CYTOLOGY

Premed 2018 - JU

◉ Sheet ○ Slides

Number

19

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Extra Cellular Matrix (ECM)

- It is the material that is outside cells. It fills spaces between cells and binds cells and tissues together.
- It is composed of different proteins and polysaccharides; these components vary between cells -*even between cells of the same tissue*-.

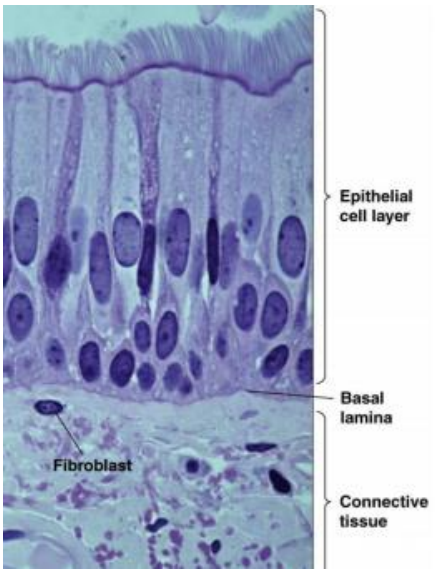
Types of extracellular matrix

1- Basal laminae (basement membranes)

- Thin, sheet like structure.
- Functions:

A- Supporting sheets of epithelial cells, since these cells rest on basal laminae which is located between epithelial and connective tissues.

B- Surrounding muscle cells, adipose cells and peripheral nerves.



2- Connective tissue (more ECM)

- Loose network of proteins and carbohydrates underneath epithelial cells and where we can find fibroblasts.
- Can be found in: muscles, tendons and cartilage.

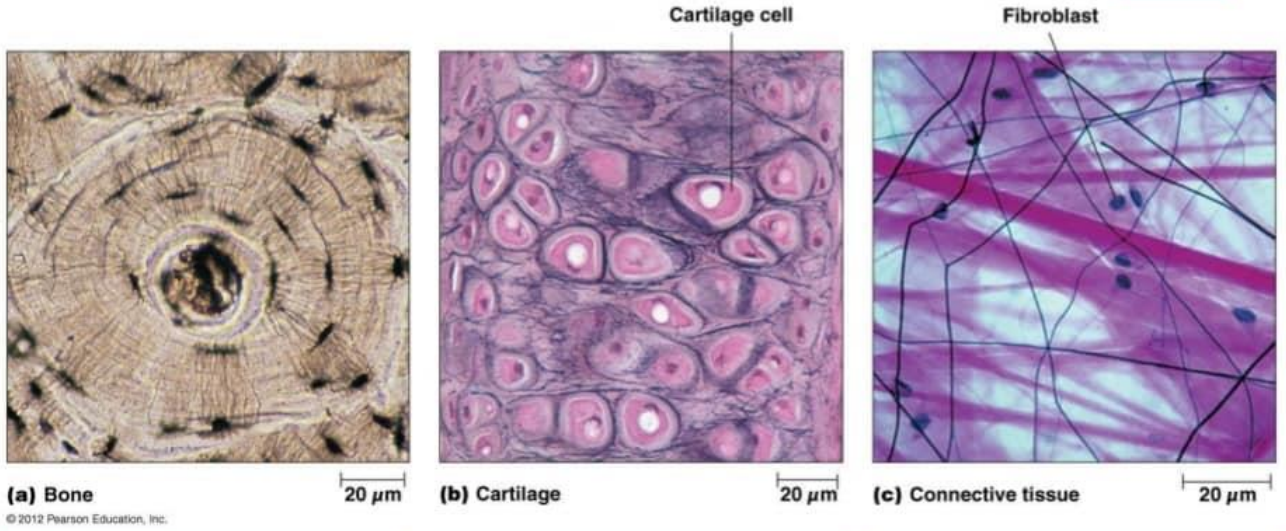
Types of matrix structural proteins:

1- Tough (fibrous proteins) embedded in a gel-like polysaccharide ground substance.

2- Adhesion proteins: **link** components of the matrix both to *each other* and to *attached cells*.

