بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Cytology & Molecular Biology | Lecture 10

The extracellular Matrix

Written by : Leen Al-Zoubi
Bushra Masalha

Reviewed by : Reem Alfaqeh

Lecture 7: the extracellular matrix and cell-cell interaction

Prof. Mamoun Ahram

School of Medicine

Second year, Second semester, 2025-2026

The extracellular matrix

The network of fibrous proteins that exist outside the cells, this network contains different types of cells as well such as fibroblasts, endothelial cells, immune inflammatory cells

What is it?

It sorta surrounds the epithelial cells and holds them in place, and this interaction stabilizes the whole tissue. You can think of it as a belt surrounding the cells and preventing them from proliferating and moving

- The extracellular matrix fills the spaces between cells, binds cells, and forms tissues.
- Types:
  - Basal laminae: thin, sheet-like, structure upon which layers of epithelial cells rest

Underneath the epithelial cells

    - It supports the sheets of epithelial cells
    - It surrounds muscle cells, adipose cells, and peripheral nerves.

Each of these cells or fibers is wrapped by its own basal laminae

  - Connective tissues: Loose network of proteins and carbohydrates underneath the epithelial cell layers where fibroblasts are distributed.

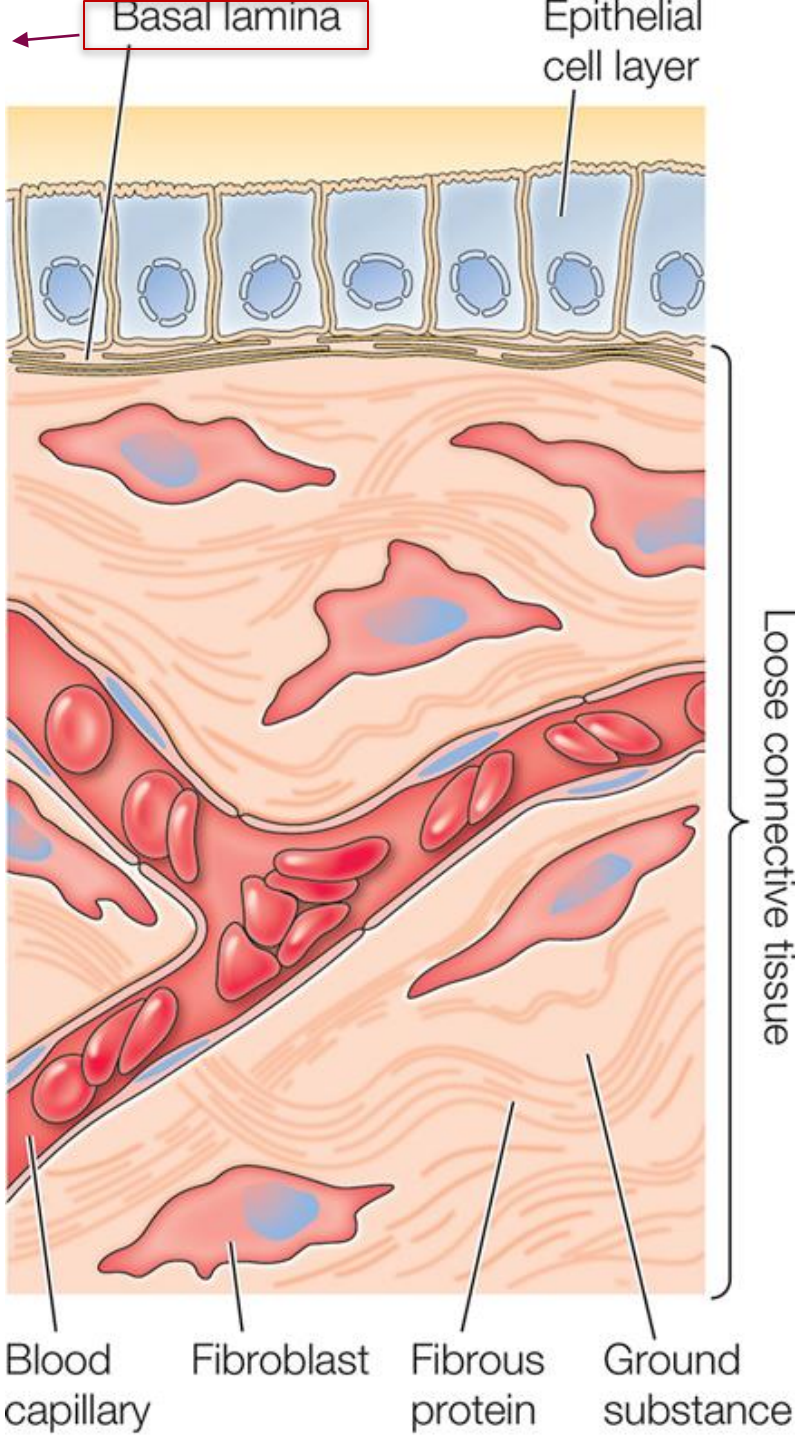
fibrous

And different types of cells

Different types of connective tissues such as:

    - Others: bone, tendon, and cartilage.

The basal laminae contain matrix components that differ from those in the connective tissues.



Benign Tumors? How does it happen?

Loss of control in one of the epithelial cells --> uncontrolled proliferation and division --> formation of tumor(mass of cells) in a certain place or region --> this is called "in situ carcinoma" , "in situ" means "in place" , this is also known as benign (الورم الحميد)
These tumor cells degrade the basal laminae leading to an interaction between the tumor (abnormal) cells and the connective tissue, instead of the normal interaction between the epithelial cells and the basal laminae proteins, this abnormal interaction has its effect on the cells as well. What is this effect? different signaling! integrins which interact with matrix proteins send different signals to the cells, what is the effect of the abnormal signaling on the cells? 1. they become mesenchymal 2.elongated 3.fibroblast-like 4.motile(these cells reach the blood vessels --> metastasize(meaning they spread from their original site to other parts of the body))

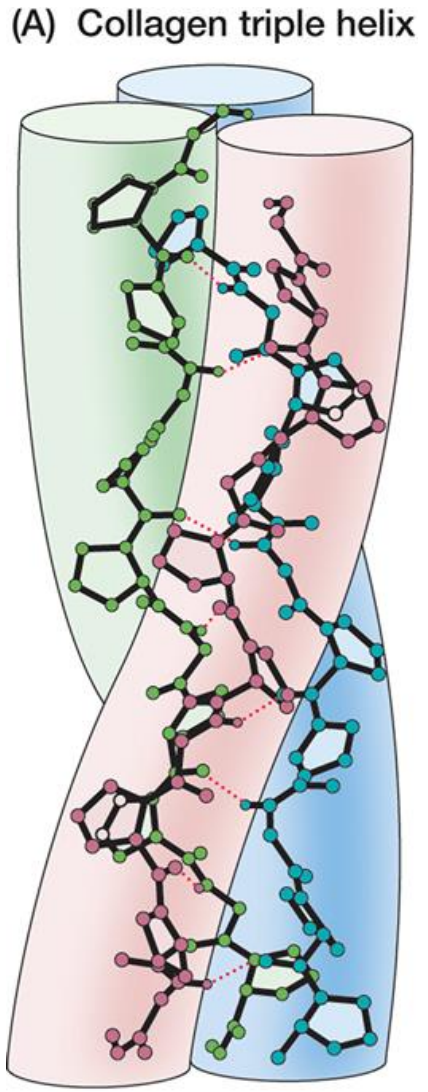
Why are we mentioning this? To highlight the importance of basal laminae in controlling cells

Components of ECM

- Matrix proteins
  - Examples: Collagen, elastin Hydrophobic in general
    - Tough fibrous proteins embedded in a gel-like polysaccharide ground substance.
- Adhesion proteins
  - Examples: Fibronectin, laminin
    - These proteins link components of the matrix to one another and to the cells.
- Glycosaminoglycans.

