Histochemistry (304 C)

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Extra Cellular Matrix (ECM)

Collagen and elastin

(Structure, Synthesis, Function, Disease)

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The Extra Cellular Matrix: ECM

- Extra Cellular: outside the cell
  Matrix: structure made from a network of interacting components

The ECM is composed of an interlocking mesh of fibrous proteins and glycosaminoglycans (GAGs).

Components of the ECM are produced intracellularly by resident cells, and secreted into the ECM via exocytosis.

Functions of ECM

1-Role in establishing and maintaining cell shape, migration, mechanical support

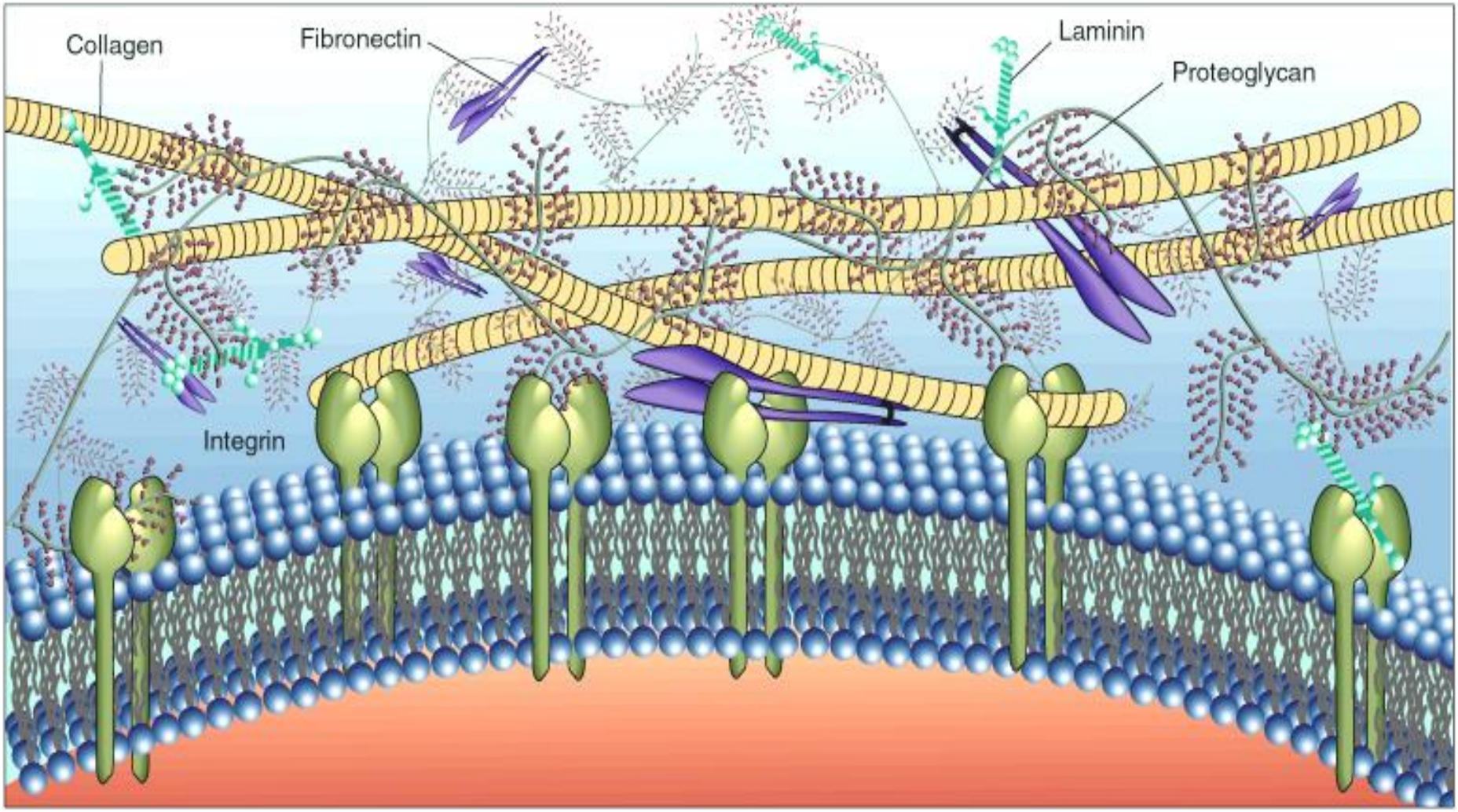
2-Anchorage for cells, segregating tissues from one another, and regulating intercellular communication

3-Sequesters a wide range of cellular growth factors, and acts as a local depot for them

4-Essential for processes like growth, wound healing etc

What are the major proteins of the ECM?

