, you simply need to be able to differentiate between them. For this, here's a tip: stick to the roots of names. For example, auto means "self", juxta denotes "adjacent", endo means "within etc".

Integration of Cells into Tissues

So! Here we go *drumroll*. Presenting, ladies and gentlemen, what happens in your body all the time!

- **Autocrines:** These are cell produced substances that have effect on the cells that produce them. (جس تہالی میں کھایا اسی میں چھیدک یا)
- **Paracrines:** These are signals or hormones that are localized i.e. they function only in the vicinity of the gland that secretes them.
- **Endocrines:** These you already know about. Period.
- **Juxtacrines:** In these, the signal producing cell is adjacent to the cell that has the receptor for the signals. Much like a person sharing a hematoxylin pencil only with an adjacent feller who needs that specific type of pencil. (they must be med students).

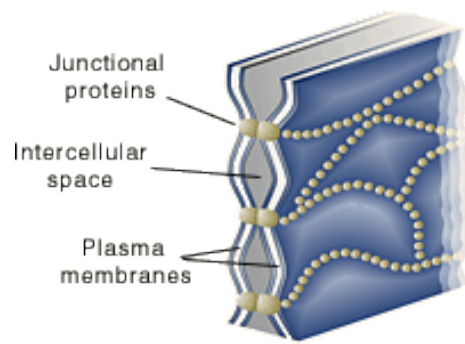
Cells Communicate by Cell Junctions:

Finally an interesting thing. As far as our original topic goes, cell junctions are not really required to be understood at all. But since we need to study them in histology as well as physiology, so I'll give a somewhat detailed overview of them here:

We will discuss only animal cells here.
Plants have plasmodesmata by thousands that bridge cells together, but we will not discuss them.

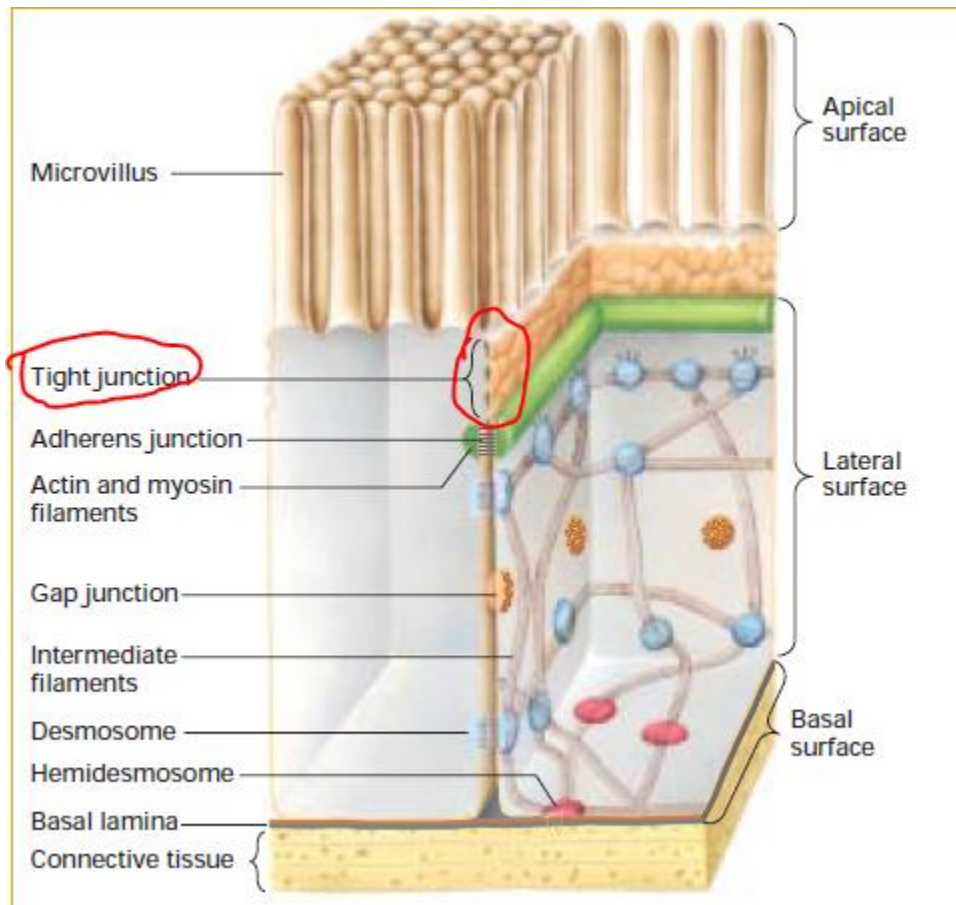
1. **Anchoring Junctions:** As their name suggests, they anchor cells together in a tissue. They have three components:
 - a. **Adhesive proteins (like CAMs and ARs)**
 - b. **Adapter Proteins: actin filaments that connects CAMs to cytoskeletal filaments**
 - c. **Cytoskeletal filaments themselves**
2. **Tight Junctions:** They control the flow of solutes between cells. They are nearly impermeable and prevent most molecules from passing into the intercellular space. To get past them, you would have to perform quite a lot of complicated steps {I shouldn't wonder} Major types of proteins in them include the claudins and the occludins (don't remember these names!).