The collagens

- The most abundant proteins in mammals (25% of the total protein mass).
- Long, stiff, triple-stranded helical structure made of three α chains
- A basic unit of mature collagen is called tropocollagen.
- Rich in glycine (33%), proline (13%), and hydroxyproline (9%)
- It contains hydroxylysine (attachment of polysaccharides)
- Crosslinking of chains via lysine and aldolysine via the action of lysyl oxidase



Collagen composition

-Purpose of glycine: it proximate the chains to one another making them close
-Purpose of proline: provides toughness and rigidity to the structure plus the helical structure depends on it
-Purpose of hydroxyproline: similar to proline it provides rigidity and the helical structure + the hydroxyl group forms hydrogen bonds strengthening the tropocollagen
-Purpose of Hydroxylysine: attachment point for polysaccharides / sugars (all collagens are glycoproteins!)

In addition, lysine undergoes oxidation outside cells --> allowing for covalent linkage between :

1. Lysine-lysine
2. Aldolysine-aldolysine
3. Aldolysine-hydroxylysine

Again, strengthening the molecule

Types of collagens

- More than 40 types of collagen that resist tissue stretching.
- Types:
  - Fibrillar collagens — Elongated collagen fibers
  - Fibril-associated collagens — Collagens that link the fibrillar collagens together
  - Network-forming collagens — Collagens that give us a three-dimensional structure outside the cell
  - Anchoring fibrils — Collagens that form an interaction between matrix and basal laminae
  - Transmembrane collagens

Types of fibrillar collagens

Most abundant type

- Type I: most connective tissues (long, aligned in parallel to each other in a regular staggered array to form fibrils), and rigid (fit to be in bone structure)
- Type II: cartilage and vitreous humor
  - Smaller in diameter than type I and oriented randomly in the viscous proteoglycan matrix
  - Rigid macromolecules, but compressible (to resist large deformations in shape and absorb shocks)

Found in cartilage as a sort of protection for the bone structure

Read only

- *Type III: extensible tissues (skin and lung)*
- *Type XI: cartilage*
- *Type XXIV: bone and cornea*
- *Type XXVII: eye, ear, and lung*

Why do we have different types of collagen ?
Because each collagen is made from a unique combination of alpha chains giving it a distinct structure and function (ex: collagen type two has three identical alpha chains)

Synthesis of collagen type I

Synthesis of preprocollagen

Removal of pre-region during synthesis

Folding

Hydroxylation and glycosylation

Each chain is called protocollagen

Formation of a triple helical molecule

Vesicular exocytosis of procollagen

Now, it is called tropocollagen

Terminal propeptides are cleaved

Tropocollagen is now hydrophobic

Lysines are oxidized by lysyl oxidase

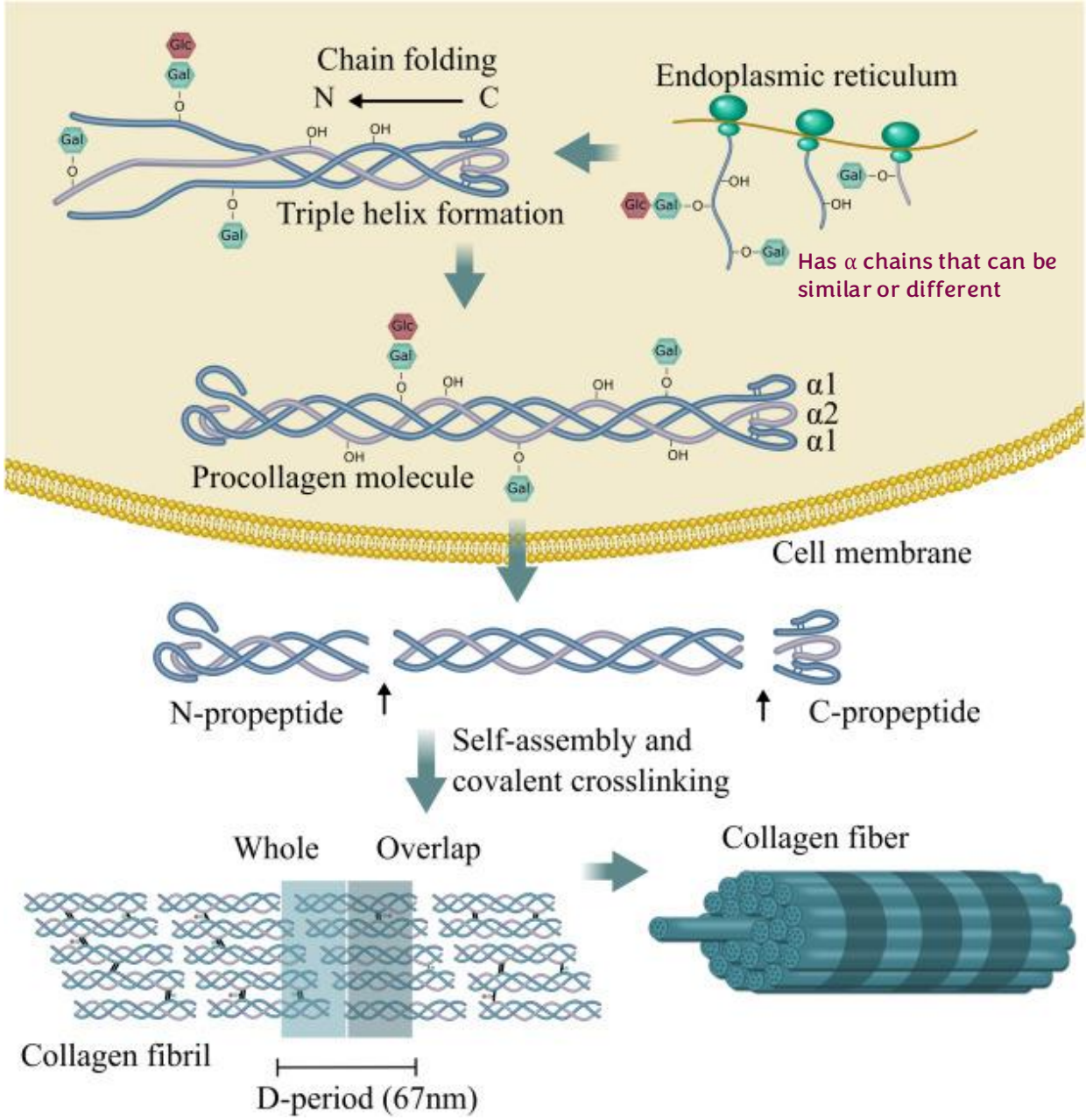
Copper is needed

Deficiency of Copper = Deficiency in the formation of collagen matrix

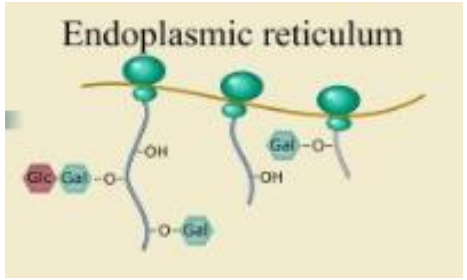
Crosslinking of lysines and hydroxylysines

