Histology

faculty of medicine - JU2015

Done by:

Fahed Al Karmi and Rahaf Al Qaryouti

lecture #7

Fibers of the connective tissue are collagen, elastic and reticular fibers

Collagen fibers

- Collagen is a protein, 30% of the proteins in our body is **collagen**. it is the most common protein in our body
- There are 28 types of collagen and are identified according to their distribution, location and function. These types differ in their amino acids sequence, structure and the protein modifications.
- In this sheet we will focus on collagen I, II, III, IV, and VII.
- Collagen III is found in the reticular lamina
- Collagen IV is found in basal lamina (lamina densa).
- Collagen VII is an anchoring protein that anchors collagen III with collagen IV (anchors the basal lamina with the reticular lamina of the basement membrane).
- Collagen II is the most common type in cartilages
- Collagen I is the most common type of collagen (90%) and the strongest one, that is why it is found in areas that are subjected to mechanical forces and stresses that need strength like tendons, skin (dermis) and sub mucosa.

-The epithelial layer of the skin is called epidermis and the connective layer is called dermis which is under the epithelium.

-Mucus membrane lines the cavities that open to the outside. The **submucosa** is a thin layer of c.t tissue that supports the mucosa (mucous membrane), it has high amount of collagen I

-Leather is very strong and is derived from the dermis of large mammals (collagen fibers 1)

- Only **collagen type 1** can form collagen bundles, while collagen type 3 forms fibers (thin fibers), collagen type 2 forms fibrils, collagen type 4 in basal lamina forms sheets.
- Note that each molecule of tropocollagen has head and tail, so the arrangement is (head to tail.. head to tail and so on), also there is a regular gap between two tropocollagens, so when looking at a collagen fibril by electron microscope cross striations will appear; these striations are formed by the gaps between tropocollagen molecules because of the accumulation of the stain in these gaps.
- The longitudinal areas of completely overlapping tropocollagen are called "overlapping areas".
- The longitudinal areas where there is gaps between tropocollagens are called non-overlapping areas

Tropocollagen ---->Fibrills ----> fibers ----> bundles

-Different combination between 3 helical alpha chains gives different types of collagen.

-each alpha chain is composed of 1000 amino acids. In collagen type 1 each third amino acid is glycine, and the other amino acids are proline and lysine.

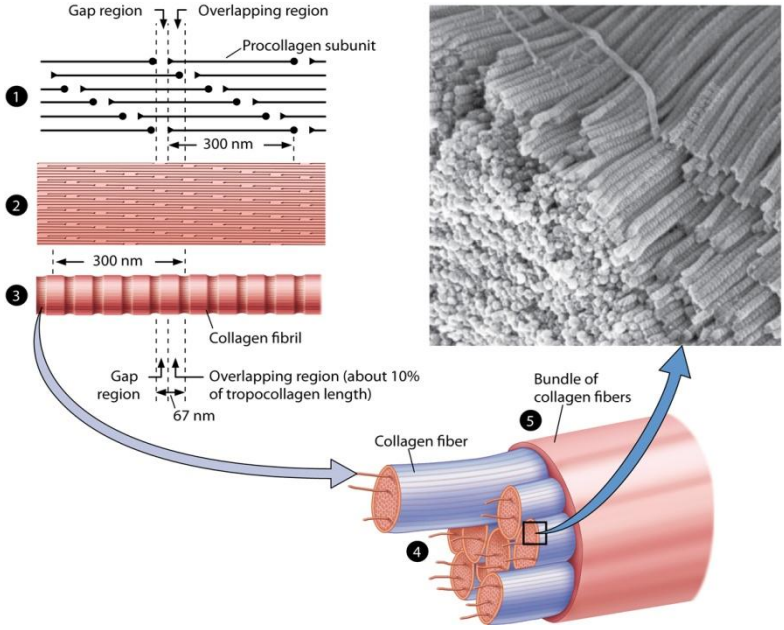
-Collagen fibers type 1 are seen under LM with H&E staining as acidophilic structures (pink). In anatomy, the organs with collagen appear white in color.

