بسم الله الرحمن الرحيم

BioChemistry | FINAL 3

Proteins pt.3 & Fibrous proteins

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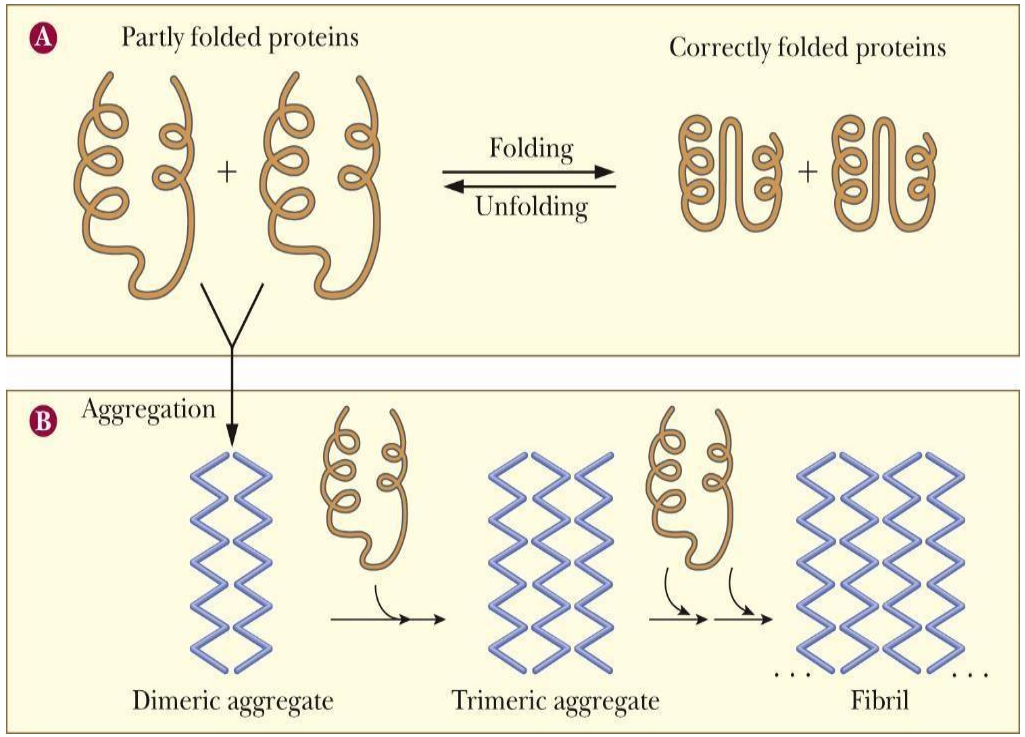
THE PROBLEM OF MISFOLDING

- When proteins do not fold correctly, their internal hydrophobic regions become exposed and interact with other hydrophobic regions on other molecules, and form aggregates.



If the thing that has undergone misfolding is sth new to the body & I cannot recognize it, then

What is the outcome ?

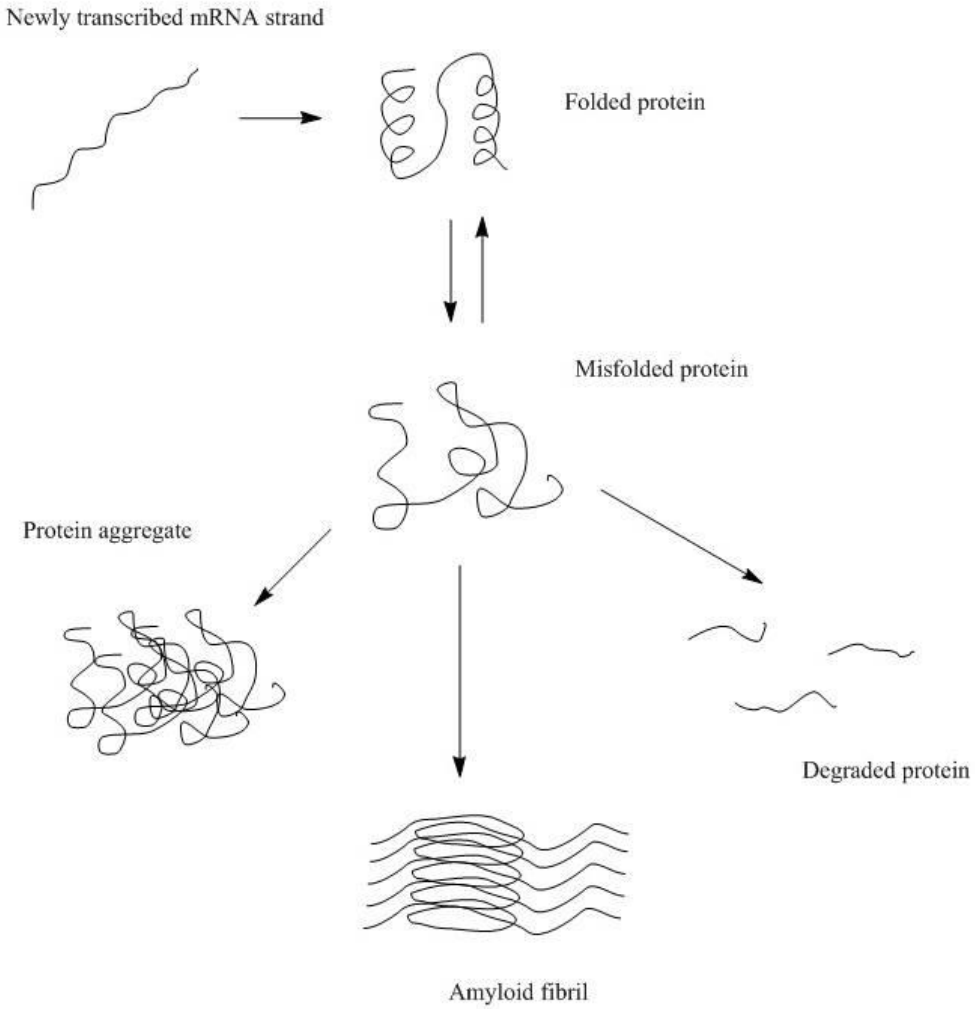
It will **accumulate;** it won't be degraded! There is no pathway for degradation to get it back to amino acids so I can benefit from it..

It will accumulate because the hydrophobic (non-polar) regions كانوا مخبّيين جوا صاروا –> Exposed; which is unstable, so non-polar is gonna attach with other non-polar regions فبصير عندي –> aggregates.. أهلًا وسهلًا مش زعلانين

But Aggregates will also accumulate because I cannot deal with them .. ☹

OUTCOME OF PROTEIN MISFOLDING

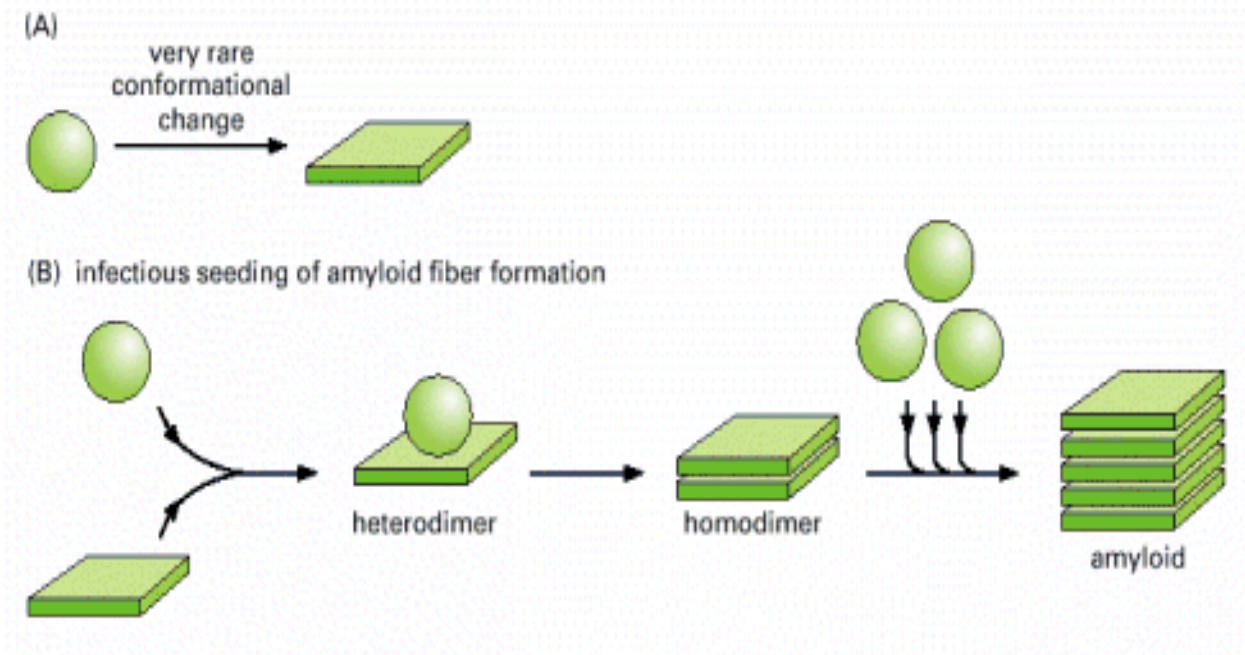
- Partly folded or misfolded polypeptides or fragments may sometimes associate with similar chains to form aggregates.
- Aggregates vary in size from soluble dimers and trimers up to insoluble fibrillar structures (amyloid).
- Both soluble and insoluble aggregates can be **toxic** to cells.



PRION DISEASE :

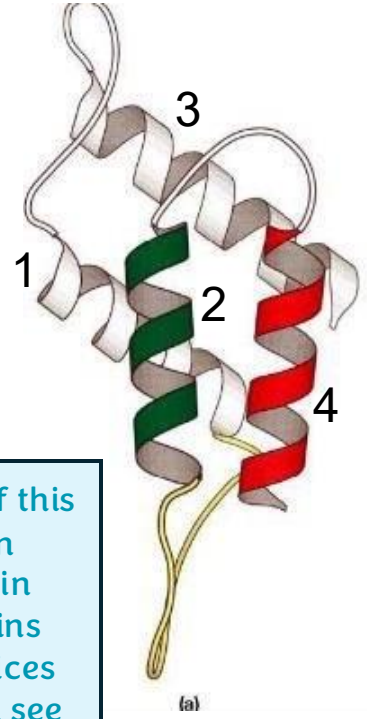
A disease that affects a protein called **prion.** Misfolding happens due to a problem (common through all diseases) that results in misfolding of the protein; which is replacement of **Methionine**^{129} OR some changes may occur to it.

- Striking examples of protein folding-related diseases are prion diseases, such as :
- Creutzfeldt-Jacob disease
- (in humans), and mad cow disease
- (in cows), and scrapie (in sheep)
- Today it is recognized that prion diseases are protein conformation diseases
- Pathological conditions can result if a brain protein known to as prion protein (PrP) is misfolded into an incorrect form called PrPsc (Met^{129})
- PrP_C has a lot of α-helical conformation, but PrPsc has more β strands forming aggregates



PRION DISEASE:

Regardless of the cause, it can be an infectious disease, genetic disease
Apparently in all of them (all prion diseases), it has been noticed that this specific residue (Met #129 in the protein sequence) undergoes mutation to another amino acid (missense mutation)
Or it may undergo modification (adding/removing a chemical group)

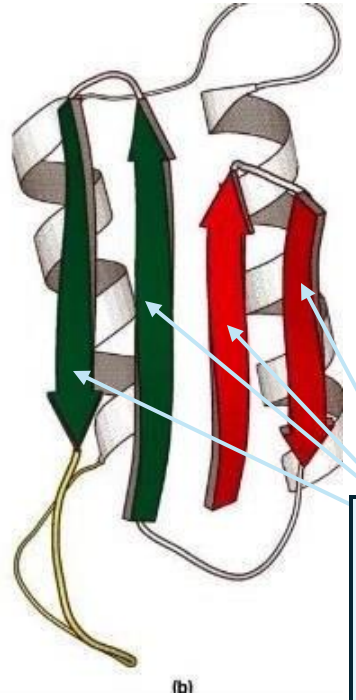


Shape of this prion protein contains 4 α helices as u can see over here

Modifications happen on **Met 129**

So u can tell it's an essential amino acid in the folding of prion

To become like this: **(2α helices & 4β strands)**



These strands will attach to each other forming aggregates

ALZHEIMER'S DISEASE

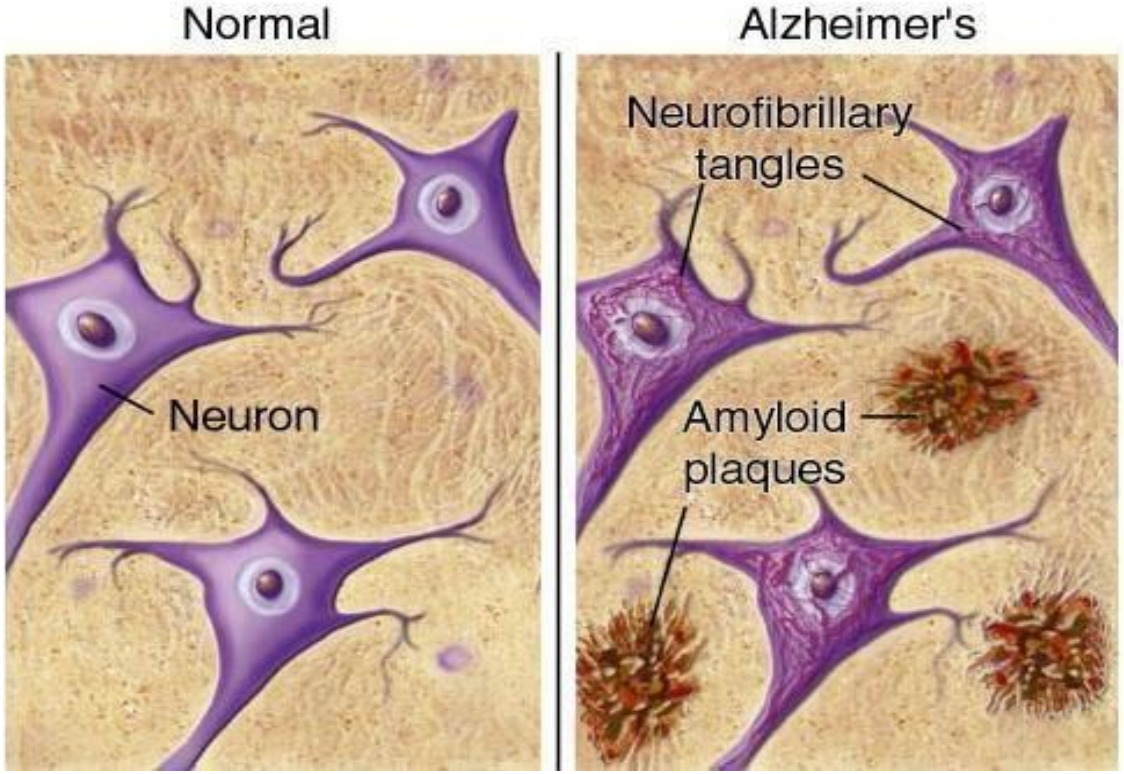
- Not transmissible between individuals
- Extracellular plaques of protein aggregates of a protein called tau and another known as amyloid peptides (Aβ) damage neurons.

