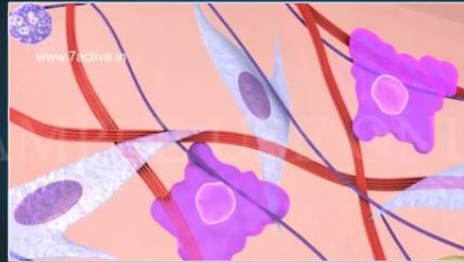


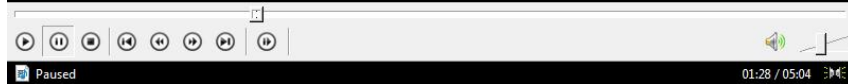
CONNECTIVE TISSUE

1. Loose Connective Tissue

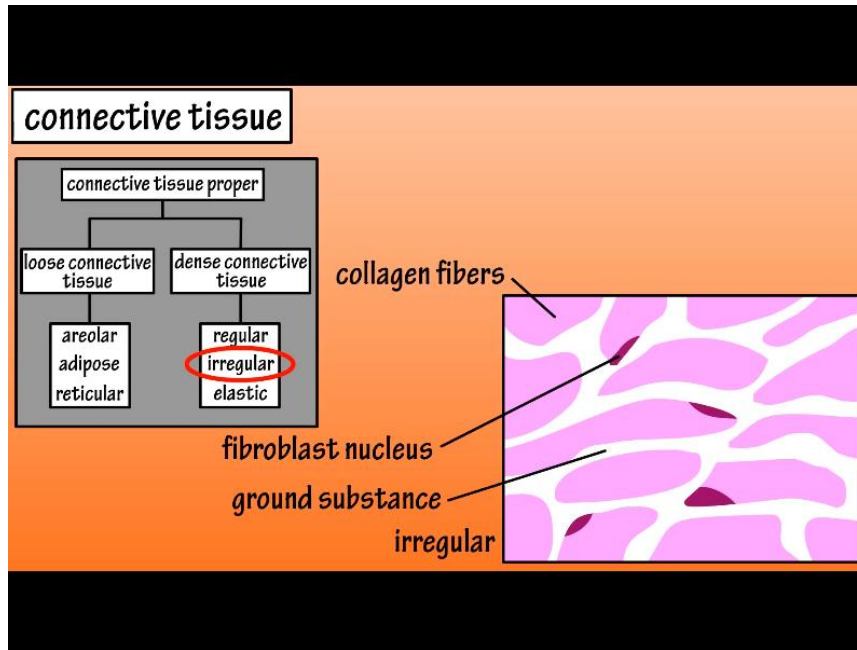
⇒ Areolar tissue



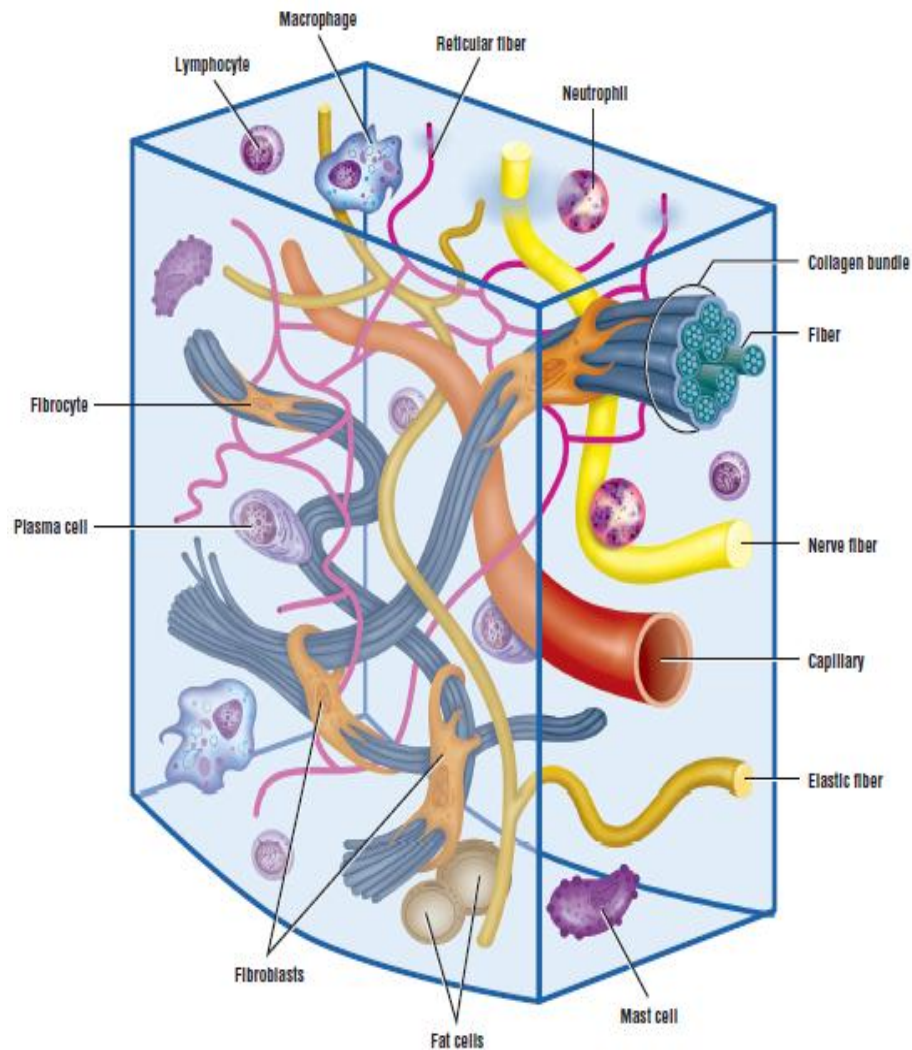
It is present beneath the skin, serves as a support frame work for epithelium. It contains fibroblasts, macrophages and mast cells.



CONNECTIVE TISSUE PART 01.mp4



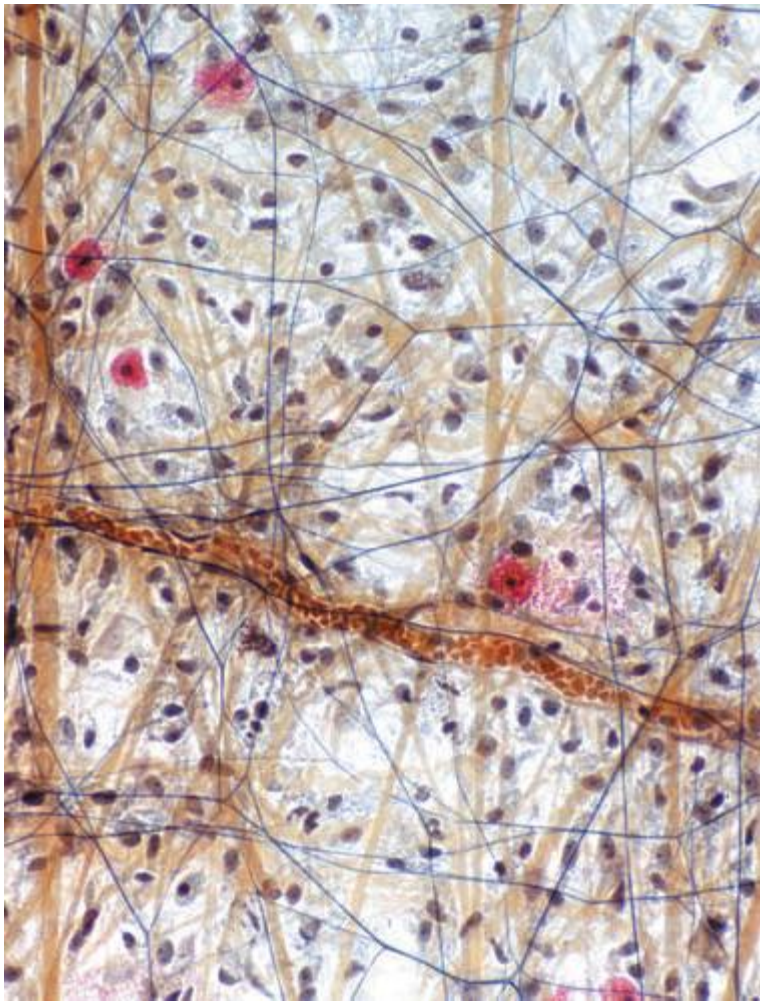
Types Of Connective Tissue - What Is Connective Tissue - Functions Of Connective Tissue.mp4



Connective tissue is formed by three classes of components:

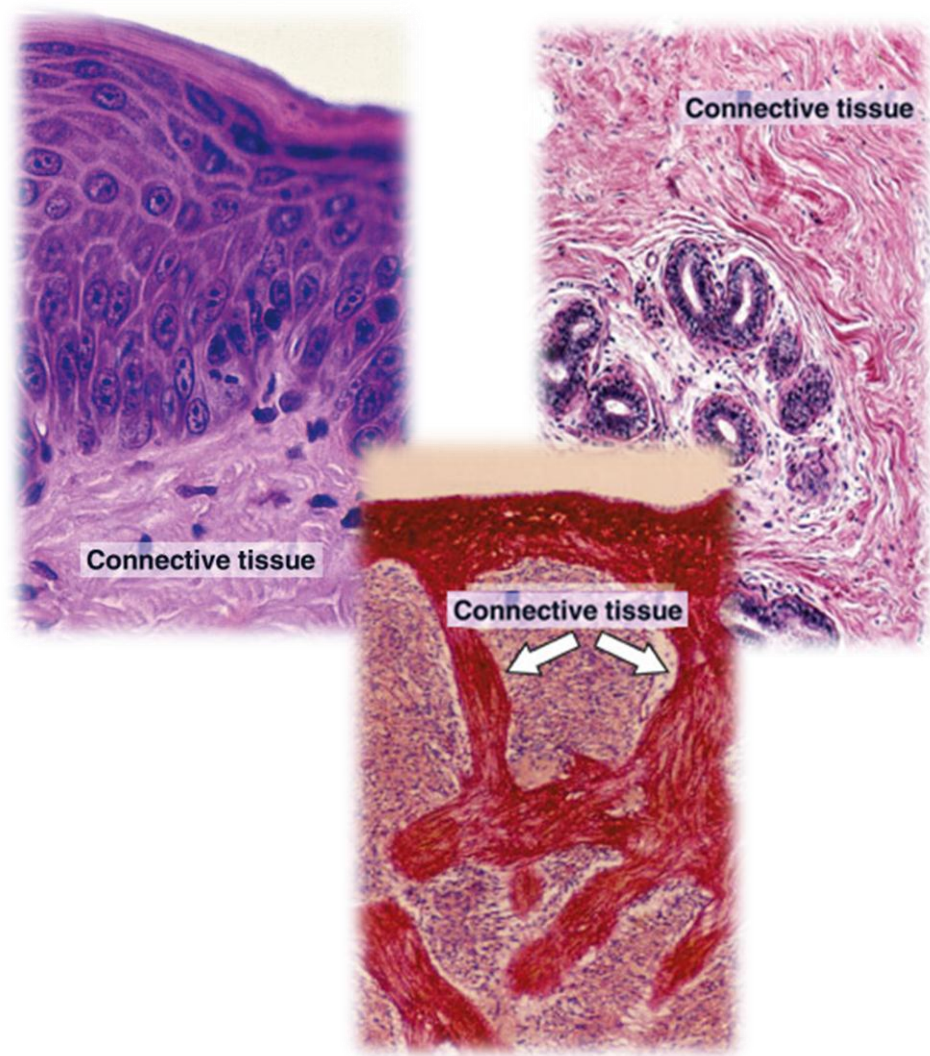
- **Cells;**
 - **Fibers;**
 - **Ground substance.**
- } extracellular
matrix

Extracellular matrices consist of different combinations of **protein fibers** (collagen, reticular, and elastic) and **ground substance**.



Fibers, predominantly composed of collagen, constitute tendons, aponeuroses, capsules of organs, and membranes, forming the most resistant component of the **stroma**, or supporting tissue of organs.

Ground substance is a highly hydrophilic, viscous complex of anionic macromolecules (glycosaminoglycans and proteoglycans) and glycoproteins (laminin, fibronectin, and others) that imparts strength and rigidity to the matrix. The connective tissue matrix is also the medium through which nutrients and metabolic wastes are exchanged between cells and their blood supply.



Connective tissue forms a vast and continuous compartment throughout the body, bounded by the basal laminae of the various epithelia and by the basal or external laminae of muscle cells and nerve-supporting cells. Functioning mechanically, they provide a matrix that connects and binds the cells and organs.

Write this text

Connective tissue is formed by three classes of components: **Cells, Fibers, Ground substance**.

Fibers, predominantly composed of collagen, constitute **tendons, aponeuroses, capsules of organs**, forming component of the **stroma**, or supporting tissue of organs.

Ground substance is a complex of anionic macromolecules (**glycosaminoglycans and proteo-glycans**) and glycoproteins (**laminin, fibronectin, and others**).