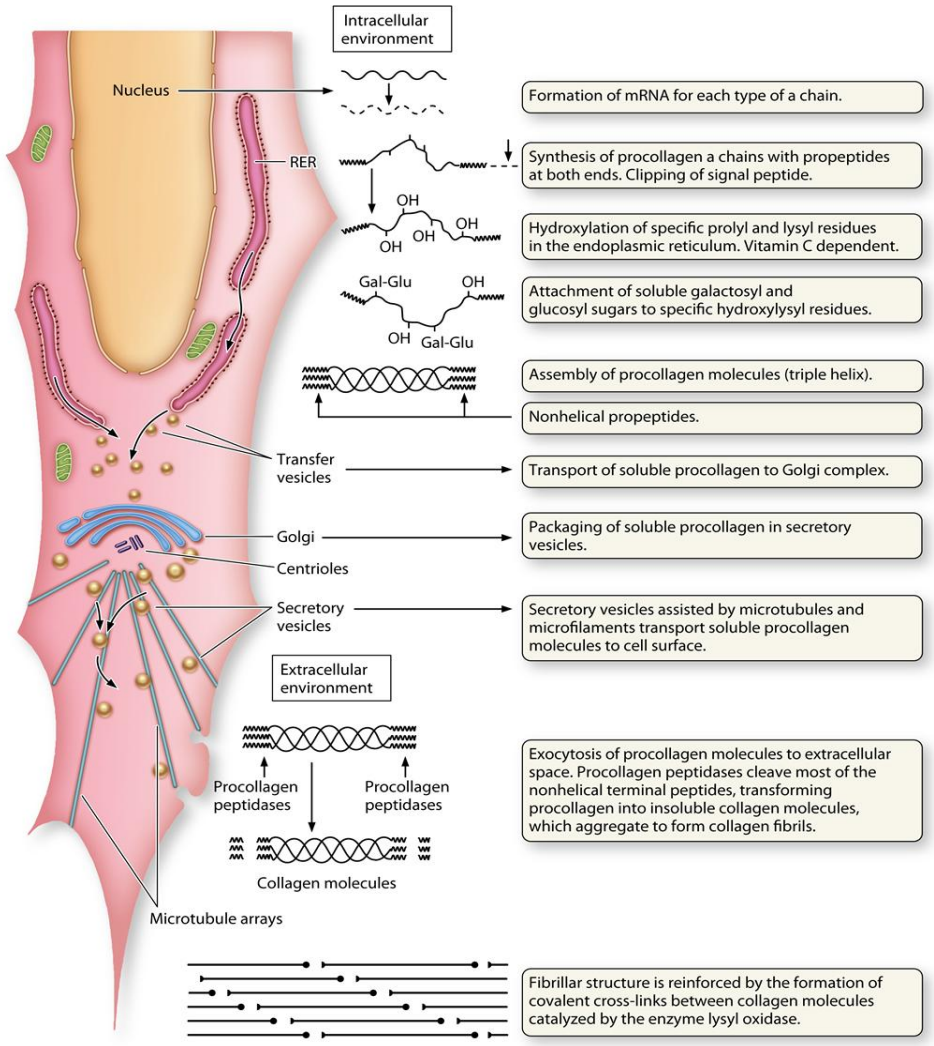
-Clinical applications

1- Keloid: once the fibrocytes are stimulated by injury, they differentiate into fibroblasts and start producing collagen fibers. In the surgical incision site for example, the connective tissue is going to replace this defect by collagen type 1, this is called scar formation. But in some people the production of collagen is very excessive and result in excessive accumulation of collagen fibers. The scar area appears large, protruded from the surface (exotic), pinkish -color and shiny, this is called Keloid. Keloid is common in Africans.

