

# Histology

**faculty of medicine - JU2015**

LECTURE#6

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# Connective tissue

Tissue is a group of cells and extracellular matrix (ECM).

**Connective tissue:** is composed of cells with a large amount of ECM

- The connective cells are widely separated from each other, unlike the epithelium cells which are tightly packed together by junctions. And this is the main difference between the two tissues.

-No cell junctions between the cells in ordinary C.T.

-The epithelium tissue can be derived from the three embryonic layers, while the C.T. is derived from the middle layer of the embryo only (mesoderm).

**The ECM of CT is composed of 2 main components:**

1- Fibers

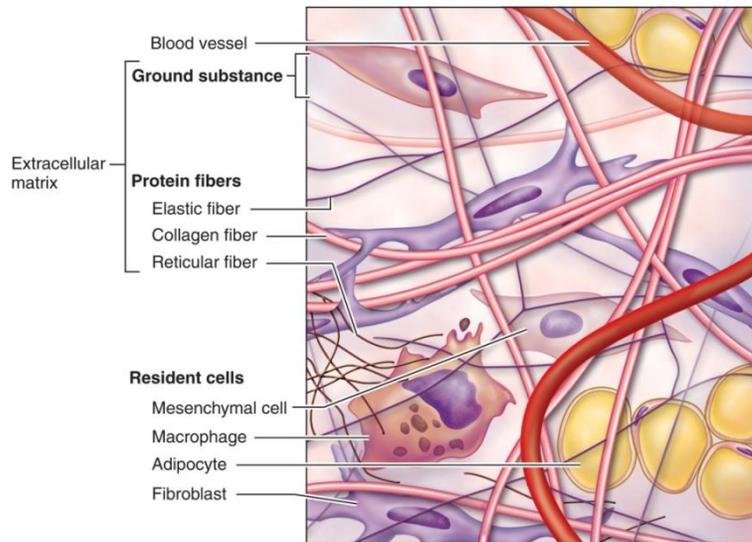
2- Ground substance

The **fibers** are composed of proteins which polymerize to form an elongated structure called fiber (ex. Collagen, elastic and reticular fibers).

The **ground substance:** is mainly water with other macromolecules where the cells and fibers are embedded in. So it's a medium for transport.

**Features of CT:**

- Highly vascular
- Have variable regenerative power
- Originated from mesenchyme



There are different types of CT classified according to their main **component**:

If we have cells/ ground substances more than fibers	If we have fibers more than cells
<b>Loose CT</b>	<b>Dense CT</b>
	<b>More collagen: Collagen CT</b>
	<b>More elastic: Elastic CT</b>
	<b>More reticular: Reticular CT</b>

And there are **special** types of CT:

- Blood
- Bone
- Cartilage
- Adipose tissue

**Functions of CT:**

- 1- **Support:** support the epithelium cells  
Mechanical support and Nutritional support
- 2- **Defense & protection:** CT contains inflammatory cells involved in immune response.
- 3- **Storage:** adipose tissue for example stores lipid
- 4- **Transport:** CT acts as a transport medium for gases and small molecules

**CT cells are divided into two groups:**

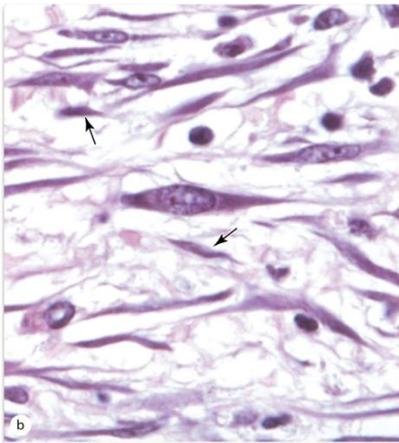
- Fixed cells:  
Always found in CT.
  
- Transient cells:  
They leave the blood and enter the CT in case of injury/ sites of tissue inflammation.
  
- **Fixed cells:**
  - Fibroblasts.
  - Adipose cells.
  - Mast cells.
  - Macrophages.
- **Transient cells:**
  - Plasma cells.
  - White blood cells (Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes).
  - Macrophages.