Classification of connective tissue

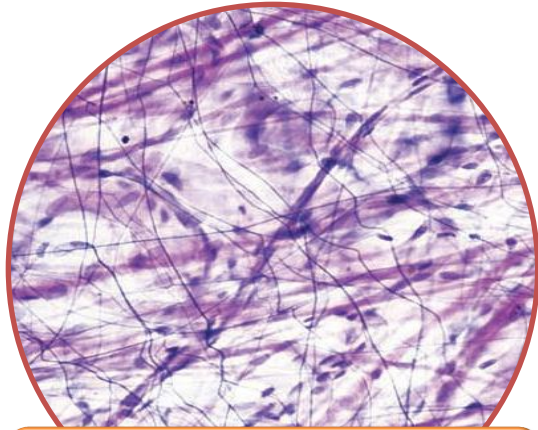
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graph TD; A[Classification of connective tissue] --> B[Connective tissue proper]; A --> C[Specialized connective tissue]
```

Connective tissue proper

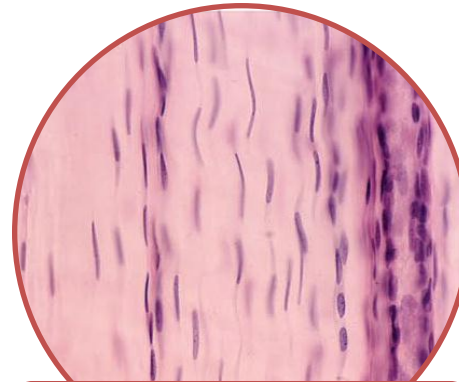
Specialized connective tissue

**Connective tissue
proper**

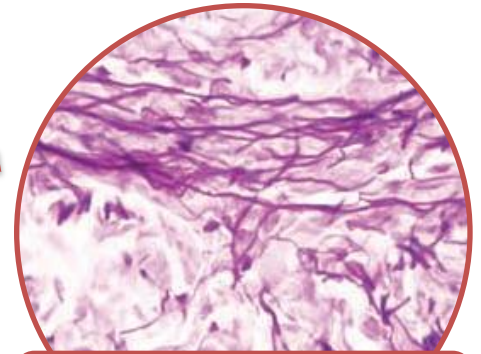
**Dense connective
tissue**



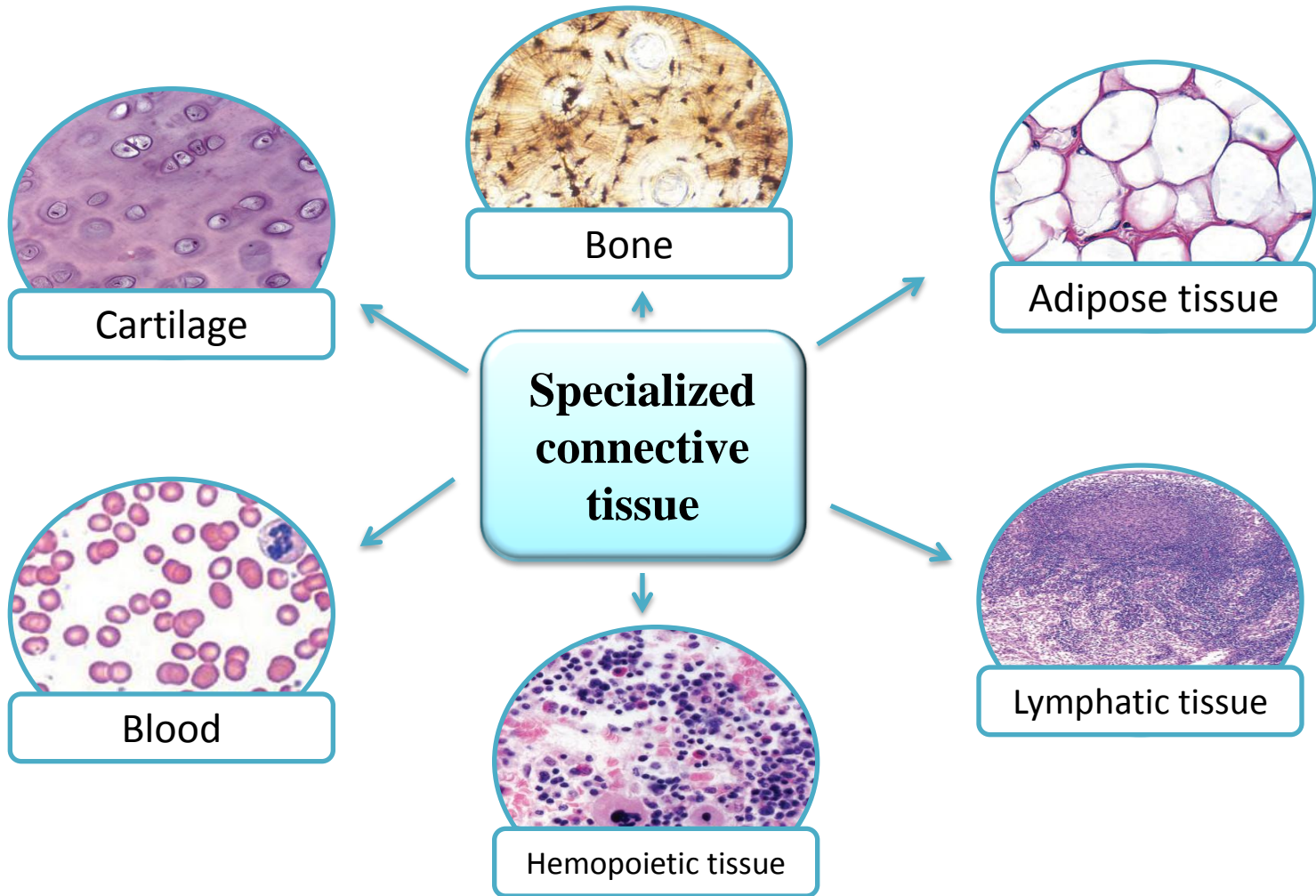
**Loose connective
tissue**



**Dense regular
connective tissue**



**Dense irregular
connective tissue**



Write this text

Classification of connective tissue

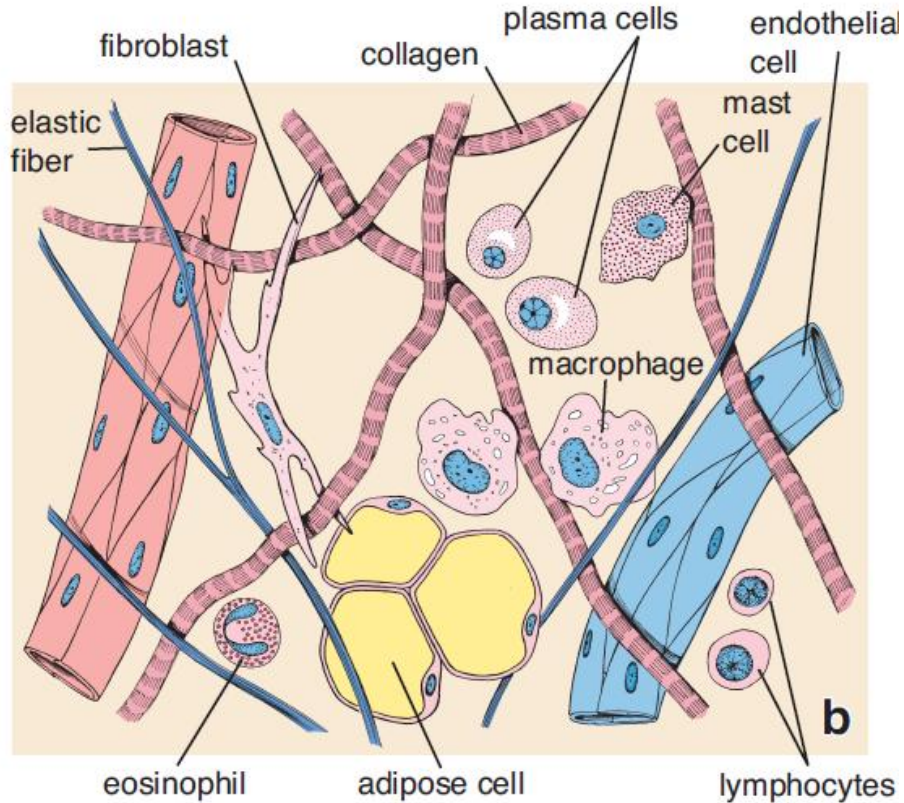
1. Connective tissue proper:

- **Loose** connective tissue
- **Dense** connective tissue (dense irregular connective tissue and dense regular connective tissue)

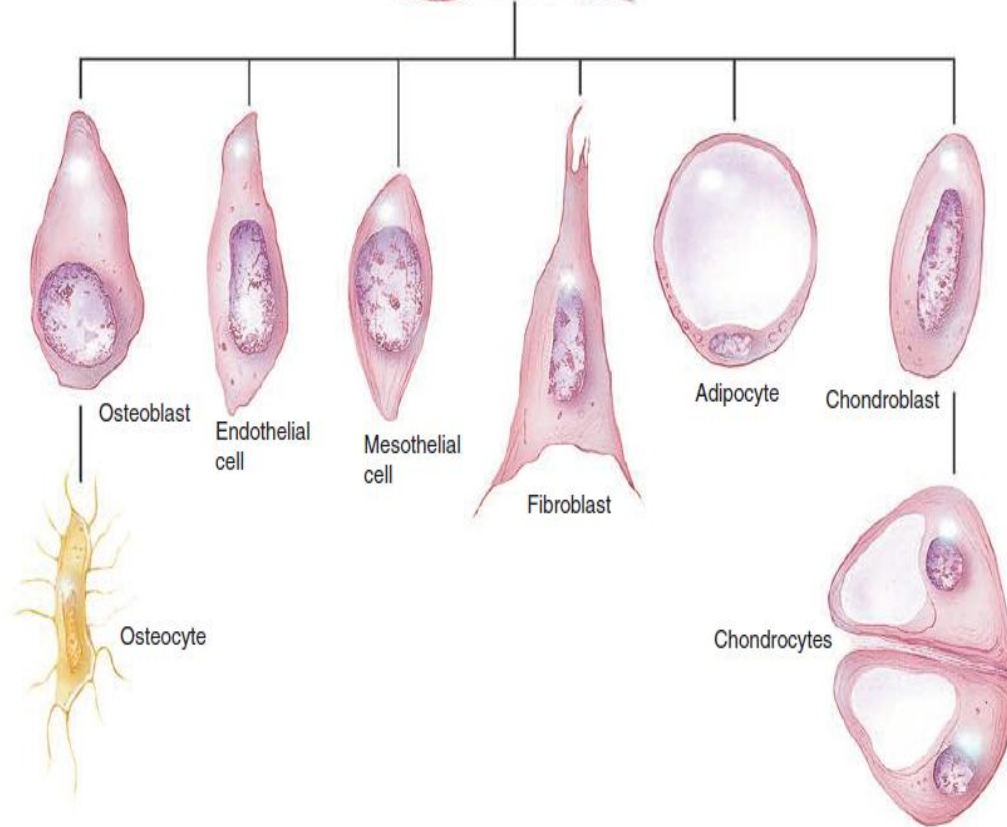
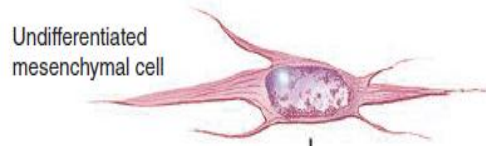
2. Specialized connective tissue:

- Cartilage
- Bone
- Adipose tissue
- Blood
- Hemopoietic tissue
- Lymphatic tissue

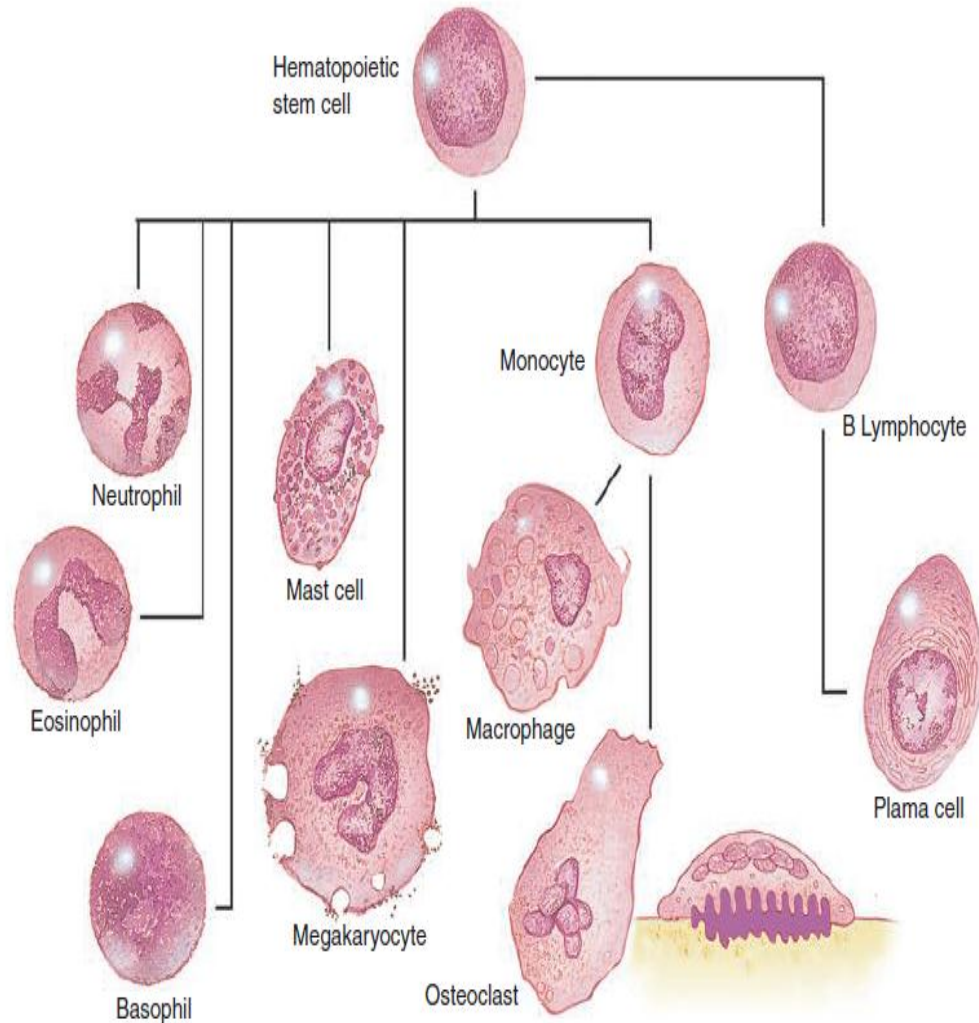
Cells of the Connective Tissue



Various types of cells are present in connective tissue. These can be classed into two distinct categories:



1. Cells that are intrinsic components of connective tissue:
In typical connective tissue the most important cells are ***fibroblasts***. Others present are ***undifferentiated mesenchymal cells, pigment cells, and fat cells***. Other varieties of cells are present in more specialized forms of connective tissues.



2. Cells that belong to the immune system and are identical or closely related with certain cells present in blood and in lymphoid tissues. These include *macrophage cells* (or *histiocytes*), *mast cells*, *lymphocytes* *plasma cells*, *monocytes*, and *eosinophils*.

Write this text

Various types of cells are present in connective tissue.

1.Cells that are intrinsic components of connective tissue:

- **Fibroblasts**
- **Mesenchymal cells**
- **Pigment cells**
- **Fat cells**

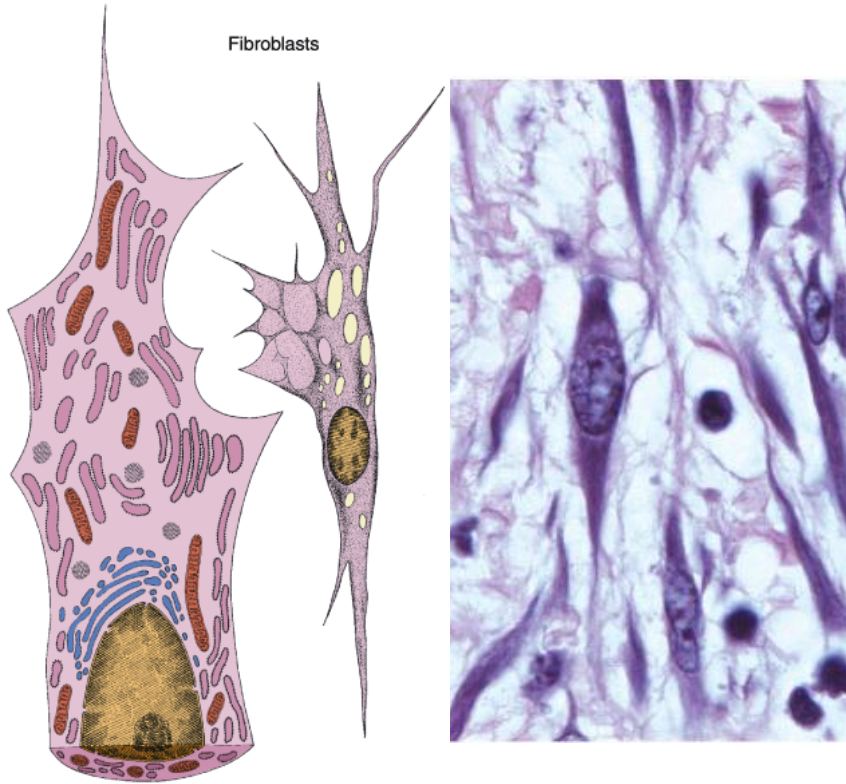
2.Cells that belong to the immune system with certain cells present in blood and in lymphoid tissues:

- **Macrophage cells (or histiocytes)**
- **Mast cells**
- **Lymphocytes**
- **Plasma cells**
- **Monocytes**
- **Eosinophils**

Table 1. Functions of Connective Tissue Cells

Cell Type	Representative Product or Activity	Representative Function
Fibroblast, chondroblast, osteoblast	Production of fibers and ground substance	Structural
Plasma cell	Production of antibodies	Immunological (defense)
Lymphocyte (several types)	Production of immunocompetent cells	Immunological (defense)
Eosinophilic leukocyte	Participation in allergic and vasoactive reactions, modulation of mast cell activities and the inflammatory process	Immunological (defense)
Neutrophilic leukocyte	Phagocytosis of foreign substances, bacteria	Defense
Macrophage	Secretion of cytokines and other molecules, phagocytosis of foreign substances and bacteria, antigen processing and presentation to other cells	Defense
Mast cell and basophilic leukocyte	Liberation of pharmacologically active molecules (eg, histamine)	Defense (participate in allergic reactions)
Adipose (fat) cell	Storage of neutral fats	Energy reservoir, heat production

