

Connective Tissue

Textbook of Histology, 4th ed.

Gartner

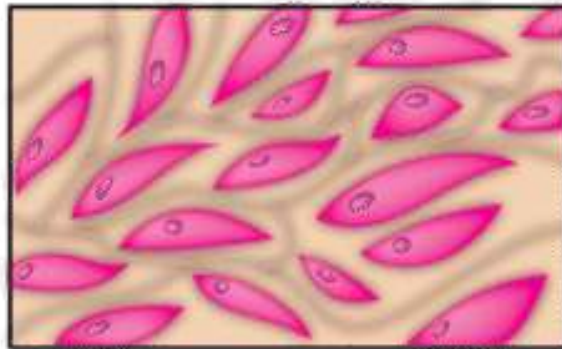
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- <https://gestioneval.unibo.it/rilevazioni-docenti>

Four basic tissue types

Four Types of Tissues

Provides support



Connective tissue

To cover and protect the body



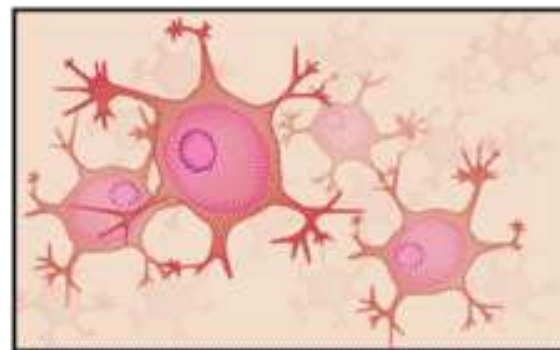
Epithelial tissue

Movement



Muscle tissue

Provides control and communication



Nervous tissue

Definition of Connective Tissue

The connective tissue provides the supportive and connecting framework (or stroma) for all the other tissues of the body.

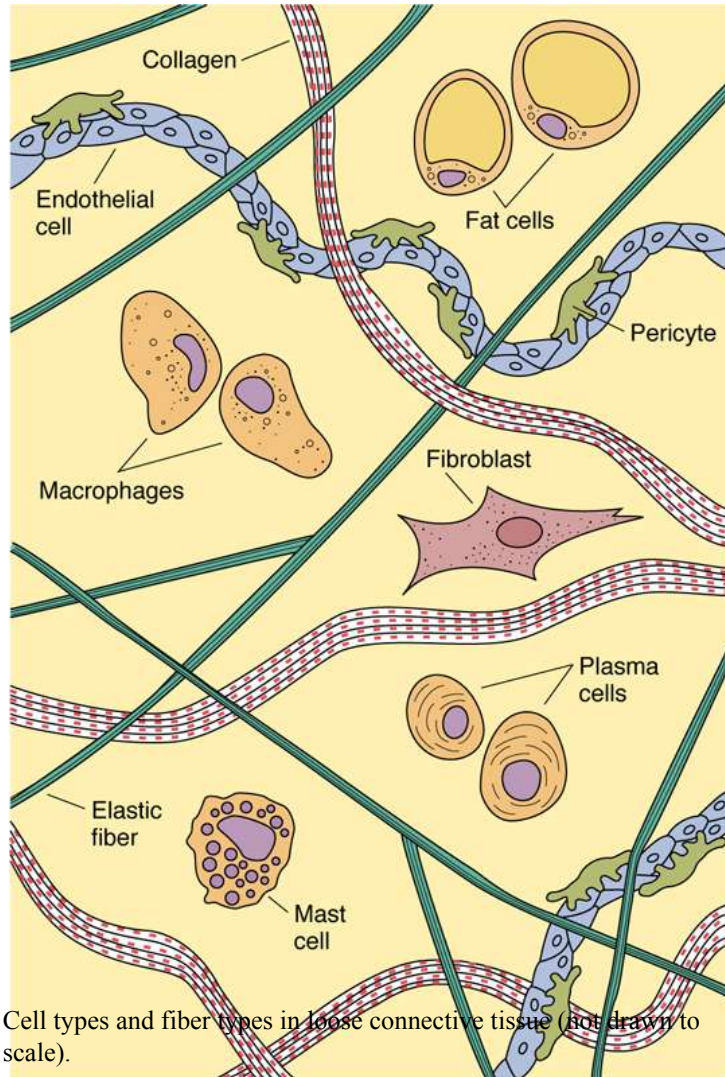
The connective tissue is formed by:

- **cells**
- **fibers**
- **extracellular matrix (ECM).**

The ECM or ground substance represents a combination of **collagens, non-collagenous glycoproteins** and **proteoglycans surrounding** the cells of the connective tissue.

We distinguish resident cells of the connective tissue: the **fibroblasts**. *Immigrant cells* to the connective tissue include **macrophages, mast cells** and **plasma cells**.

Connective Tissue Proper



Cell types and fiber types in loose connective tissue (not drawn to scale).

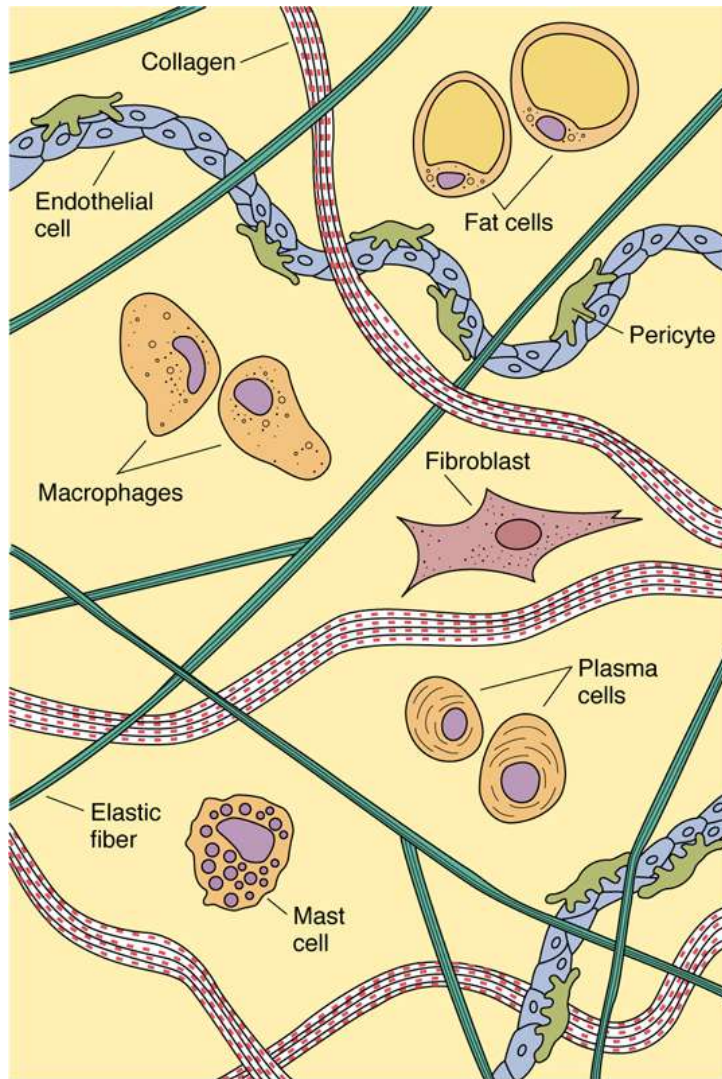
Connective tissue is composed of **cells** and **extracellular matrix (ECM)** consisting of ground substance and fibers.

The cells are the most important components in some connective tissues.

For example, fibroblasts are the most important components of **loose connective tissue**; these cells manufacture and maintain the fibers and ground substance composing the extracellular matrix.

Cell/fibers → high (loose)

Connective Tissue Proper



Cell types and fiber types in loose connective tissue (not drawn to scale).

In contrast, fibers are the most important components of the **dense connective tissue**.

Dense connective tissue contains **more collagen fibers than cells**.

Cell/fibers → low (dense)

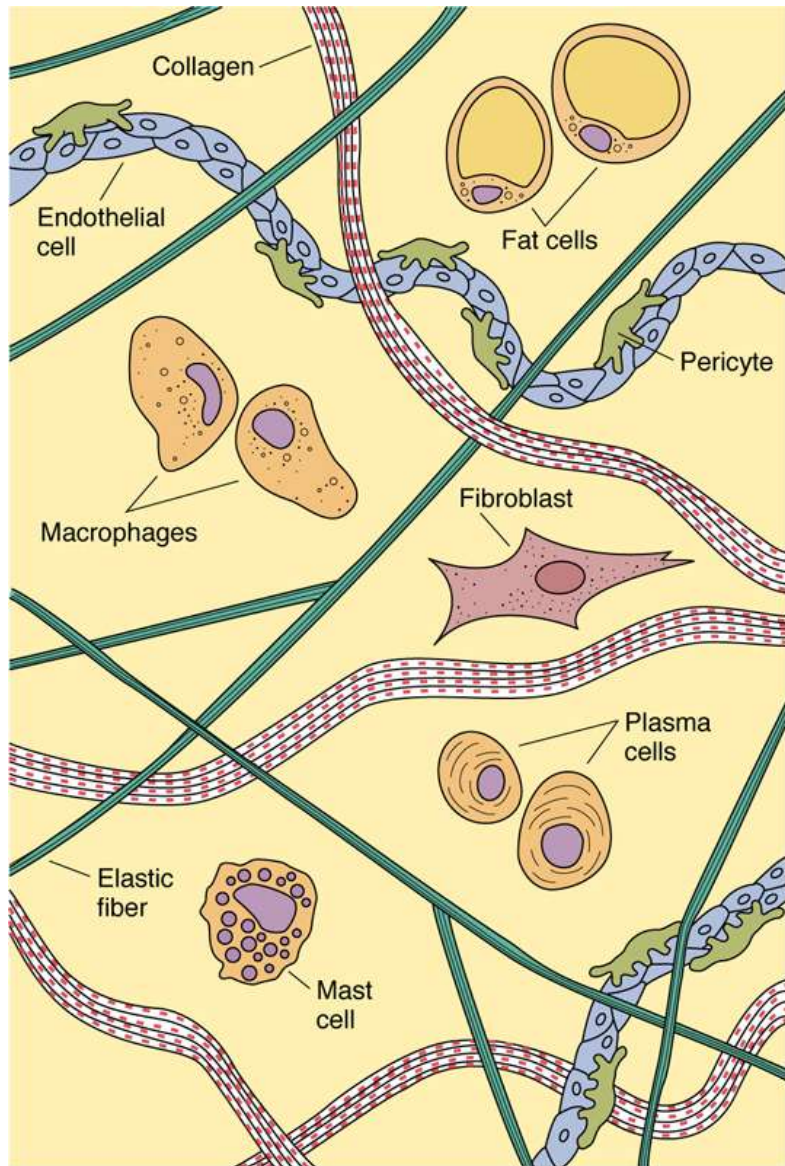
When the collagen fibers are

- preferentially oriented, as in tendons, ligaments and the cornea, the tissue is called **dense regular connective tissue**.

