بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

BioChemistry

وَلَقَدْ خَلَقْنَا الْإِنسَانَ وَنَعْلَمُ مَا تُوَسْوِسُ بِهِ نَفْسُهُ ۖ وَنَحْنُ أَقْرَبُ إِلَيْهِ مِنْ حَبْلِ الْوَرِيدِ

Final | Lecture 4

Fibrous Proteins

Written by : Ali Al-sharaeah
Yamen Aljarrah

Reviewed by : Abdullah Saffarini

Color coding used in the modified:

- *Black: the original slides*
- *Blue: the doctor's explanation/words*
- *Gray: additional information and explanation*
- *Red: important information*

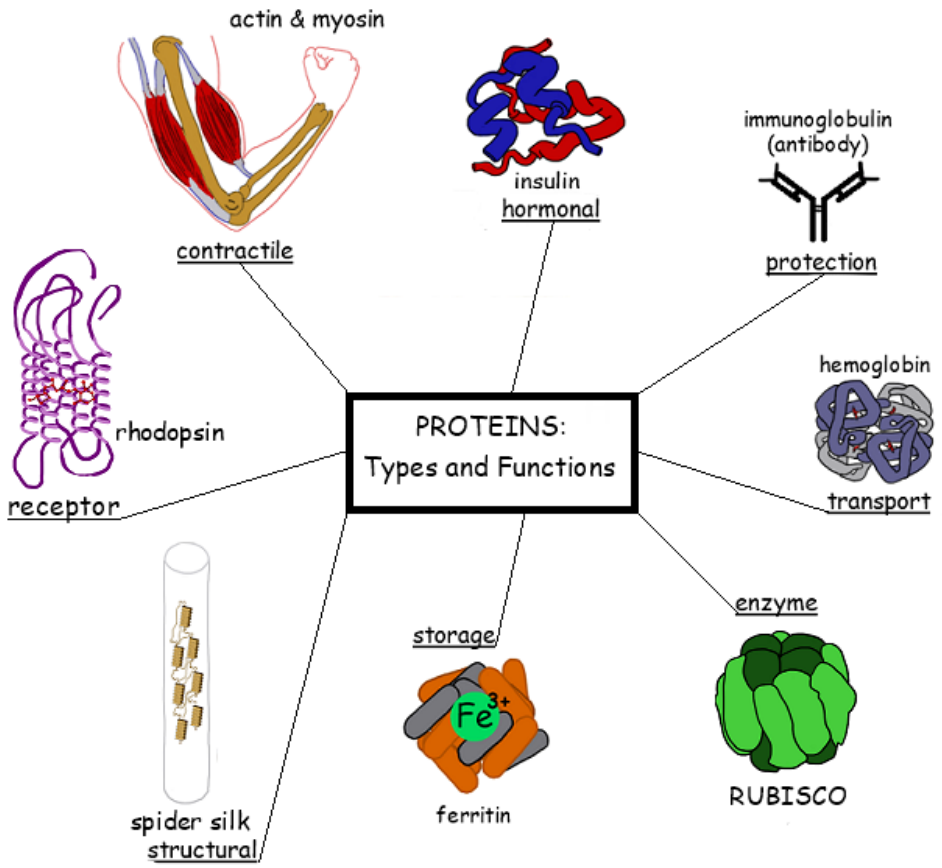
Structure-function relationship:
Fibrous proteins

Prof. Mamoun Ahram

Biological Functions of Proteins

we can classify proteins according to structure and function

- Enzymes--catalysts for reactions
- Transport molecules— transportation of O2 and CO2
  - hemoglobin; channel proteins
- Contractile/motion—
  - myosin; actin
- Structural—
  - Collagen, keratin and elastin (extracellular), actin (intracellular)
- Defense—antibodies antigens and immunoglobulins
- Signaling—hormones, receptors
- Toxins--diphtheria; enterotoxins



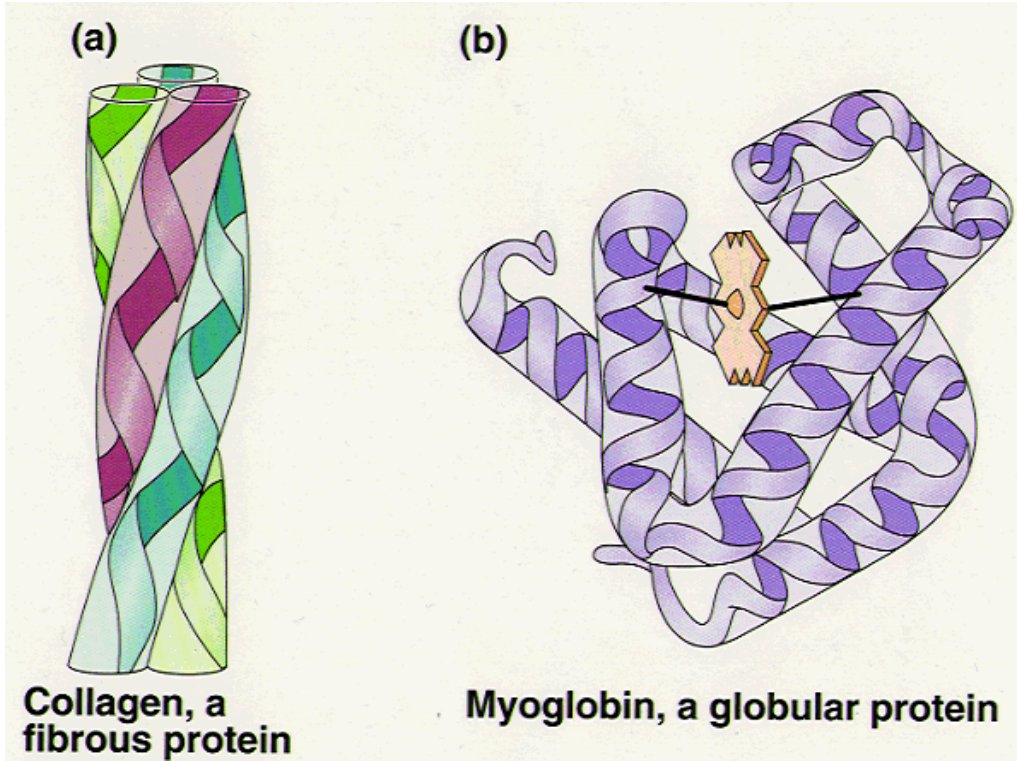
Types of proteins

- Proteins can be divided into two groups according to structure:
  - fibrous (fiber-like with a uniform secondary-structure only, elongated, mainly structural)
  - globular (globe-like with three-dimensional compact structures, enzyme transport storage, and so on)

Examples

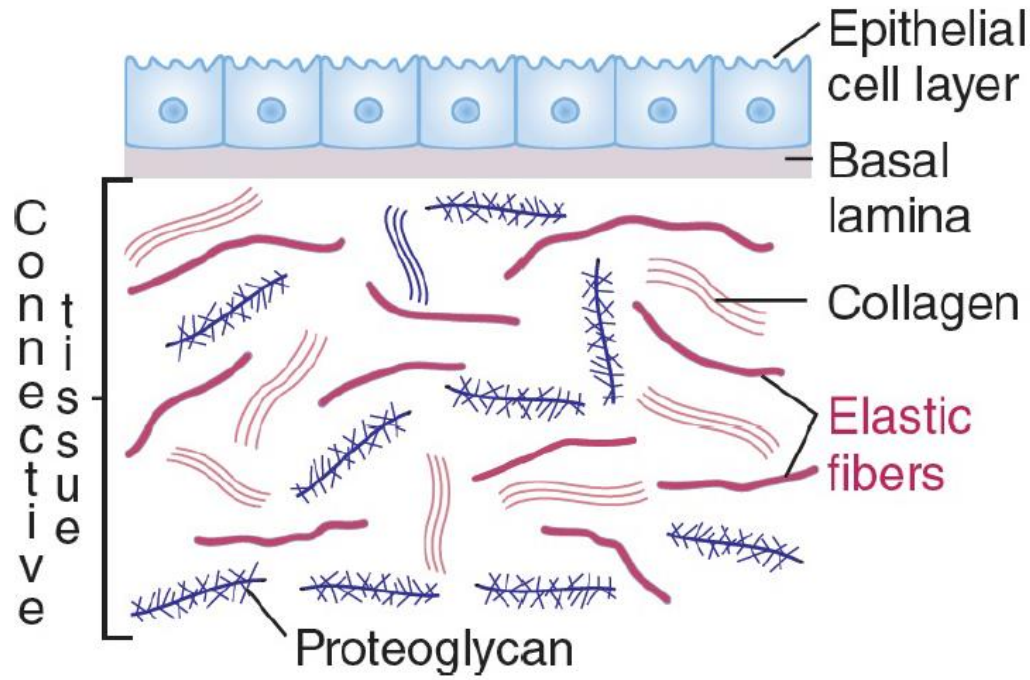
- Fibrous proteins mainly: collagens, elastin, and keratins

- Globular proteins: myoglobin, hemoglobin, and immunoglobulin



The extracellular matrix

- The extracellular space is largely filled by an intricate network of macromolecules including proteins and polysaccharides that assemble into an organized meshwork in close association with the cell surface.

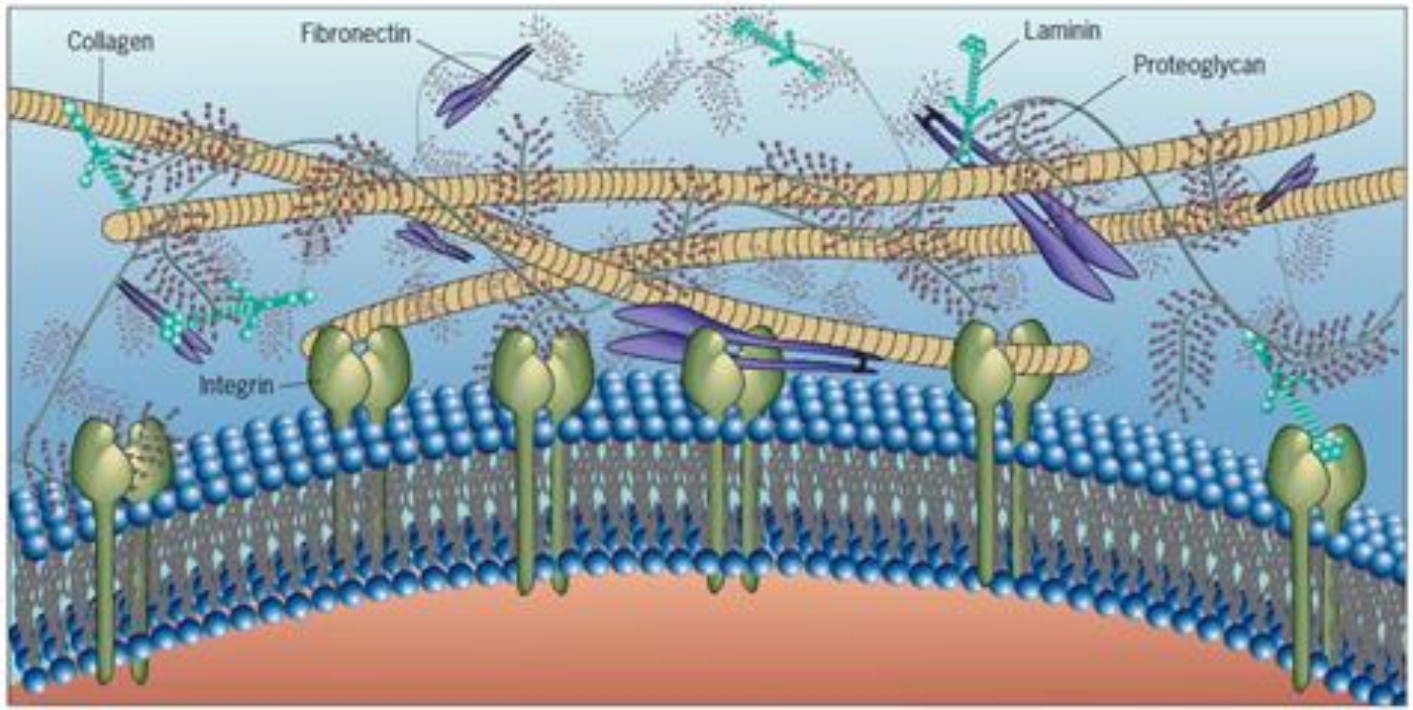


- Basal lamina: the basal membrane that is thick, extracellular and contains compact proteins. epithelial cells rest on this membrane and it separates the epithelial cells from the other cells in the connective tissue such as fibroblasts and inflammatory cells.