Tight Junctions



Integration of Cells into Tissues

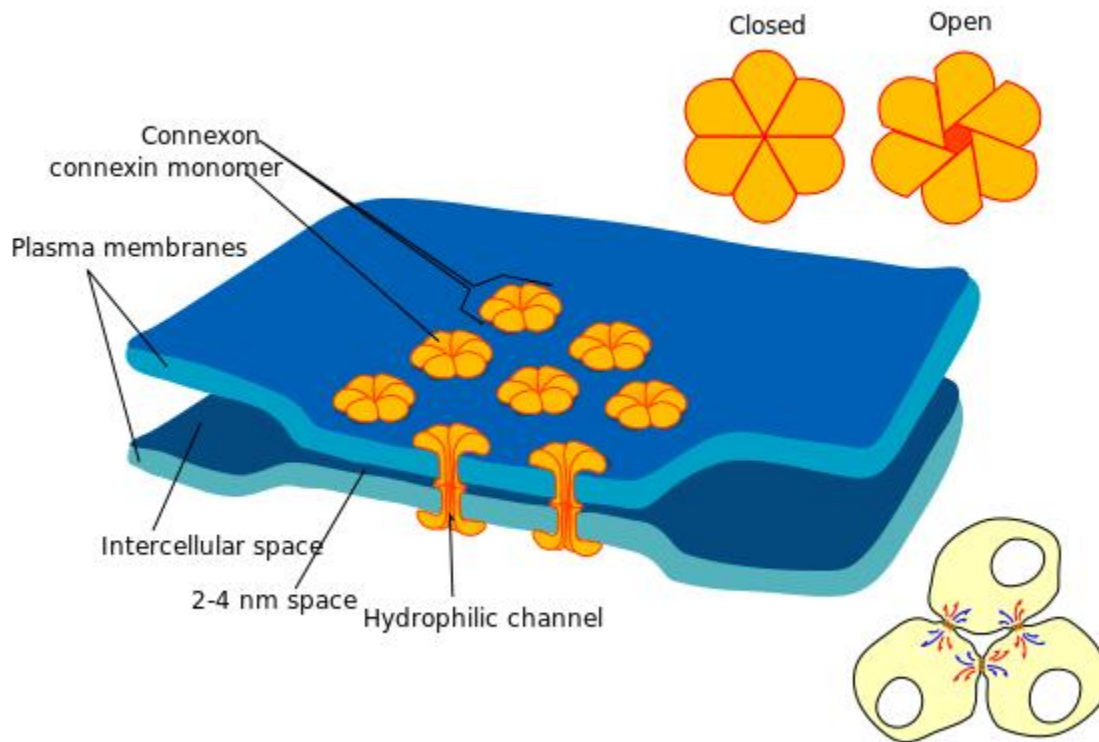
Where are they found? They are found in the apical region around the cell's circumference. To visualize that, see this:



A defining feature of tight junctions is that they are found only in epithelial cells.