Due to oxidation

Fibril then fiber formation

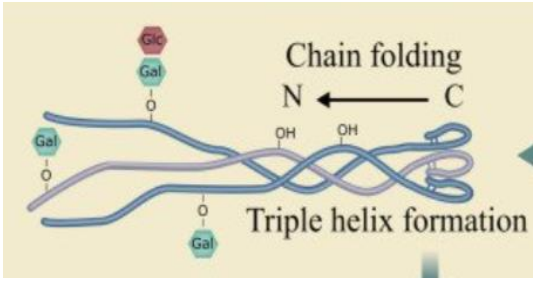


Synthesis of collagen type 1

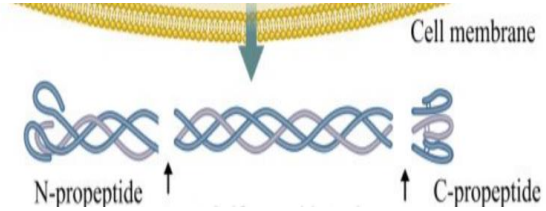


1)Formation of alpha chains on the surface of ER (preprocollagen --> procollagen) procollagen is still immature/inactive it needs further processing by cleaving the "pro region",, the term "pro" applies on both enzymes and proteins
2)Folding / hydroxylation/ glycosylation for each chain separately, each chain is called protocollagen

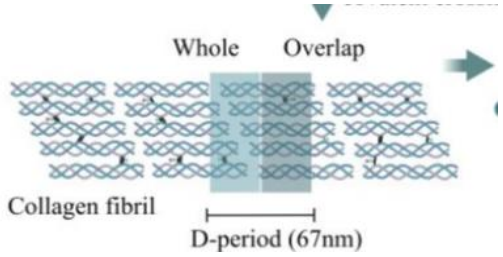
What do we call proenzymes ?
Zymogens (inactive form of an enzyme) ex: pepsinogen, trypsinogen



3)Formation of a triple helical molecule
4) this triple helical collagen molecule is transferred to Golgi apparatus and from there it will be loaded in a secretory vesicle(unregulated) ,, we did say that there is two types of secretion
a) regulated secretion ex secretion of neurotransmitters which is regulated by calcium influx
b) unregulated secretion ex secretion of procollagen (continuous from Golgi--> membrane--> outside)



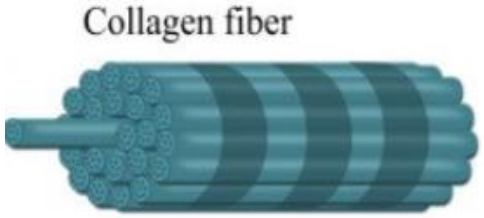
5) after secretion, the molecule is called tropocollagen (with the pro regions) ,, after secretion cleavage will occur at both N terminus and C terminus because they contain the pro regions (non-helical) by an enzyme called propeptidase , the pro regions make the protein slightly hydrophilic, without them the protein is hydrophobic \ insoluble



6) formation of fibrils

Fibrous proteins are mainly hydrophobic thus they clump together, that's why after removing the proregions, hydrophobic protocollagen molecules will aggregate together and form covalent linkages

What will happen if the proregions were cleaved inside the cells?
Clustering and aggregation of collagen inside the cell (hydrophobic molecules cluster together)--> cell death because collagen fibrils are huge in size



7) formation of fibers

Synthesis of collagen

1)They make the protein soluble

Function: 2)

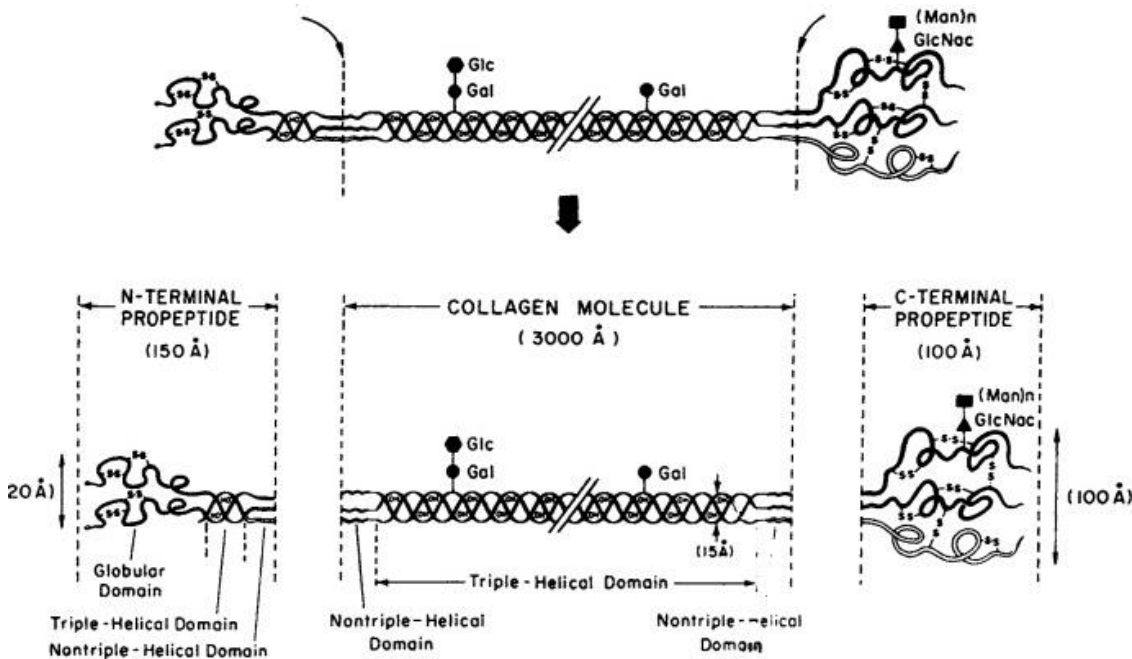
- Procollagen contains the N-terminal and C-terminal propeptides that inhibit <u>intracellular</u> fibril formation preventing the catastrophic assembly of fibrils within the cell.
  - Lysyl oxidase, which catalyzes the formation of reactive aldehydes, is an extracellular enzyme (another protective measure).

Allows covalent/ crosslinking linkages between the modified lysine residues

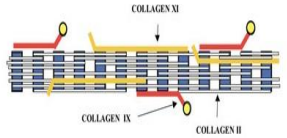
- Following exocytosis, the procollagen peptidases remove the propeptides.

- Procollagen I Intact N-Terminal (PINP) is considered the most sensitive marker of bone formation, and it is useful for monitoring bone resorption therapies.

-Normal formation of bone--> high levels of propeptides in the blood
-Osteoporosis--> a problem in forming collagen and bones--> low levels of propeptides in the blood system --> patients can be diagnosed by monitoring the levels of propeptides using PINP

