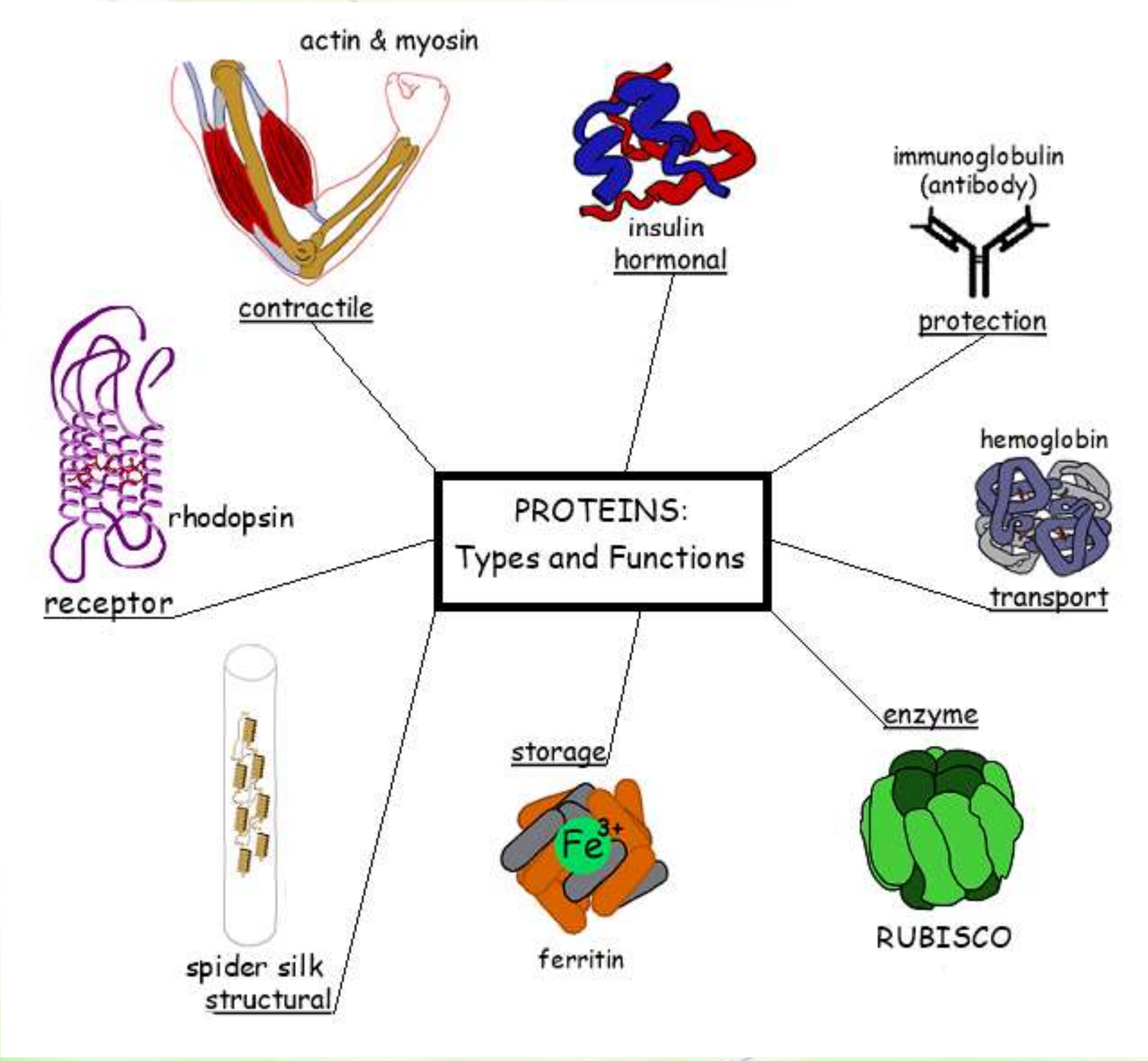
Structure-function relationship:
Fibrous proteins

Summer semester, 2023

Biological Functions of Proteins

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

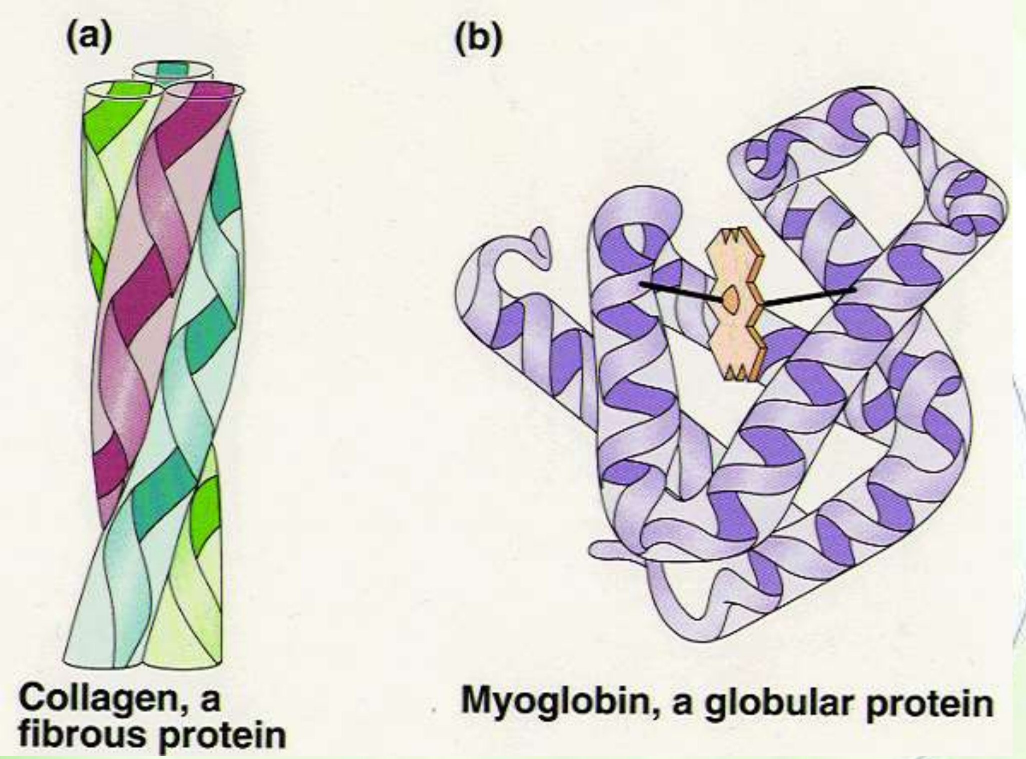


Types of proteins

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

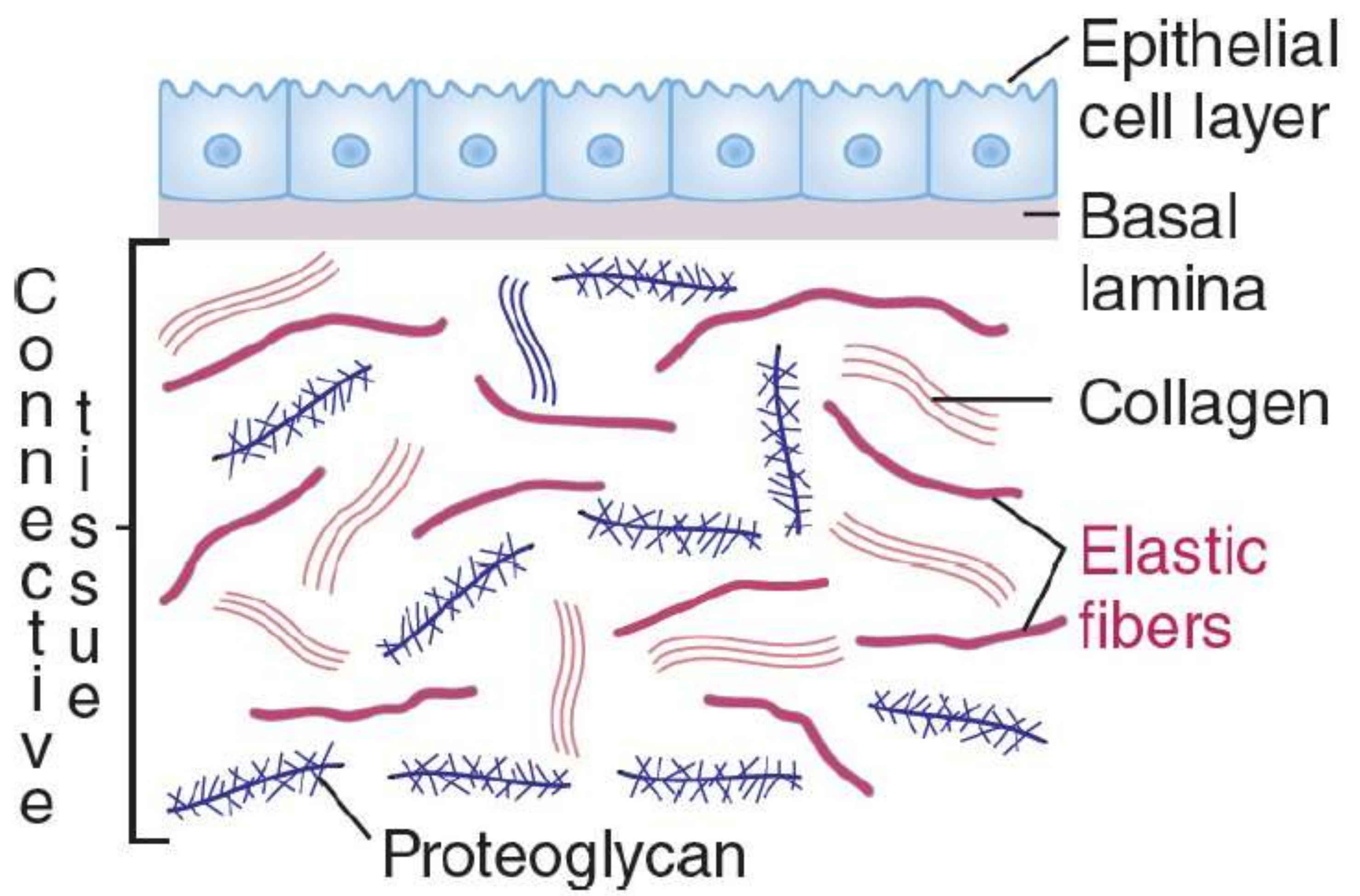
<u>Examples</u>

- Fibrous proteins: collagens, elastin, and keratins
- Globular proteins: myoglobin, hemoglobin, and immunoglobulin