- The extracellular material has collagen and elastic fibers and proteoglycan, (fibrous proteins structure) .

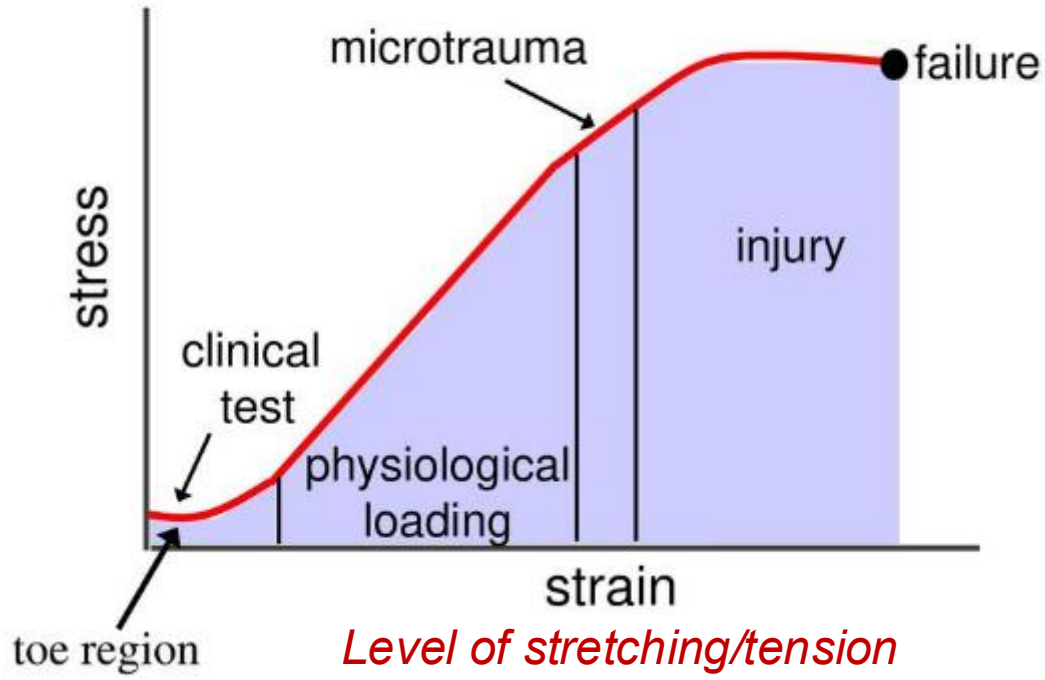
Collagens:

Thick fibers outside the cell , does interactions with other extracellular proteins and can do interactions with cell surface like integrins, they also maintain the structure.



Collagens and their properties

- A family of fibrous proteins of 40 types found in all multicellular animals
- **Most abundant proteins** in mammals (25% of the total protein mass)
- Named as type I collagen, type II collagen, type III collagen, and so on
- Main function: structural <u>support</u> to tissues,
- Primary feature: Rigid ,stiffness and tensile (stretching) strength
- tensile strength means: the highest amount of strain that we can apply on any protein without snapping (tearing)
- For example (about collagen tensile strength) is that we can pull skin but not tear it due to collagen, same with blood vessels when they dilate, they won't tear due to collagen as well. This is why it's important in bone structure.



Types of collagen

- Fibril-forming (types I, II, III, V, XI, XXIV, and XXVII)
- Network-forming (types IV, VIII, and X)
- Fibril-associated (types IX, XII, XIV, XXI, and XXII)
- Transmembrane (types XIII, XVII, XXIII, and XXV)
- Endostatin-forming (types XV and XVIII)
- Periodic beaded (type VI)

This is not for memorizing.

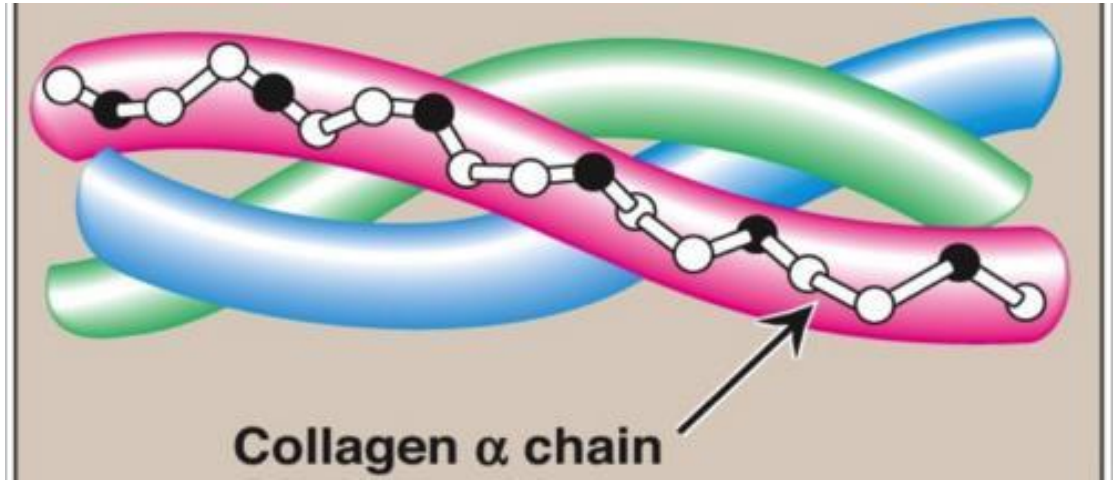
The lecture is going to focus mainly on Fibril forming collagen.

Structure (Overall Structure)

- It is a triple-stranded, helical protein where three collagen polypeptide chains, called α chains (each one of the strands comes from different gene), are wound around one another in a rope-like superhelix.
- This basic unit of collagen is called **tropocollagen**.

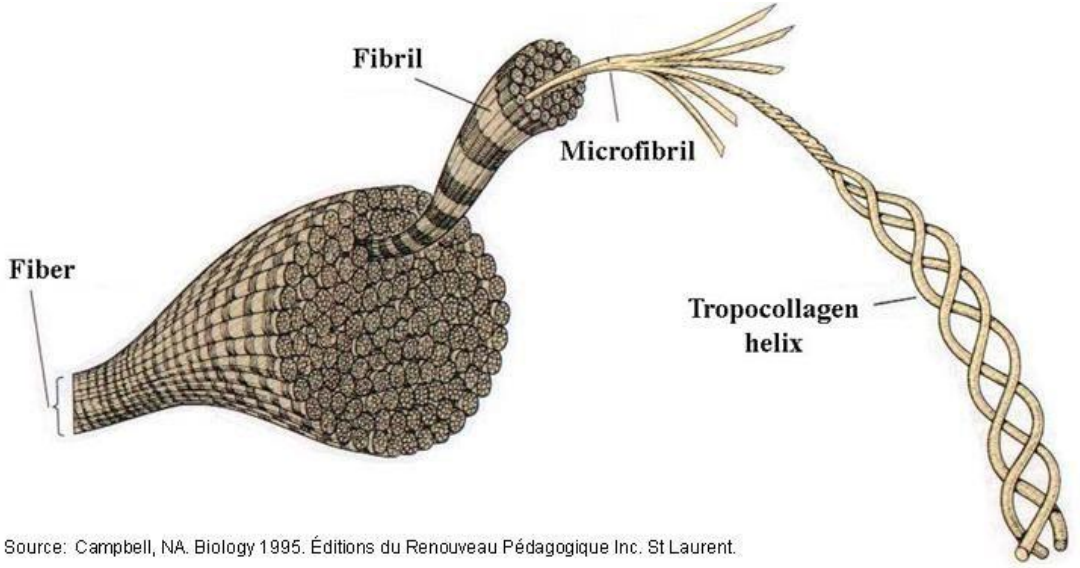
- There are 3 helical strands each called α, so we can name them α1, α2 and α3 comes from gene number 1, 2 and 3. However, there could be 2 α1 and 1 α2 in a tropocollagen meaning that there might be different combinations . This difference in 'Types of α strands' is what makes collagen varies into multiple types. The most important thing that there are 3 helical strands form the Tropocollagen.

- Compared to the α-helix (3.6 residue per turn), the collagen helix is much more extended with 3.3 residues per turn.



Formation of collagen fibers

- Following their release, 5 of the tropocollagens polymerize into a microfibril and connect with each other via covalent aldehyde links between lysine residues.
- Microfibrils align with each other forming larger collagen fibrils, which are strengthened via further cross-links.
- Fibrils then assemble into collagen fibers.

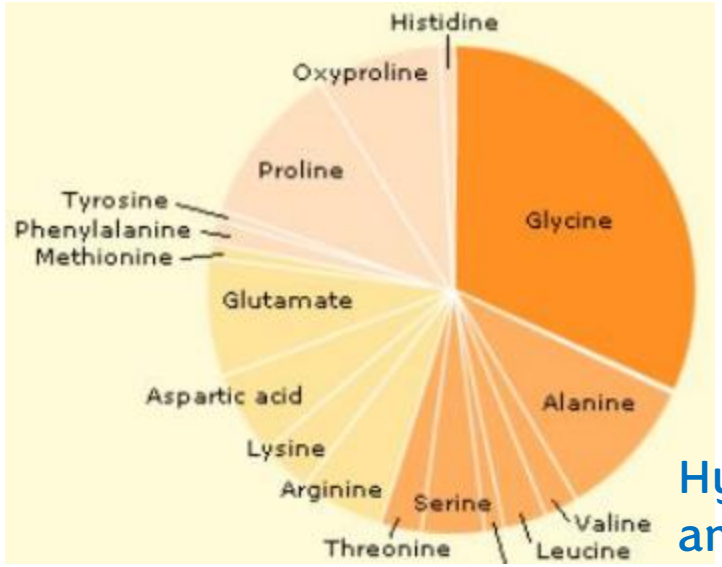


Source: Campbell, NA. Biology 1995. Éditions du Renouveau Pédagogique Inc. St Laurent.

