**Topic:
 Cell adhesion**

**Definition:**

 The attachment of a cell, either to another cell or to an underlying substrate such as the extracellular matrix via cell adhesion

 This process can occur either through direct contact between cell surfaces or indirect interaction, where cells attach to surrounding extracellular matrix, a gel-like structure containing molecules released by cell into spaces between them. Cell adhesion occurs from the interactions between cell-adhesion molecules (CAMs) , transmembrane protein located on the cell surface. Cell adhesion links cell in different ways and can be involved in signal transduction for cell to detect and respond to changes in the surroundings. Other cellular processes and lead to variety of diseases including cancer and arthritis. Cell adhesion is also essential for infectious organisms, such as bacteria or viruses, to cause disease.

**General Mechanism:**

 CAMs are classified into four major families : integrins , immunoglobulin(Ig) superfamily , cadherins and selectins. Each of these adhesion molecules have different functions and recognizes different ligands.

Cadherins and immunoglobins are homophilic CAMs, as they bind to the same kind of CAMs to the other cell, while integrins and selectins are heterophilic CAMs that bind to different types of CAMs.

Defects in cell adhesion are usually attributable to defects in expression of CAMs.

In multicellular organisms, binding between CAMs allow cells to adhere to one another and creates structure called cell junction. According to their function , the cell junctions may be classified as:

* Anchoring junctions ( adherens junction, desmosomes and hemidesmosomes), which maintain cells together and strengthens contact between cells.
* Occluding junctions (tight junctions) , which seal gaps between cells through cell- cell contact, making an impermeable barrier of diffusion.
* Channel – forming junctions ( gap junctions) , which links cytoplasm of adjacent cells allowing transport of molecules to occur between cells.
* Signal – relaying junctions, which can be synapses in the nervous system.

Accordingly , cell junctions can be categorized into two main types according to what interacts with the cell , cell-cell junctions, mainly mediated by cadherins and cell-matrix junction, mainly mediated by integrins.



Fig 1 CELL ADHESION

**Cell-cell Junctions:**

Cell-cell junctions can occur in different forms. In anchoring junctions between cells such as adherens junctions and desmosomes, the main CAMs present are the cadherins. This family of CAMs are membrane proteins that mediate cell-cell adhesion through its extracellular domains and require extracellular Ca2+ ions to function correctly. Cadherens form homophilic attachement between themselves , which results in the cells of a similar type sticking together and can lead to selective cell adhesion, allowing vertebrate cell to assemble into organized tissues. Cadherins are essential for cell-cell adhesion and cell signaling in multicellular animals and can be separated into two types : classical cadherins and non-classical cadherins.

1. **Aherens junction :**

Cell junction at which anchoring proteins (cadherins or integrins ) extend through the plasma membrane and are attached to actin filaments.

They are proteins complexes occur at cell-cell junctions in epithelial and endothelial tissues, usually more basal than tight junctions. Defined as: a cell junction whose cytoplasmic face is linked to the actin cytoskeleton. They can appear as bands encircling the cell (zonula adherens) or as spots of attachment to the extracellular matrix (adhesion plaques). Adherens junctions uniquely disassemble in uterine epithelial cells to allow the blastocyst to penetrate between epithelial cells. A similar junction in non-epithelial cells is fasci adherens . it is structurally the same but appears ribbonlike patterns that do not completely encircle the cells.

They mainly maintain the shape of tissues and hold the cell together. Cadherins between the neighboring cells interacts through the extracellular domains , which share a conserved calcium sensitive region in their extracellular domains. Hence this region meets the calcium ions , extracellular domains of cadherins undergo a conformational change from the inactive flexible conformation to more rigid conformation in order to undergo homophilic binding. Intracellular domains of cadherins are also highly conserved, as they bind to proteins called catenins , forming catenin-cadherin complexes. The protein complexes link cadherins to actin filaments. This association with actin filament is essential for adherens junction of stabilize cell-cell adhesion. Interactions with actin filaments can also promote clustering cadherins, which are involved in the assembly of adherens junction. This is since cadherin clusters promotes the assembly of adherins junctions by binding to cadherins-catenin complexes that then form at the junction. 

Fig 2 -Adheren\_junction\_showing\_homophilic\_binding\_between\_cadherins

1. **Desmosomes:**

Strong cell junction involved in cell-cell adhesion

A type of junctional complex , they are localized sot like adhesion randomly arranged on the lateral side of plasma membrane . They are one of the stronger cell-cell adhesions types and are found in tissue that experience intense mechanical stress, such as cardiac muscle tissue , bladder tissue, gastrointestinal mucosa and epithelia.

