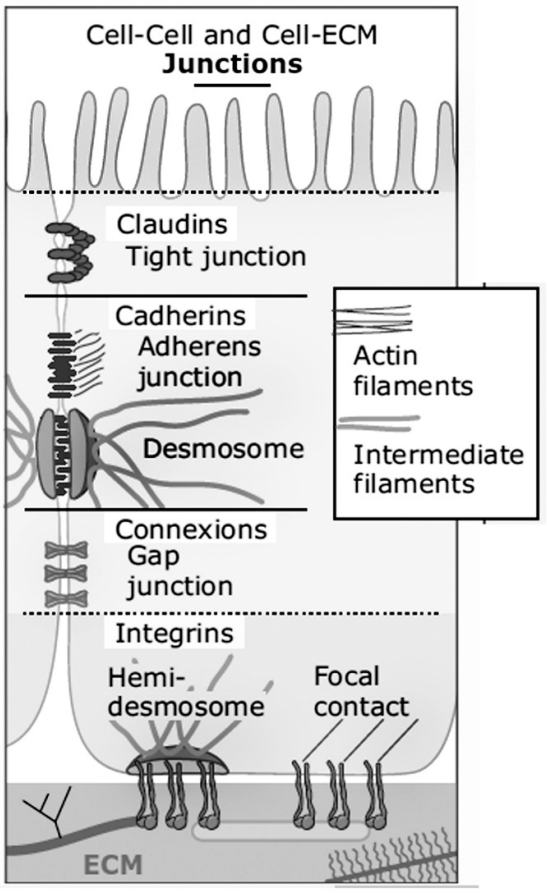
Cell-cell junctions

- A cell junction (or intercellular bridge) is a type of structure that exists within the tissue of some multicellular organisms, such as animals.
- Cell junctions consist of multi-protein complexes that provide contact between neighboring cells or between a cell and with the extracellular matrix.
  Types of Adhesion
  - Cell-cell.
  - Cell-extracellular matrix.
- Cell-cell junctions link cells to each other in tissues and regulate tissue homeostasis in critical cell processes that include tissue barrier function, cell proliferation and migration. Defects in cell-cell junctions give rise to a wide range of tissue abnormalities that disrupt homeostasis and are common in genetic abnormalities and cancers.
- Cell junction is a common feature of epithelial cells.
- During metazoan evolution, cell junctions allow multicellular organisms to form tissue compartments with distinct ionic compositions by limiting the permeability of their constituents across epithelial barriers.

Outline of various types of junctional proteins and junctions



Tight junctions link cells very closely forming a barrier that prevents the passage of molecules and ions between cells. They also prevent the movement of integral membrane proteins within the cell membrane. Hence, they are important in maintaining, for example, the polarity of the epithelial cells.

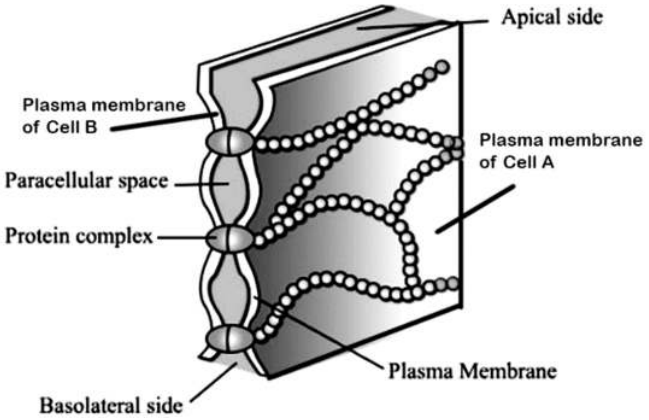
Gap junctions are a type of specialized cell junction that allows intercellular communication. In the smooth muscle of the intestine, which must contract in a coordinated manner for peristalsis to occur, the smooth muscle cells have gap junctions, which allow transmission of molecules and electrical signals between the adjacent smooth muscle cells.