Fibroblasts

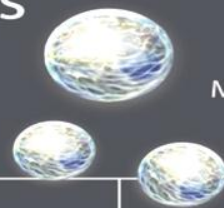


Fibroblasts synthesize collagen, elastin, glycosaminoglycans, proteoglycans, and multiadhesive glycoproteins. Fibroblasts are the most common cells in connective tissue and are responsible for the synthesis of extracellular matrix components. Two stages of activity — active and quiescent — are observed in these cells. Some histologists reserve the term fibroblast to denote the active cell and fibrocyte to denote the quiescent cell.

The Mesengenic Process

Bone Marrow/Perosteum

Mesenchymal Tissue



Mesenchymal Stem Cell (MSC)

Proliferation

Commitment

Lineage Progression

Differentiation

Maturation

Marrow Stroma

Osteogenesis

Chondrogenesis

Tendogenesis

Myogenesis

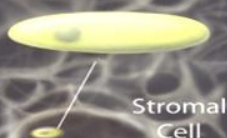
Adipogenesis



Transitory Stromal Cell



Unique Micro-niche



Stromal Cell

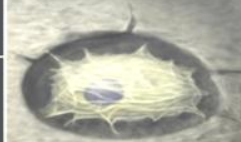
MARROW



Transitory Osteoblast

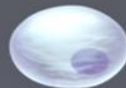


Osteoblasts

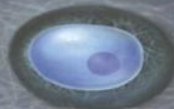


Osteocyte

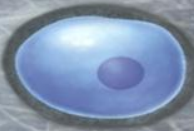
BONE



Transitory Chondrocyte

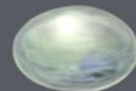


Chondrocyte



Hypertrophic Chondrocyte

CARTILAGE



Transitory Fibroblast



Fibroblast



T/L Fibroblast

TENDON



Transitory Myoblast



Myoblast Fusion



Myotube

MUSCLE



Transitory Adipocyte



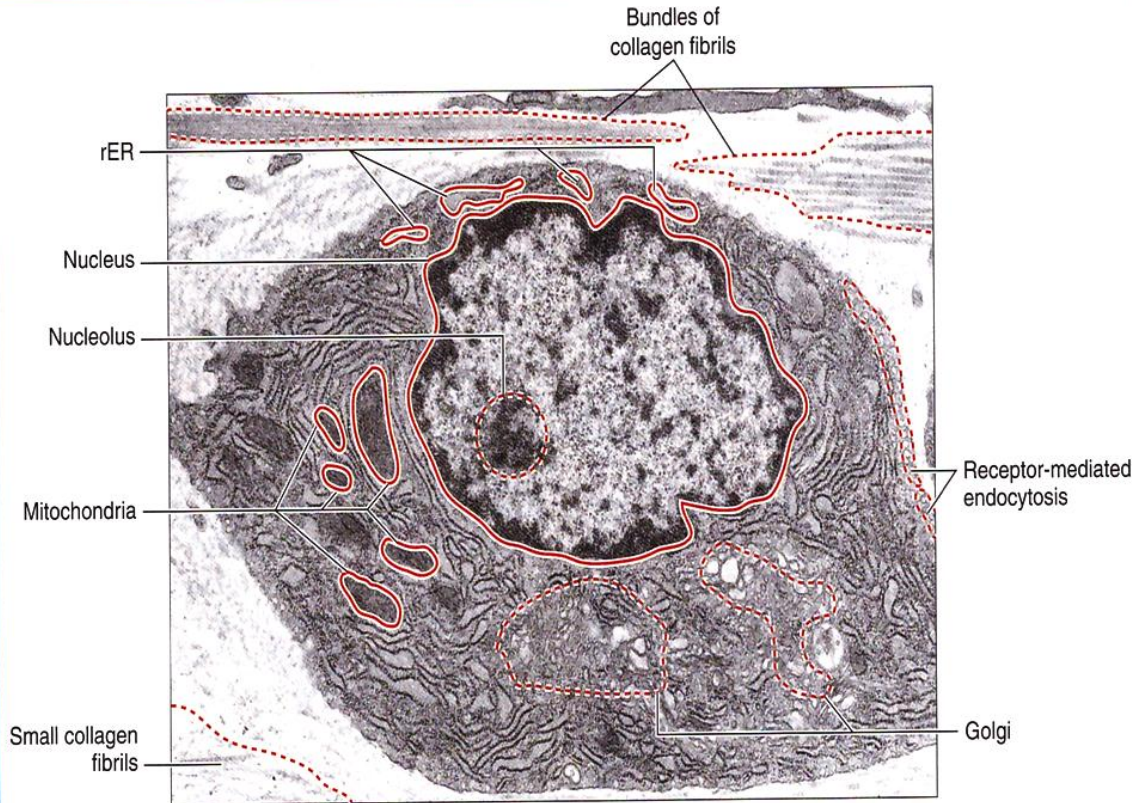
Pre-adipocyte



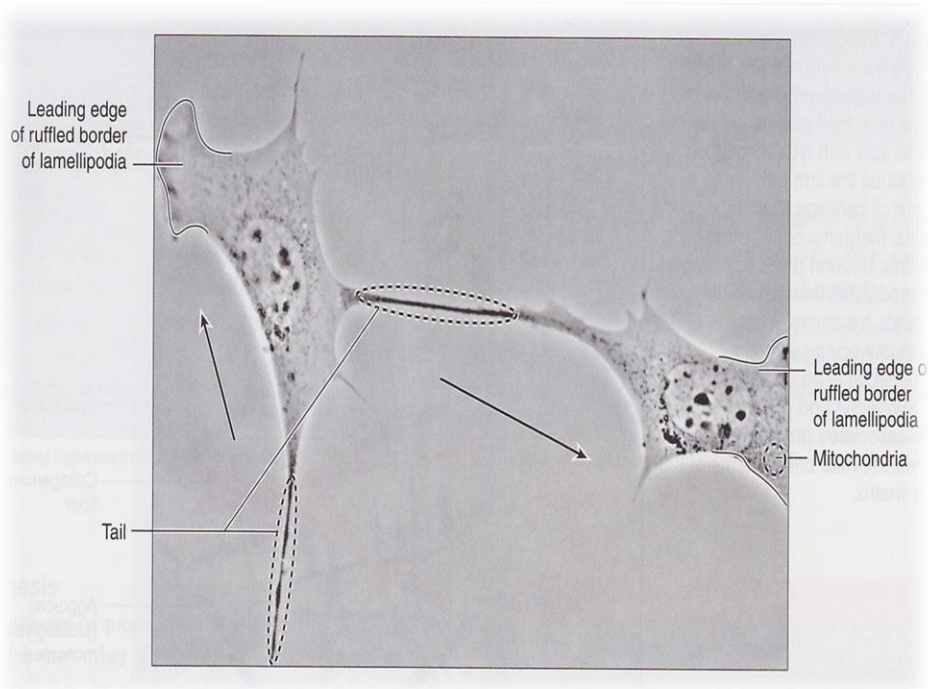
Adipocyte

FAT

Active fibroblast

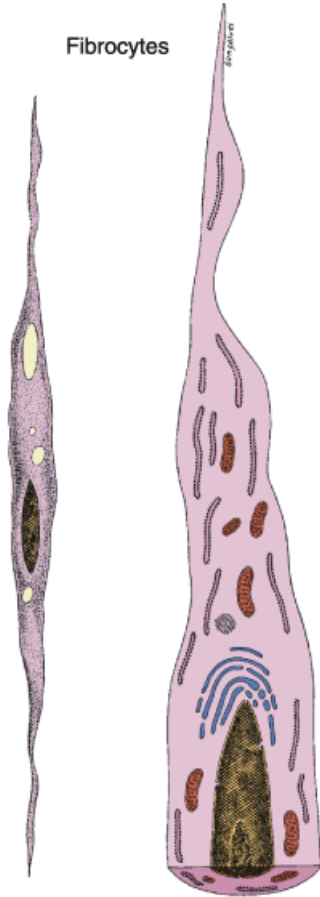


The **active fibroblast** has an abundant and irregularly branched cytoplasm. Its nucleus is ovoid, large, and pale staining, with fine chromatin and a prominent nucleolus. The cytoplasm is rich in rough endoplasmic reticulum, and the Golgi complex is well developed.



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.

Quiescent fibroblast



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

Write this text

Fibroblasts synthesize collagen, elastin, glycosaminoglycans, proteoglycans, and multiadhesive glycoproteins. Two stages of activity — **active and quiescent**:

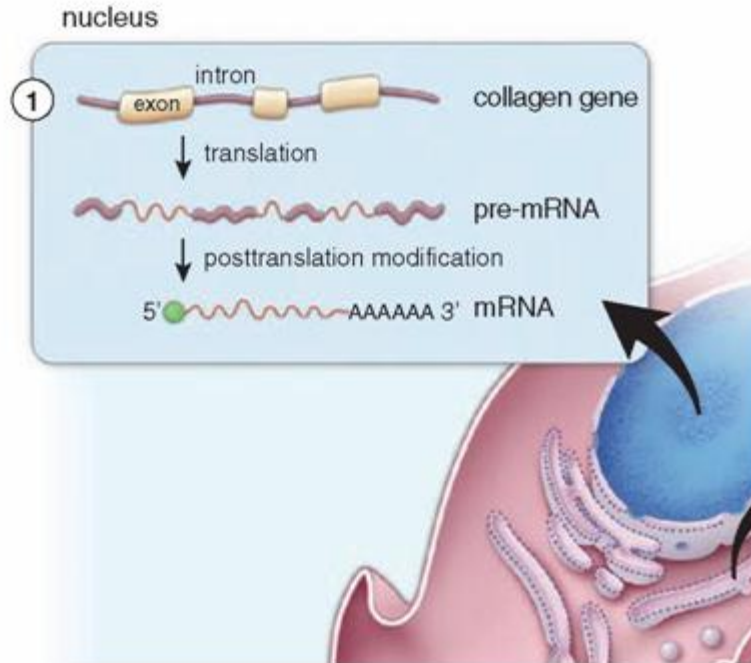
The **active fibroblast**: Branched cytoplasm; Nucleus is ovoid, with fine chromatin and a prominent nucleolus; The cytoplasm is rich in rough endoplasmic reticulum, the Golgi complex is well developed.

The **quiescent fibroblast (fibrocyte)**: Smaller than the active fibroblast; To be spindle shaped; It has a smaller darker nucleus; An acidophilic cytoplasm; Small amount of rough endoplasmic reticulum.



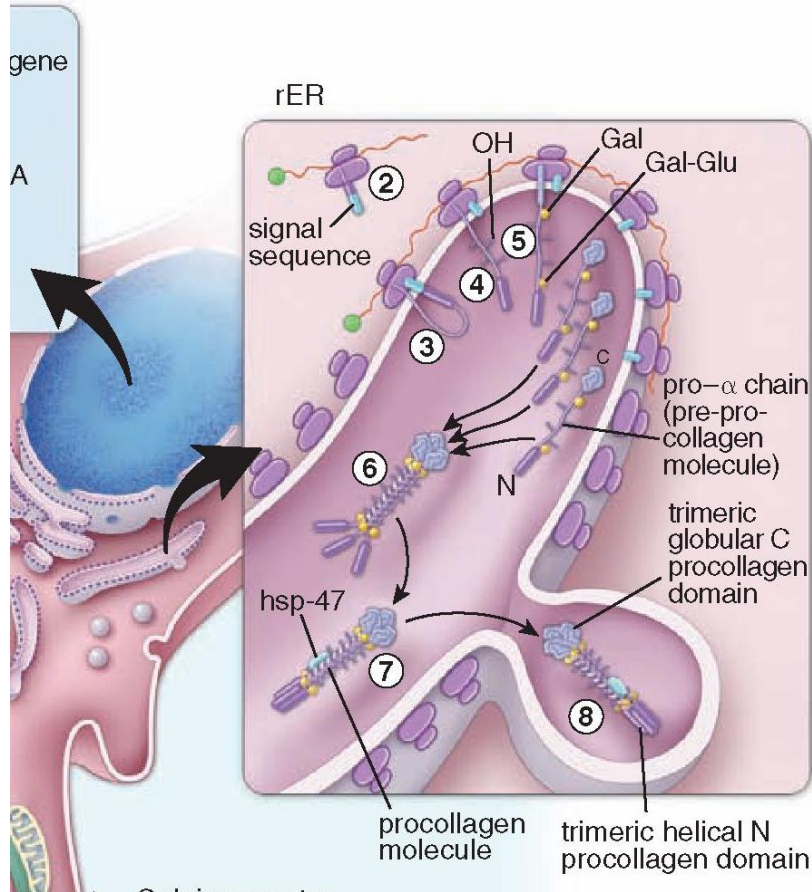
Transcription and Translation.mp4

Biosynthesis of Collagen

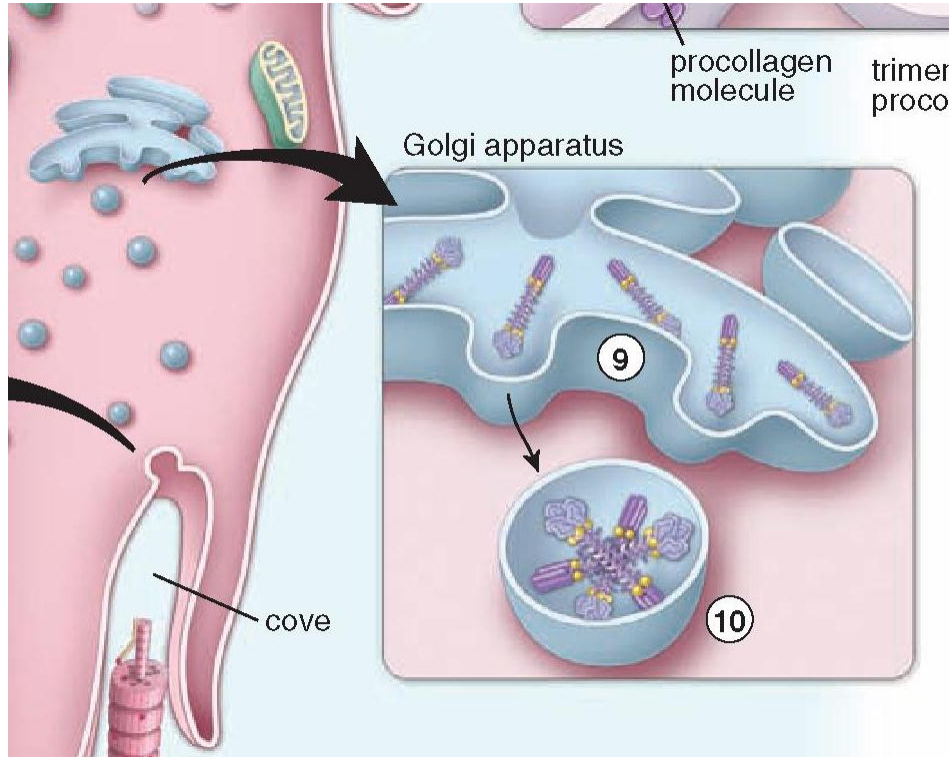


Intracellular events

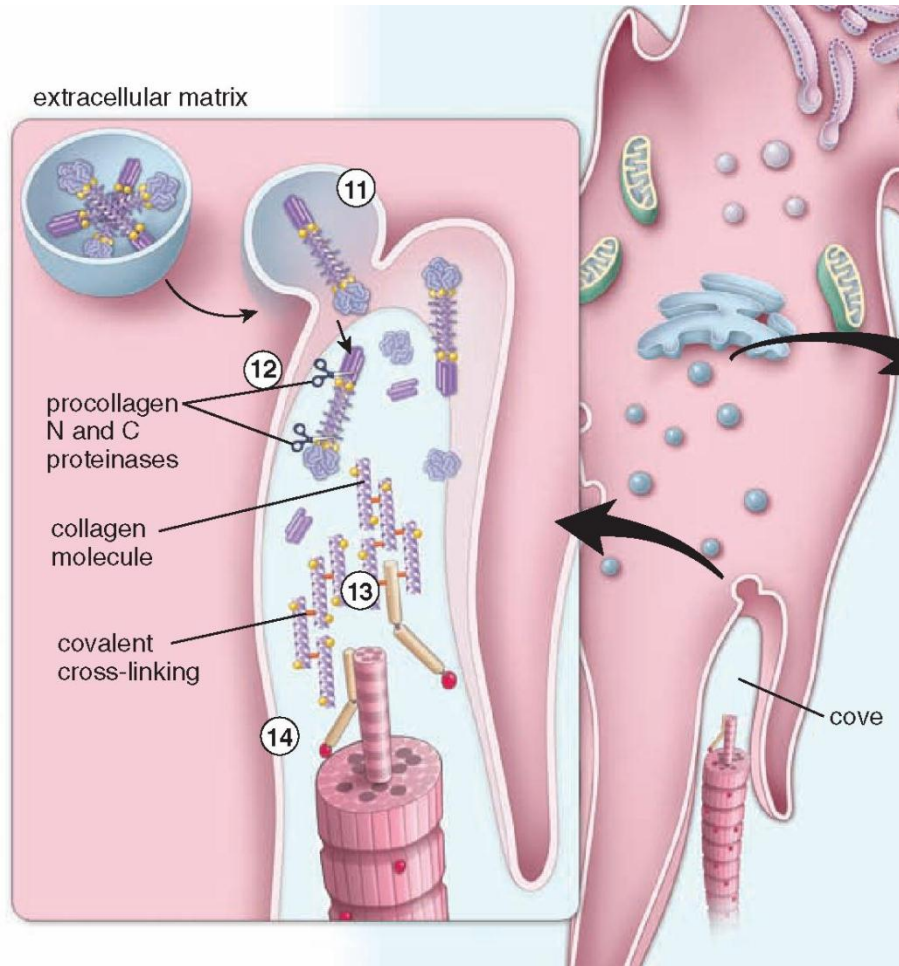
1. Formation of mRNA in the nucleus.



2. Initiation of synthesis of pro-α chains with signal sequences by ribosomes.
3. Synthesis of pro-α chains on the rER.
4. Hydroxylation of proline and lysine residues and cleavage of signal sequence from pro-α-chain.
5. Glycosylation of specific hydroxylysyl residues in the rER.
6. Formation of procollagen triple helix molecules from a C terminus toward the N.
7. Stabilization of the triple helix by formation of intra- and interchain hydrogen and disulfide bonds and chaperone proteins.