Tau tangles

–> Alzheimer's affect the function of neurons accumulating what we call **Aβ** peptide, a sequence of amino acids (~40 amino acids in length), will accumulate:

1. **inside** cells
2. **outside** cells

Amyloid plaques



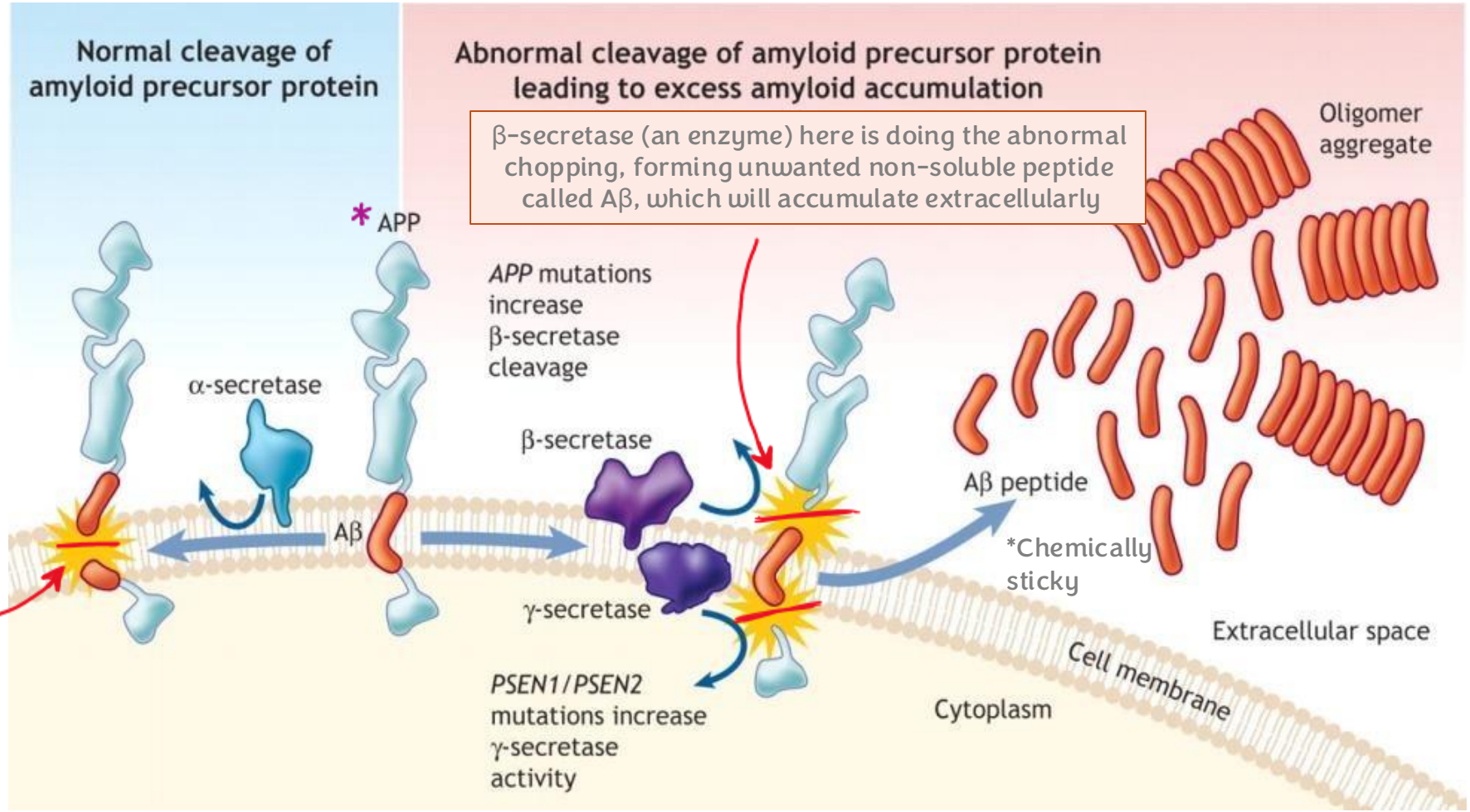
FORMATION OF PLAQUES

In Alzheimer disease patients, levels of β-amyloid become elevated, and this protein undergoes a conformational transformation from a **soluble α helix-rich state to a state rich in β sheet** and prone to self-aggregation.

* **APP = Amyloid Precursor Protein**

- In the abnormal cleavage of amyloid: γ-secretase and β-secretase will be much more effective than α-secretase
- γ-secretase produces intracellular piece and β-secretase produces the extracellular one, leading to release the peptide that was inside the membrane to be excluded outside the membrane.

Cleavage must be done here, normally
في نصّ الـAβ
By α-secretase

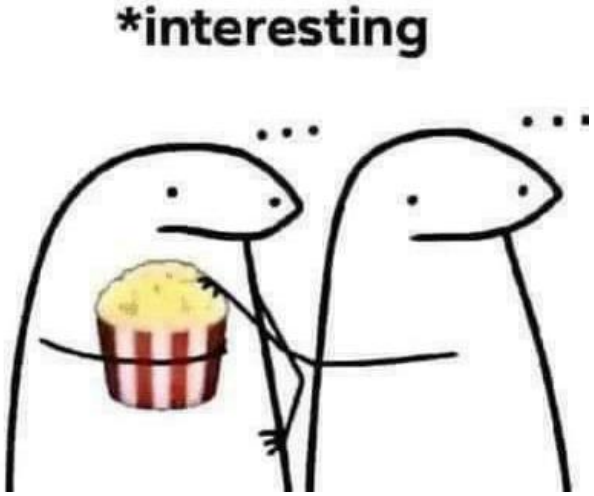


COMPLEX PROTEIN STRUCTURES

· Proteins can be attached to non-proteinous parts -as we discussed before with other structures (Carbs, Lipids)- to form what we call conjugated compounds, complex structures

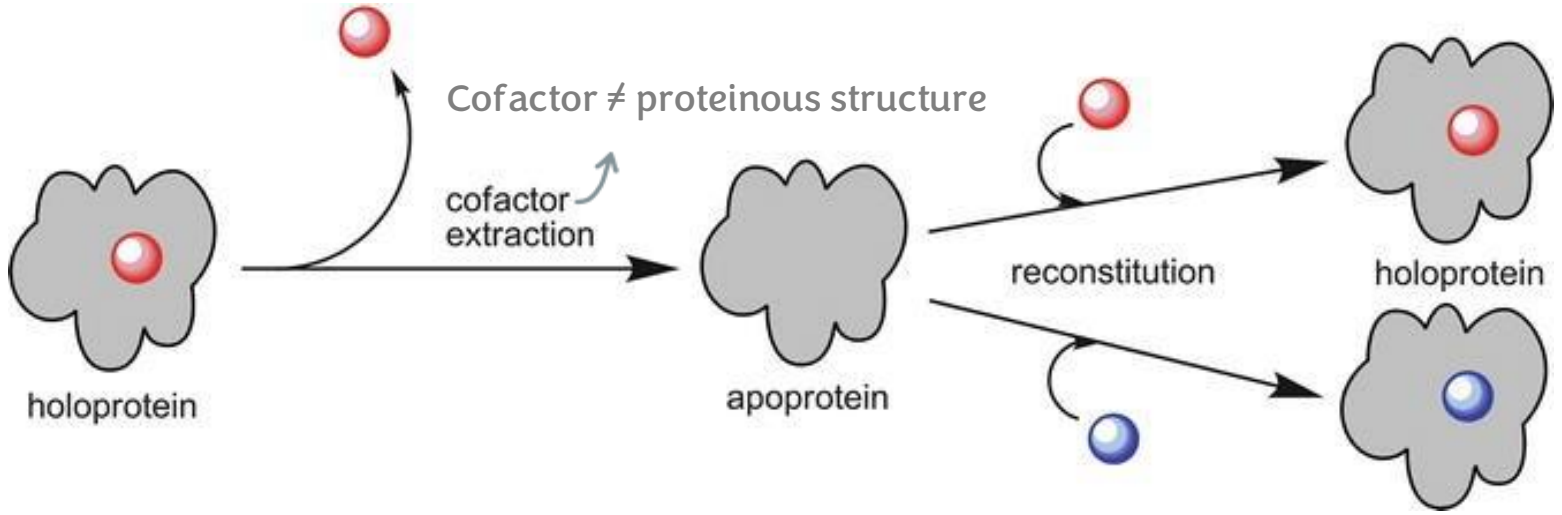
· So when they are **attached** to the non-proteinous structures—> we call them **Holoproteins**
· For proteins that are **NOT attached** to non-proteinous structures **anymore**—> we call them **Apoproteins**

· This principle likewise applies to enzymes, since -as we are all aware- enzymes are themselves a form of protein; we have Holoenzymes and Apoenzymes



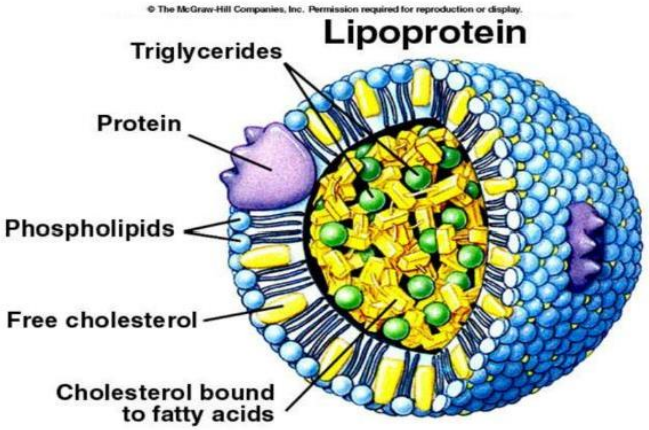
HOLO- AND APO-PROTEINS

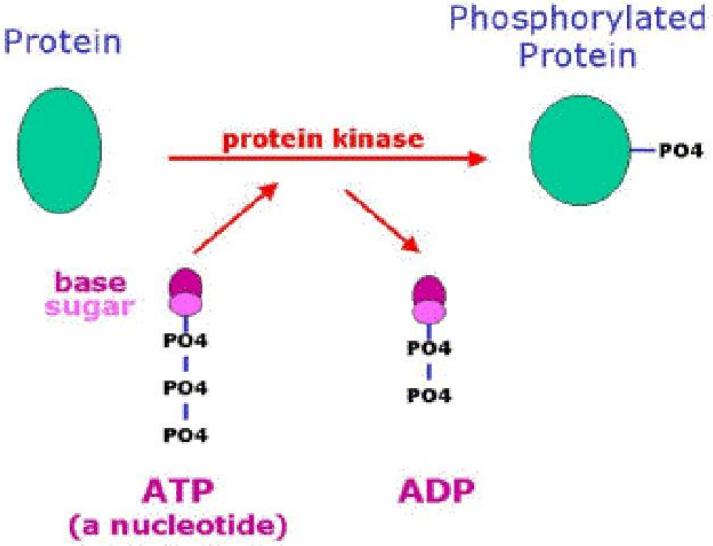
- Proteins can be linked to non-protein groups and are known as **conjugated proteins**
- When a protein is conjugated to a non-protein group covalently, the non-protein group is known as a **prosthetic group** and the protein known as a **holoprotein**
- If the non-protein component is removed, the protein is known as an **apoprotein**

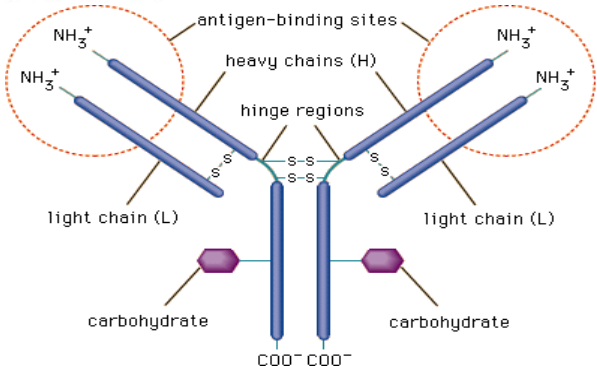


CONJUGATED . . .

