Introduction to Biochemistry and Molecular Biology

Lecture {18}

Fibrous Proteins

وَأَنزَلَ الَّذِينَ ظَاهَرُوهُم مِّنْ أَهْلِ الْكِتَابِ مِن صَيَاصِيهِمْ وَقَذَفَ فِي قُلُوبِهِمُ الرُّعْبَ فَرِيقًا تَقْتُلُونَ وَتَأْسِرُونَ فَرِيقًا (26) وَأَوْرَثَكُمْ أَرْضَهُمْ وَدِيَارَهُمْ وَأَمْوَالَهُمْ وَأَرْضًا لَّمْ تَطَئُوهَا ۚ وَكَانَ اللَّهُ عَلَىٰ كُلِّ شَيْءٍ قَدِيرًا (27). (سورة الأحزاب)

اللّهمّ نصرَكَ الّذي وعدتَ

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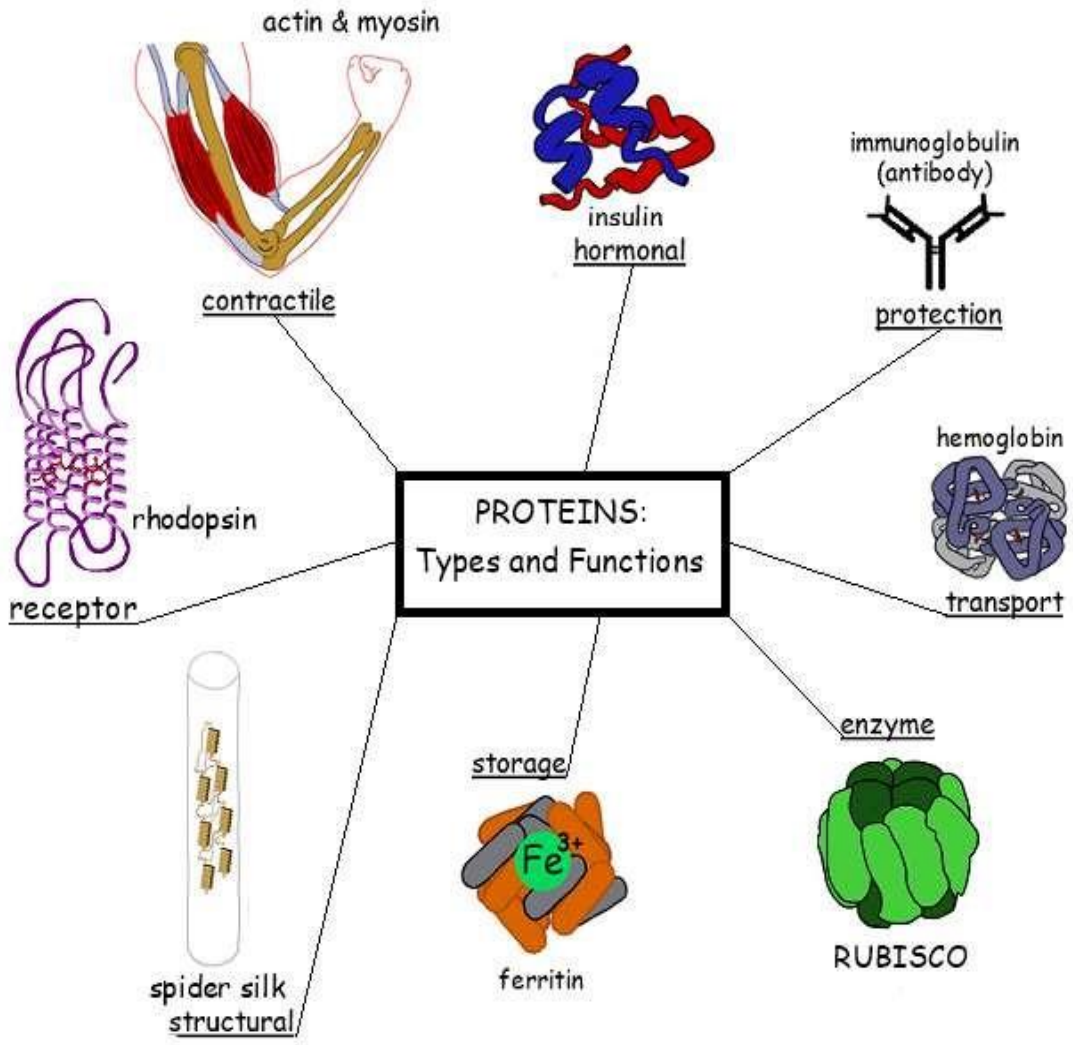
Structure-function relationship:

Fibrous proteins

Why this protein have this specific amino acid ?
what does it do ?
How can it be modified?
Why there is an Alpha helixes in this protein?

Biological Functions of Proteins

- **Enzymes--**catalysts for reactions
- **Transport molecules—** Like O2OC ,2
  - hemoglobin; channel proteins
- **Contractile/motion—** assist in muscle contraction
  - myosin; actin
- **Structural—**
  - collagen; keratin, actin, **elastin**
- **Defense**(removing antigens by antibodies)immunoglobulin)
- antibodies
- **Signaling—**hormones, receptors **Toxins--** diphtheria; enterotoxins



-collagen,keratin and elastin are extracellular while actin is intracellular

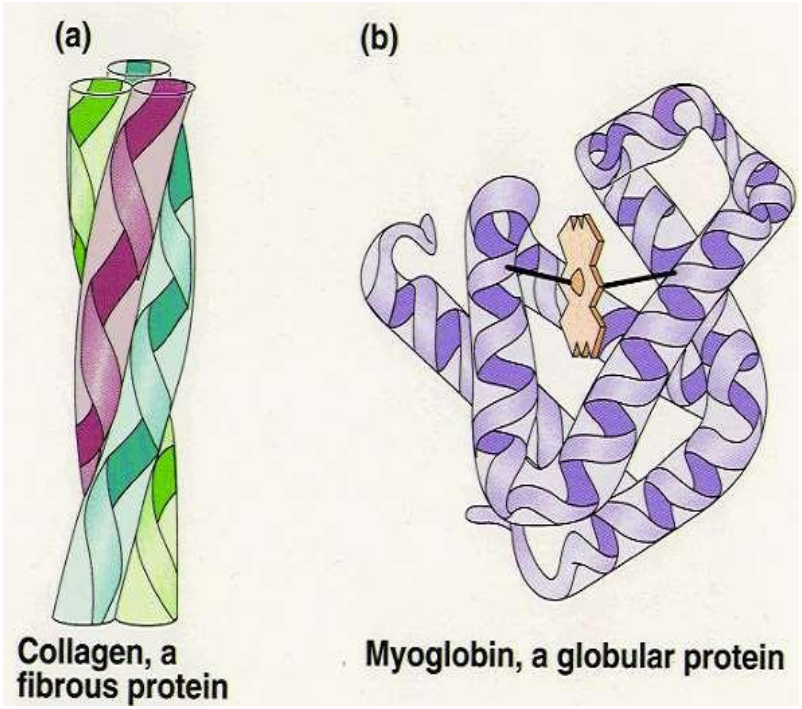
Types of proteins

- Proteins can be divided into two groups according to structure:
  - fibrous (fiber-like (elongated)with a uniform secondary-structure only)
  - globular (globe-like with three-dimensional compact structures) multi-functional (enzymes or transporter or storage)

Examples

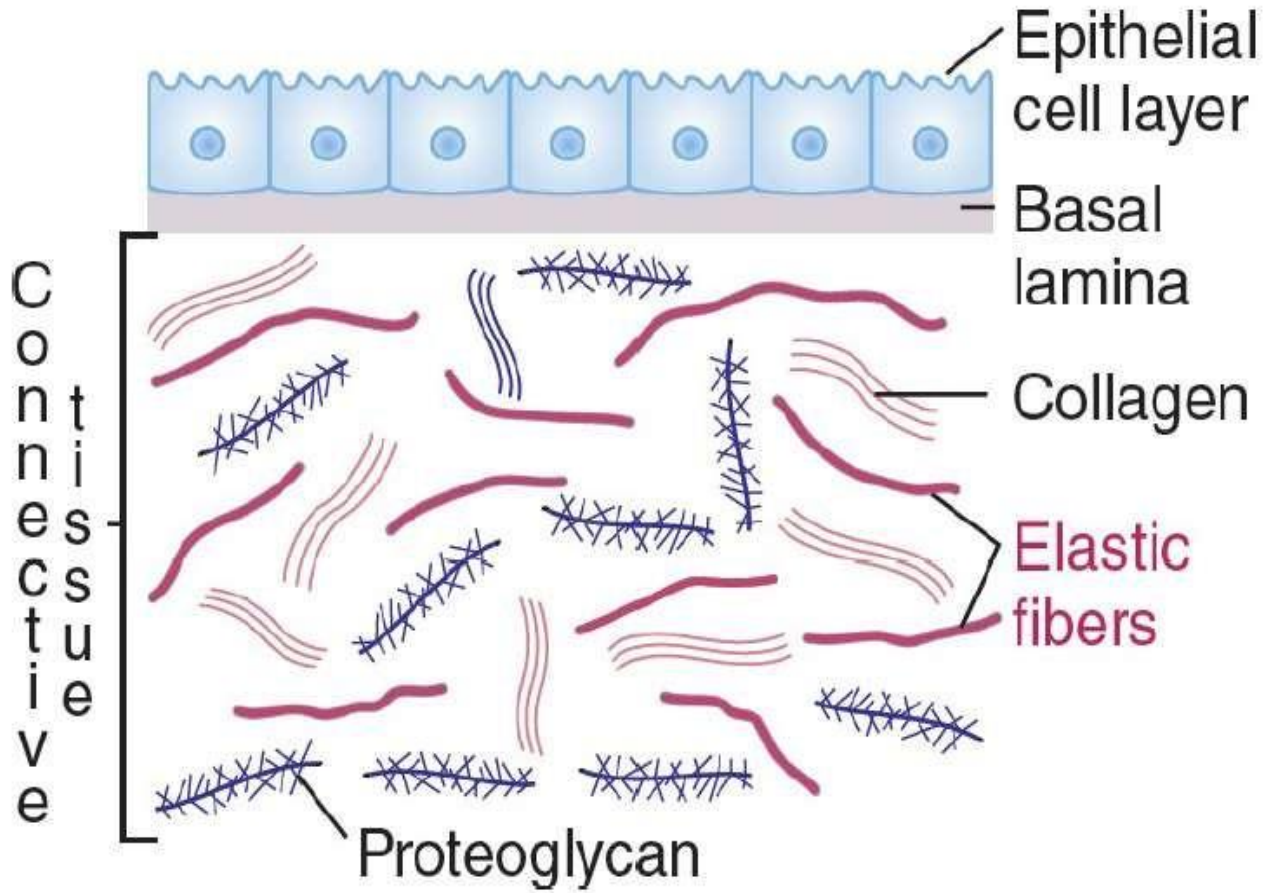
- Fibrous proteins: collagens, elastin, and keratins

- Globular proteins: myoglobin, hemoglobin, and immunoglobulin



The extracellular(out the cell) 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.



Basement membrane (basal lamina is a part of it) is composed of:

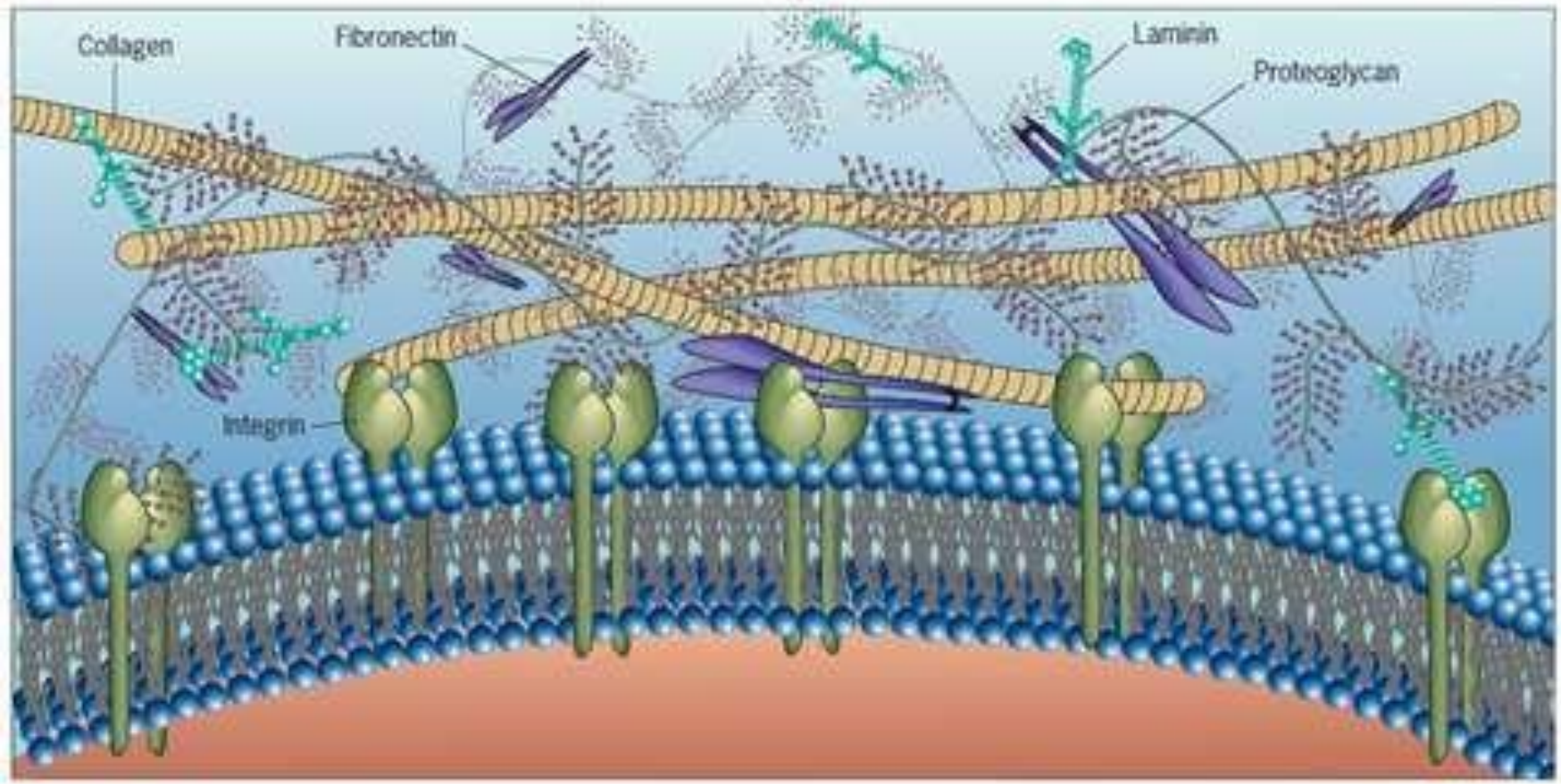
1) **thick compact fibrous proteins found under the epithelial cells. They are structural and tough (collagen and elastic fibers).**
2) **Some proteoglycans work in cell signaling.**

Also the basal lamina separates epithelial cells from other cells in the connective tissue like (fibroblast, endothelial cells and inflammatory cells)

Collagens

They are thick fibrous proteins found outside the cell, undergo some interactions with proteoglycans, other extracellular proteins and some surface receptors like integrins.