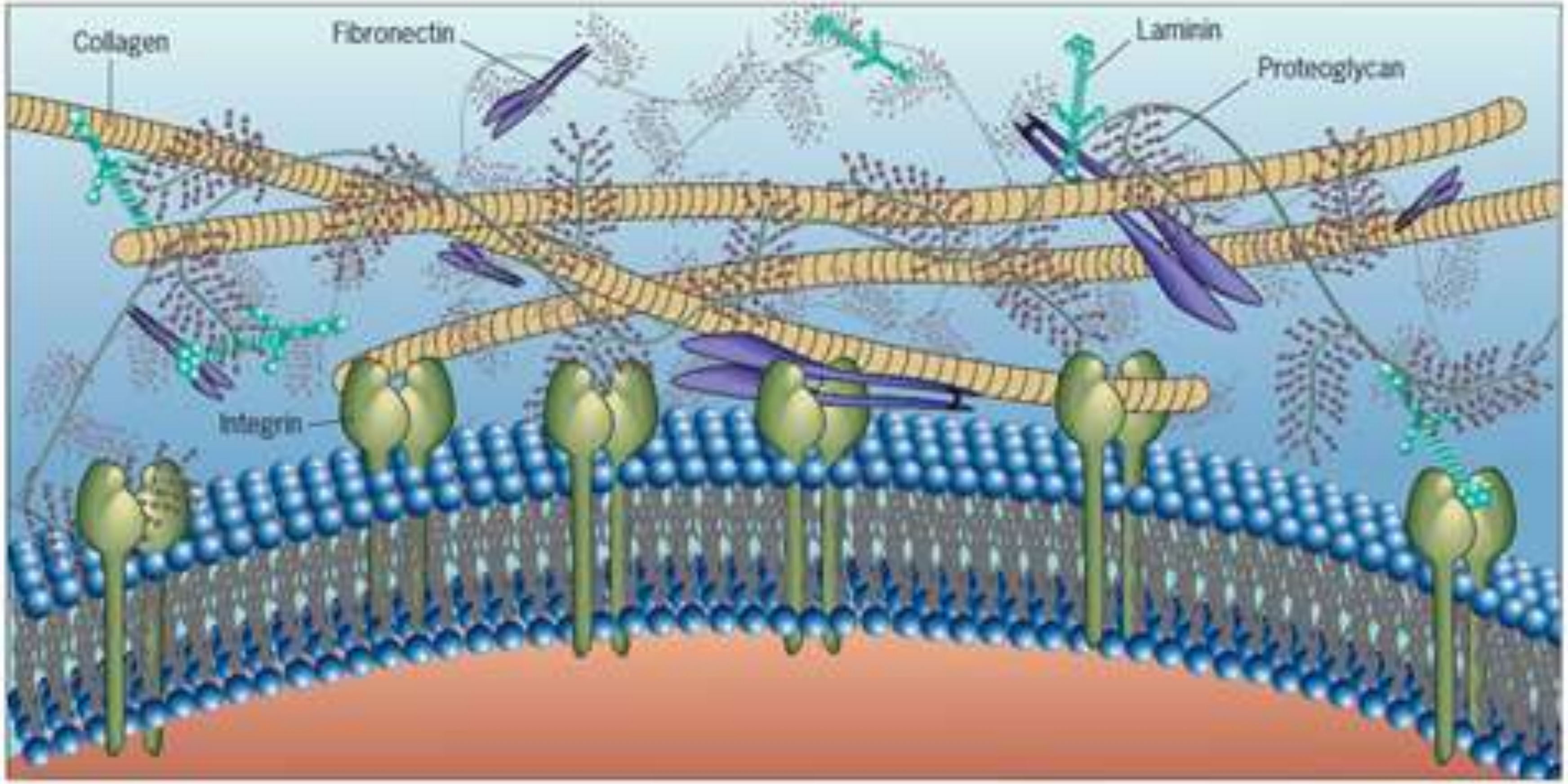


The extracellular matrix

- 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.

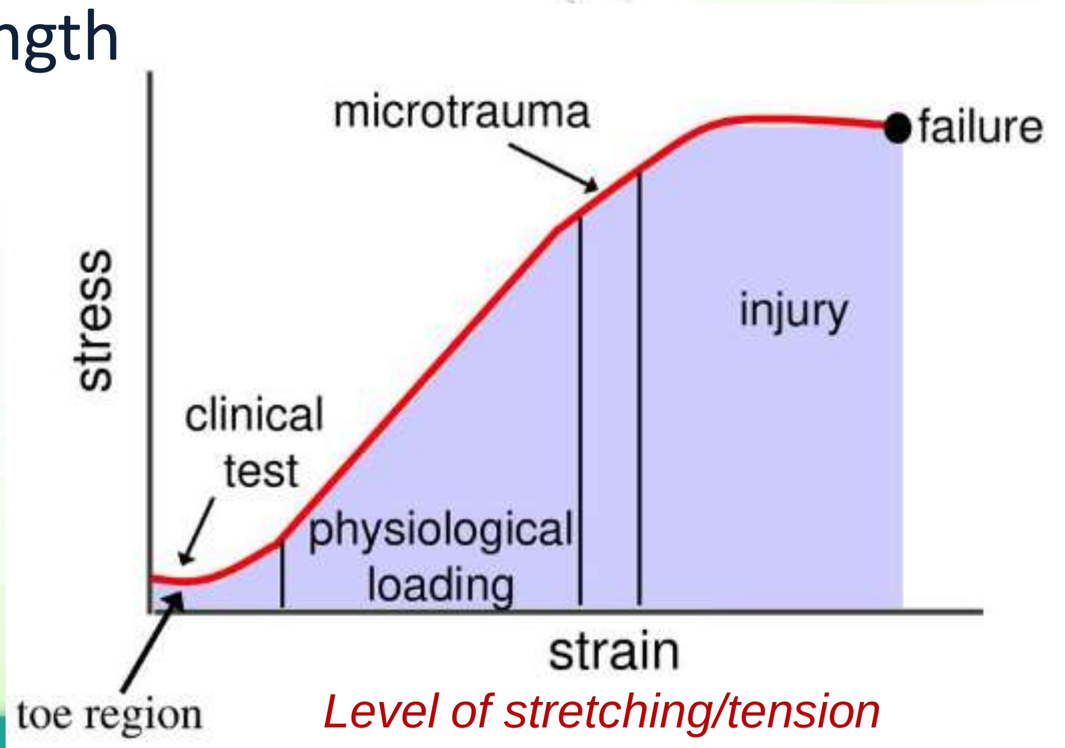


Collagens



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
- Primary feature: stiffness and tensile strength

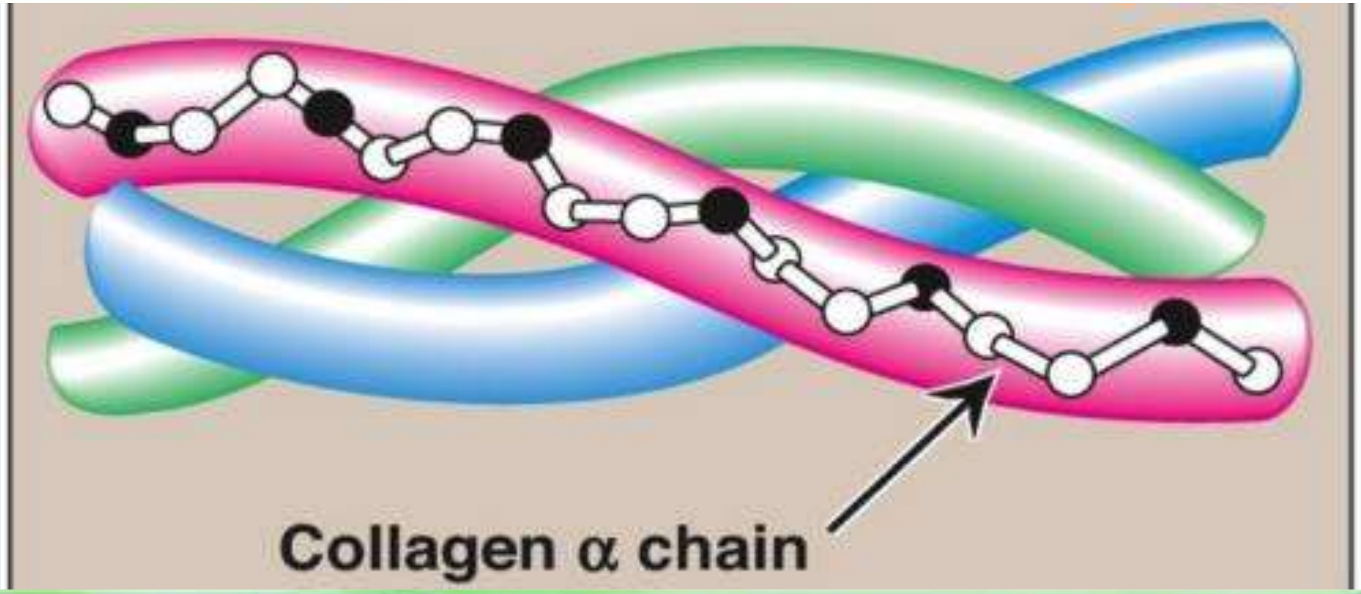


Types of collagen

- 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)

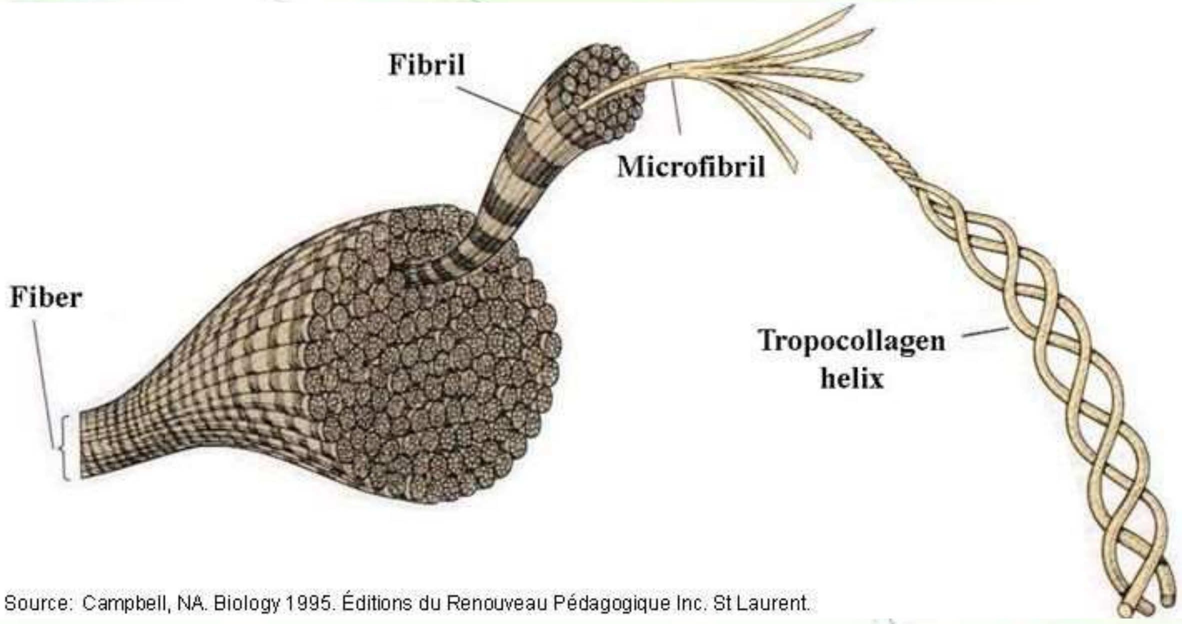
Structure

- It is a triple-stranded, helical protein where three collagen polypeptide chains, called α chains, are wound around one another in a ropelike superhelix.
- 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.