When the collagen fibers are

- **randomly oriented**, as in the dermis of the skin and submucosa of the alimentary tube, the tissue is called **dense irregular connective tissue**

Connective Tissue Proper



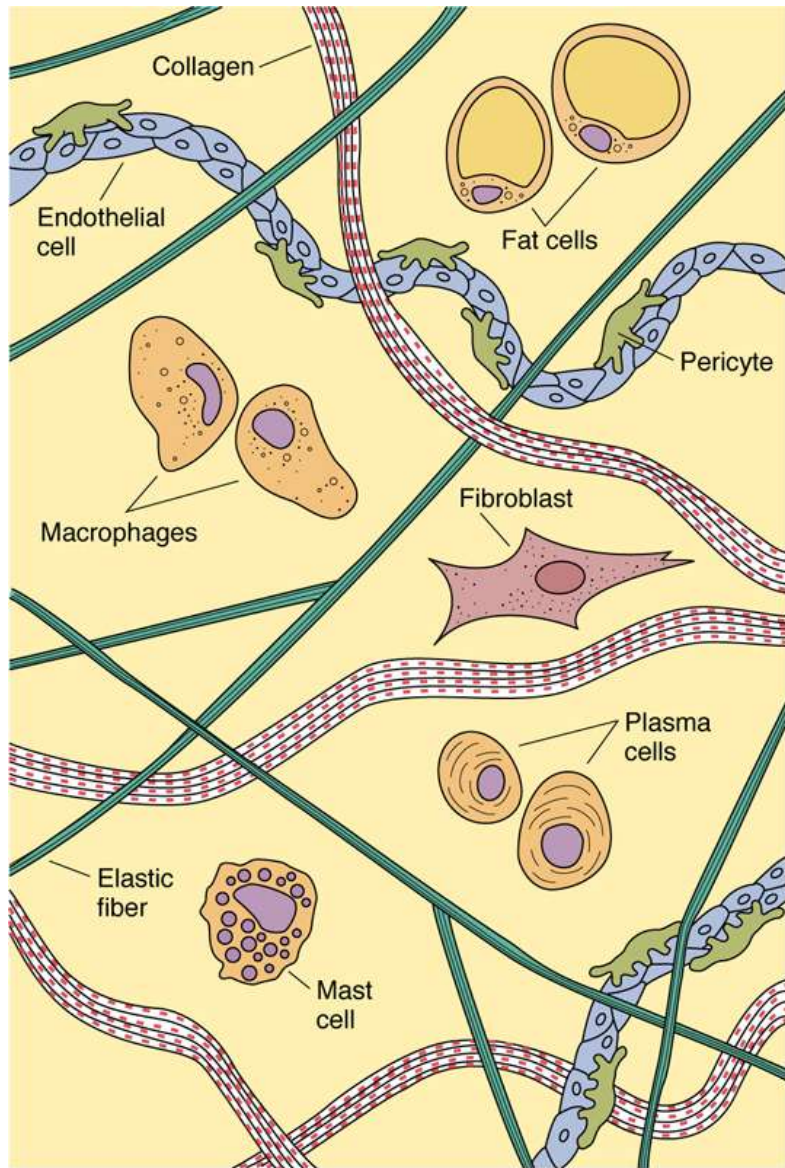
Cell types and fiber types in loose connective tissue (not drawn to scale).

Its primary function includes providing structural **support**, serving as a **medium for exchange**, aiding in the **defense** and **protection** of the body, and forming a site for **storage of fat**.

Connective tissue is classified

- connective tissue proper
- specialized connective tissue.

Connective Tissue Proper



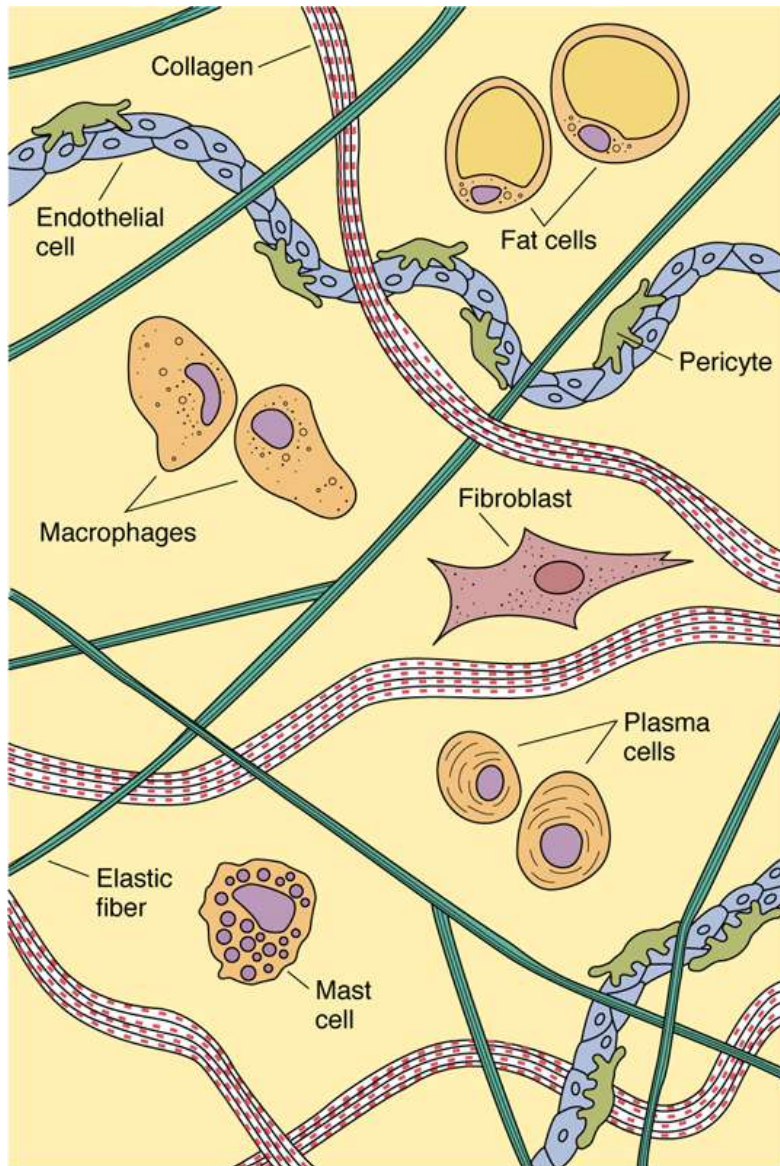
Cell types and fiber types in loose connective tissue (not drawn to scale).

Connective tissue proper is further subclassified:

- Embryonic or mucous tissue
- mesenchymal
- loose
- dense (regular and irregular)
- collagenous, elastic or reticular

Connective Tissue

Specialized



Cell types and fiber types in loose connective tissue (not drawn to scale).

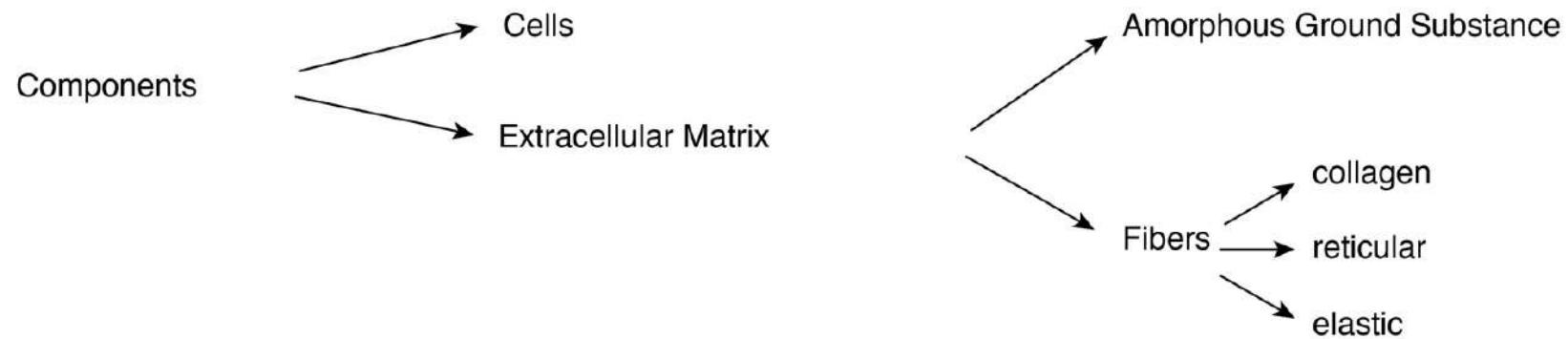
Specialized connective tissue

- cartilage
- bone
- blood
- adipose tissue

in the specialized category

**HISTOLOGY LABORATORY - Prof. Lauriola Mattia -
Morphology and Development (I.C.)**

Connective Tissues



MESENCHYME

embryonal connective tissue
pulp of young teeth

- mesenchymal cells

MUCOUS TISSUE

umbelical cords (wharton jelly)
subdermal connective tissue of embryo

- Mainly mesenchymal cells

LOOSE CONNECTIVE TISSUE

mainly cells (fibroblasts and macrophages), few fibers

DENSE CONNECTIVE TISSUE

few cells, mainly fibers

IRREGULAR

- collagen fibers are arranged in bundles without a definite orientation

**REGULAR**

- collagen fibers are arranged according to a definite pattern
- elastic fibers (wavy) are parallel arranged

**CROSSED FIBERS**

- collagen fibers are crossed (cornea)