Collagens, Proteoglycans, Elastin, Fibronectin, Laminin, Tenascin.

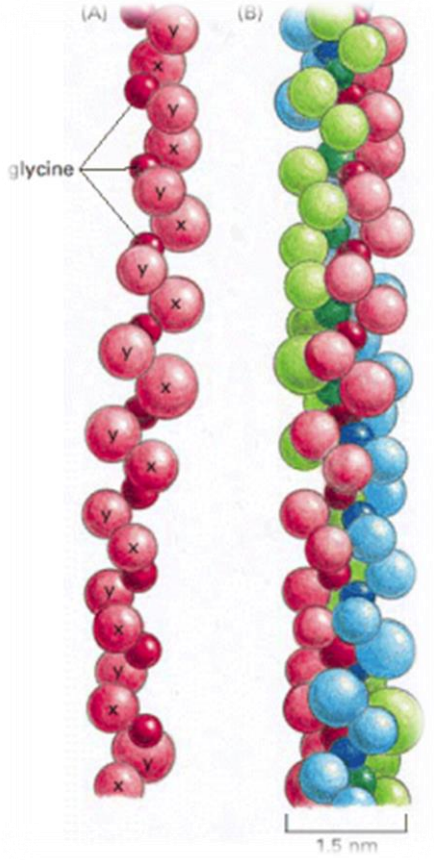


The collagens

- A family of fibrous proteins found in all multicellular animals.
- They are secreted by connective tissue cells, as well as by a variety of other cell types
- They are the most abundant proteins in mammals, constituting 25% of the total protein mass in these animals.

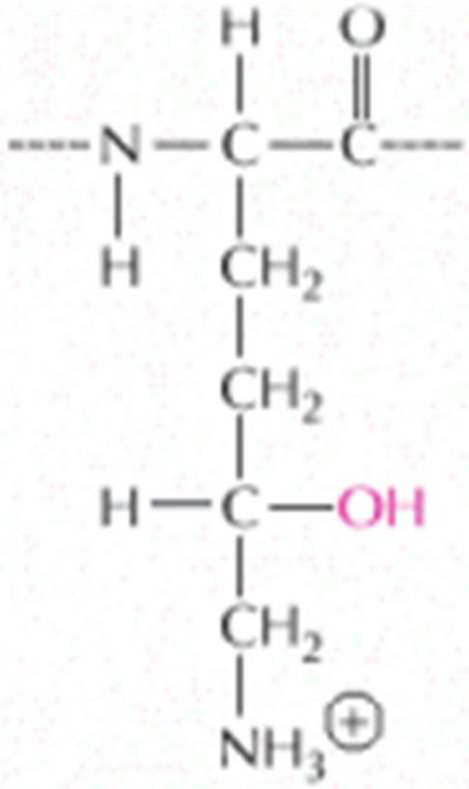
Structural features

- Long, stiff, triple-stranded helical structure,
- Three collagen polypeptide chains, called α chains, are coiled around one another in a ropelike superhelix
- A basic unit of mature collagen is called <u>tropocollagen</u>

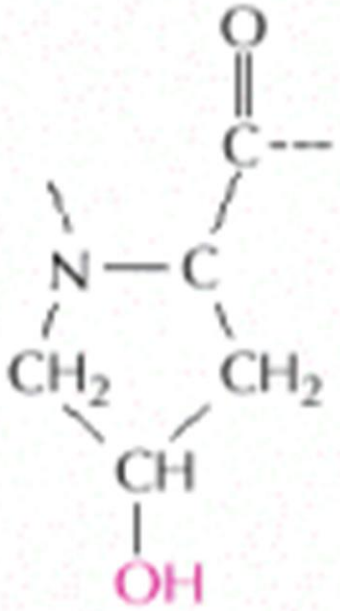


Composition of collagens

- Collagens are extremely rich in proline and glycine
- It is composed mainly of glycine (33%), proline (13%), 4-hydroxyproline (9%)
- Hydroxyproline is unique for collagen and elastin