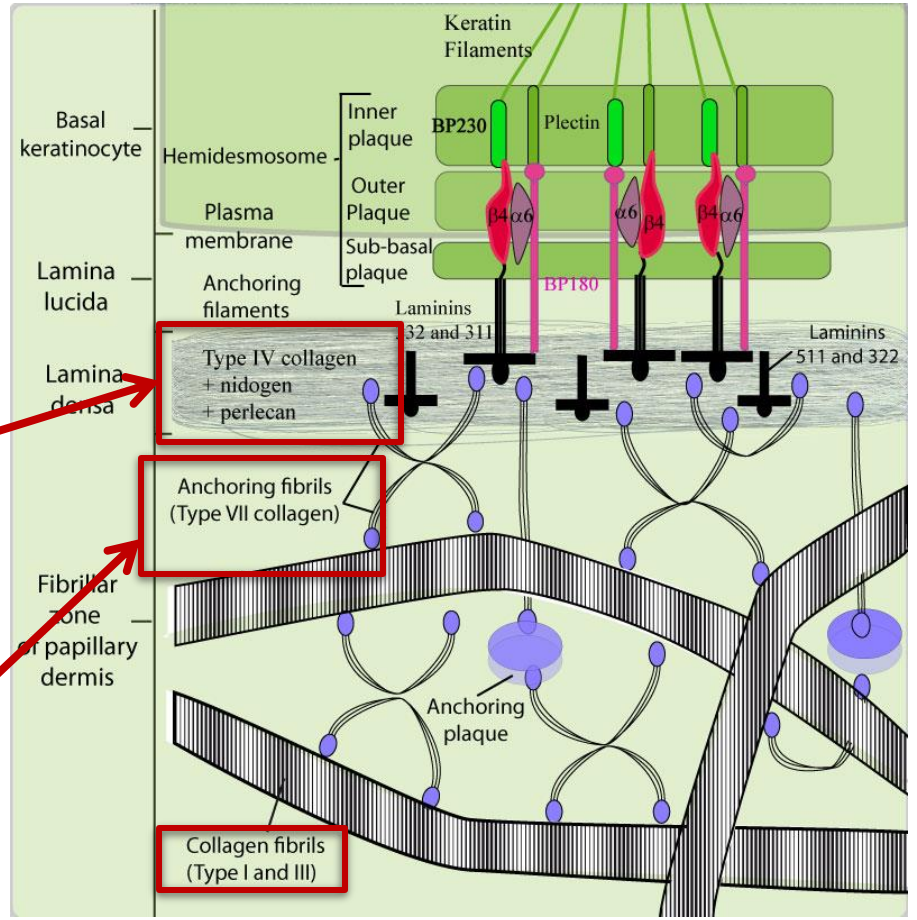


Others



- They have high ratios of glycine, proline, and hydroxyproline, but their helical region is shorter and they contain non-helical domains

- **We have different type of collagen each one has own function and structure**
- Fibril-associated collagens **(in yellow and red)**
  - The Gly-X-Y repeats interrupted by short nonhelical sequences making it flexible.
  - Collagens type IX and XI link fibrils to one another and to other components in the ECM.
- Network-forming collagens
  - Types IV: constituent of the basal laminae.
- Anchoring fibrils (type VII): link basal laminae to underlying connective tissues (network-forming collagens to fibrillar collagens).

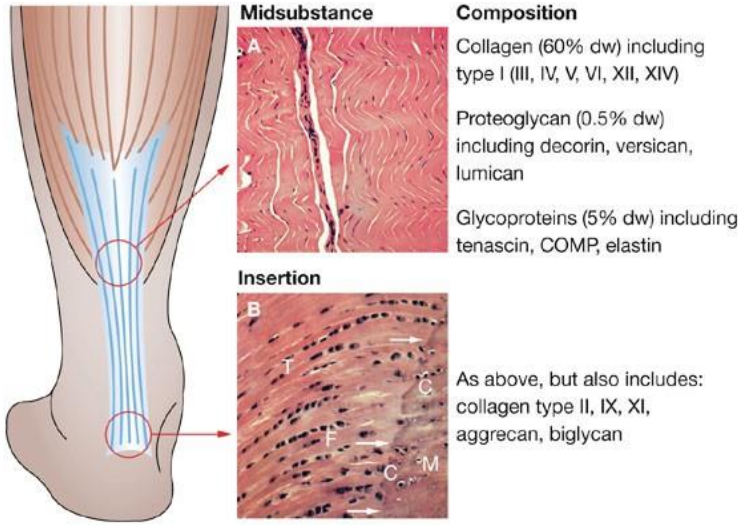


Collagen-related diseases

If we have deficits in the synthesis process of collagen molecule will lead to different conditions <u>depend on where the mutation is happened</u>

****Doctor doesn't ask about the symptoms ,he focuses on the type of protein and the mutations .**

- Collagen is highly crosslinked in tissues where tensile strength is required such as in Achilles tendon.
- Function of lysyl oxidase**(it converts the lysine into allysine which make the cross linking between lysine residues and between three strand collagen they wrapped around each other and also between three(triple) strand and other three strand of collagen or fibrils)**
- IF lysyl oxidase is mutated and crosslinking is inhibited, the tensile strength of fibers is greatly reduced, collagenous tissues become fragile, and collagen structures tend to tear (skin, tendon, and blood vessels).

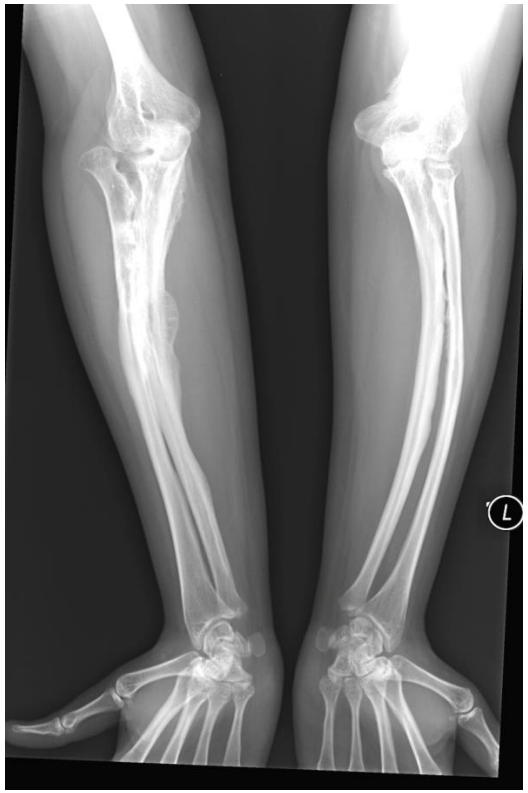


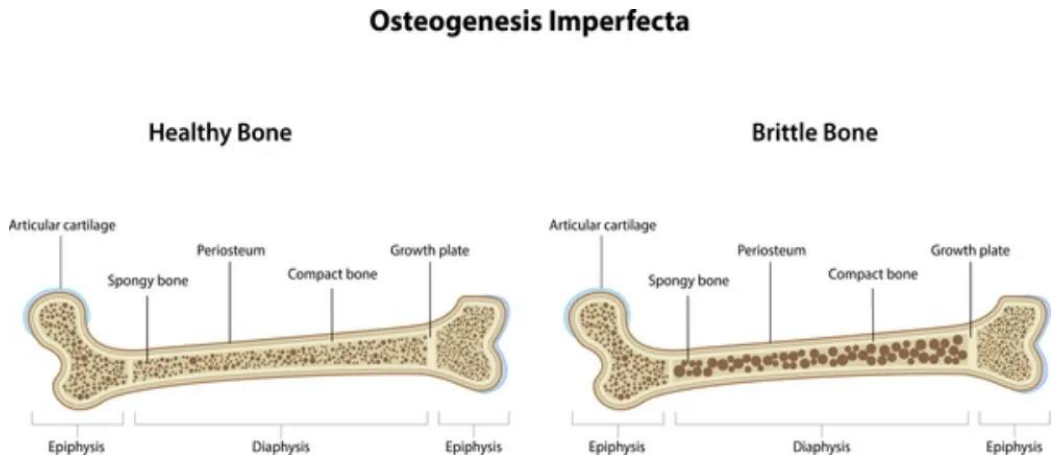
Osteogenesis imperfecta (Brittle-bone disease)

- “Osteogenesis imperfecta" = imperfect bone formation
- A genetic disorder of several forms that cause fragile, soft, brittle**(Torn)**, and easily broken bones.
- **Four types** of osteogenesis imperfecta 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.

