CONNECTIVE TISSUE

I. CONNECTIVE TISSUE

A. **Structure.** Connective tissue is formed primarily of **extracellular matrix**, consisting **of ground substance**, and **fibers**, in which various connective tissue **cells** are embedded.

B. **Function.** Connective tissue **supports** organs and cells, acts as a **medium for exchange** of nutrients and wastes between the blood and tissues, **protects** against microorganisms, **repairs** damaged tissues, and **stores fat**.

II. EXTRACELLULAR MATRIX

The extracellular matrix provides a medium for the transfer of nutrients and waste materials between connective tissue cells and the bloodstream.

A. **Ground substance** is a colorless, transparent, gel-like material in which the cells and fibers of connective tissue are embedded.

1. It is a complex mixture of glycosaminoglycans, proteoglycans, and glycoproteins (see Chapter 4 for details of these components).
2. Ground substance serves as a lubricant, helps prevent invasion of tissues by foreign agents, and resists forces of compression.

B. **Fibers (collagen, reticular, and elastic)** are long, slender protein polymers present in different proportions in different types of connective tissue.

1. Collagen fibers. Although there are at least 25 different types of collagen, the most common collagen types in connective tissue proper are type I and type III collagen, both consisting of many closely packed tropocollagen fibrils. The diameter of individual type I collagen fibrils varies greatly (10–300 nm). These fibrils may aggregate and form cablelike structures up to several centimeters in length and display 67-nm periodicity

a. Collagen fibers are produced in a two-stage process, involving both intracellular and extracellular events.

b. Collagen fibers have great tensile strength, which imparts both flexibility and strength to tissues containing them.

c. Bone, skin, cartilage, tendon, and many other structures of the body contain collagen fibers.

2. Reticular fibers are extremely thin (0.5–2.0 m) in diameter and are composed primarily of type III collagen; they have higher carbohydrate content than other collagen fibers.

a. Type III collagen fibers constitute the architectural framework of certain organs and glands.

b. Because of their high carbohydrate content, they stain black with silver salts.

3. Elastic fibers are coiled branching fibers 0.2 to 1.0 m in diameter that sometimes form loose networks.

a. These fibers may be stretched up to 150% of their resting length.

b. They are composed of elastin and microfibrils of fibrillin

c. Elastic fibers require special staining to be observed by light microscopy.

III. CONNECTIVE TISSUE CELLS

Connective tissue cells include many types with different functions. Some originate locally and remain in the connective tissue (fixed cells), whereas others originate elsewhere and remain only temporarily in connective tissue (transient cells).

Fixed connective tissue cells include **fibroblasts**, **pericytes**, **adipose cells**, **mast cells, and fixed macrophages**.

Transient connective tissue cells include **certain macrophages, lymphocytes, plasma cells, neutrophils, eosinophils, and basophils.**

A. Fixed Cells of Connective Tissue

1. Fibroblasts arise from mesenchymal cells and are the predominant cells in connective tissue proper. They often possess an oval nucleus with two or more nucleoli. Fibroblasts seldom undergo mitosis except in wound healing. They may differentiate into other cell types under certain conditions. Active fibroblasts are spindle shaped (fusiform) and contain well-developed rough endoplasmic reticulum (RER) and many Golgi complexes. Myosin is located throughout the cytoplasm, and actin and α-actinin are located at the cell periphery. Synthetically active, they produce procollagen and other components of the extracellular matrix.

2. Pericytes are derived from embryonic mesenchymal cells and may retain a pluripotential role.

a. They possess characteristics of endothelial cells as well as smooth muscle cells because they contain actin, myosin, and tropomyosin, suggesting that they may function in contraction.

b. They are smaller than fibroblasts and are located mostly along capillaries, yet they lie within their own basal lamina.

c. Pericytes contain actin, myosin, and tropomyosin and may function as contractile cells that modify capillary blood flow.

d. During blood vessel formation and repair, they may differentiate into smooth muscle cells as well as endothelial cells.

e. In response to injury, pericytes may give rise to endothelial cells, fibroblasts, and smooth muscle cells of blood vessel walls.