hydroxylysine
in protein



hydroxyproline
in protein

Amino acid sequence

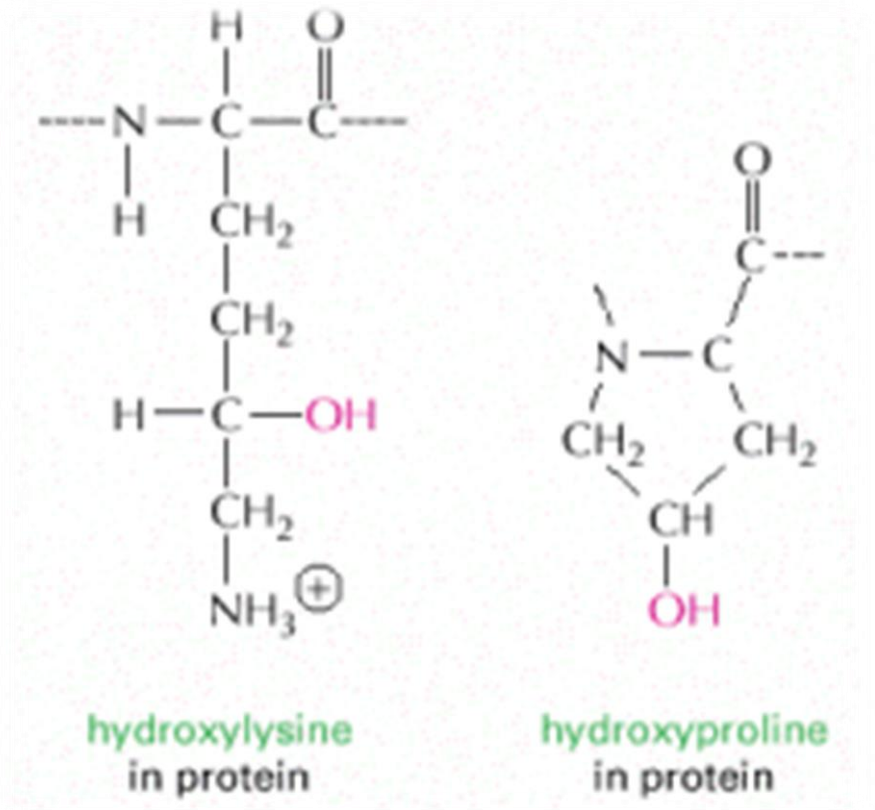
- Every third residue is glycine which lies in the center of the triple helix, with the preceding residue being proline or hydroxyproline in a repetitive fashion
  - pro-Gly-X
  - hydroxypro-Gly-X

Functions of amino acids

- Proline stabilizes the helical conformation in each α chain
- Glycine allows the three helical α chains to pack tightly together to form the final collagen superhelix

Hydroxylysine

- Collagen is also composed of hydroxylysine, which serves as attachment sites of polysaccharides making collagen a glycoprotein