The main function is : maintaining the tissue structure.

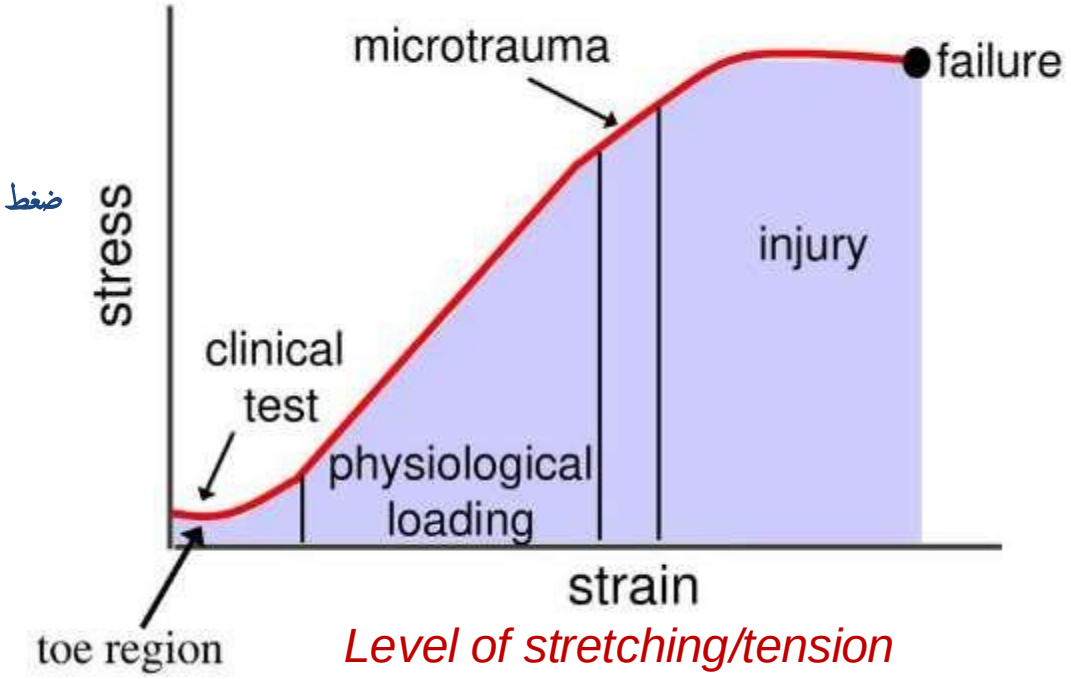


Collagens and their properties

- 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 support to tissues (**rigidity**) **and provide a really high strength, for example, bone strength comes from collagen in addition to Ca &Po4**
- Primary feature: stiffness and tensile strength

tensile strength : the maximum applicable amount of pressure)strain)a protein can withstand before breaking

ضغط أو توتر أو شد على البروتين



-Stretching skin does not lead to damaging it. Also when heart beats, blood vessels won't rupture due to its collagen content.

Types of collagen

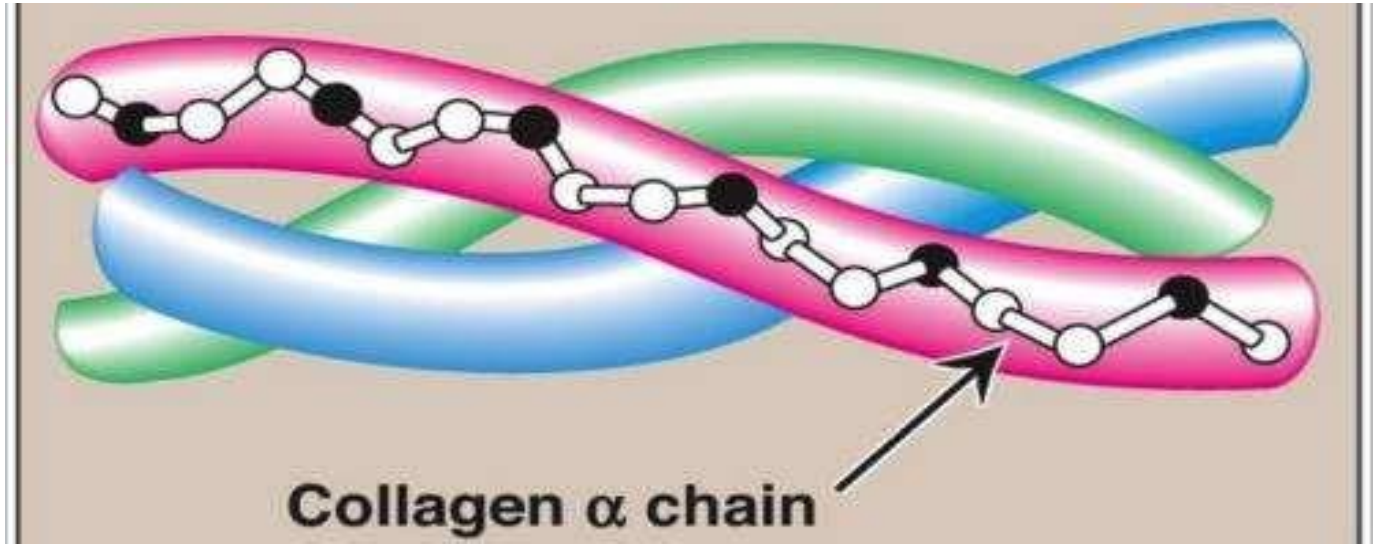
You don't have to memorize this slide

- 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)

Overall structure

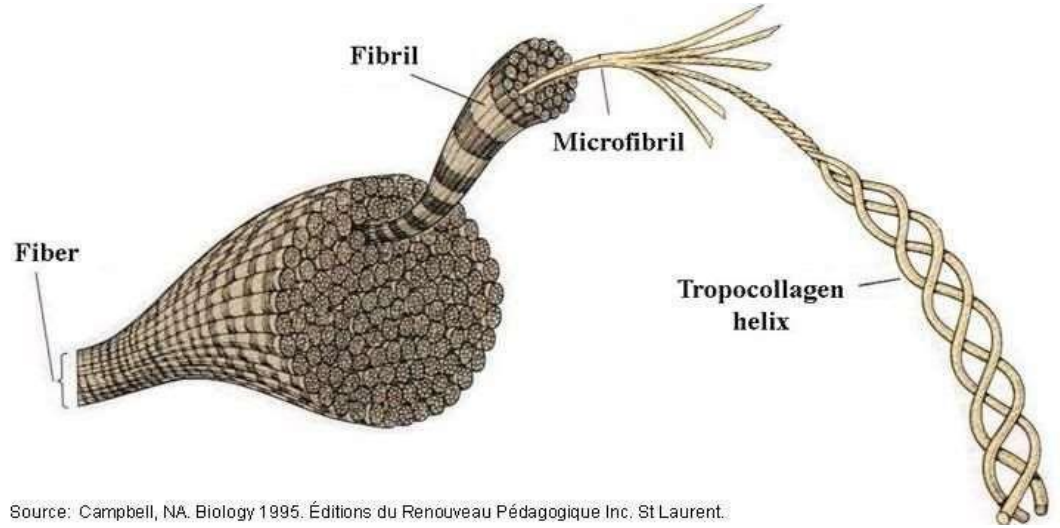
- It is a triple-stranded, helical protein where three collagen polypeptide chains, called α chains, are wound around one another in a ropelike superhelix. each one of these strands comes from separate gene and has different numbers (alpha 1,2,3)
  then,you may have a molecule with three (alpha1) strands,
  or a molecule with two (alpha2) and one (alpha1) strands
  this is the reason behind the diversity of collagen molecules!
- This basic unit of collagen is called tropocollagen (the three strands).
- Compared to the α-helix, the collagen helix is much more extended with 3.3 residues per turn.(extended helical protein compered to alpha helix).

REMEMBER
alpha helix has 3.6 residues per full 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.



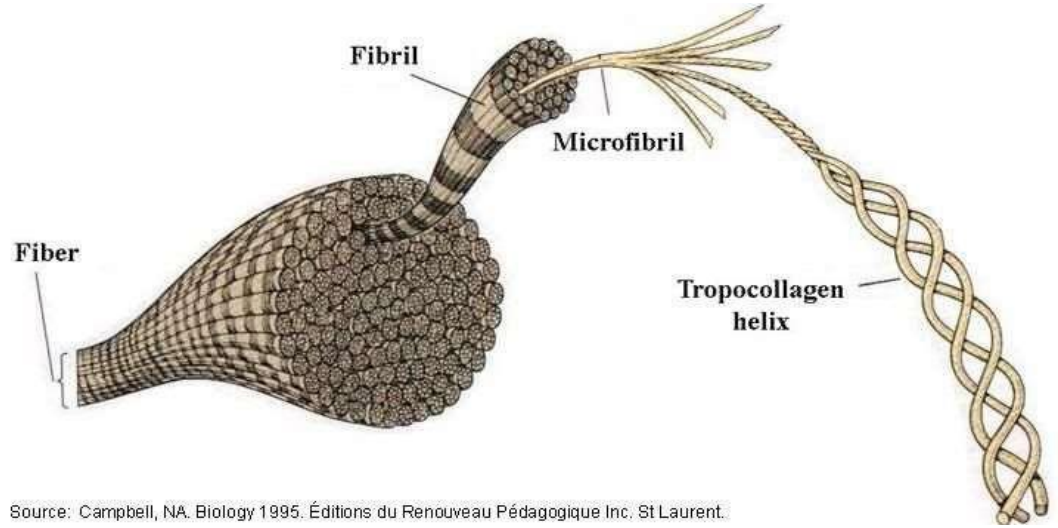
Source: Campbell, NA. Biology 1995. Éditions du Renouveau Pédagogique Inc. St Laurent.

• Recall that the basic unit of collagen is **tropocollagen** which is a helical triple stranded molecule.
• Tropocollagen consists of three alpha chains in which all alpha chains within the same tropocollagen can come from different genes.
• When the formation of tropocollagen is completed, 5 molecules of it assemble and connect with each other via covalent aldehyde links between lysine residues to form a **microfibril**.
• Several microfibrils cluster, aggregate and align with each other forming **larger collagen fibrils**, which are strengthened via further covalent cross-links.
• Several fibrils then assemble together forming the **collagen fiber.**

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.

Different genes → Different/similar alpha chains → Tropocollagen →Microfibrils → Fibrils → Collagen fiber



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

Note: The covalent linkages within/between the tropocollagens and between the microfibrils pack them together closely & strengthen their interactions with each other, as well as they strengthen & tighten the collagen molecule overall

The primary structure of collagens :The amino acid sequence in collagen molecules

We are going to discuss the primary structure of fibril-forming collagen molecules, ex. Collagen type 1, type 2 & type 3.

Collagens are rich in glycine (33%) and proline (13%).

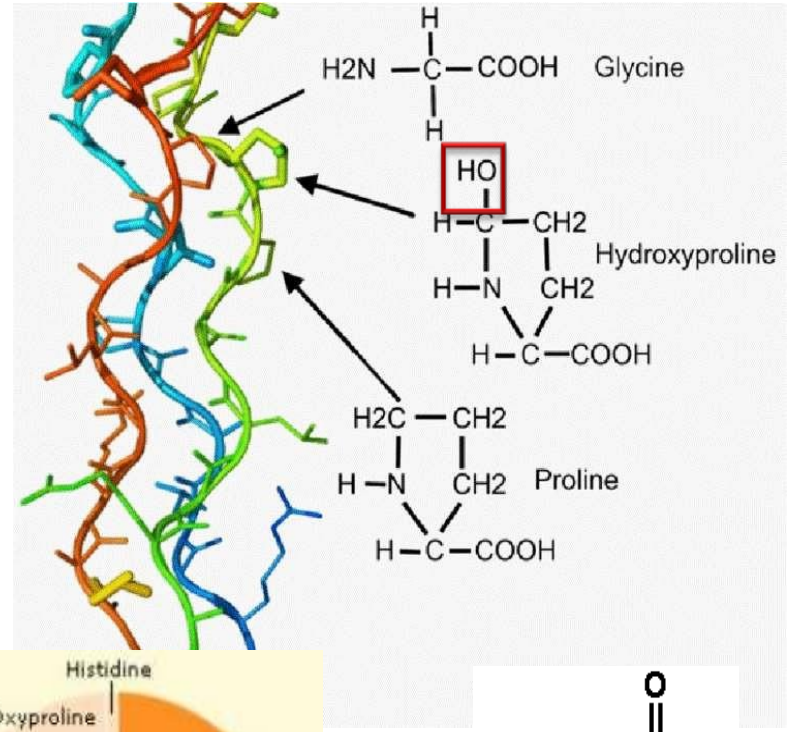
Every third residue is a glycine.