2-Scurvy: is due to absence of vitamin C which is necessary for the hydroxylation step, the skin of the patient in this case is yellowish because of Anemia. Also the patient has bleeding gums and hemorrhage at different areas because of defective collagen (remember that collagen adds strength to the tissue).

3-Hypermobility Ehlers-Danlos syndrome: there are many types of this disease (defect in different steps of collagen synthesis), this type is characterized by joint hypermobility and luxation.



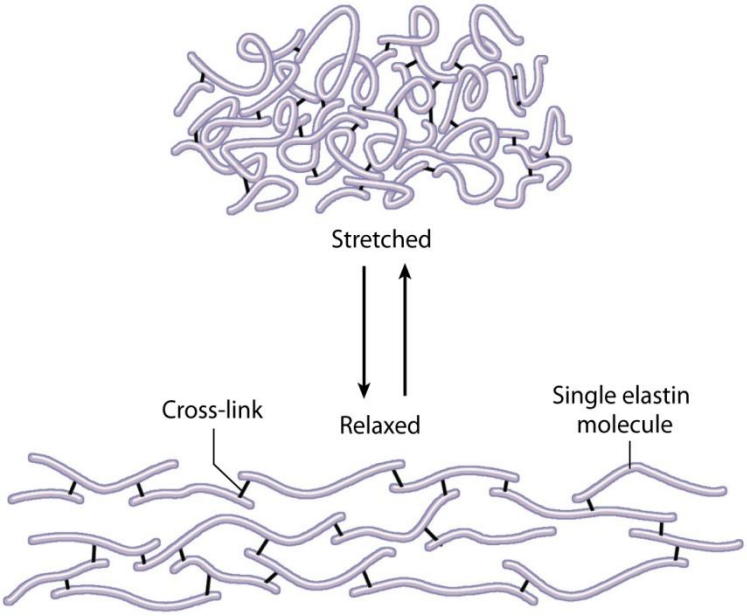


Elastic fibers

- Elastic fibers provide elasticity which means the ability to restore the original shape after stretching
- Elastic fibers are like the rubber bands, when you apply a certain force, they stretch. When you release the force, they return back to their original shape
- They are found in organs that are subjected to bending and stretching forces such as blood vessels especially the large arteries, the presence of elastic fibers in aorta will allow it to recoil after distension/dilation.
- In general, Elastic fibers are made by fibroblasts, except in certain places like the wall of large arteries, elastic fibers are produced by smooth muscle cells
- Elastic fibers are mainly composed of two proteins:

1- Fibrillin 10%: fibrilin forms microfibrils (aggregation of fibrillin protein). It is important for stability of the elastic fiber
2- Elastin 90%: coiled protein which is responsible for the elasticity of the elastic fiber.

- Coiled elastin proteins start to deposit around microfibrils. elastin proteins are connected by special cross links called desmosine.
- Elastin fibers are digested by elastase (a pancreatic enzyme), they are also affected by sun exposure and age.
- We also find collagen I with elastic fibers to provide strength and prevent over-stretching when exposed to severe stress.
- Elastic fibers are found in all types of connective tissues but in some tissues they are the predominant fibers and the tissue is called elastic tissue
- In anatomy, any tissue that has a high concentration of elastic fibers appears yellow.
- Elastic tiissue is found in the external ear (elastic cartilage), it is also found in certain ligaments (remember that tendons attach muscles to bones while ligaments attach bones to bones), ligaments are considered as collagenous CT type I, except the ligamentum flavum (connects the vertebrae of the vertebral column), where *flavum* = yellow, ligamentum flavum is an elastic ligament
- Elastic fibers are electron dense, so they appear black under the EM. Under LM, some special stains are used such as elastin stain because elastic fibers are poorly stained with H&E.



Reticular fibers

Because of their different staining characteristics, reticular fibers were initially thought to be completely different from collagen fibers. Cross-striations with the same periodicity as in collagen I are however visible using EM. Reticular fibers consist of collagen III. Reticular fibers are very delicate and form fine networks instead of thick bundles (branched fibers).