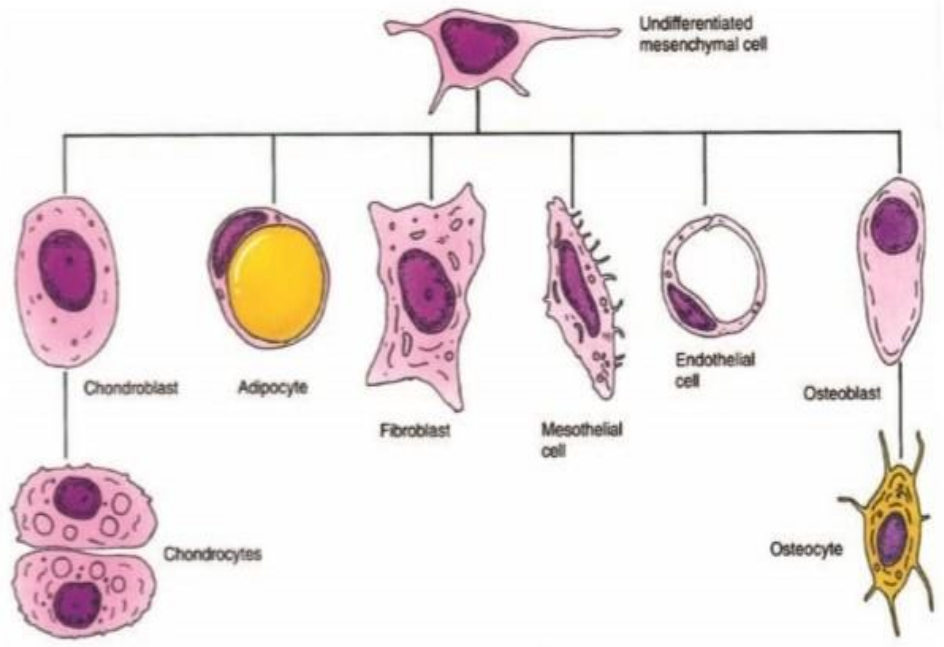
3. Adipose cells (adipocytes) arise from mesenchymal cells and perhaps from fibroblasts. They do not normally undergo cell division because they are fully differentiated cells. However, they do increase in number in early neonatal life. There is debate about normal proliferation of adipocytes beyond 2 years after birth. They are surrounded by a basal lamina and are responsible for the **synthesis**, **storage, and release of fat**.

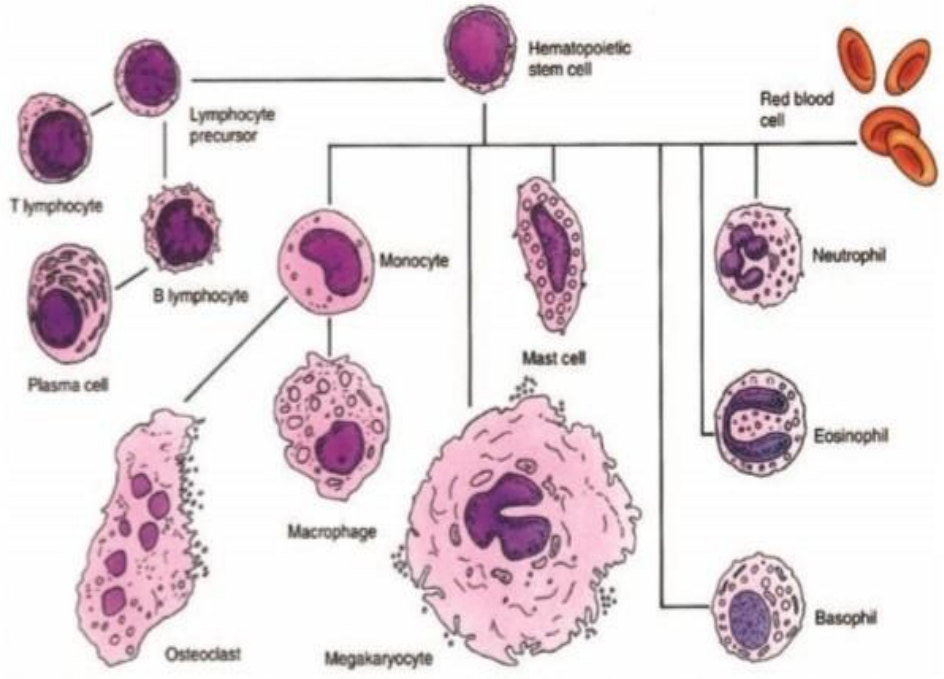
a. Unilocular adipose cells (white adipose tissue) contain a single large fat droplet. To accommodate the droplet, the cytoplasm and nucleus are squeezed into a thin rim around the cell's periphery.