- Note: differences in the amount and type of components leads to different types and functions of ECM.

Different ECM composition



In bone, the extracellular matrix is hardened by deposition of calcium phosphate crystals.	Cartilage contains a high concentration of polysaccharides that form a firm compression-resistant gel.	Tendons contain a high proportion of fibrous proteins.

- **Notes for better understanding:**

For picture a: the **darker** places are cells, while other **lighter** ones are ECM.

Question: Why are bones hard and rigid?
Because the ECM contains a lot of ions especially calcium and phosphate.

For picture b: polysaccharides give cartilage a flexible structure because water molecules interact with polysaccharides by ***hydrogen bonds*** making a gel-like structure.

Clinical case

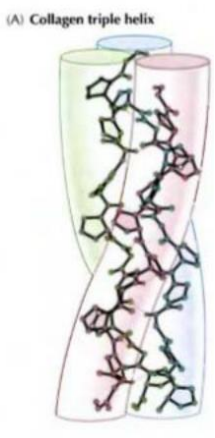
- Why do children have less chance of getting their bones fractured *e.g. when they fall*?

Because their bones haven't finished ossification, so they have a larger amount of cartilages in their bodies which act as shock-absorbers.

For picture c: Tendons link muscles to bones. They are composed of protein fibers that provide enough support and flexibility to allow muscles to do their functions. These fibers are arranged in networks.

Collagen

- It the major structural proteins in ECM.
- It is the most abundant protein in mammals. (*25%* if the total protein mass)
- It is a structural protein, so it's mechanically strong.
- Found in fibrous tissues.
- Structure:
  Long, stiff, triple-stranded helical structure made of 3 **α** (alpha) chains.
- A basic unit of *mature* collagen is called **tropocollagen**
- Rich in **glycine** (33%), **proline** (13%), and **hydroxyproline** (9%).
  (Not all of its structure is glycine, proline and hydroxyproline, but most of it).



- Note that hydroxyproline is a modified proline that undergoes hydroxylation (*occurs post-translational, after the protein is synthesized*). The hydroxyl groups added to hydroxyproline are responsible for a large number of hydrogen bonding between the chains of collagen, thus providing strength and stability.

- Proline and glycine are small unbranched molecules thus they provide more compaction and support for the structure, too.

- Sequence Is (Gly-Pro-Hydroxypro)

- It also contains **lysine** which can be modified by adding hydroxyl group resulting in hydroxylysine, but here the (OH) in hydroxylysine is responsible for attachment with polysaccharide **(glycosylation)**.
- The cross linking between different chains of collagen occurs via lysine and hydroxylysine.

