

BIOCHEMISTRY

COLLAGEN

OVER VIEW

- ⦿ Collagen and Elastin are the examples of fibrous proteins.
- ⦿ These are basic structural elements.
- ⦿ These proteins have special mechanical properties.
- ⦿ They are found as components of skin, connective tissue, blood vessels, sclera and cornea of eye.

Collagen

- ⦿ It is the most abundant protein in the body.
- ⦿ It is long, rigid structure in which three polypeptides are wound around one another in a rope like fashion.
- ⦿ These polypeptides are called α -helix.

- ① They are arranged in a triple helix.
- ① They are found everywhere in the body, but their type is dictated by their structural role in a particular organ.

◎ Example:

1. Gel- extracellular matrix or vitreous humor of eye.
2. Tight bundles- Tendons
3. Stacked- as in Cornea
4. Fibers arranged at an angle- Bones

- ⦿ Polypeptide chains are held together by hydrogen bonds.
- ⦿ Variations in the amino acids sequence of the α -chain result in the different properties of the chains.

- ⦿ These α -chains are combined to form various types of collagen found in the tissues.
- ⦿ Type I - $2\alpha_1 \& 1\alpha_2$

Types of Collagen

Fibril-Forming

Collagen type I

- Found in the supporting elements of high tensile strength.
- Found in bone, skin, tendon, muscles, cornea and walls of blood vessels.

Collagen type II

- Found in cartilaginous tissues.
- found in inter vertebral disk, vitreous body and hyaline cartilage.

Collagen type III

- Found in distensible tissues.
- fetal skin, blood vessels.

Network- Forming

Collagen type IV

- Found in the basement membranes and muscles.

Collagen type VII

- Beneath stratified squamous epithelia

Fibril- Associated

Collagen type IX

- Found in cartilage

Collagen type XII

- Tendon, ligaments

STRUCTURE OF COLLAGEN

- ⦿ Amino Acid Sequence
- ⦿ Triple- helical structure
- ⦿ Hydroxyproline & Hydroxylysine
- ⦿ Glycosylation

Amino Acid Sequence:

- Collagen is a glycoprotein containing galactose and glucose as the carbohydrate content.

- Glycine is one - third of total amino acid content of collagen followed by hydroxyproline and proline account for another one-third of amino acid content of collagen.

- ⦿ Proline - facilitate the formation of helical conformation of α - chain, because its ring structure causes kink in the peptide chain.
- ⦿ Glycine- found in every third position of the polypeptide chain. It fits into the restricted spaces where the three chains of the helix come together.

- ⦿ Glycine is the part of the repeating sequence.

Gly- X-Y

- ⦿ X- is frequently proline
- ⦿ Y- hydroxy proline or hydroxylysine.

Triple- helical structure:

- ⦿ Amino acids side chains are on the surface of the triple helical molecule.
- ⦿ This allows bond formation between the exposed R- groups of neighboring collagen monomers- This leads to aggregation into fibrils.

Hydroxyproline & Hydroxylysine:

- ④ Hydroxylation of Proline & lysine residues after their incorporation into the polypeptide chains.
- ④ Thus called post translational modification.
- ④ Causes stabilization of triple helical structure.

Glycosylation:

- Hydroxyl group of hydroxylysine residues of collagen are enzymatically glycosylated.
- Most commonly glucose and galactose are attached.

BIOSYNTHESIS OF COLLAGEN

Precursors:

- ① Collagen is one of the proteins that functions outside the cell.
- ① Polypeptide Precursors of the collagen molecule are formed in Fibroblast, osteoblasts and chondroblasts.
- ① These are secreted into the extracellular matrix.

1. Formation of Pro- α -chains:

- ⦿ **Pre-pro α -chains-** contain a special amino acid sequence at their N-terminal.
- ⦿ This sequence acts as a signal that the newly synthesized polypeptide is destined for function outside the cell.

- ⦿ This sequence facilitate the binding of ribosomes to the rough endoplasmic reticulum (RER), and direct the Pre-pro α -chain into the lumen of the RER.

- ⦿ This sequence is cleaved in the lumen of RER and after its cleavage Precursor of collagen is formed.
- ⦿ This precursor is called **Pro α -chain**.

2. Hydroxylation:

- Processing of Pro α -chains occur by a number of enzymic steps in the lumen of **RER**, while the polypeptides are still being synthesized.
- Proline and lysine residues are hydroxylated.
- This reaction requires O₂ and vitamin C.