Formation of collagen fibers

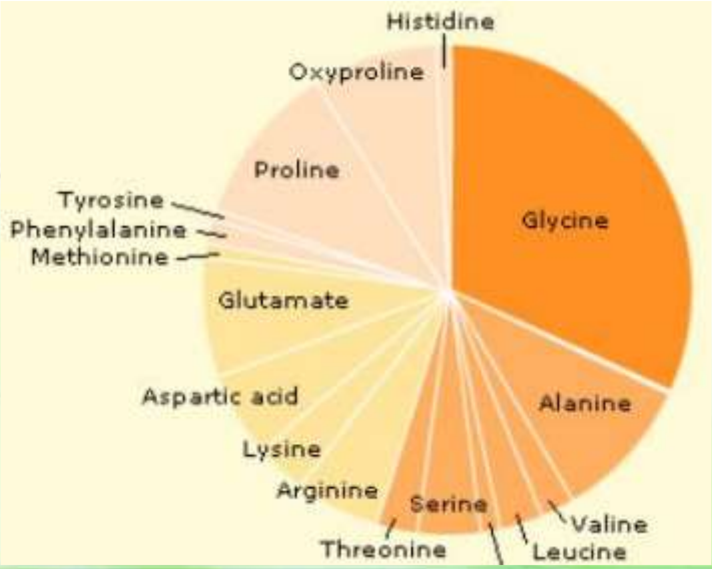
- Following their release, 5 of the protocollagens polymerize into a microfibril and connect with each other via covalent aldehyde links between lysine residues.
- Microfibrils align with each other forming larger collagen fibrils, which are strengthened via further cross-links.
- Fibrils then assemble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

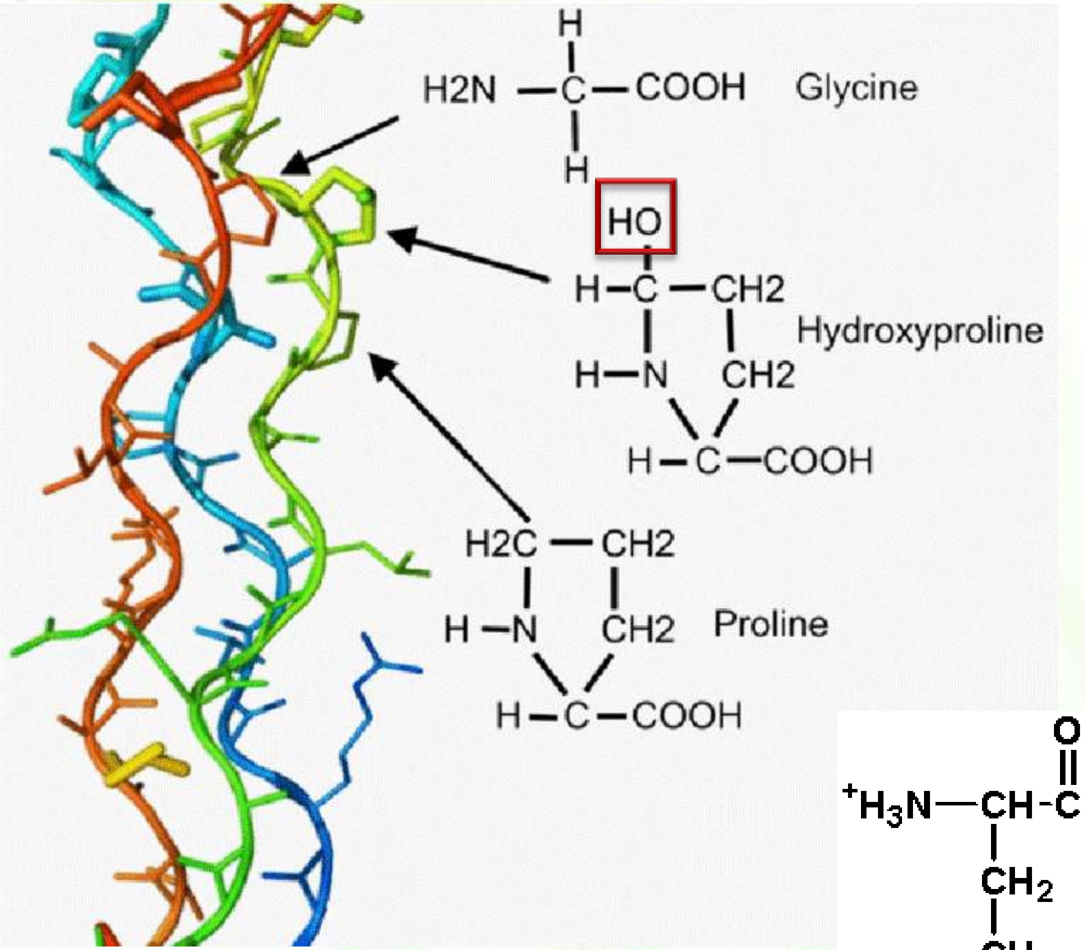


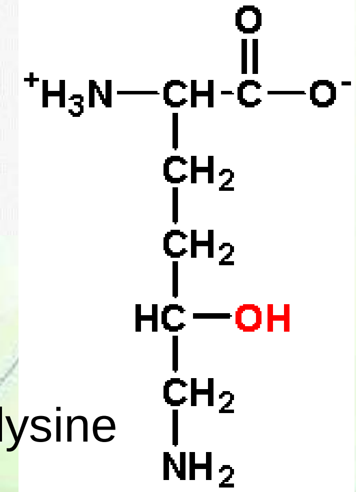
Source: Campbell, NA. Biology 1995. Éditions du Renouveau Pédagogique Inc. St Laurent.