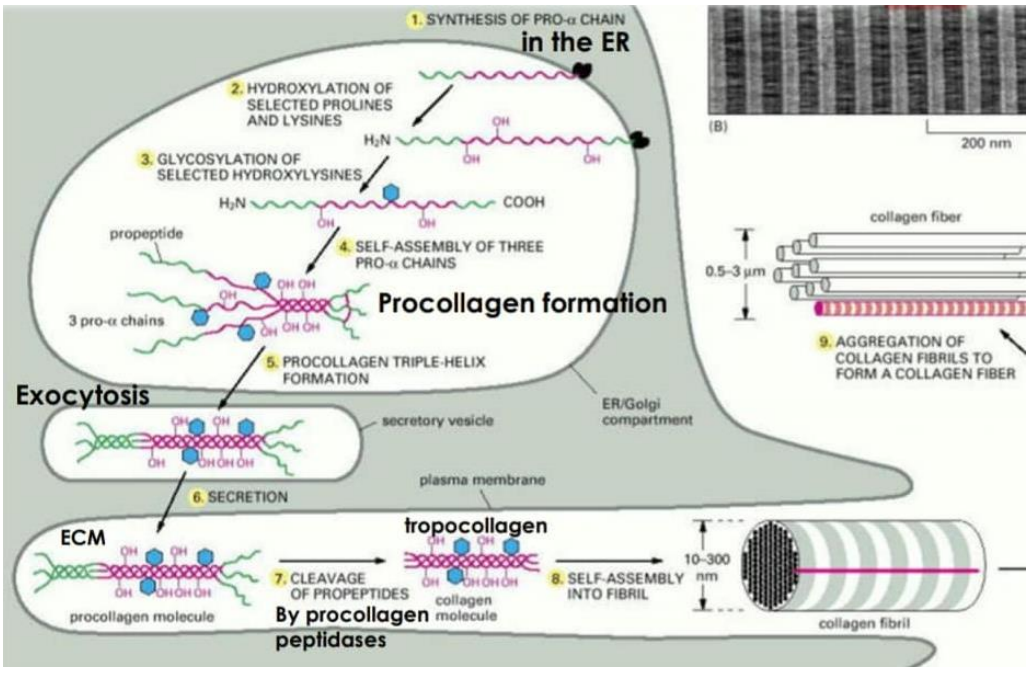
Types of collagen

- There are *30* collagen genes that form more than 20 types of collagen that resist tissue stretching.

- Types of collagens:
  1- **Fibril-forming (fibrillary) collagens** *such as* **collagen I,** which is the most common type.
  2- **Fibril-associated collagens:** links collagen fibrils (**Collagen I**) to each other and to ECM components. *Example:* collagen **IX** and collagen **XII**.
  3- **Network-forming collagens:** They are flexible because they are interrupted by non-helical short domains *such as* type **IV** which is the main constituent of basal lamina.
  4- **Anchoring fibrils:** associate and connect network-forming collagens and fibril forming collagens (*1 and 3*).
  5- **Transmembrane collagens:** attaches the cell with ECM (participate in cell matrix interactions).