They are usually structurally like adherens junctions but composed if different components. Instead of classical cadherins , non-classical cadherins such as desmogeins and desmocollins act as adhesion molecules and they are linked to intermediate filaments instead of actin filaments. No catenin is present in desmosomes as intracellular domains of desmosomal cadherins interact with desmosomal plaque proteins, which forms the thick cytoplasmic plaques in the desmosomes and link cadherins to intermediate filaments. Desmosomes provide strength and resistance to mechanical stress by unloading forces onto the flexible but resilient intermediate filament, something that cannot occur with the rigid actin filaments. This makes desmosomes important in tissues that encounter high levels of mechanical stress , such as heart muscles and epithelia.

1. **Tight junction:**

Tight junctions are (also known as occluding junctions) are multiprotein junctional complexes whose general function is to prevent leakage of transported solutes and water seals the paracellular pathway. Tight junctions may also serve as leaky pathways by forming selective channels from small cations , anions or water. Tight junctions are present mostly in vertebrates. The corresponding junctions that occur in invertebrates are separate junctions.

**Functions :**

They perform vital functions:

* They hold cells together.
* Barrier function , which can be further subdivided into protective barriers and functional barriers serving purpose such as material transport and maintenance of osmotic balance:
* Tight junctions help to maintain polarity of the cell by preventing the lateral diffusion of integral membrane proteins between the apical and lateral surface, 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. The aims to preserve the transcellular transport.
* Tight junctions prevent the passage of molecules and ions through the space between plasma membrane of adjacent cells, so materials must enter the cells ( by diffusion or active transport) in order to pass through the tissue. Investigation using freeze-fracture methods in electron microscopy is deal for revealing the lateral extent of light junctions in cell membranes and has been useful in showing how tight junctions are formed. The constrained intracellular pathway exacted by the tight junction barrier system allows precise control over which substances can passthrough tissues. (tight junction plays this role in maintaining the blood-brain barrier) at the present time, it is still unclear whether the control is active or passive and how these pathways are formed. In one study for paracellular transport across the tight junction in kidney proximal tubule , a dual pathway model is proposed; large slit breaks formed by infrequent discontinuities in the TJ complex and numerous small circular pores.
1. **Gap junctions:**

Cell-cell junction composed of two different families of channel-forming proteins.

It is a specialized intercellular connection between a multitude of animal cell types. They directly connect the cytoplasm of two cells , which allows various molecules , ions and electrical impulses to directly pass through the regulated gate between cells. One gap junction composed of two connexons ( or hemichannels) which connect across the intercellular space. Gap junctions are analogous to plasmodesmata that join plant cell.

Gap junctions occur in virtually all tissues of the body ,with the exception of fully developed skeletal muscle and mobile cell types such as sperms or erythrocytes. Gap junctions are however not found in simpler organisms such as sponges and slime molds.

**Functions :**

Gap junctions are composed of channels called connexons, which consist of transmembrane proteins called connexins clustered in groups of six. Connexons are from adjacent cells form continuous channels when they come in contact and align with each other. These ions allow transport of ions and small molecules between cytoplasm of two adjacent cells , apart from holding cells together and provide structural stability like anchoring junctions. Gap junctions’ channels are selectively permeable to specific ions depending on which connexins form the connexons, which allows gap junctions to be involved in cell signaling cascades. Channels can respond to many different stimuli and are regulated dynamically either by rapid mechanisms , such as voltage gating or by slow mechanism such as altering number of channels present in gap junctions.



Fig 3 Gap\_cell\_junction

1. **Adhesion mediated by selectins:**

Transmembrane proteins which are lectin-like domain, an epidermal growth factor like domain , and a variable number of domains homologous to complement regulatory proteins.

They are family of adhesion molecules. All selectins are single chain transmembrane glycoproteins that share similar properties to C-type lectins due to a related amino terminus and calcium dependent binding. They bind to sugar moieties and so are a type of lectin, cell adhesion proteins that binds to sugar polymers.

**Functions:**

They mainly mediate the movement of white blood cells in blood stream by allowing the white blood cells to roll on endothelial cells through reversible binding of selectins. They undergo heterophilic bindings , as its extracellular domain binds to carbohydrates on adjacent cells instead of other selectins , while it also requires cells instead of other selectins , while it also require Ca2+ ions to function same as cadherins . cell-cell adhesion of leukocytes to endothelial cells is important for immune responses as leukocytes can travel to sites off infection or injury through this mechanism. At these sites, integrins on the rolling white blood cells are activated and bind firmly to the local endothelial cells, allowing the leucocytes to stop migrating and move across the endothelial barrier.