8. Transport of procollagen molecules to Golgi apparatus.



9. Packaging of procollagen molecules by Golgi into secretory vesicles.
10. Movement of vesicles to plasma membrane, assisted by molecular motor proteins associated with microtubules.



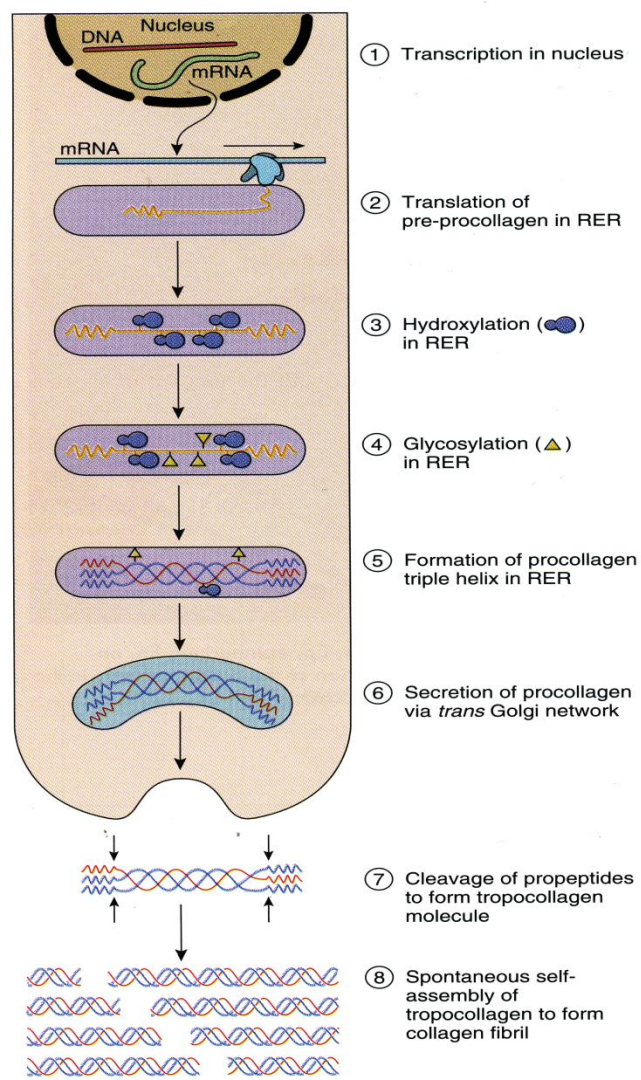
Outside the cell:

11. Exocytosis of procollagen molecules.

12. Cleavage of trimeric globular C- and helical N-procollagen domains by procollagen N- and C-proteinases.

13. Polymerization (self-assembly) of collagen molecules into collagen fibrils (in cove of fibroblast) with development of covalent cross-linking.

14. Incorporation of other collagens into collagen fibrils.

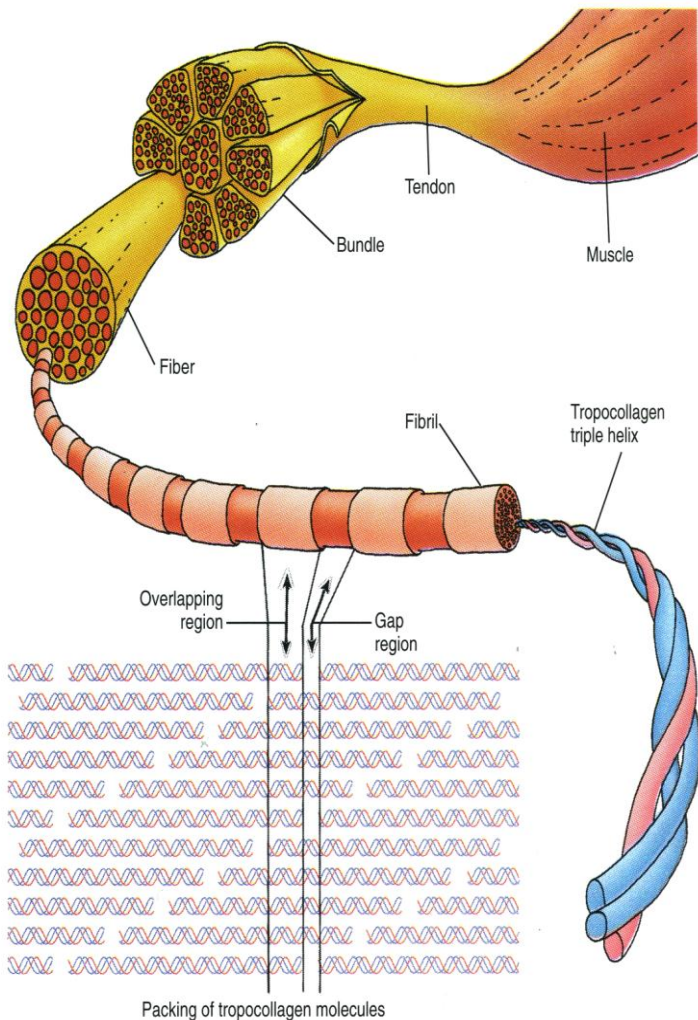


Collagen synthesis involves several steps:

1. **Polypeptide chains** are assembled on polyribosomes bound to rough endoplasmic reticulum membranes and injected into the cisternae as **preprocollagen molecules**. The signal peptide is clipped off, forming **procollagen**. A single **collagen molecule** consists of three polypeptides known as – **α -chains**. The α -chains intertwine, forming **triple helix**. **Hydroxylation** of proline and lysine occurs after these amino acids are incorporated into polypeptide chains.

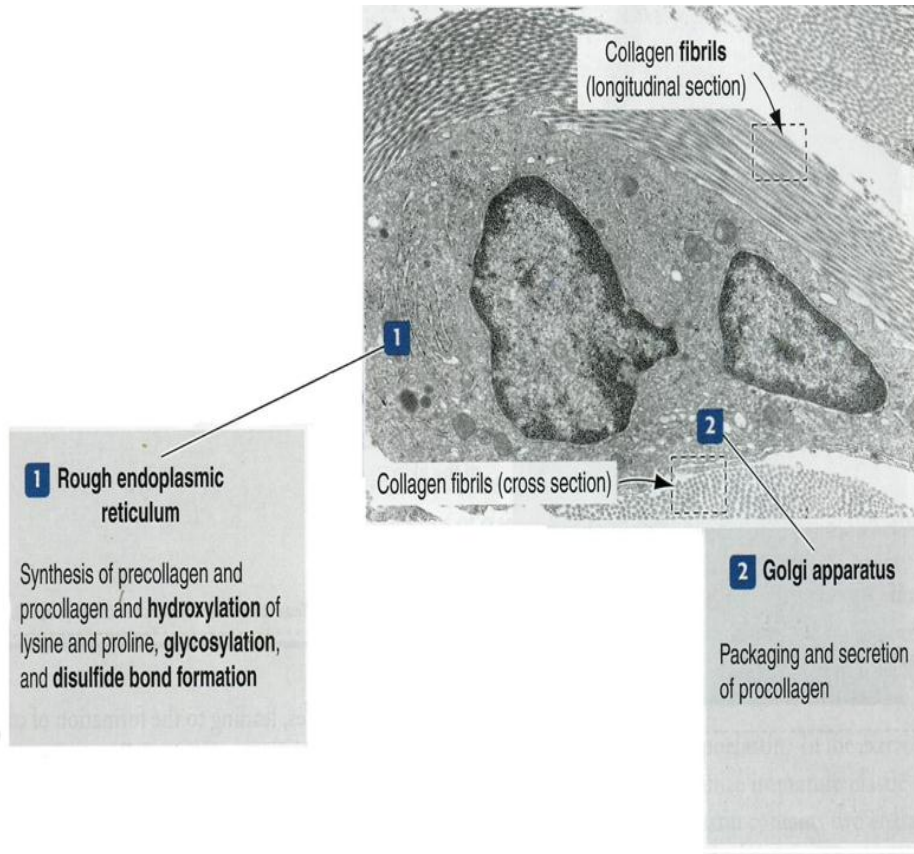
2. **Glycosylation** of hydroxylysine occurs after its hydroxylation.

3. Each chain is synthesized with an extra length of peptides called **registration peptides on both the amino-terminal and carboxyl-terminal end**.



4. Outside the cell, specific proteases called **procollagen peptidases** remove the registration peptides. The altered protein, known as **tropocollagen**, is able to assemble into polymeric **collagen fibrils**. The hydroxyproline residues contribute to the stability of the tropocollagen triple helix, forming hydrogen bonds between its polypeptide chains.

5. Collagen fibrils aggregate spontaneously to form **fibers**. Proteoglycans and structural glycoproteins play an important role in the aggregation of tropocollagen to form fibrils and in the **formation of fibers from fibrils**.



6. The fibrillar structure is reinforced by the formation of covalent cross-links between tropocollagen molecules. This process is catalyzed by the action of the enzyme lysyl oxidase, which also acts in the extracellular space.

The synthesis of collagen involves a cascade of unique posttranslational biochemical modifications of the original procollagen polypeptide. All these modifications are critical to the structure and function of normal mature collagen.

Write this text

Biosynthesis of Collagen

Intracellular events:

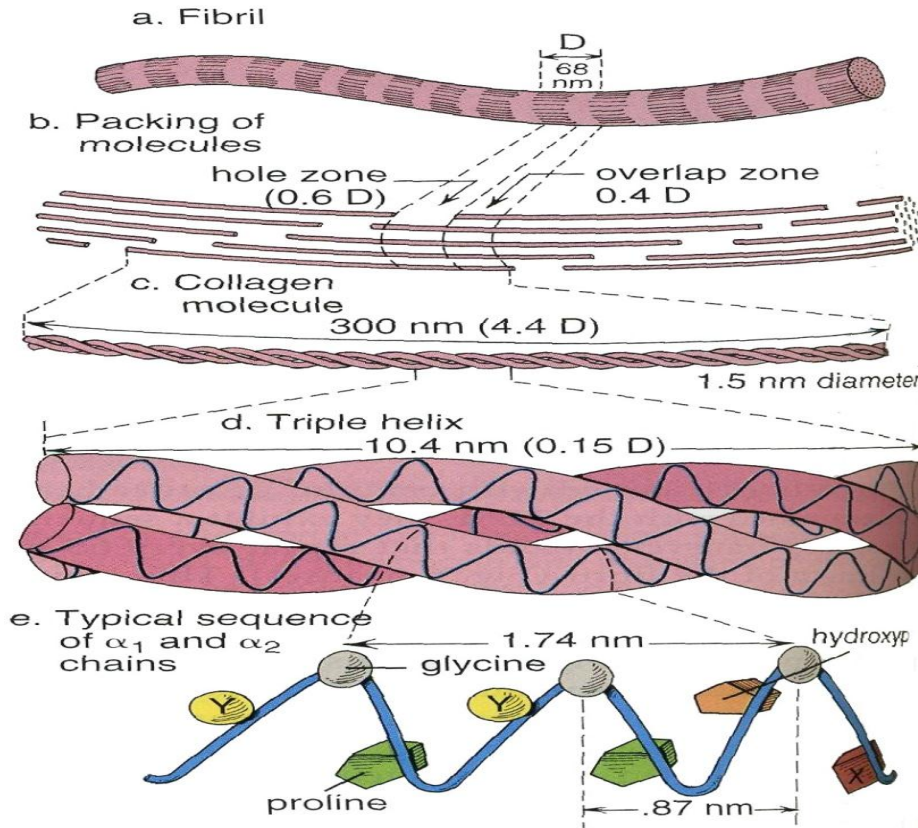
1. Formation of **mRNA** and synthesis of **pro- α -chains** with signal sequences by ribosomes on the rER.
2. **Hydroxylation** of proline and lysine in RER.
3. **Glycosylation and formation of procollagen triple helix molecules,**
4. **Transport** of procollagen molecules to Golgi apparatus.
3. **Packaging** of procollagen molecules into **secretory vesicles.**
movement of vesicles to plasma membrane.
4. **Exocytosis** of procollagen molecules.

Write this text

Outside the cell:

1. Procollagen peptidases remove the **registration peptides**.