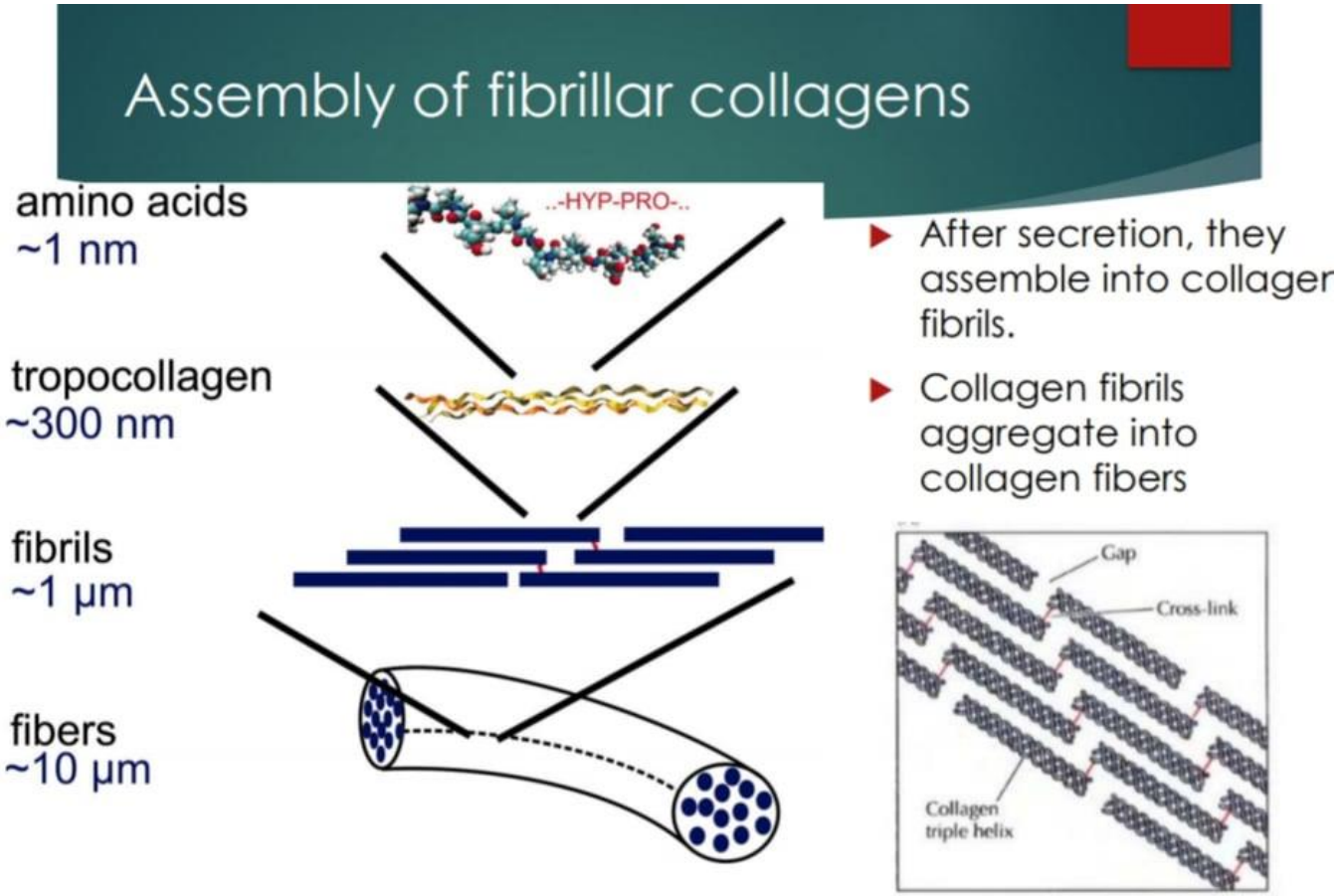
Synthesis of collagen

- Firstly, the individual polypeptide chains are synthesized into the **ER** as a pro-α chain (*a protein is composed of polypeptide chains*) *as in* ***step 1*****.**
- Also in the ER, selected prolines and lysines are hydroxylated and some of the hydroxylysines are glycosylated. *As in steps* ***2 and 3*****.**



- Steps 1,2 and 3 produce **pro-α chain**.
- Three of pro-α chains are combined to form a triple helix called **procollagen**. *Step* ***4 and 5***.
  - *Note*: **pro** means *pre* or *before* so procollagen is premature collagen which needs more modification.
- The procollagen is then secreted outside the cell by *exocytosis* via secretory vesicles to undergo more modifications. These modifications include cleavage of the **pro-peptides** (*amino acids sequence that is supposed to be removed*) by enzymes called ***procollagen peptidases*** (when we find the word **peptidase** in any enzyme we have

to know that its job is **cleaving and breaking a peptide bond**). >> *After* the cleavage of pro-peptides, the procollagen becomes **tropocollagen** which is the basic unit of collagen.



- After producing **tropocollagen**, many of these molecules assemble into **fibrils >>** Fibrils are then assembled into **fibers.**

- Gaps between **tropocollagen** units are not **aligned** together in order to prevent the formation of weak points within fibrils. (This gives the protein a mechanically strong structure).

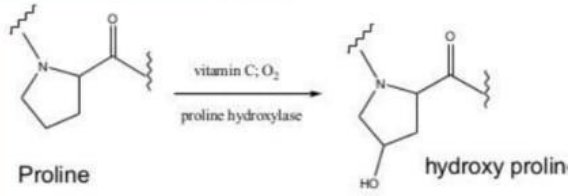
  - Question: why aren't collagen fibers formed inside the cell?
    Answer: because of size limitations, only tropocollagens are formed inside cells, while fibers are formed outside since they are big in size.

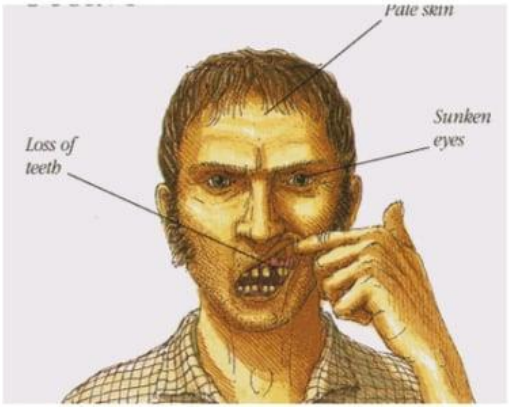
Clinical cases

1)