Recall that:

- ➤ Glycine is the smallest & simplest amino acid.
- ➤ Glycine has a hydrogen atom as its R group.
- ➤ Glycine is achiral.

Recall that:

- ➤ Proline is the only cyclic amino acid.
- ➤proline is a rigid molecule.
- ➤Proline within a polypeptide doesn't have a hydrogen bond donor



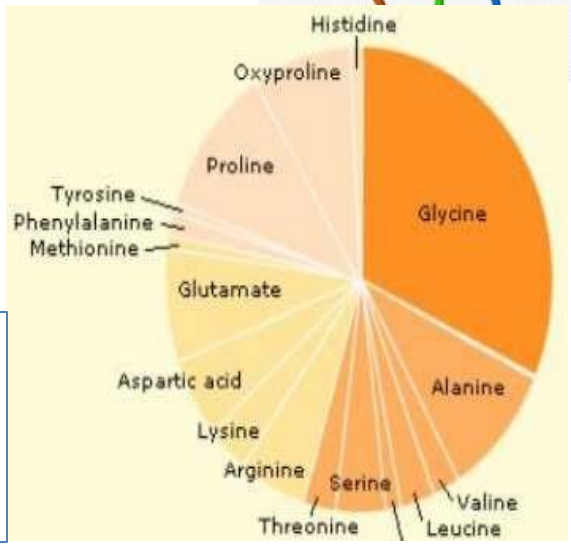
They unusually in contain hydroxyproline (9%) and hydroxylysine.

Because glycine constitutes 1/3 of the primary structure, we can say that every three amino acids within the primary structure of collagens, there is a glycine residue

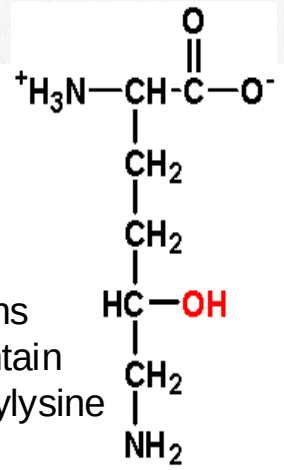
In simple words,we can say that the primary structure of the collagen molecule consists of a repeating unit of 3 amino acids:**Primary structure: Gly X-Y**

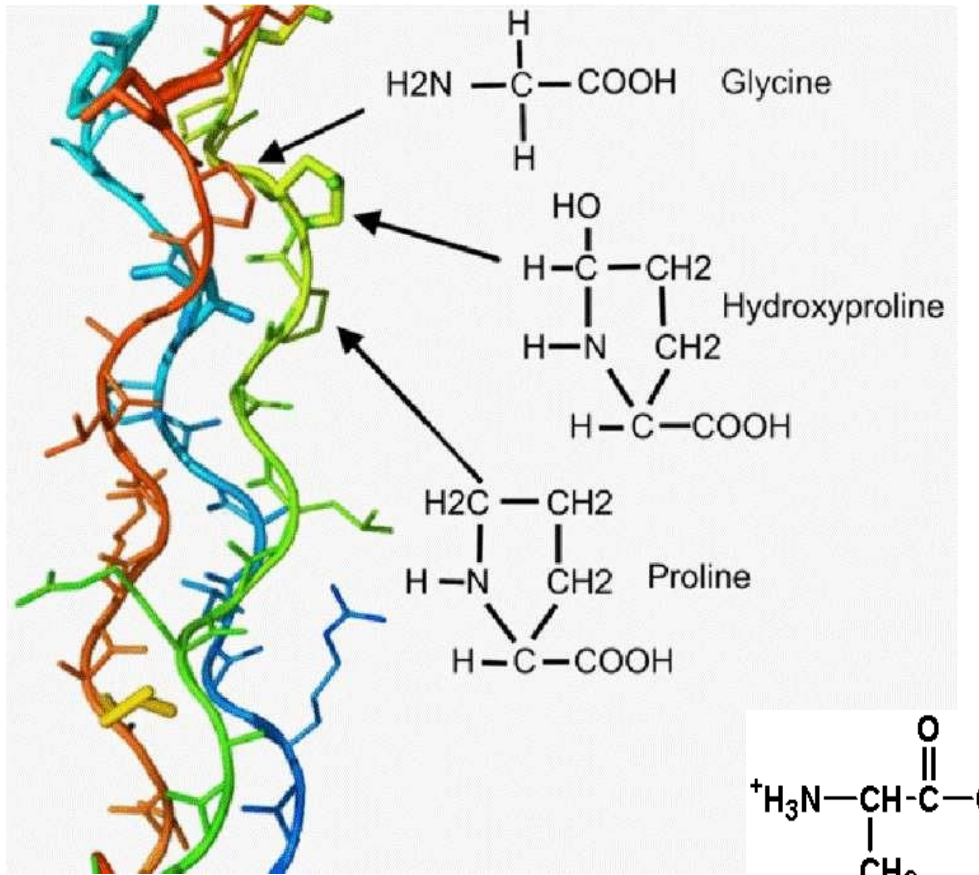
X is often proline or hydroxyproline**.**

About one-fourth or one-fifth of the primary structure of the collagen molecule are proline (13%) & hydroxyproline (9%) amino acid residues.

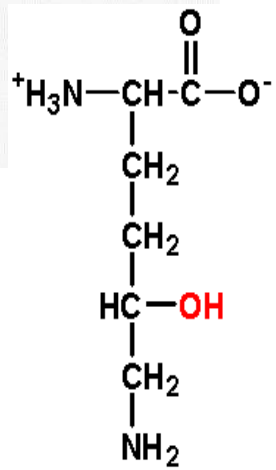


Collagens also contain .Hydroxylysine





Notice the large amounts hydrophobic amino acids, in which each one of them constitute approximately (25%) of the primary structure of collagen.



Hydroxylysine

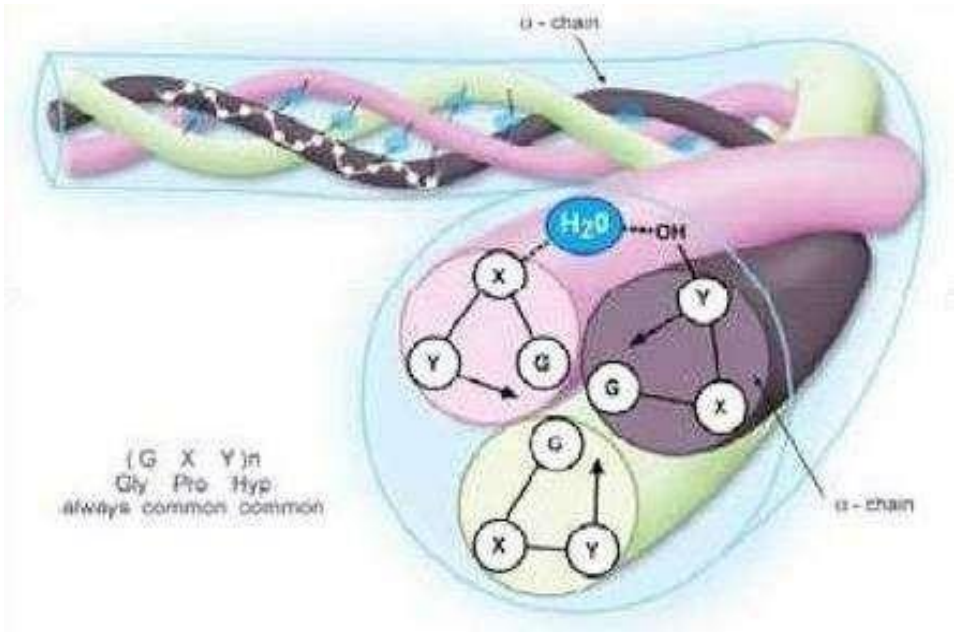
The hydroxyl group in hydroxy-amino acids is significant for functional purposes which we will discuss later on.

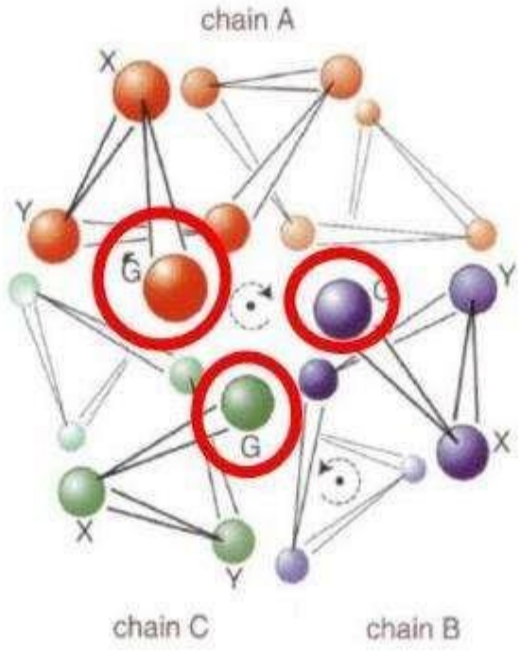
Functional purposes of amino acids

Why does glycine constitute 1/3 of the primary structure of collagen?
Because glycine is small and simple, it does not create repulsion

Notice in the organization of glycine residues within the tropocollagen how glycine is present internally (in the interior) in a very stacked form, while other groups are present externally relative to the tropocollagen molecule.
Because glycine lacks an R-group:

1) **It allows the triple helical alpha-chains to pack tightly & closely together**
2) **It provides flexibility as it can rotate freely giving the alpha-chains the ability to rotate around each other as glycine is very small.**

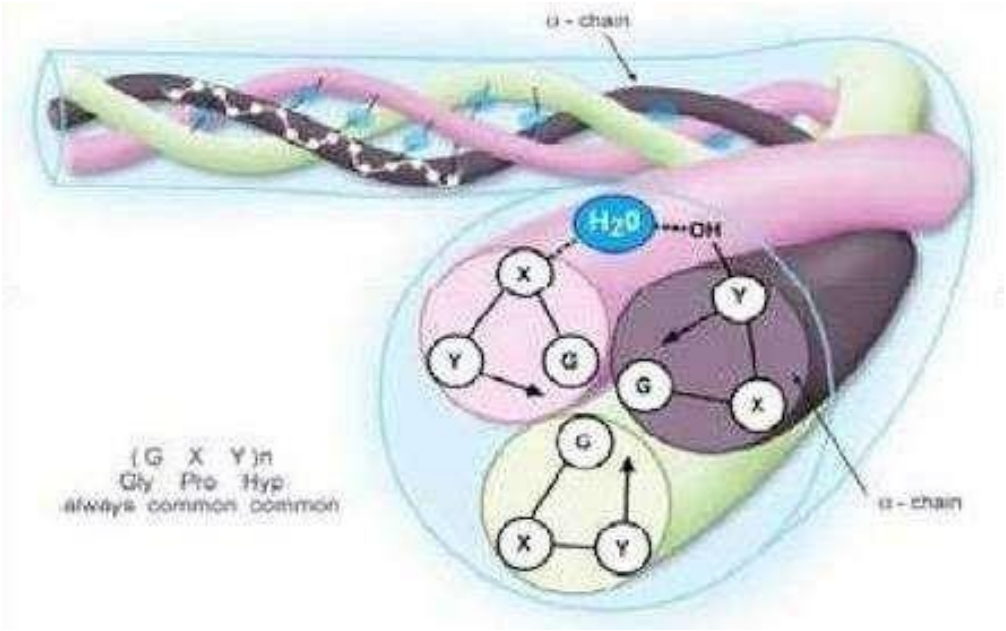


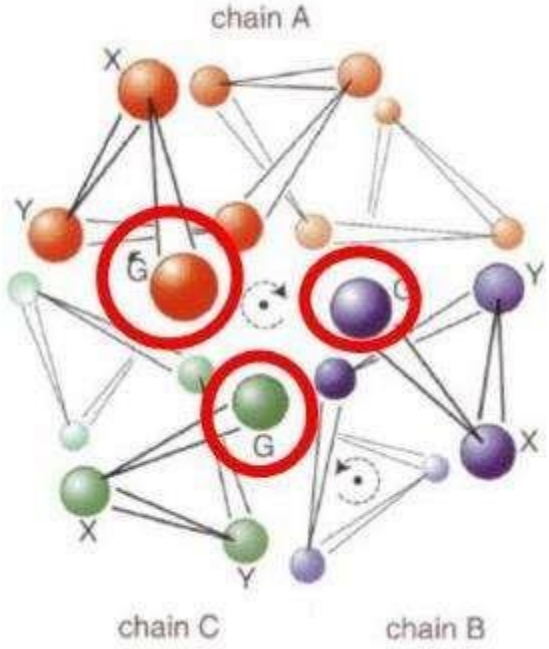


Functional purposes of amino acids

How about proline, why does it constitute about 1⁄4 of the primary structure of tropocollagen along with hydroxyproline?