3. **Gap Junctions:** You must have seen gap junctions in the above diagram. Briefly speaking, then, these junctions are like tiny gaps (not actually), regulated by Ca^{+2} ions concentration, that allow diffusion of small water soluble molecules between adjacent cells. See this:

Integration of Cells into Tissues



There are connexons between the two cell membranes that allow transport of materials (a connexon is made of an assembly of 6 connexin proteins. 2 connexons form one complete gap junction). When the connexons are open, they allow transport of substances, when closed, they disallow. This is simple, and if you don't find it so, simply put your head in a pool of freezing water. That's it. Feeling better?

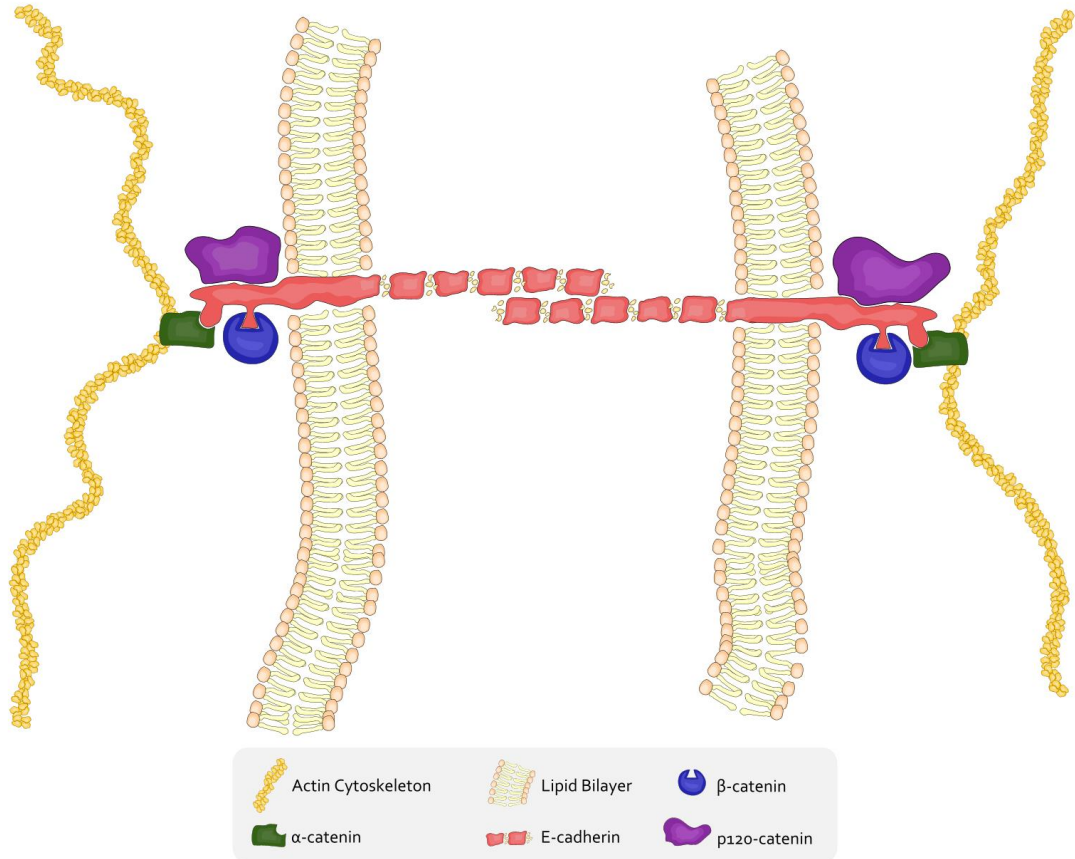
Gap junctions (as you might have judged if you emerged sound from the pool) are analogous to **plasmodesmata** in plant cells.

4. **Adherens Junctions:** There are, as you know already, actin filaments which are part of the cytoskeleton. Imagine two cells, lying adjacent to each other, each with the cytoskeleton inside the confines of the plasma membrane. What they need to connect is a bridge. Adherens junctions provide just that sort of bridge.

Adherens junctions are important when it comes to connecting cytoskeletons of adjacent cells.

