CHAPTER 14

14.0 Cell Junctions, Cell Adhesion, and the Extracellular Matrix

Objectives

a) Explain how cell combine to form massive structures
b) Explain how cells assemble

Physical cellular traits

i) cells are small
ii) deformable
iii) motile objects
iv) filled with an aqueous medium
v) enclosed in a flimsy plasma membrane
vi) combine in their millions to form a structure as massive, as strong, and as strictly ordered as a horse or a tree.

Organism are formed of many types of *tissues,* in which the cells are assembled and bound together in different ways.

14.1 Extracellular matrix (ECM).

The ECM is a complex structural entity surrounding and supporting cells that are found within mammalian tissues. It is also found in plants The ECM is often referred to as the connective tissue. The ECM is composed of 3 major classes of biomolecules:

- **Structural proteins**: collagen and elastin.
- **Specialized adhesion proteins;** which are also important matrix fibrillin, fibronectin, and laminin.
- **Proteoglycans:** molecule contributing to the mechanical behavior of the tissue. These are composed of a protein core to which is attached long chains of repeating disaccharide units termed of glycosaminoglycans (GAGs) forming extremely complex high molecular weight components of the ECM

Functions of Extracellular matrix

i) forms a supporting framework.
ii) Helps in holding the cells and tissues together
iii) in animals, it provides an organized environment within which migratory cells can move and interact with one another in orderly ways.

Major types tissues in vertebrate are: ***nerve, muscle, blood, lymphoid, epithelial, and connective tissues.*** *Connective tissue has plentiful extracellular matrix and cells are sparsely distributed within it. The matrix is rich in fibrous polymers, especially collagen, and it is the matrix—rather than the cells—that bears most of the mechanical stress to which the tissue is subjected. Direct attachments between one cell and another are relatively rare.*

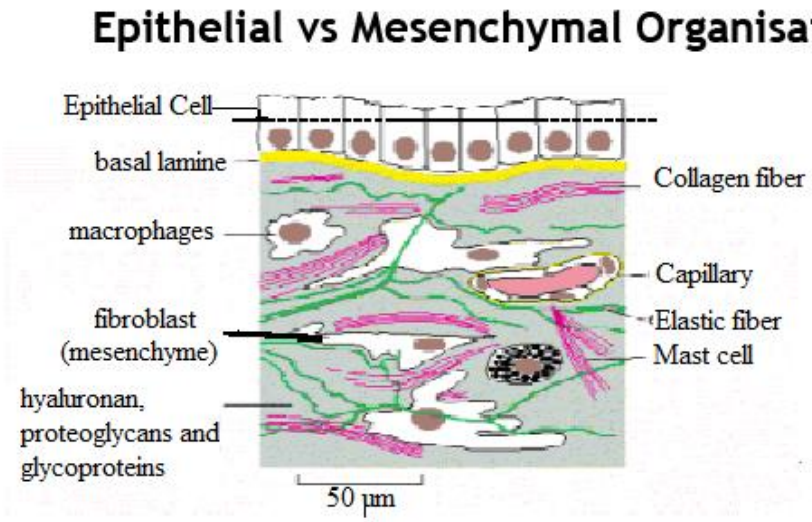


Figure. The connective tissue underlying an epithelium. This tissue contains a variety of cells and extracellular matrix components. The predominant cell type is the fibroblast, which secretes abundant

14.1.1 Collagens

Collagens is a long and thin diameter rod-like protein e.g. type I collagen is 300nm long, 1.5nm in diameter.

a) Characteristics

- Collagens are the most abundant proteins found in the animal kingdom.
- It is the major protein comprising the ECM.
- Are controlled by about **30 different collagen genes** dispersed through the human genome. Genes code for proteins that combine in a variety of ways to create over **20 different** types of collagen fibrils. Types **I, II and III** are the most abundant and form fibrils of similar structure. Type IV collagen forms a two-dimensional reticulum and is a major component of the basal lamina. Collagens are predominantly synthesized by fibroblasts but epithelial cells also synthesize these proteins.
- Lateral interactions of collagens result in the formation of **fibrils** roughly 50nm diameter. Collagens are synthesized as **longer precursor** proteins called procollagens.