The primary structure of collagens

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



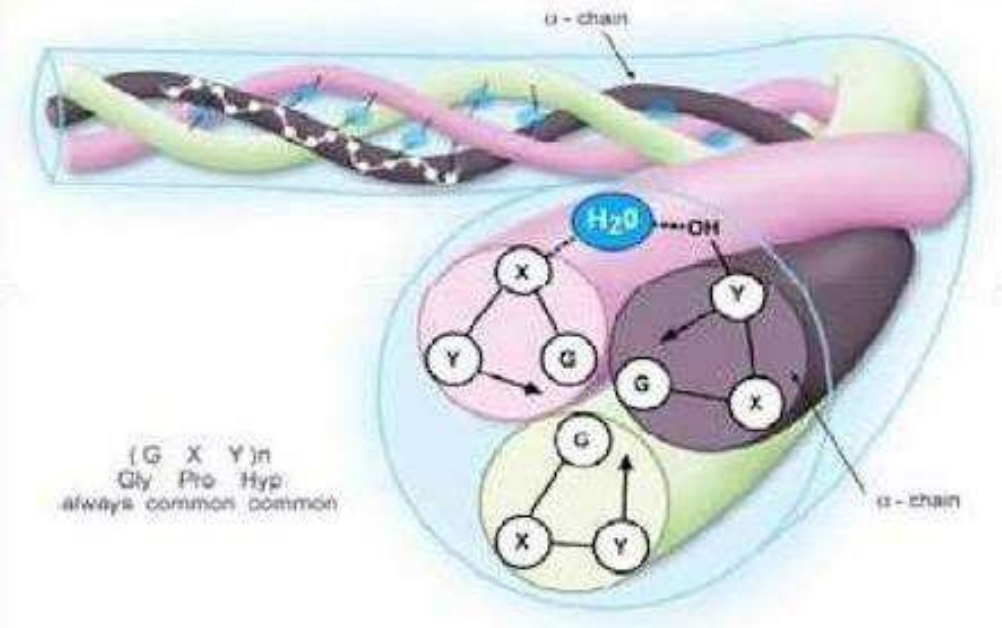


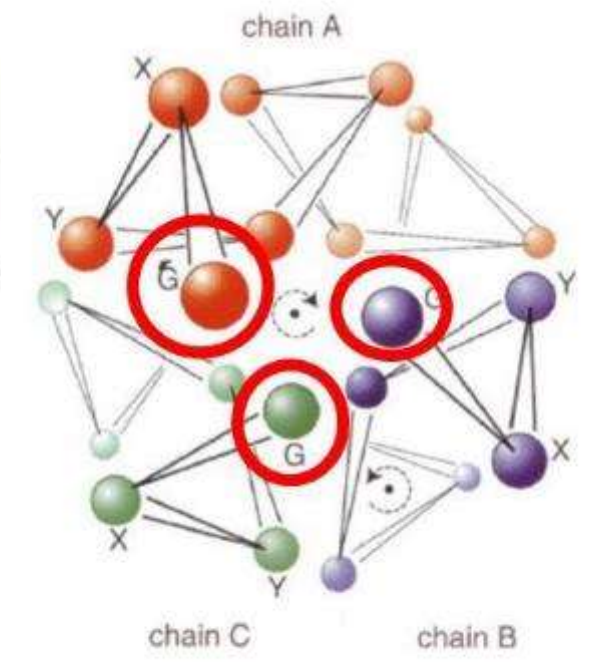


Hydroxylysine

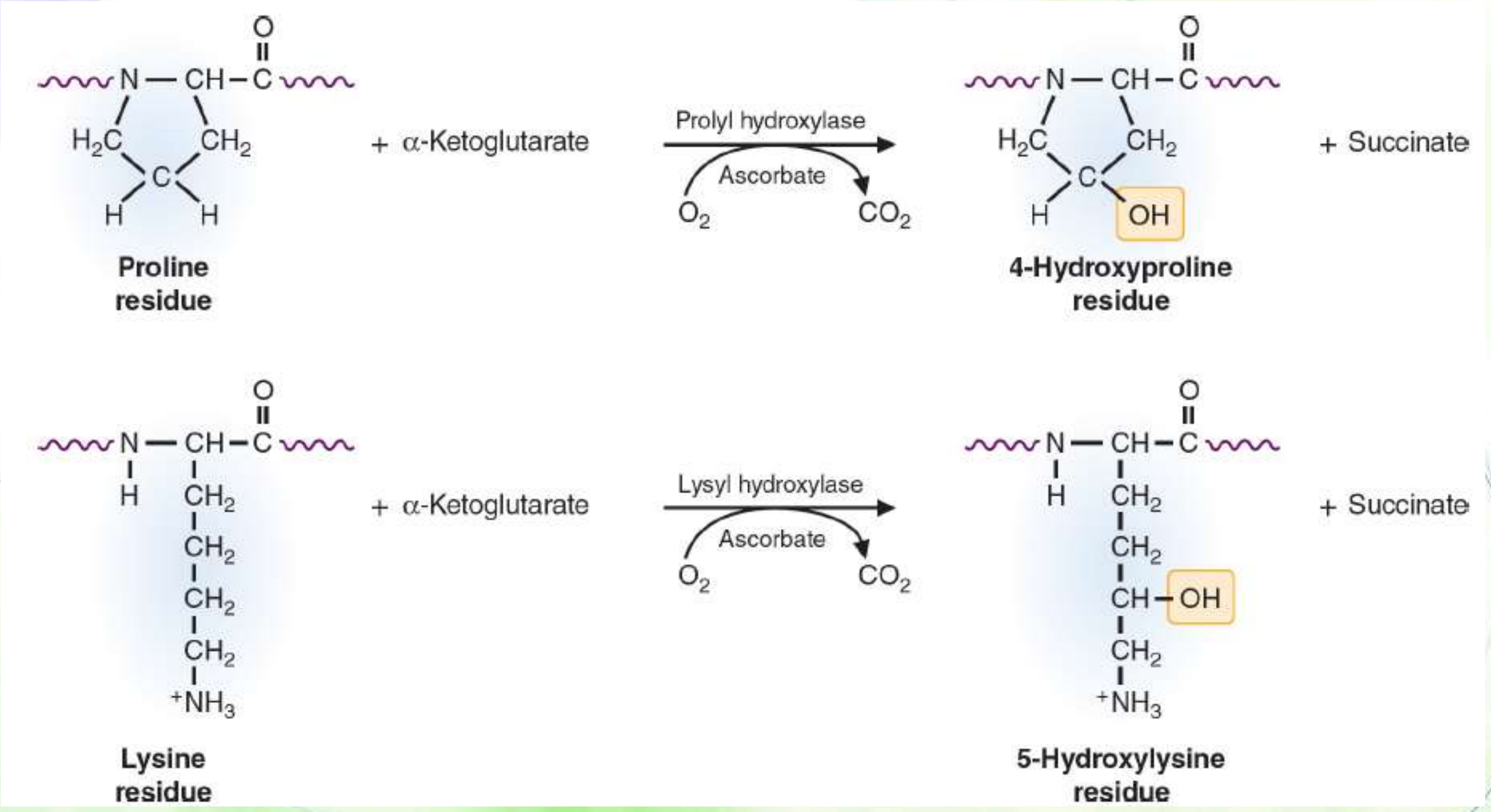
Functional purposes of amino acids

- 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.



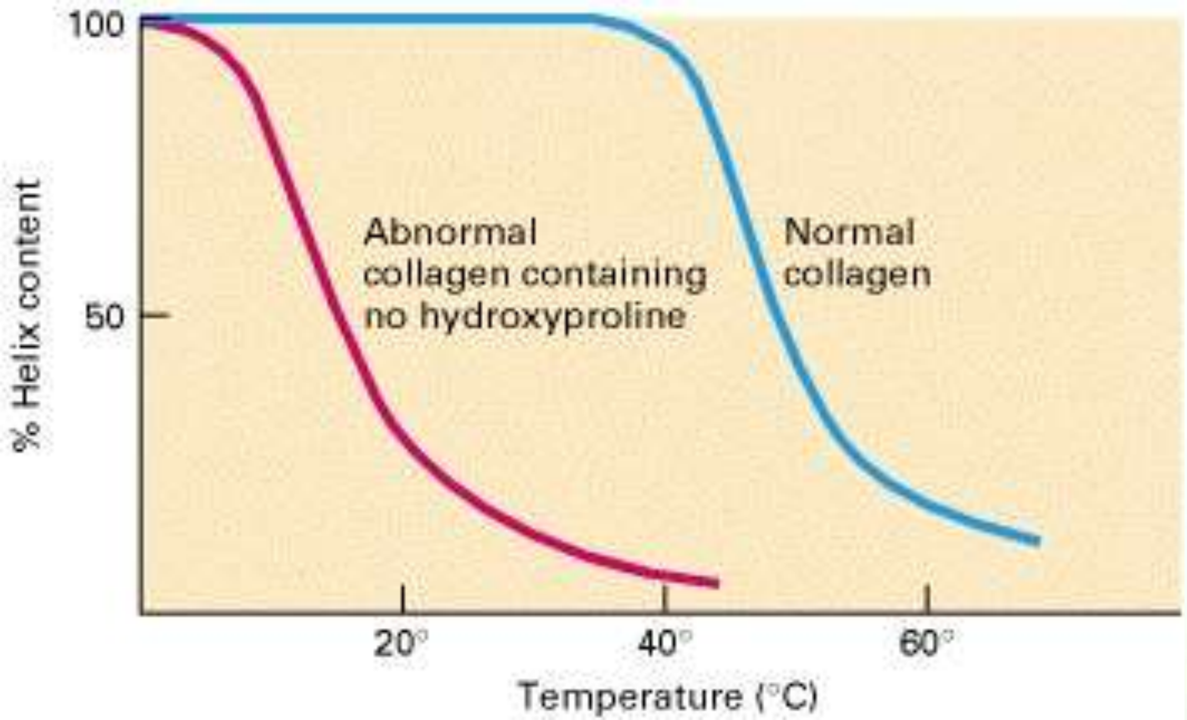


Hydroxylation of proline and lysine



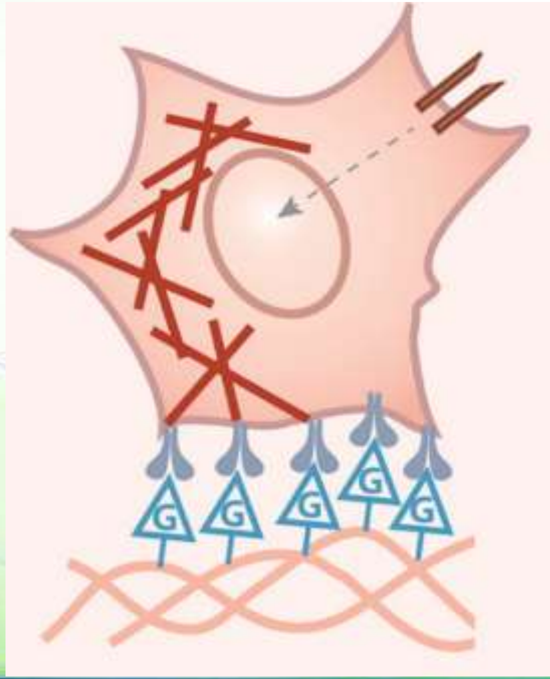
Purpose of hydroxyproline

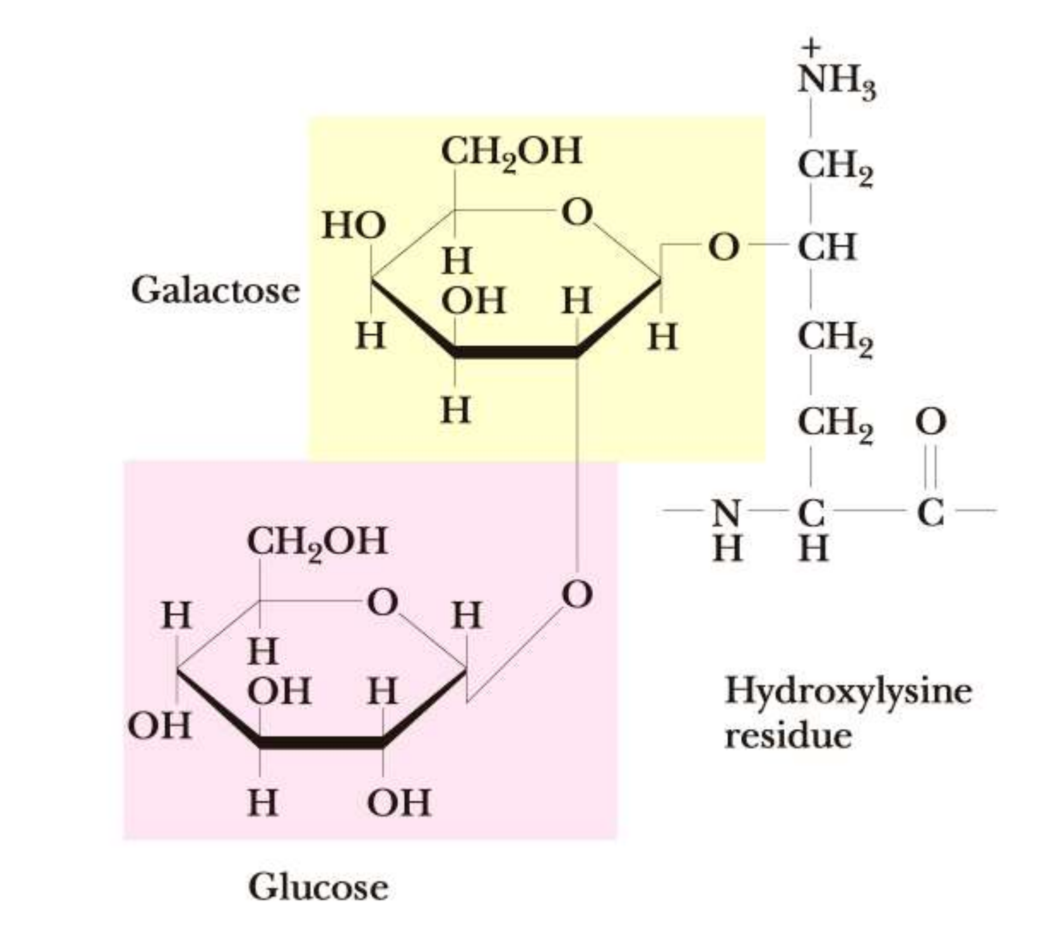
- Normal collagen is stable even at 40°C.
- Without hydrogen bonds between hydroxyproline residues, the collagen helix is unstable and loses most of its helical content at temperatures above 20°C.



