Connective Tissue

The different types of connective tissues are responsible for *providing and maintaining form in the body*. Functioning mechanically, they provide a matrix that connects and binds the cells and organs and ultimately gives support to the body. Structurally, connective tissue is formed by three classes of components: cells, fibers, and ground substance. Unlike the other tissues (epithelium, muscle, and nerve), which are formed mainly by **cells**, the major constituent of connective tissue is the **extracellular matrix.** Extracellular matrices consist of different combinations of **protein fibers** (collagen, reticular, and elastic) and **ground substance.**

Fibers: predominantly composed of **collagen**, constitute *tendons, capsules of organs, and membranes that envelop the central nervous system (**meninges**)*. They also make up the trabeculae and walls inside several organs, forming the most resistant component of the ***stroma,*** or supporting tissue of organs. As well as **elastic** and **reticular** fibers.

Ground substance is a highly hydrophilic, viscous complex of anionic macromolecules (glycosaminoglycans and proteoglycans) and multiadhesive glycoproteins (laminin, fibronectin, and others) that imparts strength and rigidity to the matrix by binding to receptor proteins (**integrins**) on the surface of cells and to the other matrix components. In addition to its conspicuous structural function, the molecules of connective tissue serve other important biological functions, such as serving as a reservoir for hormones controlling cell growth and differentiation.

The connective tissue matrix is also the medium through which *nutrients and metabolic wastes are exchanged between cells and their blood supply*.

The wide variety of connective tissue types in the body reflects variations in *the composition and amount of the three components (cells, fibers, and ground substance)* that are responsible for the remarkable structural, functional, and pathological diversity of connective tissue

1- Cells of the Connective Tissue

A variety of cells with different origins and functions are present in connective tissue. **Fibroblasts** originate locally from undifferentiated mesenchymal cells and spend all their life in this tissue; other cells such as **mast cells, macrophages,** and **plasma cells** originate from hematopoietic stem cells in the bone marrow, circulate in the blood, and move to connective tissue, where they remain and execute their functions. Blood **leukocytes,** which are transient cells of connective tissue, also originate in bone marrow. They usually migrate to connective tissue where they reside for a few days and die.

Fibroblasts

*Fibroblasts synthesize collagen, elastin, glycosaminoglycans, proteoglycans, and multiadhesive glycoproteins.**Fibroblasts are the most common cells in connective tissue and are responsible for the synthesis of extracellular matrix components***. Two stages of activity active and quiescent are observed in these cells. Cells with intense synthetic activity are morphologically distinct from the quiescent fibroblasts that are scattered within the matrix they have already synthesized. Some histologists reserve the term **fibroblast** to denote the active cell and **fibrocyte** to denote the quiescent cell.

The active fibroblast has an abundant and irregularly branched cytoplasm. *Its nucleus is ovoid, large, and pale staining, with fine chromatin and a prominent nucleolus. The cytoplasm is rich in rough endoplasmic reticulum, and the Golgi complex is well developed.*

The quiescent fibroblast, or fibrocyte, is smaller than the active fibroblast and tends to be spindle shaped. *It has fewer processes; a smaller, darker, elongated nucleus; an acidophilic cytoplasm; and a small amount of rough endoplasmic reticulum.*

Fibroblasts synthesize proteins, such as collagen and elastin, that form collagen, reticular, and elastic fibers, and the glycosaminoglycans, proteoglycans, and glycoproteins of the extracellular matrix. *Fibroblasts are also involved in the production of **growth factors** that influence cell growth and differentiation*. In adults, fibroblasts in connective tissue rarely undergo division; however, mitoses are observed when the organism requires additional fibroblasts.

Macrophages & the Mononuclear Phagocyte System

Macrophages were discovered and initially characterized by their phagocytic ability. Macrophages have a wide spectrum of morphological features that corresponds to their state of functional activity and to the tissue they inhabit. When a vital dye such as trypan blue or India ink is injected into an animal, macrophages engulf and accumulate the dye in their cytoplasm in the form of granules or vacuoles visible in the light microscope.