Blast in histology → active cell

Cyte → inactive cell

1-**Fibroblast:** (most common type)

Active in ECM synthesis, they synthesize the fibers and the ground substance components. When these cells finish the synthesis of ECM, they become inactive cells, retired cells, mature cells and called fibrocytes



Differences between fibroblast & fibrocyte:

<b>Fibroblast</b>	<b>Fibrocyte</b>
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Spindle in shape	Spindle in shape
Many process	Few process
Good amount of organelles	Little amount of cytoplasm
Nucleus more euchromatic	Nucleus more heterochromatic
Larger	Smaller

If fibrocytes are stimulated by damage to the surrounding tissue, the fibrocyte is altered into a fibroblast to repair the tissue damage. The site of injury is filled mainly with collagen fibers.

### 2-Myofibroblast:

- Myo means muscle
- They contain high amount of actin & myosin in the cytoplasm.
- Has features of both smooth muscles and fibroblasts.
- Their contraction is responsible for wound contraction.

### 3- Mast cell: (alarm cell) (fixed cell)

- Derived from precursors produced by hematopoiesis in bone marrow
  - Mast cells are “**alarm cells**” scattered within C.T, any slight disturbance of the tissue makes them release their content in order to recruit the inflammatory cells and trigger the Process of inflammation
  - Rounded cell.
  - Euchromatic nucleus.
  - Cytoplasm has high amount of secretory vesicles/granules
- Some thought it was a phagocytic material or ingested food from the outer environment so they called it Mast cells (The word "mast" refers to food)
- The secretory granules contain inflammatory mediators like:
    - Histamine:** (important in allergic reactions): it increases blood flow which means increasing diameter of blood vessel and the permeability.
    - Heparin:** anticoagulant at the site of inflammation
    - Leukotrienes**
    - Eosinophil chemotactic factor: Eosinophil** are white blood cells that increase at parasite infection.
    - Neutrophil chemotactic factor:** which are phagocytic cells

Blood is composed of blood cells & blood plasma.

#### **Blood has two main types of cells:**

- 1-Red blood cells: carrying o<sub>2</sub>& co<sub>2</sub>.
- 2-White blood cells: important for the immune system.

- They are seen in **2 places ( places exposed to antigens):**
- **Perivascular mast cells** which surround blood vessels.
- **Mucosal mast cells** which are in mucous membrane lining the cavities that open to the outside like in GI tract.
- They're waiting for any disturbance or allergen to secrete their granules; Allergies are caused (in part) by inappropriate sensitivity of mast cells. The symptoms are treated with *antihistamines*, chemicals which interfere with the action of histamine
- Under LM the nucleus appear rounded and pale (euchromatic) and you can't see cytoplasm, because it's filled with secretory granules which are called **metachromatic granules.**
- **Metachromatic granules:** able to change the color of the stain (ex: change the color of toluidine blue from blue to red purple (violet)).
- This property is called **Metachromasia** refers to the ability of changing the color of the dye.