Hydroxylysine

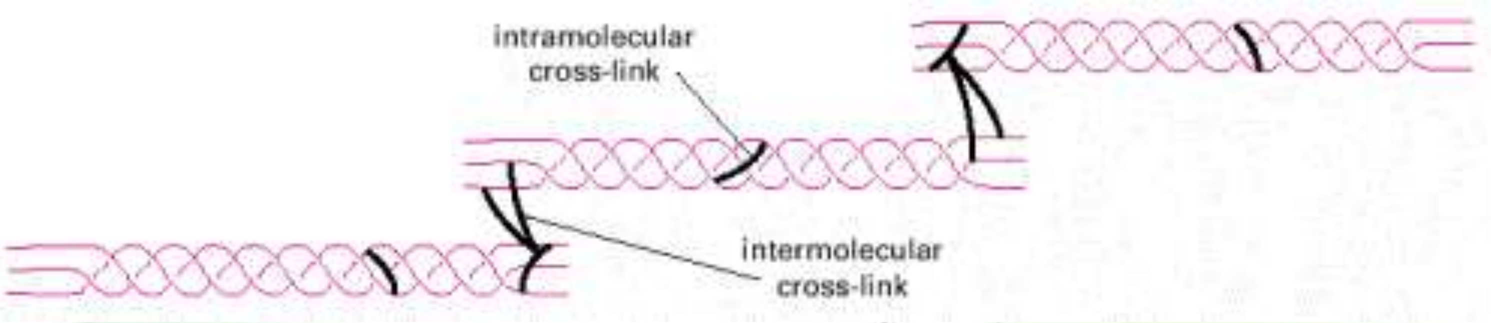
- Hydroxylysine serves as attachment sites of polysaccharides making collagen a glycoprotein.
- Sugars allows collagen to recognize and interact with cell surface receptors.

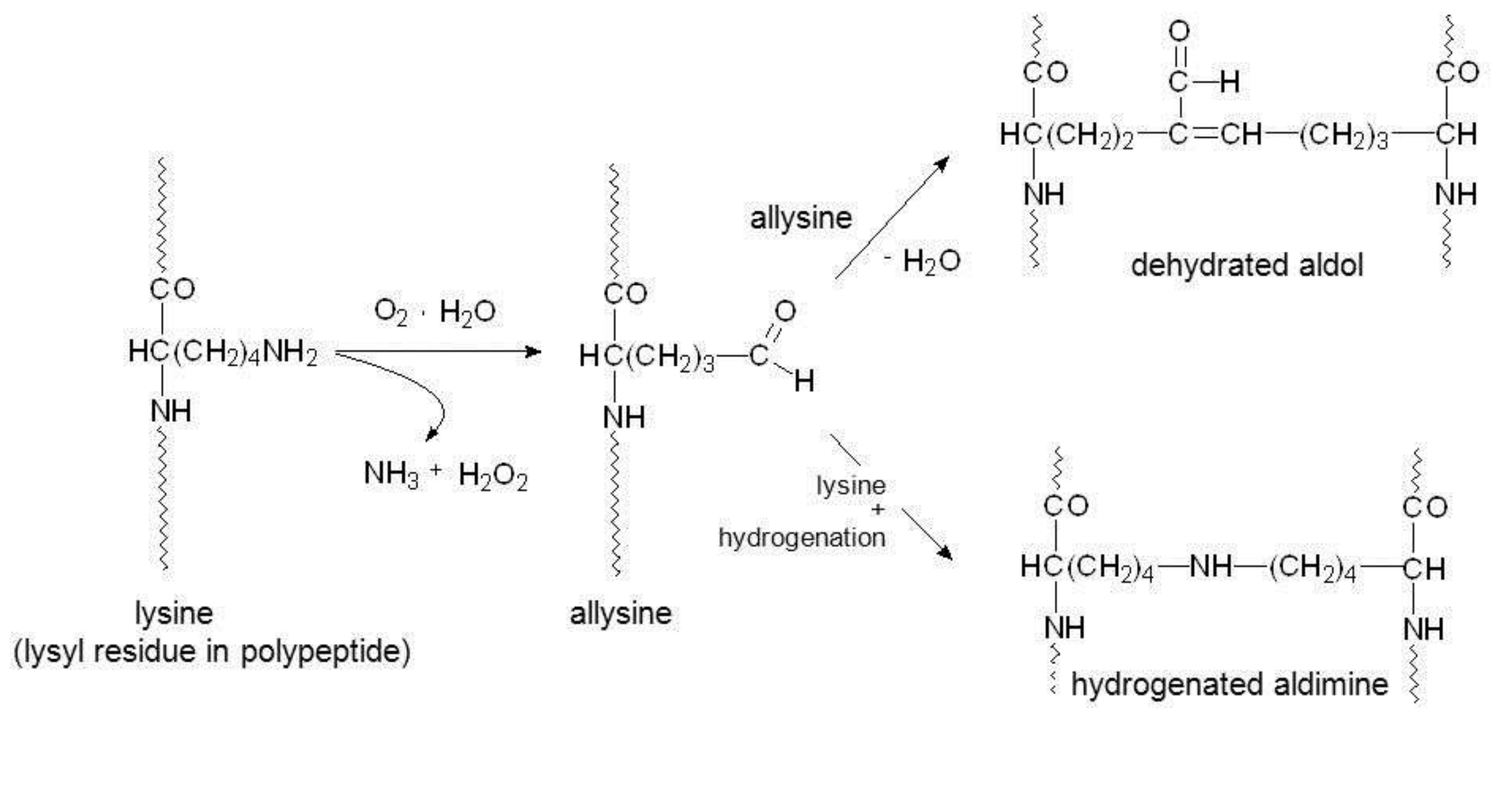




Oxidation of lysine

- 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.



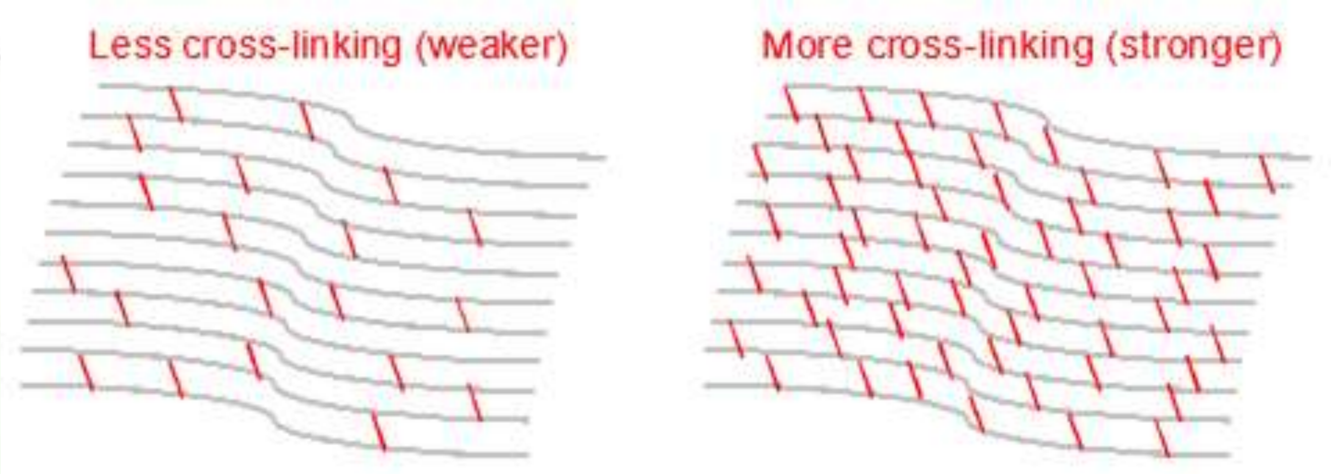


Deficient cross-linking

- 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.

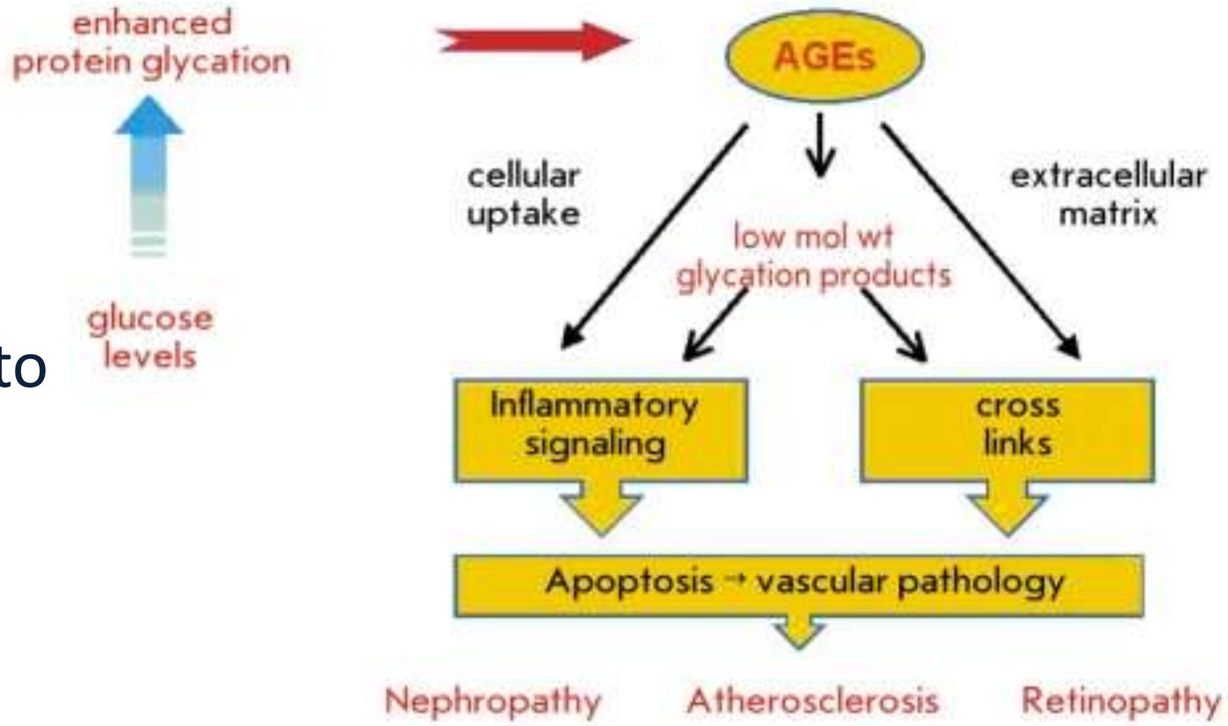
More on cross-linking

- 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.