- Collagen fibers begin to assemble in the ER and Golgi complexes.

- Procollagens are processed and secreted into the extracellular space where extracellular enzymes remove the pro-domains and the collagen molecules then polymerize to form collagen

fibrils. Accompanying fibril formation is the oxidation of certain lysine residues by the extracellular enzyme lysyl oxidase forming reactive aldehydes. These reactive aldehydes form specific cross-links between two chains thereby, stabilizing the staggered array of the collagens in the fibril.

b) Clinical Significance of Collagen Disorders

Collagens are the most **abundant proteins** in the body. Alterations in collagen structure resulting from abnormal genes or abnormal processing of collagen proteins results diseases like:

a) **Alport syndrome, Larsen syndrome, and numerous chondrodysplasias** as well as the more commonly known clusters of related syndromes of osteogenesis imperfecta (bone fragility) and Ehlers-Danlos syndrome (skin fragility and hyperextensibility- extension of a body party beyond its limit and joint hypermobility – excessive mobility of stomach or intestine).
b) **Marfan syndrome (MFS)** manifests itself as a disorder of the connective tissue. It results from mutations in the extracellular protein, **fibrillin**, which is an integral constituent of the non-collagenous microfibrils of the extracellular matrix. Leads to Skeletal Abnormalities e.g individuals look taller than their age, Cardiovascular Abnormalities e.g Mitral valve prolapse (MVP)
c) **Pulmonary Abnormalities e.g.** reduction in lung volume- this can lead to spontaneous pneumonia
d) **Ocular Abnormalities -** displacement of the lens from the center of the pupil (ectopia lentis)

Types of Collagen

Type	Chain Composition	Gene Symbol(s)	Structural Details	Localization
I	$[\alpha1(I)]_2[\alpha(I)]$	COL1A1, COL1A2	300nm, 67nm banded fibrils	skin, tendon, bone, etc.
II	$[\alpha1(II)]_3$	COL2A1	300nm, small 67nm fibrils	cartilage, vitreous humor
III	$[\alpha1(III)]_3$	COL3A1	300nm, small 67nm fibrils	skin, muscle, frequently with type I
IV	$[\alpha1(IV)_2[\alpha2(IV)]$	COL4A1 thru COL4A6	390nm C-term globular domain, nonfibrillar	all basal lamina
V	[α1(V)][α2(V)][α3(V)]	COL5A1, COL5A2, COL5A3	390nm N-term globular domain, small fibers	most interstitial tissue, assoc. with type I
VI	[α1(VI)][α2(VI)][α3(VI)]	COL6A1, COL6A2, COL6A3	150nm, N+C term. globular domains, microfibrils, 100nm banded fibrils	most interstitial tissue, assoc. with type I

VII	$[\alpha1(VII)]_3$	COL7A1	450nm, dimer	epithelia
VIII	$[\alpha1(VIII)]_3$	COL8A1, COL8A2		some endothelial cells
IX	[α1(IX)][α2(IX)][α3(IX)]	COL9A1, COL9A2, COL9A3	200nm, N-term. globular domain, bound proteoglycan	cartilage, assoc. with type II
X	$[\alpha1(X)]_3$	COL10A1	150nm, C-term. globular domain	hypertrophic and mineralizing cartilage
XI	[α1(XI)][α2(XI)][α3(XI)]	COL11A1, COL11A2	300nm, small fibers	cartilage
XII	α1(XII)	COL12A1		interacts with types I and III

14.1.2 Fibronectin

Composition

Fibronectins are dimers of 2 similar peptides. Each chain is 60-70nm long and 2-3nm thick. At least 20 different fibronectin chains have been identified.

Function

a) attach cells to a variety of extracellular matrices. Fibronectin attaches cells to all matrices except type IV that involves laminin as the adhesive molecule.