- Lipoproeins: Proteins associated with lipids
- Phosphoproteins: proteins that are phosphorylated leading to either activation or deactivation (PO ≠ proteinous)
- Hemoproteins: proteins with heme (not amino acids in their nature. heme = iron + porphyrin, non-protein component tightly bound to certain proteins–giving them their specific function)
- Nucleoproteins: proteins with a nucleic acid (Histones)
- Glycoproteins: proteins with carbohydrate groups (Carbs can be attached to proteins in an organized way, not randomly, as we studied in Carbohydrates before (Next slide)

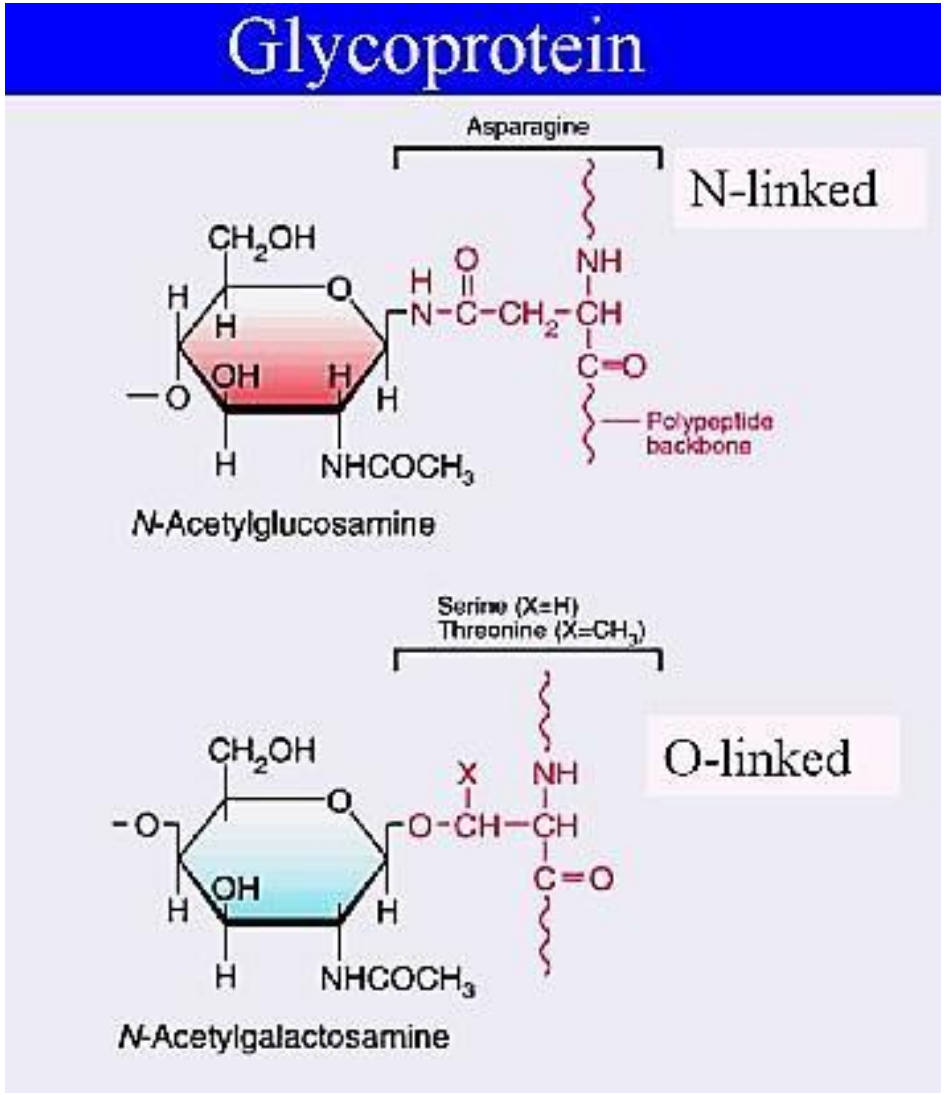




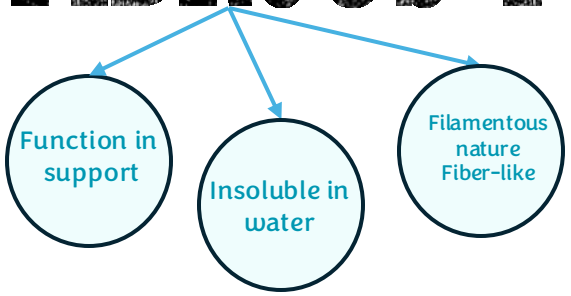


CLASSES OF GLYCOPROTEINS

- N-linked sugars
  - The amide nitrogen of the R-group of asparagine
- O-linked sugars
  - The hydroxyl groups of either serine or threonine
  - Occasionally to hydroxylysine

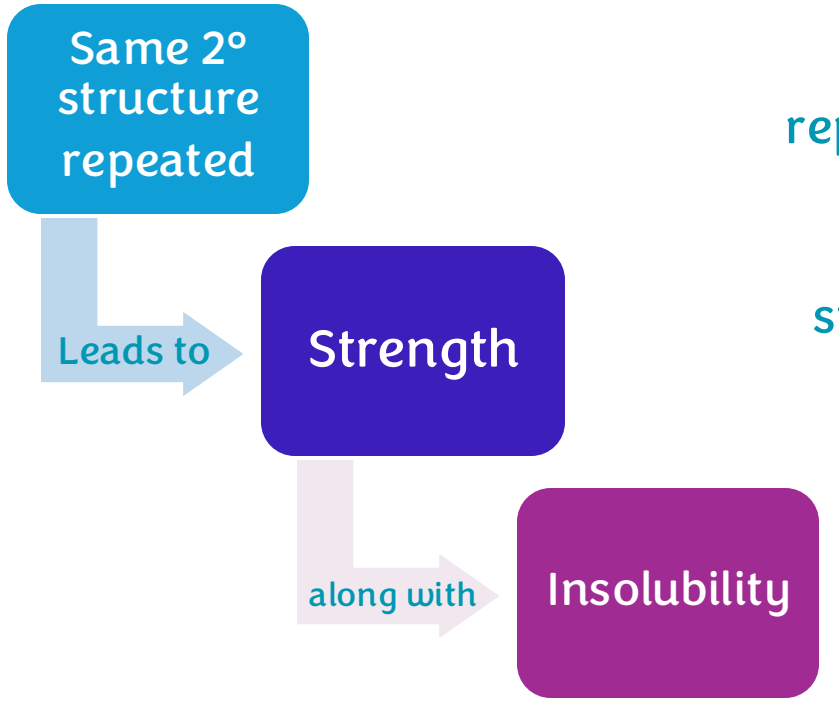


STRUCTURE-FUNCTION RELATIONSHIP: FIBROUS PROTEINS



الآن لو طُلب منك تعبّي صندوق معيّن بقطع ألعاب أومكعّبات ليغو وعندك الخيار تختار أحجامهم؛ فأنسب شيء يكونوا كلهم بنفس الحجم حتّى تتعبّى الفراغات جميعها داخل الصندوق

وهذه تمامًا الفكرة في الـ **FIBROUS PROTEINS**



They all contain only **One type** of a **secondary** structure which is being repeated over & over again contributing to their strength

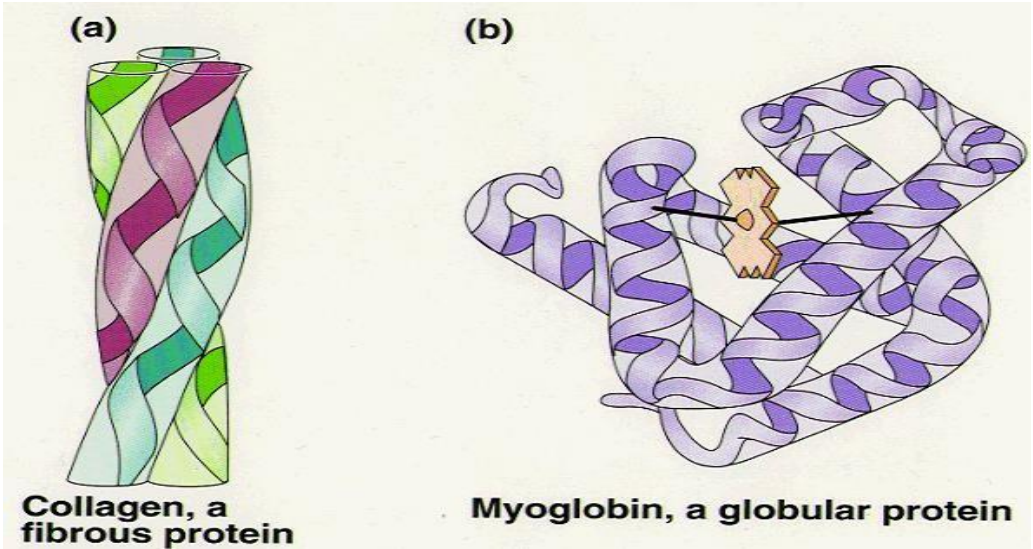
By packing & stacking secondary structures u r excluding water, so they r now insoluble

BIOLOGICAL FUNCTIONS OF PROTEINS

- Enzymes--catalysts for reactions
- Transport molecules--hemoglobin; lipoproteins, channel proteins
- Contractile/motion--myosin; actin Structural--collagen; keratin, actin
- Defense--antibodies
- Signaling—hormones, receptors Toxins--diphtheria; enterotoxins

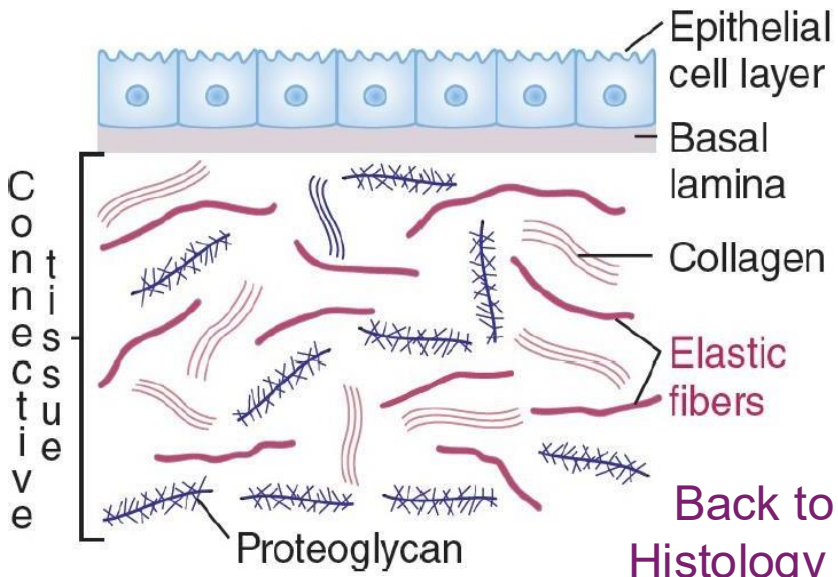
TYPES OF PROTEINS

- Structure:
  - Fibrous (fiber-like with a uniform secondary-structure only),even though their variety is not big but their amounts are very high compared to all proteins
  - Globular (globe-like with three-dimensional compact structures)
- Examples
- Fibrous proteins: collagens, elastins, 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 cell surface.



Back to Histology ☹

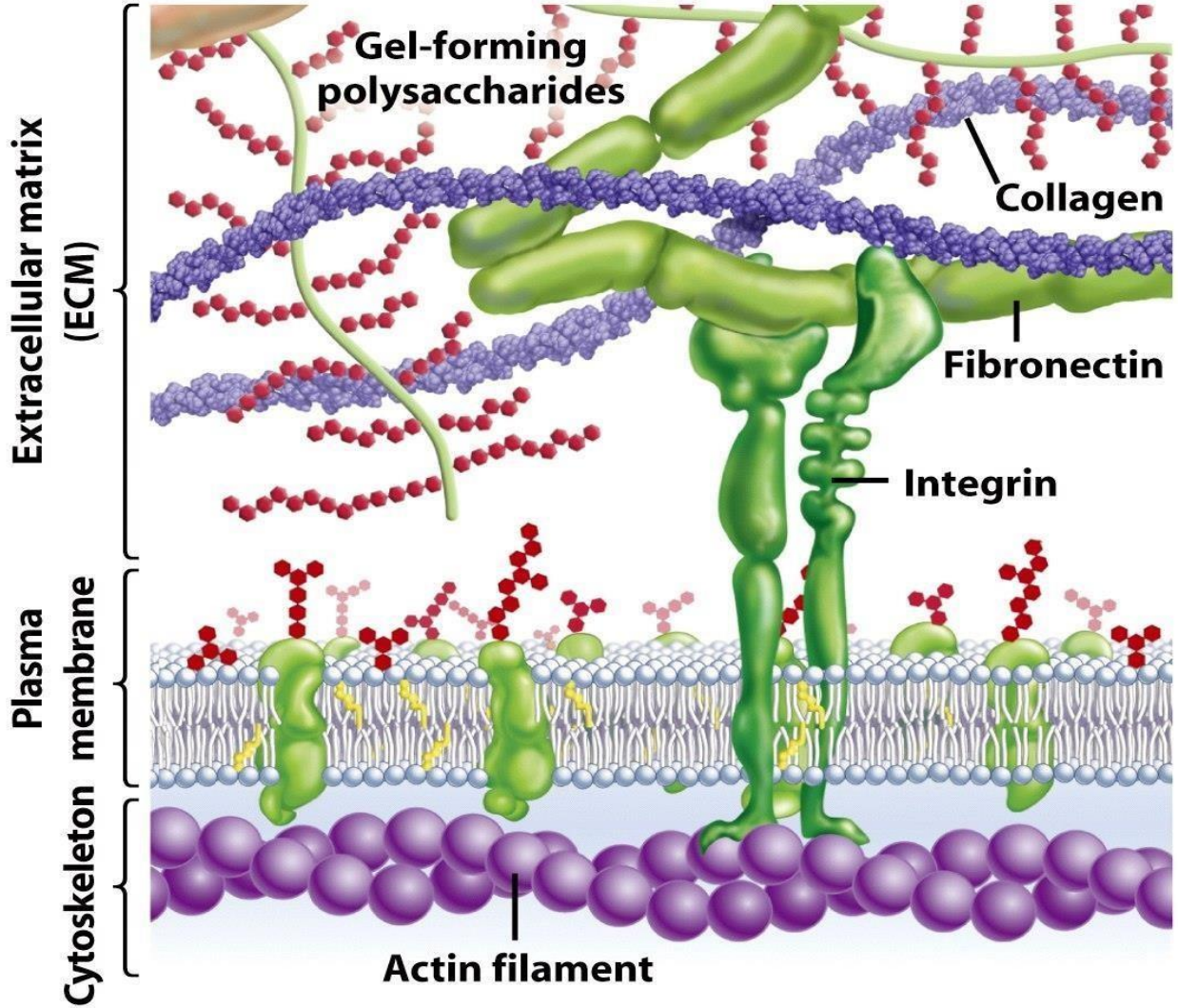
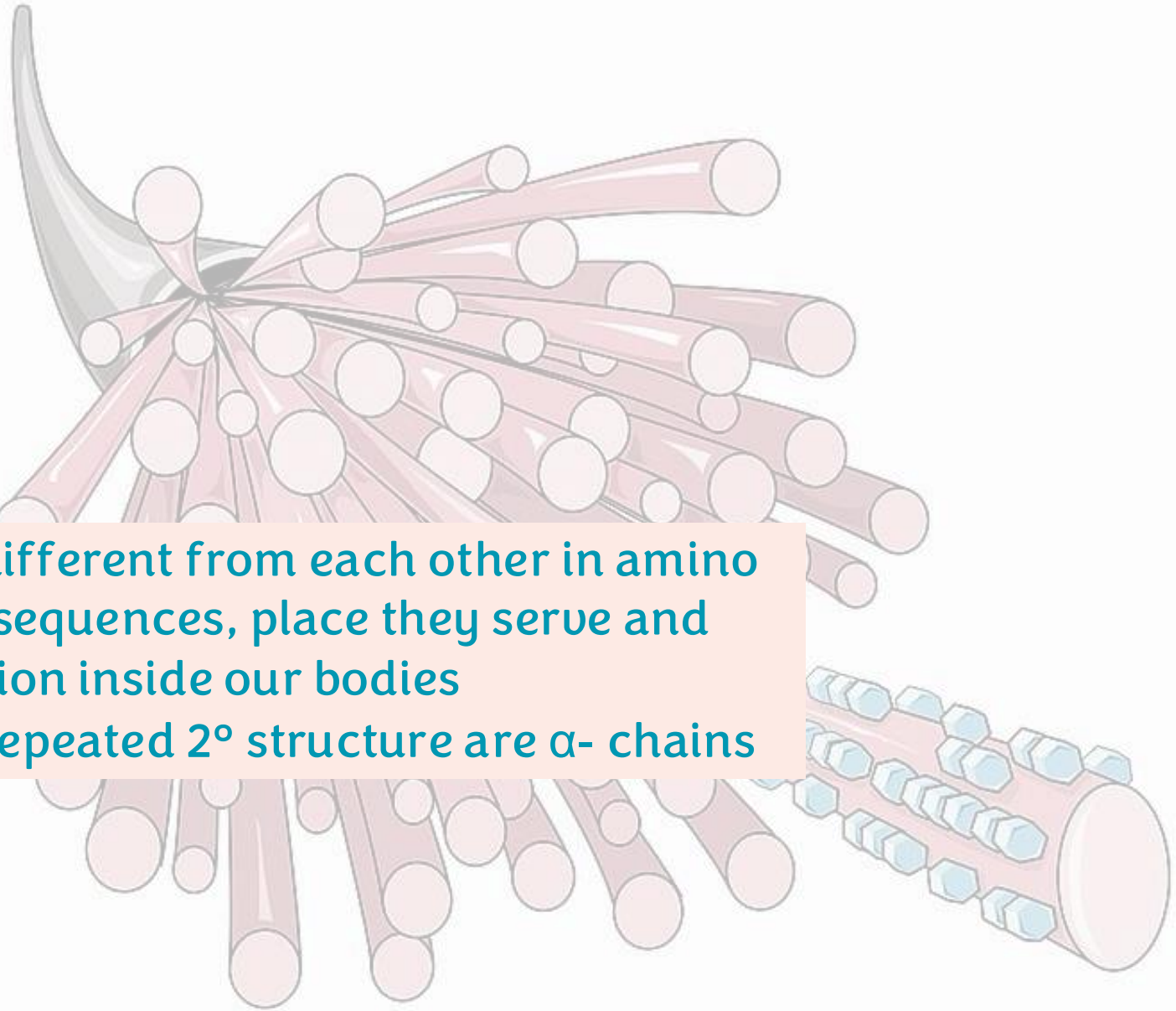