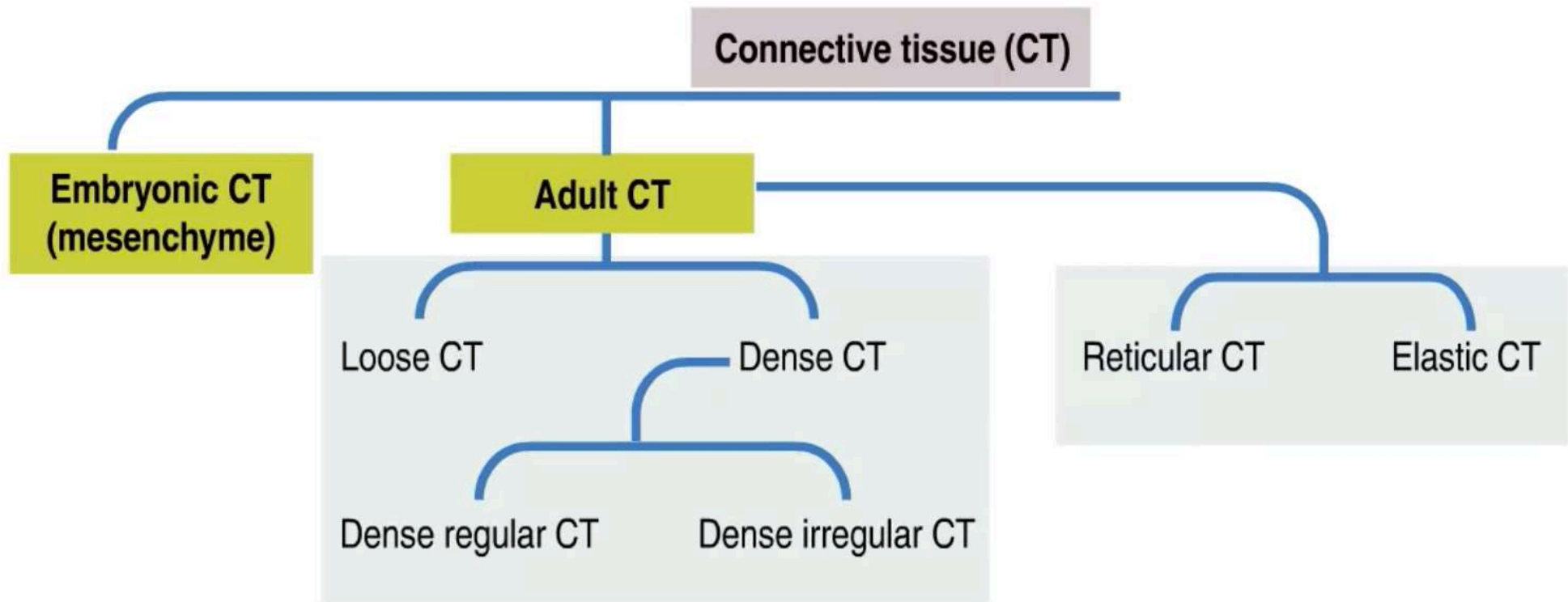


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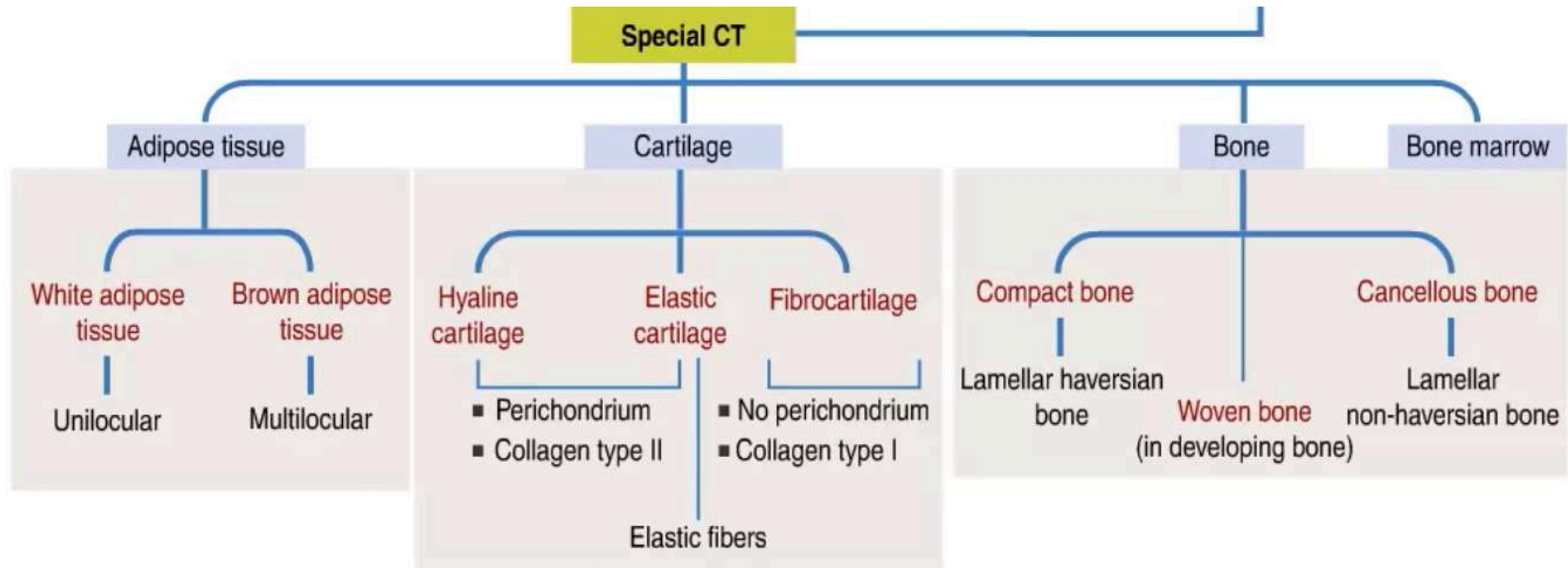
RETICULAR TISSUE

- elaborate a fine matrix of branched reticular fibers

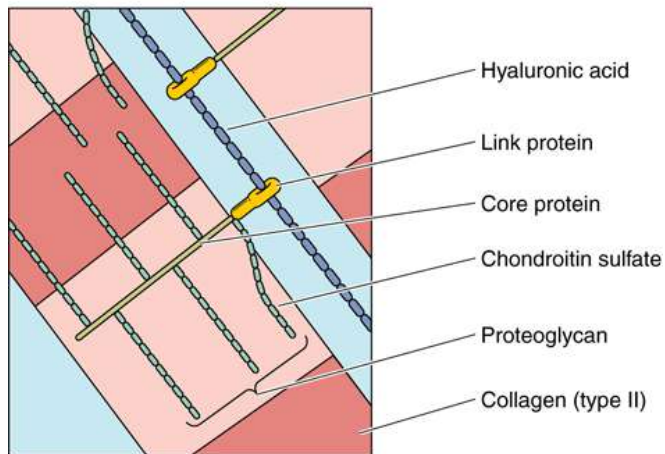
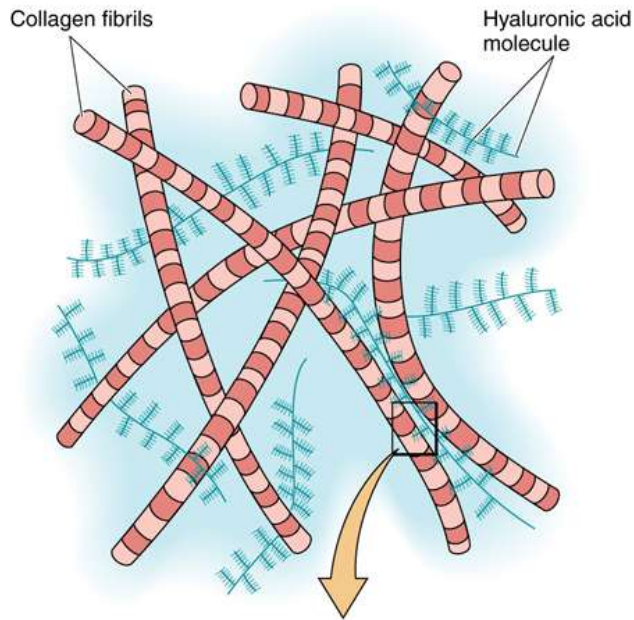
Connective Tissue (CT) proper



Special Connective Tissues



Extracellular Matrix



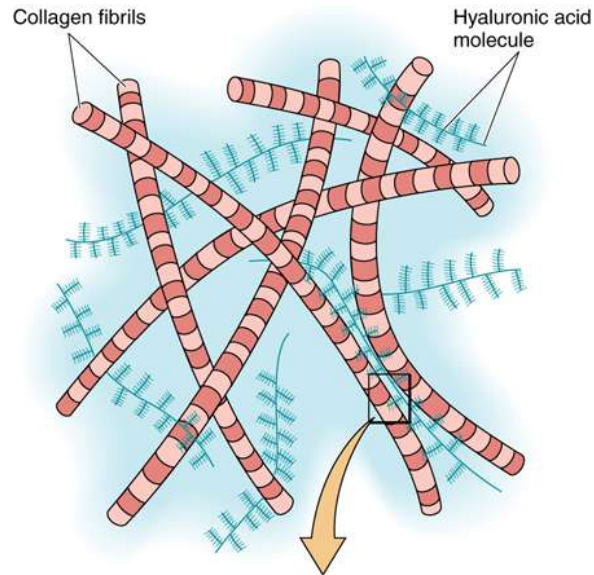
The extracellular matrix, composed of ground substance and fibers, resists compressive and stretching forces.

Ground substance is a hydrated, amorphous material that is composed of **glycosaminoglycans (GAG)**, **proteoglycans**, and **adhesive glycoproteins**, large macromolecules.

Glycosaminoglycans are of two major types:

- **sulfated**, including keratan sulfate, heparan sulfate, heparin, chondroitin sulfates, and dermatan sulfate;
- **nonsulfated**, including *hyaluronic acid*.

Extracellular Matrix-ECM

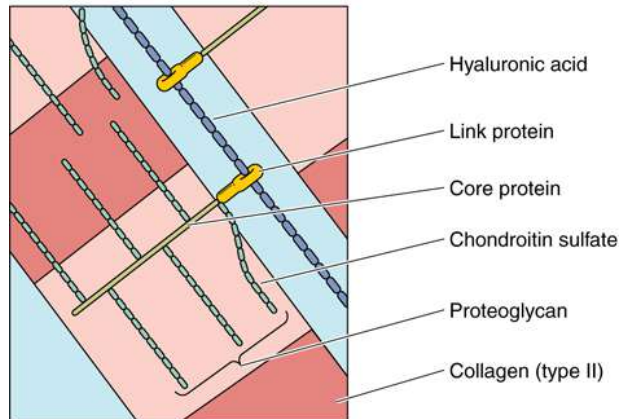


Proteoglycans are covalently linked to hyaluronic acid, forming huge macromolecules called **aggrecan aggregates**, which are responsible for the gel-state of the extracellular matrix.

Adhesive glycoproteins are of various types.

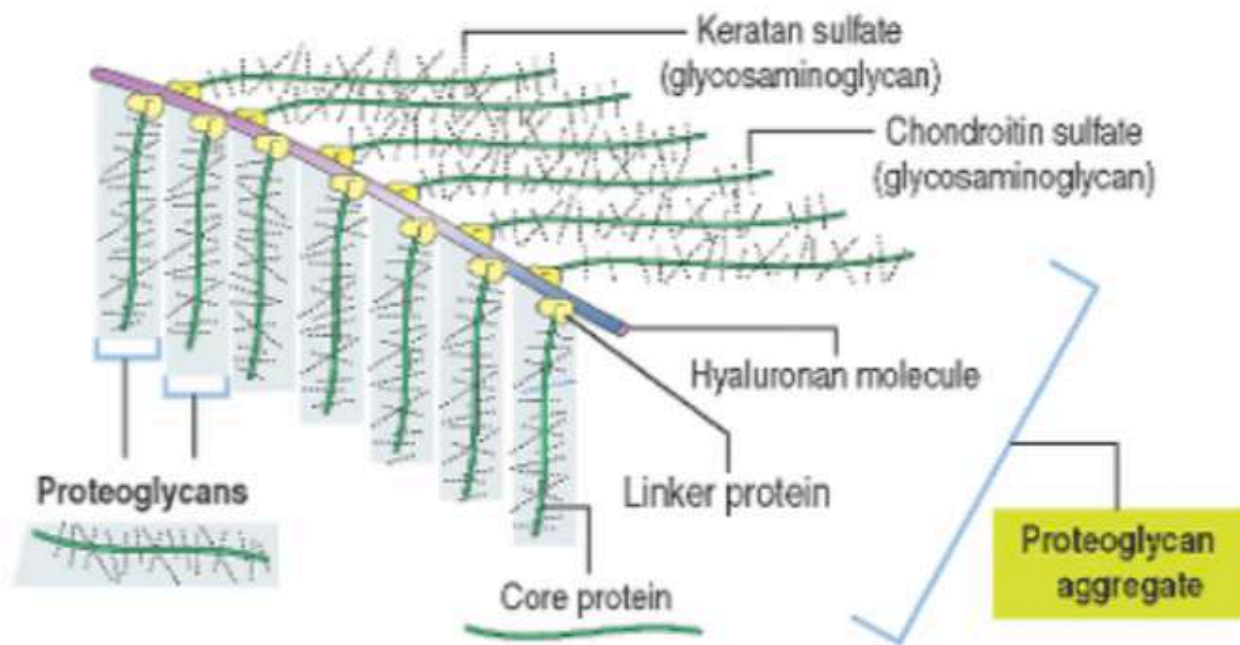
Some are localized preferentially to the basal lamina, such as **laminin**. In cartilage **chondronectin** and bone, such as **osteonectin**,

Still others are generally dispersed throughout the extracellular matrix, such as **fibronectin**.