In the electron microscope, they are characterized by an *irregular surface with pleats, protrusions, and indentations, a morphological expression of their active pinocytotic and phagocytic activities. They generally have a well-developed Golgi complex, many lysosomes, and a prominent rough endoplasmic reticulum*.

Distribution and Main Functions of the Cells of the Mononuclear Phagocyte System.		
Cell Type	**Location**	**Main Function**
Monocyte	*Blood*	*Precursor of macrophages*
Macrophage	*Connective tissue, lymphoid organs, lungs, bone marrow*	*Production of cytokines, chemotactic factors, and several other molecules that participate in inflammation (defense), antigen processing and presentation*
Kupffer cell	*Liver*	*Same as macrophages*
Microglia cell	*Nerve tissue of the central nervous system*	*Same as macrophages*
Langerhans cell	*Skin*	*Antigen processing and presentation*
Dendritic cell	*Lymph nodes*	*Antigen processing and presentation*
Osteoclast	*Bone (fusion of several macrophages)*	*Digestion of bone*
Multinuclear giant cell	*Connective tissue (fusion of several macrophages)*	*Segregation and digestion of foreign bodies*

Macrophages derive from bone marrow precursor cells that divide, producing **monocytes** that circulate in the blood. In a second step, these cells cross the wall of venules and capillaries to penetrate the connective tissue, where they mature and acquire morphological features of **macrophages.** Therefore, monocytes and macrophages are the same cell in different stages of maturation. Tissue macrophages can proliferate locally, producing more cells.

Mast Cells

Mast cells are oval to round connective tissue cells, 10–13 µm in diameter, whose cytoplasm is filled with basophilic secretory granules. The rather small, spherical nucleus is centrally situated; it is frequently obscured by the cytoplasmic granules.

The secretory granules are 0.3–2.0 µm in diameter. Their interior is heterogeneous in appearance, with a prominent scroll-like substructure that contains preformed mediators such as histamine and heparin, a highly acidic, sulfated glycosaminoglycan. The principal function of mast cells is the storage of chemical mediators of the inflammatory response.

Although they have similar morphology, there are at least two populations of mast cells in connective tissues. One type, called the **connective tissue mast cell,** is found in the skin and peritoneal cavity; these cells measure 10–12 µm in diameter and their granules contain the **anticoagulant heparin**. The second type, the so-called **mucosal mast cell,** is present in the connective tissue of the intestinal mucosa and in the lungs. These cells are smaller (only 5–10 µm) than the connective tissue mast cells and their granules contain *chondroitin sulfate instead of heparin.*

Plasma Cells

Plasma cells are large, ovoid cells that have a basophilic cytoplasm ***due to their richness in rough endoplasmic reticulum.*** The juxtanuclear Golgi complex and the centrioles occupy a region that appears pale in regular histological preparations.

The nucleus of the plasma cell *is spherical and eccentrically placed, containing compact, coarse heterochromatin alternating with lighter areas of approximately equal size.* This configuration resembles the face of a clock, with the heterochromatin clumps corresponding to the numerals. Thus, the nucleus of a plasma cell is commonly described as *having a clock-face appearance*. There are few plasma cells in most connective tissues.

Adipose Cells

Adipose cells (adipocytes; L. *adeps,* fat, + Gr. *kytos*) are connective tissue cells that have become specialized for storage of neutral fats or for the production of heat. Often called **fat cells**.