Adherens junctions link the actin cytoskeleton of adjacent cells together, often forming a belt-like arrangement around each of the cells in an epithelial sheet. The link occurs via transmembrane proteins known as cadherins, and intracellular proteins that link cadherins to the cytoskeleton.

Anchoring junctions (called **desmosomes**) link adjacent cells together, while hemidesmosomes link cells to the extracellular matrix. Again, these links occur via cadherins. In this case, however, the link is to intermediate filaments of the cytoskeleton rather than actin filaments.

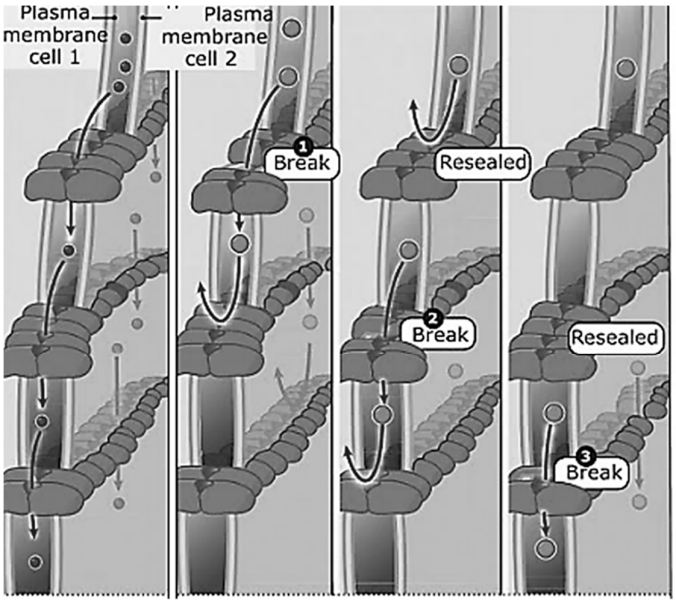
Tight junction

- Tight junctions are part of the junctional complex that forms **between adjacent epithelial cells or endothelial cells.**
- Tight junctions (TJ) **regulate transport** of particles between epithelial cells.
- Tight junctions also **preserve epithelial cell polarity** by serving as a "fence" that **prevents diffusion of plasma membrane proteins between the apical and basal regions.**
- The Tight Junction is located at the **apex of the lateral plasma membranes** between adhering cells.
- The TJ encircles each cell, **forming a proteinaceous seal** that regulates the diffusion of ions and solutes between cells (the **paracellular pathway**).
- The TJ is composed of 2 families of transmembrane proteins: **claudin and occludin, which form homotypic claudin-claudin and occludin-occludin complexes between cells.**
- **Claudin and occludin bind directly to cytoplasmic adaptor proteins that in turn bind to the actin cytoskeleton. These adaptor proteins comprise a family of Zonula occludens-1 (PDZ) domain proteins (ZO-1, -2, -3), cingulin and additional proteins.**
- The claudin family of proteins are relatively small, between 20–27 kDa and show four transmembrane domains, a significantly longer first extracellular loop of ~53 amino acids, a second extracellular loop of ~24 amino acids and a short carboxyl intracellular tail.
- **The junctional adhesion molecule (JAM) proteins are immunoglobulin (Ig)-like molecules found in the TJs of epithelial and endothelial cells.** Their extracellular domains mediate cell–cell adhesion. Their cytosolic regions in turn associate with a set of adaptor molecules including ZO-1, ZO-2 and ZO-3, forming a link to the F-actin cell cytoskeleton.