Collagen-related diseases
Scurvy

- Deficiency of vitamin C results in **insufficient formation of hydroxyproline** and, hence, poor synthesis of collagen, formation of unstable triple helices.
- Non-hydroxylated procollagen chains are then degraded within the cell.
- Symptoms: skin and gum lesions and weak blood vessels





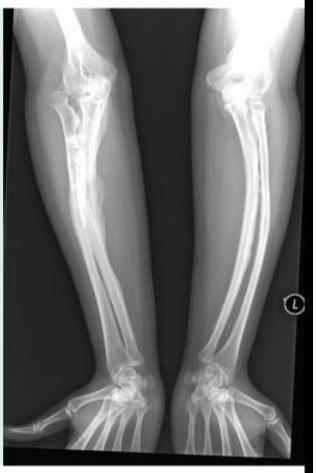
- Important notes:
  - Vitamin C is an important factor in the reaction of proline hydroxylation in order for it to become hydroxyproline. So, if there is deficiency in vitamin C, there will be lack in the amount of hydroxyproline which *contains hydroxyl group that are important for hydrogen bonding between chains of collagen*. We conclude that the structure of collagen will be weaker if there is lack in vitamin C.

  - Collagen is the most abundant protein in our body (it can be found in the skin) so abnormalities in its structure leads to ruptures in the skin or somewhere else.)

2)

Collagen-related diseases
Osteogenesis imperfect (OI)
(Brittle-bone disease)

- "Osteogenesis imperfecta" = imperfect bone formation
- A genetic disorder that cause fragile, soft, brittle, and easily broken bones due to mutations in COL1A1 and COL1A2 genes that interfere with the assembly of type I collagen.
- Four types of OI designated as type I through type IV
  - Type I: the mildest form of the condition
  - Type II: the most severe form that results in death in utero or shortly after birth
  - Milder forms generate a severe crippling disease



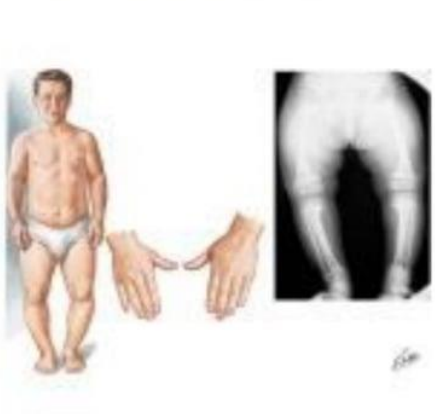
- ✓ **Autosomal dominant pattern of inheritance**
  - ✓ **One copy of the altered gene is sufficient to cause the condition**

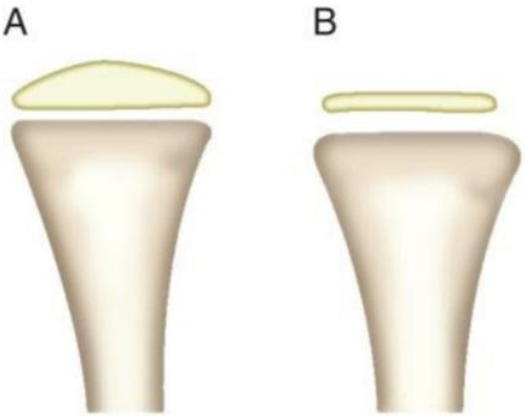
- Notes:
  - Osteo means bone and genesis means generation (formation).
  - Collagen type **A1** and **A2** are specifically important for the structure of bone.
  - This disease obeys autosomal dominant pattern which means that if the child carries one copy of the altered gene, he's going to be affected and show symptoms of the disease.

3)

Collagen-related diseases
Chondrodysplasias

- Mutations affecting type II collagen cause chondrodysplasias, characterized by abnormal cartilage, which leads to bone and joint deformities.