Figure 8-4 Biological Science, 2/e

COLLAGENS



- Are different from each other in amino acid sequences, place they serve and location inside our bodies
- The repeated 2° structure are α- chains

COLLAGENS AND THEIR PROPERTIES

- The collagens are a family of fibrous proteins with **25** different types found in all multicellular animals. (25 types are discovered Until now, naming them with numbers: I, II, III…)
- They are the most abundant proteins in mammals, constituting **25%** of the total protein mass in these animals.
- Collagen molecules are named as type I collagen, type II collagen, type III collagen, and so on.
- The main function of collagen molecules is to provide **structural support** to tissues.
- Hence, the primary feature of a typical collagen molecule is its stiffness.

STRUCTURE

- It is a left-handed, triple-stranded, helical protein, in which three collagen polypeptide chains, called α- chains, are wound around one another in a ropelike superhelix.
- This basic unit of collagen is called **tropocollagen**.
- Compared to the α -helix, the collagen helix is much more extended with 3.3 residues per turn.

3 α- chains, 3 structures
3 polypeptide chains

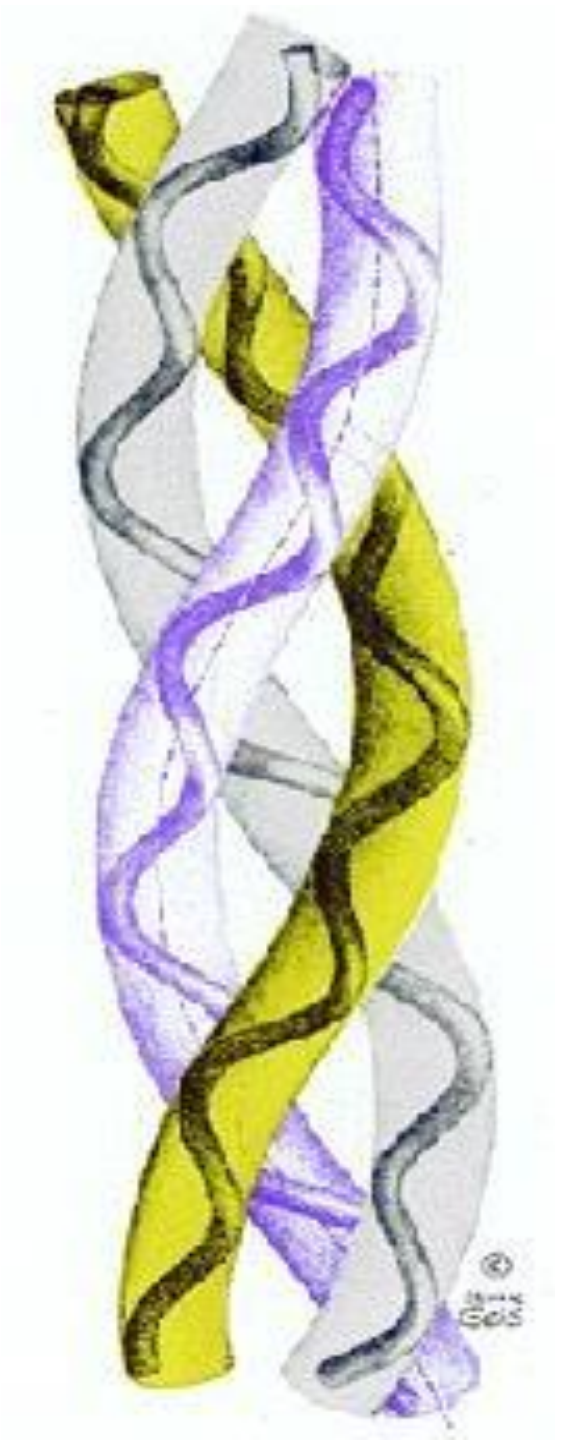
Measurements found in α-chain which are not found in α- helix:

1. It's left-handed not right-handed
2. 3.3 amino acids per turn, helix contains 3.6 amino acids. So α-chain is more relaxed since it has less # of amino acids per turn than the helix

STRUCTURE

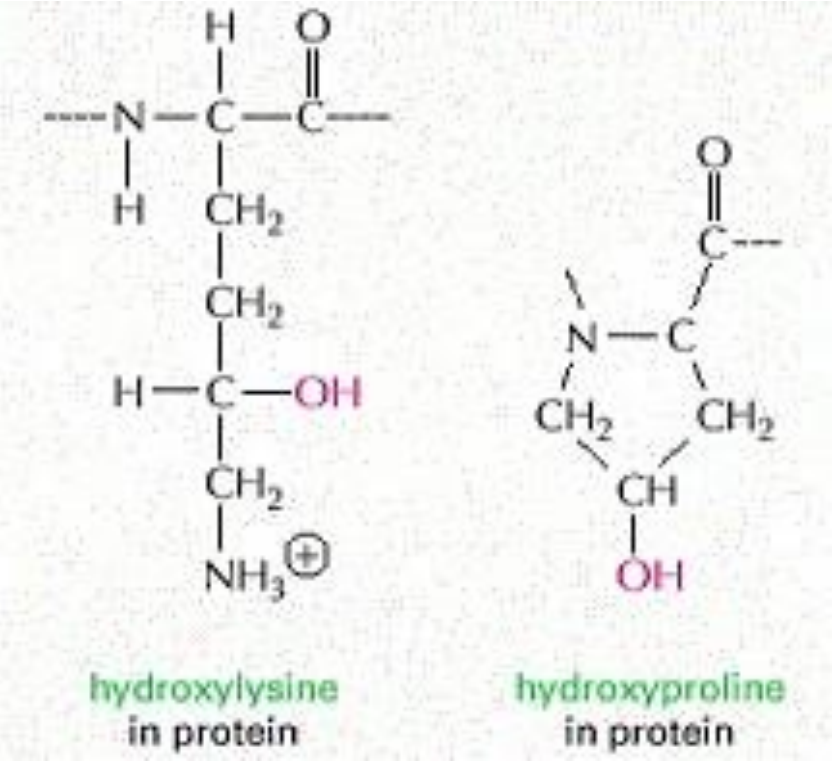
· Each polypeptide chain composed of ~800-1000 amino acids, depending on the type of collagen
· Each polypeptide chain is helical in its structure, alpha chain for each
· The way how being built –> زي اللي بجدّل الشعر
· The way how it looks : relaxed area and then a knot (عقدة) being repeated
· **how can u fit 3 amino acids in a very small place (the knot) ?** By having **Glycine residues** in each polypeptide chain of them so they can be packed or stacked in top of each other.

Glycine as we said is a breaker of the alpha helix because of its instability by itself, but here it's soo important. It constitues 1/3 of all amino acids in collagen, every 2 amino acids there must be a Glycine residue between them,where the knot comes all the time

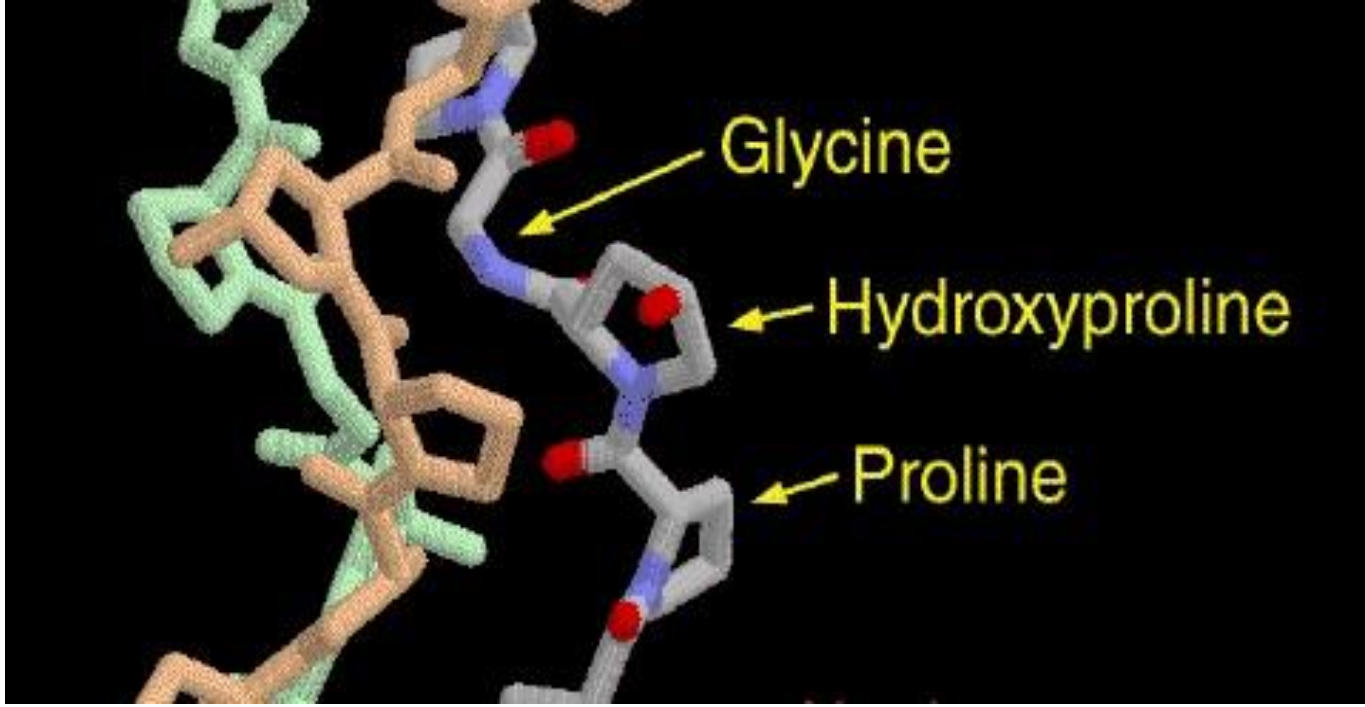


COMPOSITION OF COLLAGENS

- Collagens are rich in glycine (33%) and proline (13%).
- It is also unusual in containing hydroxyproline (9%) and hydroxylysine.
- Every third residue is glycine, which, with the preceding residue being proline or hydroxyproline in a repetitive fashion as follows:
- Gly-pro-Y
- Gly-X-hydroxyproline

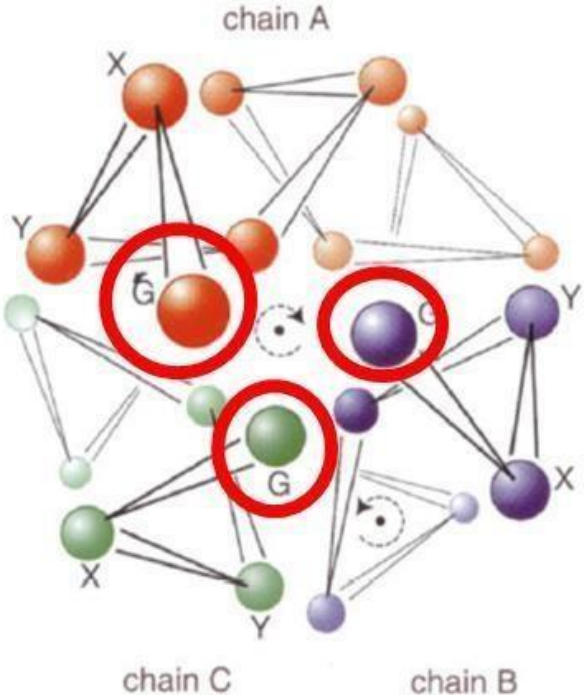


FUNCTIONAL PURPOSE OF AMINO ACIDS



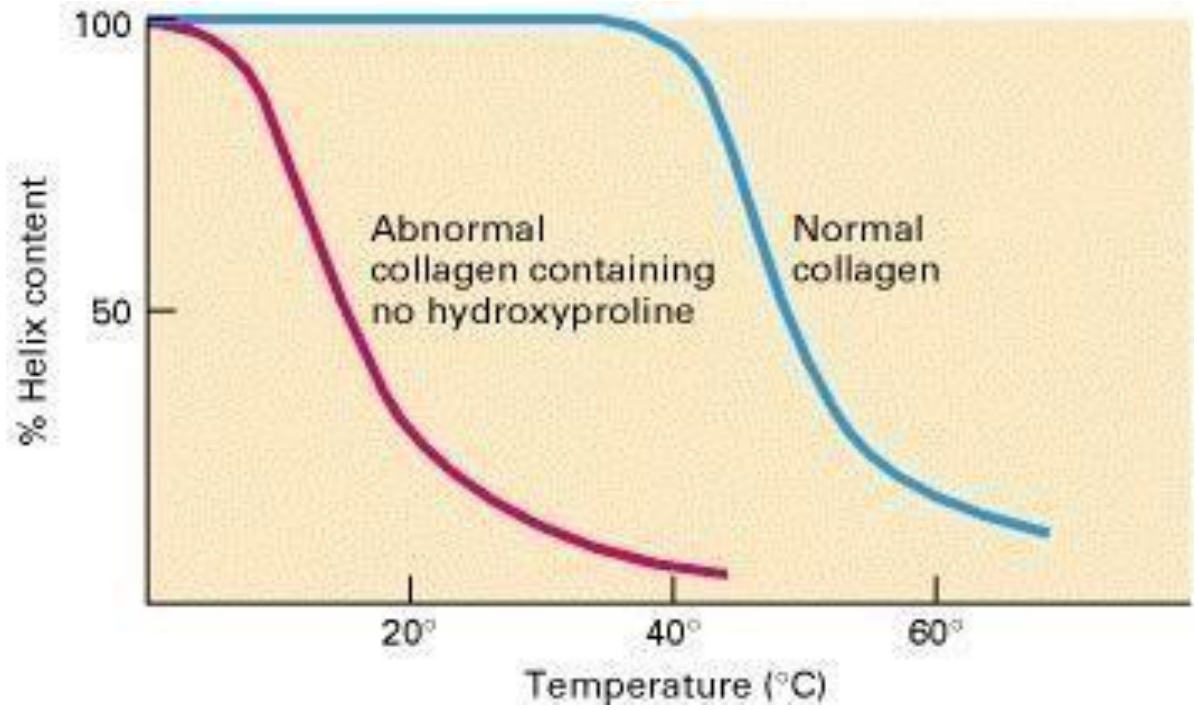
- Glycine allows the three helical a chains to pack tightly together to form the final collagen superhelix.
- Proline creates the kinks and stabilizes the helical conformation in each a chain.