Fibronectins contain at least 6 tightly folded domains each with a high affinity for a different substrate such as heparan sulfate, collagen (separate domains for types I, II and III), fibrin and cell-surface receptors. The cell-surface receptor-binding domain contains a consensus amino acid sequence, **RGDS** (Arg-Gly-Asp tripeptide).

14.1.3 Laminin

All basal laminae contain a common set of proteins and GAGs (Glycosaminoglycans). These are type IV collagen, heparan sulfate proteoglycans, entactin and laminin. The basal lamina is often refered to as the type IV matrix. Each of the components of the basal lamina is synthesized by the cells that rest upon it.

Function : Laminin anchors cell surfaces to the basal lamina.

Representative matrix types produced by vertebrate cells

Collagen	Anchor	Proteoglycan	Cell-Surface Receptor	Cells
I	fibronectin	chondroitin and dermatan sulfates	integrin	fibroblasts
II	fibronectin	chondroitin sulfate	integrin	chondrocytes
III	fibronectin	heparan sulfate and heparin	integrin	quiescent hepatocytes, epithelial; assoc. fibroblasts
IV	laminin	heparan sulfate and heparin	laminin receptors	all epithelial cells, endothelial cells, regenerating hepatocytes
V	fibronectin	heparan sulfate and heparin	integrin	quiescent fibroblasts
VI	fibronectin	heparan sulfate	integrin	quiescent fibroblasts

14.2 Cell-cell junctions and cell adhesion

Cell junctions play a major row in **epithelial tissue** where cells are tightly bound together into sheets called **epithelia**. The extracellular matrix is scanty, consisting mainly of a thin mat called the ***basal lamina,*** which underlies the epithelium. The cells are attached to each other by **cell-cell adhesions**, which bear most of the mechanical stresses. For this purpose, strong intracellular protein filaments (components of the cytoskeleton) cross the cytoplasm of each epithelial cell and attach to specialized junctions in the plasma membrane. The junctions, in turn, tie the surfaces of adjacent cells either to each other or to the underlying basal lamina. In animals especially, the cells of most tissues are bound directly to one another by *cell-cell junctions.*

i) provide mechanical attachment
ii) bear mechanical stress
iii) maintain cells together to form the body (with cell junctions bodies would disintegrate).

14.2.1 Functional Classification of Cell Junctions

a) Occluding (shutting) junctions

i) tight junctions (vertebrates only)

ii) septate junctions (invertebrates mainly)

b) Anchoring junctions

i) Actin filament attachment sites

- cell-cell junctions (adherens junctions)
- cell-matrix junctions (focal adhesions)

ii) Intermediate filament attachment sites

- cell-cell junctions (desmosomes)
- cell-matrix junctions (hemidesmosomes)

c) Communicating junctions

1. gap junctions
2. chemical synapses

a) Anchoring Junctions: can be between adjacent cells or between cells and basal lamina

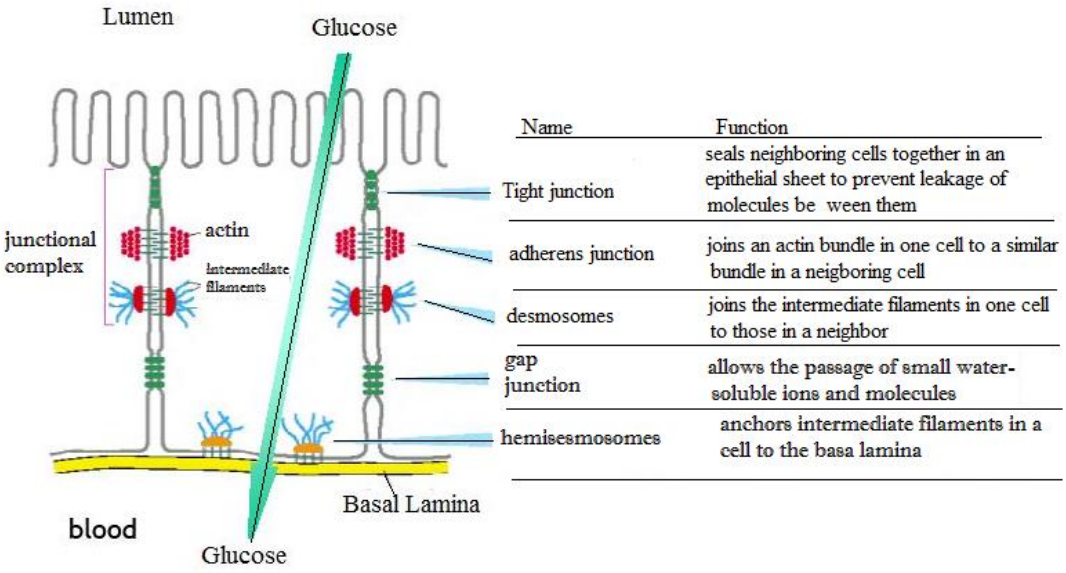
Basic principles of adhesion:

- mediated by multiple multi-protein complexes

- integral membrane receptor (homophilic or heterophilic)
- strengthened by linkage to cytoskeletal elements with/without

  lateral clustering of receptors

- linked to cytoskeleton by adaptor proteins



A summary of the various cell junctions found in a vertebrate epithelial cell. The drawing is based on epithelial cells of the small intestine.

Anchoring Junctions

JUNCTION	TRANSMEMBRAN ADHESION PROTEIN E	EXTRACELLULAR LIGAND	INTRACELLULA CYTOSKELETAL R ATTACHMENT PROTEINS	INTRACELLULAR ANCHOR
Cell-Cell				
Adherens junction	cadherin (E-cadherin)	cadherin in neighboring cell	actin filaments	α β-,
Desmosome	cadherin(desmoglein, desmocollin)	desmogleins, desmocollins in neighboring cell	intermediate filaments	desmoplakins, plakoglobin (γ-)
Cell-Matrix				
Focal adhesion	Integrin	extracellular matrix proteins	actin filaments	talin, vinculin, α-
Hemidesmosome	integrin α6β4	extracellular matrix proteins	intermediate filaments	plectin, BP230

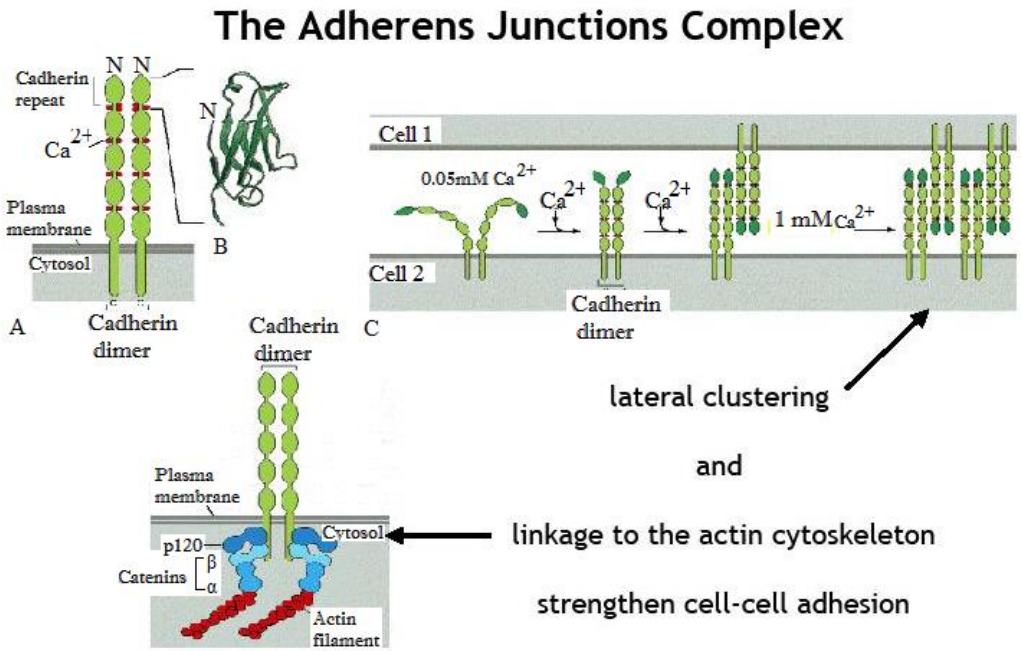


Figure showing the structure and function of cadherins. (A) A classical cadherin molecule. The protein is a homodimer, with the extracellular part of each polypeptide folded into five cadherin repeats. There are Ca2+-binding sites between each pair of repeats. (B) The crystal structure of a single cadherin repeat, which resembles an immunoglobulin (Ig) domain. (C) The influence of extracellular Ca2+. As the amount of Ca2+ increases, the extracellular parts of the cadherin chains become more rigid. When enough Ca2+ is bound, the cadherin dimer extends from the surface, where it can bind to a cadherin dimer on a neighboring cell. If Ca2+ is removed, the extracellular part of the protein becomes floppy and is degraded by proteolytic enzymes

Epithelial cell sheets line all the cavities and free surfaces of the body. The specialized junctions between the cells enable epithelia to form barriers that inhibit the movement of water, solutes, and cells from one body compartment to another (Figure above), epithelia almost always rest on a supporting bed of connective tissue. This supporting bed may in turn attach them to other tissues, such as the muscle shown in the figure above. In this way, tissues join together in various combinations to form larger functional units called *organs*.

14.2.2 Cell adhesions