Integration of Cells into Tissues

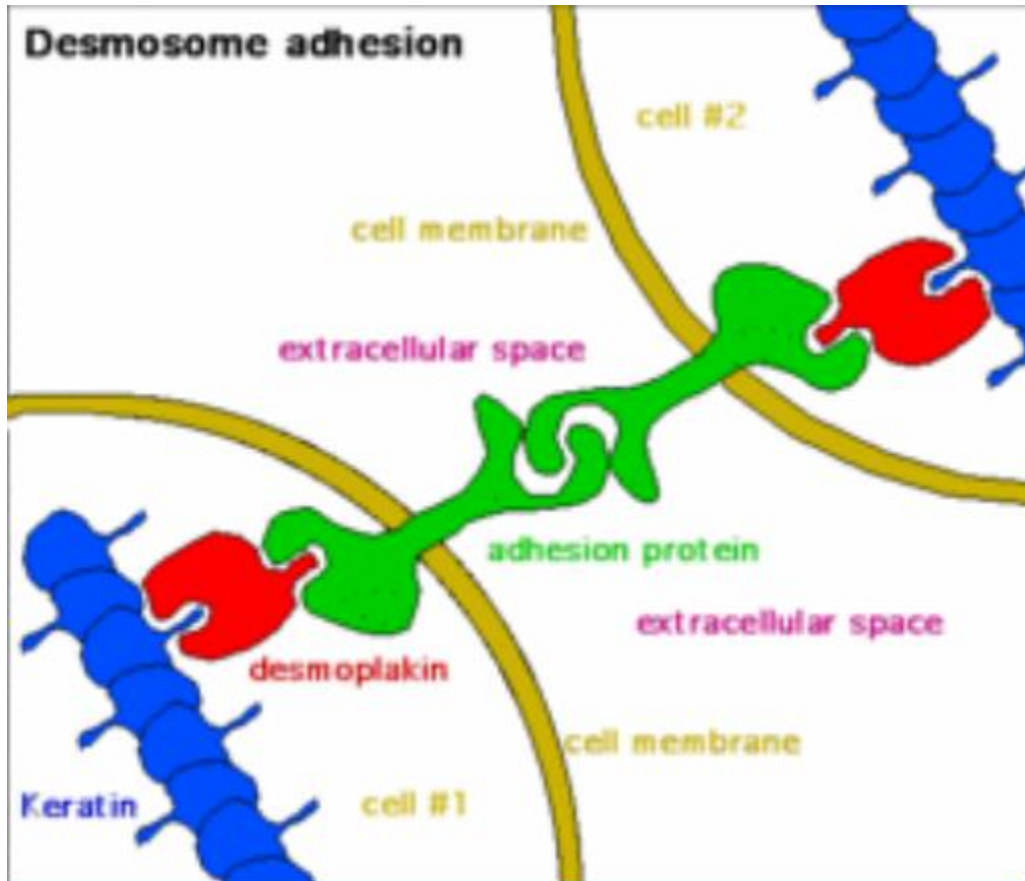
How they do this is visualized in the figure:



Their position is directly (not so much!) below the tight junctions in epithelial cells.

Integration of Cells into Tissues

5. **Desmosomes:** To follow these, consider:



So desmosomes are actually complexes. They are complexes of adhesion proteins and linking proteins (like the **desmoplakin** you see here) that bind adhesion proteins (like CAMs) to intracellular keratin cytoskeletal filaments. In this way, they resist shearing forces (forces that pull two parts of the body in opposite directions). They are, thus, found in heart and muscle cells. Mutations in specific genes can lead to desmosomal structural faults that lead to heart problems like Arrhythmogenic right ventricular cardiomyopathy ([ARVC](#)).

6. **Hemidesmosomes:** They appear very much like desmosomes. They connect one cell to the ECM, unlike desmosomes that link two cells together. You can think of them as nails that hold down carpets in halls such as our beloved Old Auditorium.

That's all, I believe, that is to be said about this topic. We have said much and learnt much, and I hope it helps us and future generations from despairing following some clueless lectures. Adieu!