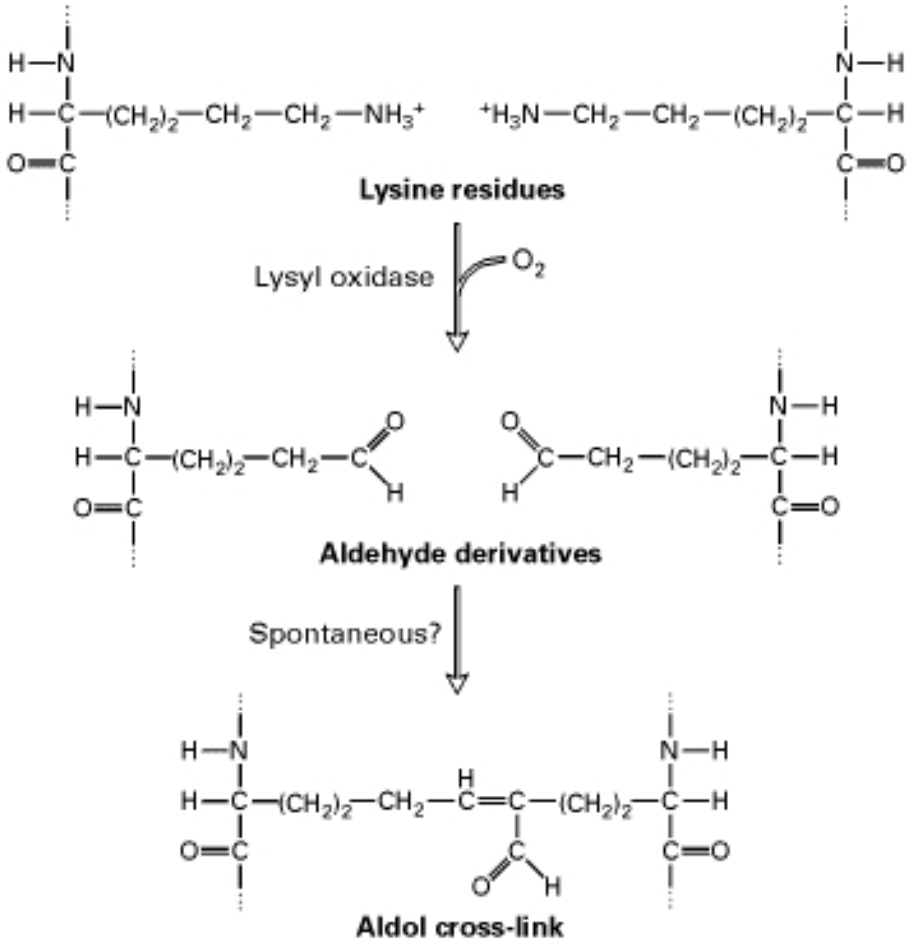


Lysine

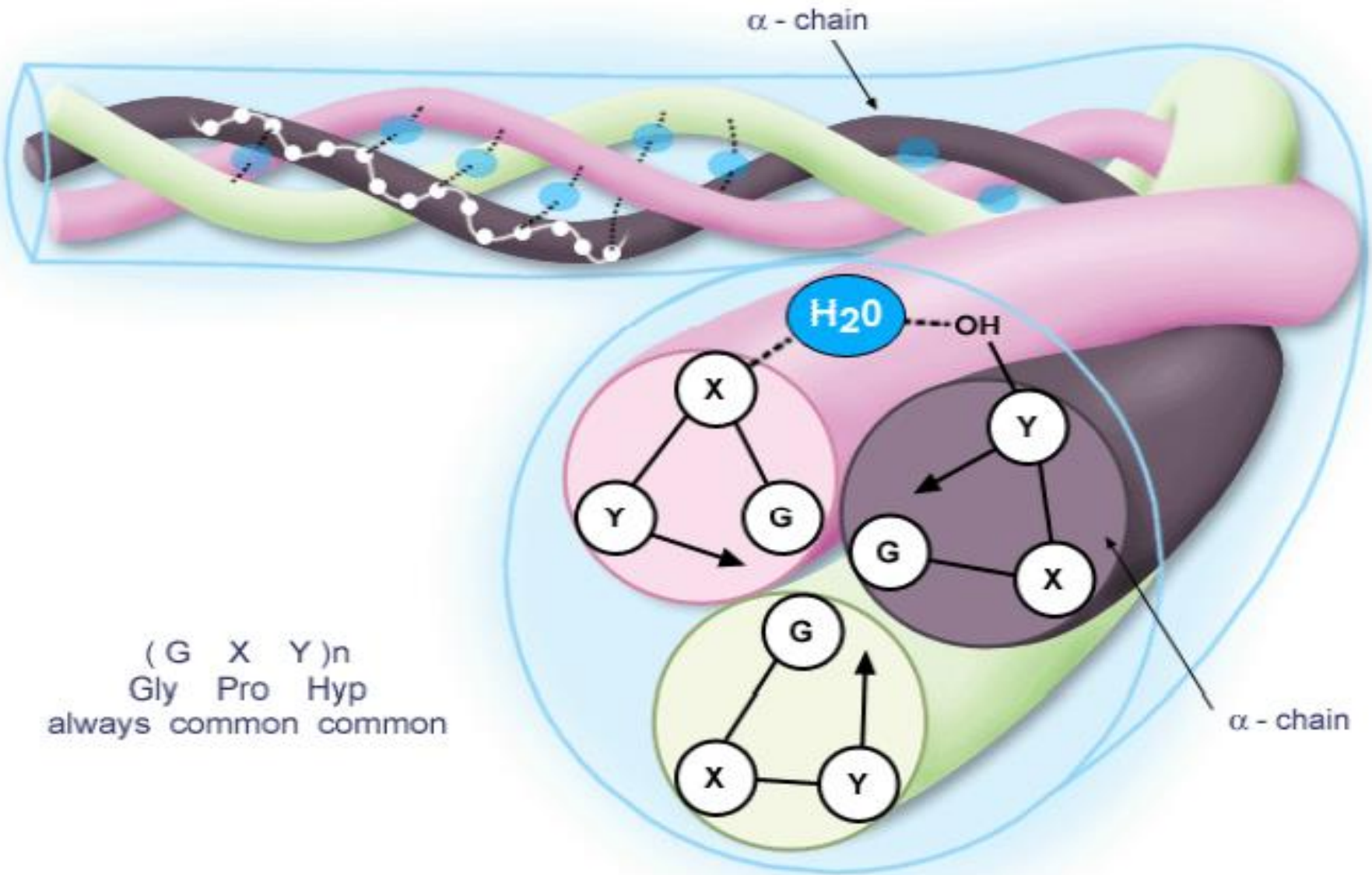
- Part of the toughness of collagen is accounted by the cross-linking of chains via lysine residues