-Proline provides rigidity to collagens.
- Proline creates the kinks and stabilizes the helical conformation in each alpha-chain. In other words, proline creates the helical structure





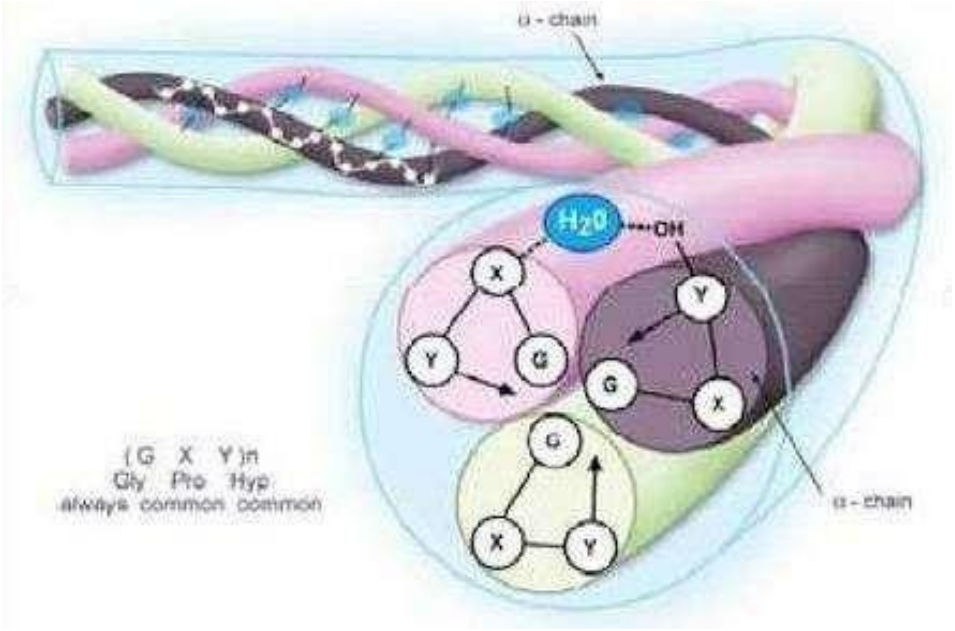
Functional purposes of amino acids

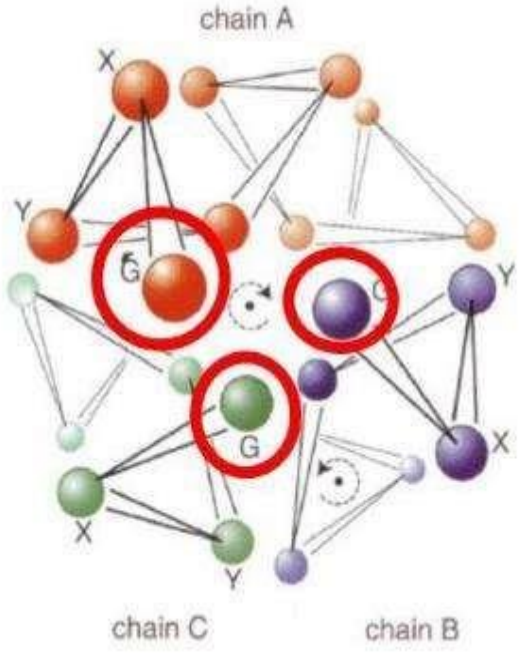
➤ But, we studied previously that proline breaks alpha-helices because it doesn't have a hydrogen bond donor, and also because of its rigidity. So, how does it differ in the case of collagen?
➤ Actually, in the case of collagen, proline creates a kink because of its rigidity. And when it is followed by a glycine amino acid, the molecule is allowed to rotate. And when the glycine is also followed by another proline molecule, another kink will be present. With another proline molecules, further kinks will be found.
➤ Also, because the proline is a rigid amino acid, it can make the collagen a rigid molecule. Furthermore, it stabilizes the conformation of the helical structure.
➤ The kinks formed by proline along with the ability to rotate provided by glycine, they both contribute to the helical conformation of alpha chains.
➤ So, this way proline assist in the formation of the helical structure of the collagen molecule (not alpha-helices!).

Functional purposes of amino acids

Glycine allows the three helical a chains to pack tightly together since it lacks an R group and provides flexibility because it can rotate freely.

Proline creates the *kinks*, stabilizes the helical conformation in each α chain, and provides rigidity to collagens.





Hydroxylation of proline and lysine

You do NOT have to memorize these reactions , but you should memorize the enzymes included

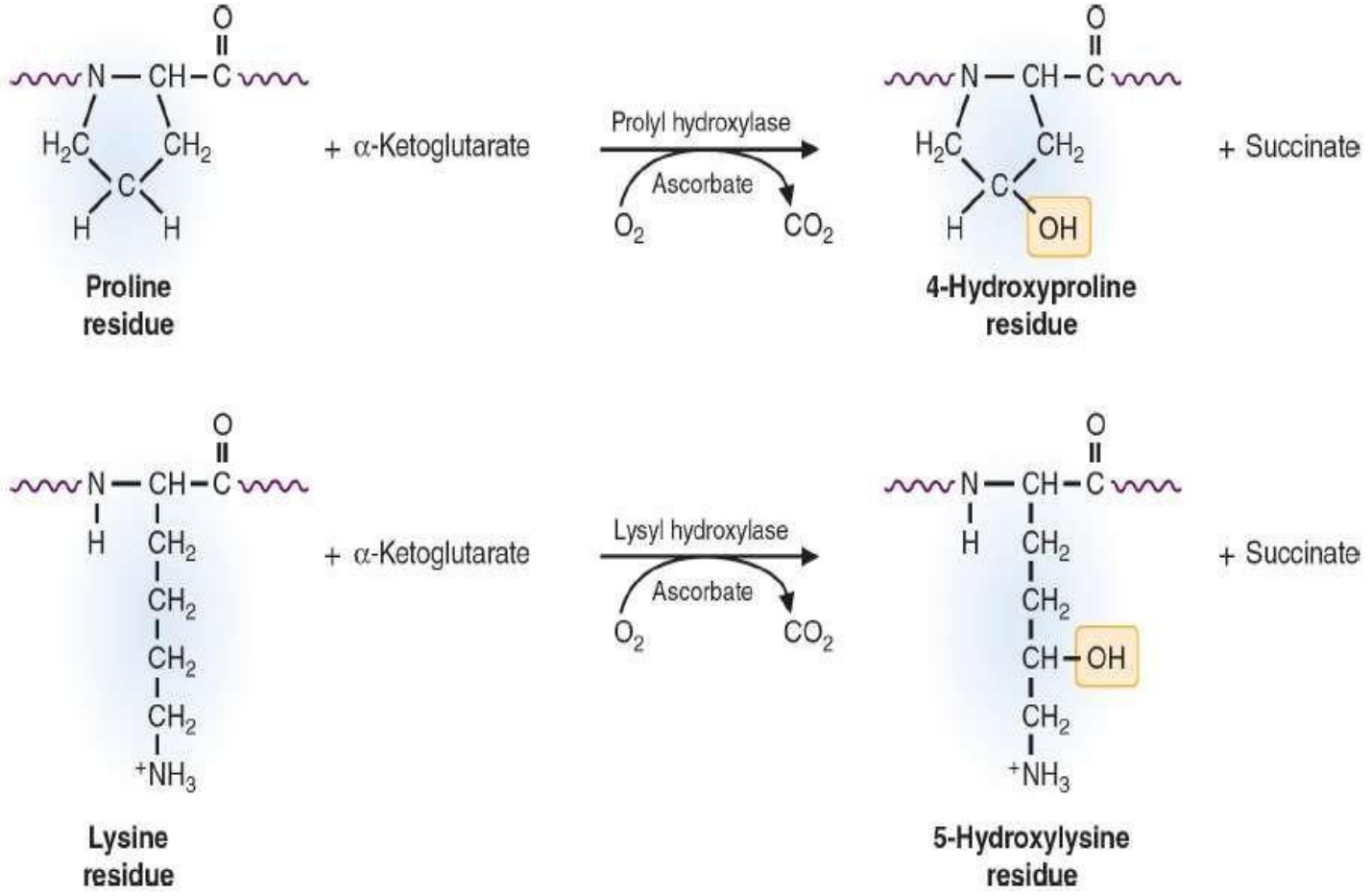
One of the important features of the collagen molecule, is that it contains hydroxylysine and hydroxyproline.

Hydroxylation here simply starts with a proline or lysine, and ends by the addition of a hydroxyl group to the reacted amino acid residue.
Hydroxylation of proline or lysine is a post-translational modification which takes place after the translation and the formation of the polypeptide

Notice that ascorbate (which is vitamin C) is needed for the hydroxylation reactions

We need hydroxylase enzymes for the reaction to occur:

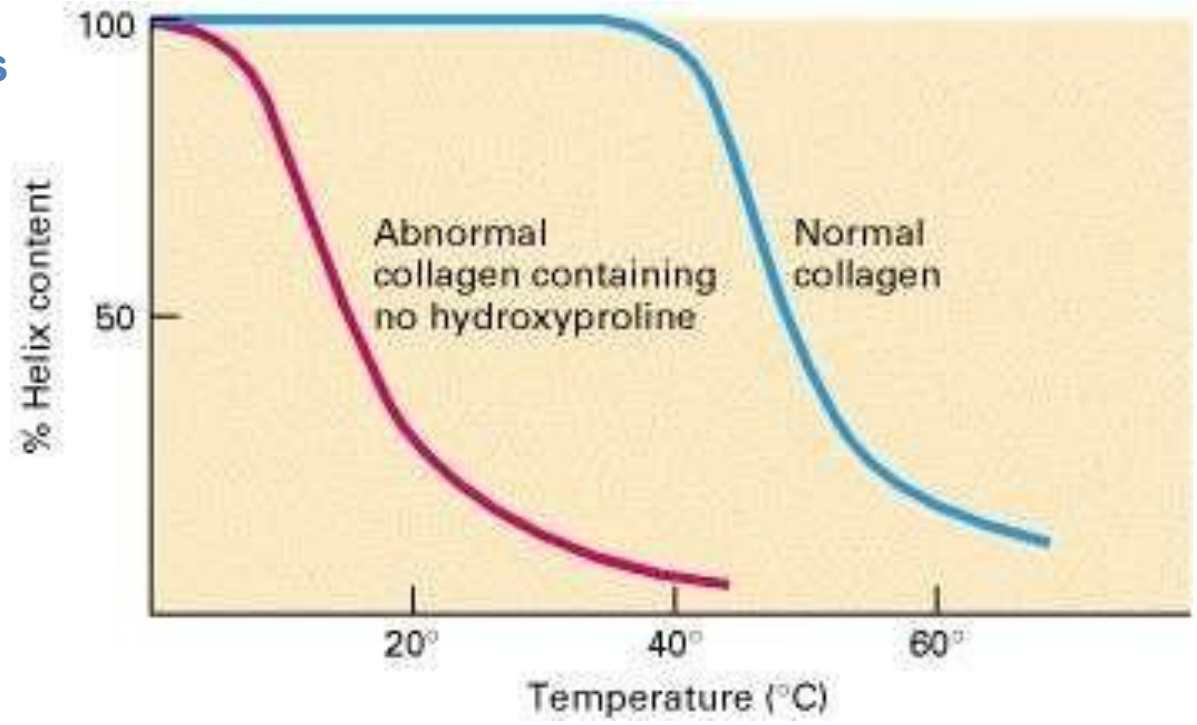
1. Prolyl hydroxylase for proline.Succinate
2. 2. Lysyl hydroxylase for lysine



Purpose of hydroxyproline

we are connecting the structure of the collagen with its function, we want the collagen to be highly packed, strong and rigid, so that proline gives the structure rigidity and glycine helps in packing as we said . Also, the presence of hydroxyl group assists in increasing the number of hydrogen bonds between molecules (amino acids residues)

- we can notice the importance of hydroxyproline when there is a deficiency in proline hydroxylation (prolyl hydroxylase is defected or there is a deficiency of vitamin C).In this case, what will happen to collagen? Collagen will be easily broken down(fragile) because tropocollagen and alpha chains are not packed together so they aren't strong enough



Normal collagen is stable even at 40°C.

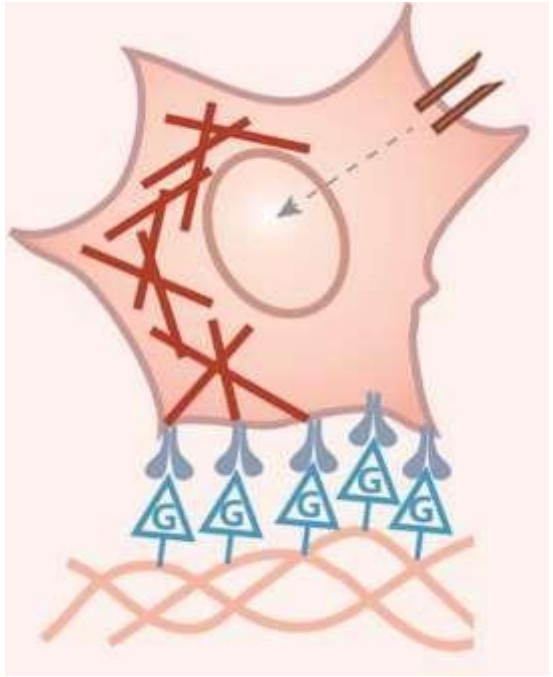
Without hydrogen bonds between hydroxyproline residues, the collagen helix is unstable and loses most of its helical content at temperatures above 20°C.

