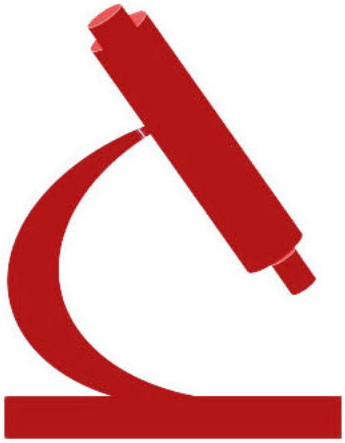

CYTOLOGY

Premed 2018 - JU

◉ Sheet ○ Slides

Number

20

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➢ Extra Cellular Matrix (Recap) :

- The extracellular matrix fills the spaces between cells and binds cells and tissues together
- It is composed of different polysaccharides and proteins.
- There are many types of ECM depending on the type of tissue.
- Some tissues –like connective tissues- are mostly made of ECM. For example: bones and cartilages.
- Other tissues (e.g: epithelium) have a very small amount of ECM and it is mostly located at the basal lamina.
- Proteins of the ECM are either arranged into fibers –like collagen- or they link components of the matrix both to one another and to attached cells (adhesion proteins).

➢ Protein Fibers :

1) Collagen:

- Collagen is the most abundant protein in our body. It has many shapes meaning that it doesn't always form fibers.
- It's discussed in details in sheet 19.

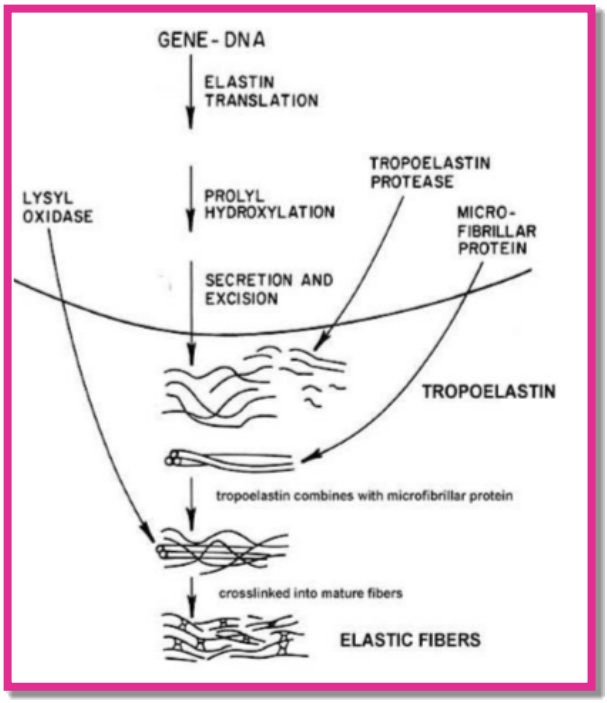
2) Elastic Fibers:

- Abundant in organs to allow them to stretch then return to their original shape, e.g. lungs.
- They form a loose network of fibers in the ECM that shares **some** characteristics with collagen fibers.
- In general, elastic fibers are more flexible than collagen that's why wherever flexibility is needed, there are more elastic fibers than collagen in the structure of ECM.
- The main component of elastic fibers is elastin.
- Elastin, as a protein, is rich in proline and glycine. It contains hydroxyproline but in less amount than in collagen.
- Hydroxyproline contributes to the strength and the structure of the molecule but it doesn't make it as strong as collagen.
- Lysine is present in elastin but hydroxylysine isn't.
- Hydroxylation of lysine occurs only in collagen for the attachment of sugars, it doesn't occur in elastic fibers **(no hydroxylation of lysine)** which means that there's no attachment of sugars on elastic fibers. **(No glycosylation on elastin).**

- Elastin has two types of short segments that alternate along the polypeptide chain:
  1. **Hydrophobic segments,** which are responsible for the elastic properties of the molecule.
  2. **Segments rich in alanine and lysine (a-helical segments),** which form cross-links between elastic fiber networks and between elastic fibers and adjacent molecules.

➢ Formation of Elastic Fibers :

- Elastic fibers are made of elastin protein.
- DNA contains elastin gene which is transcribed into m-RNA. m-RNA is then translated, and post-translational modifications occur.
- One of the post-translational modifications is hydroxylation of proline (doesn't happen as frequent as in collagen) to form hydroxyproline.
- Again, there's no hydroxylation of lysine and no glycosylation.
- After these modifications, elastin is secreted (Secretion and excision).
- After secretion, elastin will have other modifications :
  - Tropoelastin protease (an enzyme) cuts parts of the tropoelastin that don't contribute to the final structure of the protein.
  - After removing parts of the tropoelastin, tropoelastin is then transformed into a mature form that can form fibers.