How?

- Some of the lysine side chains are oxidized to aldehyde derivatives, which react with another lysine or another oxidized lysine via the action of lysyl oxidase

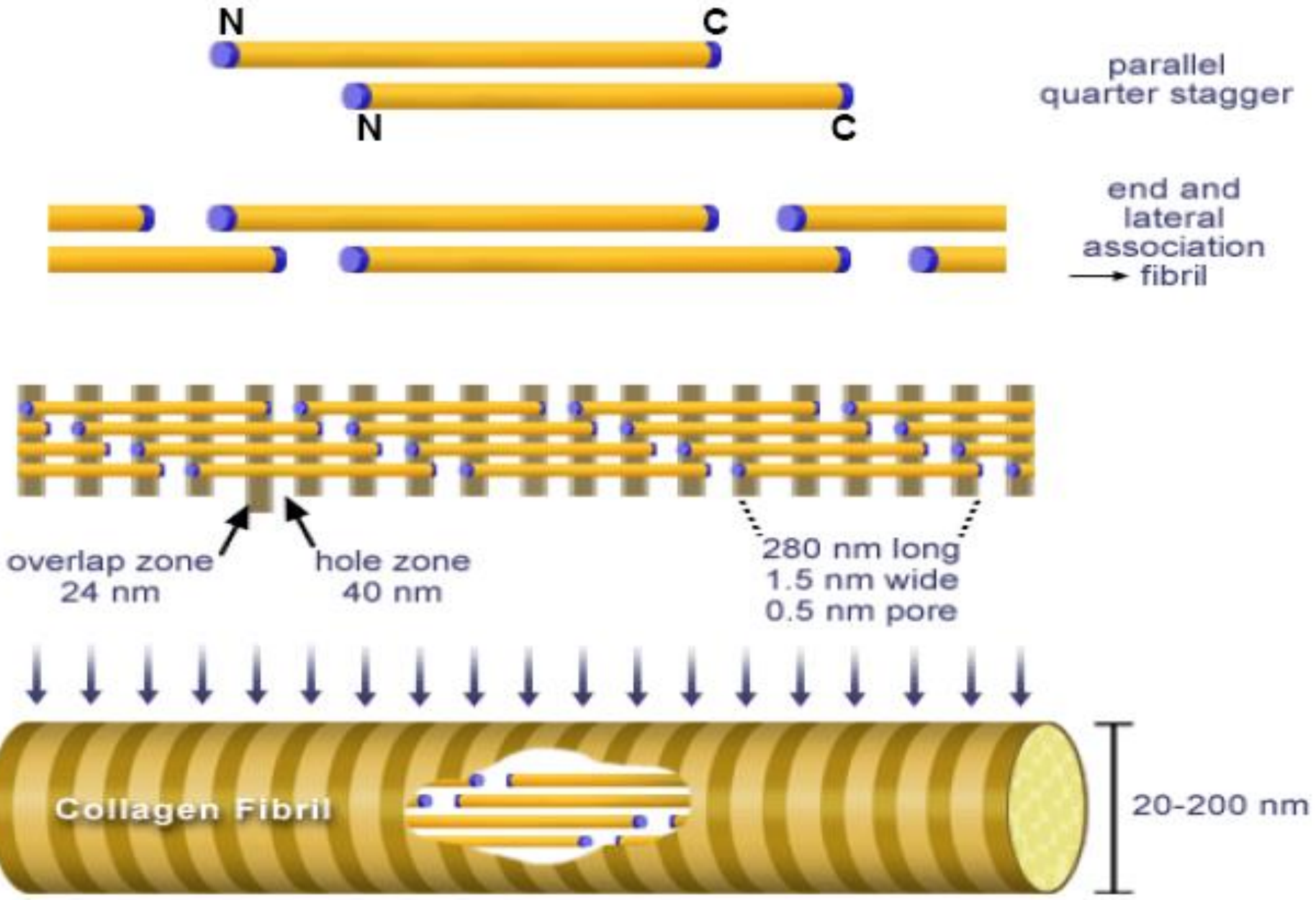


Collagen Triple Helix



(G X Y)n
Gly Pro Hyp
always common common

Collagen Fibrils



Types of collagens

- There are about 40 collagen genes dispersed throughout the genome and the protein products combine to form more than 28 different types of collagen.

- The various collagens and the structures they form all serve the same purpose, to help tissues resist stretching.

Synthesis of collagen

- Individual collagen polypeptide chains are synthesized on membrane-bound ribosomes and injected into the lumen of the endoplasmic reticulum (ER) as larger precursors, called *pro-α chains*