U need proline to keep the kinking process, to achieve the helical shape
U need hydroxyproline to be able to do hydrogen bonding to prserve the helical shape
U need lysine for connecting tropocollagens together and alpha chains together



PURPOSE OF HYDROXYPROLINE

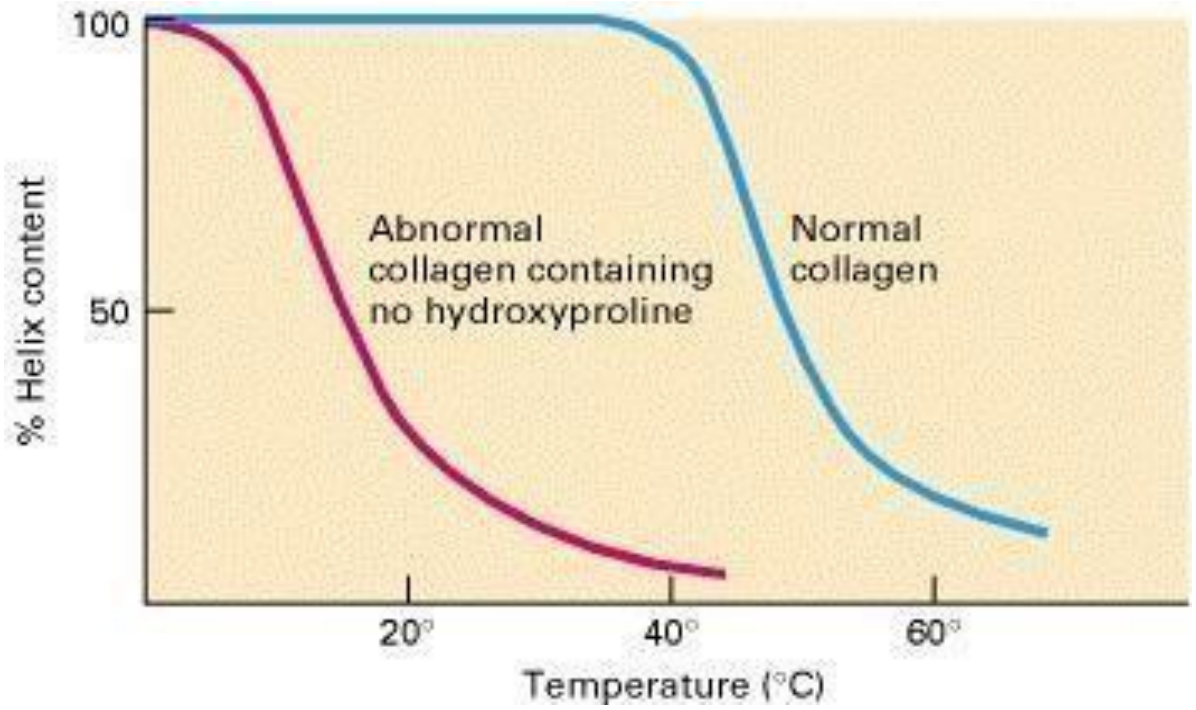
- Normal collagen is stable even at 40 °C.
- Without hydrogen bonds between hydroxyproline residues, the collagen helix is unstable and loses most of its helical content at temperatures above 20 °C



The chart shows the effect of temperature on the helical content of normal collagen versus collagen lacking hydroxyproline.

As temperature increases, the percentage of helix content decreases in both types, because hydrogen bonds are disrupted by heat.

PURPOSE OF HYDROXYPROLINE



- Normal collagen remains stable at 100% helix content up to about 40 °C. Its helical content then gradually decreases, reaching about 50% at 50 °C.

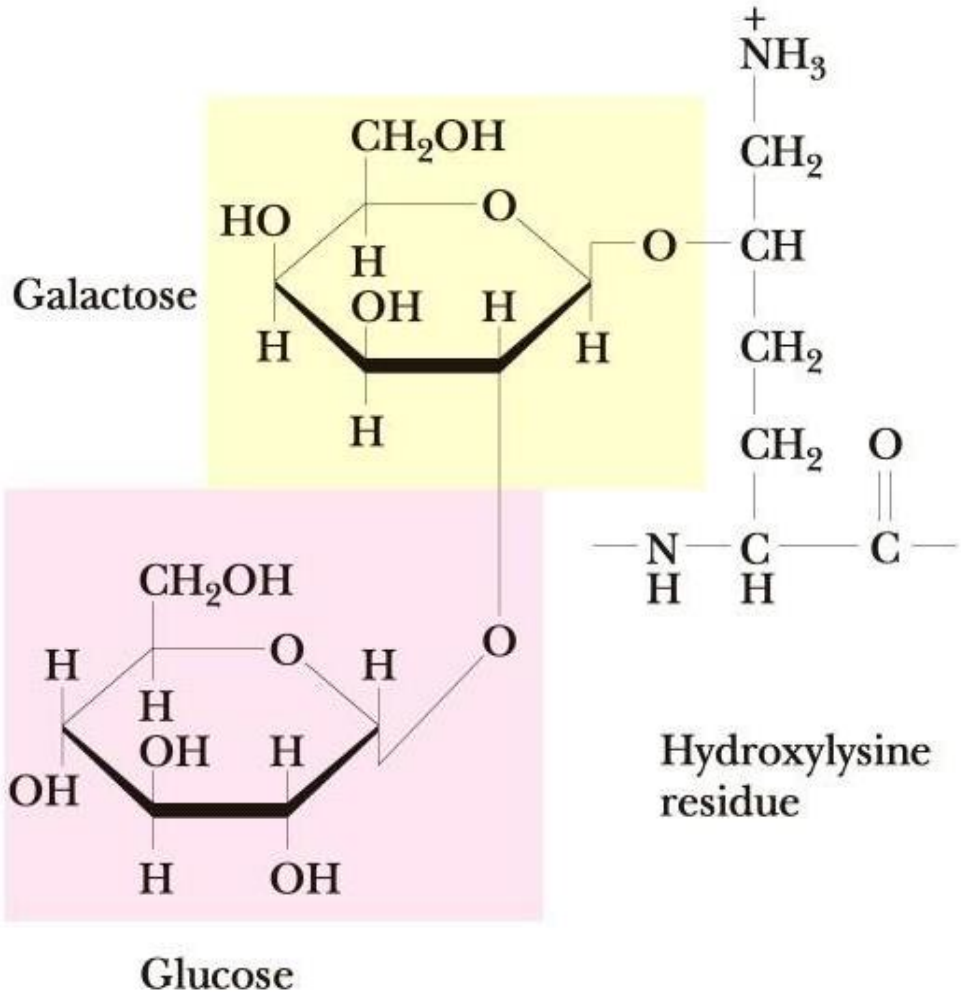
- Collagen without hydroxyproline begins losing its helical content almost immediately as temperature rises, dropping sharply above 20 °C.

This difference occurs because hydroxyproline forms additional hydrogen bonds, increasing thermal stability. Without it, there are fewer hydrogen bonds, so the collagen helix is more easily disrupted.
So, we conclude that Hydroxyproline plays a crucial role in **maintaining the stability and helical structure** of collagen at higher temperatures.

HYDROXYLYSINE: An amino acid found in collagen

- Hydroxylysine serves as attachment sites of polysaccharides (glycosylation) making collagen a glycoprotein.

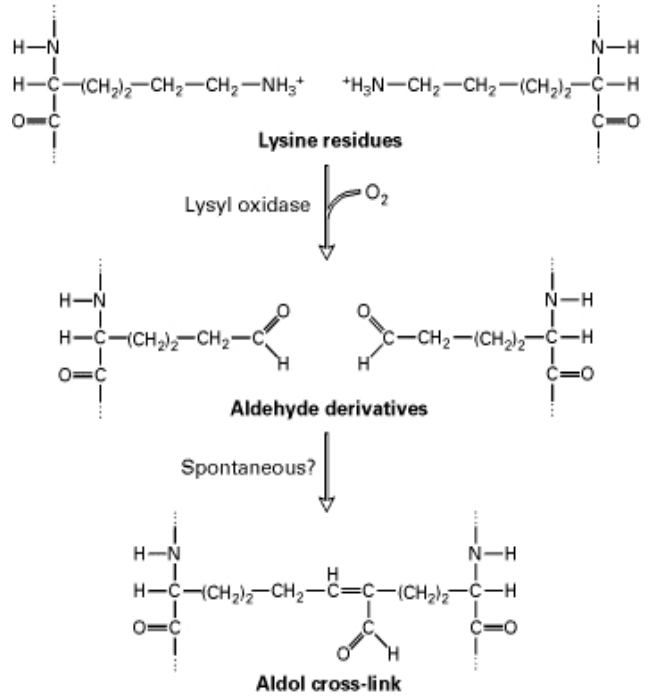
Glycosylation of hydroxylysine plays an important role in the stability and function of collagen.

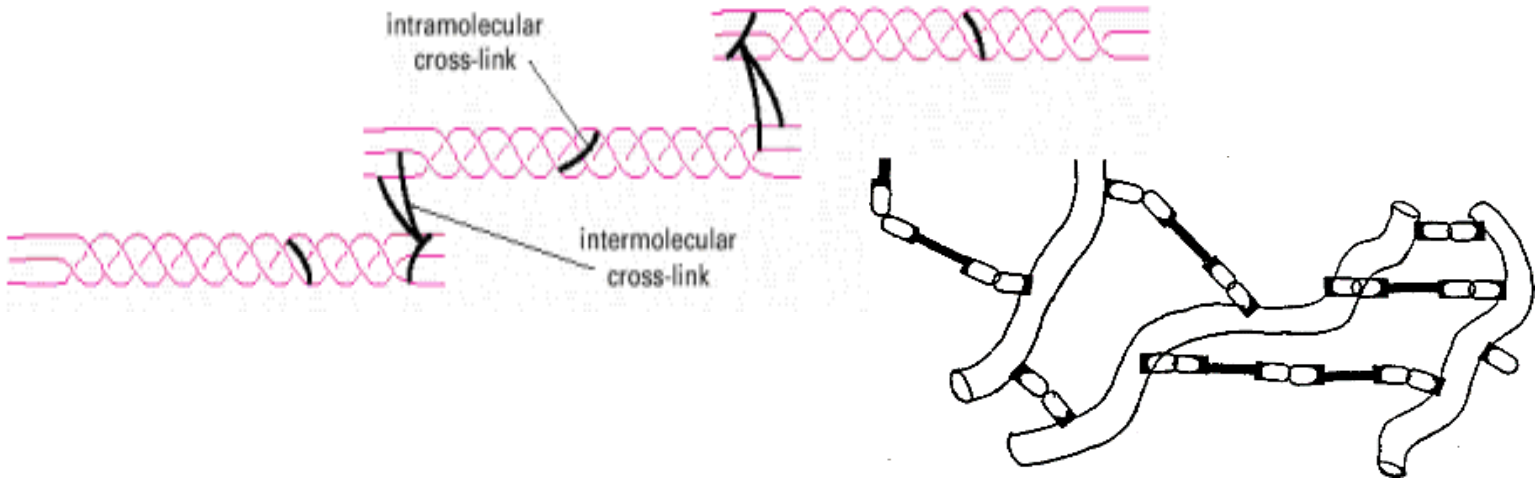


OXIDATION OF LYSINE

- Covalent aldol cross-links form between hydroxylysine residues and lysine or another oxidized lysine (between individual collagen helices (intramolecular) and between separate tropocollagen molecules(intermolecular))

These covalent cross-links strengthen collagen. Cross-linking is usually catalyzed by enzymes, but it can also occur spontaneously over time, although much more slowly.

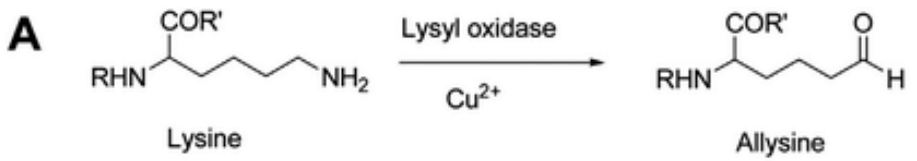




OXIDATION OF LYSINE

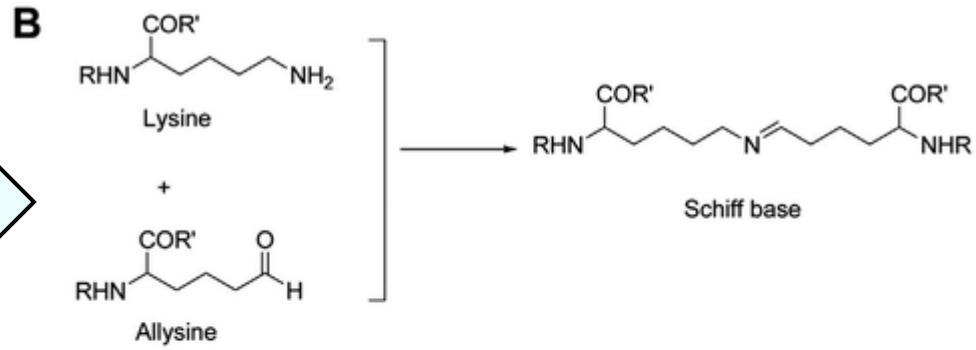
- Some of the lysine side chains are oxidized (through Lysyl oxidase) to aldehyde derivatives known as allysine (aldehyde form of lysine)

Lysine can also be hydroxylated by the enzyme lysyl hydroxylase, similar to how proline is hydroxylated.