Fig 4 Pselectin

1. **Adhesion mediated by members of immunoglobin superfamily** :

Large super family of cell surface and soluble proteins superfamily of cell surface and soluble proteins that are involved in the recognition, binding or adhesion processes of cells

Molecules are categorized as members of this superfamily based on shared structural features with immunoglobins ( also known as antibodies). They all possess a domain known as an immunoglobulin domain member of IgSF include cell surface antigen receptors, co-receptors and co-stimulatory molecules of the immune system , molecules involved in antigen presentation to lymphocytes , cell-adhesion molecules. Certain cytokine receptors and intracellular muscle proteins. They are commonly associated with roles in the immune system .

**Functions:**

The immunoglobulin superfamily (IgSF) is one of the largest superfamily of proteins in the body and it contains many diverse CAMs involved in different functions. These transmembrane proteins have one or more [immunoglobulin-like domains](https://en.wikipedia.org/wiki/Immunoglobulin_domain) in their extracellular domains and undergo calcium-independent binding with ligands on adjacent cells. Some IgSF CAMs, such as [neural cell adhesion molecules](https://en.wikipedia.org/wiki/Neural_cell_adhesion_molecules) (NCAMs), can perform homophilic binding while others, such as [intercellular cell adhesion molecules](https://en.wikipedia.org/wiki/Intercellular_adhesion_molecule) (ICAMs) or [vascular cell adhesion molecules](https://en.wikipedia.org/wiki/VCAM-1) (VCAMs) undergo heterophilic binding with molecules like carbohydrates or integrins. Both ICAMs and VCAMs are expressed on vascular endothelial cells and they interact with integrins on the leukocytes to assist leukocyte attachment and its movement across the endothelial barrier.

1. **Cell-matrix junction :**

Cell junctions (or intercellular bridges) are a class of cellular structures consisting of [multiprotein complexes](https://en.wikipedia.org/wiki/Multiprotein_complexes) that provide contact or adhesion between neighboring [cells](https://en.wikipedia.org/wiki/Cell_%28biology%29) or between a cell and the [extracellular matrix](https://en.wikipedia.org/wiki/Extracellular_matrix) in animals. They also maintain the paracellular barrier of [epithelia](https://en.wikipedia.org/wiki/Epithelia) and control [paracellular transport](https://en.wikipedia.org/wiki/Paracellular_transport). Cell junctions are especially abundant in epithelial tissues. Combined with [cell adhesion molecules](https://en.wikipedia.org/wiki/Cell_adhesion_molecule) and [extracellular matrix](https://en.wikipedia.org/wiki/Extracellular_matrix), cell junctions help hold [animal cells](https://en.wikipedia.org/wiki/Animal_cells) together.

Cell junctions are also especially important in enabling communication between neighboring cells via specialized protein complexes called [communicating (gap) junctions](https://en.wikipedia.org/wiki/Gap_junction). Cell junctions are also important in reducing stress placed upon cells.

In plants, similar communication channels are known as [plasmodesmata](https://en.wikipedia.org/wiki/Plasmodesma), and in [fungi](https://en.wikipedia.org/wiki/Fungus) they are called [septal pores](https://en.wikipedia.org/wiki/Septal_pores)

Cells creates extracellular matrix by releasing molecules into its surrounding extracellular space. Cells have specific CAMs that will bind to molecules in the extracellular matrix and link the matrix to the intracellular [cytoskeleton](https://en.wikipedia.org/wiki/Cytoskeleton). Extracellular matrix can act as a support when organizing cells into tissues and can also be involved in cell signaling by activating intracellular pathways when bound to the CAMs. Cell–matrix junctions are mainly mediated by integrins, which also clusters like cadherins to form firm adhesions. Integrins are transmembrane heterodimers formed by different α and β subunits, both subunits with different domain structures. Integrins can signal in both directions: inside-out signaling, intracellular signals modifying the intracellular domains, can regulate affinity of integrins for their ligands, while outside-in signaling, extracellular ligands binding to extracellular domains, can induce conformational changes in integrins and initiate signaling cascades. Extracellular domains of integrins can bind to different ligands through heterophilic binding while intracellular domains can either be linked to intermediate filaments, forming hemidesmosomes, or to actin filaments, forming [focal adhesions](https://en.wikipedia.org/wiki/Focal_adhesions).