- In the lumen of the ER, selected prolines and lysines are hydroxylated to form hydroxyproline and hydroxylysine, respectively, and some of the hydroxylysines are glycosylated

- Each pro-a chain then combines with two others to form a hydrogen-bonded, triple-stranded, helical molecule known as *procollagen*

(Continued)

Synthesis of collagen

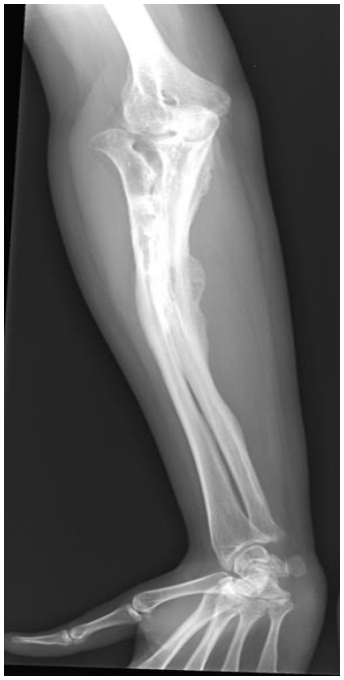
- During or following exocytosis, extracellular enzymes, the procollagen peptidases, remove the N-terminal and C-terminal propeptides
- The resulting protein, often called tropocollagen (or simply collagen), consists almost entirely of a triple-stranded helix.
- Excision of both propeptides allows the collagen molecules to polymerize into normal fibrils in the extracellular space

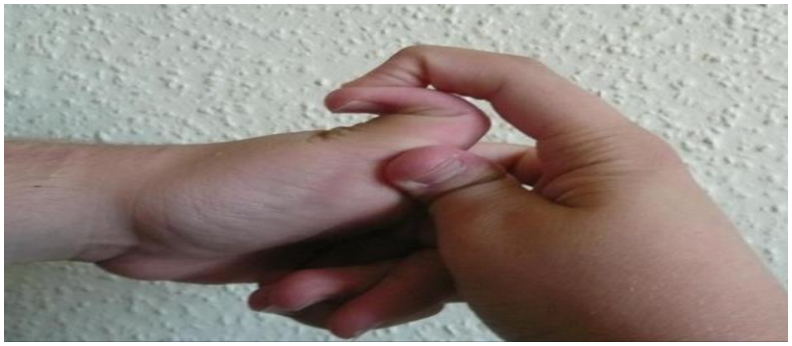
Collagen-related diseases

- Collagen is highly cross-linked in tissues where tensile strength is required such as Achilles tendon