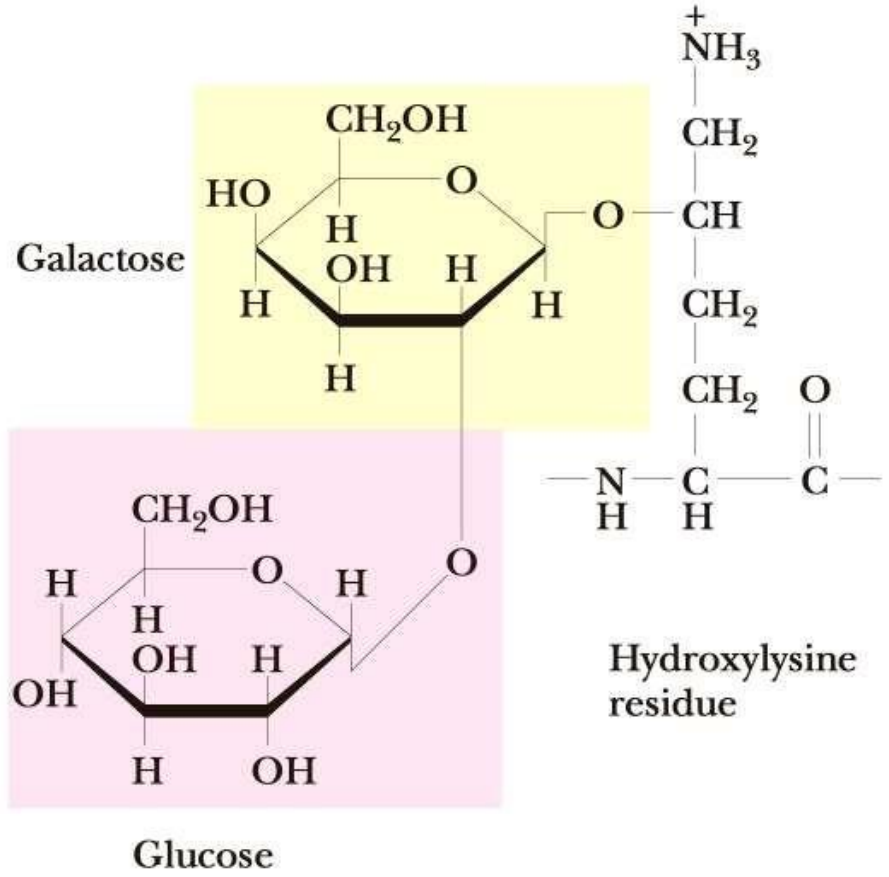
At low temperature, helix content or helical conformation of the collagen molecule will be compromised (abnormal)so as we see in the image it will dissociate even at very low temperature

Hydroxylysine

- Hydroxylysine serves as attachment sites of polysaccharides making collagen a glycoprotein.
- Sugars allows collagen to recognize and interact with cell surface receptors.

We can add sugar molecules to hydroxylysine (on the hydroxyl group specifically) that makes collagen glycosylated protein (glycoprotein)
Why sugar molecules are important? They allow collagen to recognize and interact with cell surface receptors which helps in signaling ....How? The cell will be alerted if any change occurs in the environment (collagen and matrix) so it (the cell) will adapt according to the change that occurs in the collagen molecule.





Oxidation of lysine

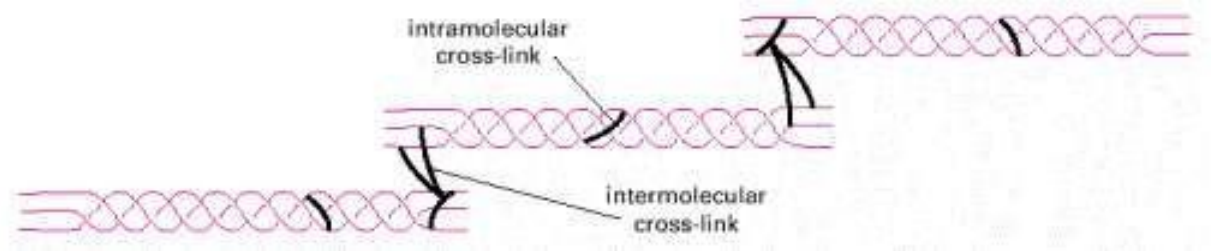
- Some of the lysine side chains are oxidized to aldehyde derivatives known as allysine.
- Allysine cross-links with another allysine, hydroxylysine, or lysine residues within the same or with another tropocollagen.
- These cross-links stabilize the side-by-side packing of collagen molecules and generate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

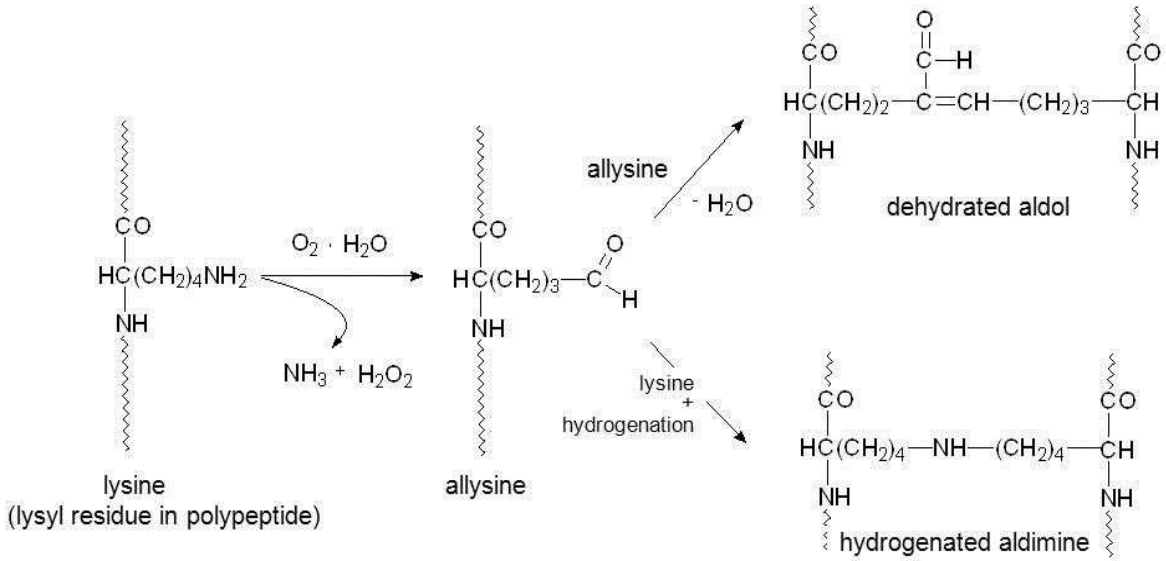
As we said before that there are covalent crosslinking between alpha chains and fibrils ,, from where we get that crosslinking ?
From oxidation of lysine

Lysine has an amino group that will be converted to an aldehyde group when it is oxidized, with that group the molecule now is called allysine (al:aldehyde)

Allysine will crosslink with another allysine to get dehydrated aldol (the linkage between aldehyde groups is covalent) or it can interact with the amino group of lysine to get hydrogenated aldimine, these crosslinking will take place within tropocollagen, between tropocollagens or between the fibrils.

These cross-links will increase the strength and rigidity of the collagen molecule, which stabilize the side-by-side packing of collagen molecules and generate a strong fibril.





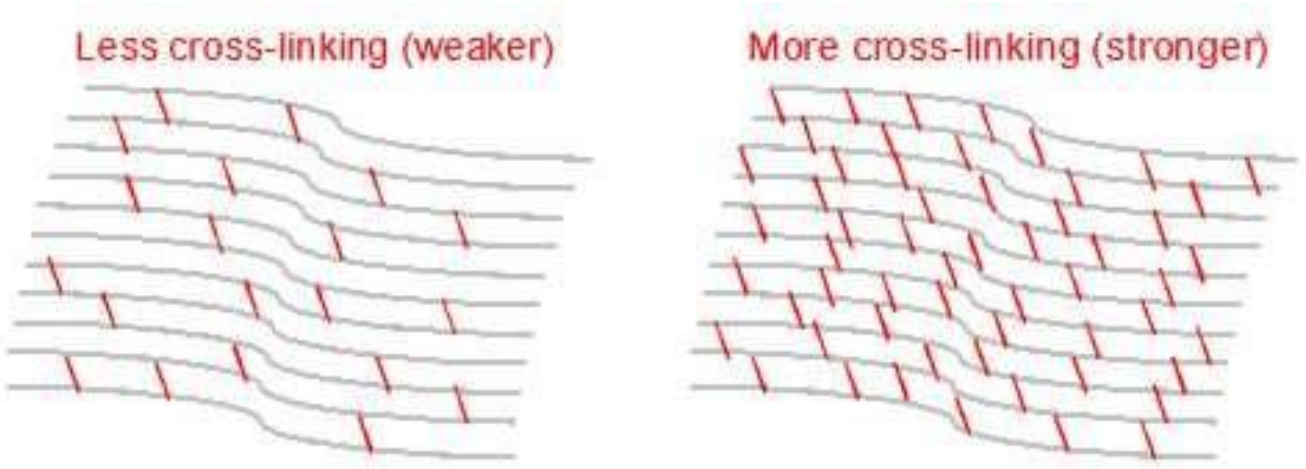
Deficient cross-linking

- If cross-linking is inhibited, the tensile strength of the fibrils is drastically reduced (below normal); collagenous tissues become fragile, and structures such as skin, tendons, and blood vessels (& bones) tend to tear (easy to be broken up).
- Deficiency of hydroxylation can cause diseases such as Ehlers-Danlos syndrome. This syndrome causes hyper-mobility to extend or stretch their arms or legs. Also, they can be taller than normal. They exceed at gymnastics, taekwondo, and swimming.

More on cross-linking

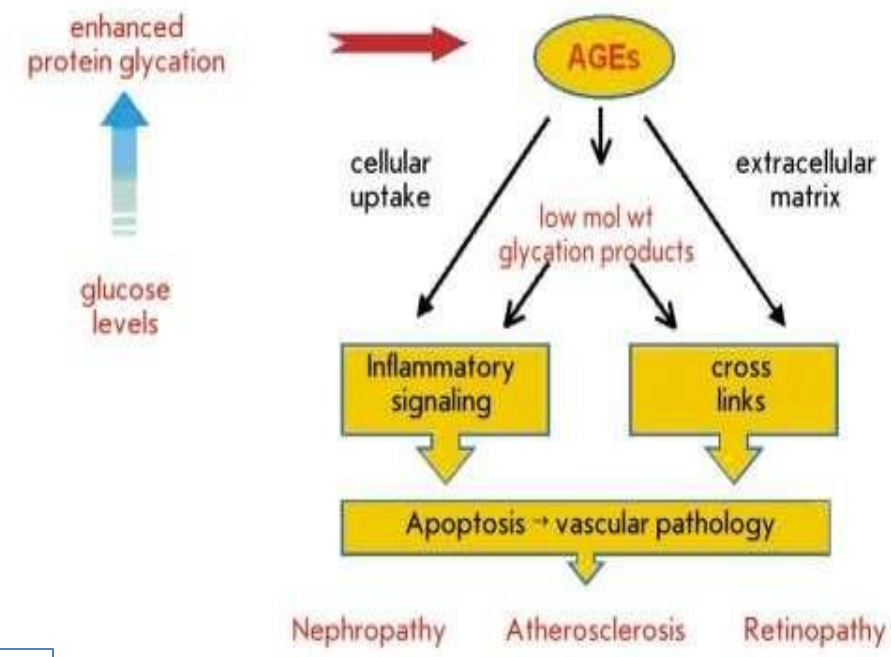
- The amount of cross-linking in tissue increases with age.

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



Advanced glycation end products

- Proteins (e.g., collagen 'remember collagen is the most abundant protein in the body!' and hemoglobin(we will talk about it next year)) can be nonenzymatically glycated producing glycosylated proteins that are difficult to turn over.
- Glycation is proportionate to glucose level.
  - Hyperglycemia increases the levels of glycated proteins.