Leukocytes

The normal connective tissue contains leukocytes that migrate from the blood vessels by diapedesis. Leukocytes, or white blood corpuscles, are the wandering cells of the connective tissue. They migrate through the walls of capillaries and postcapillaryvenules from the blood to connective tissues by a process called **diapedesis.** This process increases greatly during inflammation. ***Inflammation****is a vascular and cellular defensive reaction against foreign substances, in most cases pathogenic bacteria or irritating chemical substances.* Inflammation begins with the local release of **chemical mediators of inflammation,** substances of various origin (mainly from cells and blood plasma proteins) that induce some of the events characteristic of inflammation, eg, **increase of blood flow** and **vascular permeability, chemotaxis,** and **phagocytosis.**

2- Fibers

The connective tissue fibers are formed by proteins that polymerize into elongated structures. The three main types of connective tissue fibers are **collagen, reticular,** and **elastic.** Collagen and reticular fibers are formed by the protein **collagen,** and elastic fibers are composed mainly of the protein **elastin.** These fibers are distributed unequally among the types of connective tissue. Actually, there are two systems of fibers: the collagen system, consisting of collagen and reticular fibers, and the elastic system, consisting of the elastic, elaunin, and oxytalan fibers. In many cases, the predominant fiber type is responsible for conferring specific properties on the tissue.

Collagen fibers

Collagen is the most abundant protein in the human body, representing 30% of its dry weight. Based on their structure and functions, they can be classified into the following groups.

1-Collagens, That Form Long Fibrils

The molecules of long fibril–forming collagens aggregate to form fibrils clearly visible in the electron microscope. These are collagen types I, II, III, V, and XI. Collagen type I is the most abundant and has a widespread distribution. It occurs in tissues as structures that are classically designated as **collagen fibers** and ***that form structures such as bones, dentin, tendons, organ capsules, and dermis.***

2-Fibril-Associated Collagens

Fibril-associated collagens are short structures that bind collagen fibrils to one another and to other components of the extracellular matrix. They are collagen types IX, XII, and XIV.

3-Collagens That Form Networks

The molecules of network-forming collagen, or type IV collagen, assemble in a meshwork that constitutes the structural component of the basal lamina.

In many parts of the body, collagen fibers are organized in parallel to each other, forming collagen bundles. Because of the long and tortuous course of collagen bundles, their morphological characteristics are better studied in spread preparations than in histological sections. The collagen fibers in a spread preparation appear as elongated and tortuous cylindrical structures. In the light microscope, collagen fibers are acidophilic; they stain pink with eosin,

Reticular Fibers

Reticular fibers, which consist mainly of collagen type III, are extremely thin, with a diameter between 0.5 and 2 µm, and they form an extensive network in certain organs. They are not visible in hematoxylin and eosin (H&E) preparations but can be easily stained black by impregnation with silver salts. Because of their affinity for silver salts, these fibers are called **argyrophilic**.

Reticlar fibers are particularly abundant in smooth muscle, endoneurium, and the framework of hematopoietic (or hemopoietic) organs (eg, spleen, lymph nodes, red bone marrow) and constitute a network around the cells of parenchymal organs (eg, liver, endocrine glands). The small diameter and the loose disposition of reticular fibers create a flexible network in organs that are subjected to changes in form or volume, such as the arteries, spleen, liver, uterus, and intestinal muscle layers.

The Elastic Fiber System

The elastic fiber system is composed of three types of fibers ***oxytalan, elaunin, and elastic***. The elastic fiber system, by using different proportions of microfibrils and elastin, constitutes a family of fibers whose variable functional characteristics are adapted to local tissue requirements. It appear as fine , single, and branch fibers.

3- Ground Substance

The intercellular ground substance is a highly hydrated, colorless, and transparent complex mixture of macromolecules. It fills the space between cells and fibers of the connective tissue and, because it is viscous, acts as both a lubricant and a barrier to the penetration of invaders. When adequately fixed for histological analysis, its components aggregate and precipitate in the tissues as granular material that is observed in electron microscopic preparations as electron-dense filaments or granules. The ground substance is formed mainly of three classes of components: **glycosaminoglycans, proteoglycans,** and **multiadhesive glycoproteins.**

Types of Connective Tissue

There are several types of connective tissue that consist of the basic components already described: fibers, cells, and ground substance. The names given to the various types denote either the component that predominates in the tissue or a structural characteristic of the tissue.