The association of aggrecan molecules with collagen fibers. *Inset* displays a higher magnification of the aggrecan molecule, indicating the core protein of the proteoglycan molecule to which the glycosaminoglycans are attached. The core protein is attached to the hyaluronic acid by link proteins. (Adapted from Fawcett DW: *Bloom and Fawcett's A Textbook of Histology*, 11th ed. Philadelphia, WB Saunders, 1986.)

Proteoglycan aggregate-ECM



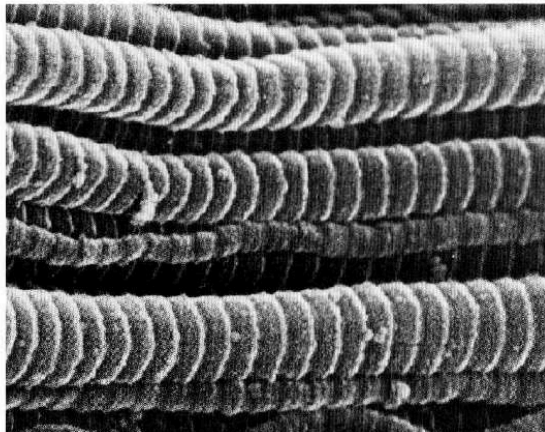
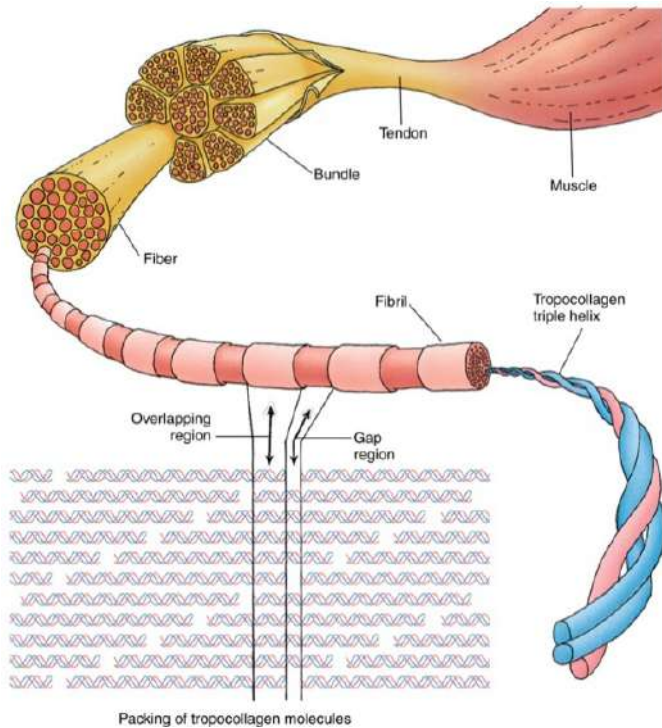
Proteoglycans are extracellular protein complexes of glycosaminoglycans

Proteoglycan aggregates are formed by:

- (1) An axial **hyaluronan molecule**.
- (2) **Core proteins** attached to the hyaluronan molecule by a **linker protein**.
- (3) **Glycosaminoglycans** attached to a core protein.

Several chains of glycosaminoglycans bound to the core protein form a proteoglycan. The molecular mass of a proteoglycan is about 10^8 kd.

Fibers of Connective Tissue



Fibers of the extracellular matrix are

- Collagen and reticular
- elastic fibers.

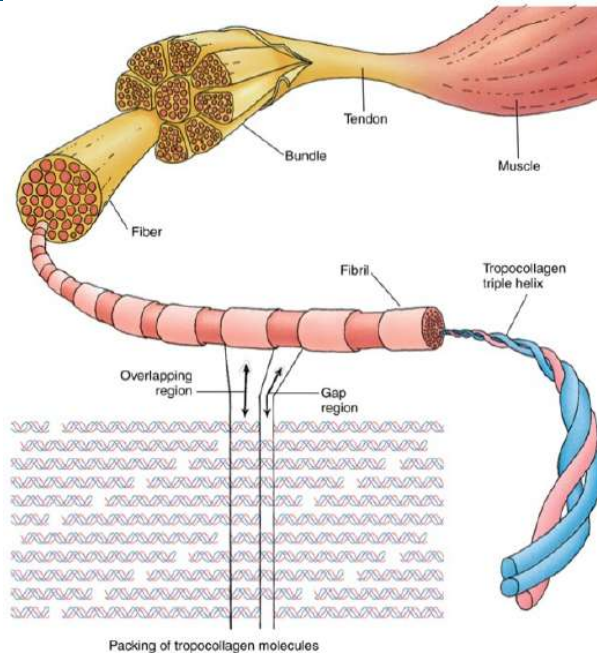
Components of a collagen fiber. The ordered arrangement of the tropocollagen molecules gives rise to gap and overlap regions, responsible for the 67-nm cross-banding of type I collagen.

The *gap region* is the area between the head of one tropocollagen molecule and the tail of the next.

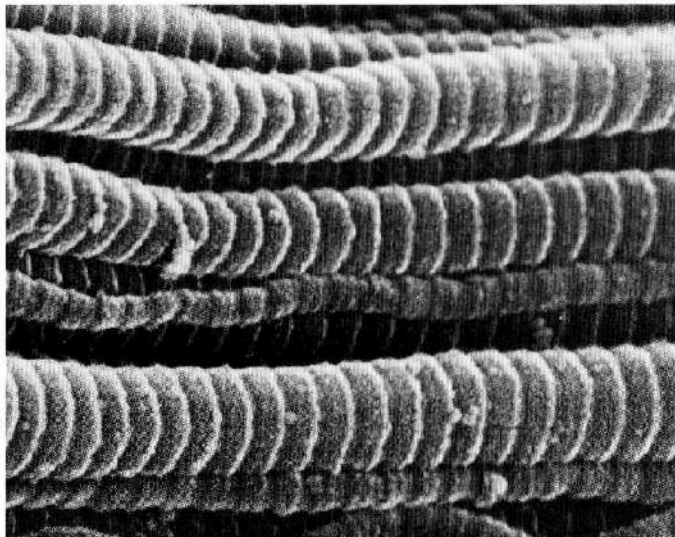
The *overlapping region* is the area where the tail of one tropocollagen molecule overlaps the tail of another in the row above or below.

In three dimensions, the overlap region coincides with numerous other overlap regions, and the gap regions coincide with numerous other gap regions.

Fibers of Connective Tissue- Collagen



The heavy metals that are used in electron microscopy precipitate into the gap regions and make them visible as the 67-nm cross-banding. Type I collagen is composed of two identical $\alpha 1(I)$ chains (*blue*) and one $\alpha 2(I)$ chain (*pink*).



Collagen fibers are *inelastic* and possess great **tensile strength**.

Each fiber is composed of fine subunits, the tropocollagen molecule, composed of three α -chains wrapped around one another in a helical configuration.

At least 20 different types of collagen fibers are known, which vary in the amino acid sequences of their α -chains. The six major collagen types are:

Type I: in connective tissue proper, bone, dentin, and cementum

Type II: in hyaline and elastic cartilages

Type III: reticular fibers

Type IV: lamina densa of the basal lamina,

Type V: associated with type I collagen and in the placenta

Type VII: attaching the basal lamina to the lamina reticularis.

Table 6.1 MAJOR TYPES AND CHARACTERISTICS OF COLLAGEN

Molecular Type	Molecular Formula	Synthesizing Cells	Function	Location in Body
I (fibril-forming); most common of all collagens	$[\alpha 1(I)]_2\alpha 2(I)$	Fibroblasts, osteoblasts, odontoblasts, cementoblasts	Resists tension	Dermis, tendon, ligaments, capsules of organs, bone, dentin, cementum
II (fibril-forming)	$[\alpha 1(II)]_2$	Chondroblasts	Resists pressure	Hyaline cartilage, elastic cartilage
III (fibril-forming); also known as reticular fibers; highly glycosylated	$[\alpha 1(III)]_2$	Fibroblasts, reticular cells, smooth muscle cells, hepatocytes	Forms structural framework of spleen, liver, lymph nodes, smooth muscle, adipose tissue	Lymphatic system, spleen, liver, cardiovascular system, lung, skin
IV (network-forming); do not display 67-nm periodicity, and alpha chains retain propeptides	$[\alpha 1(IV)]_2\alpha 2(IV)$	Epithelial cells, muscle cells, Schwann cells	Forms meshwork of lamina densa of basal lamina to provide support and filtration	Basal lamina
V (fibril-forming)	$[\alpha 1(V)]_2\alpha 2(V)$	Fibroblasts, mesenchymal cells	Associated with type I collagen, also with placental ground substance	Dermis, tendon, ligaments, capsules of organs, bone, cementum, placenta
VII (network-forming); form dimers that assemble into anchoring fibrils	$[\alpha 1(VII)]_2$	Epidermal cells	Forms anchoring fibrils that fasten lamina densa to underlying lamina reticularis	Junction of epidermis and dermis

Reticular Connective Tissue

Reticular connective tissue contains **reticular fibers**, which form the **stroma** of organs of the lymphoid-immune system (for example, lymph nodes and spleen), the hematopoietic bone marrow and the liver.

This type of connective tissue provides a delicate meshwork to allow passage of cells and fluid.

Type III: reticular fibers

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x=31524&y=3317&z=33.8](http://www.histologyguide.com/slideview/MH-078-lymph-node/03-quiz-1.html?x=31524&y=3317&z=33.8)

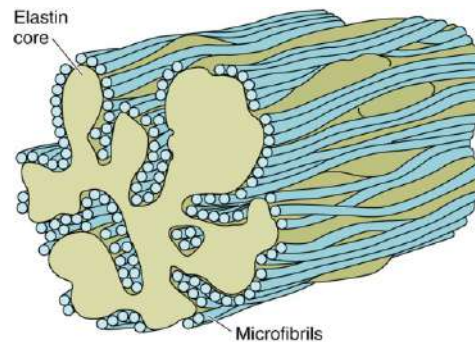
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Fibers of Connective Tissue - Elastic

Elastic connective tissue contains irregularly arranged elastic fibers. These are found in ligaments of the vertebral column or concentrically arranged **laminae** in the wall of the aorta. This type of connective tissue provides **elasticity**.