Model of fast and slow transport of solutes through tight junctions

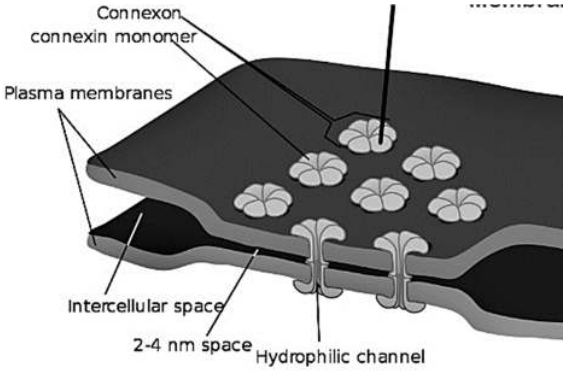
Tight junction permeability barriers are composed of rows of charge-selective pores that form the web of fragile strands. Cataions (small) pass through spaces between claudins. **Fast transport (continuous)** of some ions occurs through ion channels embedded within the fibrous strands of the junction. Larger molecules pass through the breaks in the tight junctions. **Slow transport (stepwise)** of the solutes that cannot pass through channels occurs when the strands break, allowing these solutes to flow through the breaks. Because there are many layers of strands, this form of transport occurs in stages.

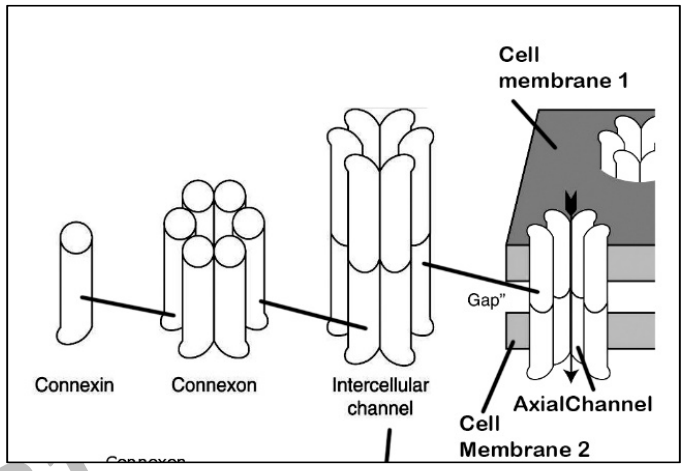


Function

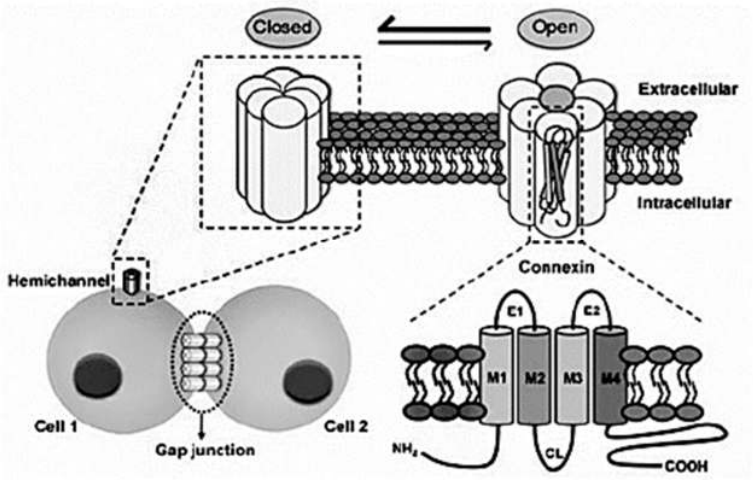
1. They **hold cells together**.
2. **Barrier function**: Functions as protective barriers and functional barriers serving purposes such as material transport and maintenance of osmotic balance.
3. **Polarity of cells**: Tight junctions help to maintain the polarity of cells by preventing the lateral diffusion of integral membrane proteins between the apical and lateral/basal surfaces, allowing the specialized functions of each surface (for example receptor-mediated endocytosis at the apical surface and exocytosis at the basolateral surface) to be preserved. This aims to preserve the transcellular transport.
4. **Tight junctions prevent the passage of molecules and ions through the space between plasma membranes of adjacent cells**, so materials must actually enter the cells (by diffusion or active transport) in order to pass through the tissue.
5. **Paracellular transport across the tight junction:** TJs functions as a "molecular sieve" through which extracellular molecules are filtered as they cross epithelial and endothelial boundaries. the cutoff size for free diffusion across tight junction ranges between approximately 4 and 40 Å, depending on the tissue in which they are found. tight junction permeability barrier is composed of rows of charge-selective pores that form the web of fragile strands. Ions are transported through the pores, but other solutes must wait until the strands break before they can move through the junction. As the strands break and reseal, the solutes move stepwise through the barrier