Connective Tissue Proper

There are two classes of connective tissue proper: ***loose and dense***

Loose connective tissue supports many structures that are normally under pressure and low friction. A very common type of connective tissue, it fills spaces between groups of muscle cells, supports epithelial tissue, and forms a layer that sheathes the lymphatic and blood vessels.

Loose connective tissue is also found in the papillary layer of the dermis, in the hypodermis, in the serosal linings of peritoneal and pleural cavities, and in glands and the mucous membranes (wet membranes that line the hollow organs) supporting the epithelial cells.

Loose connective tissue comprises all the main components of connective tissue proper. There is no predominant element in this tissue. The most numerous cells are fibroblasts and macrophages, but all the other types of connective tissue cells are also present. A moderate amount of collagen, elastic, and reticular fibers appears in this tissue. Loose connective tissue has a delicate consistency; it is flexible, well vascularized, and not very resistant to stress.

Dense connective tissue is adapted to offer resistance and protection. It consists of the same components found in loose connective tissue, but there are fewer cells and a clear predominance of collagen fibers. Dense connective tissue is less flexible and far more resistant to stress than is loose connective tissue. It is known as **dense irregular** connective tissue when the collagen fibers are arranged in bundles without a definite orientation. The collagen fibers form a three-dimensional network in dense irregular tissue and provide resistance to stress from all directions. This type of tissue is encountered in areas such as the dermis.

The collagen bundles of **dense regular** connective tissue are arranged according to a definite pattern. The collagen fibers of this tissue are aligned with the linear orientation of fibroblasts in response to prolonged stresses exerted in the same direction; consequently they offer great resistance to traction forces.

Tendons are the most common example of dense regular connective tissue. These elongated cylindrical structures attach striated muscle to bone; by virtue of their richness in collagen fibers, they are white and inextensible. They have parallel, closely packed bundles of collagen separated by a small quantity of intercellular ground substance. Their fibrocytes contain elongated nuclei parallel to the fibers and sparse cytoplasmic folds that envelop portions of the collagen bundles. The cytoplasm of these fibrocytes is rarely revealed in H&E stains, not only because it is sparse but also because it stains the same color as the fibers.

The collagen bundles of the tendons (**primary bundles**) aggregate into larger bundles (**secondary bundles**) that are enveloped by loose connective tissue containing blood vessels and nerves. Externally, the tendon is surrounded by a sheath of dense connective tissue. In some tendons, this sheath is made up of two layers, both lined by squamous cells of mesenchymal origin. One layer is attached to the tendon, and the other lines the neighboring structures. A cavity containing a viscous fluid (similar to the fluid of synovial joints) is formed between the two layers. This fluid, which contains water, proteins, glycosaminoglycans, glycoproteins, and ions, is a lubricant that permits the tendon to slide easily within its sheath.

Elastic Tissue is composed of bundles of thick, parallel elastic fibers. The space between these fibers is occupied by thin collagen fibers and flattened fibroblasts. The abundance of elastic fibers in this tissue is the cause of its typical yellow color and great elasticity. Elastic tissue, which occurs infrequently, is present in the yellow ligaments of the vertebral column and in the suspensory ligament of the penis.

Reticular Tissue The very delicate reticular tissue forms three-dimensional networks that support cells. Reticular tissue is a specialized loose connective tissue consisting of reticular fibers intimally associated with specialized fibroblasts called reticular cells. Reticular tissue provides the architectural framework that creates a special microenvironment for hematopoietic organs and lymphoid organs (bone marrow, lymph nodules and nodes, and spleen). The reticular cells are dispersed along this framework and partially cover the reticular fibers and ground substance with cytoplasmic processes. The resulting cell-lined trabecular system creates a spongelike structure within which cells and fluids are freely mobile.

In addition to the reticular cells, cells of the mononuclear phagocyte system are strategically dispersed along the trabeculae. These cells monitor the slow flow of materials through the sinuslike spaces and remove invaders by phagocytosis.