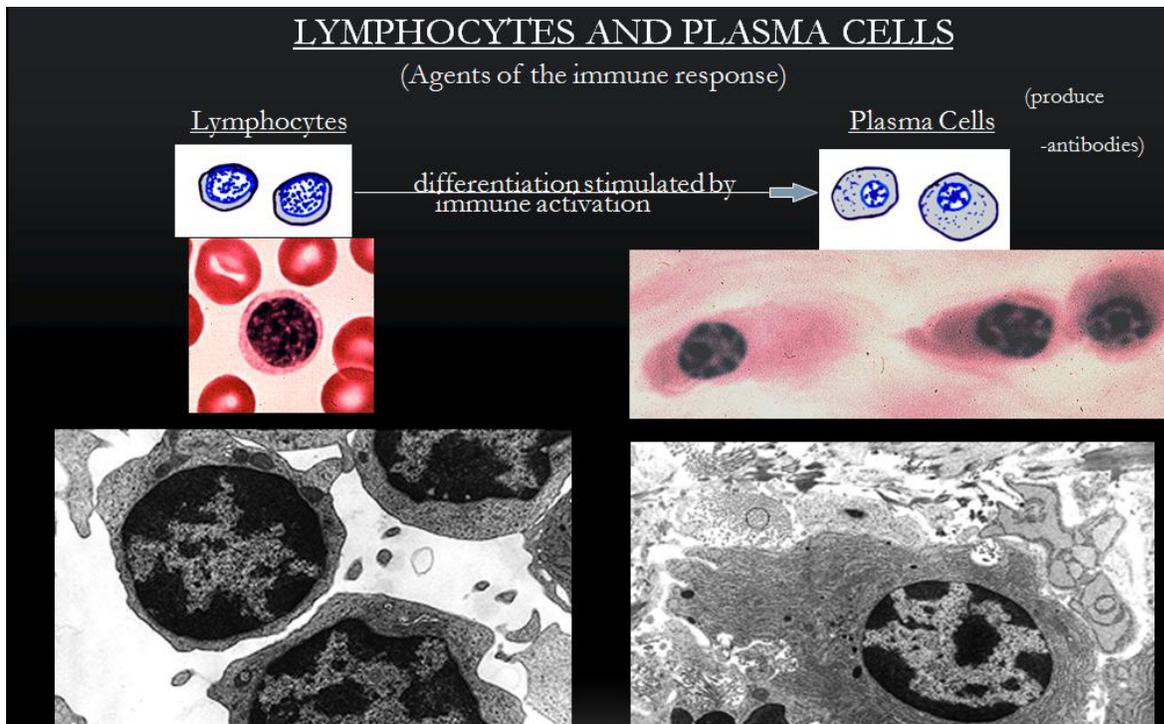
### **Plasma cells:**

- **Lymphocytes** (are small white blood cells with large nucleus, little cytoplasm and can enter and exit C.T easily).
- These lymphocytes are very important weapons in our immune system; they give 2 types (T, B).
- **B lymphocytes** give the plasma cells (origin).
- Plasma cells are seen in **chronic inflammation areas** due to their function (producing Antibodies "proteins") how?

When a certain antigen enters like bacteria, these cells will synthesize antibodies against them so when dealing with the same antigen again we don't need to produce new antibodies. As they synthesize antibodies they are **Protein synthesizing cells.**

- **For describing plasma cells:**

- Large rounded cells.
- Its Nucleus is Euchromatic and Eccentric (not in the center) it is toward the periphery (near the plasma membrane of the cell.)
- Cytoplasm is full with organelles (indicating the activity of the cell):
- Prominent RER for the synthesis of proteins= cytoplasm is **Basophilic**.
- prominent Golgi apparatus for packaging of these proteins (-ve Golgi stain; it appears pale or non-stained because it's composed of lipids and can't be stained with H & E or aqueous stains).
- Nucleolus presence indicates the activity of the cells.
- The heterochromatin of plasma cells is typically clumped in a characteristic "spoke-wheel" arrangement which also aids plasma cell recognition. This appearance is called: Cart wheel appearance (nucleolus at the center and there's heterochromatin lines going outside it). Or Clock-face appearance

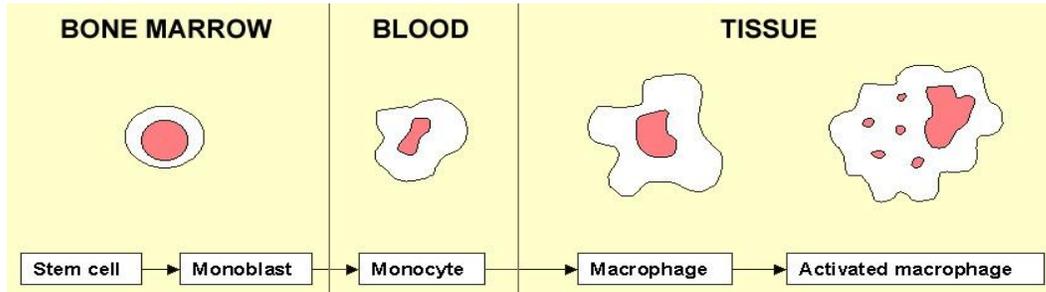


### Macrophages:

- Fixed+ transient cells
- Function: phagocytosis. SO we predict the presence of lysosomes in its cytoplasm

- Origin: (Monocytes from bone marrow)

Stem cells in bone marrow give Monocytes which are released into blood (circulating cells), once they enter C.T they become Macrophages (fixed cells in C.T), when an antigen enters it activates them (active form of Macrophages).