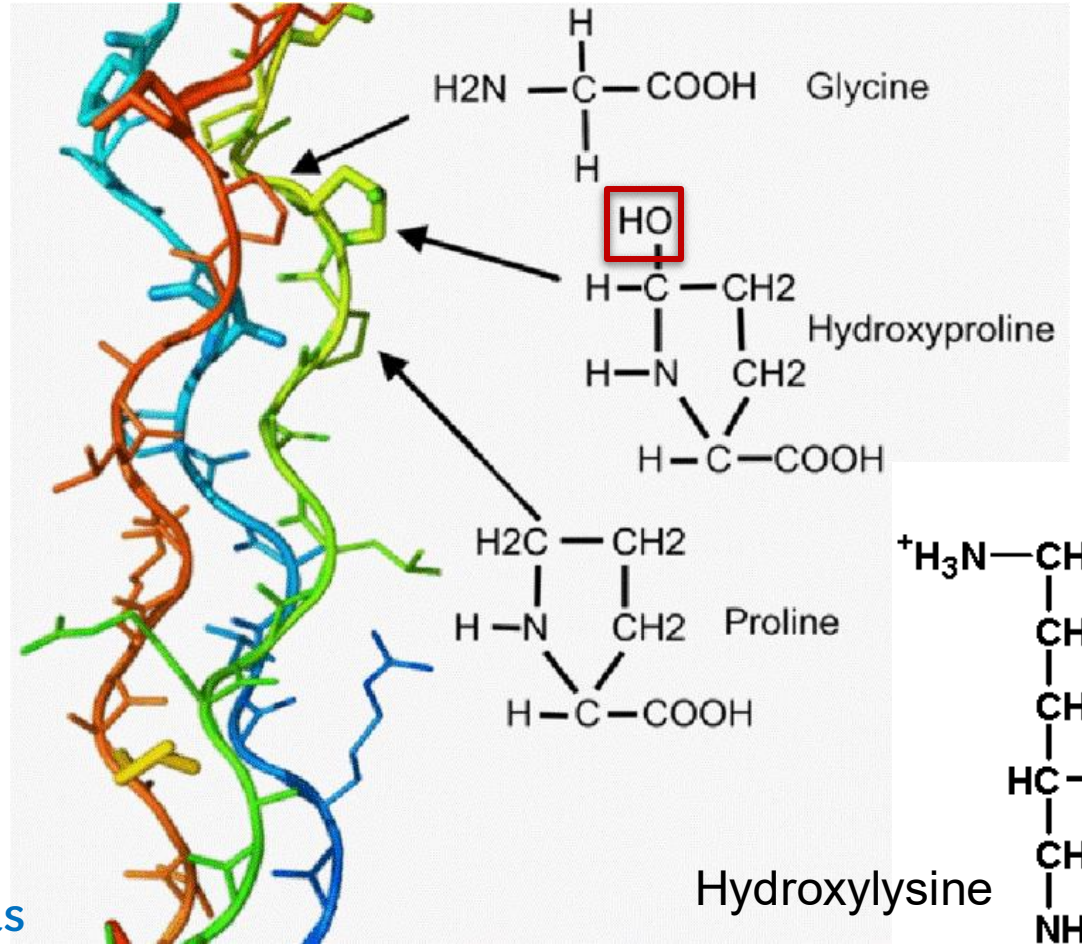
5 tropocollagens → microfibril → several microfibril → fibrils → several fibrils → fiber.

The primary structure of collagens (amino acid sequence)

- Collagens are rich in glycine (33%) and proline (13%) residues.
  - **Every third residue is a glycine.**
- They unusually contain hydroxyproline (9%) and hydroxylysine.
- Primary structure: Gly X-Y
  - **X** is often proline or hydroxyproline.

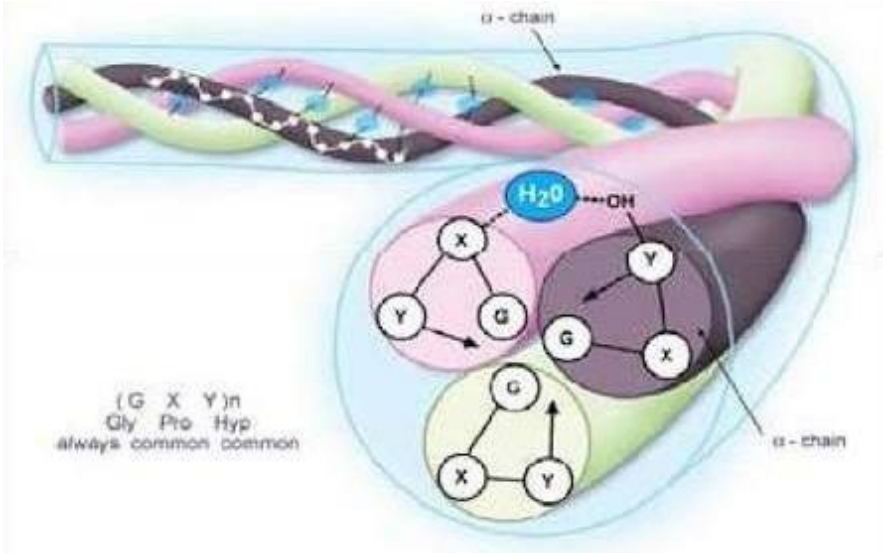


Hydrophobic amino acids as well. (1/4)

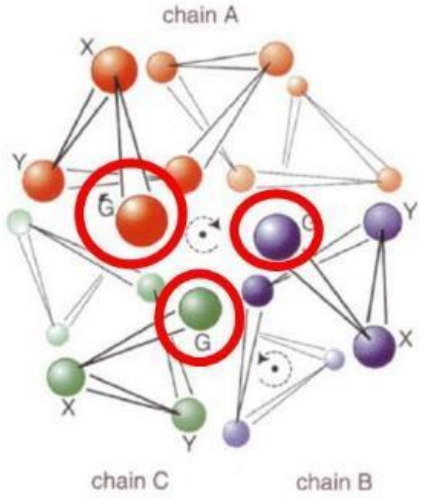


Functional purposes of amino acids

- Glycine allows the three helical α chains to pack tightly together since it lacks an R group and provides flexibility because it can rotate freely.
- Proline creates the kinks (creating the helical structure, in the collagen structure), stabilizes the helical conformation in each α chain, and provides rigidity to collagens.

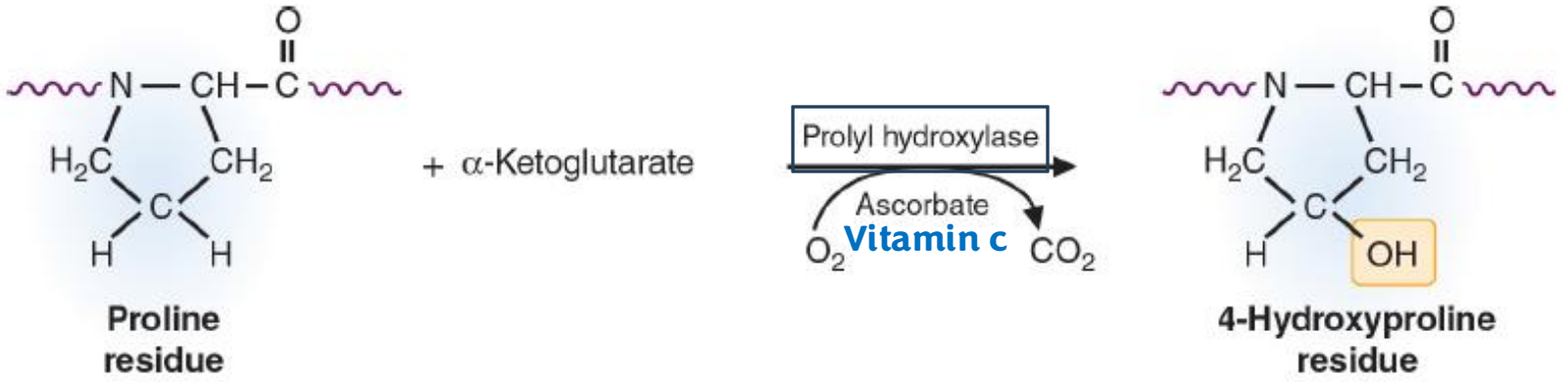


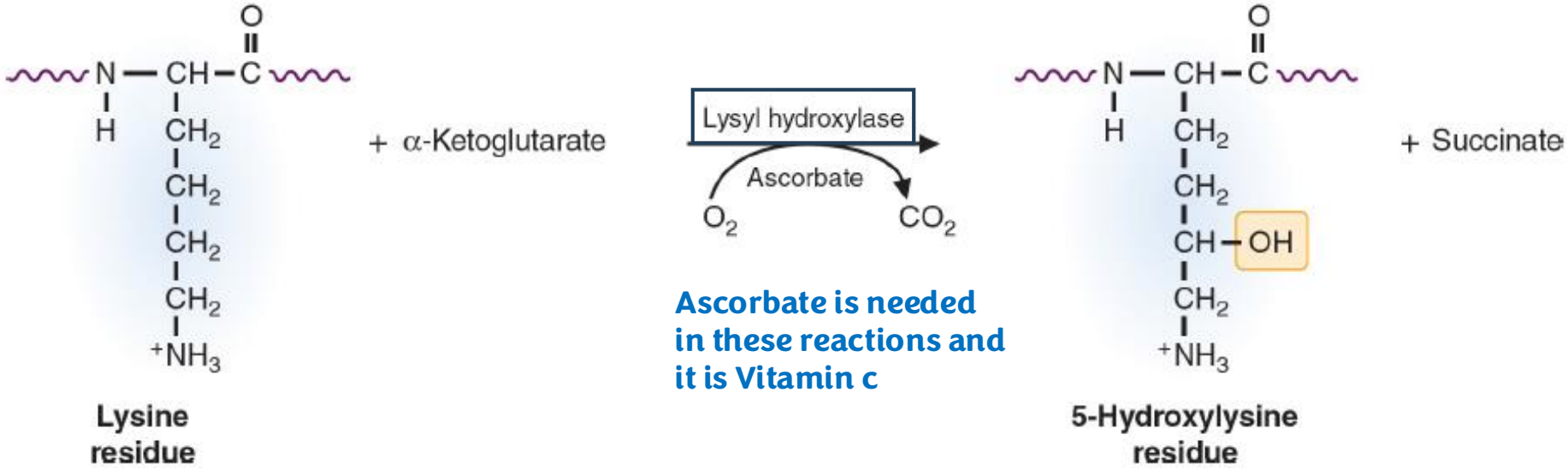
Glycine is
←internal
→



Hydroxylation of proline and lysine

No need to memorize the reaction just know the enzymes

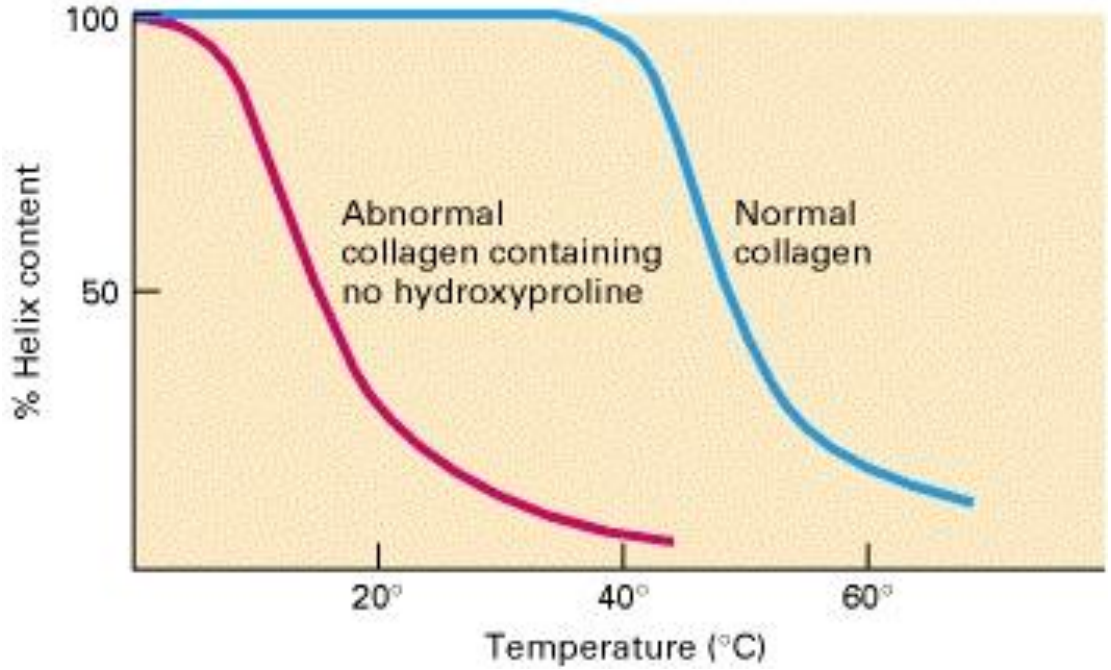




Ascorbate is needed in these reactions and it is Vitamin c

Purpose of hydroxyproline

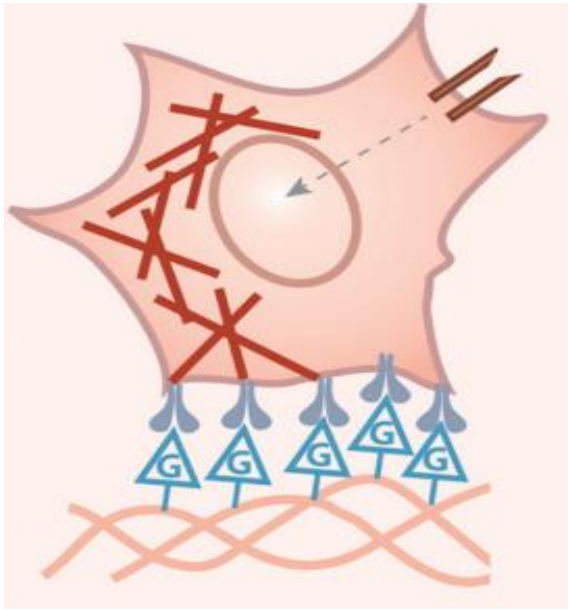
- Normal collagen is stable even at 40°C.
- Without the hydrogen bonds between the hydroxyproline residues, the collagen helix is unstable ,easy to break, and it loses most of its helical content at 20°C.
- Hydroxyl group helps with formation hydrogen bonds between molecules (amino acid residues)