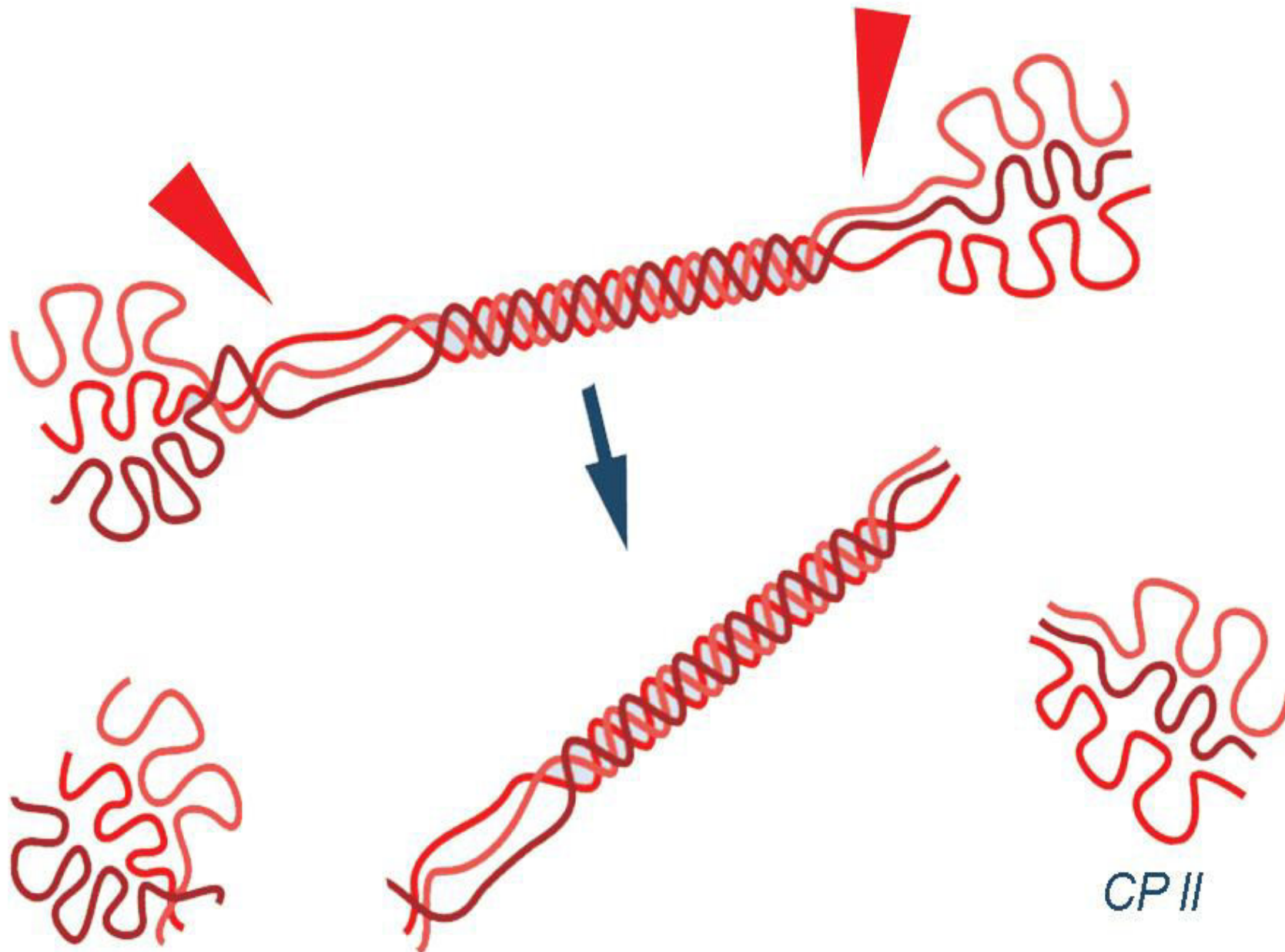
- ⦿ Enzymes are prolyl hydroxylase and lysyl hydroxylase.
- ⦿ In Vit C deficiency, collagen fibers cannot cross link- and tensile strength is decreased (scurvy).

3. Glycosylation:

- ⦿ Modified by glycosylation with glucose or galactose residues.