Gap junctions

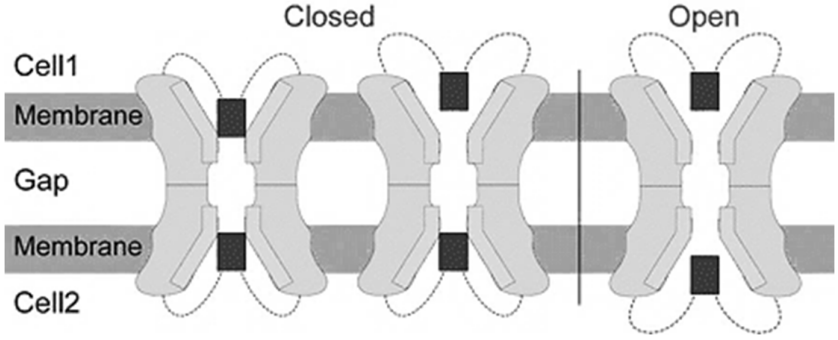




- Gap junctions are aggregates of **intercellular channels that permit direct cell–cell transfer of ions and small molecules.** Initially described as low-resistance ion **pathways joining excitable cells (nerve and muscle),** gap junctions are found joining virtually all cells in solid tissues.
- Gap junctions are clusters of intercellular channels that **allow direct diffusion of ions and small molecules between adjacent cells.**
- Six proteins called the **connexins (Cx) forms a hexameric structure (Connexon or hemichannel) with a hydrophilic channel inside.**
- **Connexin α-helixes span the membrane four times,** with a single cytoplasmic loop and two extracellular loops, and have their amino and carboxy terminals (CTs) inside the cell.



- The intercellular channels are formed by **head-to-head attachment of those hexameric structures in adjacent cells.**
- The **connexin complexes docks closely leaving a narrow ∼2 nm extracellular "gap" between the adjacent plasma membranes. For this gap the junction are called Gap junctions.**
- It is hypothesized that gap junctions can be **regulated by plug gating or channel gating** as seen in Connexin 26 in human. The gap junction is open only when the plugs in both hemichannels are displaced from the channel constriction



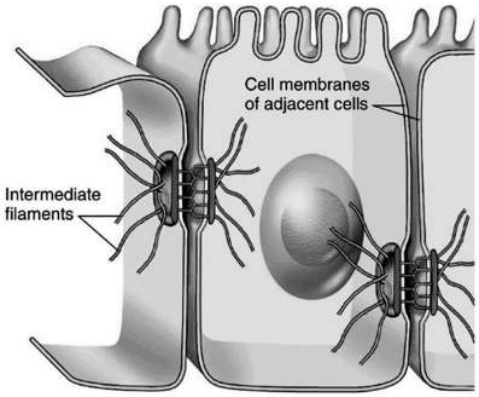
formed by the innermost helices toward the cytoplasmic side. Channel gating controlled by protein kinases that phosphorylate connexin subunits, change the intracellular pH and alterations in intracellular calcium concentration.