Cellular adhesion is the binding of a cell to another cell or to a surface or matrix. Cellular adhesion is regulated by specific cell adhesion molecules that interact with other molecules.

Functions

- In cell recognition, one cell specifically binds to another cell of a certain type.
- In cell adhesion, the relationship between the two cells is “cemented”.
- Tissue-specific and species-specific aggregation occur because of plasma membrane recognition proteins.

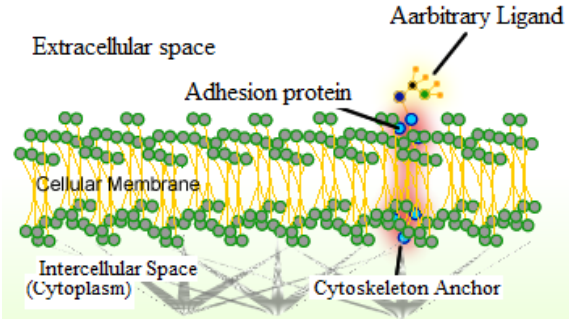
There are two general ways that cell adhesion molecules work:

i) **Homotypic** binding occurs when both cells possess the same type of cell surface receptor and their interaction causes them to stick together.
ii) **Heterotypic** binding occurs between two different but complementary proteins and resembles a plug and socket.

Adhesion in prokaryotes: Prokaryotes have adhesion molecules usually termed "adhesins". Adhesins may occur on pili (fimbriae), flagellae, or the cell surface. Adhesion of bacteria is the first step in colonization and regulates tropism (tissue- or cell-specific interactions).

Adhesion in viruses: Viruses also have adhesion molecules required for viral binding to host cells. For example, influenza virus has a hemagglutinin on its surface that is required for recognition of the sugar sialic acid on host cell surface molecules. HIV has an adhesion molecule termed gp120 that binds to its ligand CD4, which is expressed on lymphocytes.

Adhesion in eukaryotic: Eukaryotic protozoans also express multiple adhesion molecules. E.g. malarial parasite (*Plasmodium falciparum*), which uses one adhesion molecule called the **circumsporozoite** protein to bind to liver cells, and another adhesion molecule called the **merozoite** surface protein to bind red blood cells. In human cells, which have many different types of adhesion molecules, the major classes are named integrins, Ig superfamily members, cadherins, and selectins.



Clinic importance of adhesion proteins

a) inability to express adhesion proteins may lead to genetic disease like **leukocyte adhesion deficiency-I (LAD-I)**, where patients do not express the **integrin** required for leukocytes to adhere to the blood vessel wall during inflammation in order to fight infection.
b) Tumor metastases ; tumors that spread through the circulatory system use mechanisms of cell adhesion to establish new tumors in the body.