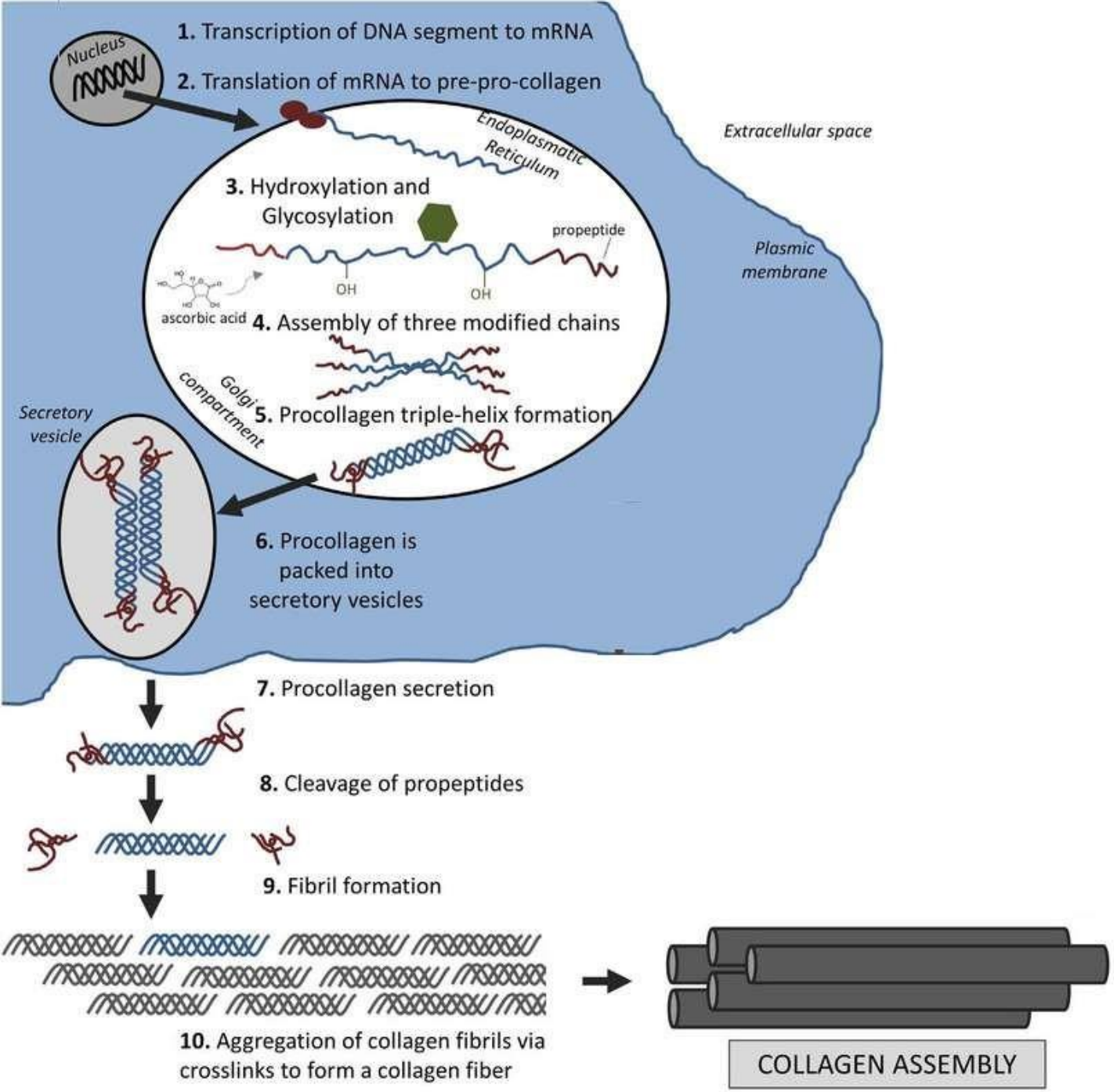
As the concentration of sugars in blood or tissues increases, as the protein glycation occurs,
which is the addition of glucose to protein (this addition is non-enzymatic)

Uncontrolled diabetics suffer from cardiomyopathy

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

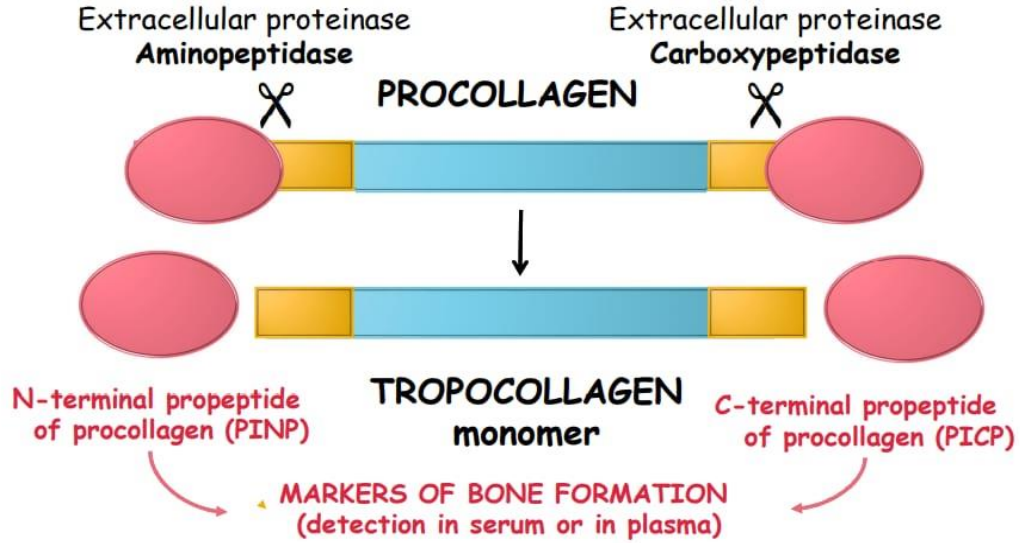
When the cross links and aggregation increase between AGEs that will lead to an increase in the oxidative stress, also inflammatory cytokines will be released, that will cause a damage to tissues (such as: cardiac muscle) -{Nephropathy: damage in the kidneys/Atherosclerosis: it will lead to heart attack/Retinopathy: damage in the retina (eye)}

So if someone has uncontrolled diabetes+increase in glycation of proteins including collagen+increased AGEs = cardiomyopathy.



1. Transcription of DNA segments to mRNA collagen G.
2. Translation of mRNA to pre-pro-collagen, which occurs on the surface of ER, then collagen enters into ER
3. In ER hydroxylation of proline and lysine and Glycosylation of hydroxylysine.
4. Assembly of three modified chains inside Golgi compartment WITHOUT aggregation of tropocollagen because the propeptides (the ends of collagen strands) prevent aggregation.
5. Procollagen triple-helix formation
6. Procollagen is packed into secretory vesicles.
7. Procollagen(immature collagen) secretion
8. Cleavage of propeptides termini (left and right) of the procollagen forming the mature collagen molecule which is tropocollagen.
9. Fibril formation (cross-linking)

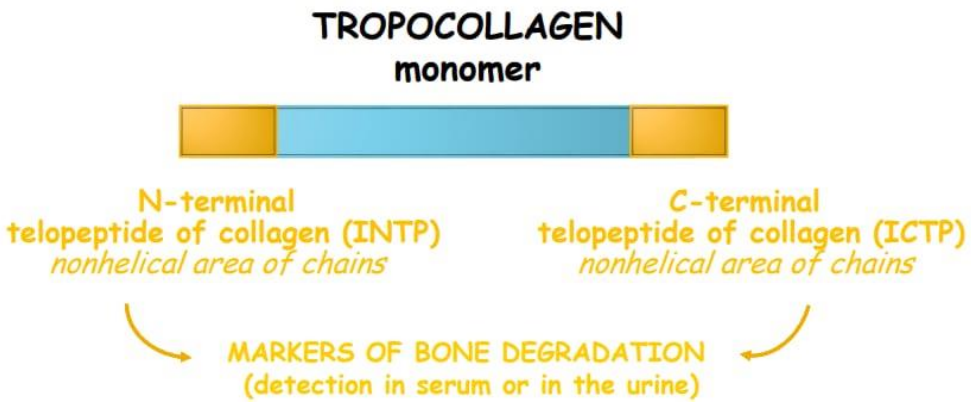
Synthesis of collagen



Extra images from doctor.
Note the difference between Telopeptide and Propeptide.

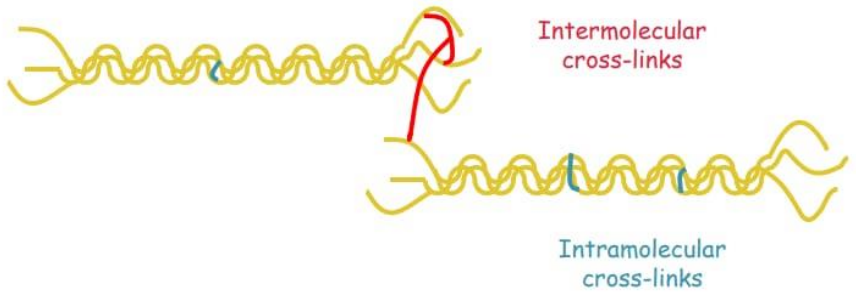
Tropocollagen

- Greek *tropé* - turn, induce a turn
- monomer of the collagen – mature molecule of collagen
- Mr = 300 000



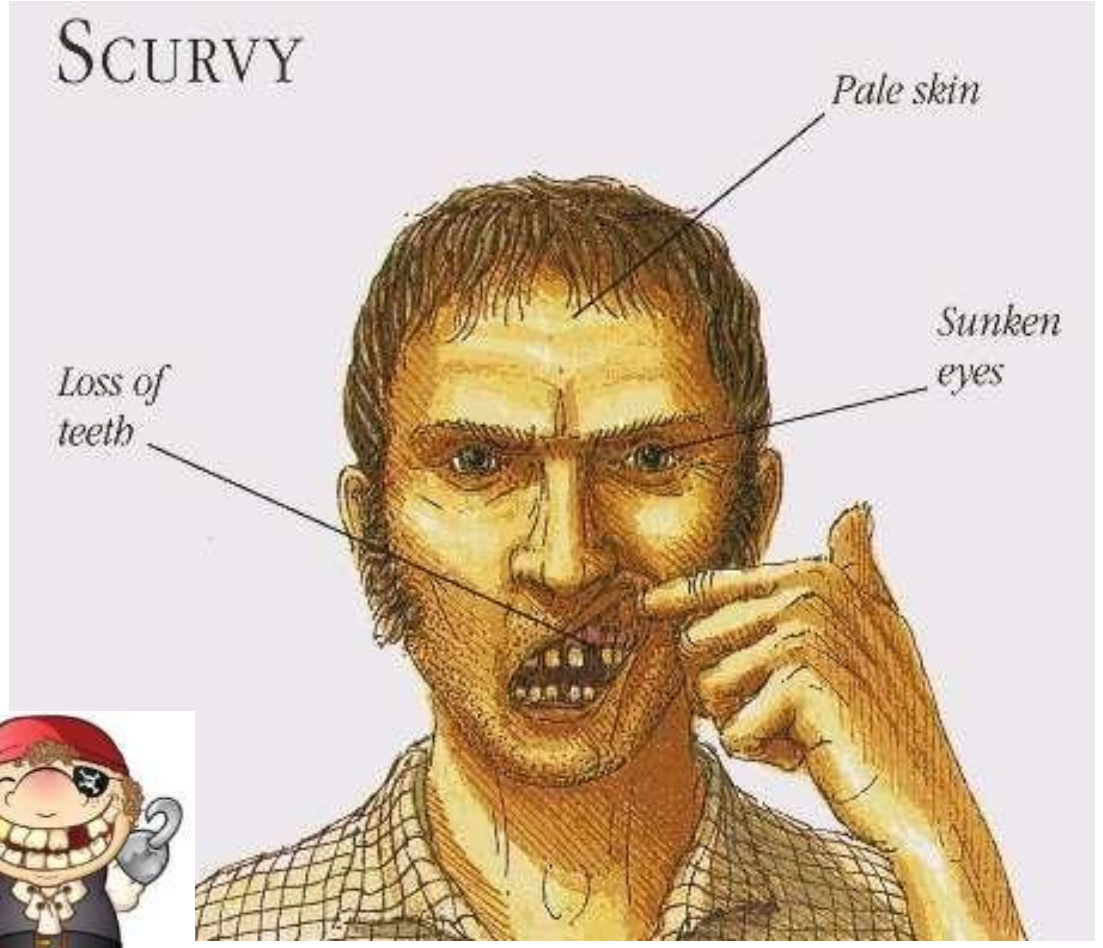
Formation of cross-links

Collagen fibers are stabilized by formation of the covalent cross-links, which can be formed either within the tropocollagen molecule between the three chains – intramolecular cross-links and between the tropocollagen molecules – intermolecular cross-links.



Scurvy

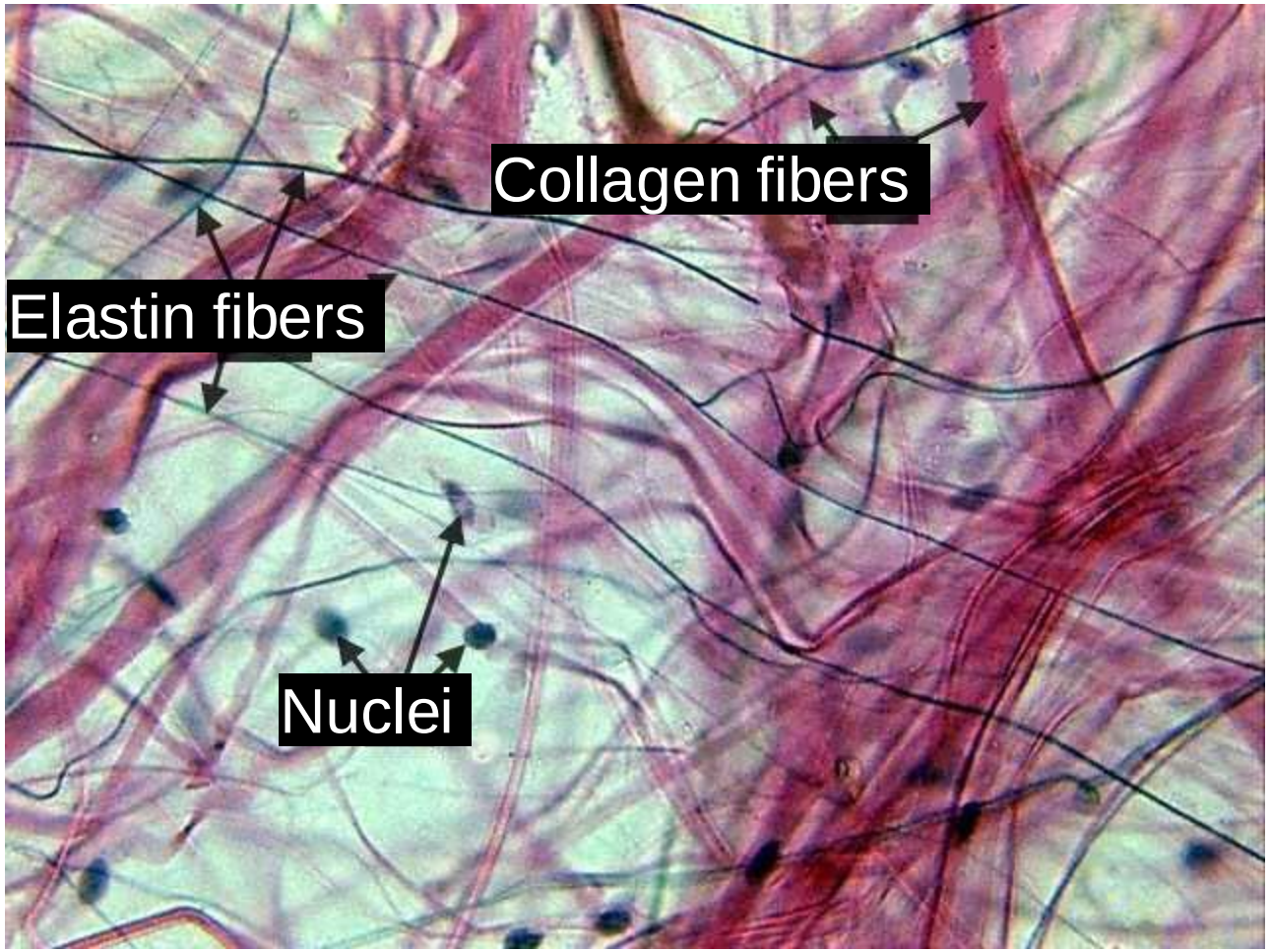
- Deficiency of ascorbic acid (vitamin C) prevents proline hydroxylation forming defective pro-α chains that fail to form a stable triple helix. **So collagen will be fragile.**
- This causes scurvy.
- Blood vessels become extremely fragile, and teeth become loose in their sockets. **All tissues that depend on collagen molecule will become fragile including bone, skin, gum, blood vessels, and so on.**



Scurvy was common among sailors, because they didn't have a source of vitamin C.