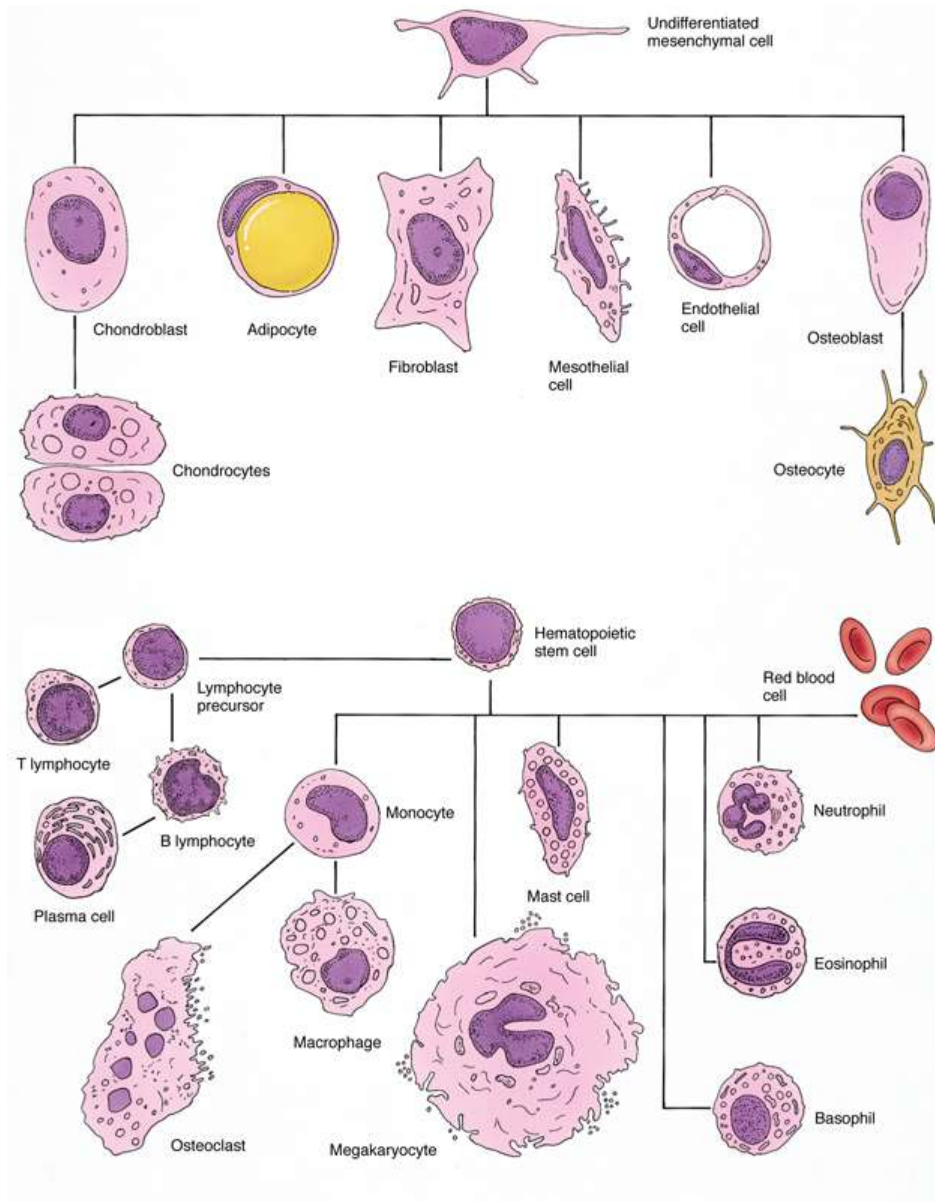
Elastic fibers are composed of **elastin** and **microfibrils**. These fibers are highly elastic and may be stretched to 150% of their resting length without breaking. **Elastin** is an amorphous material whose main amino acid components are **glycine** and **proline**. Additionally, elastin is rich in lysine, the amino acid responsible for the formation of the highly deformable **desmosine residues** that impart a high degree of elasticity to these fibers.

An elastic fiber, showing microfibrils surrounding the amorphous elastin..



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Cells of Connective Tissue Proper



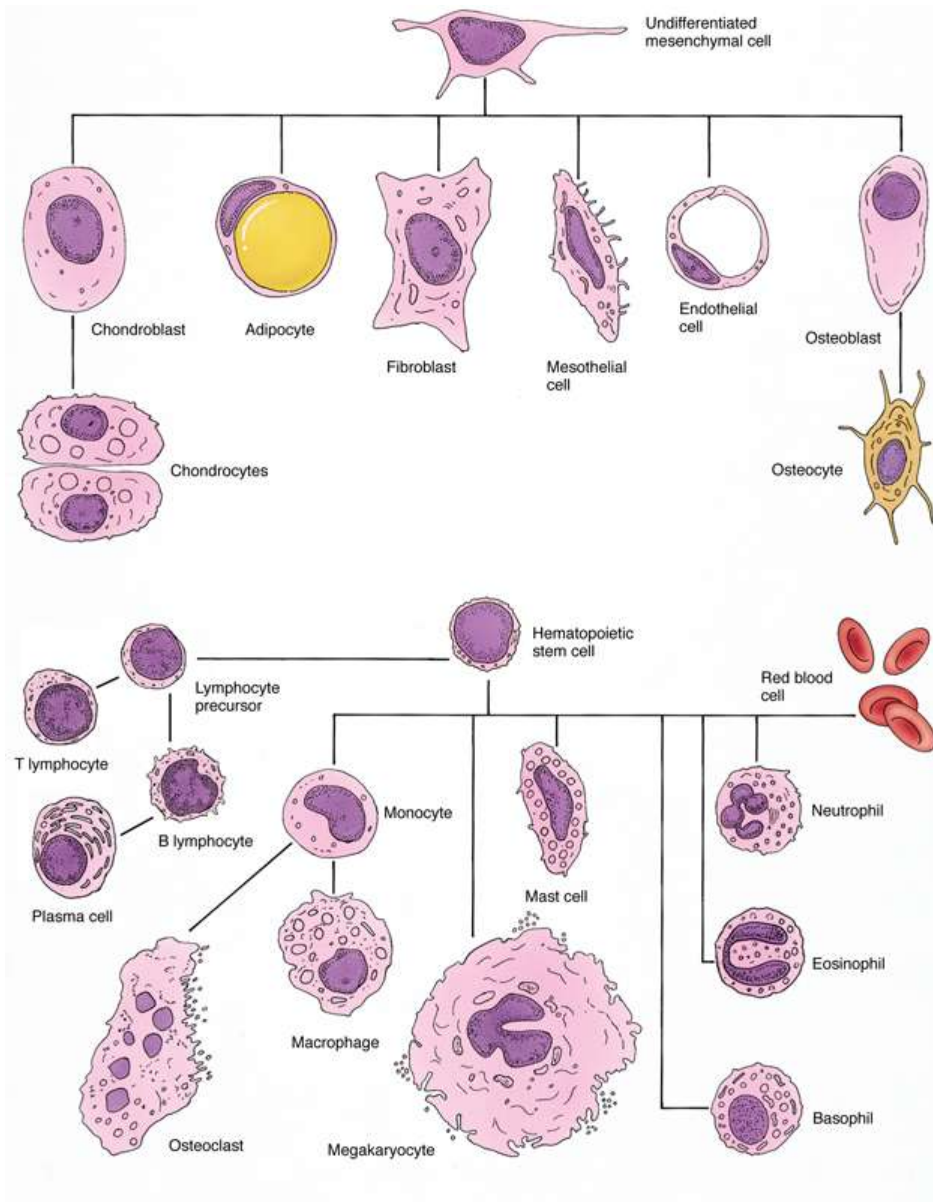
Origins of connective tissue cells (not drawn to scale).

The cells in connective tissues are grouped into two categories, **fixed (resident) cells** and **transient cells**.

Fixed cells are a resident population of cells that have developed and remain in place within the connective tissue, where they perform their functions. The fixed cells are a stable and long-lived population that include:

- fibroblasts,
- adipose cells,
- pericytes,
- mast cells
- macrophages.

Cells of Connective Tissue Proper



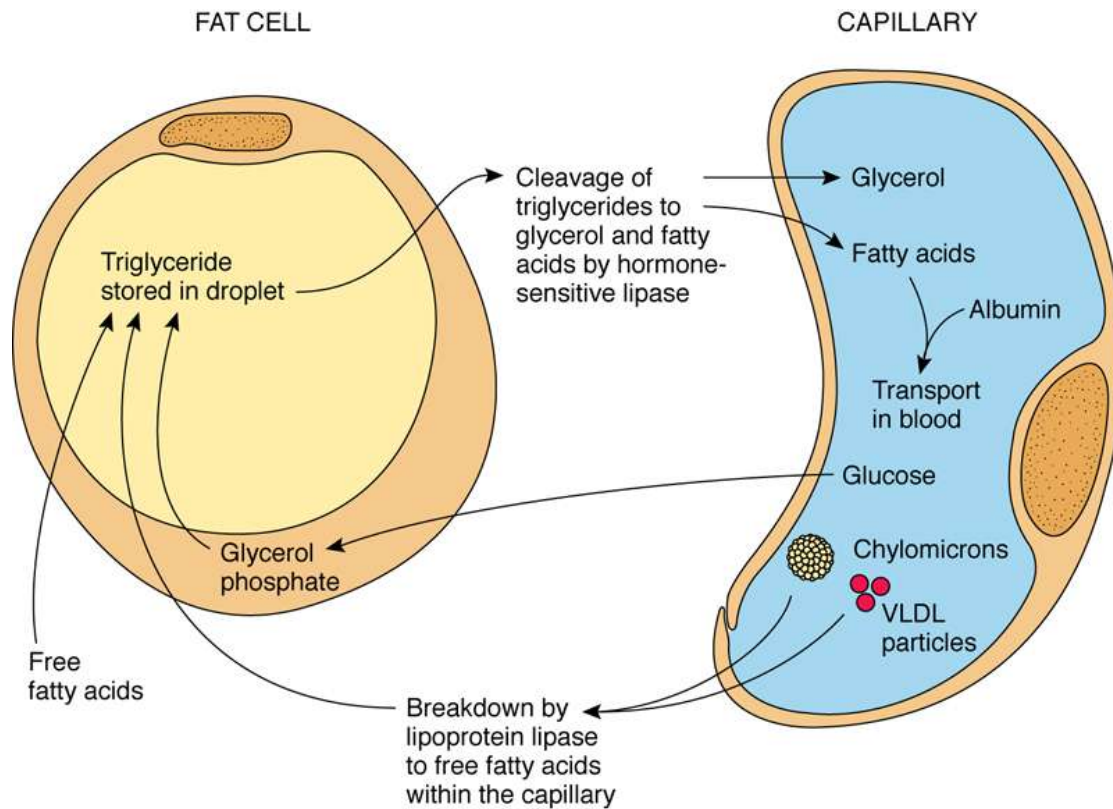
Origins of connective tissue cells (not drawn to scale).

Transient cells (free or wandering cells) originate mainly in the bone marrow and circulate in the bloodstream.

Upon receiving the proper stimulus or signal, these cells leave the bloodstream and migrate into the connective tissue to perform their specific functions. Because most of these motile cells are usually short-lived, they must be replaced continually from a large population of stem cells. Transient cells include:

- *plasma cells,*
- *lymphocytes,*
- *neutrophils,*
- *eosinophils,*
- *basophils,*
- *monocytes,*
- *Macrophages!!* Note that some macrophages are fixed whereas others are transient.