Location of reticular fibers:-

1- They are found mainly in the reticular lamina of the basement membrane.
2- They are found in RES organs (Reticulo endothelium system) such as bone morrow, liver, lymph nodes and spleen, which consists of blood channels supported by reticular fibers. These organs have a meshwork of reticular fibers which acts as the framework of these organs (supportive stroma and supporting individual cells) .

- It was thought that reticular fibers are not collagen fibers because they are stained positively by PAS stain due to their high amount of carbohydrates. and they are also stained positively by silver nitrate, there is a method of staining called silver impregnation which is adding silver to the tissue, because these fibers have a high amount of carbohydrates, and these carbohydrates are negatively charged, thus, they are going to interact with the silver and cause its reduction, which results in deposition of silver inside the tissue, so that the reticular fibers can be seen as black threads, reticular fibers are argyrophilic (silver loving).

- Note that all collagen fibers types contain carbohydrates but in minimal amount (about 1% only) , that's why collagen fibers are considered as glycoproteins , but collagen III which forms reticular fibers contains much higher amount of carbohydrates (10% carbohydrates) .

- The cells that are specialized in secreting reticular fibers are called reticular cells, which are modified fibroblasts.

- Functions of reticular fibers :-

1- Supporting the tissue
2 - Allowing the movement of cells and molecules, for example, lymphoid tissue which is found in lymph nodes, is filled with cells called lymphocytes. So, these fibers form spaces in which lymphocytes can move freely within the tissue.

Medical application-Edema

- It is the accumulation of the interstitial fluid inside the extracellular matrix of the CT.
- Extracellular matrix of connective tissue is the ground substance and fibers and it has fluid called interstitial fluid in between the cells.
- There are many causes of edema but in general:
- Any capillary has an arterial side and a venous side, many forces act on the movement of fluid from blood lumen to the extracellular fluid. When blood passes through arterial side it is controlled by hydrostatic force produced by high blood pressure of arterial side (from pumping of the heart) this will force fluid and nutrients to move from capillary to extracellular matrix (interstitial fluid). what is left inside a capillary in its venous side are plasma proteins which will exert another type of pressure called osmotic pressure, this

pressure will force fluids to pass from extracellular matrix back to the venous side of a capillary.

- Not all of the left fluid will be picked up by the venous side, there is something called lymphatic capillaries that pick up the remnant of this fluid.
- Any defect in this system (problem in the hydrostatic pressure in the arterial side, venous side or lymphatic side) causes edema

Classification of CT

A) Proper CT: loose (cells and ground substance are more than fibers or all have the same proportions) and dense (more fibers)
B) Embryonic CT: Mesenchyme CT and mucus CT.
C) Special CT: bone, cartilage, blood, adipose, reticular and elastic

A) <u>Proper CT</u> :-

1- Loose CT:- Composed of all types of fibers, fibroblasts and inflammatory cells and ground substance.

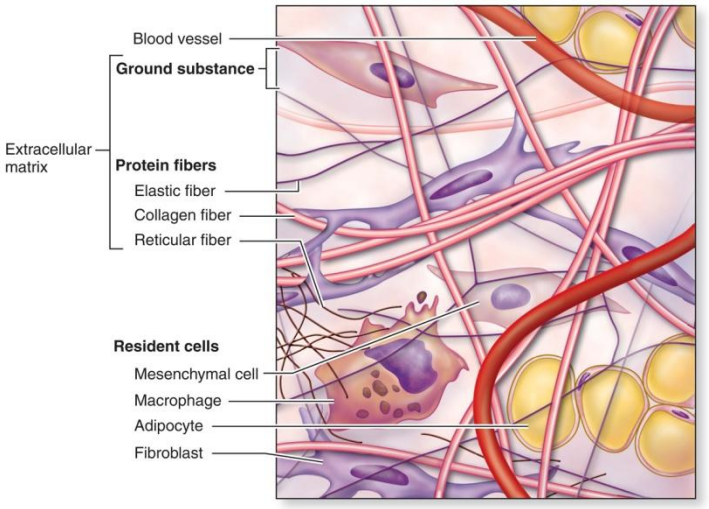
Function:

1- Diffusion (medium for transport) because it has a lot of spaces filled with ground substance. It is found around blood vessels, directly under epithelium layer, highly vascular (high amount of capillaries in order for the molecules to pass from the blood vessels to the epithelium and backward.

2- Second line of defense below basement membrane of epithelial cells because it has inflammatory cells (ex macrophages)

3-fills spaces inside any organ

- found in lamina propria of mucus membrane below epithelium (special name for the loose CT of mucus membrane)
- it is a flexible structure, because it has high amount of ground substance, high amount of water, extracellular matrix, gel like structure.
- not resistant to stress because it has low amount of collagen, flexible but not very strong (the function is diffusion and defense).
- Loose CT has high regenerative power and is highly vascularized.



Dense CT:- Dense CT is formed mainly from fibers and a little amount of cells (mainly fibroblasts). The main function is to provide strength. Dense CT has low regenerative power and is less vascularized.

Irregular :- found in areas subjected to forces from more than one direction such as dermis of the skin, capsules of organs and sub mucosa

Regular :- found in areas subjected to forces from one direction such as tendons, ligaments, and aponeurosis (ex.abdominal flat tendons).

Dense irregular connective tissue

- mostly comprised of collagen fibers
- collagen fibers are arranged haphazardly (randomly)
- Collagen fibers add strength to the connective tissue so it's very resistant to compressional forces and tensile forces
- provide powerful resistance in **many directions** (according to the orientation of the fibers)
- location: 1-skin dermis (exposed to many different forces in multiple directions)
  The superficial layer of connective tissue is loose, the deeper layer is dense irregular connective tissue (to give strength for loose ct and epithelium). Note: Epithelium of the skin is epidermis, and the connective tissue of the skin is dermis
  2-Organ capsules
  3-submucosa of digestive tract

Dense regular connective tissue

- fibers oriented in certain direction
- provide resistant to stress in one direction
- fewer cells and ground substance and most of the cells found are fibroblasts not inflammatory cells
- Locations: **ligaments**: connect bone to bone, usually are collagenous (whitish in color) dense regular type of connective tissue except certain types of ligaments (elastic/yellowish in color).**Tendons**: connect muscle to bone. **Aponeurosis**: flat tendon (sheet like) instead of cord like structure.

B) Embryonic connective tissue:

- It contains star or spindle shaped mesenchymal cell, gel like ground substance with fine fibers (more ground substance than fibers).
- If you go back to developing embryo you will see three germinal layers; ectoderm, endoderm (inner side) and in between them there is a filling material (mesoderm or Mesenchyme). It is the common origin of all other connective tissue
- With fetal development, mesenchyme forms the connective tissue between and within the developing tissues and organs
- Remember that epithelium is derived from the three germinal layers which is a characteristic for it, while connective tissue is derived from mesenchyme (or mesoderm).
- Mesenchymal tissue or embryonic tissue is a tissue found only in embryo while after birth we can't find mesenchymal tissue because all mesenchymal tissue has differentiated into different types of connective tissue. EXCEPT in certain places; in the pulp of the tooth (be careful we talk now about a tissue not individual stem cells) and the umbilical cord
- If we see a section shows mesenchymal tissue we will expect that this section is taken from embryo or pulp of the tooth or umbilical cord.
- Mesencymal cells can differentiate into osteoblasts which form the bone or fibroblasts which form the connective tissue or adipoblasts which form the adipose tissue or……etc. So these cells are stem cells which can differentiate into many types of connective tissue cells. The extra cellular matrix of mesenchymal c.t contains more ground substance than fibers (gel like structure because it has large amount of hyalourinic acid, chondriotin sulphate (sulfated GAG) and water)
- Mesenchymal stem cells are characterized by having a little amount of cytoplasm with fine processes and large oval or rounded nuclei.
- The mesenchymal c.t of the umbilical cord is called also mucoid connective tissue (also called Wharton's jelly). The wide extracellular space between the mesenchymal cells is occupied by ground substance, which can be stained

with dyes that also stain mucin - hence the alternative name of this tissue type: mucoid connective tissue