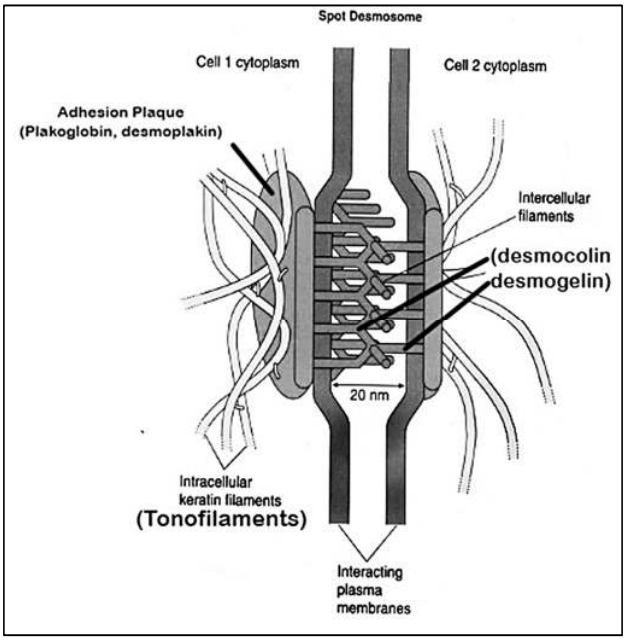
- **Hemichannels**
  Hexameric high-conductance plasma membrane channels made by same connexins that are normally closed and can act as a conduit to release paracrine signaling molecules such as ATP, NAD^+, glutamate, and prostaglandins when opened.

Function

1. Facilitate the **direct transfer of ions and small molecules** between adjacent cells.
2. Gap junctions allow **free diffusion of molecules 1,200 Da in size and exclude passage of molecules 2,000 Da in size. i.e: ions, salts, amino acids, sugars and other solute within MW 1000 Da can pass through.**
3. Gap junctions can be **found at the "electrical synapses": gap junctions between pre- and postsynaptic membranes permit current to flow passively through intercellular channels.**
4. Gap junctions allow nearly instantaneous exchange of ions, and it helps in carefully controlled timing of contraction by heart muscle fibers is mediated by rapid exchange of ions as well.