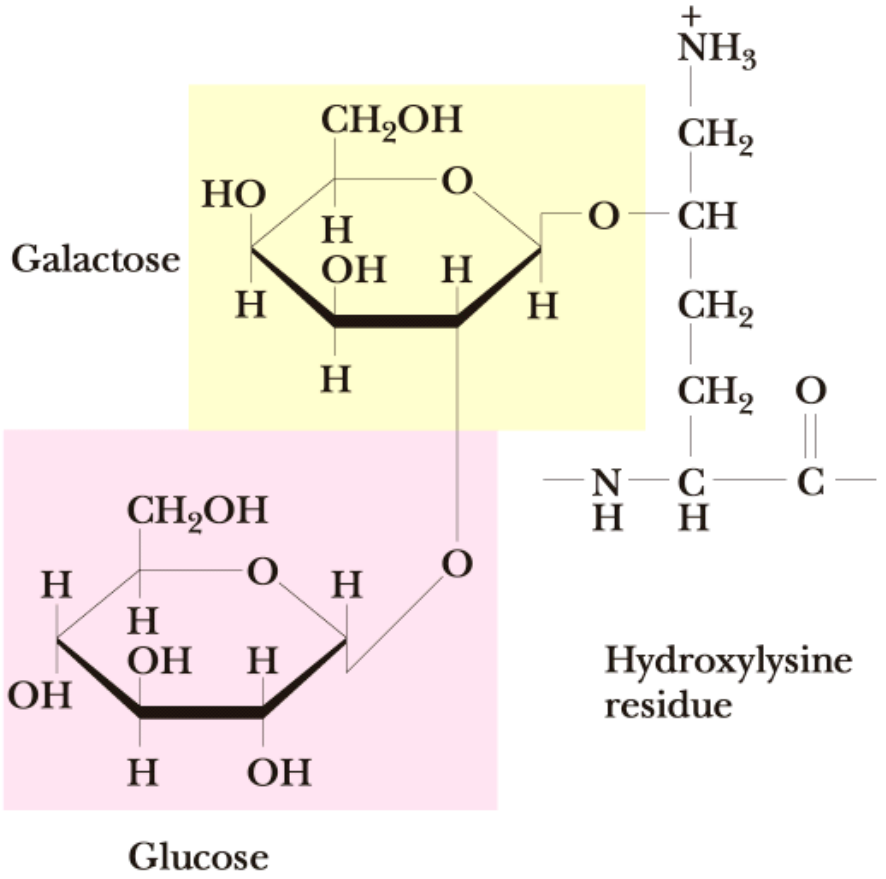


Hydroxylysine

- Hydroxylysines serve as attachment sites of polysaccharides making collagen a glycoprotein.
- Sugars allow collagen to recognize and interact with cell surface receptors.
  (signaling, if something happens to the matrix a message will be delivered through this connection to the cell)

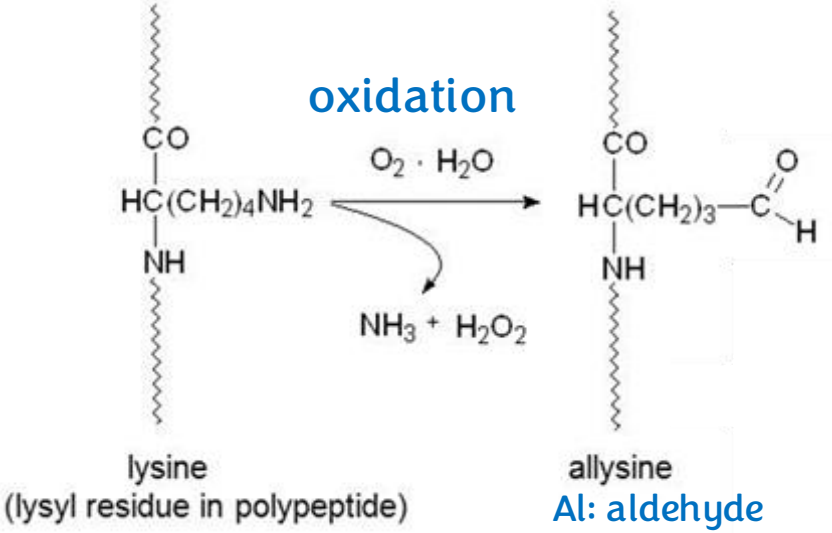
- Hydroxylysine is also important for collagen stability and strength.

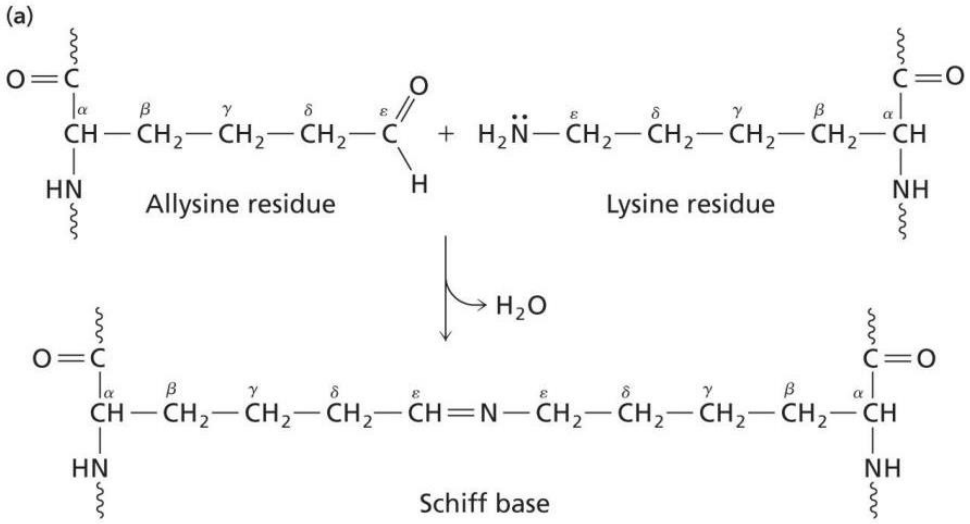


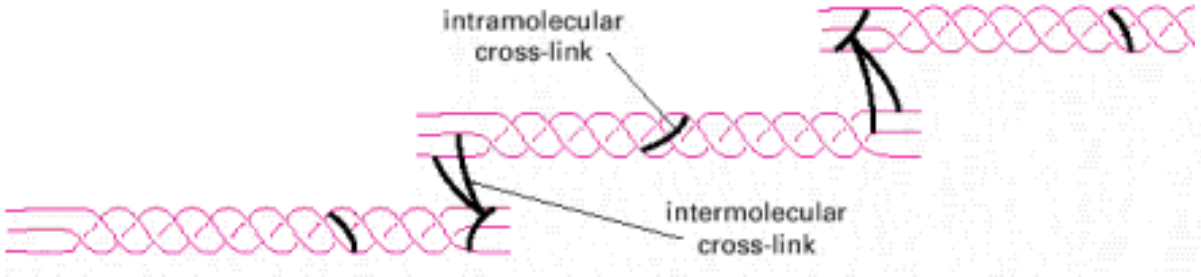


Oxidation of lysine

- Some of the lysine side chains are oxidized to aldehyde derivatives known as allysine.
- Allysine cross-links (covalent) with another allysine, hydroxylysine, or lysine residues within the same or with another tropocollagen.
- These cross-links stabilize the packing of collagen molecules generating a strong fibril.







Explanation of the professor for the previous slide:

- Allysine might react or cross-link with:

A. Another allysine , forming a dehydrated aldol (this was in the recorded lecture but it's removed from the slides).

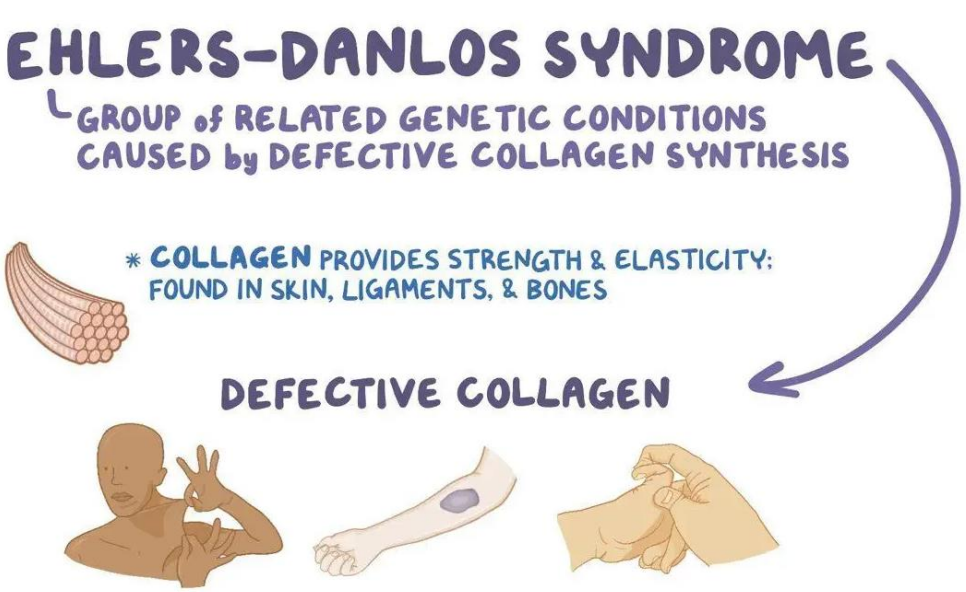
B. With lysine, forming schiff base. (It is a condensation reaction)

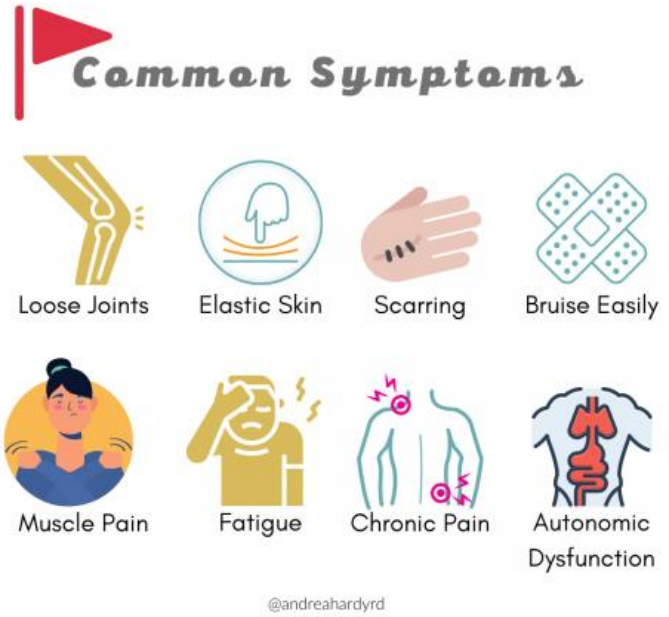
C. With hydroxylsine.