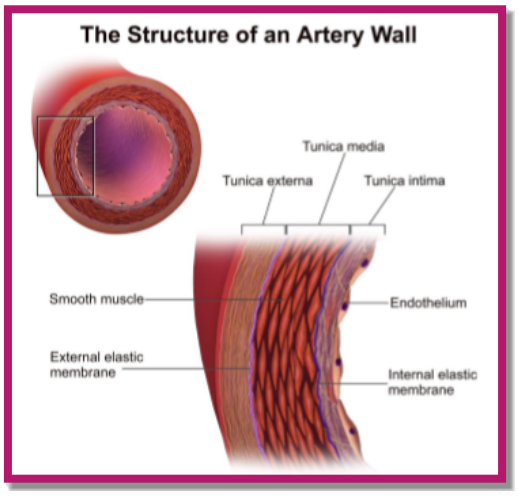


- Microfibrillar proteins are needed for the assembly of elastic fibers. They facilitate and aid in the formation of elastic fibers.
- Tropoelastin gets cross-linked with microfibrillar proteins through **covalent bonding** between **lysine** residues.
- Lysine residues facilitate the cross-linking by the formation of covalent bonds between them.

Collagen	Elastic Fibers
Hydroxylation of lysine.	No hydroxylation of lysine.
Glycosylation.	No Glycosylation.
No proteins are needed for the assembly of collagen.	Microfibrillar proteins are needed for the assembly of elastic fibers.
Stronger.	More flexible.

➢ Importance of elastic fibers in blood vessels :

- Walls of blood vessels contain muscles and elastic fibers which are necessary for them to be able to constrict (vasoconstriction) and dilate (vasodilation) to regulate blood pressure and maintain homeostasis.
- Elastin is the dominant ECM protein in arteries.
- Elastic fibers contribute to the flexibility of the walls of blood vessels. This flexibility allows the diameters of blood vessels to change in response to change in blood pressure.
- The normal elasticity (flexibility) of an artery restrains the proliferation of smooth muscle cells.
- If a patient has a deficiency in elastic fibers or the amount of elastic fibers is less than normal in the walls of blood vessels, the smooth muscles in the walls of blood vessels will proliferate (become bigger). Smooth muscles aid in constriction and dilation but they're not as flexible as elastic fibers. Consequently, the flexibility of the walls will decrease and they'll constrict causing the blood vessels to narrow → higher blood pressure.



- Abnormality or deficiency of the elastin results in excessive proliferation of smooth muscle cells in the arterial wall and narrowing of the arteries.

➢ Microfibrils :

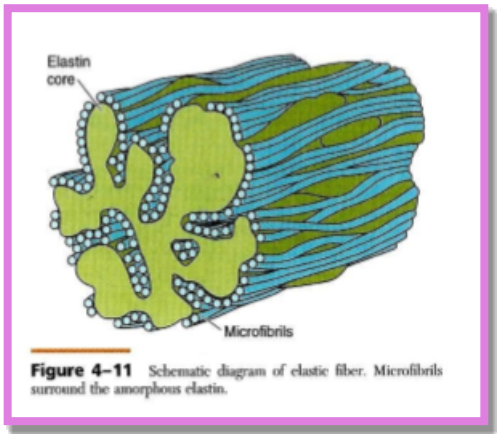


Figure 4–11 Schematic diagram of elastic fiber. Microfibrils surround the amorphous elastin.

- An elastin core is covered with a sheath of microfibrils.
- Microfibrils are composed of a number of distinct glycoproteins, including the large glycoprotein fibrillin, which binds to elastin and is essential for the integrity of elastic fibers.
- Microfibrils are present in hair and sperm tail.
- Remember that elastin doesn't contain sugar (no glycosylation) but the proteins that facilitate its assembly do.

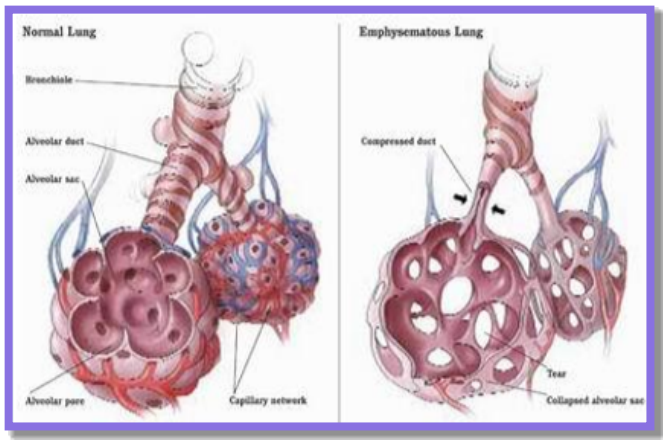
➢ Marfan's Syndrome :

- Cause: mutation of fibrillin.
- The mutation affects the microfibrillar proteins that help with the assembly of elastic fibers.
- Rapture of aorta.
- Signs and symptoms:
  1) A tall, thin build Long arms, legs, fingers, and toes.
  2) Flexible joints Scoliosis, or curvature of the spine.
  3) A chest that sinks in or sticks out.
  4) Crowded teeth.
  5) Flat feet.