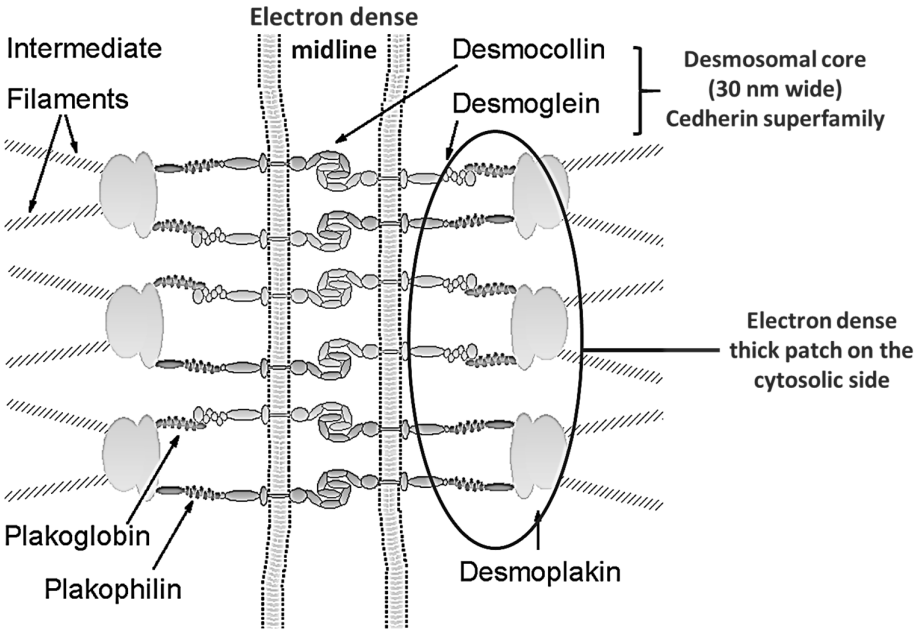
Anchoring junction





Desmosome/ macula adherens

- Desmosomes are one of four intercellular junctions present on the **lateral side of neighboring polarized epithelial cells.**
- Desmosomes are found subjacent to the adherens Junctions and are more widely distributed along the lateral membranes.
- **Desmosomes appear as multi-layered, bilaterally symmetrical structures featuring a pair of electron-dense plaques that sandwich an extracellular region of ∼20 nm in width. This extracellular space is bisected by a central dense line (dense midline) comprising the desmosomal cadherin ectodomains.**
- The major components of desmosomes come from three protein families: **cadherins, armadillo proteins and plakins.**
- Desmosomal Cadherins are subdivided into **desmogleins 1-4 (Dsg1-Dsg4) and desmocollins 1-3 (Dsc1-Dsc3). Dsgs and Dscs** contain a series of highly conserved extracellular repeat (EC) domains, followed by a short transmembrane domain (TM**).**
- On the extracellular face of the plasma membrane, the desmosomal **cadherins** engage in calcium (Ca^{2+})-dependent adhesive interactions.
- On the cytoplasmic side, desmosomal cadherins are indirectly linked to the Intermediate Filament **(IF)** cytoskeleton via their interactions with **armadillo** and **plakin** family members.
- Desmosomal armadillo family members **include Pg (Plakoglobin) and Pkps 1-3 (Plakophilins 1,2,3).**
- **Plakoglobins and Plakophilins** binds desmosomal cadherins and the N-terminus of the Intracellular Filament-anchoring protein **desmoplakin (DP).**
- Four plakin family members have been reported to associate with desmosomes **(Desmoplakin, plectin, envoplakin and periplakin),** DP is indispensable for desmosome assembly and IF anchorage.

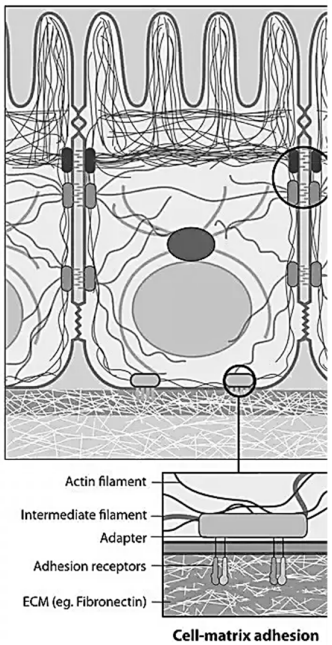


Function

1. Desmosomes are intercellular junctions of epithelia and cardiac muscle.
2. They resist mechanical stress because they adopt a strongly adhesive state in which they are said to be hyper-adhesive and which distinguishes them from other intercellular junctions.
3. Desmosomes are specialized for strong adhesion and their failure can result in diseases of the skin and heart.
4. They are also dynamic structures whose adhesiveness can switch between high and low states during processes such as embryonic development and wound healing, the switching being signaled by protein kinase C.
5. Desmosomes may also act as signaling centers, regulating the availability of signaling molecules and thereby participating in fundamental processes such as cell proliferation, differentiation and morphogenesis.

Note: Hemidesmosome (HD)

- Hemidesmosomes are multiprotein complexes that facilitate the stable adhesion of **basal epithelial cells to the underlying basement membrane.**
- The mechanical stability of hemidesmosomes relies on multiple interactions of a few protein components that form a membrane-embedded tightly-ordered complex.
- The major adhesion molecule of hemidesmosomes is α6β4 integrin. Also present is a type II membrane protein (NH2-terminal cytoplasmic, COOH-terminal extracellular) called BP180. (BP represents bullous pemphigoid, an autoimmune blistering disorder in which the autoantibodies target this 180-kDa protein.)
- Within the plaque, two molecules are involved in linking to cytokeratin, BP230 and plectin, both members of the plakin family and related to desmoplakin.



Cell-matrix adhesion

- Outside the membrane, the anchoring filaments appear to be composed of a member of the laminin family of ECM proteins, laminin 5, and form the substrate for α6β4 integrin binding.
- The anchoring fibrils are composed of collagen type VII, a specialized member of the collagen family.