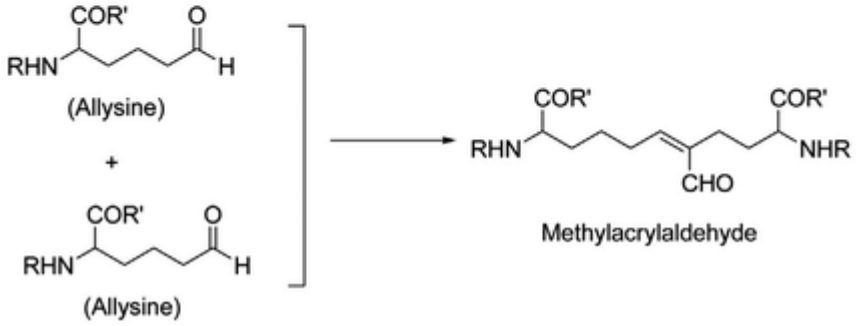


Cross-linking can then occur in two main ways:

1. An **unmodified** lysine reacts with an **oxidized** lysine via a Schiff base reaction, forming a covalent double bond.

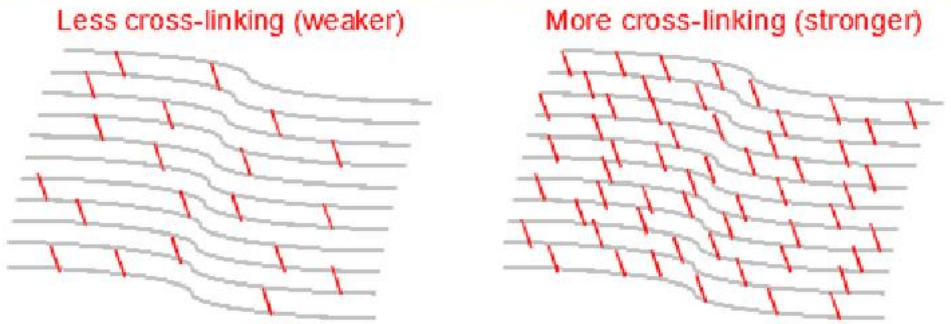


2. **Two oxidized** lysines react, with one remaining in the aldehyde form and the other forming a double bond.



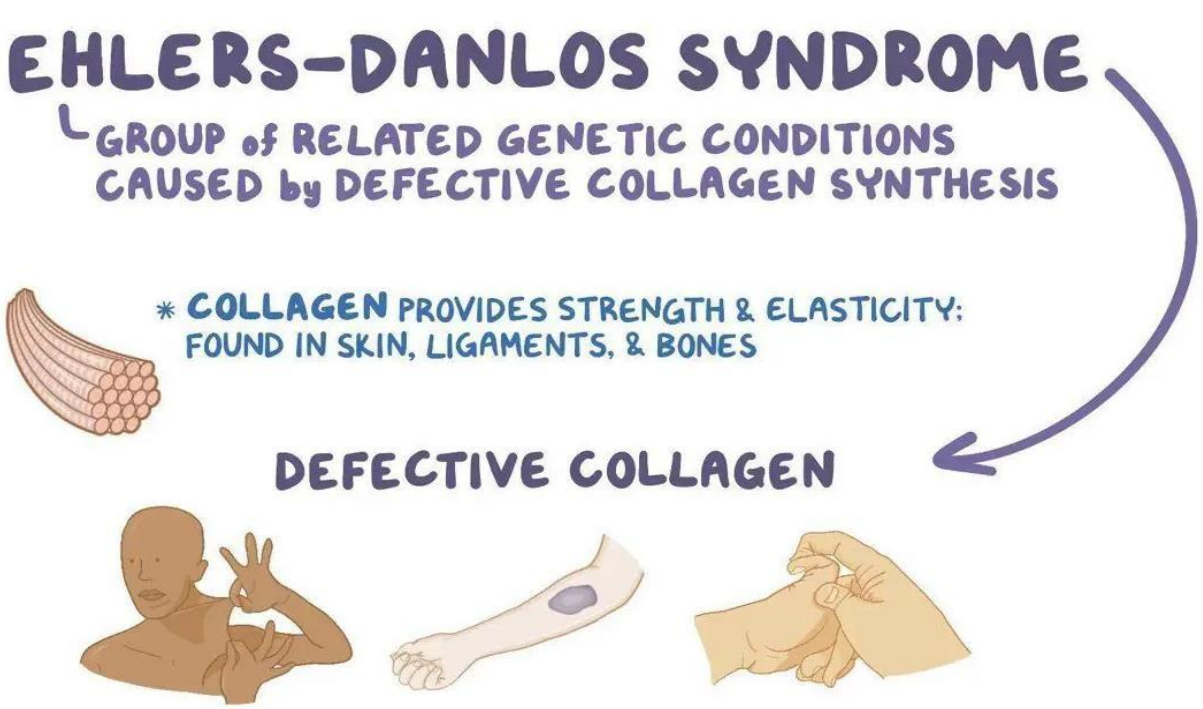
FUNCTION OF CROSS-LINKING

- These cross-links stabilize the side-by-side packing of collagen molecules and generate a strong fibril
- The amount of cross-linking in a tissue increases with age. That is why meat from older animals is tougher than meat from younger animals.
- The same principle applies in the body; more cross-linking over time leads to stiffer tissues, such as in aging blood vessels.



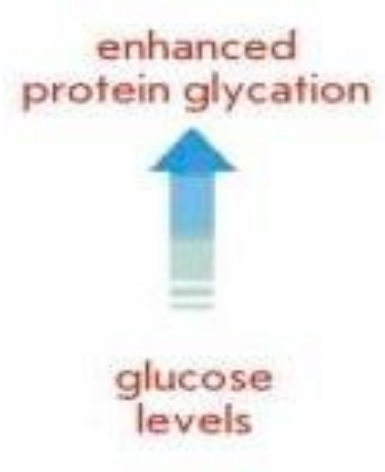
DEFICIENT CROSS-LINKING

- 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. (A genetic disorder—result from defective cross-linking, leading to weaker collagen.Along with the common symptoms, it may also lead to bone fractions)



ADVANCED GLYCATION END PRODUCTS (AGES)

- Proteins (e.g., collagen) can be nonenzymatically glycated (where sugars, especially when present at high concentrations, bind spontaneously to amino acids such as serine, threonine, hydroxylysine, or lysine
- This process is unregulated, thus, producing glycosylated 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.

Uncontrolled diabetics suffer from cardiomyopathy

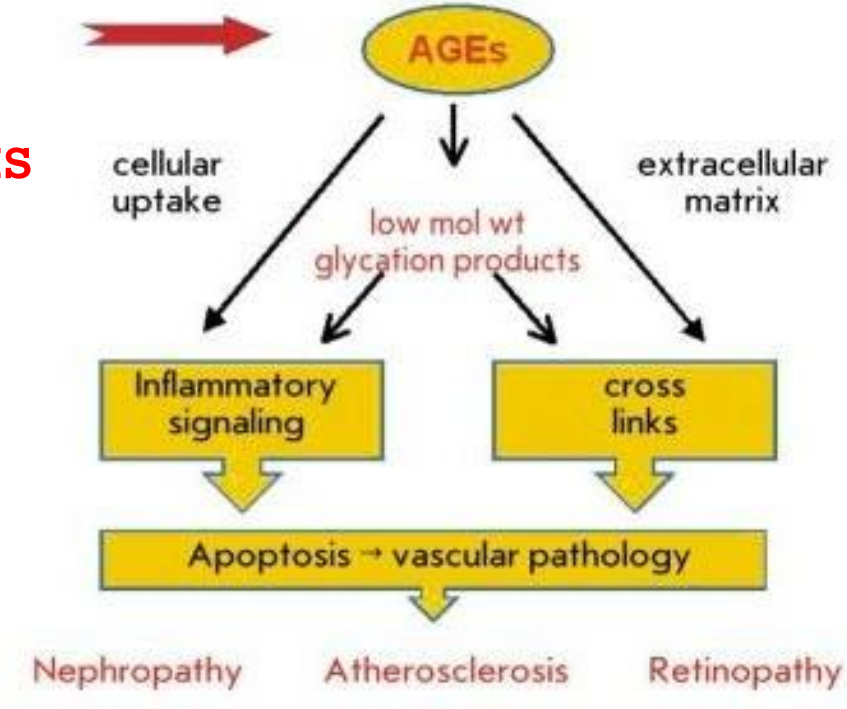
- In proteins with a short half-life, glycation has little effect, but in long-lived proteins, accumulation can lead to structural stiffness and increased oxidative stress.

Clinically, this principle is used in the hemoglobin A1c test (Diabetes test), which measures the percentage of glycated hemoglobin. A value above 5% suggests higher average blood glucose levels, as seen in poorly controlled diabetes.

ADVANCED GLYCATION END PRODUCTS (AGES)

- Glycated proteins in tissues are further modified by nonenzymatic oxidation forming additional cross-links.

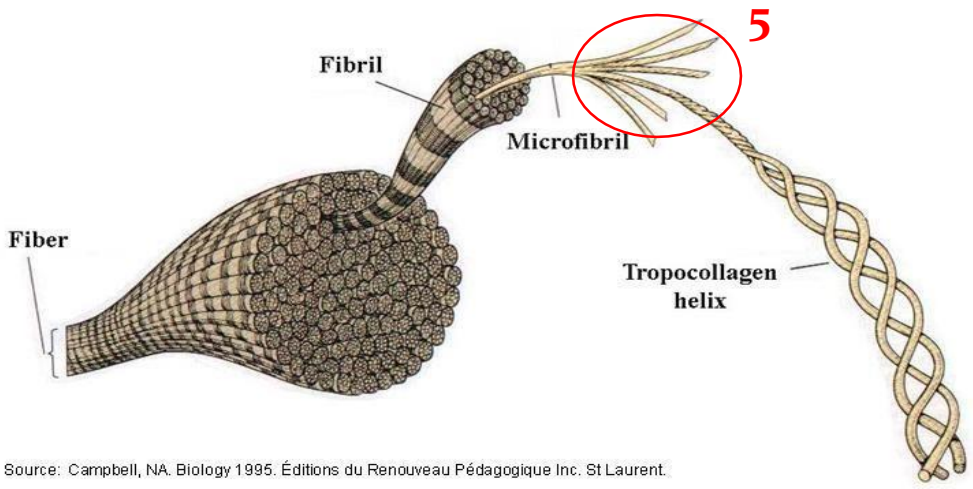
- The net result is the formation of large protein aggregates termed advanced glycation end products (AGEs), which increase cellular oxidative stress.



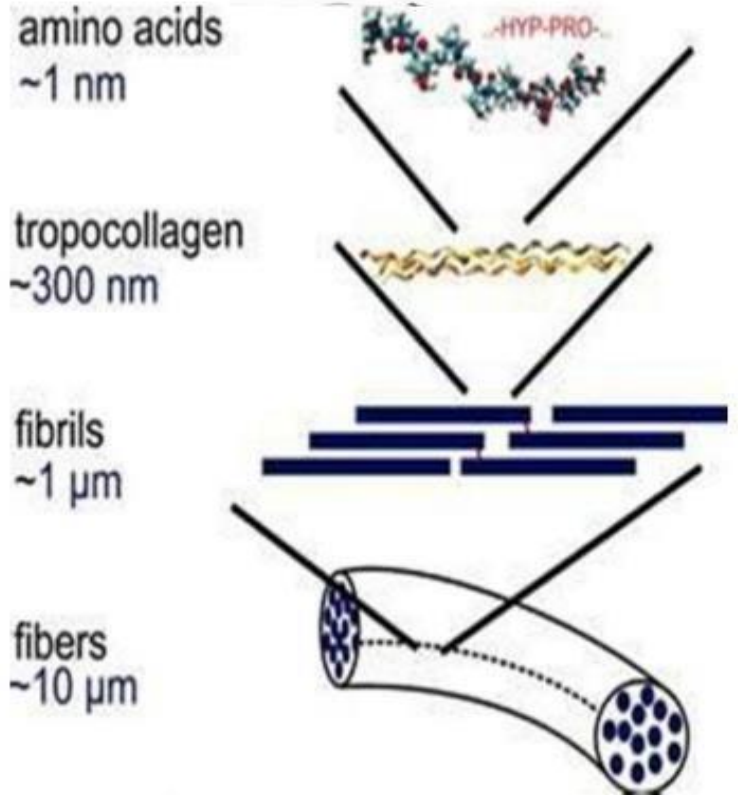
These aggregates raise oxidative stress, contributing to tissue stiffness and vascular damage seen in chronic complications such as nephropathy, retinopathy, atherosclerosis, and cardiomyopathy in uncontrolled diabetes.

FORMATION OF COLLAGEN FIBERS

- Following cellular release of protocollagen, 5 of them polymerize into a microfibril, that get connected with each other via aldehyde links.
- Microfibrils align with each other forming larger collagen fibrils, which are strengthened by the formation of covalent cross-links between lysine residues.
- Microfibrils assemble into collagen fibers.