(1) These cells have plasmalemma receptors for insulin, growth hormone, norepinephrine, and glucocorticoids to control the uptake and release of free fatty acids and triglycerides.

(2) They are surrounded by a basal lamina and are responsible for the synthesis, storage, and release of fat.

b. Multilocular adipose cells (brown adipose tissue) are smaller than unilocular adipose cells and the fat is stored as many small fat droplets, and thus the spherical nucleus is centrally located.


Undifferentiated mesenchymal cell
Chondroblast
Adipocyte
Fibroblast
Mesothelial cell
Endothelial cell
Osteoblast
Chondrocytes
Osteocyte


Hematopoietic stem cell
Red blood cell
Lymphocyte precursor
T lymphocyte
B lymphocyte
Plasma cell
Monocyte
Mast cell
Neutrophil
Eosinophil
Basophil
Macrophage
Osteoclast
Megakaryocyte

4. Mast cells : arise from **myeloid stem** cells in bone marrow and usually reside near small blood vessels. Although they share many structural and functional characteristics with basophils, they develop from different precursors and are not related.

a. These cells are one of the largest cells of connective tissue proper. They possess a central spherical nucleus; their cytoplasm is filled with coarse, deeply stained metachromatic granules; their contents (known as primary mediators)

b. Their surfaces are folded, and in electron micrographs they have a well-developed Golgi complex, scant RER, and many dense lamellated granules. Two populations of mast cells exist. **Connective tissue mast cells** possess secretory granules containing heparin. The other population, the smaller **mucosal mast cells** whose secretory granules contain chondroitin sulfate, is located in the mucosa of the alimentary canal and of the respiratory tract.

c. When mast cells become activated during a type I hypersensitivity reaction, phospholipids of their cell membranes can be converted into arachidonic acid by the enzyme phospholipase A2. Arachidonic acid is, in turn, converted into secondary mediators.

Major Mediators Released by Mast Cells

Substance	Intracellular Source	Action
Primary mediators		
Histamine	Granules	Vasodilator; increases vascular permeability; causes contraction of bronchial smooth muscle; increases mucus production
Heparin	Granules	Anticoagulant; inactivates histamine
Eosinophil chemotactic factor	Granules	Attractant for eosinophils to site of inflammation
Neutrophil chemotactic factor	Granules	Attractant for neutrophils to site of inflammation
Aryl sulfate	Granules	Inactivates leukotriene C_4, limiting inflammatory response
Chondroitin sulfate	Granules	Binds and inactivates histamine
Neutral proteases	Granules	Protein cleavage to activate complement; increases inflammatory response
Secondary mediators		
Prostaglandin D_2	Membrane lipid	Causes contraction of bronchial smooth muscle; increases mucus secretion; vasoconstriction
Leukotrienes C_4, D_4, E_4	Membrane lipid	Vasodilators; increases vascular permeability; contraction of bronchial smooth muscle
Bradykinins	Membrane lipid	Causes vascular permeability; responsible for pain sensation
Thromboxane A_2	Membrane lipid	Causes platelet aggregation; vasoconstriction
Platelet-activating factor	Activated by phospholipase A_2	Attracts neutrophils and eosinophils; causes vascular permeability; contraction of bronchial smooth muscle

d. Mast cells mediate immediate(type I) hypersensitivity reactions (anaphylactic reactions) as follows:

(1) After the first exposure to an allergen, plasma cells manufacture immunoglobulin E (IgE) antibodies, which bind to Fc receptors (FceRI receptors) on the surface of mast cells and basophils, causing these cells to become sensitized. Common antigens that may evoke this response include plant pollens, insect venoms, certain drugs, and foreign serum.