Fig 5 -Cellular\_tight\_junction

1. **Hemidesmosomes:**

Hemidesmosomes are very small stud-like structures found in [keratinocytes](https://en.wikipedia.org/wiki/Keratinocyte) of the [epidermis](https://en.wikipedia.org/wiki/Epidermis_%28skin%29) of skin that attach to the [extracellular matrix](https://en.wikipedia.org/wiki/Extracellular_matrix). They are similar in form to [desmosomes](https://en.wikipedia.org/wiki/Desmosome) when visualized by [electron microscopy](https://en.wikipedia.org/wiki/Electron_microscope), however, desmosomes attach to adjacent cells. Hemidesmosomes are also comparable to focal adhesions, as they both attach cells to the extracellular matrix. Instead of [desmogleins](https://en.wikipedia.org/wiki/Desmoglein) and [desmocollins](https://en.wikipedia.org/wiki/Desmocollin) in the extracellular space, hemidesmosomes utilize [integrins](https://en.wikipedia.org/wiki/Integrin). Hemidesmosomes are found in epithelial cells connecting the basal epithelial cells to the [lamina lucida](https://en.wikipedia.org/wiki/Lamina_lucida), which is part of the [basal lamina](https://en.wikipedia.org/wiki/Basal_lamina). Hemidesmosomes are also involved in signaling pathways, such as [keratinocyte](https://en.wikipedia.org/wiki/Keratinocyte) migration or [carcinoma](https://en.wikipedia.org/wiki/Carcinoma) cell intrusion.

In hemidesmosomes, integrins attach to extracellular matrix proteins called [laminins](https://en.wikipedia.org/wiki/Laminins) in the [basal lamina](https://en.wikipedia.org/wiki/Basal_lamina), which is the extracellular matrix secreted by epithelial cells. Integrins link extracellular matrix to [keratin](https://en.wikipedia.org/wiki/Keratin) intermediate filaments, which interacts with intracellular domain of integrins via adapter proteins such as [plectins](https://en.wikipedia.org/wiki/Plectin) and BP230. Hemidesmosomes are important in maintaining structural stability of epithelial cells by anchoring them together indirectly through the extracellular matrix.



Fig 6 -Hemidesmosomes\_showing\_interaction\_between\_integrins\_and\_laminin

1. **Focal adhesions**

In [cell biology](https://en.wikipedia.org/wiki/Cell_biology), focal adhesions (also cell–matrix adhesions or FAs) are large [macromolecular assemblies](https://en.wikipedia.org/wiki/Macromolecular_assemblies) through which mechanical force and regulatory signals are transmitted between the [extracellular matrix](https://en.wikipedia.org/wiki/Extracellular_matrix) (ECM) and an interacting cell. More precisely, focal adhesions are the sub-cellular structures that mediate the regulatory effects (i.e., signaling events) of a cell in response to ECM adhesion.

Focal adhesions serve as the mechanical linkages to the ECM, and as a biochemical signaling hub to concentrate and direct numerous signaling proteins at sites of [integrin](https://en.wikipedia.org/wiki/Integrin) binding and clustering.

Focal adhesions are integrin-containing, multi-protein structures that form mechanical links between intracellular actin bundles and the extracellular substrate in many cell types. Focal adhesions are large, dynamic [protein complexes](https://en.wikipedia.org/wiki/Protein_complexes) through which the [cytoskeleton](https://en.wikipedia.org/wiki/Cytoskeleton) of a cell connects to the ECM. They are limited to clearly defined ranges of the cell, at which the plasma membrane closes to within 15 nm of the ECM substrate. Focal adhesions are in a state of constant flux: proteins associate and disassociate with it continually as signals are transmitted to other parts of the cell, relating to anything from [cell motility](https://en.wikipedia.org/wiki/Cell_motility) to [cell cycle](https://en.wikipedia.org/wiki/Cell_cycle). Focal adhesions can contain over 100 different proteins, which suggests a considerable functional diversity. More than anchoring the cell, they function as signal carriers (sensors), which inform the cell about the condition of the ECM and thus affect their behavior. In [sessile](https://en.wiktionary.org/wiki/sessile) cells, focal adhesions are quite stable under normal conditions, while in moving cells their stability is diminished: this is because in motile cells, focal adhesions are being constantly assembled and disassembled as the cell establishes new contacts at the leading edge, and breaks old contacts at the trailing edge of the cell. One example of their important role is in the [immune system](https://en.wikipedia.org/wiki/Immune_system), in which [white blood cells](https://en.wikipedia.org/wiki/White_blood_cells) migrate along the connective [endothelium](https://en.wikipedia.org/wiki/Endothelium) following cellular signals to damaged [biological tissue](https://en.wikipedia.org/wiki/Biological_tissue).