➢ Emphysema (destructive lung disease) :

- It has a genetic cause and a cause related to smoking. Smoking does the same effect as the genetic cause.
- Lungs expand and contract during breathing.
- Lungs are composed of sacs that are highly flexible and thin. They contain lots of elastic fibers.

- If these sacs lose their flexibility, breathing becomes harder and not enough oxygen will reach the cells. Low concentration of O_2 in the brain could cause brain death.
- Cause: a dysfunctional Alpha(α) 1-antitrypsin.
- α 1-antitrypsin is dysfunctional in smokers who suffer from emphysema due to the oxidation of specific methionine residues. These methionine residues are essential for the functionality of α 1-antitrypsin.
- The lysine to-glutamate mutation causes protein misfolding, formation of an aggregate and block of ER export.
- The inactivation of α 1-antitrypsin will increase the activity of elastase which causes the destruction of the structure of elastin fibers.
- Consequently, lungs lose their flexibility and breathing becomes harder.
- Cigarette smoking also inactivates α 1-antitrypsin by oxidizing essential methionine residues, decreasing the enzyme activity by a factor of 2000.



➢ Matrix Polysaccharides :

- In the ECM polysaccharides are present in glycoproteins and proteoglycan.
- Proteoglycans are composed of proteins (small portion) and carbohydrates (large portion).
- The major component of proteoglycan is sugar.
- They contain a core protein + Glycosaminoglycans (GAGs).
- Glycosaminoglycans (GAGs): Polysaccharides of repeated disaccharides in which fibrous proteins are embedded.
- GAGs share some common characteristics :
  - ✓ Complex structure.
  - ✓ One of the parts of disaccharide is either N-acetylglucosamine or N-acetylgalactosamine. (sugars modified by amino groups).

- ✓ The other sugar has other modifications :
  1) **Oxidation**: transforms –for example- one of the carbonyl groups to carboxyl forming carboxylic sugar. Carboxylic sugar is acidic and will give up a proton becoming highly negatively charged (COO^-).
     -For example: glucuronic acid or iduronic acid.
  2) **Addition of a sulfate group**: sulfate also has a negative charge.
     -For example: dermatan sulfate, chondroitin sulfate, keratan sulfate, heparin sulfate.
- ✓ The original molecules are polar (glucose or galactose) but after these modification they become even more polar.
- ✓ That's why GAGs attract water molecules around them and interact with them either by hydrogen bonds, dipole-dipole interactions or dipole-charged interactions forming a gel like structure.

- GAGs form a gel like structure that functions as a shock absorber (like a sponge) which explains why in cartilages there are more polysaccharides than in bones.
- After modification, 2 sugars unite as a disaccharide unit (one is amino modified and the other is either oxidized (acidic) or a sulfate group was added to it).
- Disaccharide units are repeated forming a polysaccharide structure. After the formation of the polysaccharide, the core protein is added making up the proteoglycan. Proteoglycans then exit the cell and join the ECM.
- Some Proteoglycans are cell surface proteins with either transmembrane domains (syndecans) or GPI anchors (glycipans) interacting with integrins.
- Proteoglycans will interact with proteins found on the cell and they'll be affected by the cell's internal environment.
- Hyaluronan: is the only GAG with a single long polysaccharide chain.

➢ **Additional lecture notes that aren't mentioned in the slides :**

- Proteoglycans will interact with proteins found on the cell and they'll be affected by the cell's internal environment.
  - For example : when there's eye pressure, the tissue responsible for regulating eye pressure senses changes in pressure as mechanical stress and they send a message (signal) to produce a response. The cell will

respond by synthesizing certain proteins. These proteins (some are enzymes) will be secreted into the ECM.

- You can imagine the ECM as though it's a street and the GAGs present in it are making the street narrower. A large amount of fluid is passing in this street causing pressure.
- The fluid causes pressure while passing because of the GAGs and their branches which made the street narrow.
- Proteins secreted by the cell (as a response) cut down these GAGs and lessen their branches making the street wider so that the fluid passes without causing pressure.

- Hyaluronic acid is present is the synovial fluid around joints. It provides lubrication and it makes the movement of these joint frictionless. It's also present in the vitreous humor of the eyes.

Best of wishes. Good luck.