Mutations of osteogenesis imperfecta

- Mutations in **two genes** the COL1A1 and COL1A2 genes (and others) interfere with the assembly of **type I collagen**.
- Defective collagen weakens connective tissues, particularly bone, resulting in the characteristic features of OI.

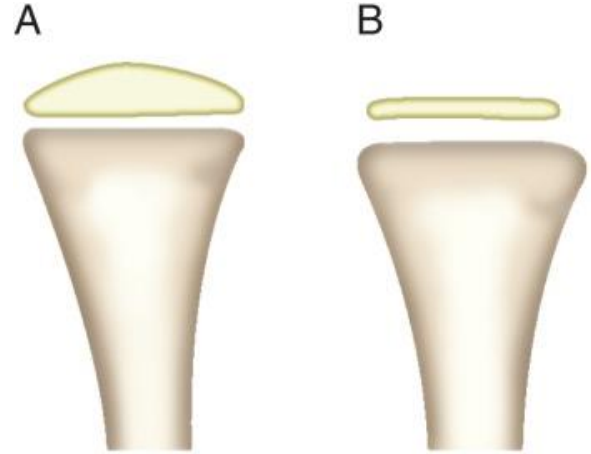




Chondrodysplasias

- Collagen type II is a spongy collagen that absorbs shock.
- It is formed by homotrimers of collagen, type II, alpha 1 chains.
- It makes up 50% of all protein in cartilage and 85–90% of the collagen of articular cartilage.
- Mutations affecting **collagen type II** cause chondrodysplasias, characterized by abnormal cartilage, which leads to bone and joint deformities.

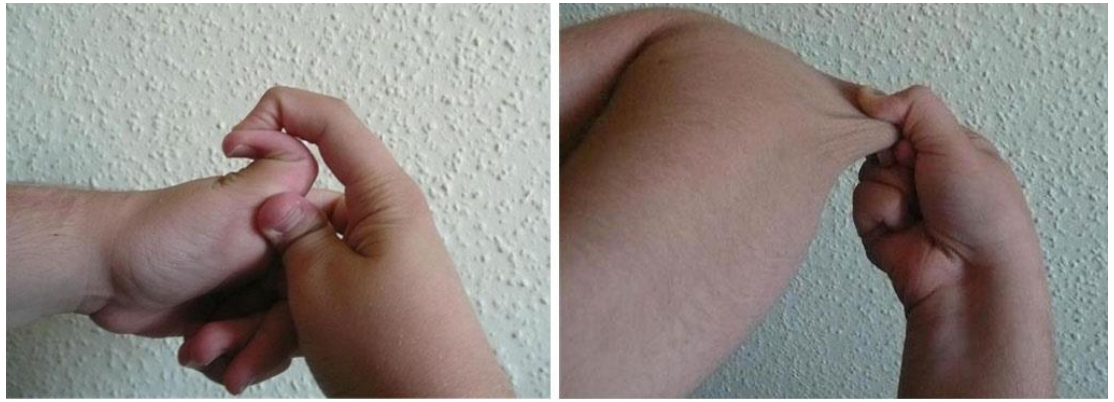
Ttype 2 collagen is abundant in cartilage, therefore affecting bones and joints



Ehlers-Danlos syndrome

- A heterogeneous group of disorders that affect the skin **(can be stretched out)** , bones**(be bent easily make hypermobility)**, 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 collagens type I, III, or V or in the collagen processing enzymes like procollagen N-peptidase or lysyl hydroxylase (**they are EC enzymes**

Major manifestations are skin fragility and hyperextensibility and joint hyper-mobility.



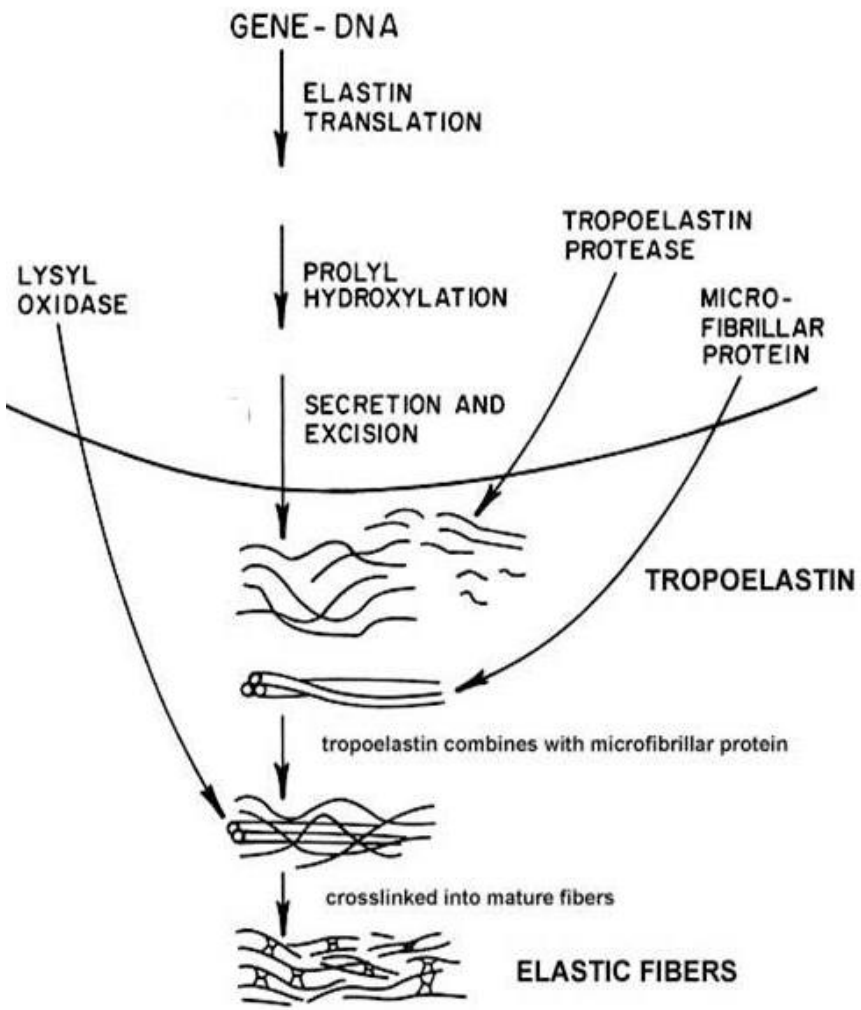
Type III EDS

- 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 it result in fragile blood vessels.

- Other symptoms include stretchy skin and hypermobile joints.
- **this things may give some advantages like in Taekwondo.**