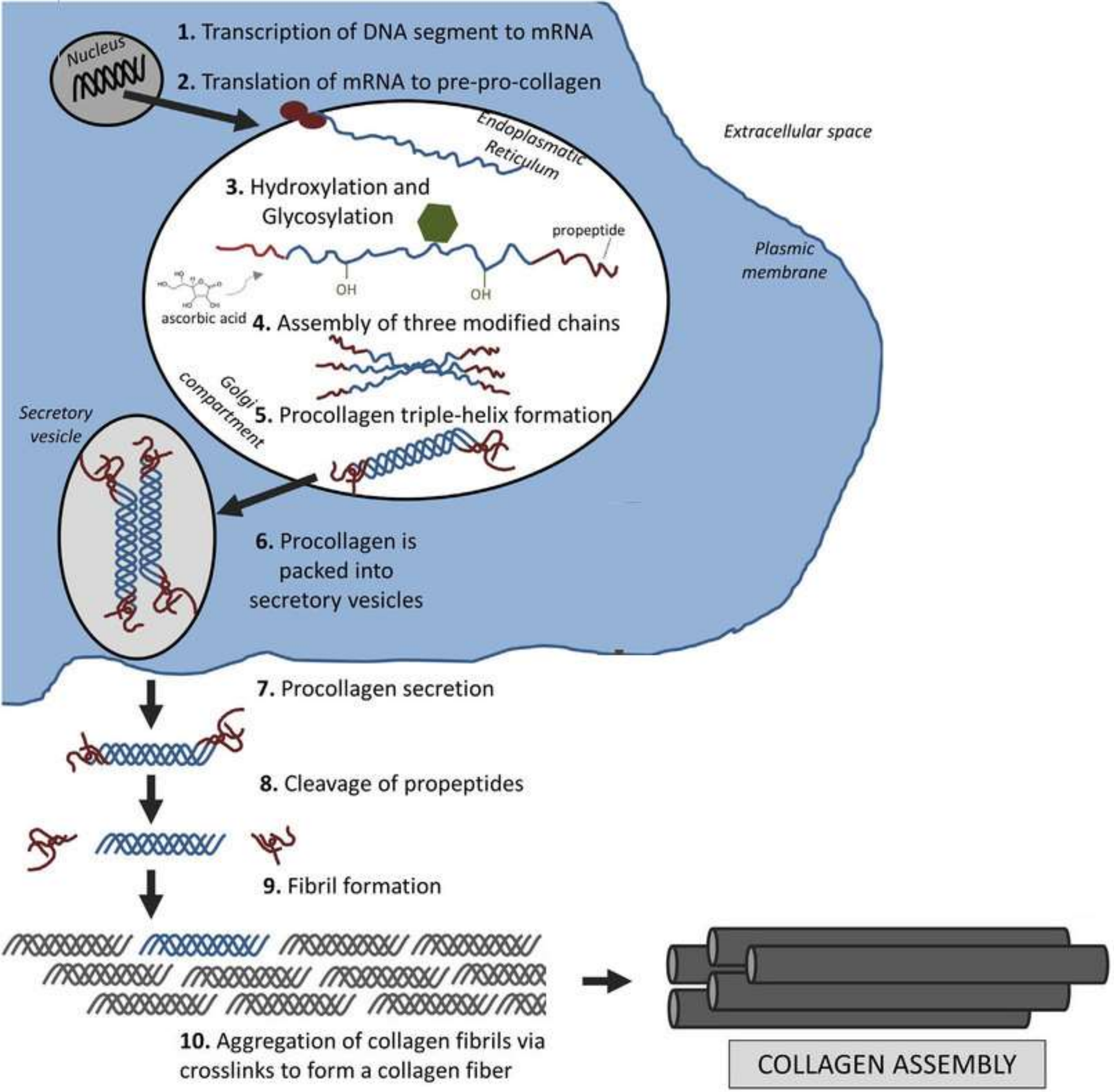
Advanced glycation end products

- Proteins (e.g., collagen) 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.



Uncontrolled diabetics suffer from cardiomyopathy

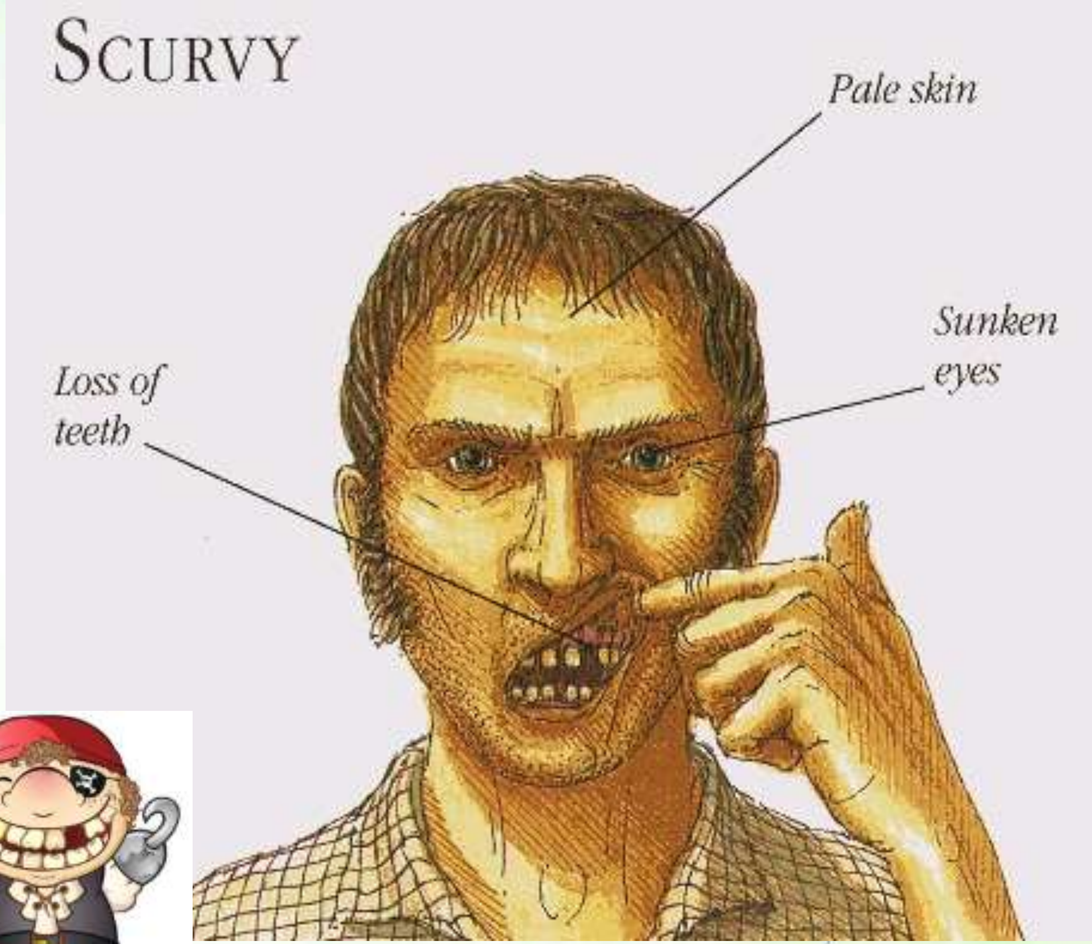
- Glycated proteins in tissues are further modified by nonenzymatic oxidation forming additional cross-links.
- The net result is the formation of large protein aggregates termed advanced glycation end products (AGEs), which increase cellular oxidative stress.