2. The altered protein, known as tropocollagen, is able to assemble into polymeric collagen fibrils.
3. The fibrillar structure is reinforced by the formation of **covalent cross-links** between tropocollagen molecules.
4. Collagen fibrils aggregate to form fibers.
5. Formation of fibers from fibrils.

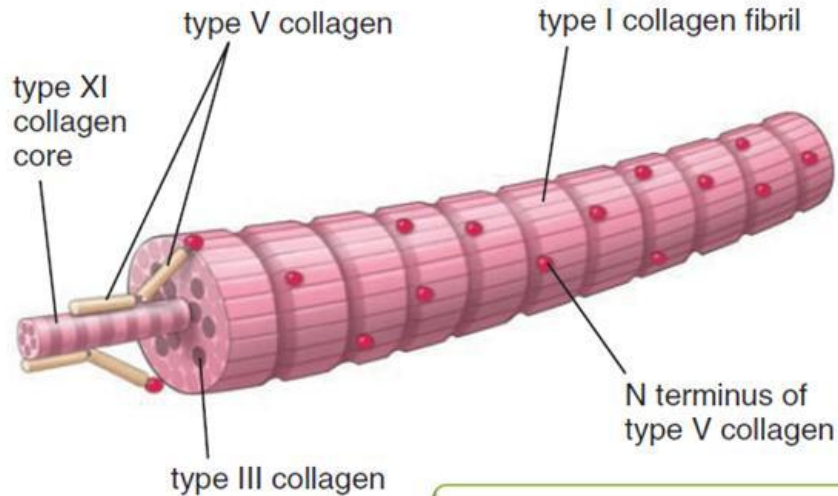
Collagen Fibers



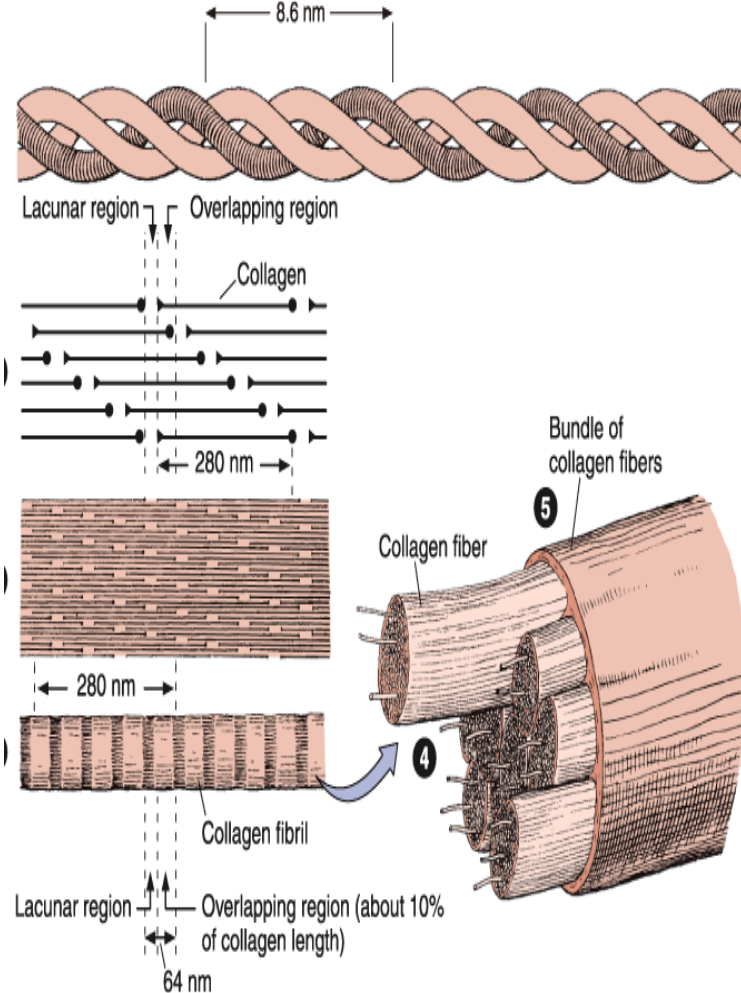
The collagens the primary examples among its various types are present in the skin, bone, cartilage, smooth muscle, and basal lamina. The collagens comprise a family of more than 25 members that are produced by several cell types and are distinguishable by their molecular compositions, morphological characteristics, distribution, functions, and pathologies.

Collagens That Form Long Fibrils

Collagen type I occurs in tissues as structures that form structures such as bones, dentin, tendons, organ capsules, and dermis. Type I collagen fibril. The type I collagen fibril contains small amounts of other collagen types such as types II, III, V, and XI. Note that the core of the fibril contains collagen types V and XI, which help initiate the assembly of the type I fibril.



Type I collagen fibril



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.

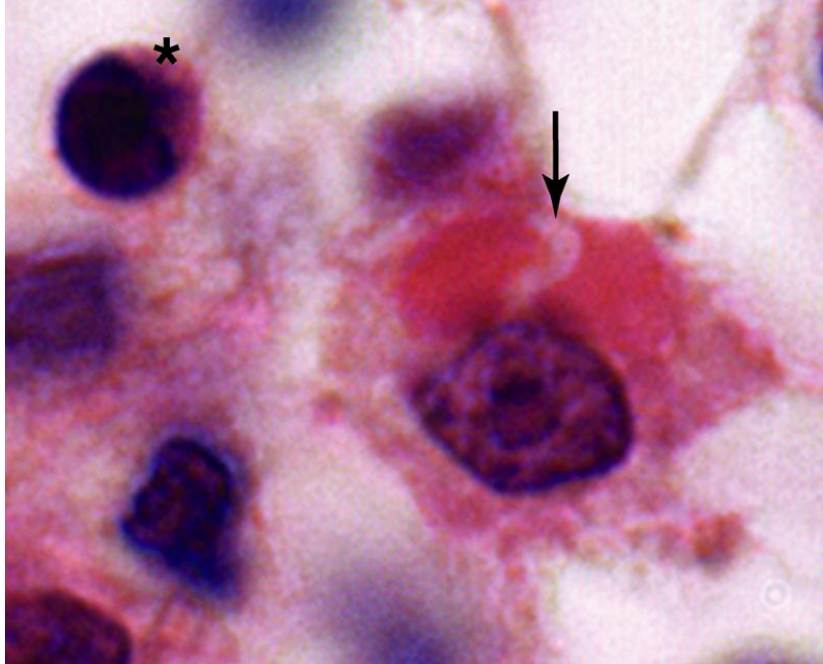
Collagens That Form Networks

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

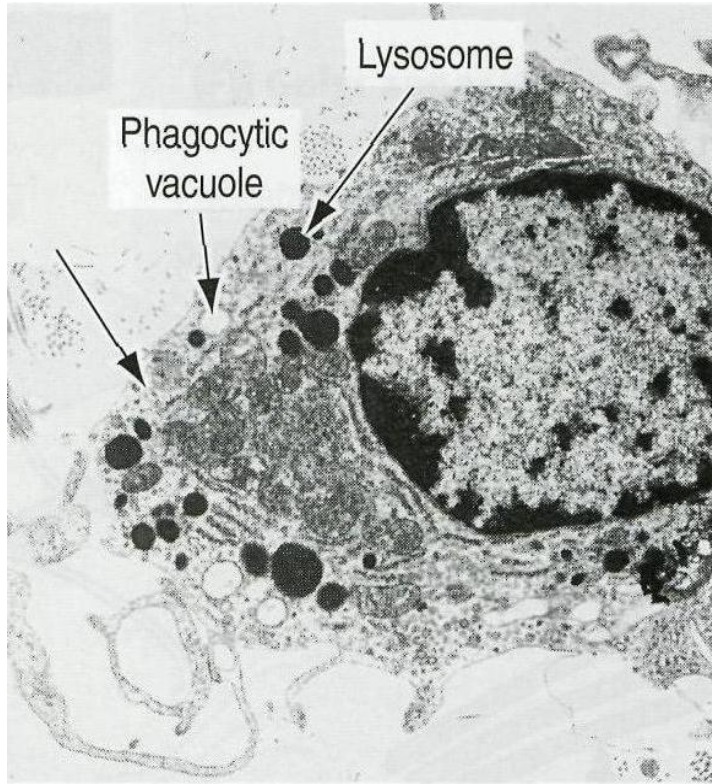
Collagens That Form Anchoring Fibrils

Anchoring collagen, or type VII collagen, is present in the anchoring fibrils that bind collagen fibers to the basal lamina.

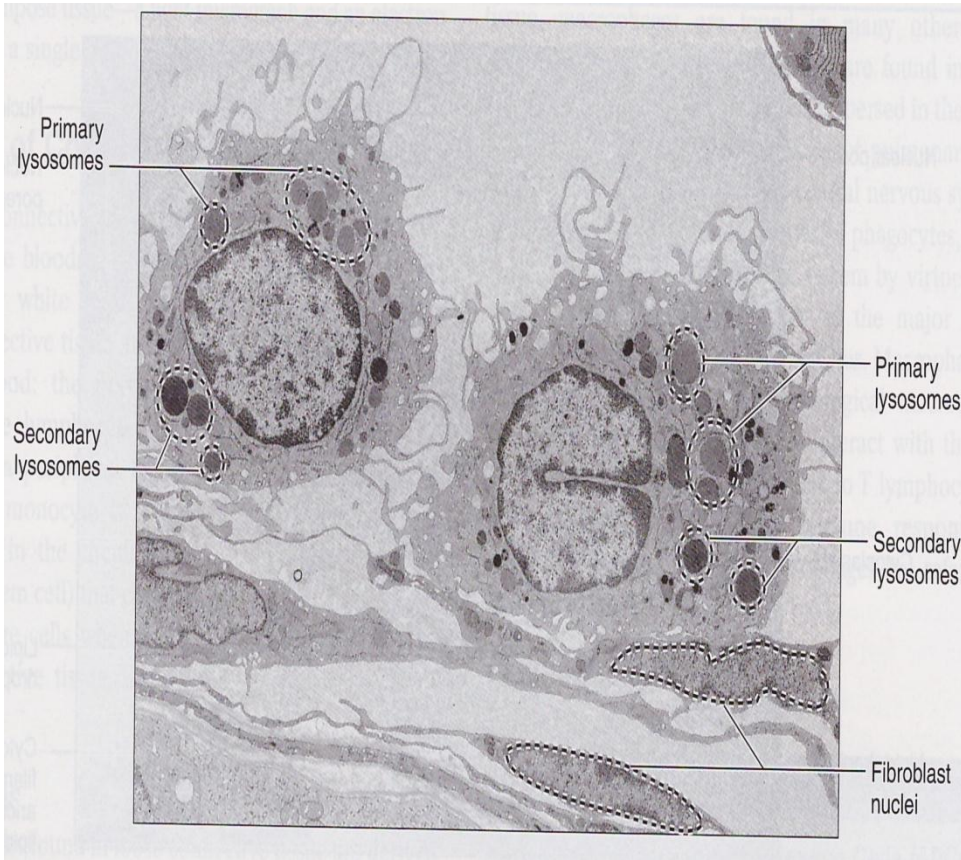
Macrophages



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. Macrophages measure between 10 and 30 μm and usually have an oval or kidney-shaped nucleus located eccentrically.



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.

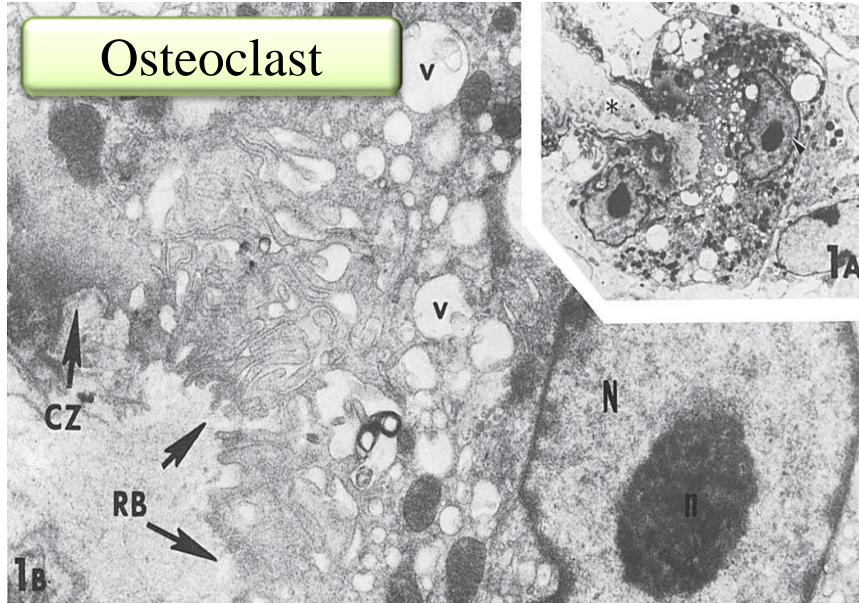


Macrophages derive from bone marrow precursor cells that divide, producing **monocytes** that circulate in the blood. In a second step, these cells cross the wall of venules and capillaries to penetrate the connective tissue, where they mature and acquire morphological features of **macrophages**.

Macrophages, which are distributed throughout the body, are present in most organs and constitute the **mononuclear phagocyte system**. They are long-living cells and may survive for months in the tissues.

Table 2. Distribution and Main Functions of the Cells of the Mononuclear Phagocyte System

Cell Type	Location	Main Function
Monocyte	Blood	Precursor of macrophages
Microglia cell	Nerve tissue of the central nervous system	Same as macrophages
Dendritic cell	Lymph nodes	Antigen processing and presentation
Multinuclear giant cell	Connective tissue (fusion of several macrophages)	Segregation and digestion of foreign bodies

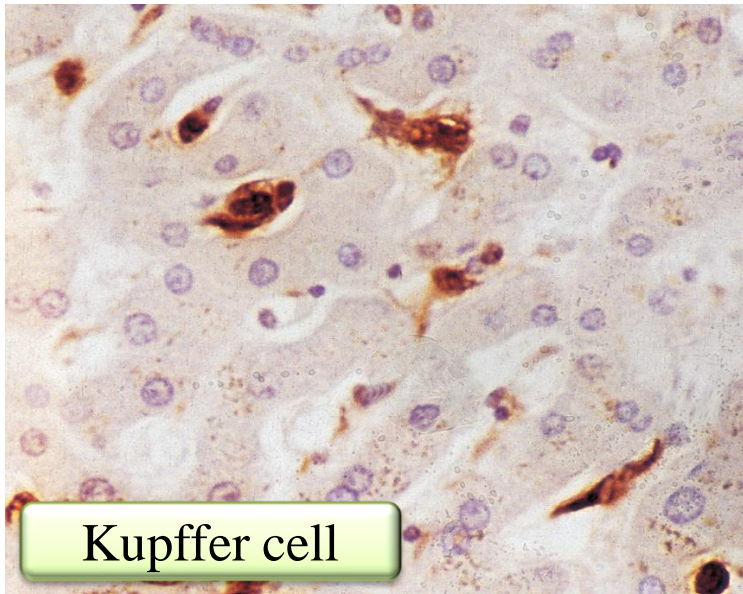


Location

Bone (fusion of several macrophages)

Main Function

Digestion of bone



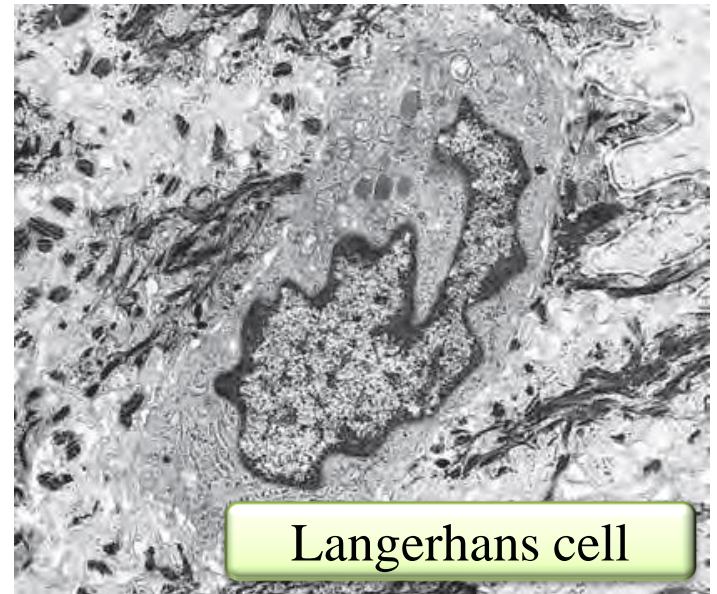
Kupffer cell

Location

Liver

Main Function

Production of cytokines, chemotactic factors, and several other molecules that participate in inflammation (defense), antigen processing and presentation



Langerhans cell

Location

Lymph nodes

Main Function