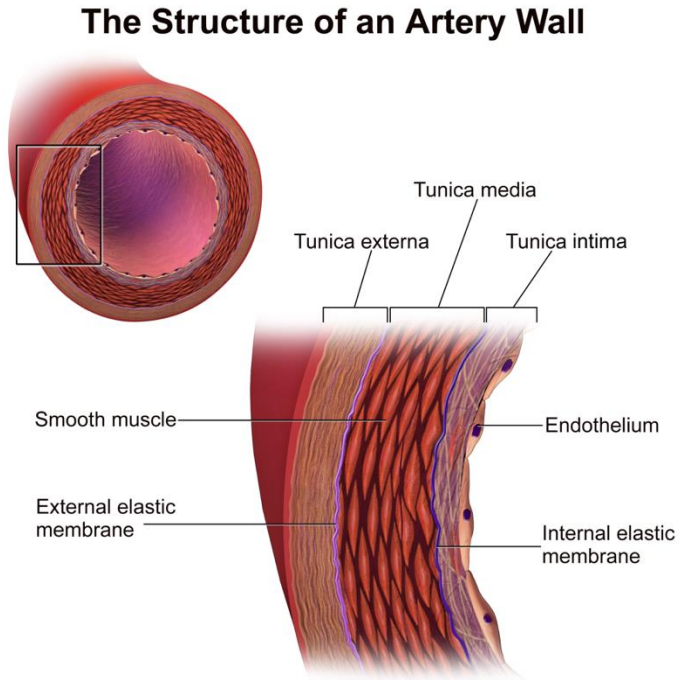
Elastin

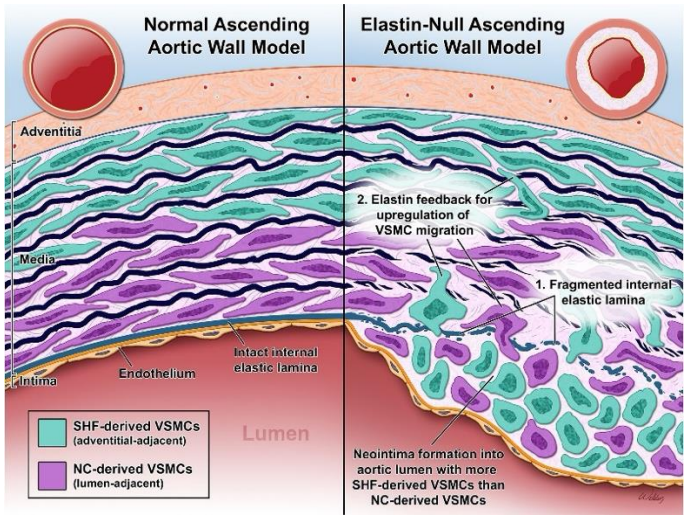
- The main component of elastic fibers is elastin **(give the flexibility for the tissue, arteries)**
- Highly hydrophobic
- Rich in proline and glycine.
- Contains some hydroxyproline, but no hydroxylysine
- Not glycosylated
- Secretion of tropoelastin
- Assembly into elastic fibers
- Crosslinking via lysines



Function of elastic fiber

- Elastin is the dominant extracellular matrix protein in arteries **(allow them to expand when blood clot)**
- The normal elasticity of an artery restrains **(prevent)** the proliferation of smooth muscle cells.
- Abnormal or deficiency of elastin results in excessive proliferation of smooth muscle cells **(thick layer)** in th arterial wall and narrowing of the aorta **which make a problem in blood pressure.**





Microfibrils and fibrillin

- The elastin core is covered with a sheath of microfibrils, which are composed of several glycoproteins, including the large glycoprotein fibrillin.
- Fibrillin binds to elastin and is essential for its integrity (**structure of elastin molecules), without fibrillin the elastin will be much flexible .**
- The main job of microfibrils is to make the connective tissue strong and rigid.
- Their secondary job is to help control growth and development.

- Fibrillin surrounds the elastin core and provides it with structural rigidity

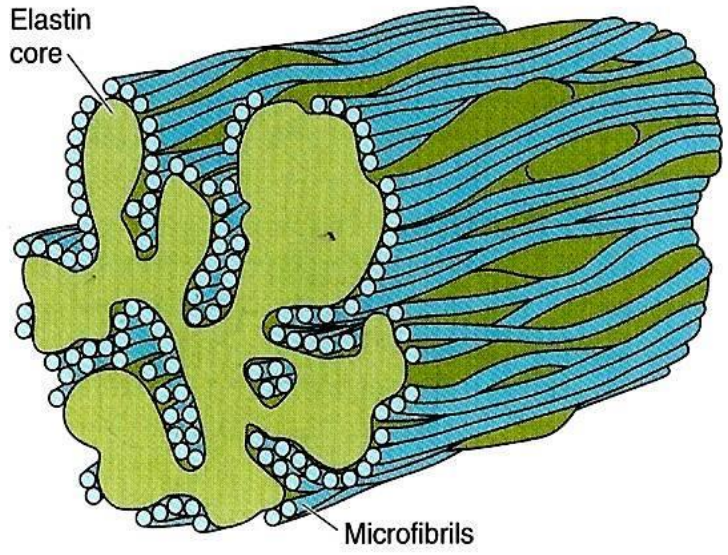


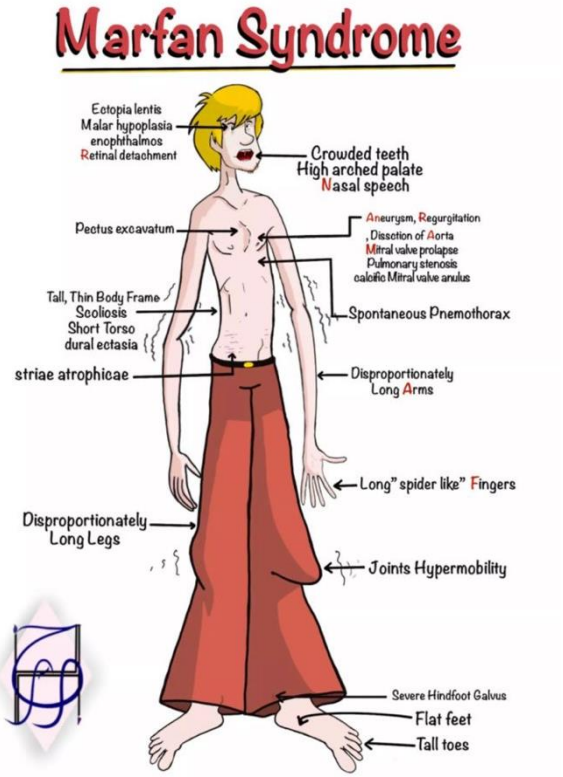
Figure 4–11 Schematic diagram of elastic fiber. Microfibrils surround the amorphous elastin.

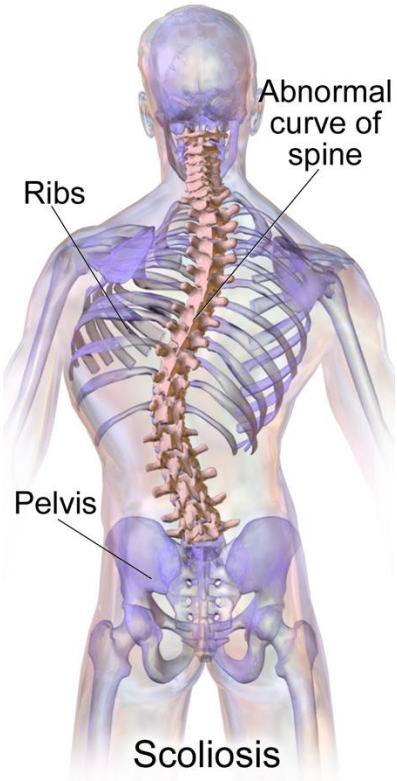
Marfan's syndrome

- Due to mutated fibrillin **(lead to loss of control for the cell growth)**
- Rupture of aorta **(the result of too much stretch of elastin)**

- لما يمدوا ايديهم بالعرض بتكون المسافة بين الاصابع اكثر من طولهم

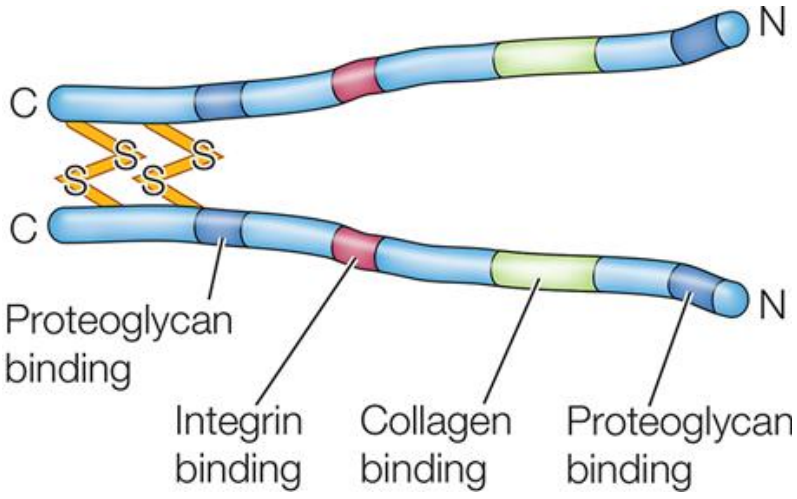
- Others: A tall, thin build; Long arms, legs, fingers, and toes and flexible joints; Scoliosis, or curvature of the spine (**looks normal , unless we use X-ray)**;
- A chest that sinks in or sticks out; Crowded teeth; Flat feet.