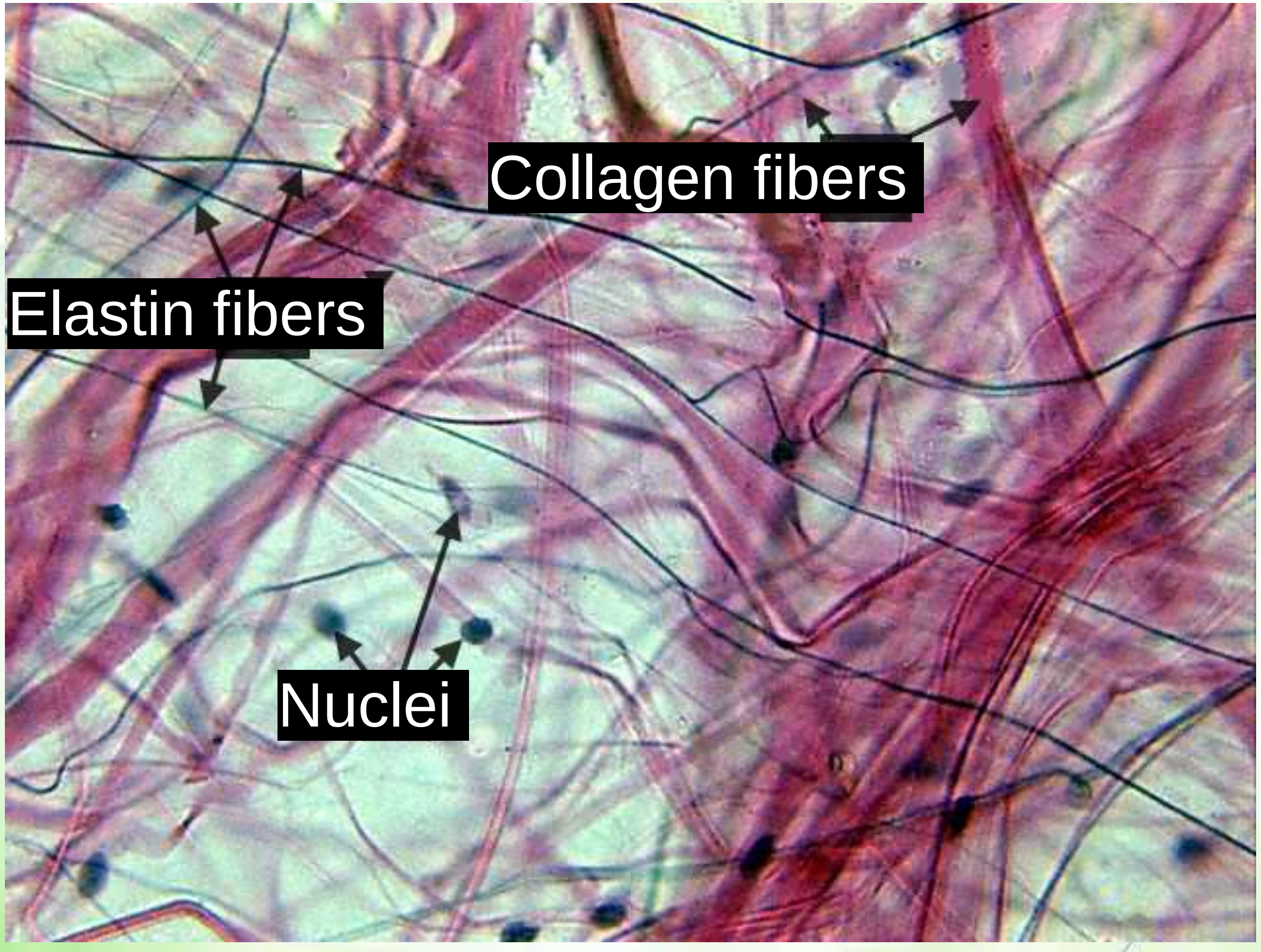
Synthesis of collagen

Scurvy

- Deficiency of ascorbic acid (vitamin C) prevents proline 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.

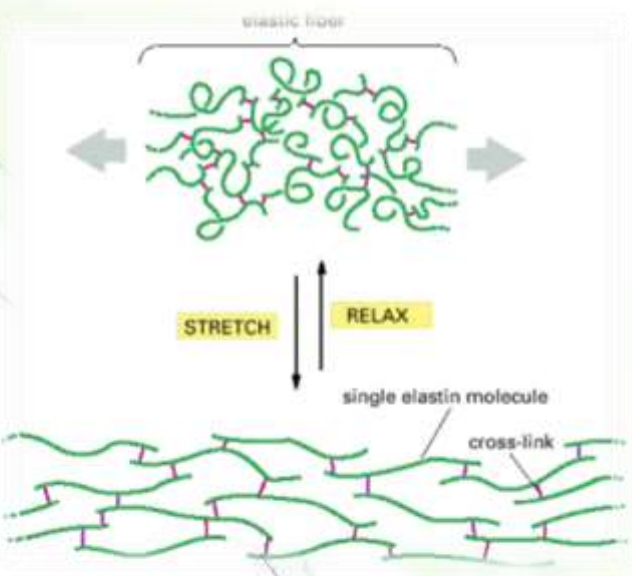


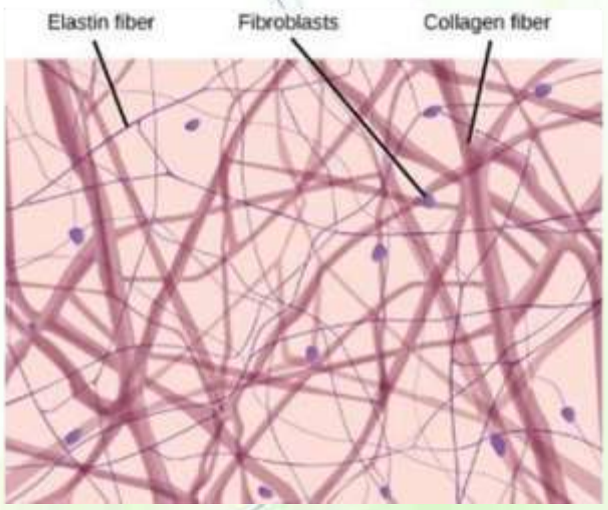
Elastin



Resilience vs. flexibility

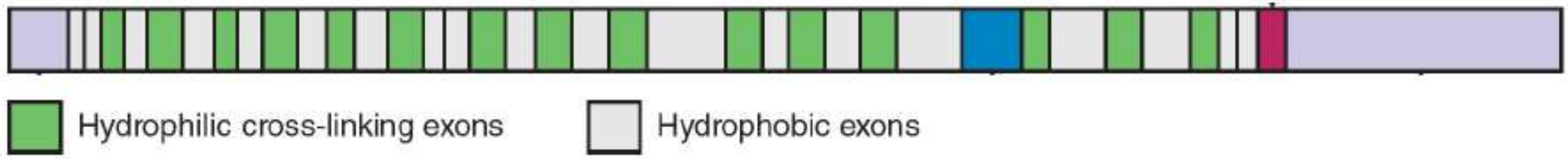
- Many tissues, such as skin, blood vessels, and lungs, need to be both strong and elastic in order to function.
- A network of elastic fibers in the extracellular matrix of tissues gives them the required resilience so that they can recoil after transient stretch.
- Long, inelastic collagen fibrils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





The primary structure of elastin

- Elastin has a highly cross-linked, insoluble, undefined structure.
- Its precursor, tropoelastin, is a molecule of high solubility, and contains repeated, alternating domains of two alternating types:
  - Lysine and alanine–rich hydrophilic domains.
  - Hydrophobic domains that are rich in valine, proline, and glycine.
- Elastin is, thus, a highly hydrophobic protein.



Elastin

- Elastin contains some hydroxyproline, but no hydroxylysine.
  - It is not glycosylated.
- Upon secretion from the cell, the tropoelastin is aligned with the microfibrils, and lysyl oxidase initiates cross-linking between lysines to one another.

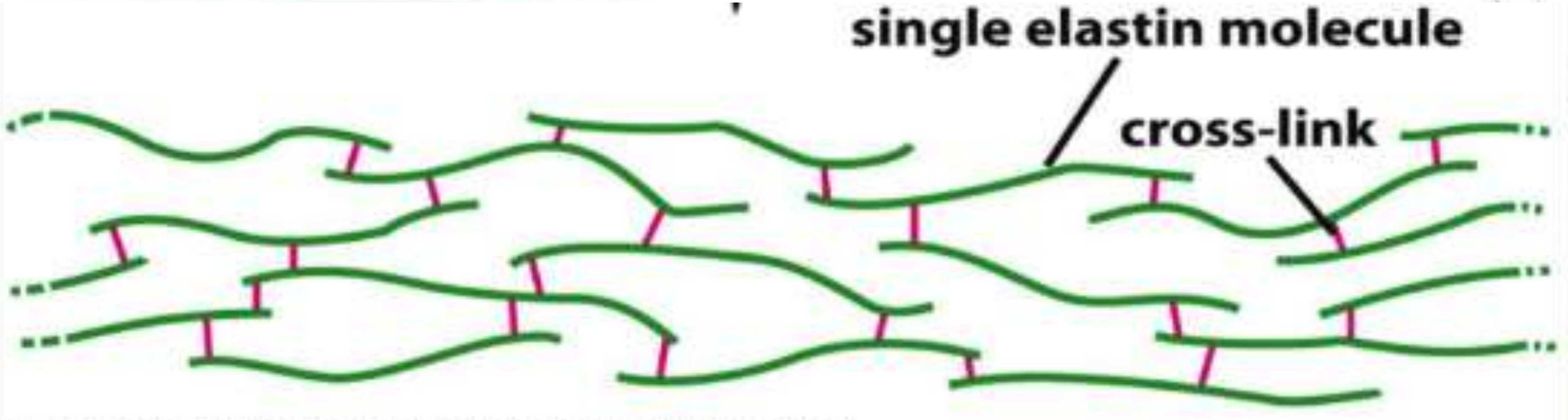


Figure 19-71 Molecular Biology of the Cell 5/e (© Garland Science 2008)

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.