Antigen processing and presentation

Write this text

Macrophages were initially characterized by their pinocytotic and phagocytic ability and constitute the **mononuclear phagocyte system**.

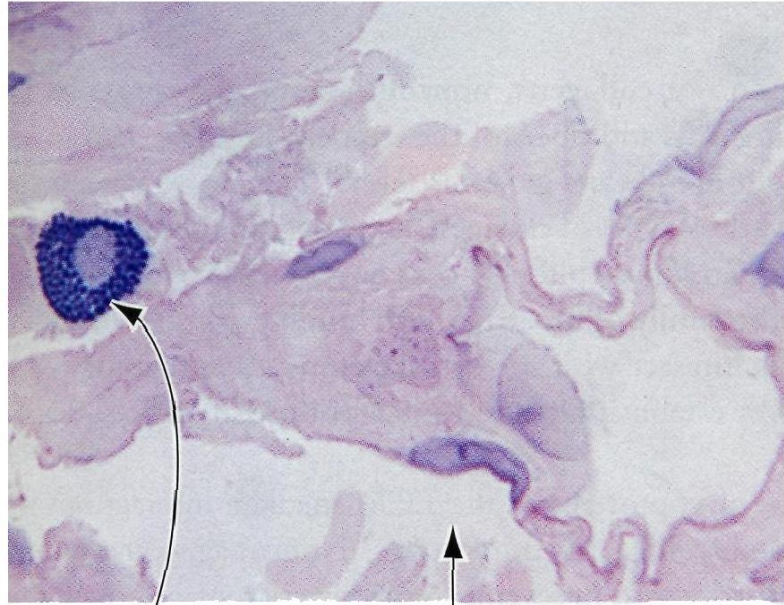
Macrophages :

- Measure between 10 and 30 μm
- Have an **oval or kidney-shaped** nucleus located eccentrically
- Have a **well-developed Golgi complex**
- **Many lysosomes**
- A prominent **rough endoplasmic reticulum**.



Macrophages, b-cells, pathogens, Antibody Immune Response.mp4

Mast Cells

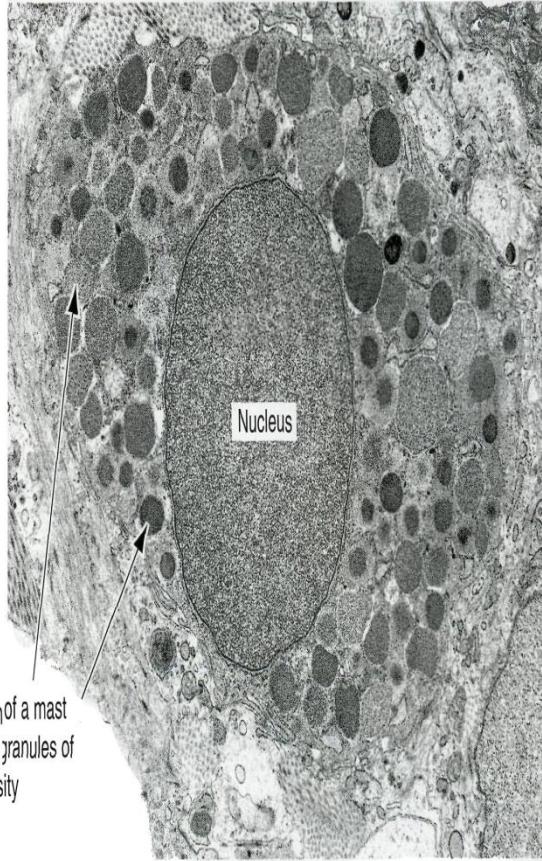


Mast cell with
metachromatic granules
in the cytoplasm

Blood vessel

Electron micrograph
cell with cytoplasmic

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.

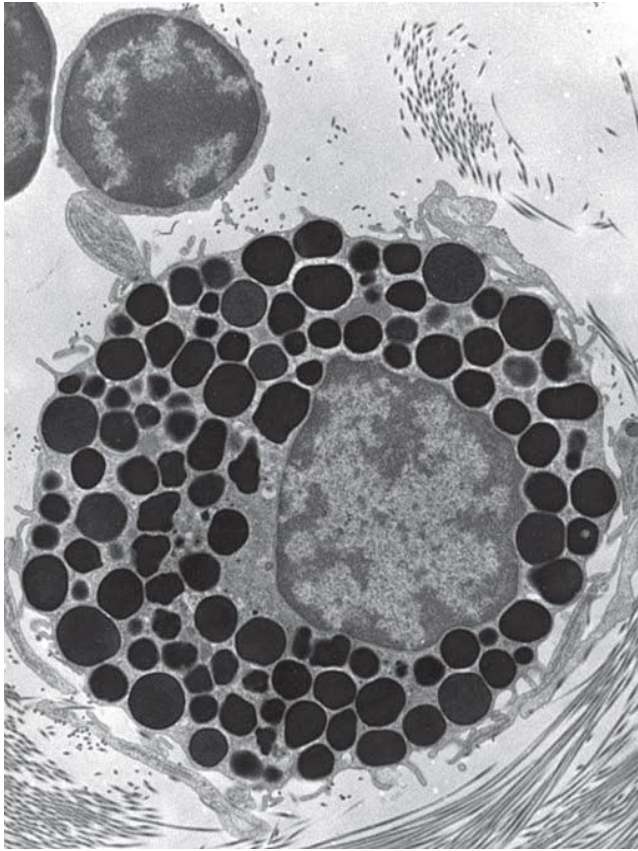


Electron micrograph of a mast cell with cytoplasmic granules of different density

Mast cells contain intensely basophilic granules that store chemical substances - **mediators of inflammation**. The secretory granules are 0.3–2.0 μm in diameter.

Mediators produced by mast cells are divided into two categories:

Preformed mediators that are stored in secretory granules and released upon cell activation and **newly synthesized mediators** that are often absent in the resting cells.

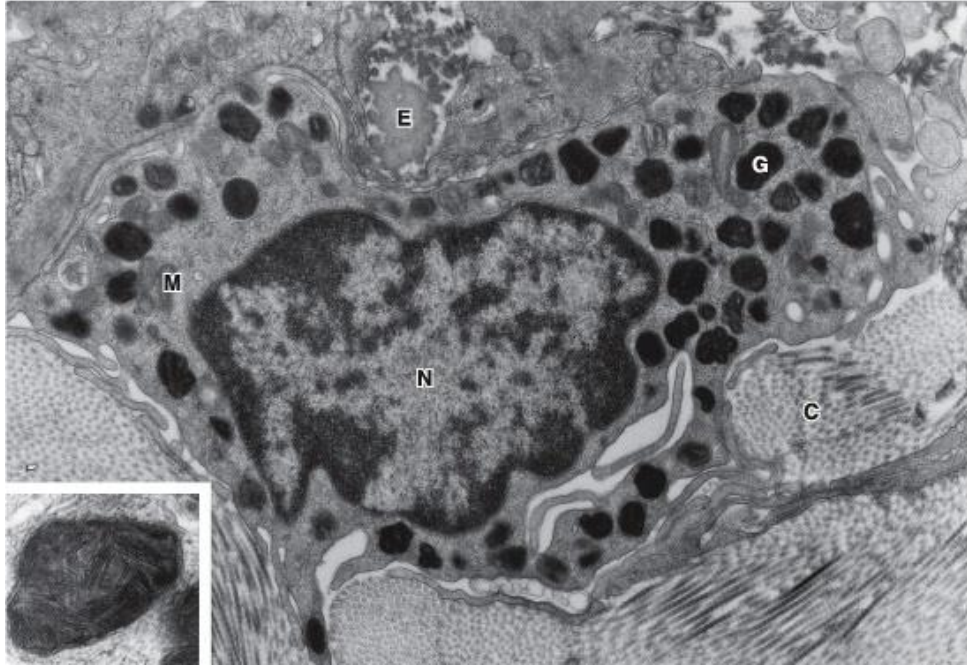


Preformed mediators found inside mast cell granules are the following:

1. **Histamine** is a biogenic amine that increases the permeability of small blood vessels, causing edema in the surrounding tissue and a skin reaction demonstrated by an itching sensation.

2. **Heparin** is a sulfated GAG that is an anticoagulant.

3. **Serine proteases** (tryptase and chymase). *Tryptase* is selectively concentrated in the secretory granules of human mast cells (but not basophils). It is released by mast cells together with histamine and serves as a marker of mast cell activation. *Chymase* plays an important role in generating angiotensin II in response to vascular tissue injury.



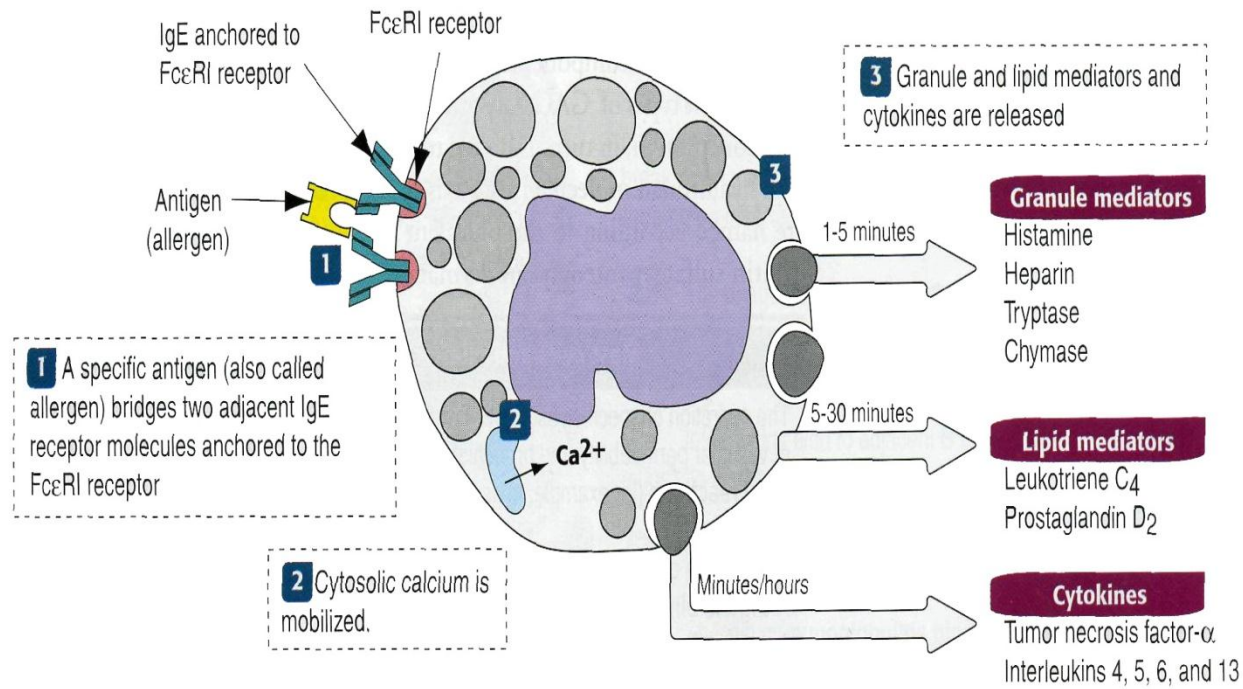
4. Leukotriene.

5. Tumor necrosis factor.

6. Interleukins (IL-4,-3 -5, -6, -8 and -16).

7. Growth factors (GM-CSF).

8. Prostaglandin D2 (PGD2).



After activation —binding of a specific antigen to two adjacent IgE receptors— mast cells:

1. Release histamine, proteases, and proteoglycans.
2. Synthesize mediators derived from arachidonic acid through the cyclooxygenase and lipoxygenase pathways.

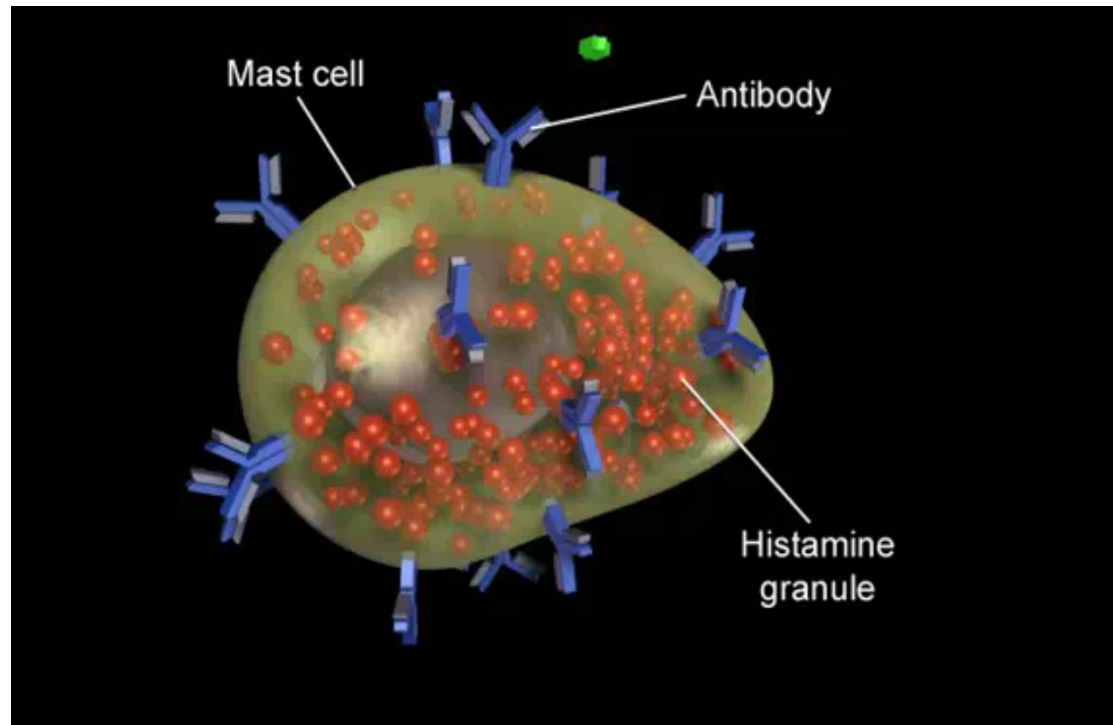
Write this text

Mast cells are connective tissue cells that store chemical substances - **mediators of inflammation**.

- 10–13 μm in diameter
- Small, spherical nucleus is centrally situated
- Cytoplasm is filled with basophilic secretory granules (0.3–2.0 μm)

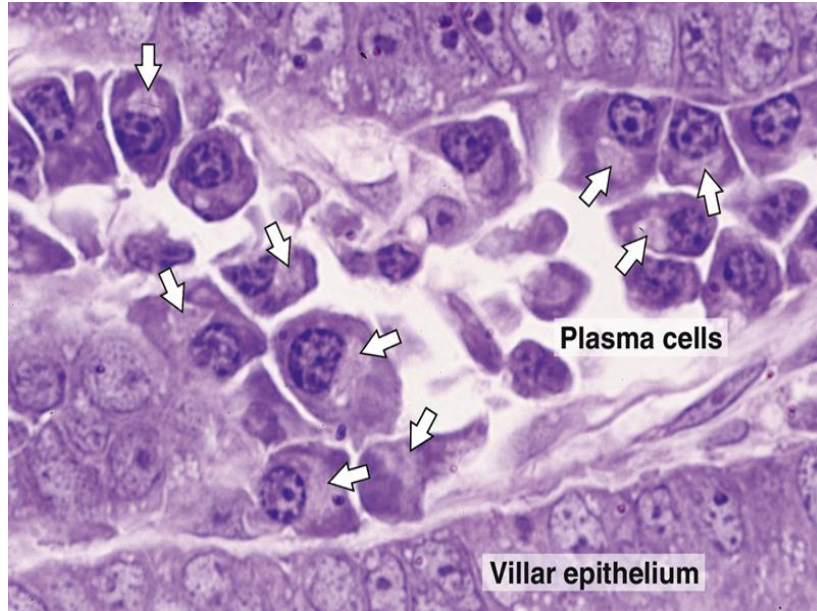
Preformed mediators found inside mast cell granules are :

1. Histamine
2. Heparin
3. Serine proteases
4. Interleukins.

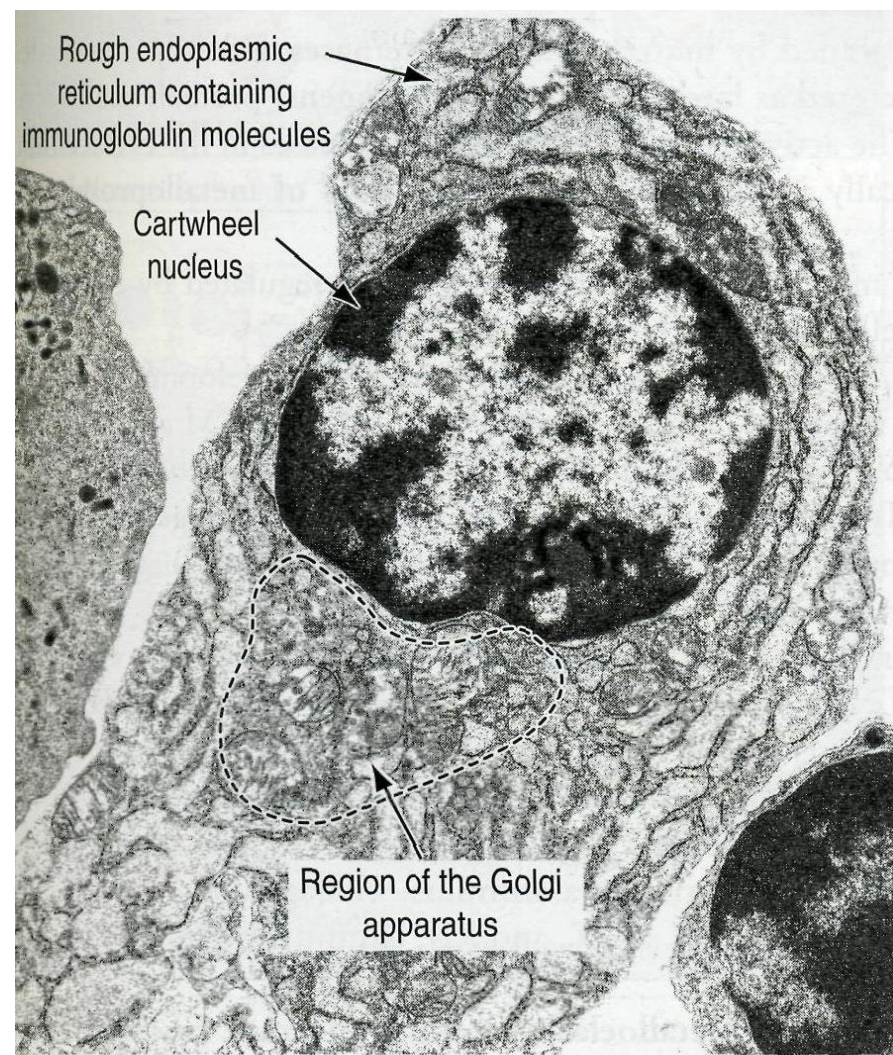


Mast Cell.mp4

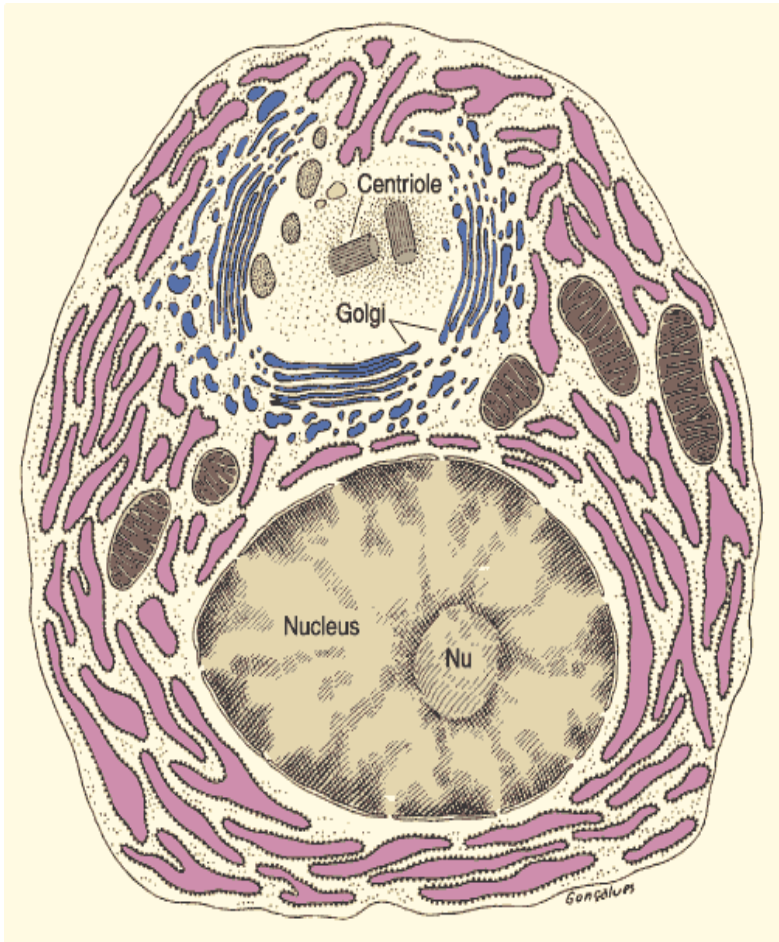
Plasma Cells



Lymphocytes represent one variety of leukocytes (white blood cells) present in blood. Large aggregations of lymphocytes are present in lymphoid tissues. They reach connective tissue from these sources, and are specially numerous when the tissue undergoes inflammation. They are of two types. ***B-lymphocytes*** pass through blood to reach other tissues directly. Some B-lymphocytes mature into ***plasma cells*** described below. The second type of lymphocytes, called ***T-lymphocytes***.