(2) During the second exposure to the same allergen, the membrane-bound IgE binds the allergen. Subsequent cross-linking and clustering of the allergen-IgE complexes trigger degranulation of mast cells and the release of primary and secondary mediators.

B. Transient Cells of Connective Tissue

1. **Macrophages** are the principal phagocytosing cells of connective tissue. They are responsible for removing large particulate matter and assisting in the immune response. They also secrete substances that function in wound healing.

a. Macrophages originate in the bone marrow as monocytes, circulate in the bloodstream, then migrate into the connective tissue, where they mature into functional macrophages. Macrophages increase in number because of the activity of the macrophage colony-stimulating factor (M-CSF). In addition, the colony-forming unit monocyte (CFU-M) facilitates the mitosis and differentiation of monocytes to form macrophages.

b. Macrophages are members of the mononuclear phagocyte system. They display FceRI receptors and receptors for complement.

c. When activated, they display filopodia, an eccentric kidney-shaped nucleus, phagocytic vacuoles, lysosomes, and residual bodies.

d. When stimulated, they may fuse to form foreign body giant cells. These multinucleated cells surround and phagocytose large foreign bodies.

2. Lymphoid cells : arise from lymphoid stem cells during hemopoiesis. They are located throughout the body in the subepithelial connective tissue and accumulate in the respiratory system, gastrointestinal tract, and elsewhere in areas of chronic inflammation.

a. T lymphocytes (T cells) initiate the cell-mediated immune response.

b. B lymphocytes (B cells), following activation by an antigen, differentiate into plasma cells, which function in the humoral immune response.

c. Natural killer cells (NK cells) lack the surface determinants characteristic of T and B lymphocytes but may display cytotoxic activity against tumor cells.

3. Plasma cells are antibody-manufacturing cells that arise from activated B lymphocytes and are responsible for humoral immunity.

a. These ovoid cells contain an eccentric nucleus possessing clumps of heterochromatin, which appear to be arranged in a wheel-spoke fashion.

b. Their cytoplasm is deeply basophilic because of an abundance of RER.

c. A prominent area adjacent to the nucleus appears pale and contains the Golgi complex (negative Golgi image).

d. They are most abundant at wound entry sites or in areas of chronic inflammation.

4. Granulocytes are white blood cells that possess cytoplasmic granules and arise from myeloid stem cells during hemopoiesis. At sites of inflammation, they leave the bloodstream and enter the loose connective tissue, where they perform their specific functions.

a. **Neutrophils** phagocytose, kill, and digest bacteria at sites of **acute inflammation.** Pus is an accumulation of dead neutrophils, bacteria, extracellular fluid, and additional debris at an inflammatory site.

b. **Eosinophils** bind to antigen–antibody complexes on the surface of **parasites** (e.g., helminths) and then release cytotoxins that damage the parasites.

(1) They are most prevalent at sites of chronic or allergic inflammation.

(2) Eosinophils are attracted by eosinophil chemotactic factor (ECF), which is secreted by mast cells and basophils, to sites of allergic inflammation. There, eosinophils release enzymes that cleave histamine and leukotriene C, thus moderating the allergic reaction.

(3) These cells also phagocytose antibody–antigen complexes.

c. **Basophils** are similar to mast cells in that they possess FceRI receptors; their granules house the same primary mediators; and the same secondary mediators are manufactured de novo from the phospholipids of their plasmalemma. They differ, however, in that they circulate via the bloodstream, whereas mast cells do not.