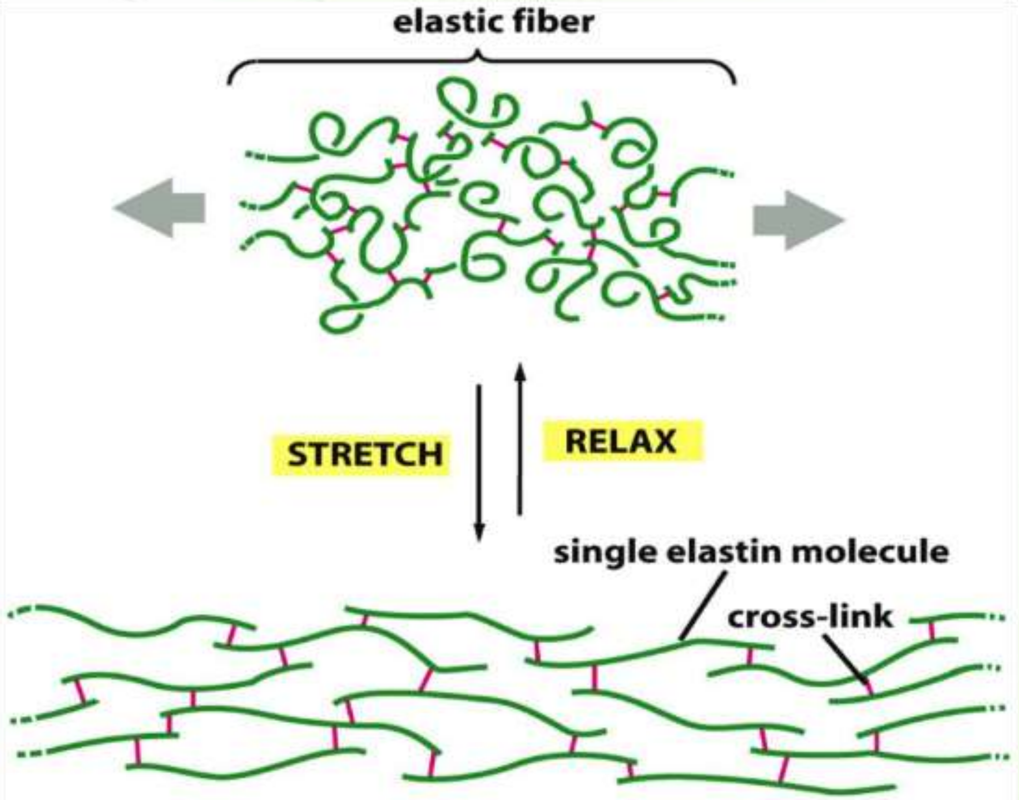
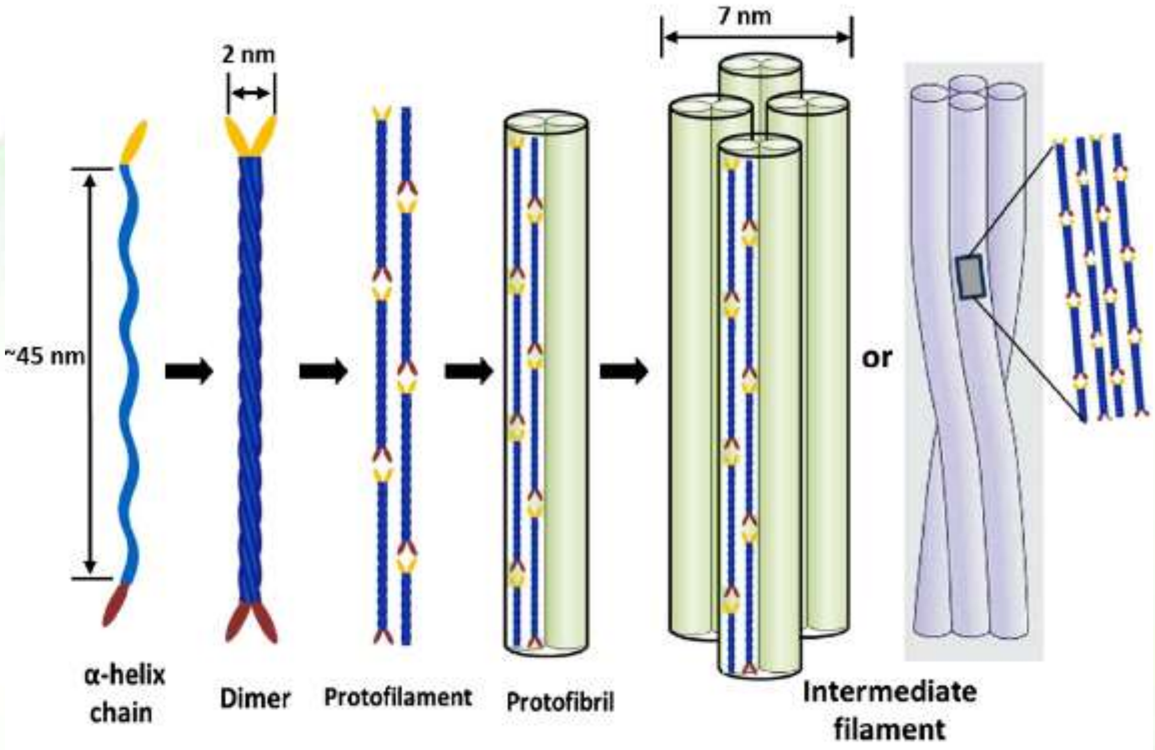


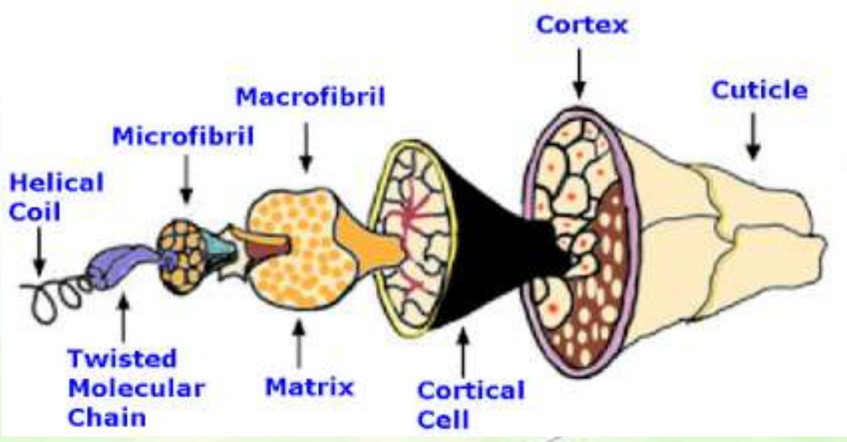
Figure 19-71 Molecular Biology of the Cell 5/e (© Garland Science 2008)

α-Keratins

α-keratins structure (hair vs. fingernails)

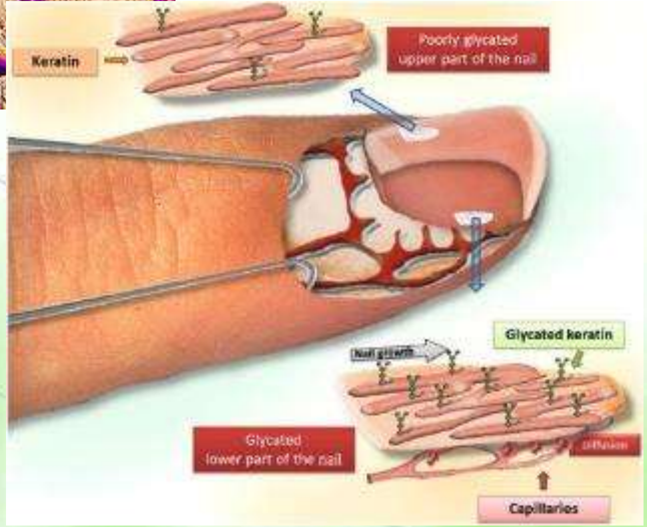
- Two helical α-keratin molecules form a coiled-coil dimer, which has sulfur cross-links.
- Two coiled-coil dimers associate forming a tetramer and tetramers associate head-to-tail forming protofilaments, which have nonhelical N- and C-termini that are rich in cysteine residues and cross-link.
- Two 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.

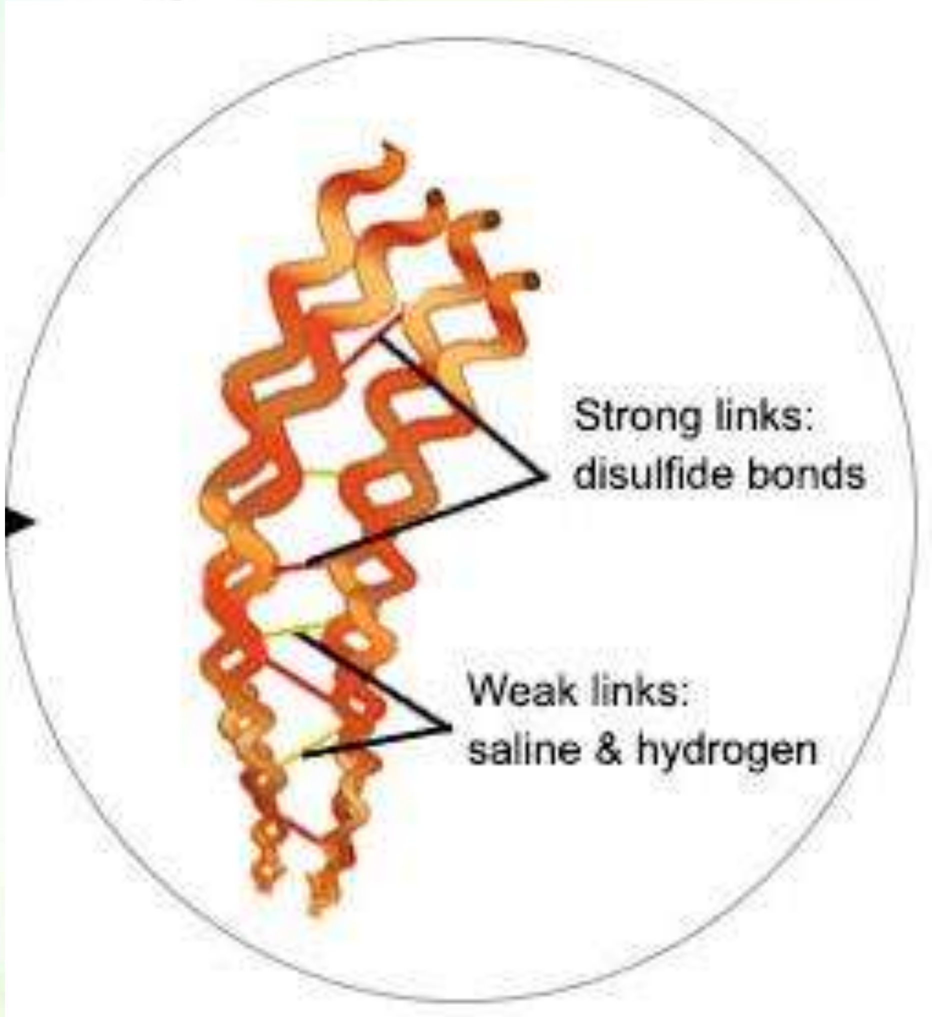




Keratin in nails

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



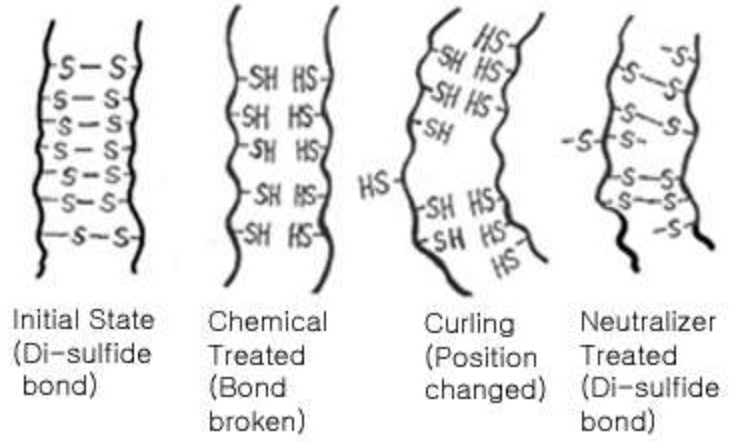


Looking beautiful?

Having a hair design?

<u>**Temporary Wave**</u>

- 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.



<u>**Permanent wave**</u>

- 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.