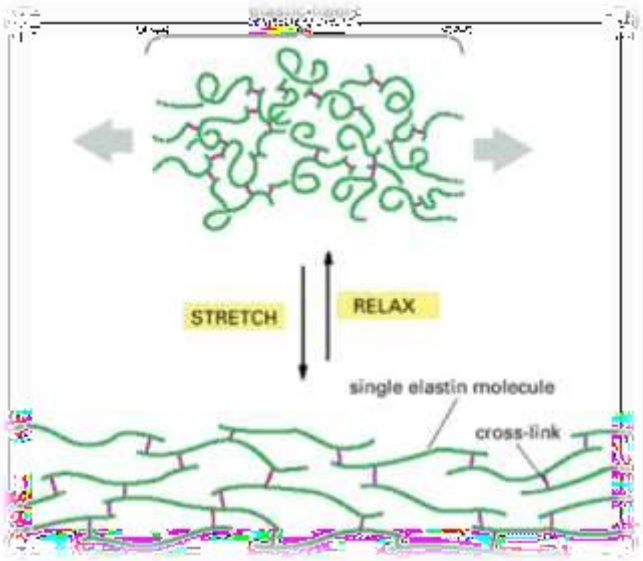
Elastin

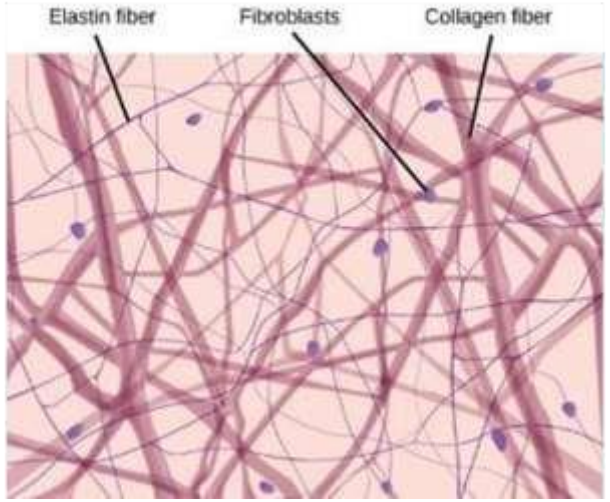
Second type of fibrous proteins
Elastin is thin & found in ECM and mixed with collagen fibers which are thick.
The major protein in Elastic Fibers.



Resilience vs. flexibility

- Many tissues, such as skin, blood vessels, and lungs, need to be both strong and elastic in order to function.
- 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.



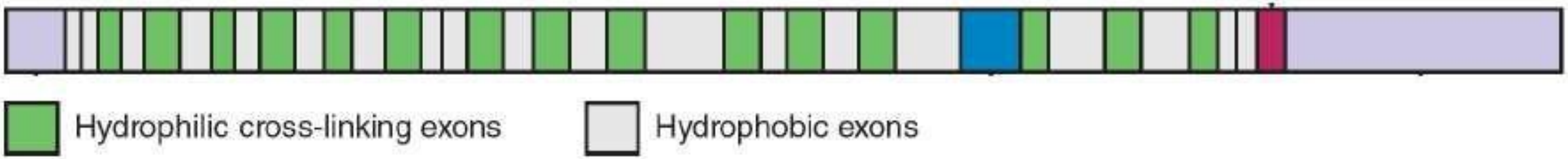


Resilience: the ability of a substance or object to spring back into shape, the structure doesn't change because of the presence of elastic fibers. Flexibility: the quality of bending, stretching easily without breaking.

The presence of collagen fibers embedded and interwoven with the elastic fibers. Elastic fibers will provide flexibility, but collagen fibers prevent the tearing of the tissue.

The primary structure of elastin

- Elastin is a highly cross-linked, hence insoluble because of it hydrophobic domains, protein with an undefined structure.
- Its precursor, tropoelastin, is a soluble 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).



Elastin is, thus, a highly hydrophobic molecule.

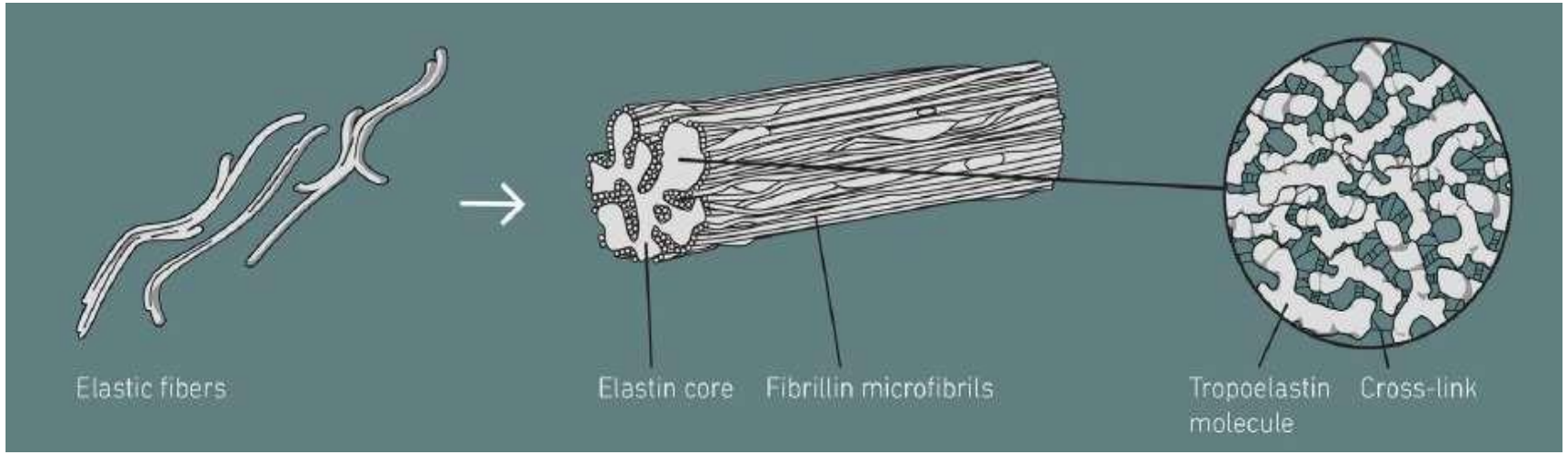
Elastin

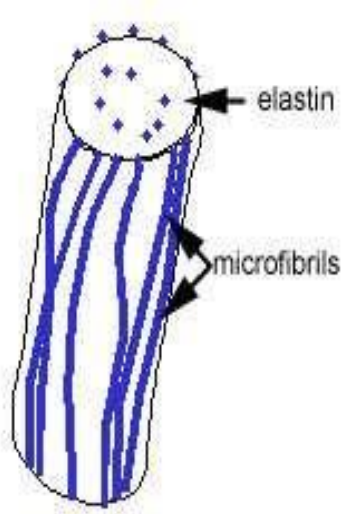
*Doesn't form triple helix.
*hydrogen bonding between different elastic fibers.

- Elastin contains some hydroxyproline, but no hydroxylysine.

  It is not glycosylated. It is not a glycoprotein.

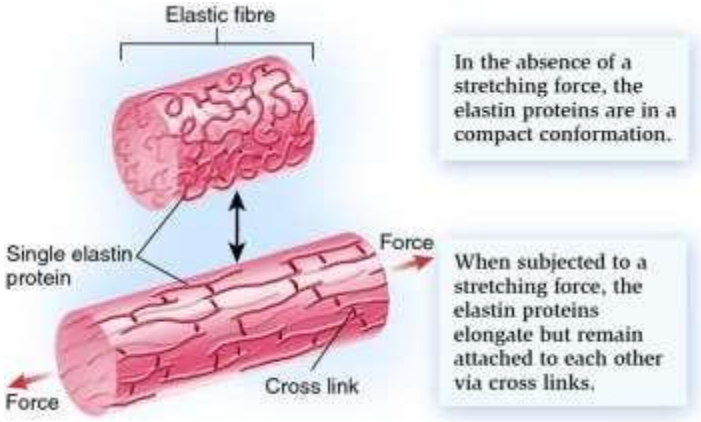
- Upon secretion from the cell, the tropoelastin is aligned with microfibrils, and lysyl oxidase (the same enzyme that oxidized the amino group of Lysine to an aldehyde group) to initiates cross-linking between lysines to one another and forming elastic fibers.

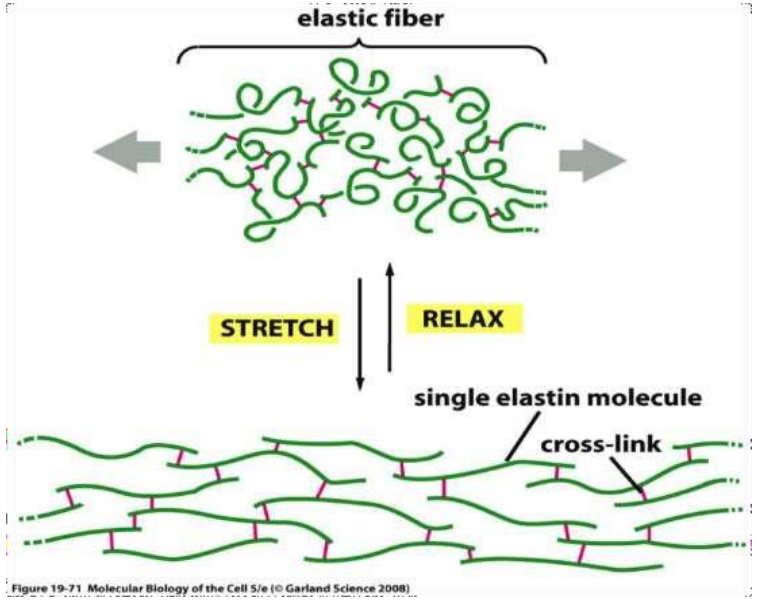




How it functions

- 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 this stretched structure to reform.



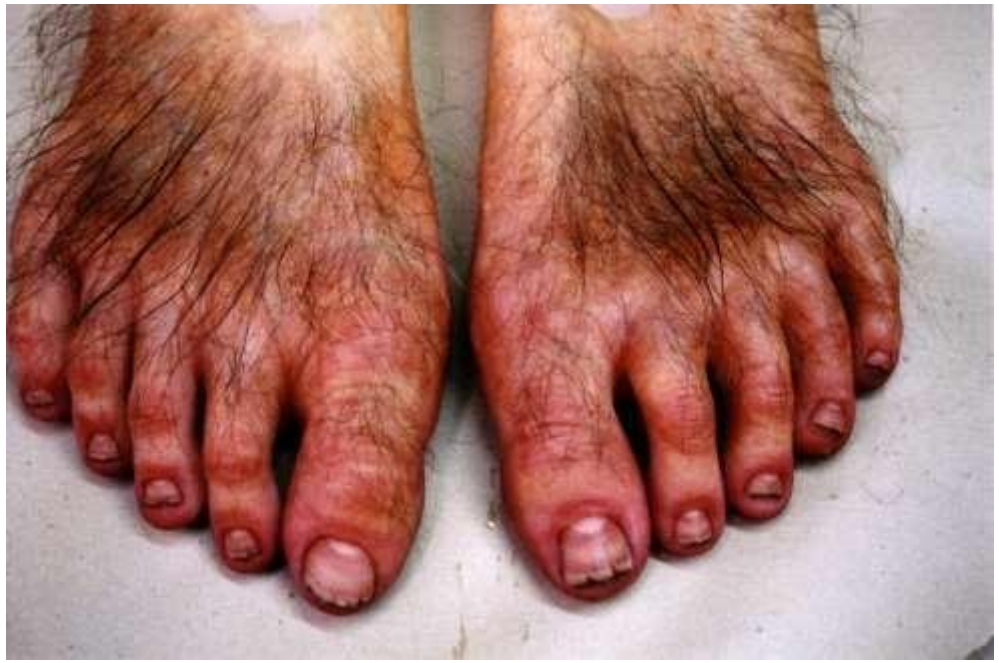


Function of elastin is to provide resilience and flexibility and the reason is that the molecule is hydrophobic and that is the key on how its function! Basically when we stretch the elastic fibres, the stretching seems to be limited due to the cross linking, but what happens after that; after the pressure is released, they cluster together because the environment they're in is hydrophilic so they come back together forming the original structure of the tissue. To sum up, the hydrophobic effect is the primary force that allows the stretchy structure to reform.