Fat Cell



There are two types of fat cells, which constitute two types of adipose tissue.

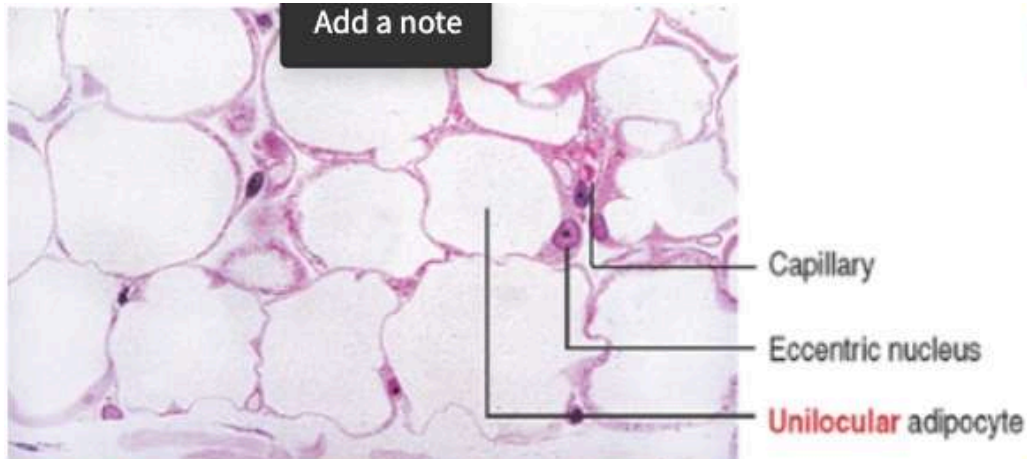
Cells with a single, large lipid droplet, called **unilocular fat cells**, form **white adipose tissue**, and cells with multiple, small lipid droplets, called **multilocular fat cells**, form **brown adipose tissue**.

White fat is much more abundant than brown fat.

Transport of lipid between a capillary and an adipocyte. Lipids are transported in the bloodstream in the form of chylomicrons and very-low-density lipoproteins (VLDLs). The enzyme lipoprotein lipase, manufactured by the fat cell and transported to the capillary lumen, hydrolyzes the lipids to fatty acids and glycerol. Fatty acids diffuse into the connective tissue of the adipose tissue and into the lipocytes, where they are reesterified into triglycerides for storage. When required, triglycerides stored within the adipocyte are hydrolyzed by *hormone-sensitive lipase* into fatty acids and glycerol. These then enter the connective tissue spaces of adipose tissue and from there into a capillary, where they are bound to albumin and transported in the blood. Glucose from the capillary can be transported to adipocytes, which can manufacture lipids from carbohydrate sources.

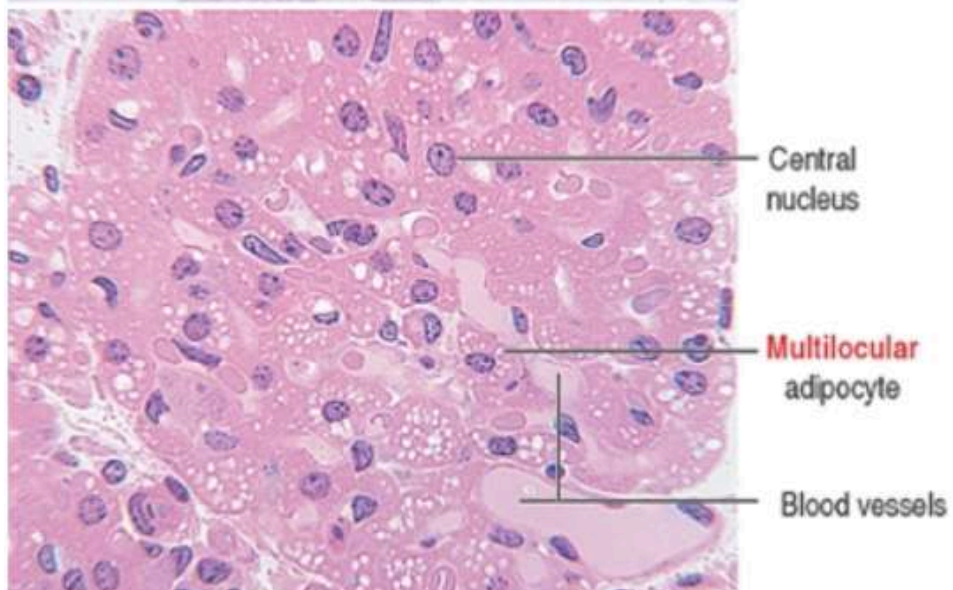
There are two classes of adipose tissue:

- 1. White adipose tissue (WAT), the major reserve of long-term energy and also an endocrine tissue.**
- 2. Brown adipose tissue (BAT), which participates in thermogenesis and also endocrine secretion.**



White adipose tissue (WAT) | Unilocular adipocyte

A **single large fat inclusion**, resulting from coalescing multiple lipid droplets, pushes the nucleus to an eccentric position. WAT in this preparation is unstained.



Brown adipose tissue (BAT) | Multilocular adipocyte

Aggregates of epithelial-like **multilocular, mitochondria-rich adipocytes surrounded by abundant blood vessels** are characteristic of brown fat.

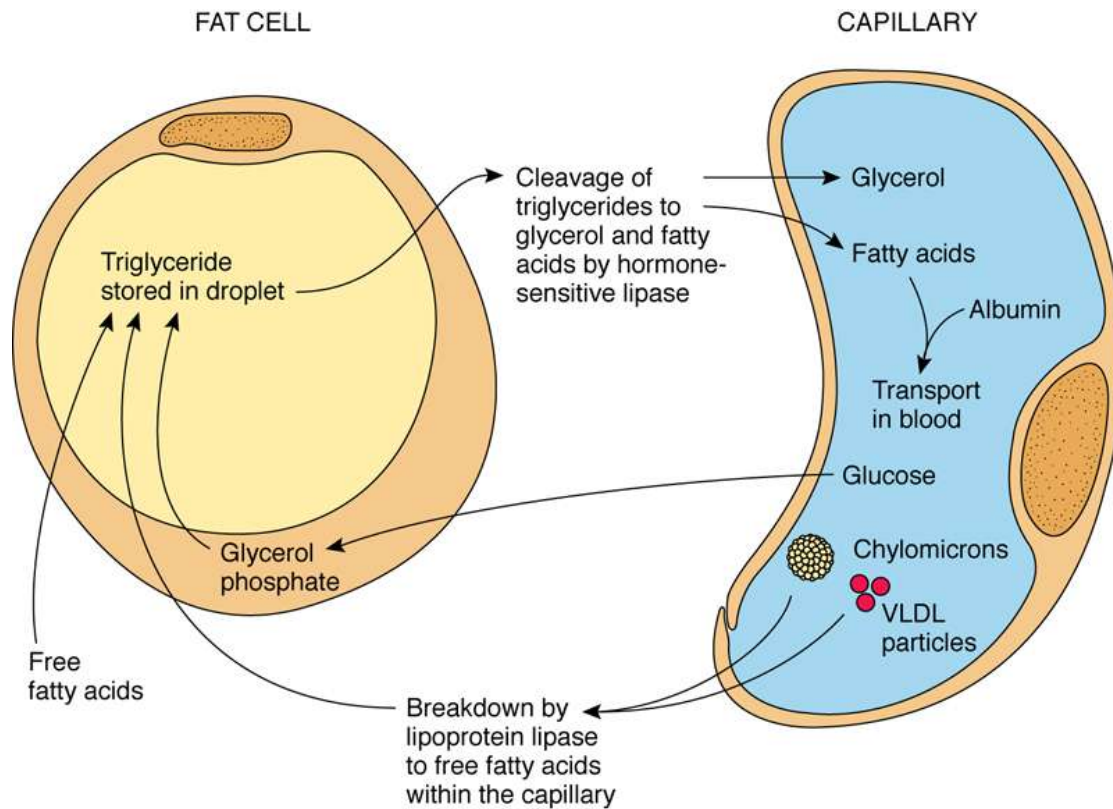
The main function of BAT is to dissipate energy instead of storing it as does WAT. Heat is generated by uncoupling the production of ATP from the movement of H^+ across the inner mitochondrial membrane down the concentration gradient.

Uncoupling protein-1 (UCP-1) activates the uncoupling.

Elevation of circulating **succinate** can activate BAT thermogenesis following exposure to cold.

Mitochondrial biogenesis and expression of **UCP-1 protein** are key features of thermogenesis by BAT.

Fat Cell



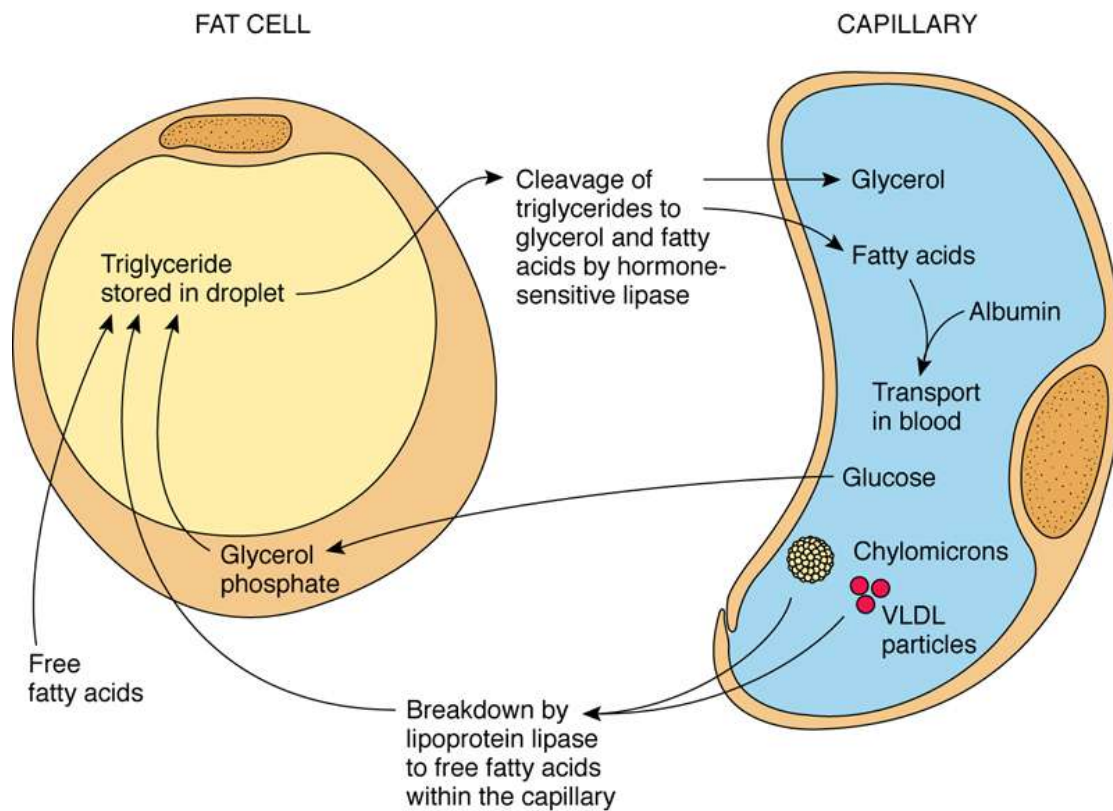
Transport of lipid between a capillary and an adipocyte. Lipids are transported in the bloodstream in the form of chylomicrons and very-low-density lipoproteins (VLDLs). The enzyme lipoprotein lipase, manufactured by the fat cell and transported to the capillary lumen, hydrolyzes the lipids to fatty acids and glycerol. Fatty acids diffuse into the connective tissue of the adipose tissue and into the lipocytes, where they are reesterified into triglycerides for storage. When required, triglycerides stored within the adipocyte are hydrolyzed by *hormone-sensitive lipase* into fatty acids and glycerol. These then enter the connective tissue spaces of adipose tissue and from there into a capillary, where they are bound to albumin and transported in the blood. Glucose from the capillary can be transported to adipocytes, which can manufacture lipids from carbohydrate sources.