- This cross-linking happens within the tropocollagen molecules, or between different tropocollagen molecules, or between the fibrils aswell. This cross-linking helps increasing the rigidity of the collagen molecule.

Deficient cross-linking

- If cross-linking is inhibited, the tensile strength of the fibrils is drastically reduced; collagenous tissues become fragile, and structures such as skin, tendons, and blood vessels tend to tear.
- Deficiency of hydroxylation can cause diseases such as Ehlers-Danlos syndrome.
  (people with this syndrome usually have hyper mobility, so they can extend and stretch their limbs way more than normal people because they have a problem with collagen. People with this syndrome are usually excellent in gymnastics, taekwondo and swimming so it's not really the end of the world if the symptoms are mild).

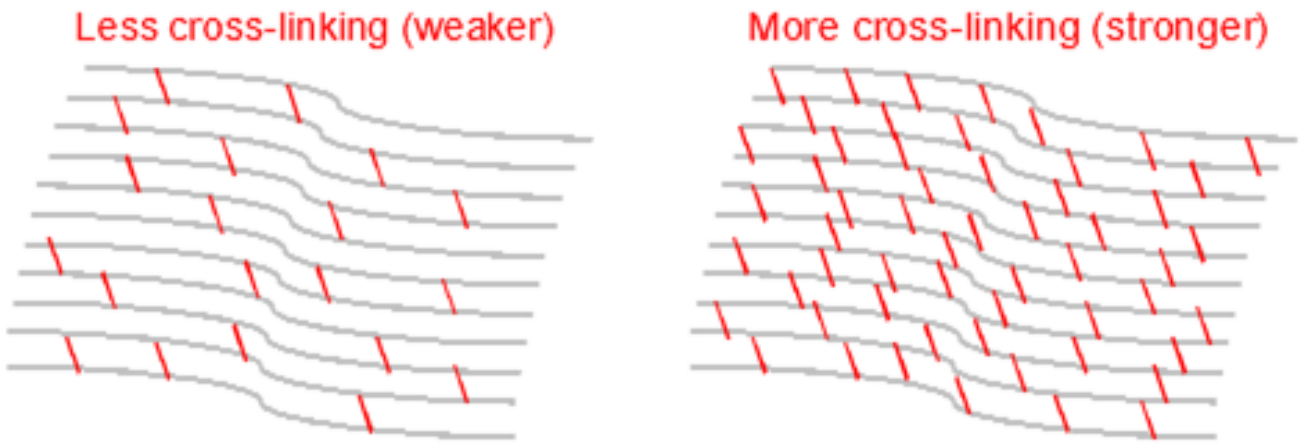




More on cross-linking

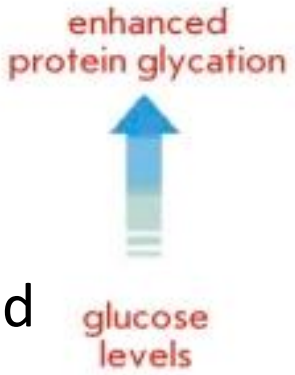
- The amount of cross-linking in tissue increases with age.

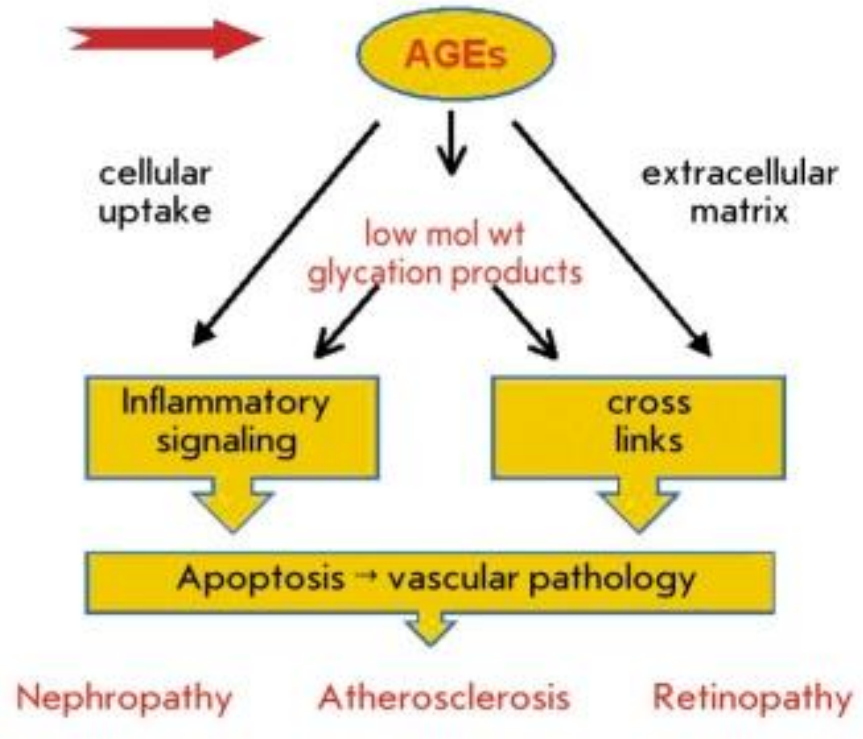
- Trivia: That is why meat from older animals is tougher than meat from younger animals.



Advanced glycation end products (AGEs)

- Proteins (e.g., collagen) can be nonenzymatically glycated producing glycated proteins that are difficult to turn over (to be degraded).
- Glycation is proportional to glucose level.
  - Hyperglycemia and diabetes increase the levels of glycated proteins.





Glycosylation: enzymatic addition of sugars
Glycation: nonenzymatic addition of sugars

Uncontrolled diabetics suffer from cardiomyopathy

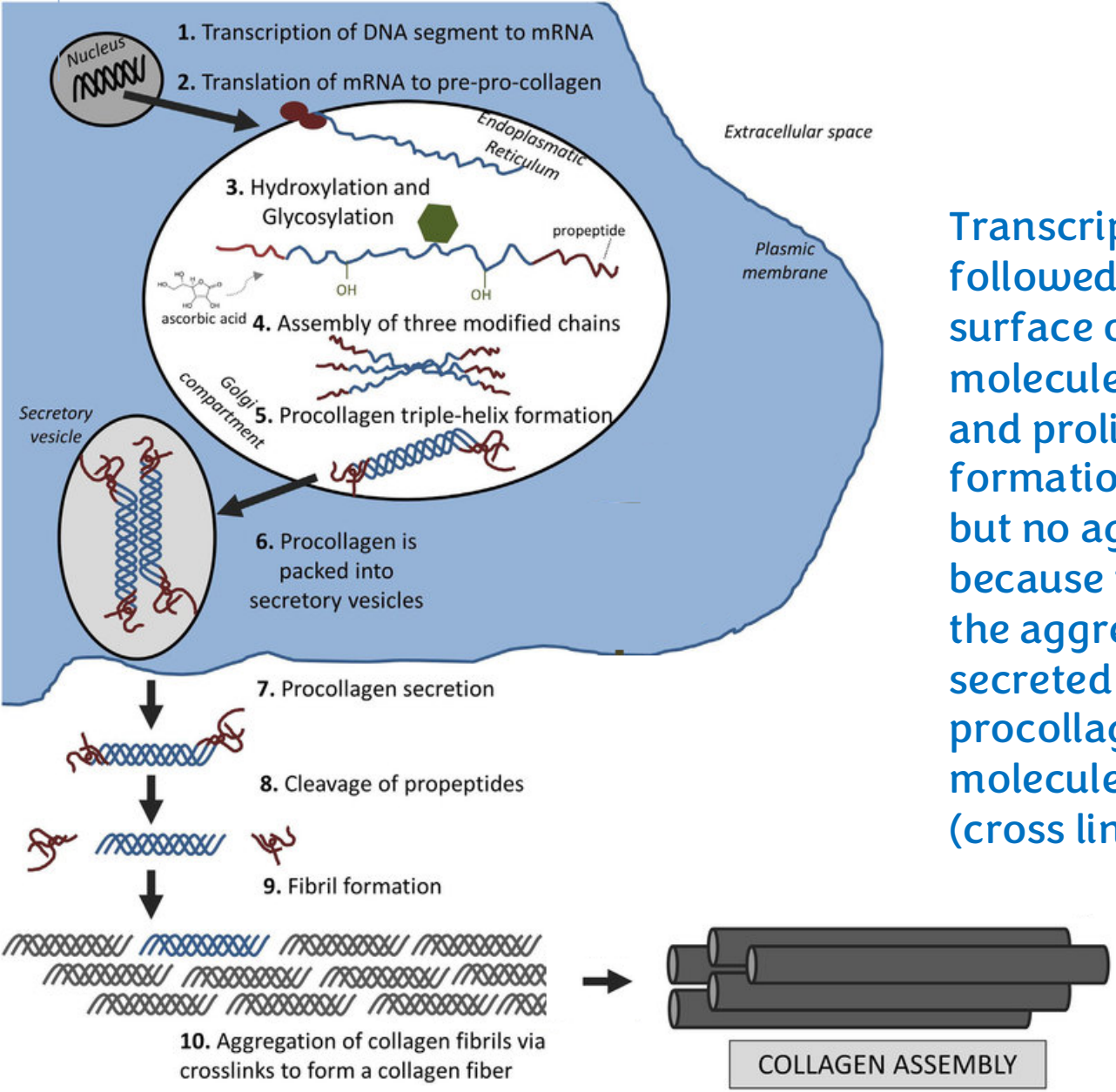
- Glycated proteins in tissues are further modified by nonenzymatic oxidation forming additional cross-links.
- The net result is the formation of large protein aggregates termed advanced glycation end products (AGEs), which increase cellular oxidative stress.

- When glucose levels increase in blood and tissues, more glycation happens (attachment of glucose to proteins , especially collagen since it's the most abundant in the body) . Glycation is a non-enzymatic reaction.

- Glycated proteins might undergo further modifications, forming cross-links between proteins. These products are called advanced glycation end products (AGEs), and when they increase this will increase oxidative stress, inflammatory response will happen and this will damage the tissues so a lot of cases can happen such as nephropathy, atherosclorsis which will lead to heart attacks, retinopathy (damage in the retina in the eye) , cardiac muscle damage and a lot more .

- When someone has uncontrolled diabetes, an increased glycation of proteins and production of AGEs, this will lead to cardiomyopathy.