- C.T usually have scattered number of macrophages (fixed) waiting for any antigen, when the C.T is exposed to an antigen (infection), more monocytes will be recruited from blood circulation to enter the c.t ( more differentiation of monocytes into macrophages) so macrophage is considered also a transient cell
- Describing Macrophages:
  - Large cells with many cell membrane projections to phagocytose (pseudopodia)
  - Eccentric nucleus, over indented (kidney shaped or oval shaped).
  - Under LM it is difficult to visualize macrophages because they don't have any special characteristics and they look like fibroblast but bigger, **Now in order to see them:**
  - Either you inject the animal with carbon particles or any type of dye, they'll deal with it as a foreign material and start phagocytosing these carbon particles, the ingested carbon particles appear as black clusters.
  - Or cells already have been very active in phagocytosis (HOW?):

**Remember:**

Primary lysosome fuses with phagosome (ingested material) to become secondary lysosome.

After digestion it will become residual body (the remaining undigested material).

When Macrophages have been very active in digestion they accumulate large amount of residual bodies in their cytoplasm so they appear pigmented.

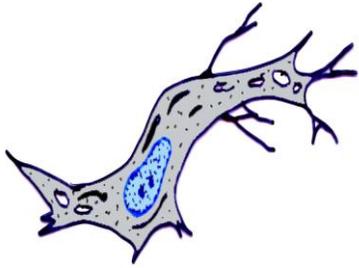
**FOR EX:** lung macrophages are exposed to antigens or dust particles in lung alveoli. We call them dust cells because they're in direct contact with inhaled air. In the lung, macrophages "patrol" the respiratory surfaces and ingest airborne particles which settle there. They can be identified by the accumulations of fine particles in their cytoplasm

- They are part of MPS “mononuclear phagocytic system”:
- MPS is a system of phagocytic cells in different locations in our body with different names and it is part of the immune system.
- In lungs : dust cells
- In liver: kupffer cells
- In central nervous system: microglial cells
- In skin: langerhans cells
- In bone : osteoclasts
- All these cells are characterized by phagocytic activity
- Some are macrophages and some look like them and have same function
- They used to name this system as Reticulo-endothelial System **but it is no longer used, why:**
- Reticulo-endothelial System is a system composed of certain organs (liver, spleen, lymph nodes) composed of blood filled channels (lined with endothelium) supported by reticular fibers, so when injecting the animal with carbon material they’ve seen the endothelium also colored with pigments SO they said that endothelial cells are the origin of macrophages or the same cells.
- but later on they’ve discovered that this is wrong and these endothelial cells only Shuttle the ingested material to the underlying C.T by endocytosis and exocytosis
- Macrophages were also named **Histiocytes**
- Also macrophages can aggregate in case of injuries to form giant cells (huge cells)

### Summary

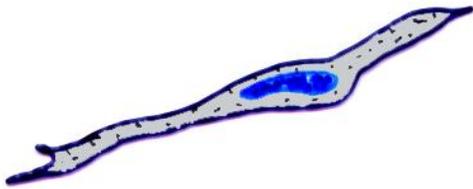
#### **Fibroblasts**

- The most numerous cells of connective tissue.
- Occur in active and inactive forms (fibrocyte).
- Originate from undifferentiated mesenchymal cells.
- Capable of some movement.
- Rarely undergo division
- Closely associated with collagen bundles.
- Elongated, fusiform, and have many processes.
- Cytoplasm is pale and difficult to be differentiated from near by tissue.
- Nucleus is large (ovoid) euchromatic, prominent nucleolus
- E.M: prominent Golgi, mitochondria, rER, actin and myosin.



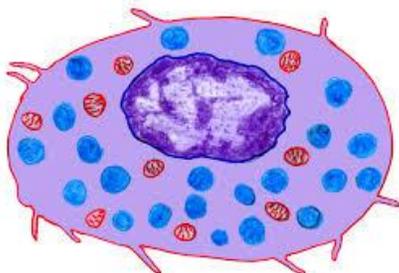
### **Fibrocytes**

- Smaller and simple shaped with acidophylic cytoplasm.
- The nucleus is smaller and darker (heterochromatic).
- Few processes.
- E.M: few rER.
- When stimulated, it may revert to fibroblast



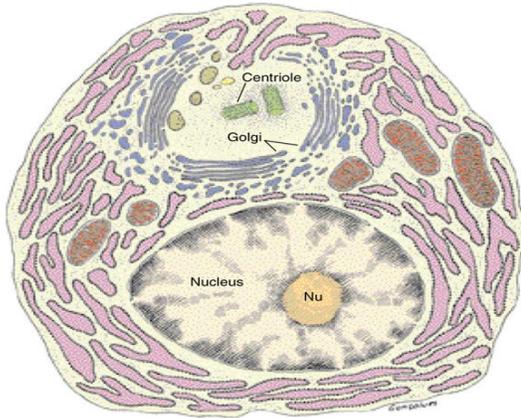
### **Mast cells**

- Large cell ~ 7-20  $\mu\text{m}$ .
- Derived from precursors in the bone marrow.
- Nucleus: central ovoid.
- Cytoplasm highly granular, metachromatic.
- Granules contain:
  - Heparin
  - Histamin
  - Leukotriens
  - Eosinophil chemotactic factor.
  - Neutrophil chemotactic factor.
  - Platelet activating factor.
  - Bradykinin.