- Mucoid connective tissue forms a compliant cushion around the vessels of the umbilical cord
- Umbilical cord banking simply involves collecting blood left in newborn's umbilical cord and storing it for future medical use (cord blood and/or tissue) (regenerative medicine).

C) Special CT :-

1- Reticular tissue which is composed of reticular fibers (discussed earlier).
2- Elastic tissue which is composed of elastic fibers (discussed earlier).
3- Bone tissue (later)
4- Cartilage (later)
5- Blood (later)
6- Adipose tissue:- It is considered a type of the connective tissue because it originates from the mesenchyme. Adipose tissue is a collection of cells that simply store lipids inside their cytoplasm (adipose tissue is the site of storage of triglycerides which consist of three fatty acids and one glycerol molecule). Adipose tissue is composed of cells called adipoblasts or adipocytes (according to the activity of the cells), these Adipocytes can be found within connective tissue proper like loose CT but when they are found in large amounts then the tissue is called adipose tissue.

There are two types of adipose tissue: white adipose CT and brown adipose CT.

	White adipose CT	**Brown adipose CT**
Location	Throughout the human body (the super facial fascia is composed of this type).	In the fetus and the newborns (brown adipose tissue decreases with age)
Collection of lipids	In a single lipid droplet filling nearly all of the cytoplasm and pushing the nucleus and the cytoplasm toward the periphery resulting in an appearance called signet ring appearance	Multi lipids droplets
Name of the tissue's	Unilocular one droplet of	Multilocular (many droplets)

adipocytes	lipid)	
Under the microscope	1-The white adipocytes are relatively large 50-150 um in diameter, compared to brown adipocytes, and are dominated by the lipid droplet 2- non-membrane bound droplet 3-unilocular cells 4-ring appearance.	1-Brown adipocytes are small cells that contain a centrally-placed nucleus and large numbers of mitochondria. 2-multilocular

- The brown adipose CT has a high amount of mitochondria that contain certain enzymes which produce the brown color, normally mitochondria produce ATP but the mitochondria in brown adipose tissue have certain enzymes that uncouple the oxidative phosphorylation & prevent the production of ATP, the result product is heat, so the main function of the brown adipose CT is to produce heat .

- Brown adipose tissue can be found in fetus. Counts for 2-5% of the body weight of the newborn located in certain areas like:-

    A. around the kidney
    B. Between the two scapulae and the back of the neck
    C. Around the heart
    D. Around large blood vessels like aortic arch, and that makes sense because production of heat will keep the blood warm.

- Brown adipose connective tissue has a high metabolic rate capable of generating relatively high amounts of heat, a process that is physiologically important to infants prior to the maturation of their thermoregulatory mechanisms.
- It is greatly reduced during childhood and adolescence. In adults it is found only in scattered areas, around kidneys and aorta.
- To differentiate between the two types under the microscope we depend on the lipid droplets: One large droplet and a peripheral nucleus indicate white adipose tissue. Multiple droplets indicate brown adipose tissue.

- White adipose tissue is the basic type of adipose tissue of the adult human and has many functions :-

    1- storage reservoir of metabolic fuel in the body
    2- thermal insulator
    3- protective cushion

- In adults, white adipose tissue is primarily distributed subcutaneously and viscerally.
- Adipocytes are surrounded by a thin external lamina containing collagen IV.