In focal adhesions, integrins attach [fibronectins](https://en.wikipedia.org/wiki/Fibronectins), a component in the extracellular matrix, to actin filaments inside cells. Adapter proteins, such as [talins](https://en.wikipedia.org/wiki/Talin_%28protein%29), [vinculins](https://en.wikipedia.org/wiki/Vinculin), [α-actinins](https://en.wikipedia.org/wiki/%CE%91-actinin) and [filamins](https://en.wikipedia.org/wiki/Filamin), form a complex at the intracellular domain of integrins and bind to actin filaments. This multi-protein complex linking integrins to actin filaments is important for assembly of signaling complexes that act as signals for cell growth and cell motility.

* **Other organisms:**
* **Eukaryotes**:

Plants cells adhere closely to each other and are connected through [plasmodesmata](https://en.wikipedia.org/wiki/Plasmodesmata), channels that cross the plant cell walls and connect cytoplasm of adjacent plant cells. Molecules that are either nutrients or signals required for growth are transported, either passively or selectively, between plant cells through plasmodesmata.

[Protozoans](https://en.wikipedia.org/wiki/Protozoans) express multiple adhesion molecules with different specificities that bind to carbohydrates located on surfaces of their host cells. cell–cell adhesion is key for pathogenic protozoans to attach and enter their host cells. An example of a pathogenic protozoan is the [malarial](https://en.wikipedia.org/wiki/Malaria) parasite ([*Plasmodium falciparum*](https://en.wikipedia.org/wiki/Plasmodium_falciparum)), which uses one adhesion molecule called the [circumsporozoite protein](https://en.wikipedia.org/wiki/Circumsporozoite_protein) to bind to liver cells and another adhesion molecule called the [merozoite surface protein](https://en.wikipedia.org/wiki/Merozoite_surface_protein) to bind [red blood cells](https://en.wikipedia.org/wiki/Red_blood_cells).

Pathogenic [fungi](https://en.wikipedia.org/wiki/Fungi) use [adhesion molecules](https://en.wikipedia.org/wiki/Fungal_adhesin) present on its cell wall to attach, either through protein-protein or protein-carbohydrate interactions, to host cells or fibronectins in the extracellular matrix.

* **Prokaryotes**:

[Prokaryotes](https://en.wikipedia.org/wiki/Prokaryote) have adhesion molecules on their cell surface termed [bacterial adhesins](https://en.wikipedia.org/wiki/Bacterial_adhesin), apart from using its [pili](https://en.wikipedia.org/wiki/Pilus) ([fimbriae](https://en.wikipedia.org/wiki/Fimbria_%28bacteriology%29)) and [flagella](https://en.wikipedia.org/wiki/Flagellum) for cell adhesion. Adhesins can recognize a variety of ligands present on the host cell surfaces and components in the extracellular matrix. These molecules also control host specificity and regulate [tropism](https://en.wikipedia.org/wiki/Tropism) (tissue- or cell-specific interactions) through their interaction with their ligands.

* **Viruses**:

[Viruses](https://en.wikipedia.org/wiki/Virus) also have adhesion molecules required for viral binding to host cells. For example, [influenza](https://en.wikipedia.org/wiki/Influenza) virus has a [hemagglutinin](https://en.wikipedia.org/wiki/Hemagglutinin) on its surface that is required for recognition of the [sugar](https://en.wikipedia.org/wiki/Sugar) [sialic acid](https://en.wikipedia.org/wiki/Sialic_acid) on host cell surface molecules. [HIV](https://en.wikipedia.org/wiki/HIV) has an adhesion molecule termed [gp120](https://en.wikipedia.org/wiki/Gp120) that binds to its ligand [CD4](https://en.wikipedia.org/wiki/CD4), which is expressed on [lymphocytes](https://en.wikipedia.org/wiki/Lymphocyte). Viruses can also target components of cell junctions to enter host cells, which is what happens when the [hepatitis C virus](https://en.wikipedia.org/wiki/Hepatitis_C_virus) targets occluding and claudins in tight junctions to enter liver cells.