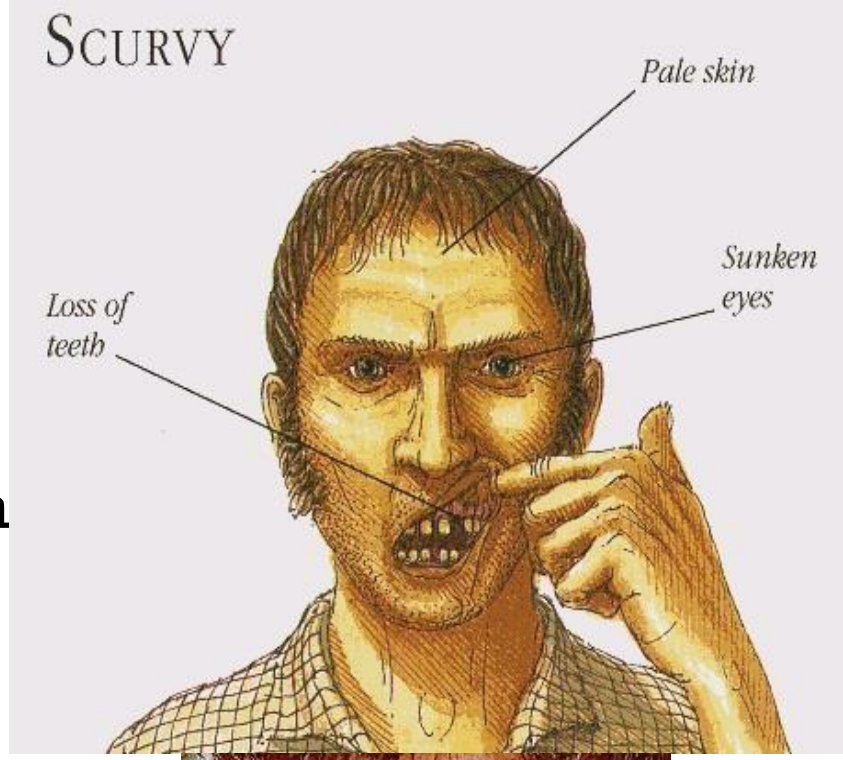
Source: Campbell, NA. Biology 1995. Éditions du Renouveau Pédagogique Inc. St Laurent.

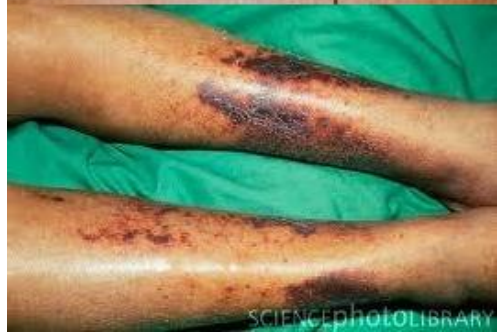


SCURVY

An acquired disease that disrupts the hydroxylation of proline and lysine during collagen synthesis, leading to weakened and deformed tissues.

- Scurvy is a disease caused by a dietary deficiency of ascorbic acid (vitamin C).
- Deficiency of vitamin C prevents proline hydroxylation
- The defective pro-α chains fail to form a stable triple helix and are immediately degraded within the cell.
- Blood vessels become extremely fragile, and teeth become loose in their sockets. (due to quick remodeling)





Existing collagen is mostly fine because it is a long-lived molecule with a half-life of about 10 years. Most body molecules undergo remodeling (breakdown and renewal), but collagen remodels slowly compared to others

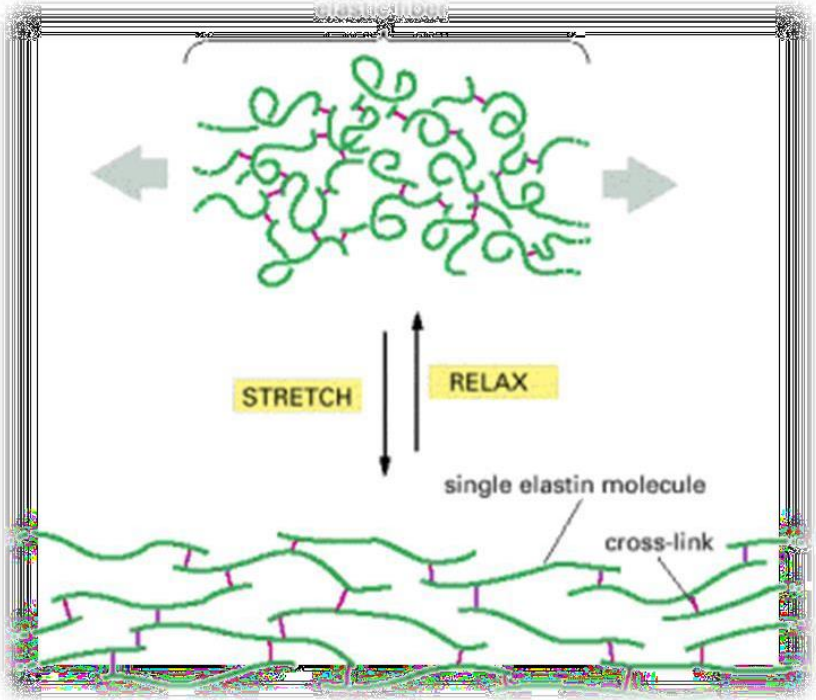
ELASTINS

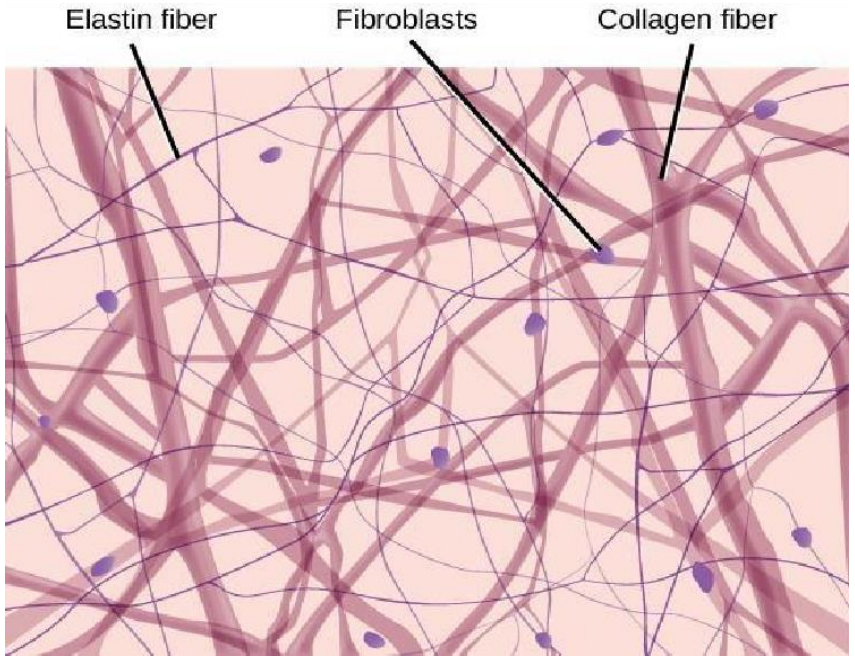
A type of protein found mainly in elastic tissues. It provides resilience and flexibility, allowing tissues to stretch and return to their original shape.

The ability of elastin to stretch comes from its structure, which contains many short segments rich in hydrophobic (non-polar) amino acids. When stretched, these hydrophobic regions become exposed to water, which is unfavorable.
Upon release of the force, they cluster together to avoid water, allowing the protein to recoil back to its original shape.

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 these 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





ELASTIN

- The main component of elastic fibers is elastin, which is a highly hydrophobic protein and is rich in proline and glycine.
- It contains some hydroxyproline, but no hydroxylysine.
- It is not glycosylated.
- The primary component, tropoelastin molecules, is cross- linked between lysines to one another.

Both collagen and elastin contain lysine residues. However, elastin lacks hydroxylysine because it does not have the enzyme lysyl hydroxylase, so its lysine cannot be hydroxylated.

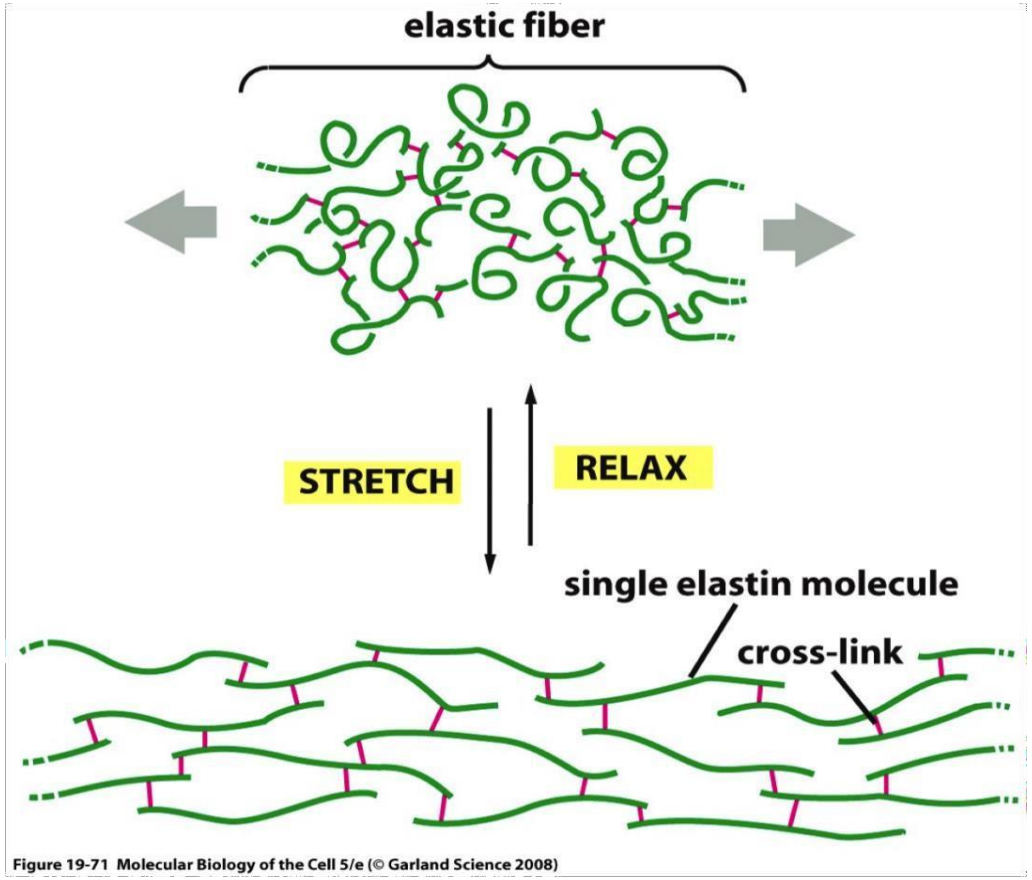
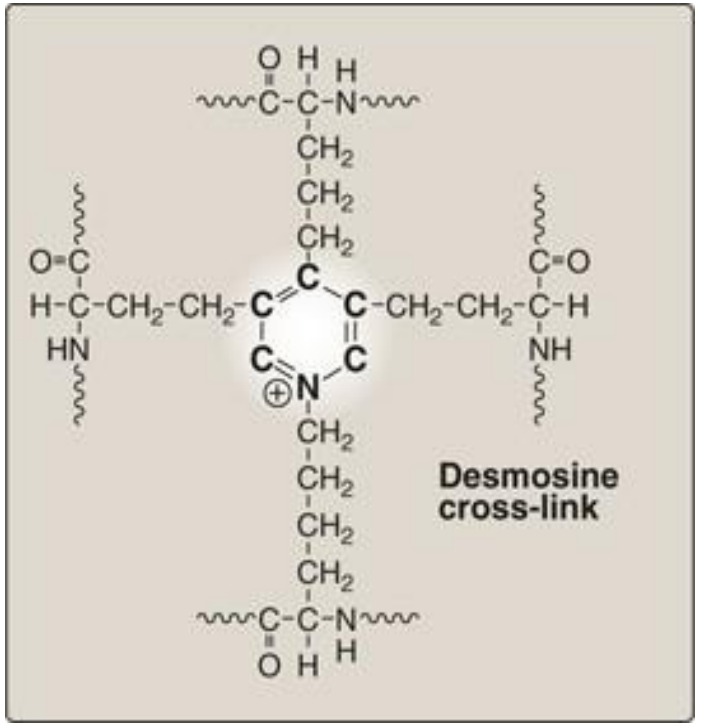


Figure 19-71 Molecular Biology of the Cell 5/e (© Garland Science 2008)

ELASTIN STRUCTURE

- The elastin protein is composed largely of two types of short segments that alternate along the polypeptide chain (secondary structure):
- Hydrophobic segments, which are responsible for the elastic properties of the molecule; and
- Alanine- and lysine-rich α- helical segments, which form cross-links between adjacent molecules

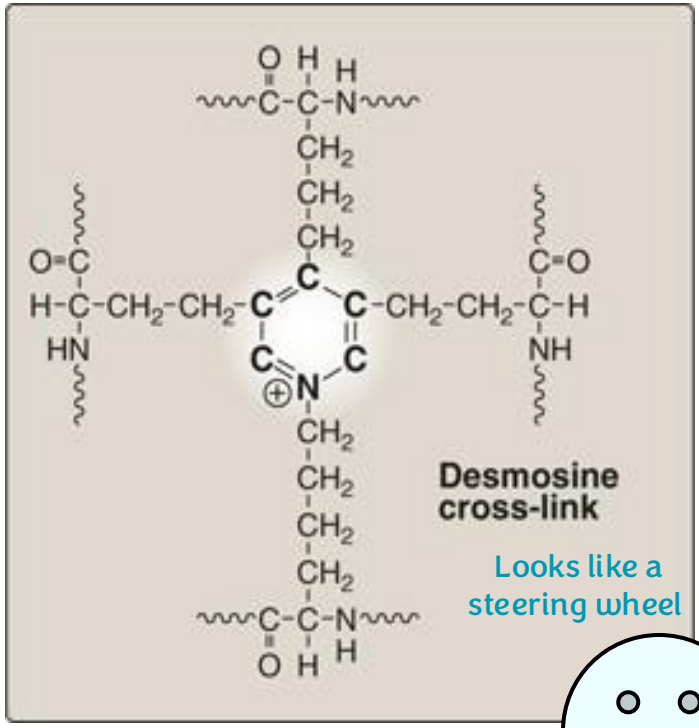


Although elastin's lysine is not hydroxylated (no lysyl hydroxylase), it is oxidized by lysyl oxidase to form allysine.