Adipocytes of white fat are large spherical cells, up to 120 μm in diameter, that become polyhedral when crowded into adipose tissue.

Once in the capillaries of adipose tissue, VLDL (very-low-density lipoproteins), fatty acids, and chylomicrons (ultra low-density lipoproteins) are exposed to **lipoprotein lipase** (manufactured by fat cells).

The fatty acids enter the connective tissue and diffuse through the cell membranes of adipocytes. These cells then **combine their own glycerol phosphate with the imported fatty acids to form triglycerides**, which are added to the forming lipid droplets within the adipocytes until needed.

Fat Cell



Epinephrine and **norepinephrine** bind to their respective receptors of the adipocyte plasmalemma, activating **adenylate cyclase** to form **cyclic adenosine monophosphate (cAMP)**, a second messenger, resulting in activation of **hormone-sensitive lipase**.

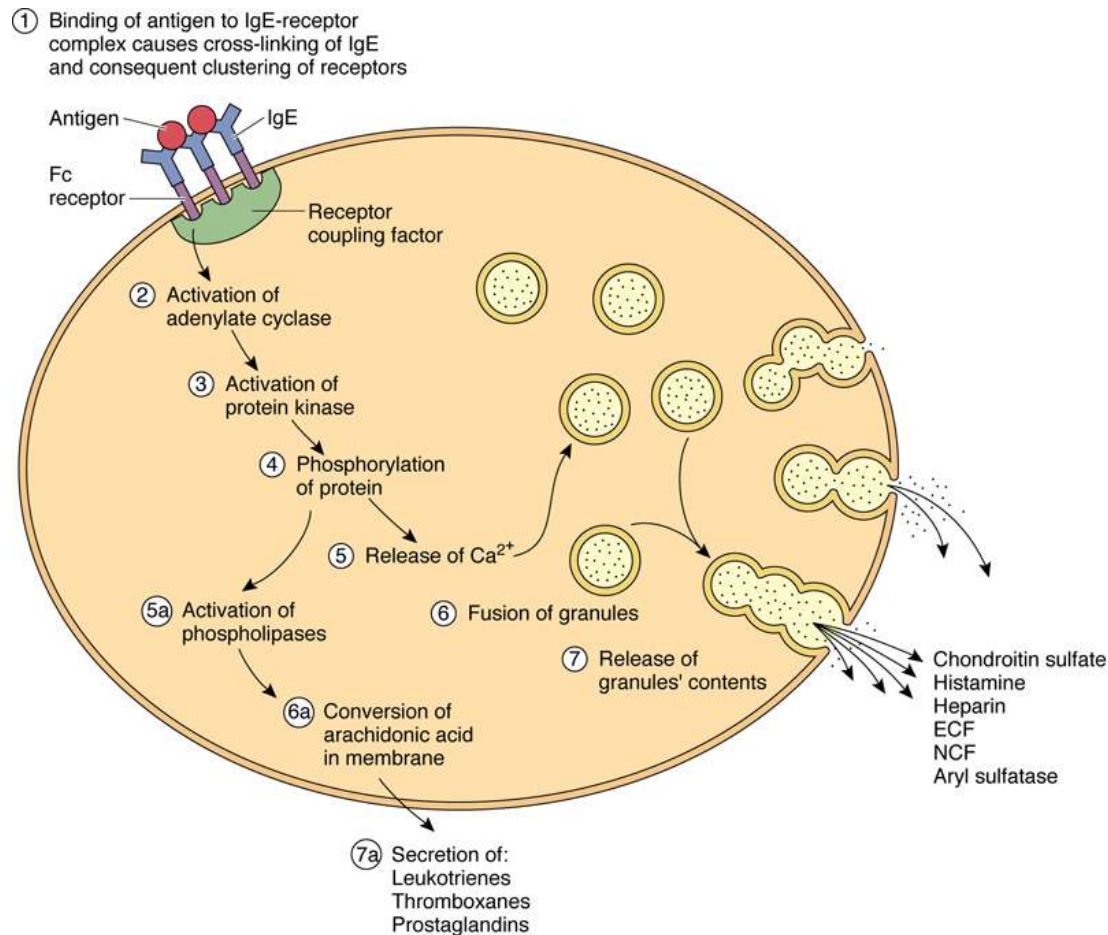
This latter enzyme cleaves triglycerides into fatty acids and glycerol, which are released into the bloodstream.

Transport of lipid between a capillary and an adipocyte. Lipids are transported in the bloodstream in the form of chylomicrons and very-low-density lipoproteins (VLDLs). The enzyme lipoprotein lipase, manufactured by the fat cell and transported to the capillary lumen, hydrolyzes the lipids to fatty acids and glycerol. Fatty acids diffuse into the connective tissue of the adipose tissue and into the lipocytes, where they are reesterified into triglycerides for storage. When required, triglycerides stored within the adipocyte are hydrolyzed by *hormone-sensitive lipase* into fatty acids and glycerol. These then enter the connective tissue spaces of adipose tissue and from there into a capillary, where they are bound to albumin and transported in the blood. Glucose from the capillary can be transported to adipocytes, which can manufacture lipids from carbohydrate sources.

Visualization of fat in histology sections

- Fat is dissolved by solvents (xylene) used during paraffin embedding, a step required for thin sectioning and preparation of histology sections. A narrow cytoplasmic rim, surrounding a central empty space where fat is stored, can be visualized.
- Fat that is fixed and stained with osmium tetroxide appears brown. This reagent is also used for the visualization of lipid-rich myelin in nerves.
- Alcoholic solutions of fat-soluble dyes (such as Sudan III or Sudan black) can also be used for the detection of aggregates of fat droplets in frozen sections.

Mast Cell



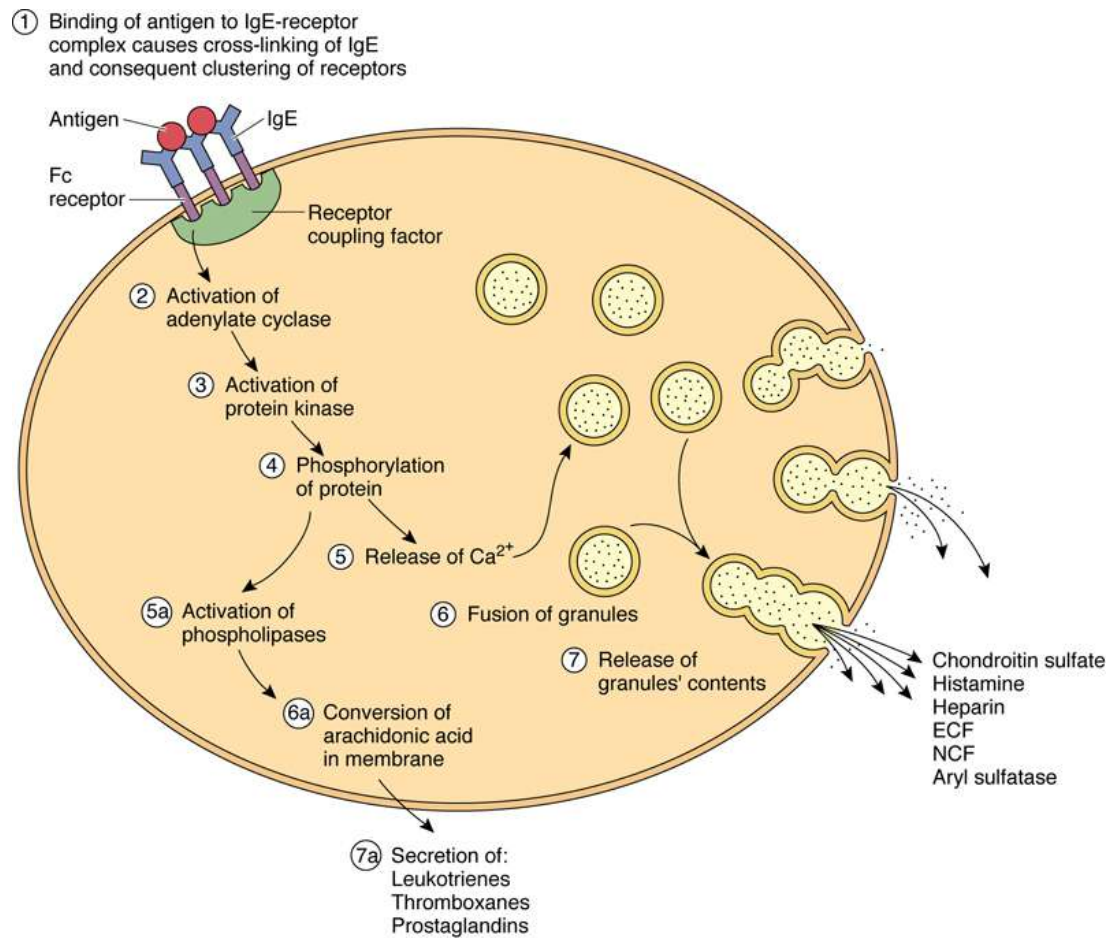
Mast cells, among the largest of the fixed cells of the connective tissue, are 20 to 30 μm in diameter, are ovoid and possess a centrally placed, spherical nucleus.

They possess membrane-bound granules that contain **heparin**, **neutral proteases**, **aryl sulfatase** (as well as other enzymes), **eosinophil chemotactic factor (ECF)**, and **neutrophil chemotactic factor (NCF)**.

These pharmacological agents present in the granules are referred to as the **primary mediators** (also known as **preformed mediators**).

Binding of antigens and cross-linking of immunoglobulin E (IgE)-receptor complexes on the mast cell plasma membrane. This event triggers a cascade that ultimately results in the synthesis and release of leukotrienes and prostaglandins as well as in degranulation, thus releasing histamine, heparin, eosinophil chemotactic factor (ECF), and neutrophil chemotactic factor (NCF).