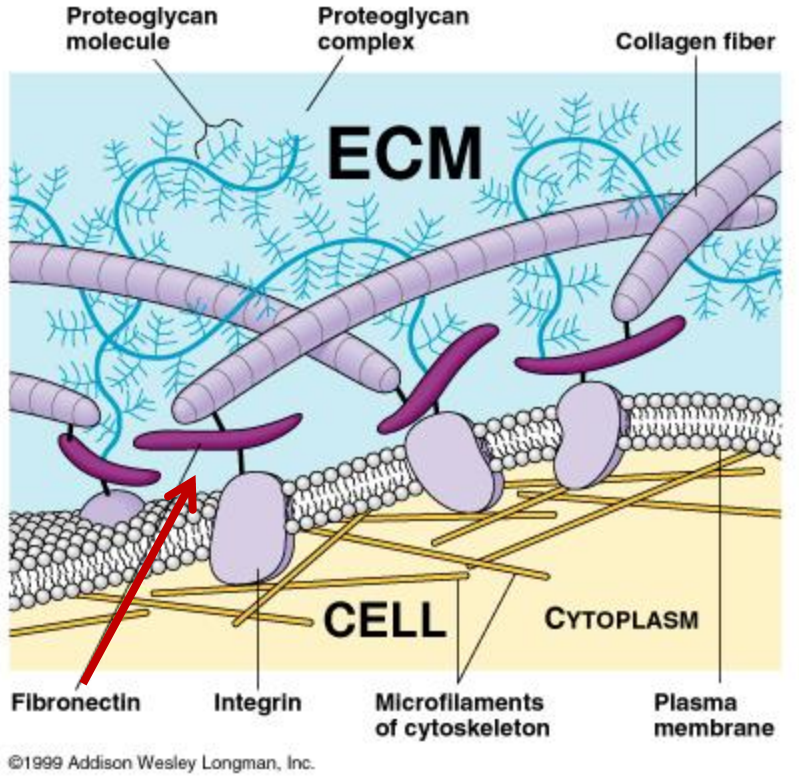




Matrix adhesion proteins

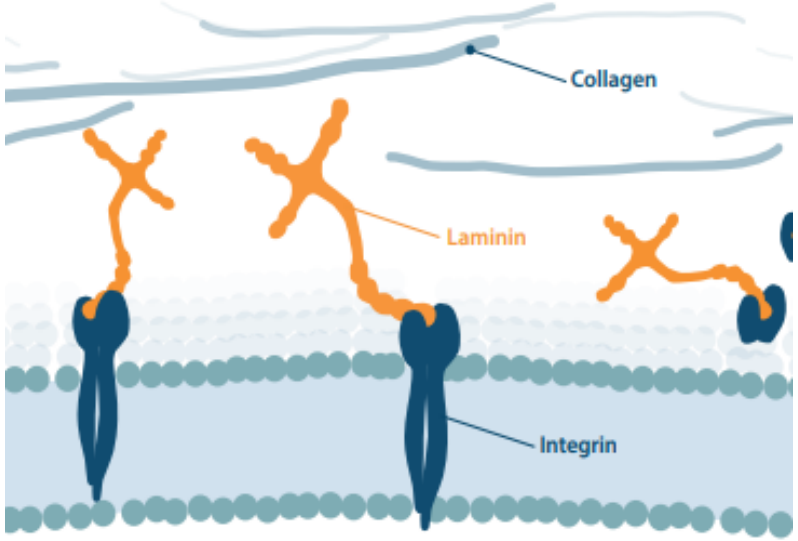
- They interact with collagen and proteoglycans and link matrix structural proteins **maintain the integrity** with one another and to the surfaces of cells.
- Fibronectin: **This protein that connect the collagen fibers to strengthen the tissue (ECM)** the principal adhesion protein of connective tissues.
  - A dimeric glycoprotein that is crosslinked into fibrils by disulfide bonds.
  - It binds to collagen and GAGs
  - It binds to cell surface proteins like integrins(
  - **(they membrane proteins as receptors present on the cell surface)**linking cells to the ECM

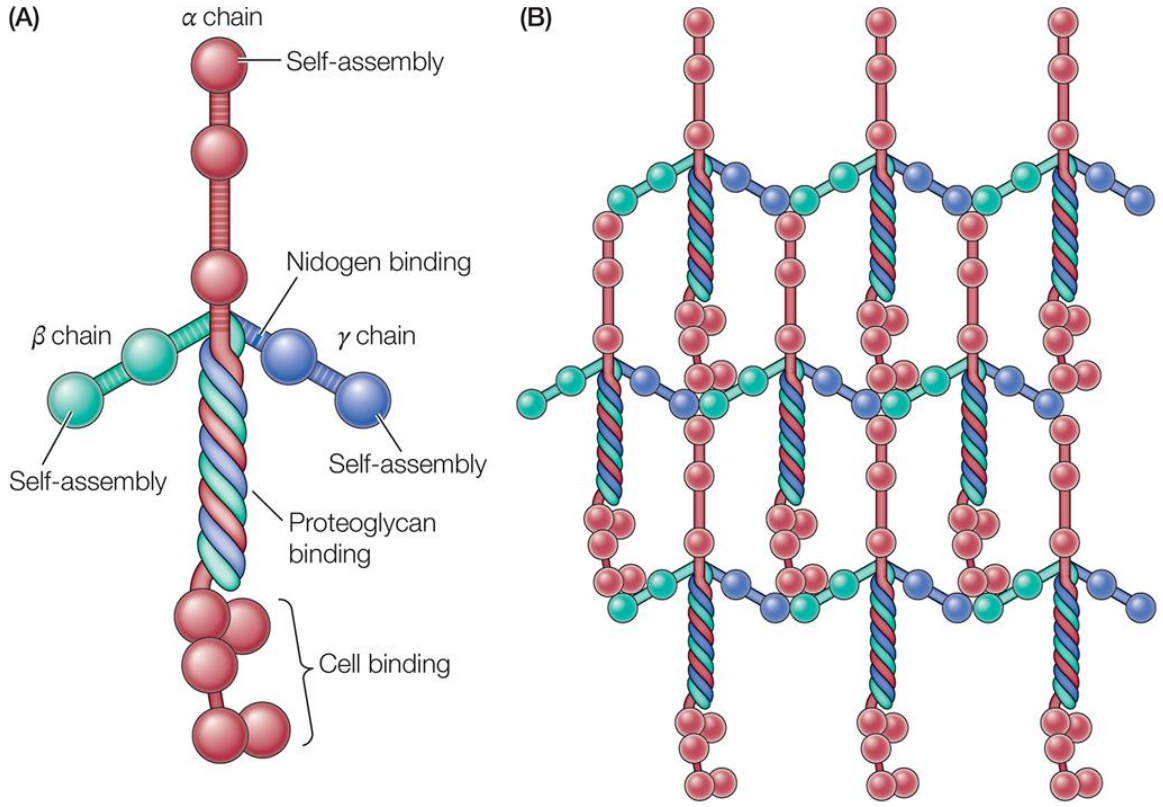




Laminin

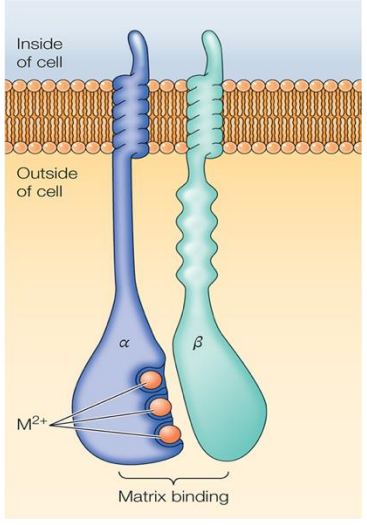
- It is found in the basal laminae.
- It forms T-shaped heterotrimers with binding sites for cell surface receptors such as integrins, type IV collagen, and GAGs.