IV. CLASSIFICATION OF CONNECTIVE TISSUE

Classification is based on the **proportion** of **cells to fibers** and on the **arrangement** and type of fibers (**embryonic connective tissue**, **connective tissue proper**, or **specialized connective tissue**).

A. Embryonic connective tissue

1. Mucous tissue (Wharton jelly) is a loose connective tissue that is the main constituent of the umbilical cord. It consists of a jellylike matrix with some collagen fibers in which large stellate fibroblasts are embedded.

2. Mesenchymal tissueis found only in embryos.It consists of a gel-like amorphous matrix containing only a few scattered reticular fibers, in which star-shaped, pale-staining mesenchymal cells are embedded. Mitotic figures are often observed in these pluripotential cells.

B. Connective tissue proper

1. Loose connective tissue (areolar tissue) possesses fewer fibers but more cells than dense connective tissue.

a. This tissue is well vascularized, flexible, and not very resistant to stress.

b. It is more abundantthan dense connective tissue and is the connective tissue that fills in the spaces just deep to the skin.

2. Dense connective tissue contains more fibers but fewer cells than loose connective tissue. It is classified by the orientation of its fiber bundles into two types:

a. Dense, irregular connective tissue (most common), which contains fiber bundles that have no definite orientation. This tissue is characteristic of the **dermis** and capsules **of many organs**.

b. Dense regular connective tissue, which contains fiber bundles and attenuated fibroblasts that are arranged in a uniform parallel fashion.

(1) It is present only in tendons and ligaments.

(2) This tissue may be collagenous or elastic.

3. Elastic tissue is composed of coarse, branching elastic fibers with a sparse network of collagen fibers and some fibroblasts filling the interstitial spaces. It is present in the **dermis**, **lungs**, **elastic cartilage**, and **elastic ligaments and in large** (conducting) **blood vessels**, where it forms fenestrated sheaths.

4. Reticular tissue consists mostly of a network of branched reticular fibers (type III collagen).

a. This tissue invests liver sinusoids, smooth muscle cells, and fat cells and forms the stroma of lymphatic organs, bone marrow, and endocrine glands.

b. It also forms the reticular lamina of basement membranes.

5. Adipose tissue is the primary site for storage of energy (in the form of triglycerides) and has a rich neurovascular supply.

a. White adipose tissue is composed of unilocular adipose cells.

(1) This tissue constitutes nearly all of the adult adipose tissue throughout the body.

(2) It stores and releases lipids as follows:

(a) Adipose cells synthesize the enzyme lipoprotein lipase, which is transferred to the luminal aspect of the capillary endothelium.

(b) Dietary fat is transported to adipose tissue as very-low-density lipoproteins (VLDLs) and chylomicrons. Lipoprotein lipase then hydrolyzes these substances into fatty acids and glycerol.

(c) The free fatty acids enter the adipose cells, where they are reesterified and stored as triglycerides (in fat droplets). Adipose cells also synthesize fatty acids from glucose.

(d) Lipid storage is stimulated by insulin, which increases the rate of synthesis of lipoprotein lipase and the uptake of glucose by adipose cells.

(e) Release of lipids is affected by neural impulses and/or adrenaline. Stored triglycerides are hydrolyzed by hormone-sensitive lipase, which is activated by cyclic adenosine monophosphate (cAMP). The free fatty acids are released into the extracellular matrix and then enter the capillary lumen.

(f) Adipose tissue also secretes leptin,a hormone that stimulates cells in the hypothalamus, to regulate appetite and to increase energy consumption.

b. Brown adipose tissue is composed of multilocular adipose cells, which contain many large mitochondria.

(1) This tissue is capable of generating heat by uncoupling oxidative phosphorylation. Thermogenin, a transmembrane protein in mitochondria, causes the release of protons away from adenosine triphosphate (ATP) synthesis, resulting in heat production.

(2) This tissue is found in **infants** (also in hibernating animals) and is much reduced in adults.

C. Specialized connective tissue

1. Cartilage and bone

2. Blood