Last fibrous protein in this lecture!

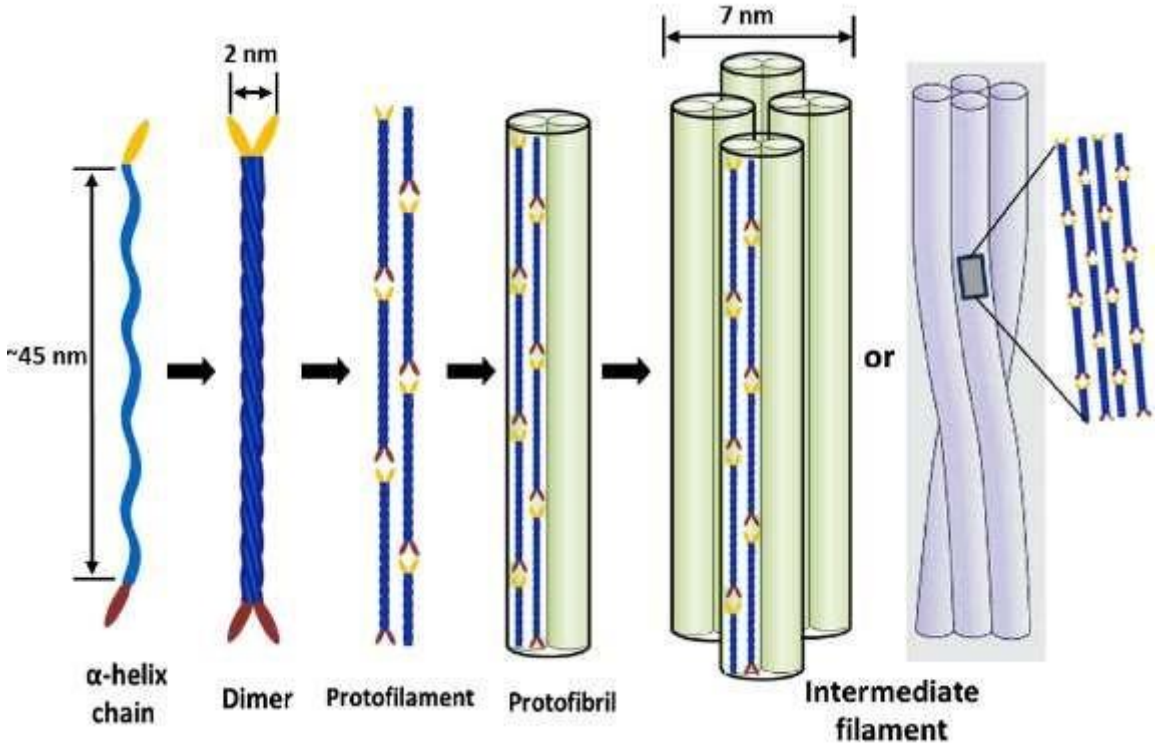
α-Keratins

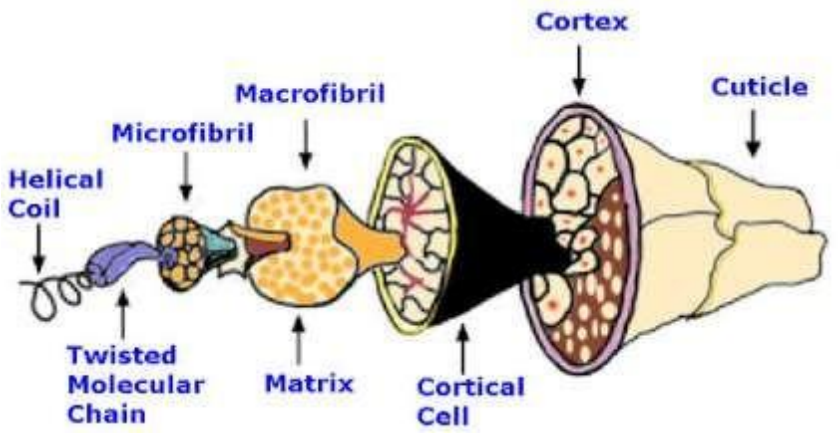
Similar to collagen, it's a family of proteins with different types. Like alpha keratin,which is present in skin, nails and hair.



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 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.





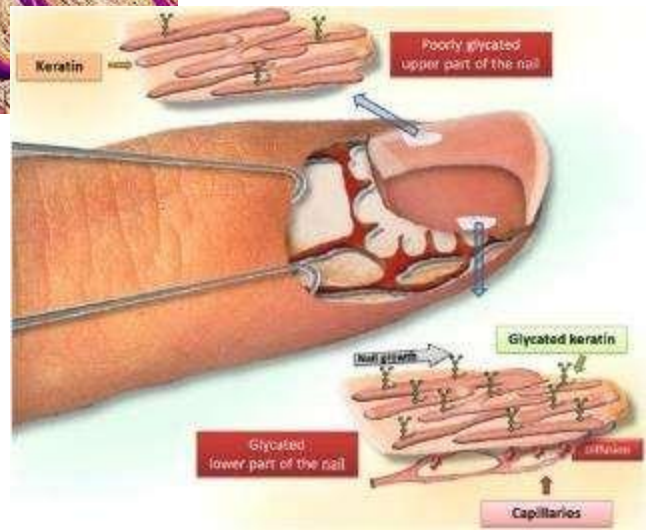
An alpha chain forms a dimer with another alpha chain resulting in a helical structure to form, this structure has ends that are like telomeres in chromosomes, called telopeptides (dimer), 2 of these telopeptides come together to form a tetramer. The lining up of different tetramers, head to tails, makes up a protofilament. What's important about the ends is that they are rich in cysteine which crosslink. While in collagen and elastin cross linking takes place between the oxidized lysine (between the allysine that has an aldehyde group). However, here in keratin because it is rich in cysteine that crosslinks and forms disulfied bonds between the cysteine residues. Two proto filament get together to form a protofibril,and 4 of these form an intermediate filament, which 8 of them come together to form a microfibril , hundreds of microfibrils are cemented into a macrofibril and finally many macrofibrils form a single hair

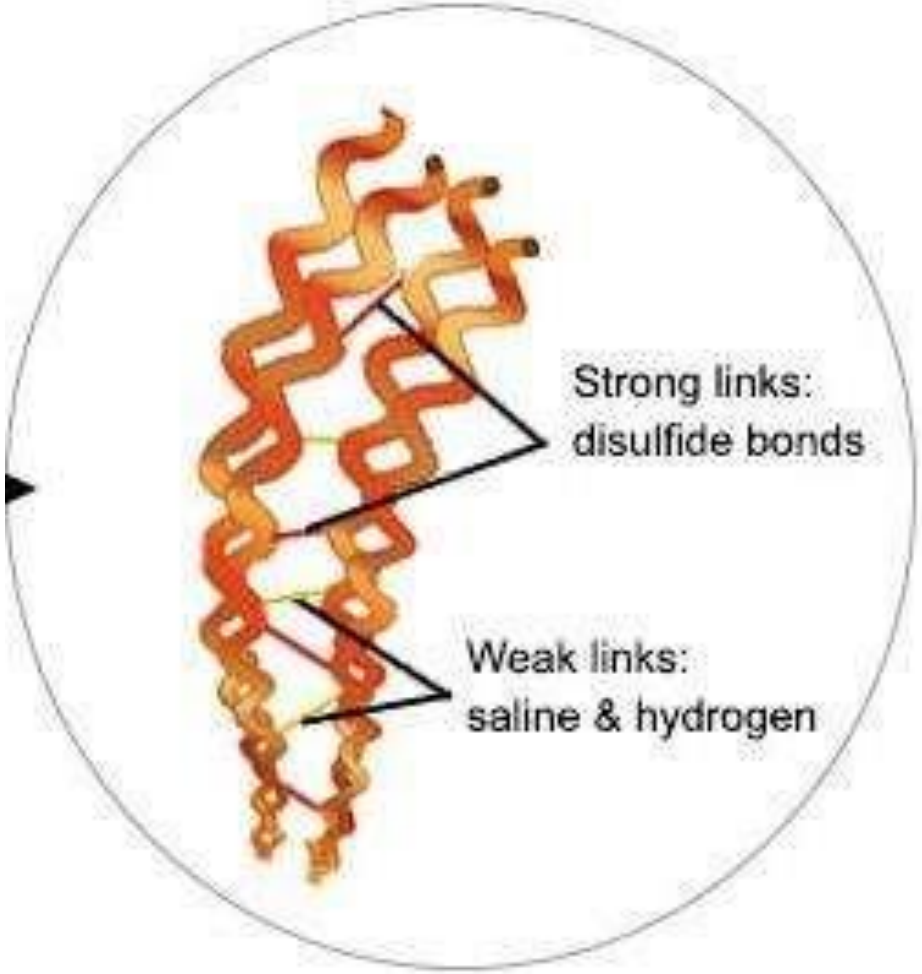
The importance of cys residues lies within the fact that as the number of them increases and the more we have cross linking between these residues, the more the rigid the structure is. Fingernail(that obviously have cysteine), for instance, are highly cross linked, so they're tough. Another example is curly or wavy hair! These textured types tend to contain a lot of cysteine residues in comparison to straight hair.

Keratin in nails

This slide shows how disulfide cross linking increases the rigidity of the structure.

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



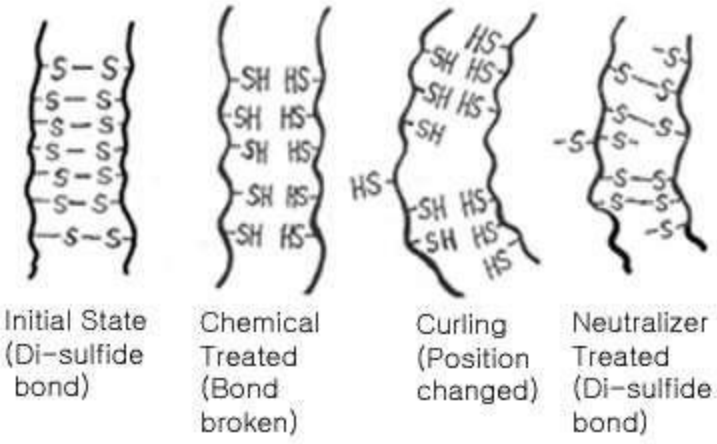


Looking beautiful?

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.

How does hair change shape? It’s all biochemistry.
There are people with wavy hair then suddenly it becomes very smooth.
There are 2 types of waves; 1)temporary waves & 2)permanent waves,

The temporary waves is dependent on non covalent interactions in the hair itself. What happens is a person wakes up and finds their hair all frizzy and stuff, they go ahead and wet it, then suddenly its straight! However, as soon as it dries it comes back to normal. Why? Its due to the hydrogen bonds that are between the keratins in the hair itself, so when we wet our hair these hydrogen bonds break and the hair becomes straight. But as soon as its dries, these hydrogen bonds reform between the keratin molecules. Thus, lining up of the alpha helices that are in the keratin molecule.

Permanent change (perms) is the reformation of the shape of the hair and lasts for a few months, it's permanent! It lasts a few months until growth of the new hair. Example, hair at the start was straight -> made perm and became wavy -> few months later after the new hair grew it became straight again. This happens by reforming the disulfide bonds. So what happens is that they add a reducing substance that is usually a certain chemical to reduce the disulfide cross links, so reduction occurs)converting ss to sh(or apply an oxidizing substance on the hair that reforms the disulfide crosslinks so oxidation occurs(converting the sh to ss). Because we wrapped the hair at a certain position, reformation of the covalent bonds occurred, so that is why it's called a perm, because the covalent bonds are fixed, in other words, it's permanent. But in the case of permanently straightening it, they apply a reducing substance to break the disulfide bonds, converting the ss bonds into sh ones.
In case of temporary wave, one could wet their hair -> wrap it -> dry it -> hair becomes wavy. However, after going through a whole day in which they sweat and move -> the wavy hair will not stay wavy, but it will return back to it's original form, because of reformation or breaking of the hydrogen bonds and reformation of the new hydrogen bonds and so on.

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

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V1 → V2	Slide 12 Slide 26	Hydrogen bond acceptor	Hydrogen bond donor Addition of 3 images
V2 → V3			
V3 → V4			

Additional Resources:

1. Marks basic medical biochemistry 5th edition pages 276-279

■https://youtu.be/H3oAFvYsuq8?si=6p6ap-P8xqIDDusp

رسالة من الفريق العلمي:

النّفسُ تبكي على الدّنيا وقدْ عَلِمَتْ
أنّ السّلامةَ فيها ترْكُ ما فيها
لا دارَ للمرءِ بعدَ الموتِ يَسكُنُها
إلّا الّتي كان قبلَ المَوتِ بانيها
أموالُنا لِذَوي الميراثِ نَجمَعُها
وَدُورُنا لِخَرابِ الدّهرِ نبنيها
كم من مدائنٍ في الآفاقِ قد بُنيَت
أمسَت خرابًا ودانَ الموتُ دانيها
لِكلّ نَفسٍ وإن كانت على وَجَلٍ
منَ المَنيّةِ آمالٌ تقوّيها
فالمرءُ يَبسُطُها والدّهرُ يقبضُها
والنّفسُ تنشُرُها والمَوتُ يَطويها

الإمام عليّ بنُ أبي طالبٍ
رضي اللهُ عنهُ وأرضاه