Synthesis of collagen

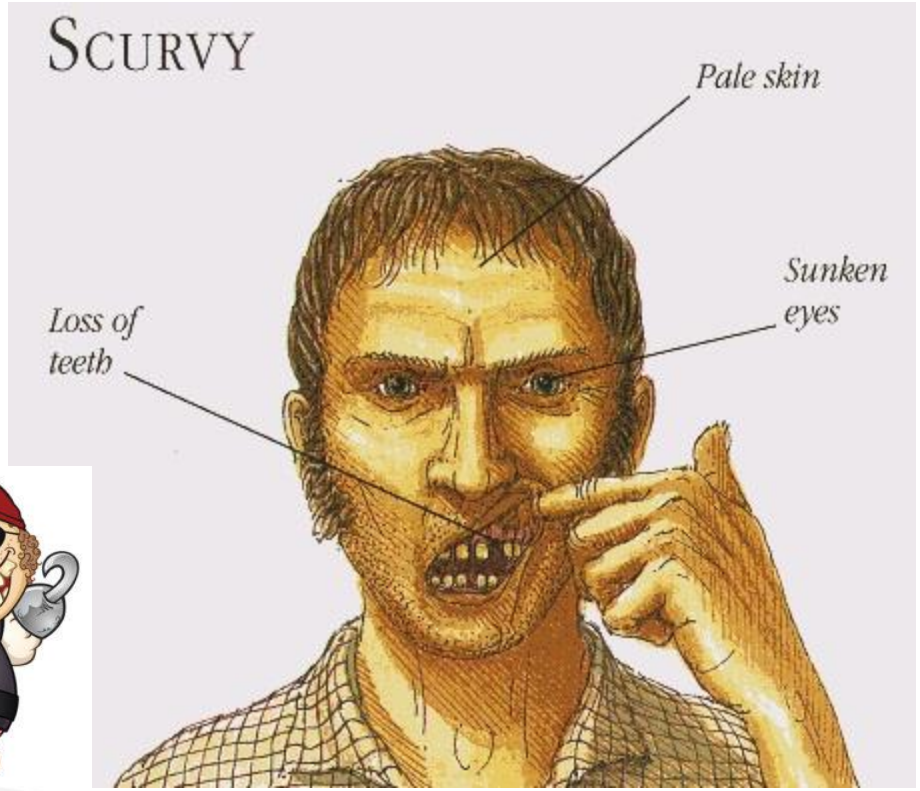


Transcription to mRNA of collagen gene happens, then it is followed by the translation that happens in ribosomes on the surface of the endoplasmic reticulum , the pro-collagen molecule enters the ER. In the ER , hydroxylation (for lysine and proline) and glycosylation (on hydroxylysine). Then the formation of the triple stranded molecule happens in the ER but no aggregation for tropocollagen molecules will happen because telopeptides (the ends of the procollagen) prevents the aggregation of tropocollagen). Then the procollagen will be secreted out the cell and then cleavage of both termini of procollagen will happen, forming the mature collagen molecule (tropocollagen). This is followed by fibril formation (cross linking between tropocollagen molecules).

Recall: prolyl and lysl hydroxylase enzymes require vitamin C.

Scurvy الإسقربوط

- Deficiency of ascorbic acid (vitamin C) prevents proline and lysine hydroxylation forming defective pro-α chains that fail to form a stable triple helix.
- This causes scurvy.
- Blood vessels become extremely fragile, and teeth become loose in their sockets.
  Bones and gum will be very fragile too.



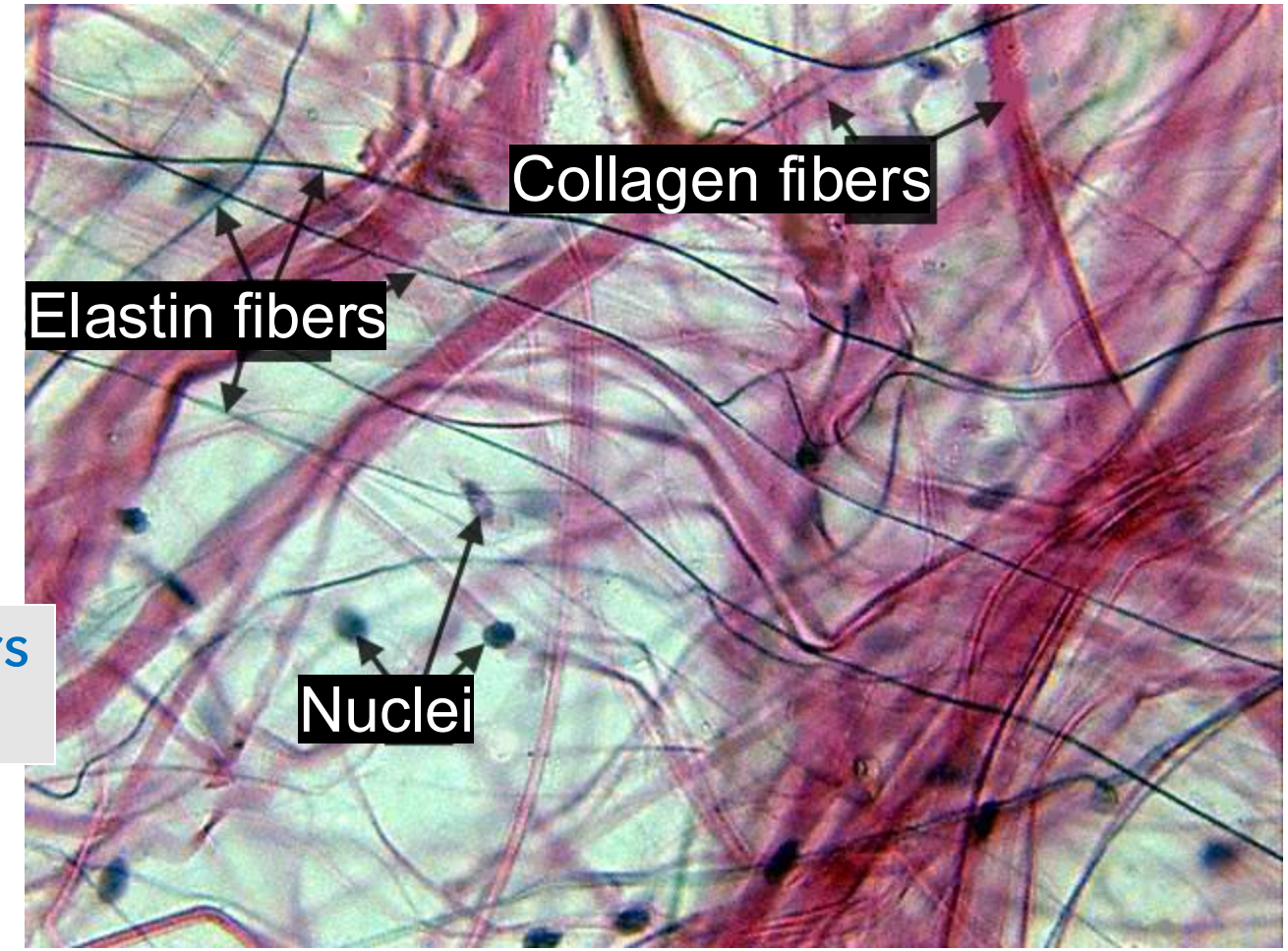
Because the collagen will be fragile .

Scurvy was very common among sailors because they don't eat fruits or other sources that have vitamin C, and that's why their teeth are usually not healthy because the collagen they have is very fragile.

Elastin

Found in the ECM with collagen fibers.

Thick strands = collagen fibers
Thin strands = elastin

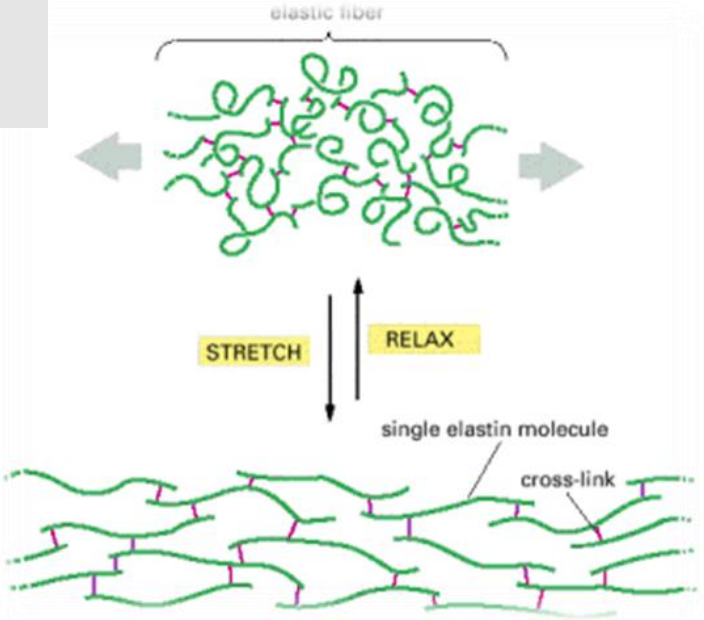


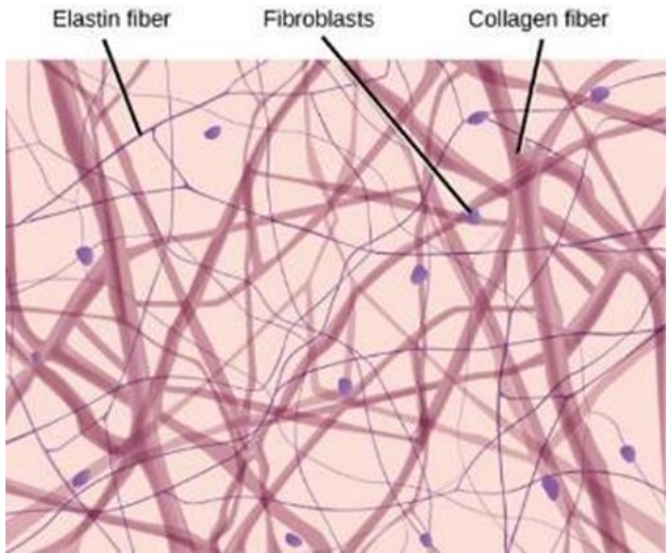
The structure will get back to its original shape or form after being stretched.

Resilience vs. flexibility

Ability to stretch an object.

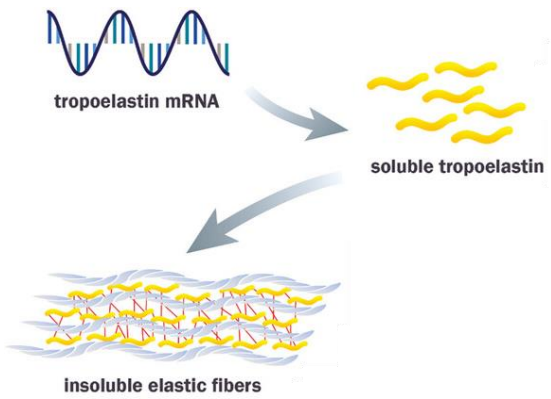
- Many tissues, such as skin, blood vessels, and lungs, need to be both strong and elastic (stretchy).
- A network of elastic fibers in the extracellular matrix of tissues gives them the required resilience so that they can recoil after transient stretch.
- Long, inelastic collagen fibrils are interwoven with the elastic fibers to limit the extent of stretching and prevent the tissue from tearing.

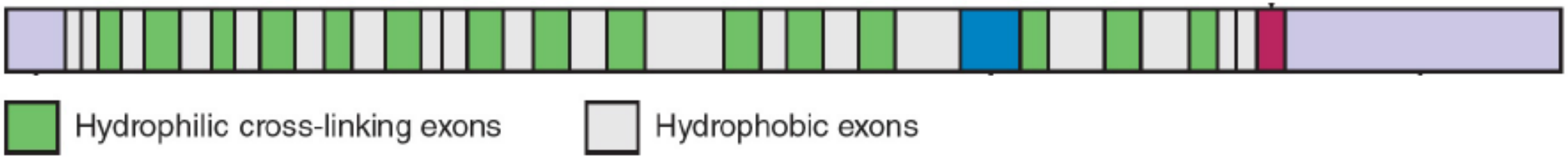




The primary structure of elastin

- Elastin is a highly cross-linked, insoluble protein (hydrophobic) with an undefined structure.
- Its precursor, tropoelastin, is a soluble precursor molecule that contains two repeated, alternating domains :
  - Lysine and alanine–rich hydrophilic domains (for cross-linking).
  - Hydrophobic domains that are rich in valine, proline, and glycine (for reversible aggregation).