- If cross-linking is inhibited, the tensile strength of fibers is greatly reduced, collagenous tissues become fragile, and structures tend to tear (skin, tendon, and blood vessels)

Diseases associated with collagen





Scurvy

The formation of hydroxyproline requires vitamin C

Deficiency of vitamin C results in insufficient hydroxylation of proto-collagen and, hence, poor synthesis of collagen, formation of unstable triple helices preventing formation of normal fibrils

Non-hydroxylated procollagen chains are then degraded within the cell

This results in weakening of the collagen resulting in skin and gum lesions and weak blood vessels

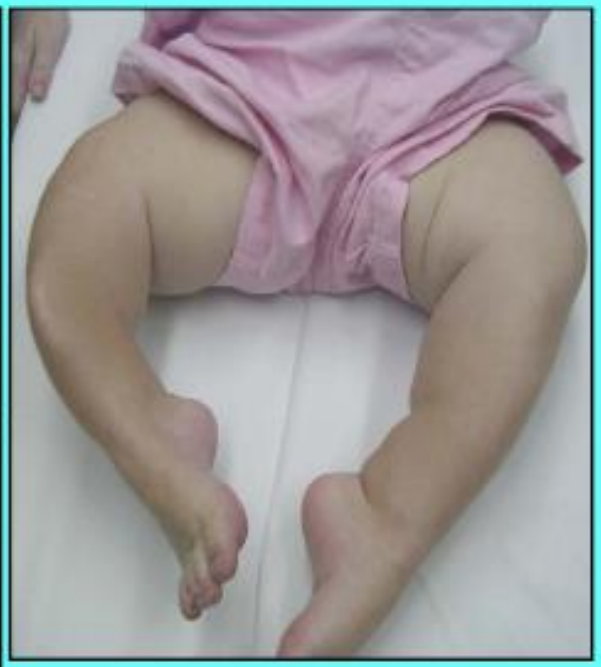
Types of OI

- At least four types of osteogenesis imperfecta
- Designated as type I through type IV
- Type I osteogenesis imperfecta is the mildest form of the condition
- Type II is the most severe results in death in utero or shortly after birth
- Milder forms generate a severe crippling disease

Osteogenesis Imperfecta

Type I

Type III



Chondrodysplasias

- Mutations affecting type II collagen cause *chondrodysplasias*, characterized by abnormal cartilage, which leads to bone and joint deformities

Elastin

- The main component of elastic fibers is elastin
- A highly hydrophobic protein, which, like collagen, is unusually rich in proline and glycine
- But, unlike collagen, is not glycosylated
- Contains some hydroxyproline but no hydroxylysine

Formation of elastic network

Soluble tropoelastin (the biosynthetic precursor of elastin) is secreted into the extracellular space and assembled into elastic fibers close to the plasma membrane

After secretion, the tropoelastin molecules become highly cross-linked to one another, generating an extensive network of elastin fibers and sheets

The cross-links are formed between lysines by a mechanism similar to that of collagen molecules

Elastin structure

- The elastin protein is composed largely of two types of short segments that alternate along the polypeptide chain:
  - hydrophobic segments, which are responsible for the elastic properties of the molecule; and
  - alanine- and lysine-rich a-helical segments, which form cross-links between adjacent molecules

Function of elastic fiber

- Elastin is the dominant extracellular matrix protein in arteries
- Mutations in the elastin gene causing a deficiency of the protein result in narrowing of the aorta or other arteries as a result of excessive proliferation of smooth muscle cells in the arterial wall
- Apparently, the normal elasticity of an artery is required to restrain the proliferation of these cells

Elastic fibers

- Mutations in elastin give rise to a variety of disorders, ranging from mild skin wrinkling to death in early childhood.