Plasma cells are large, ovoid cells that have a basophilic cytoplasm due to their richness in rough endoplasmic reticulum. Portion of a chronically inflamed intestinal villus. The plasma cells are characterized by their size and abundant basophilic cytoplasm (rough endoplasmic reticulum) and are involved in the synthesis of antibodies. A large Golgi complex (arrows) is where the terminal glycosylation of the antibodies (glycoproteins) occurs. Plasma cells produce antibodies of importance in immune reactions.



The nucleus of the plasma cell is spherical and eccentrically placed, containing compact, coarse heterochromatin alternating with lighter areas. There are few plasma cells in most connective tissues. Their average life is short, 10–20 days. Plasma cells are derived from B lymphocytes and are responsible for the synthesis of antibodies. Antibodies are immunoglobulins produced in response to penetration by antigens. Each antibody is specific for the one antigen. The results of the antibody–antigen reaction are variable. The capacity of the reaction to neutralize harmful effects caused by antigens is important.

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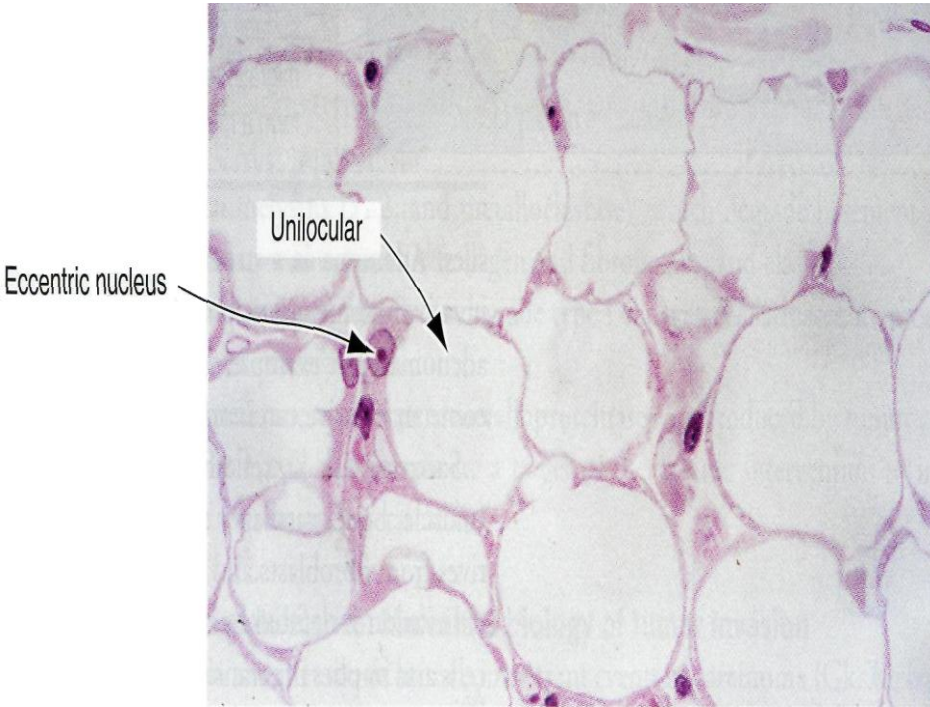
Lymphocytes migrate from the blood vessels to connective tissues by **diapedesis**. **Lymphocytes are of two types:**

- **B-lymphocytes** pass through blood to reach other tissues directly. Some B-lymphocytes mature into **plasma cells**.
- The second type of lymphocytes, called **T-lymphocytes**.

Plasma cells produce antibodies of importance in immune reactions and have a basophilic cytoplasm:

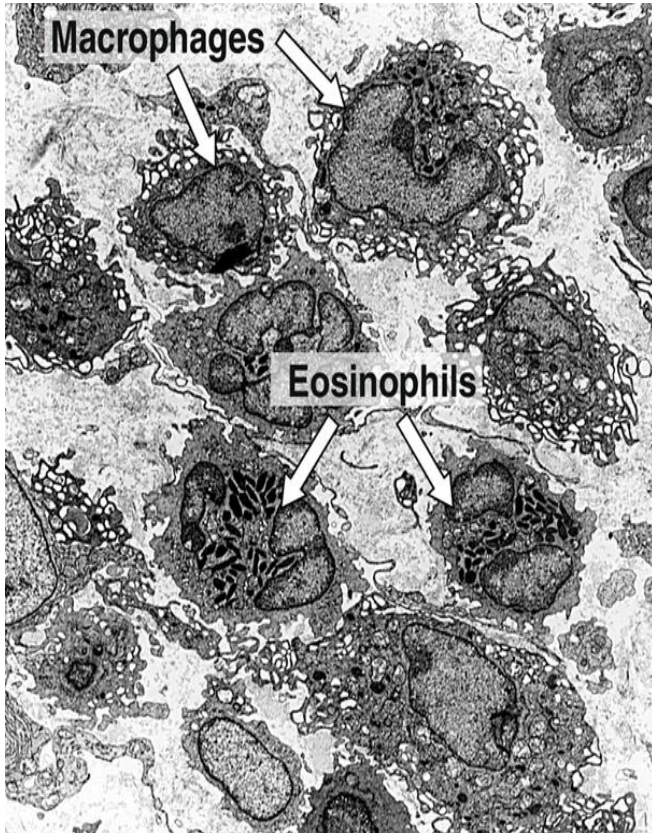
- The nucleus of the plasma cell is spherical and eccentrically placed
- Rich of rough endoplasmic reticulum
- Large Golgi complex.

Adipose Cells



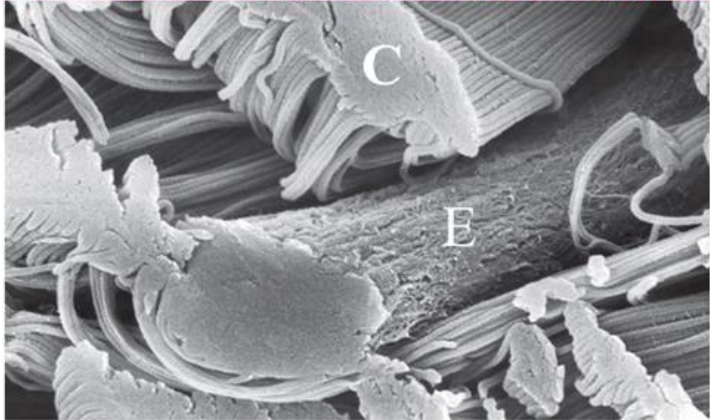
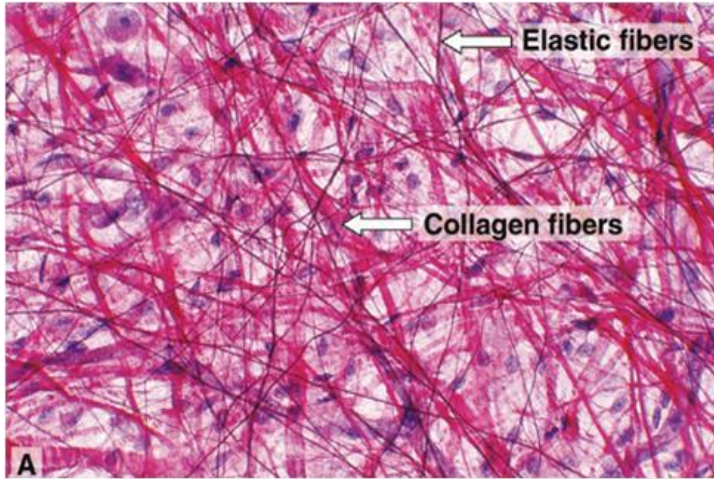
Adipose cells (adipocytes; L. *adepts*, fat, + Gr. *kytos*) are connective tissue cells that have become specialized for **storage of neutral fats** or for the production of heat. Often called **fat cells**.

Leukocytes



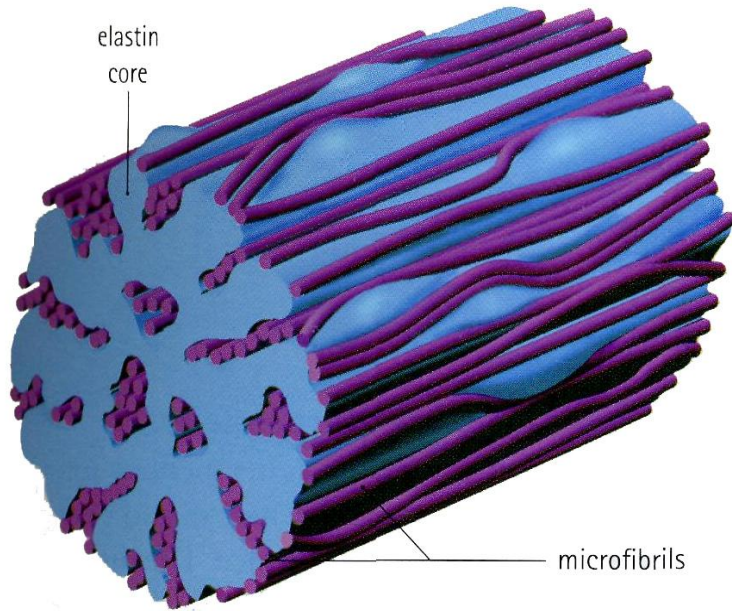
Leukocytes, or white blood corpuscles, are the wandering cells of the connective tissue. They migrate through the walls of capillaries and postcapillary venules from the blood to connective tissues by a process called **diapedesis**. Inflammation begins with the local release of **chemical mediators of inflammation**, substances of various origin (mainly from cells and blood plasma proteins) that induce some of the events characteristic of inflammation, **increase of blood flow and vascular permeability, chemotaxis, and phagocytosis**.

Fibers



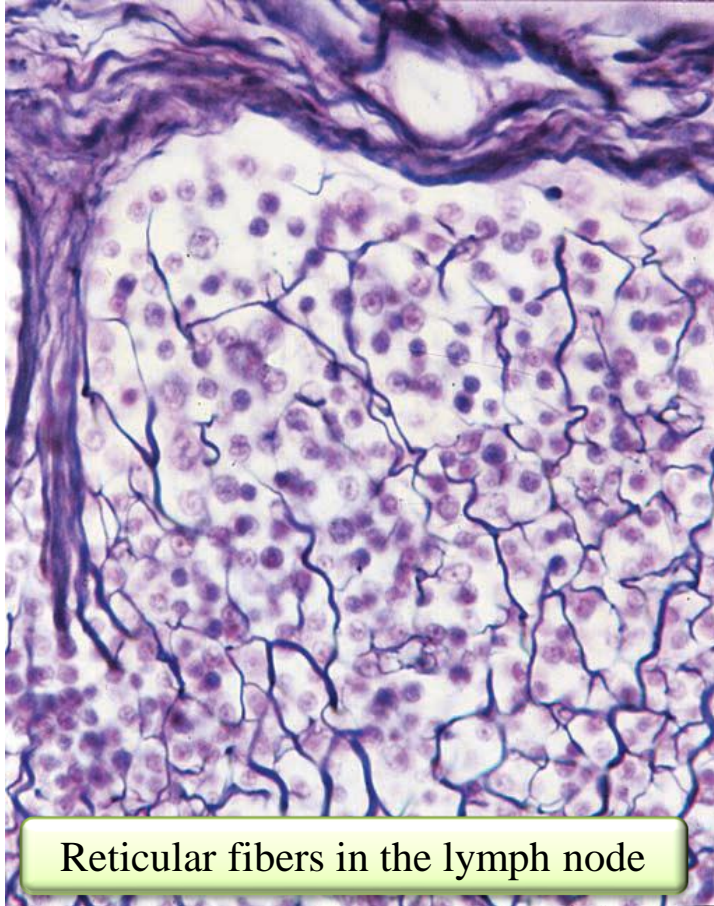
The connective tissue fibers are formed by proteins that polymerize into elongated structures. The three main types of connective tissue fibers are **collagen**, **reticular**, and **elastic**. Collagen and reticular fibers are formed by the protein **collagen**, and elastic fibers are composed mainly of the protein **elastin**.