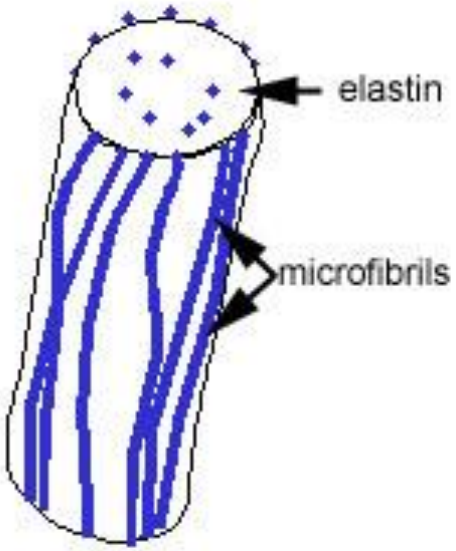


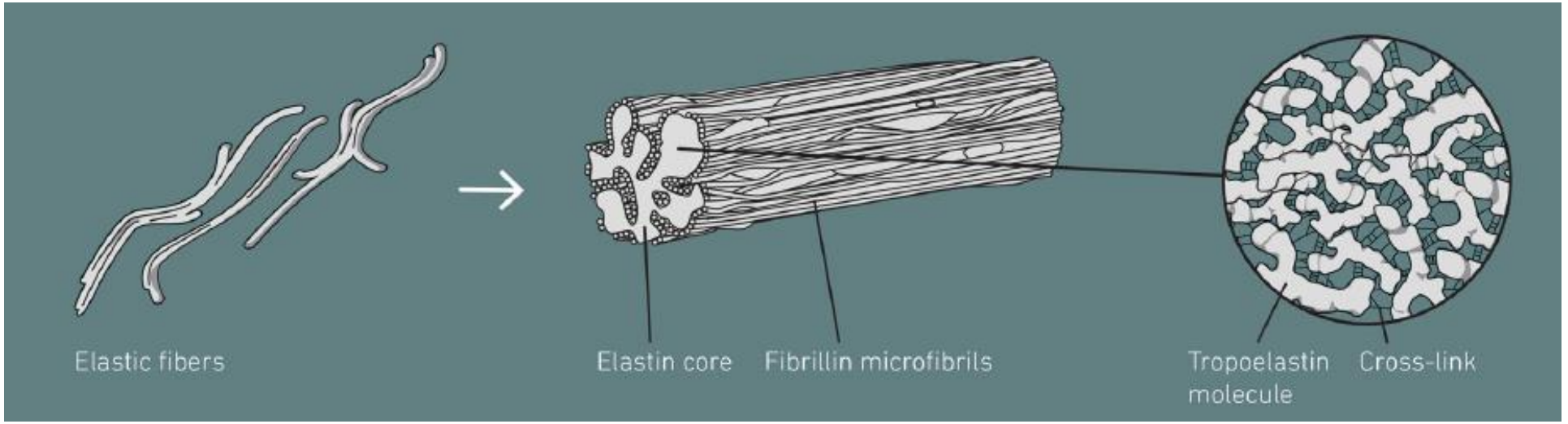


To form hydrogen bonding between different elastin fibers

Elastin

- Elastin contains some hydroxyproline, but no hydroxylysine.
  - It is not glycosylated. It is not a glycoprotein.
- Upon secretion from the cell, the tropoelastin is aligned with microfibrils, which are proteins such as fibrillin.
- The enzyme lysyl oxidase forms cross-links between lysines. (Transforms the amino group in lysine into an aldehyde forming allysine. this helps cross linking different elastin molecules together, forming cross linked elastin fibers)





How it functions

The function of elastin is to provide resilience and flexibility, and it functions because it's hydrophobic!

- When the elastic fibers are stretched, elastin structure is stretched exposing the repeating hydrophobic regions of the molecule to the aqueous environment.
- When this stretching force is removed, the elastin takes on its original structure.
- The hydrophobic effect is the primary force that allows the stretched structure to reform.

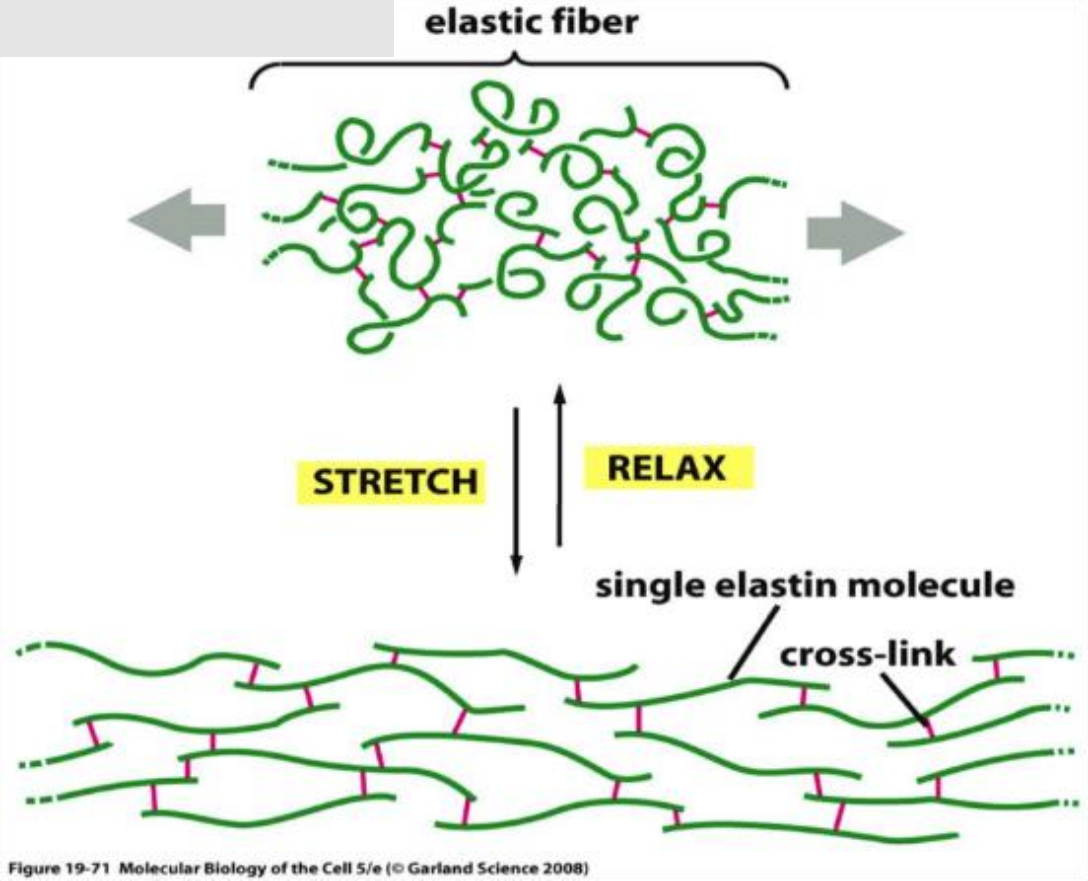
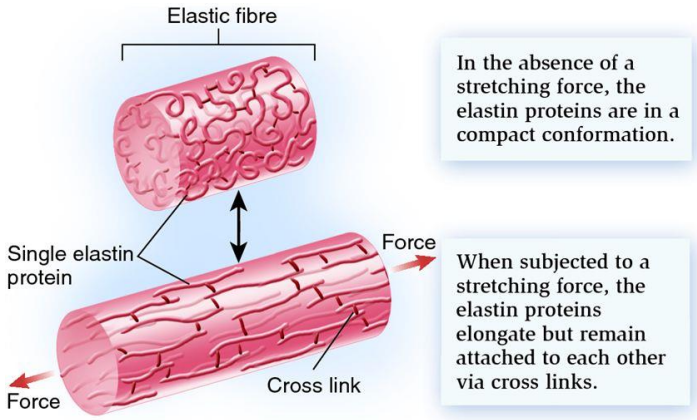


Figure 19-71 Molecular Biology of the Cell 5/e (© Garland Science 2008)

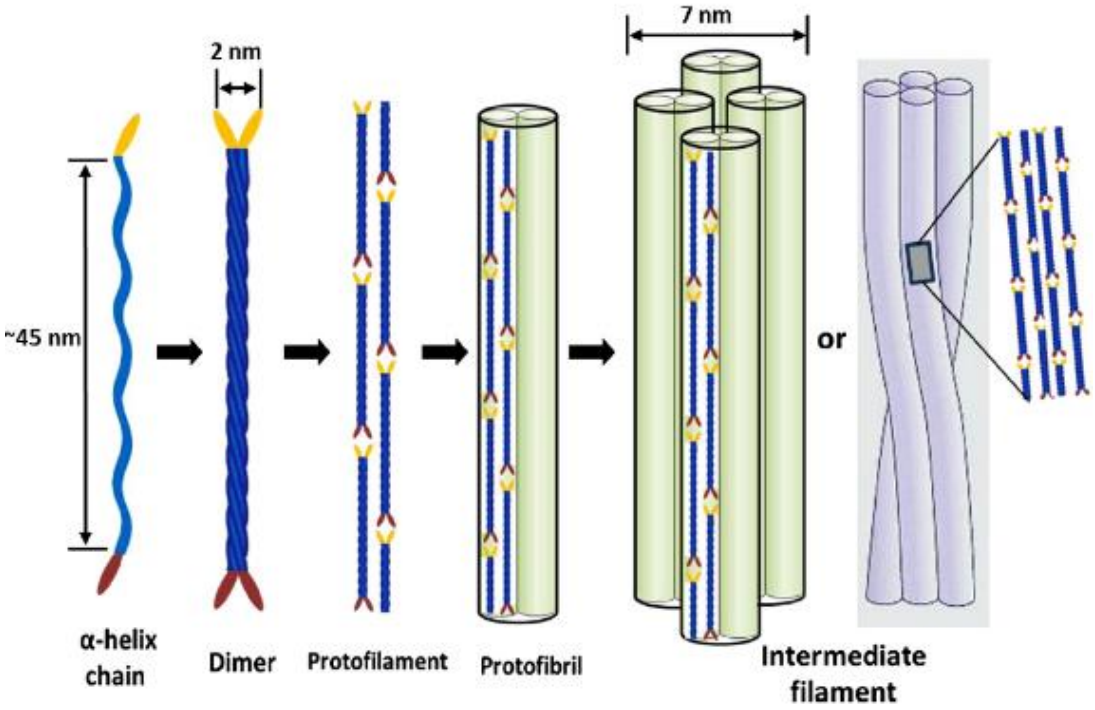


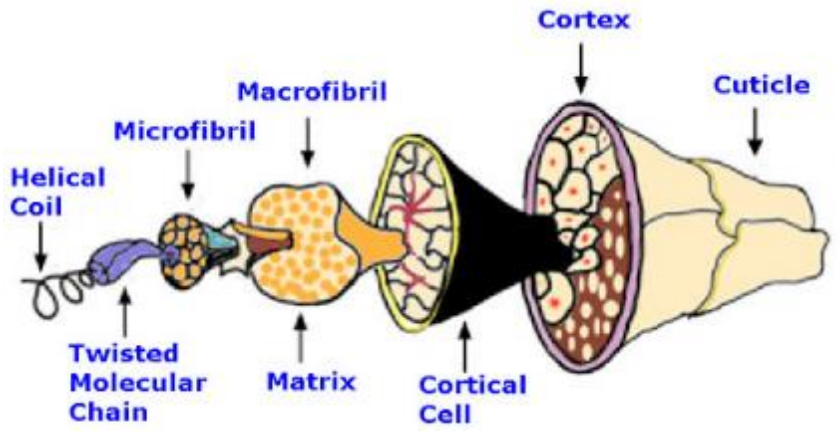
α-Keratins

A family of fibrous proteins. Found in skin, nails and hair.

α-keratins structure (hair vs. fingernails)

- Two helical α-keratin molecules form a coiled-coil dimer, which has sulfur cross-links.
- Two coiled-coil dimers associate forming a tetramer, and tetramers (not shown) associate head-to-tail forming protofilaments, which have nonhelical N- and C-termini that are rich in cysteine residues and cross-link.
- Two protofilaments twist together to form a protofibril.
- Four protofibrils form an intermediate filament.
- Eight intermediate filaments cluster to make a microfibril.
- Hundreds of microfibrils are cemented into a macrofibril.
- Many macrofibrils cluster to form a single hair.