Some notes:

- Chondro means cartilage.
- This disease is caused by a mutation and is a genetic disease.
- The ends of bones of children contain cartilages and as the child grows, ossification of cartilages occurs so that they turn into solid bones which results in growth of the human being. Those who suffer from this disease experience abnormal growth.
- Notice that the bone endings in picture A (which is a bone of normal person) contains more cartilage than bone B >>> this leads to ***friction*** between adjoining bones (*that form joints*) and thus causes pain in joints.

4)

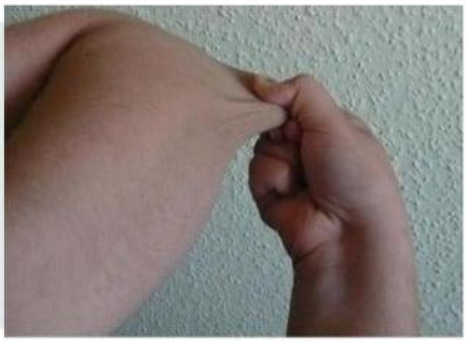
Collagen-related diseases
Ehlers-Danlos syndrome

- A heterogeneous group of disorders that affect the skin, bones, blood vessels, and other organs.
- The signs and symptoms vary from mild to life-threatening.
- All result from defects in collagen synthesis and/or processing.
  - Mutations in type I, III, or V collagen or in the synthesis of collagen processing enzymes like procollagen N-peptidase, or lysyl hydroxylase

Major manifestations:

Skin fragility and hyperextensibility

Joint hypermobility.



Collagen-related diseases
Type III EDS

- The most clinically important mutations are found in the gene of type III collagen.
- Since **type III collagen** is a major component of arteries, mutations affecting type III collagen result in fragile blood vessels.

- **Some notes:**

  - The doctor said: syndrome means that there are different symptoms in different places. So, more than one tissue is altered (as we can see there is problems in skin and joints).
  - This is an inherited disease
  - As mentioned previously, this disease can be caused by mutations that affect more then one type of collagen (types 1,3 **or** 5)
  - So, there are different symptoms and different types of the syndrome.

Now we finished what we think is important to know about in collagen

And we discussed some clinical cases

Let's move to another component of the connective tissue.

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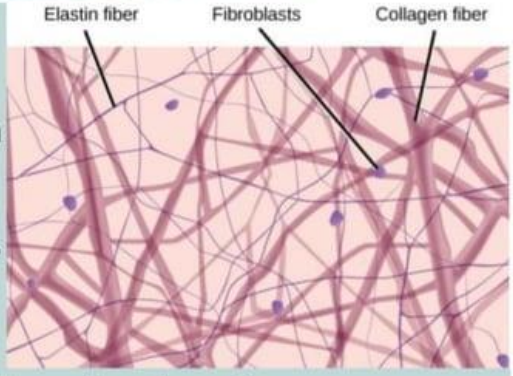
the elastic fibers

Elastic fibers structure

- Abundant in organs to allow them to stretch then return to the original shape, e.g. lungs
- The main component of elastic fibers is elastin
- Rich in proline and glycine.
- Contains hydroxyproline, but no hydroxylysine
- Not glycosylated



- 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. Alanine- and lysine-rich a-helical segments, which form cross-links between adjacent molecules

Here are some notes about the picture above:

- Elastic fibers are bundles of proteins called elastin, the word elastic is derived from elasticity which refers to flexibility. So elastic fiber is flexible.

- Elastic fibers contain hydroxyproline too but not in huge amounts (less than in collagen fibers).

- Amounts of elastic and collagen fibers differ between different tissues. E.g. in lungs is a big amount of elastic fibers.

- This is a brief introduction of elastic fibers and it will be discussed in the next sheet.
- You can contact us for any questions or in any case of misunderstanding.
- Dr Diala's lecture: https://youtu.be/ZZ6MrqrffvU

- Get to know that

where a business man works hard for more wealth

and the politician works hard for more authority

you study hard for someone else and to be sometime a hope for him… work hard for this reason…not for money.

You are a **doctor** 

كم يرفع العلم أشخاصا إلى رتب ويخفض الجهل أشرافا بلا أدب

الإمام الشافعي