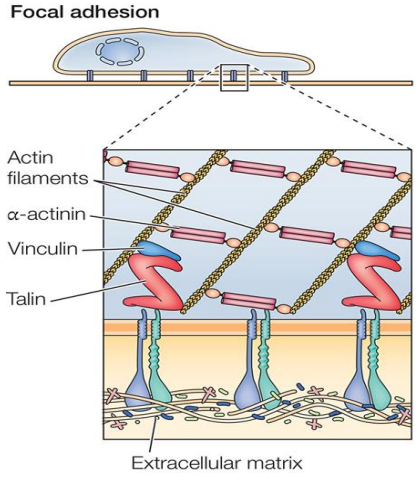


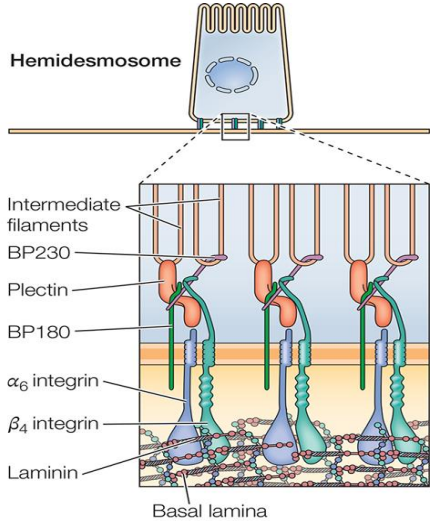
Cell-matrix interactions
Role of integrins

- integrins are a family of transmembrane heterodimers (α and β) that bind to short sequences of ECM proteins and attach cells to ECM.
- **Extra cellular domain interact with ECM proteins(fibronectin, laminine collagen), and the intracellular domain interact with filaments(cytoskeleton)**
- They also anchor the cytoskeleton at focal adhesions (cell-matrix interaction|) and hemidesmosomes (cell-basal laminae interaction).

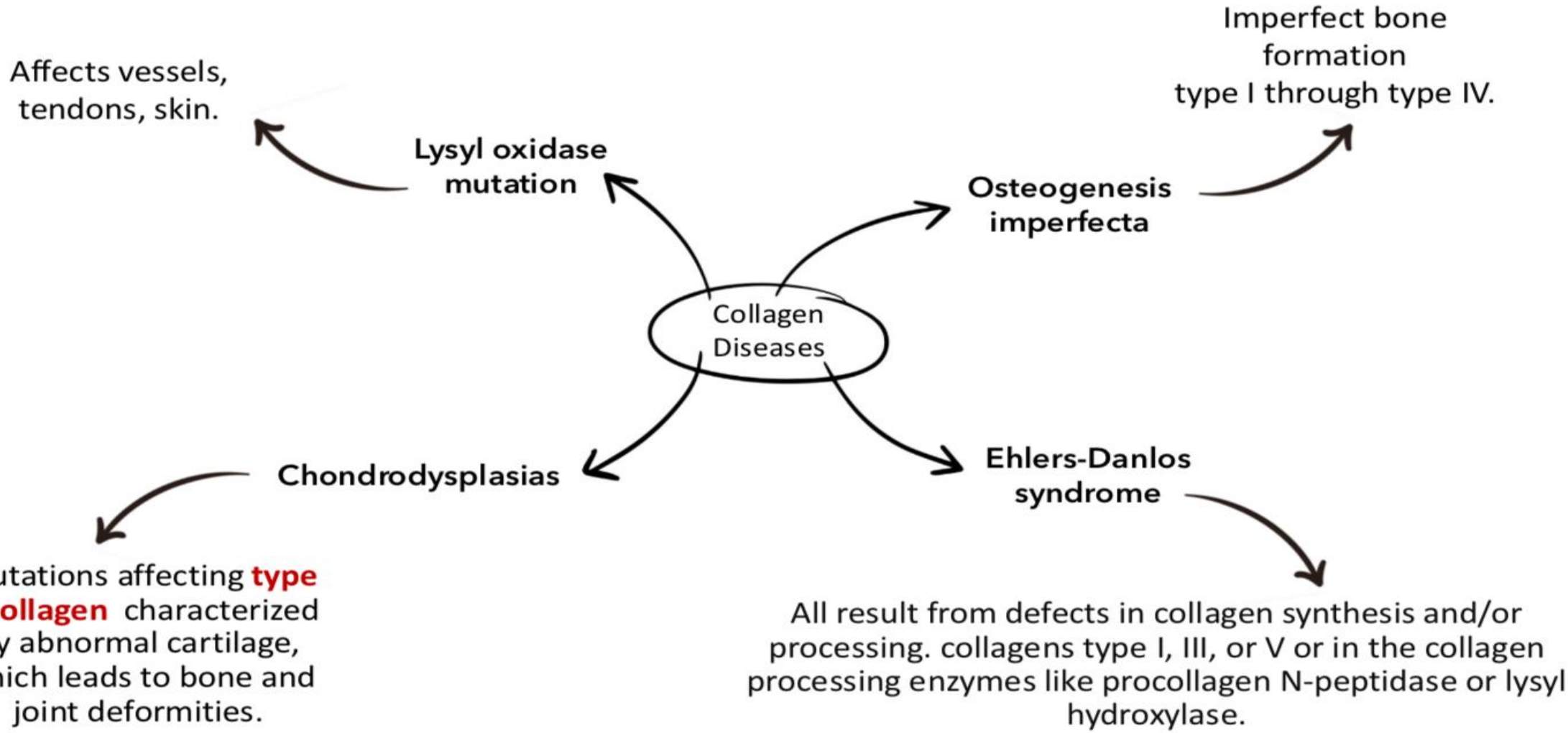


Integrins connect ECM proteins with actin binding proteins with actin filaments
Cell-Surface interaction
Cell motility.





Integrin connect with ECM proteins but inside the cell interaction with intermediate filament


Affects vessels, tendons, skin.
Lysyl oxidase mutation
Imperfect bone formation type I through type IV.
Osteogenesis imperfecta
Collagen Diseases
Chondrodysplasias
Mutations affecting type II collagen characterized by abnormal cartilage, which leads to bone and joint deformities.
Ehlers-Danlos syndrome
All result from defects in collagen synthesis and/or processing. collagens type I, III, or V or in the collagen processing enzymes like procollagen N-peptidase or lysyl hydroxylase.

رسالة من الفريق العلمي:

وَأَن لَّيْسَ لِلْإِنسَـٰنِ إِلَّا مَا سَعَىٰ

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			