## Plasma cells

- Derived from B lymphocytes following exposure to an antigen.
- Present at portal of entry of organisms and sites of chronic inflammation.
- Life span ~ 10-20 days.
- Large ovoid cells ~ 20  $\mu\text{m}$ .
- Nucleus: eccentric with clusters of heterochromatin  $\rightarrow$  cart-wheel or clock-face nucleus.
- Cytoplasm:
  - Intensely basophilic.
  - Well developed supranuclear Golgi apparatus (- ve image).
  - Well developed rER.
- Functions: secretion of specific antibodies.



## Macrophages

- Derived from monocyte.
- Large cells ~10-30  $\mu\text{m}$ .
- Surface shows many projections.
- Nucleus: eccentric, oval or indented (kidney-shaped).
- Cytoplasm: basophilic, well developed Golgi, prominent rER, many lysosomes.
- They are part of the MPS.
- Multinuclear giant cells

## Extracellular matrix (ground substance+ fibers):

### The Ground Substance:

- The ground substance is **simply composed of water** (remember that the connective tissue acts simply as a transport medium for certain molecules and waste products between blood vessels and epithelium for example).
- It's not only water because according to gravity, this water will pool in the lower part of the body so in fact it's a gel-like structure.
- With different types of C.T we'll see different components of ECM (like in blood its ECM is fluid but in bone it's solid because it has high amount of Ca ions), **but** here we are talking about ORDANIRY C.T which is located directly under epithelium (for example) not about special types of C.T.
- **3 types of ground substances** (macromolecules):

- Glycosaminoglycan(GAGs)
- Proteoglycans
- Glycoproteins

### **1.GAGs:**

- Long chains of repeating units of disaccharides (2 sugars), unbranched

- **2 types:**

-**Sulfated:** contain sulfate group such as (keratin sulfate, chondroitin sulfate, dermatan sulfate, and heparin).

-**Non-sulfated:** No sulfate group, the only one: (hyaluronic acid is the Longest one with very high molecular weight).

### **2-proteoglycans:**

Main component is sugar (GAGs) and short core of protein (a protein core attaches to many GAGs).

### **3-glycoproteins:**

Main component is protein and small amount of sugars (short chains). Branched short polysaccharides (oligosaccharides, oligo= few).

- The hyaluronic acid acts as a backbone where the other glycosaminoglycans are going to attach through a protein core, so simply the hyaluronic acid is going to interact with proteoglycans
  - Ground substance consists largely of **proteoglycans** and **hyaluronic acid**. Proteoglycans are very large macromolecules, consisting of a **core protein** to which many **glycosaminoglycan (GAG)** molecules are attached. GAGs are long-chained polysaccharides made up of repeating disaccharide units. GAGs are highly negatively charged (polyanions). The high density of negative charges attracts water, forming a hydrated gel. This gel permits the rapid diffusion of water-soluble molecules but inhibits the movement of large molecules and bacteria.
  - The large structure formed by hyaluronic acid and proteoglycans makes a spherical space; this space is called a domain. So bacteria need to pass between these domains in order to pass through the connective tissue, so that is why we say that the ground substance simply has filtering effect and prevents the spread of the bacteria. The pathogenicity of a bacterium is indeed to some extent determined by its ability to find its way through the mesh, and some of the more invasive types produce the enzyme hyaluronidase, this enzyme is able to destruct hyaluronic acid which will destruct this domain so they are able to invade the connective tissue
  - Each domain looks like a **Bottle Brush**: the handle is hyaluronic acid and the bristles are the proteoglycans
- **Functions of Proteoglycans**
  - Resistance of compression. - They are stabilizing macromolecules (little amount of it gives water solid state).
  - Retardation of movement of microorganisms.
  - Act as a filter