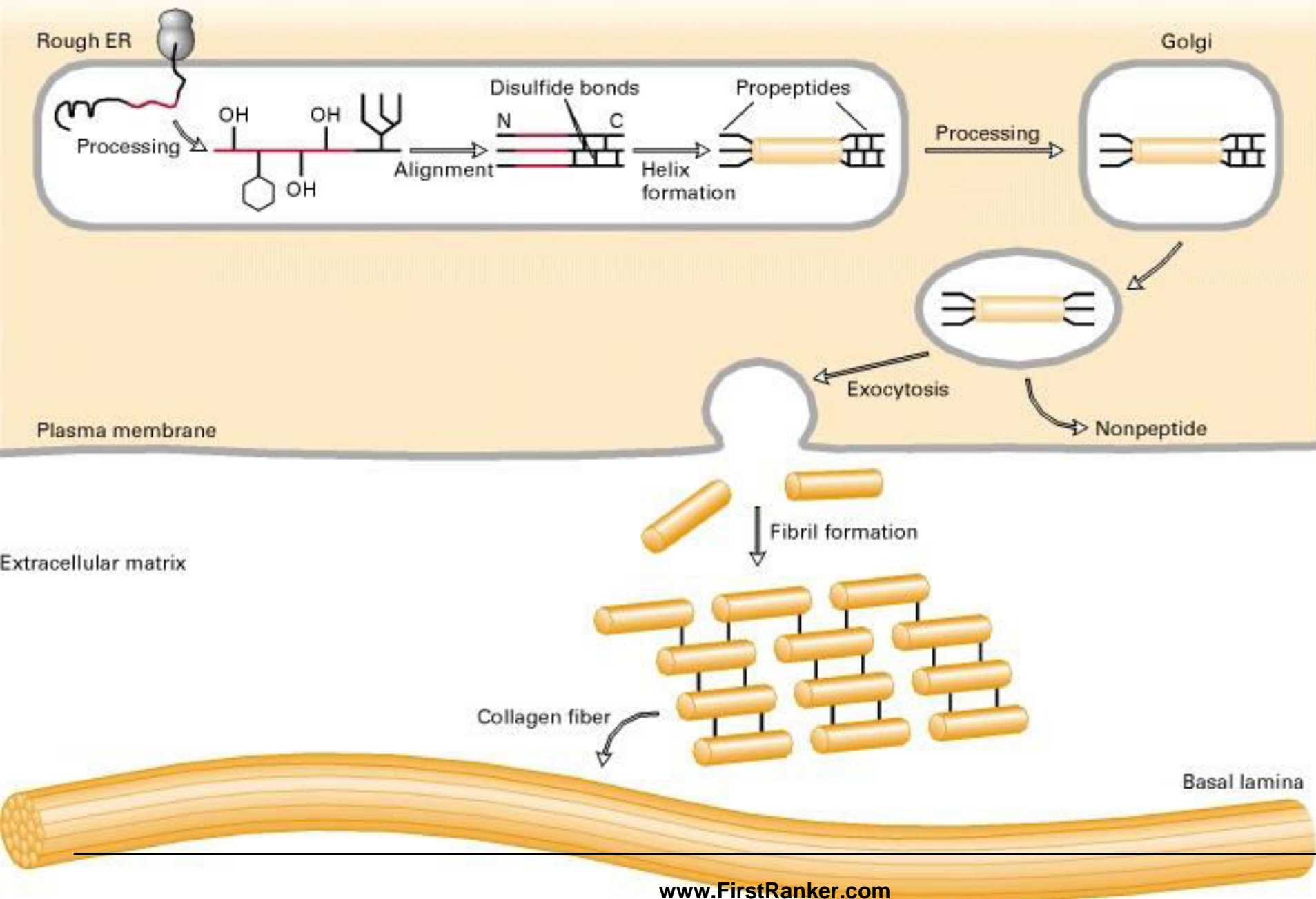
4. Assembly and Secretion:

- ⦿ After hydroxylation and glycosylation- Pro α -chains are converted to **Pro-collagen**.
- ⦿ **Pro-collagen** has a central region of triple helix and its ends have non-helical regions of amino and carboxyl terminal extensions .
- ⦿ These extensions are called **Propeptides**.



- ⦿ In the formation of procollagen interchain disulfide bonds are formed between the C-terminal extensions of the pro α -chains.
- ⦿ This alignment of pro α -chains is favorable for helix formation.
- ⦿ Then pro-collagen chains are translocated to Golgi- apparatus.

- ⦿ In the golgi they are packaged in secretory vesicles.
- ⦿ These vesicles fuse with the membrane and release the **pro-collagen molecule** into the **extracellular space**.