Mast Cell



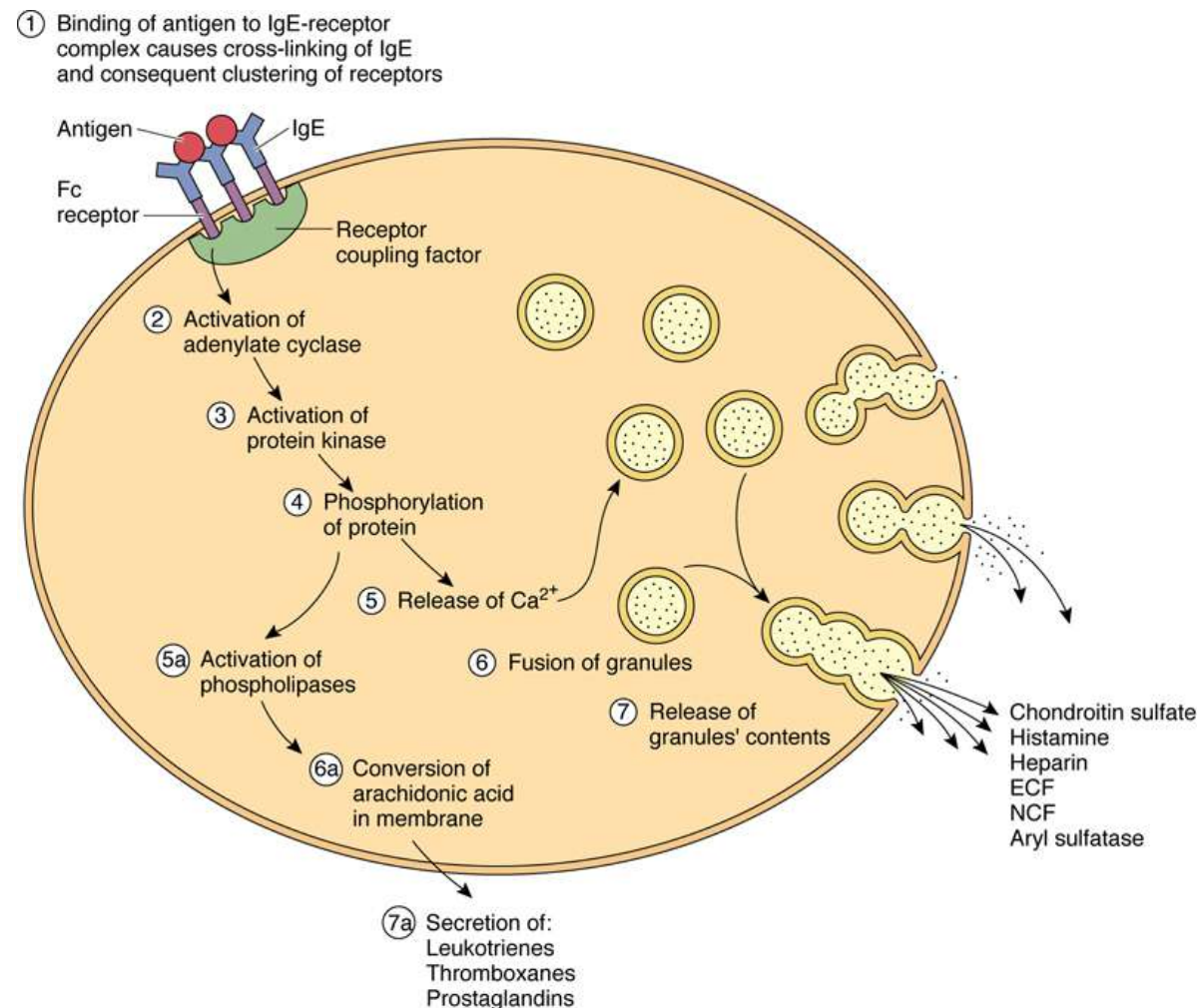
Besides the substances found in the granules, mast cells synthesize a number of mediators from membrane arachidonic acid precursors. These newly synthesized mediators include **leukotrienes, thromboxanes, and prostaglandins (PGD₂)**.

A number of other **cytokines** are also released that are not arachidonic acid precursors. All these newly synthesized mediators are formed at the time of their release and are collectively referred to as **secondary (or newly synthesized) mediators**.

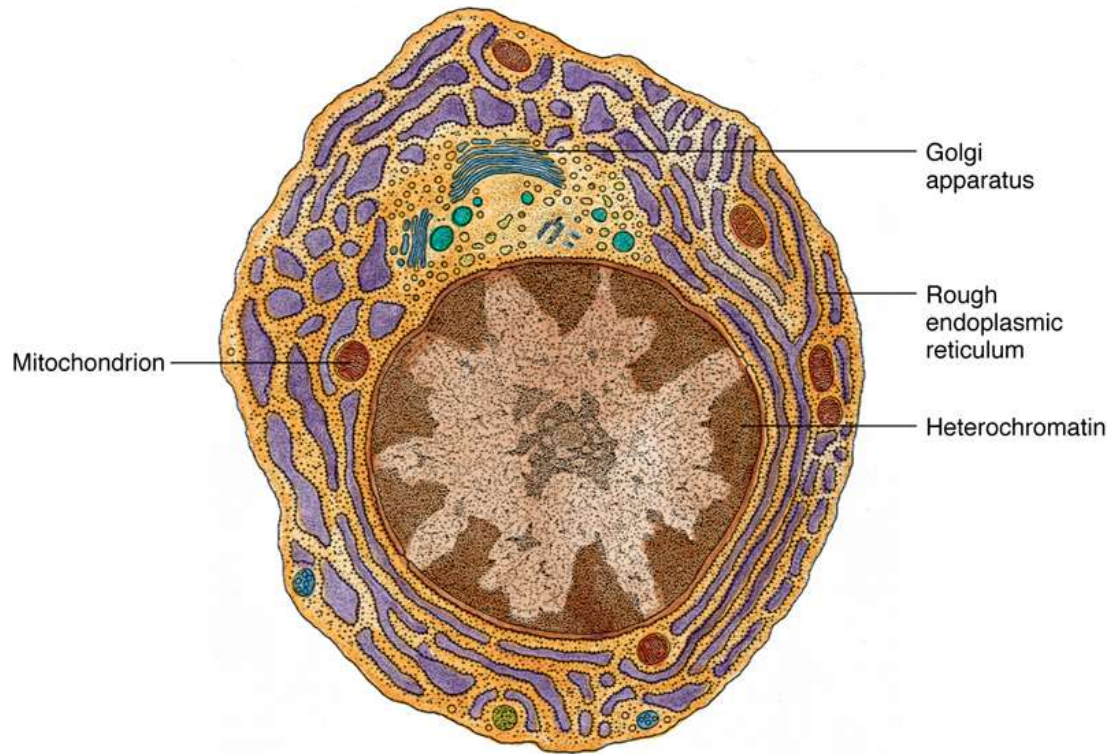
Binding of antigens and cross-linking of immunoglobulin E (IgE)-receptor complexes on the mast cell plasma membrane. This event triggers a cascade that ultimately results in the synthesis and release of leukotrienes and prostaglandins as well as in degranulation, thus releasing histamine, heparin, eosinophil chemotactic factor (ECF), and neutrophil chemotactic factor (NCF).

Mast cell activation responsible for the immediate sensitivity reaction

- Anaphylactic reaction with lethal consequences



Plasma Cell

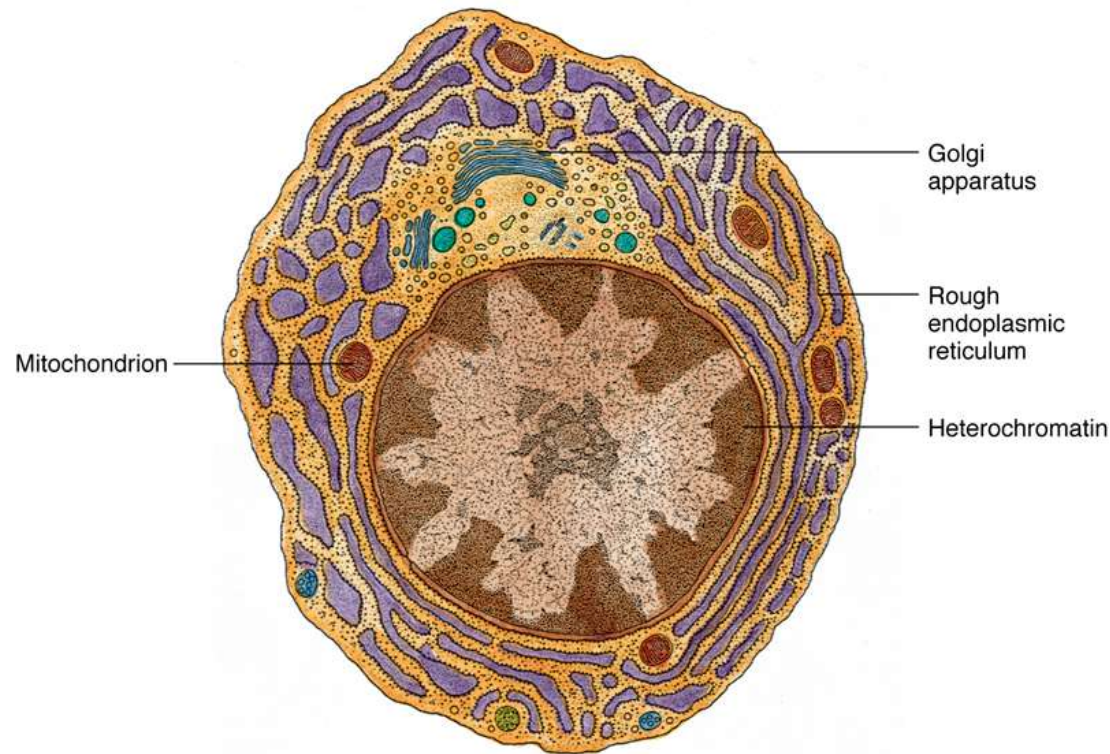


Plasma cells are scattered throughout the connective tissues; they are present in greatest numbers in areas of chronic inflammation and where foreign substances or microorganisms have entered the tissues.

These differentiated cells, which are derived from B lymphocytes that have interacted with antigen, produce and secrete antibodies. Plasma cells are large, ovoid cells, 20 μm in diameter, with an eccentrically placed nucleus that have a relatively short life span of 2 to 3 weeks.

Drawing of a plasma cell as seen in an electron micrograph. The arrangement of heterochromatin gives the nucleus a "clock face" appearance.
(From Lentz TL: *Cell Fine Structure: An Atlas of Drawings of Whole-Cell Structure*. Philadelphia, WB Saunders, 1971.)

Plasma Cell



Their cytoplasm is intensely basophilic as a result of a well-developed RER with closely spaced cisternae.

Only a few mitochondria are scattered between the profiles of RER. Electron micrographs also display a large Golgi complex and a pair of centrioles.

These structures are located in the pale-staining regions adjacent to the nucleus in light micrographs. The spherical nucleus possesses heterochromatin radiating out from the center, giving it a characteristic “clock face” or “spoked” appearance under the light microscope.

Drawing of a plasma cell as seen in an electron micrograph. The arrangement of heterochromatin gives the nucleus a “clock face” appearance.
(From Lentz TL: *Cell Fine Structure: An Atlas of Drawings of Whole-Cell Structure*. Philadelphia, WB Saunders, 1971.)

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Test

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<http://www.histologyguide.com/slideview/MH-119-ileum/02-quiz-1.html?x=30400&y=9934&z=3.7&page=1>

<http://www.histologyguide.com/slideview/MH-017-stratified-epithelia/02-quiz-1.html?x=17062&y=20672&z=31.4&page=1>

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