Mucous Tissue :The mucous tissue is found mainly in the umbilical cord. Mucous tissue has an abundance of ground substance composed primarily of hyaluronic acid. It is a jellylike tissue containing very few fibers. The cells in this tissue are mainly fibroblasts. Mucous tissue is the principal component of the umbilical cord, where it is referred to as **Wharton's jelly.** It is also found in the pulp of young teeth.

Adipose Tissue**:**Adipose tissue is a special type of connective tissue in which adipose cells (**adipocytes**) predominate. These cells can be found isolated or in small groups within the connective tissue itself; most are found in large aggregates, making up the adipose tissues that are spread throughout the body. Adipose tissue is, in a sense, one of the largest organs in the body. In men of normal weight, adipose tissue represents 15-20% of the body weight; in women of normal weight, it represents 20-25% of body weight.

Because fat is a poor heat conductor, it contributes to the thermal insulation of the body. Adipose tissue also fills up spaces between other tissues and helps to keep some organs in place. Recently, it was observed that adipose tissue secretes various types of molecules that may be carried by the blood to influence distant organs.

The two known types of adipose tissue have different locations, structures, colors, and pathological characteristics. **Unilocular** (**common,** or **yellow**) **adipose tissue** is composed of cells that, when completely developed, contain one large central droplet of yellow fat in their cytoplasm. **Multilocular** (or **brown**) adipose tissue is composed of cells that contain numerous lipid droplets and abundant brown mitochondria. Both types of adipose tissue have a rich blood supply.

Unilocular Adipose Tissue: The color of unilocular adipose tissue varies from white to dark yellow, depending on the diet; it is due mainly to the presence of carotenoids dissolved in fat droplets of the cells. Almost all adipose tissue in adults is of this type. It is found throughout the human body except for *the eyelids, the penis, the scrotum, and the entire auricle of the external ear except for the lobule*. Age and sex determine the distribution and density of adipose deposits.

Unilocular adipose cells are spherical when isolated but are polyhedral in adipose tissue, where they are closely packed. Each cell is between 50 and 150 µm in diameter. Because lipid droplets are removed by the alcohol and xylol used in routine histological techniques, each cell appears in standard microscope preparations as a thin ring of cytoplasm surrounding the vacuole left by the dissolved lipid droplet the **signet ring cell.** Consequently, these cells have eccentric and flattened nuclei. The rim of cytoplasm that remains after removal of the stored triglycerides (neutral fats) may rupture and collapse, distorting the tissue structure.

The thickest portion of the cytoplasm surrounds the nucleus of these cells and contains a Golgi complex, mitochondria, poorly developed cisternae of the rough endoplasmic reticulum, and free polyribosomes. The rim of cytoplasm surrounding the lipid droplet contains cisternae of smooth endoplasmic reticulum and numerous pinocytotic vesicles.

Although blood vessels are not always apparent in tissue sections, adipose tissue is richly vascularized. If the amount of cytoplasm in fat cells is taken into consideration, the ratio of blood volume to cytoplasm volume is greater in adipose tissue than in striated muscle.

Multilocular Adipose Tissue: Multilocular adipose tissue is also called **brown fat** because of its color, which is due to both the large number of blood capillaries in this tissue and the numerous mitochondria (containing colored cytochromes) in the cells.

Multilocular tissue cells are ***polygonal and smaller*** than cells of unilocular adipose tissue. ***Their cytoplasm contains a great number of lipid droplets*** of various sizes, a ***spherical and central nucleus***, and ***numerous mitochondria*** with abundant long cristae.

Multilocular adipose tissue resembles an endocrine gland in that its cells assume an almost epithelial arrangement of closely packed masses associated with blood capillaries. This tissue is subdivided by partitions of connective tissue into lobules that are better delineated than are unilocular adipose tissue lobules. Cells of this tissue. The main function of the multilocular adipose cells is to produce heat.