- The helical dimer structure that consists of two helical α-keratin molecules have telopeptides (peptides that are found at both ends of the dimer). These telopeptides are rich with cysteine. These cysteine residues will cross-link the dimer together via disulfide bonds (unlike elastin and collagen the cross-link happens via allysine, in α-keratin the cross-link happens via cysteine)

- Importance of cysteine residues in the termini: the rigidity of the structure containing α-keratin increases when we have more cysteine residue. That's why finger nails have a lot of cross-links between cysteine residues because they should be tough and rigid.

- People who have curly hair have a lot of cysteine residues in their hair as well. (It obviously has less cysteine than in nails but it still does have a high amount relevant to people with straight hair).

2 helical α-keratin → coiled dimer → 2 Coiled dimers –> Tetramer → Lining up of different tetramers

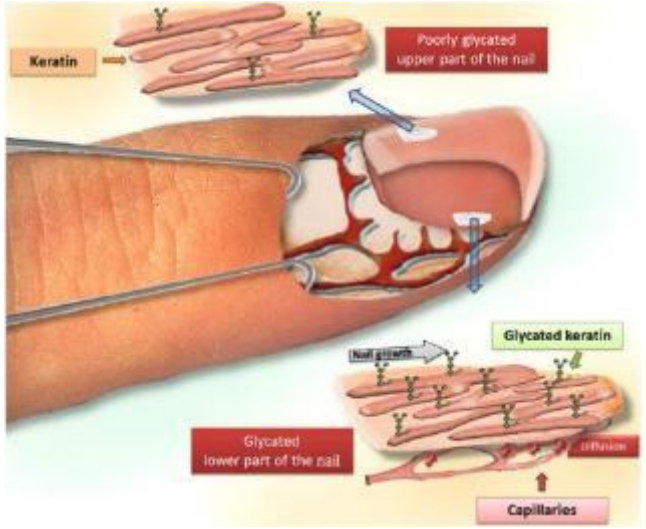
protofilaments -> 2 protofilaments → protofibril -> 4 protofibrils → Intermediate filament

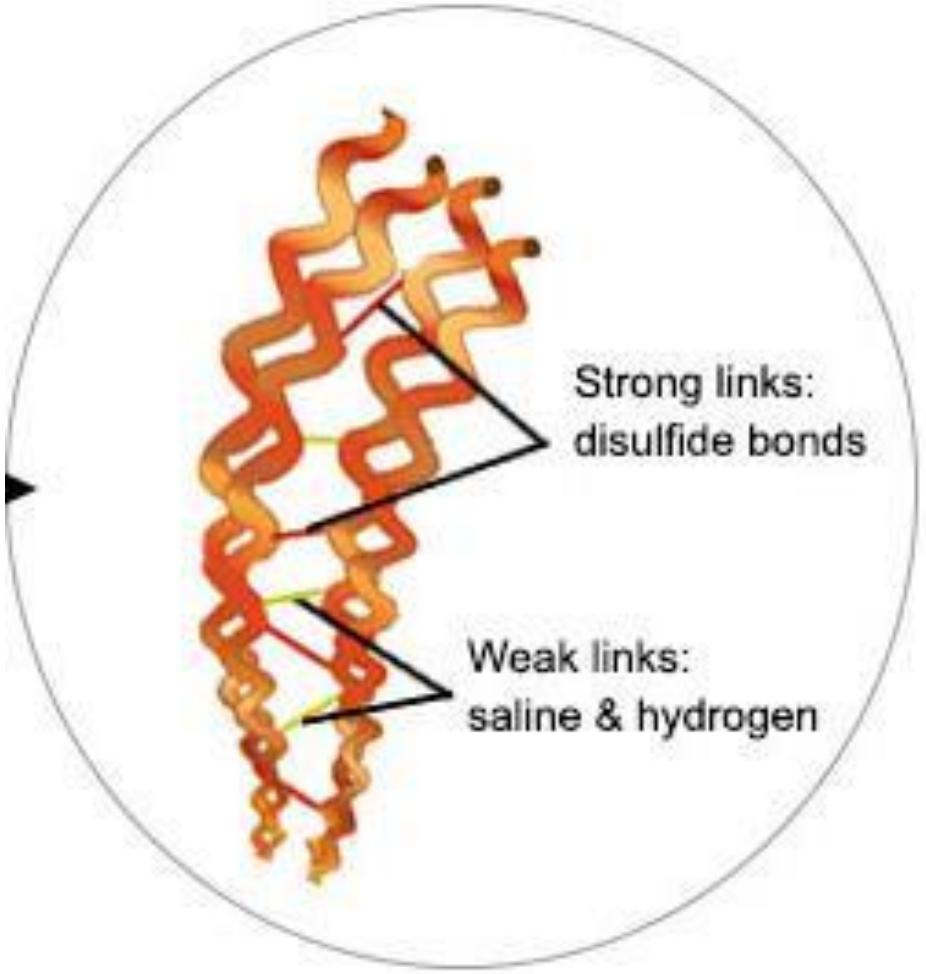
8 intermediate filaments -> Microfibril → Hundreds of microfibrils -> Macrofibril

Many macrofibrils -> A single hair

Keratin in nails

- α-keratin can be hardened by the introduction of disulfide cross-links (fingernails).



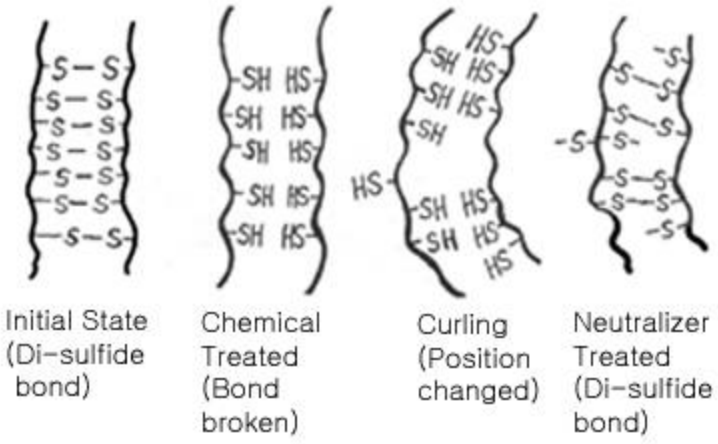


Looking beautiful?

Having a hair design?

Temporary Wave

- When hair gets wet, water molecules disrupt some of the hydrogen bonds, which help to keep the alpha-helices aligned. When hair dries up, the hair strands are able to maintain the new curl in the hair for a short time.



Permanent wave

- A reducing substance (usually ammonium thioglycolate) is added to reduce some of the disulfide cross-links. The hair is put on rollers or curlers to shift positions of alpha-helices. An oxidizing agent, usually hydrogen peroxide, is added to reform the disulfide bonds in the new positions until the hair grows out.

Clarification for the previous slide

- Temporary wave: When hair becomes wet, water molecules disrupt some of the hydrogen bonds between keratin chains, allowing the chains to move. The hair is then shaped using rollers or straightened and dried, causing new hydrogen bonds to form in the new arrangement. Because the strong disulfide bonds remain unchanged, moisture or washing can break the new hydrogen bonds, allowing the hair to return to its natural shape.

- Permanent wave: A reducing agent, usually ammonium thioglycolate, breaks some of the disulfide bonds between keratin chains by converting them into sulfhydryl (thiol) groups. The hair is then curled on rollers or held straight so that the keratin chains adopt new positions. Finally, an oxidizing agent, usually hydrogen peroxide, reforms the disulfide bonds in these new positions, fixing the new shape until the treated hair grows out.

QUIZ!

Good luck!!

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			

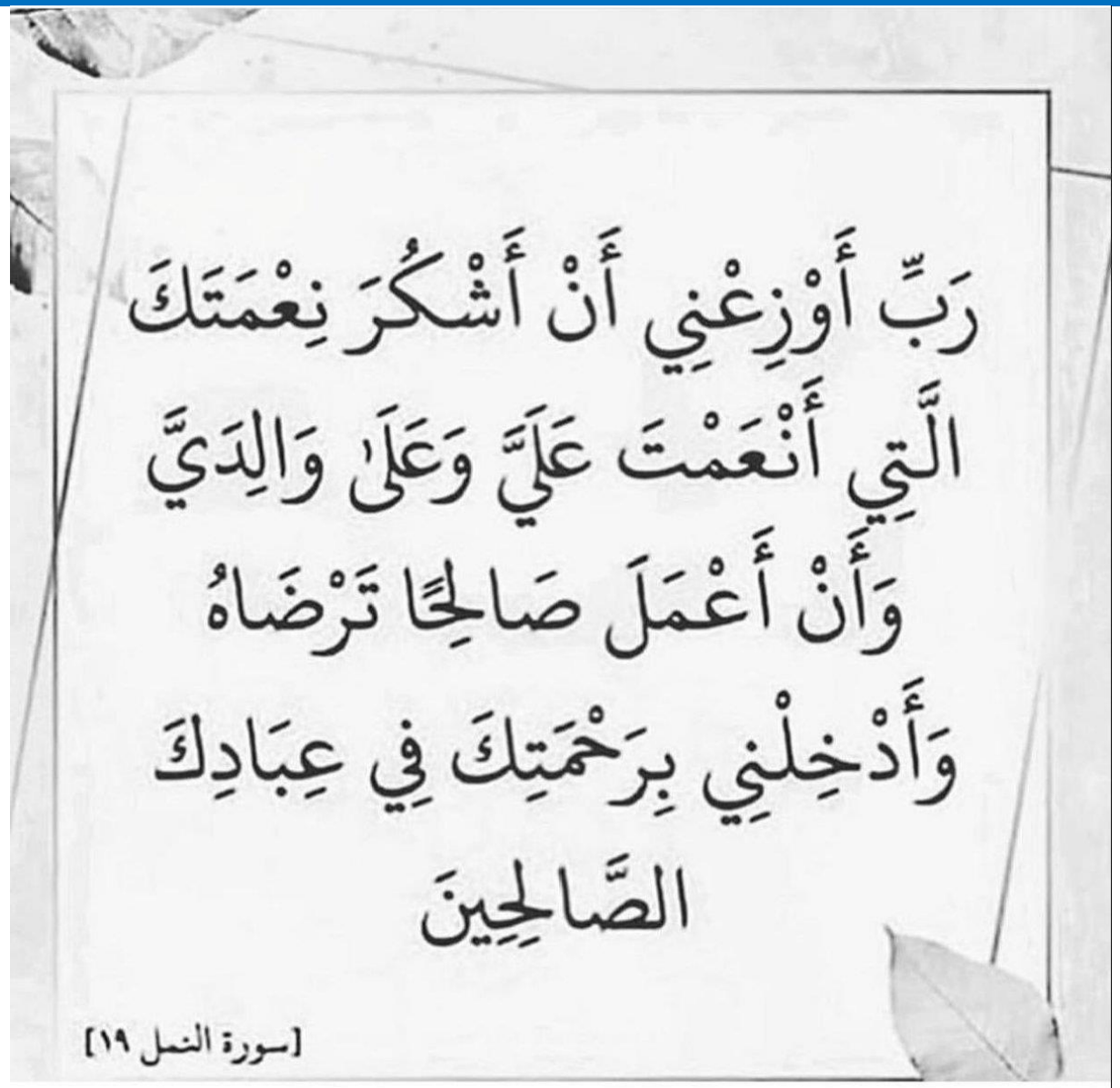
Additional Resources:

رسالة من الفريق العلمي:

Reference Used:

Prof. Mamoun Ahram recorded lecture:

"Fibrous Proteins"

Extra References for the Reader to Use:

Marks' Basic Medical Biochemistry (6th edition)