The Elastic Fiber System



The elastic fiber system is composed of three types of fibers—oxytalan, elaunin, and elastic. The structures of the elastic fiber system develop through three successive stages differentiated by the amount of the protein elastin that exists in each type of fiber.

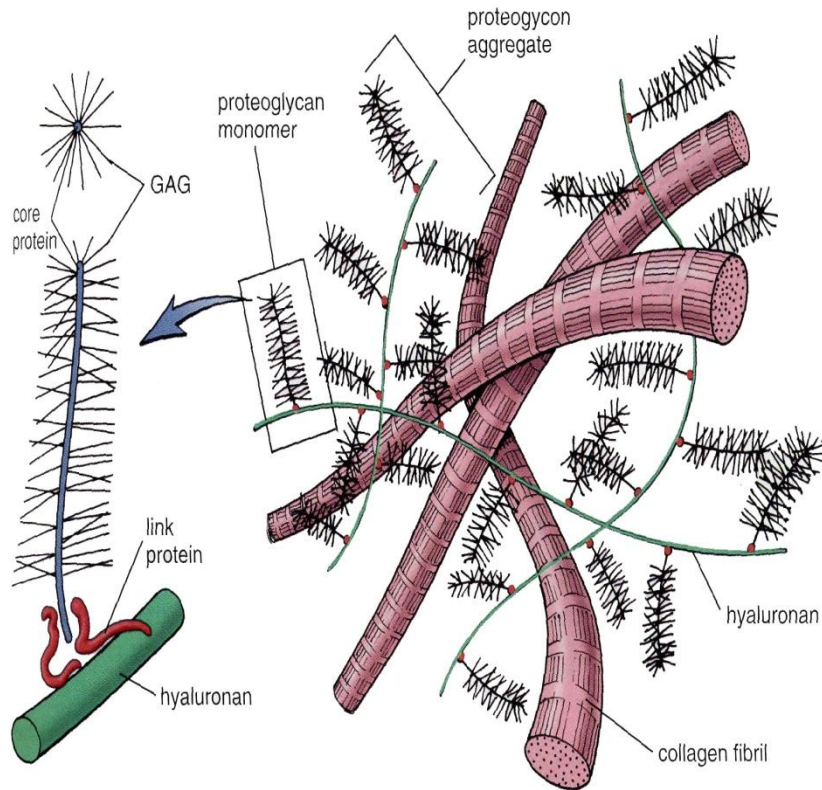
Reticular Fibers



Reticular fibers in the lymph node

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. Because of their affinity for silver salts, these fibers are called **argyrophilic**.

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. The ground substance is formed mainly of three classes of components: **glycosaminoglycans, proteoglycans, and multiadhesive glycoproteins.**

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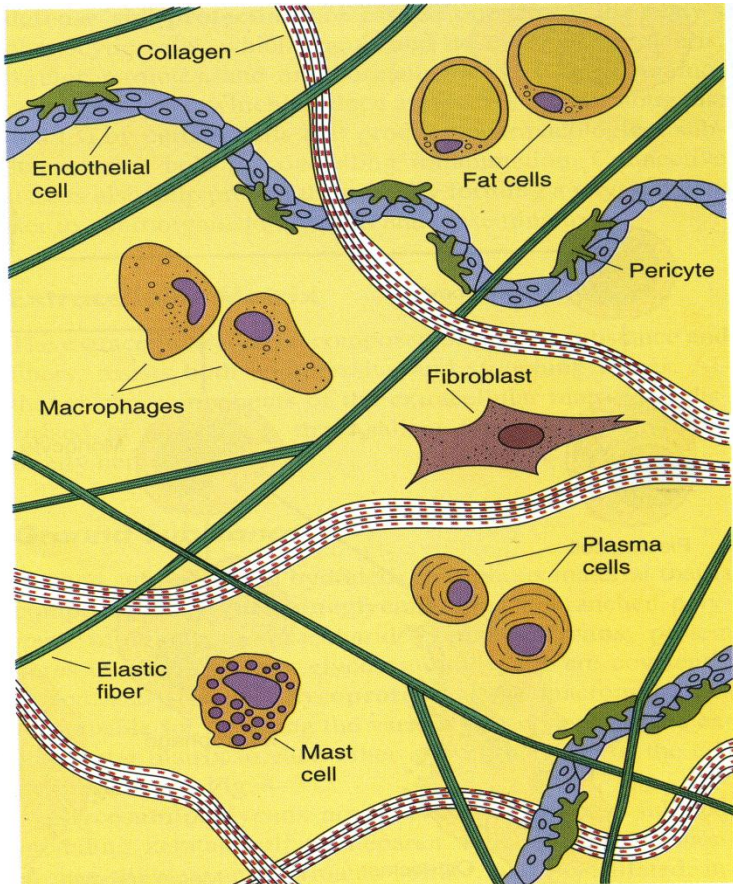
The three main types of connective tissue **fibers** are:

- **Collagen and reticular fibers** are formed by the protein **collagen**
- **Elastic fibers** are composed mainly of the protein **elastin**.

The ground substance is a highly hydrated, colorless, and transparent complex mixture of macromolecules and is formed mainly of three classes of components:

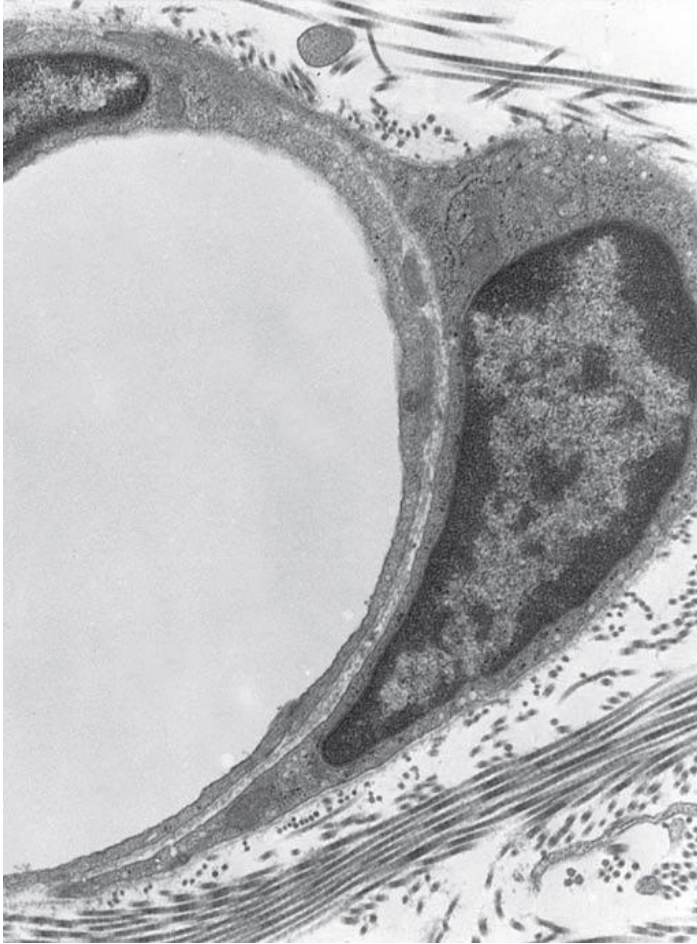
- **glycosaminoglycans**
- **proteoglycans**
- **multiadhesive glycoproteins**.

Capillaries



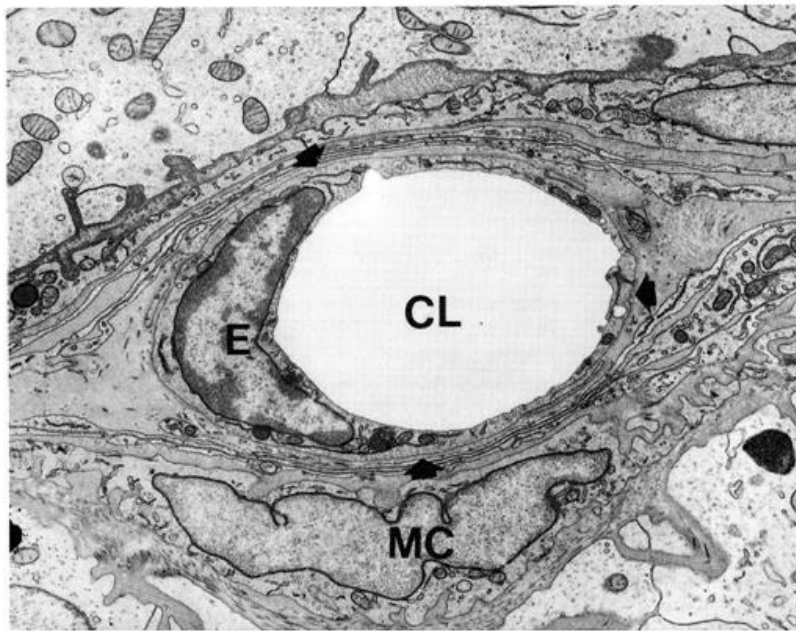
Loose connective tissue is primarily located beneath the epithelia that cover the body surfaces and line the internal surfaces of the body. It is also associated with the epithelium of glands and surrounds the smallest blood vessels.

This tissue is thus the initial site where pathogenic agents such as bacteria that have breached an epithelial surface are challenged and destroyed by cells of the immune system. Most cell types in loose connective tissue are transient wandering cells that migrate from local blood vessels in response to specific stimuli. **Loose connective tissue is, therefore, the site of inflammatory and immune reactions.**

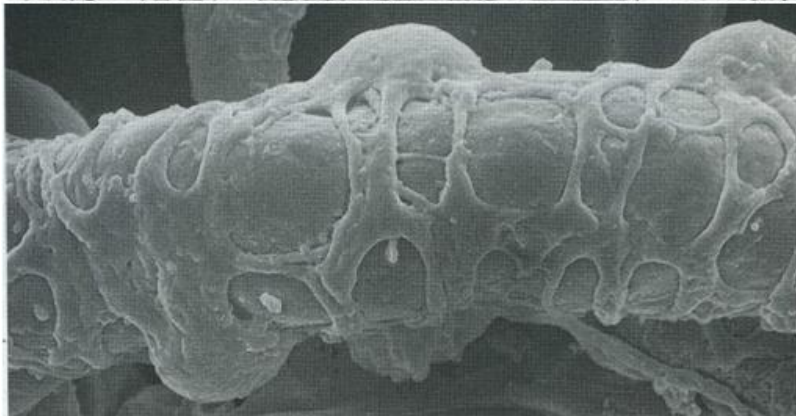


Capillaries are the smallest diameter blood vessels. Each consists of a single layer of **endothelial cells** and their **basal lamina**. Capillaries are particularly well suited for the exchange of gases and metabolites between cells and the bloodstream.

In some continuous capillaries and postcapillary venules, **pericytes** may be associated with the endothelium. The pericyte, when present, intimately surrounds the capillary, with branching cytoplasmic processes, and is enclosed by a basal lamina that is continuous with that of the endothelium.



Pericytes are contractile and are controlled by NO produced by endothelial cells. They provide vascular support and promote stability of capillaries and postcapillary venules through physical and chemical signaling with vascular endothelial cells.



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Capillaries are suited for the exchange of gases and metabolites between cells and the bloodstream:

- Capillaries are the **smallest diameter blood vessels**
- Each consists a single layer of **endothelial cells and**
- **Basal lamina**
- **Pericytes** is associated with the endothelium and is enclosed by a basal lamina.