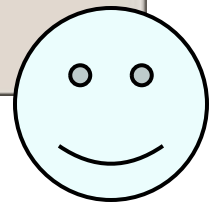
ELASTIN STRUCTURE

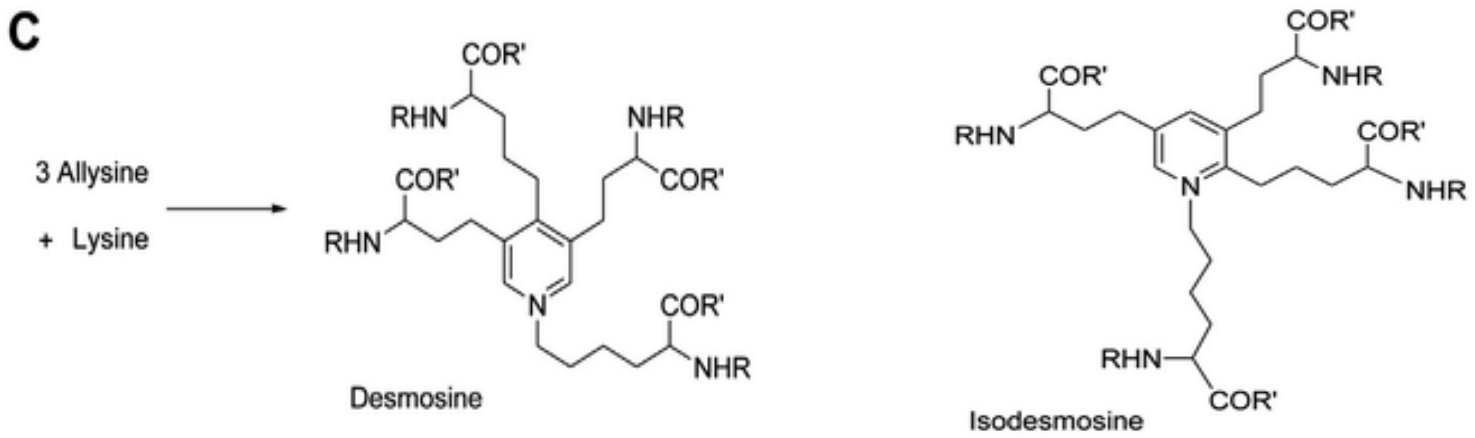
- Three allysyl side chains plus one unaltered lysyl side chain form a desmosine crosslink.

  All three allysine residues contain carbonyl groups (–CHO) in their side chains, while the unmodified lysine has an amino group (–NH2). These groups connect by forming covalent bonds that create a ring structure known as the desmosine cross-link, which stabilizes elastin's elastic network.



Looks like a steering wheel





KERATINS

KERATINS

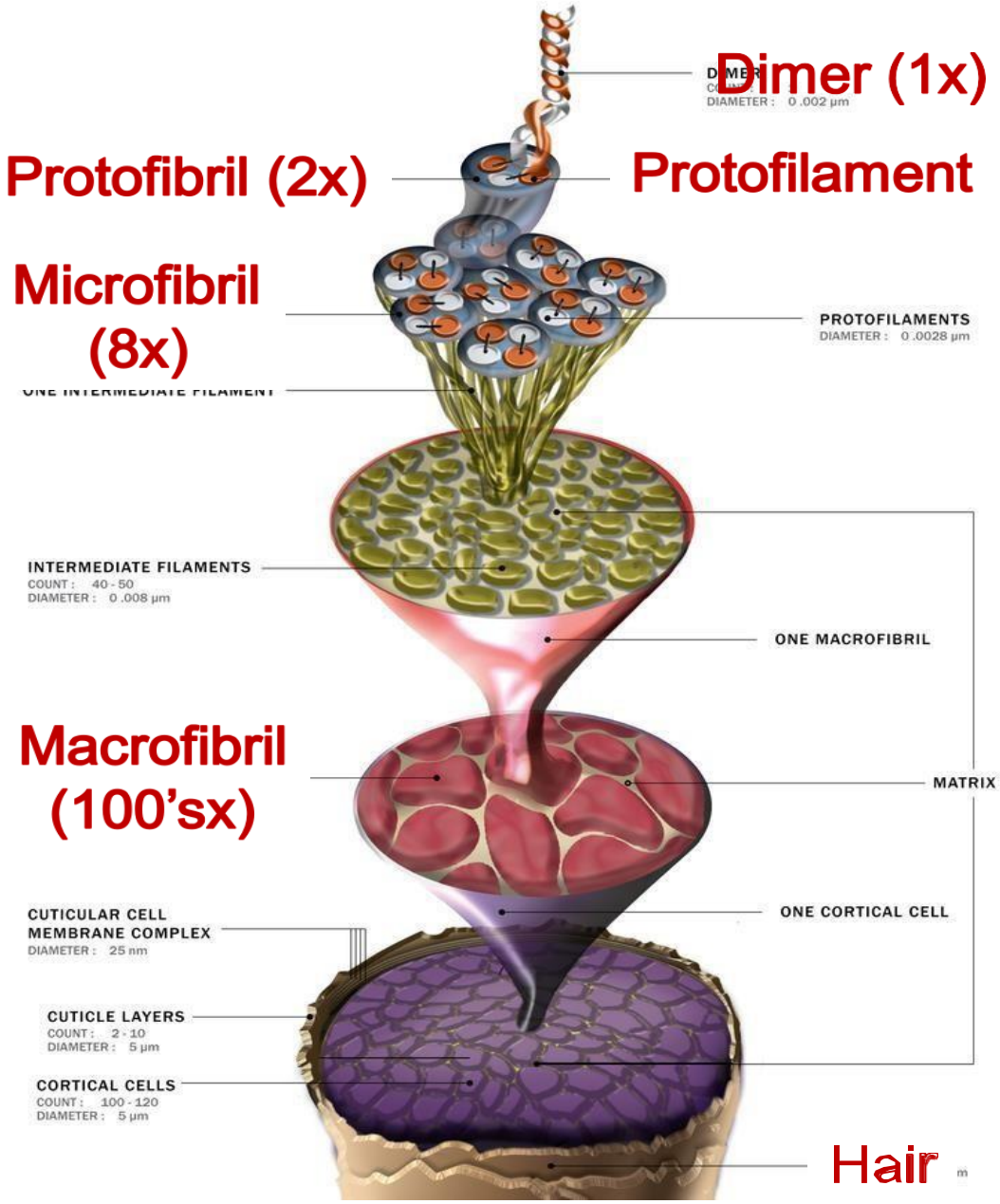
- Two important classes of proteins that have similar amino acid sequences and biological function are called α-and β-keratins (α in humans and β in birds, riptides, etc...) , which as members of a broad group of intermediate filament proteins.

- α-keratin is the major proteins of hair and fingernails as well as animal skin.
- α-keratin has an unusually high content of cysteine accordingly will be cross-linked.

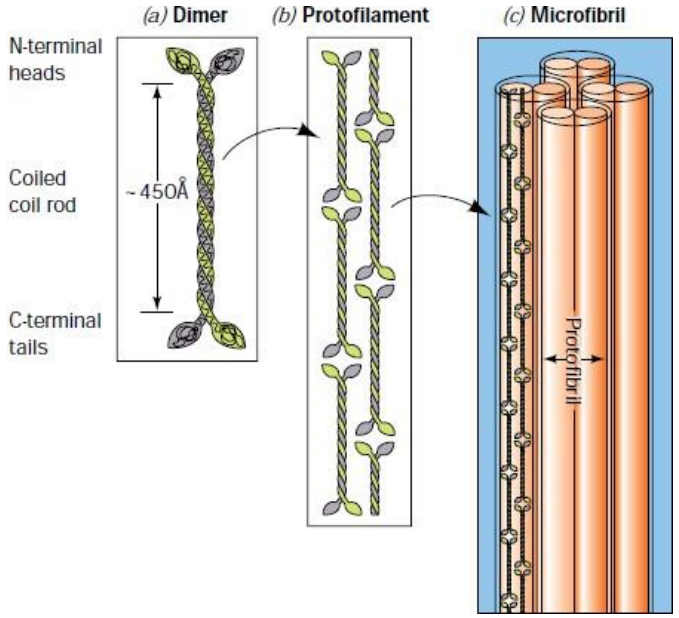
The α-helix structure in keratin is classified into:
Hard keratin: Higher cysteine content, giving greater rigidity (e.g., nails)
Soft keratin: Also rich in cysteine, but less than hard keratin resulting in more flexibility (e.g., skin)

STRUCTURE

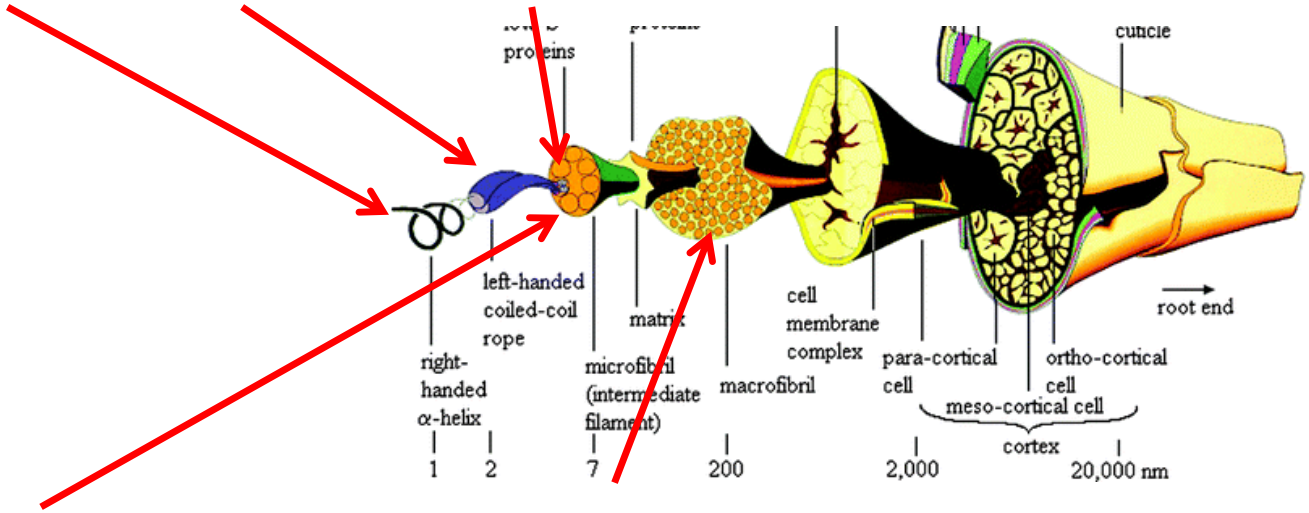
- Two helical α-keratin molecules (protofilaments) interwind forming a dimer.
- Two dimers twist together to form a 4-molecule protofibril.
- Eight protofibrils combine to make one microfibril.
- Hundreds of microfibrils are
- cemented into a macrofibril and finally, into the keratin fiber.



α-KERATINS STRUCTURE



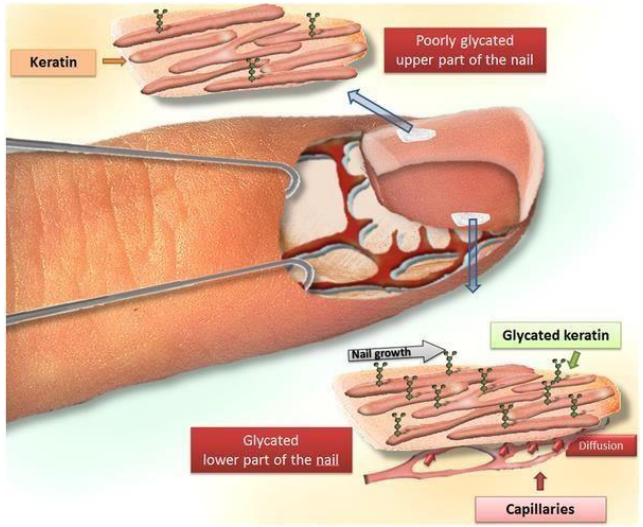
- α-helix (1), Coiled coil (2), Protofibril (4),

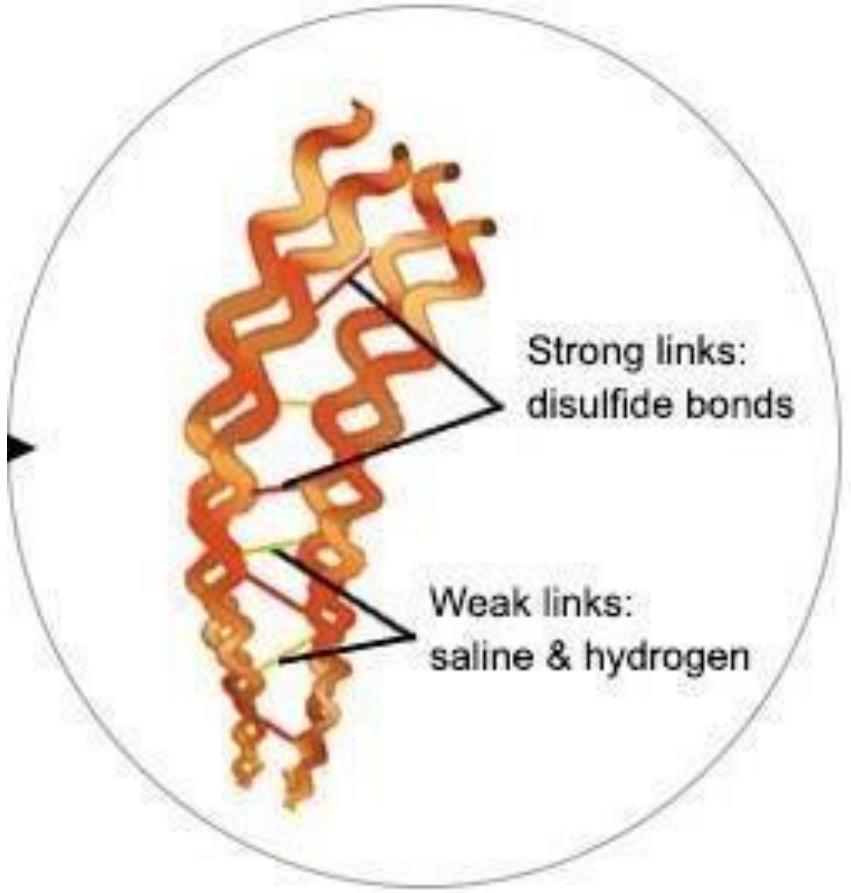


- Microfibril (28-32) (7-8 proto), Macrofibril (1000_s) (100_s micro)

KERATIN IN NAILS

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





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 (agent) (usually ammonium thioglycolate) is added to reduce some of the disulfide cross-links (break them down)(can be very high temperature, to break the covalent disulfide bonds). 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.

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:

يا فوز من نال الشّـهادة صادقاً.. تُمحى الذنوب إذا الدّمـاء تقطّرُ
وإذا الزّهور تعطّرت بعبيرها.. مسكًا تفوح جراحه وتعطّرُ
أكرِم بمن نال الشّـهادةَ مُخلِصًا.. في جنّة الفِردَوس ثاوٍ يمرحُ
نال النّعيم مُعجّلًا ومُؤجّلًا.. قد شيّعوهُ وهم بمـوتهِ يمدحوا
واللّون لون الـدمِّ لكنّ ريحـهُ.. كالمِسك ينزِف بالعبير وينضحُ
وإذا ثوى في القبر كان مُؤمَّنًا.. من فتنةٍ وعن العذابِ يُزَحزحُ
ما مـات من في الله يشري روحَهُ.. حيٌّ تُمدُّ له القُصور وتُفسَحُ
ما مات من نال الشّـهادة مخلصًا.. سيروا إلى تلك الحياة وشمّروا