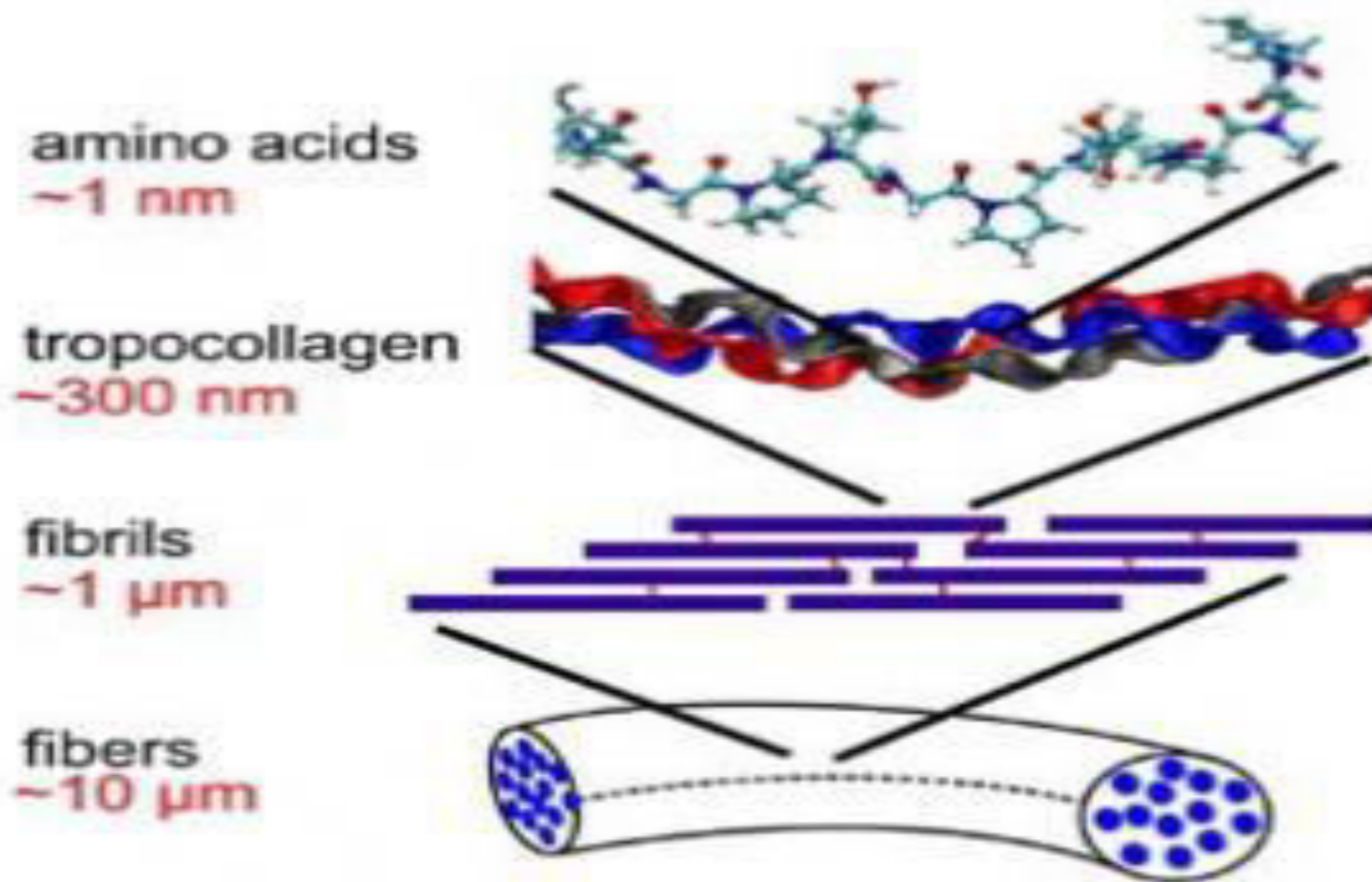


5. Extracellular cleavage of Procollagen molecules:

- ⦿ After their release the Procollagen molecules are cleaved by **N- and C Procollagen peptidases**.
- ⦿ These remove the terminal Propeptides.
- ⦿ Triple helical structure is released as **Tropocollagen**.

6. Formation of collagen fibrils:

- Tropocollagen spontaneously associate with each other and form collagen fibrils.



7. Cross-link formation:

- ⦿ The fibrils that are formed become a substrate for lysyl oxidase.
- ⦿ It contains copper.
- ⦿ It oxidatively deaminates lysyl and hydroxylslyl residues in collagen.
- ⦿ Reactive aldehydes- Allylsine and hydroxylysine are formed.

- ① These aldehydes the react with the neighboring lysyl and hydroxlysyl and covalent cross links are formed.
- ① This cross-linking leads to the formation of mature collagen.

Steps involved in collagen biosynthesis

Rough Endoplasmic Reticulum

- ⦿ Synthesis of procollagen
- ⦿ Insertion of procollagen molecule into the lumen of ER.

Lumen of ER:

- ① Hydroxylation of proline and lysine residues.
- ① Glycosylation of selected hydroxylysine residues.

Lumen of ER and Golgi apparatus:

- Self assembly of tropocollagen molecule (disulfide bond formation).

Secretory vesicles:

- ⦿ **Degradation of collagen:**
- ⦿ Collagen highly stable molecule.
- ⦿ Half life is several years.
- ⦿ Breakdown- collagenases

Collagen diseases

- ⦿ Ehlers- Danlos Syndrome
- ⦿ Osteogenesis Imperfecta syndrome.

Learning Resources

- ⦿ Lippincott's Biochemistry
- ⦿ Harpers Biochemistry
- ⦿ Teacher Notes