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Biochemistry

Fibrous proteins

❖ Biological functions of protein

- Enzymes which are catalysts for reactions
- Contractile and motive proteins such as actin and myosin
- Transport proteins such as hemoglobin, lipoproteins, channel proteins
- Structural proteins such as collagen, keratin, actin
- Defensive proteins such as antibodies
- Signaling proteins such hormones, receptors
- Toxins such as diphtheria, enterotoxins

Proteins are divided according to structure:

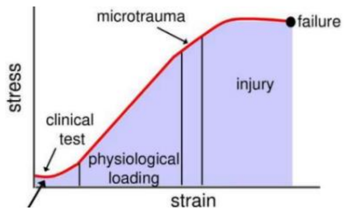
1) **Fibrous:** Elongated fiber-like proteins with only a uniform secondary structure
   - Such as collagen, elastin, keratins
   - They are mostly structural proteins
2) **Globular:** globe-like with 3D compact structures
   - Such as myoglobin, hemoglobin, immunoglobulin

- Extracellular matrix: A space largely filled by an intricate network of macromolecules such as proteins and polysaccharides that assemble into an organized meshwork closely associated with cell surface
  - Such as the basal lamina (membrane) which separates the epithelial from the underlying tissues and it is filled with compact fibrous proteins and proteoglycans

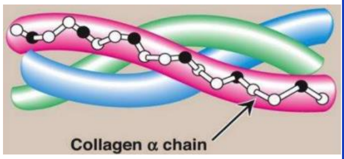
❖ Fibrous proteins

♦ Collagens

- The collagens are a family of fibrous proteins with 40 different types found in **all multicellular animals**
  - They are the **most abundant proteins** in mammals (25% of the total protein mass in them)
- Collagen molecules are named as type I collagen, type II collagen, type III collagen, and so on
  - The most important types are the fibril-forming collagens (types I, II, III, V, XI, XXIV, and XXVII)
- The main function of collagen is to **provide structural support to tissues**
  - The primary feature of a typical collagen molecule is its stiffness and tensile strength



- It is a **triple-stranded**, helical protein, in which three collagen polypeptide chains called α-chains
  - The 3 strands are wound around one another in a ropelike superhelix making the molecule stronger
  - Compared to the α-helix, the collagen helix is much more extended with 3.3 residues per turn

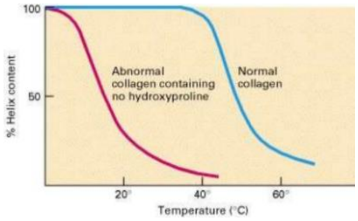


- Formation of collagen fibers:
  - This basic unit of collagen is the triple stranded structure (**tropocollagen**)
    - ✓ The 3 alpha-chains can be encoded in different genes, causing the diversity of collagen types
  - 5 tropocollagens are connected to each other by **covalent aldehyde bonds** between lysine residues forming **microfibrils**
  - Several microfibrils are aligned together via **covalent cross-links** forming **fibrils**
  - Many fibrils form collagen **fibers**

Covalent bonds strengthen the structure

- Collagens are rich in glycine (33%), proline (13%) and hydroxyproline (9%)
  - So, its primary structure is (Gly – X – Y) where X is often proline or hydroxyproline
- **Glycine** is a small and flexible (R group = H atom) amino acid that can form H-bonds allowing the three α chains to **pack tightly** together to form the final collagen superhelix
- **Proline** is a rigid structure that creates kinks and **stabilizes** the helical conformation in each a chain
- 25% of the primary structure of collagen consists of hydrophobic and charged amino acids
- **Hydroxylysine** serves as **attachment sites of polysaccharides** making collagen a glycoprotein
  - Sugars allow collagen to **recognize and interact** with cell surface receptors

- **Hydroxyproline** increase the H-bonding ability and so **stabilizes** and **strengthens** collagen
    - ✓ Normal collagen is stable even at 40 °C, but without H-bonds between hydroxyproline residues, the collagen helix is unstable and loses most of its helical content at temperatures above 20 °C
    - ✓ Prolyl and lysyl hydroxylases are dependent on ascorbate (Vitamin C)



- Some of the lysine side chains are oxidized to **allysine** (**aldehyde** derivatives)
    - Allysine form covalent aldol-cross links with other allysine, hydroxylysine or lysine residues in the same or in different tropocollagens

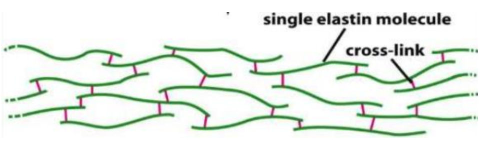
- These **cross-links stabilize** the side-by-side packing of collagen molecules generating a strong fibril
    - If cross-links are inhibited, the tensile strength of the fibrils is drastically reduced; collagenous tissues become fragile, and structures such as skin, tendons, and blood vessels tend to tear
    - Deficiency of hydroxylation can cause diseases such as **Ehlers-Danlos syndrome**
    - Dietary deficiency of ascorbic acid (vitamin C) prevents proline hydroxylation causing **Scurvy**
        - ✓ The defective pro-α chains fail to form a stable triple helix and are immediately degraded
        - ✓ Blood vessels become extremely fragile, and teeth become loose in their sockets
    - The amount of cross-linking in a tissue **increases with age**, that's why meat from older animals is tougher than meat from younger animals and that's why we have wrinkles

- Collagen synthesis:
    - DNA → RNA → PreProCollagen → hydroxylation and glycosylation in the ER → triple helix formation in Golgi → Procollagen is packed into secretory vesicles and secreted → cleavage of propeptides → Collagen forms fibril

- Proteins such as collagen can be nonenzymatically glycated producing glycosylated proteins which are difficult to turn over
    - Glycation is proportionate to glucose level (Hyperglycemia increases the levels of glycated proteins)
    - Glycated proteins in tissues undergo nonenzymatic oxidation forming additional cross-links
    - The net result is the formation of large protein aggregates called advanced glycation end products (AGEs), which **increase cellular oxidative** stress and increase the release of cytokines

♦ Elastins

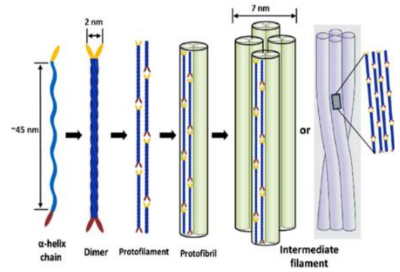
- They are strong, elastic fibrous proteins (flexible and Resilient)
    - Flexibility is the ability of bending or stretching the tissue without being broken
    - Resilience is the ability to spring back to the original shape
- Tissues such as skin, blood vessels, and lungs, need to be both **strong 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 (stretch and relax)
    - Long**,** inelastic **collagen fibrils are interwoven with the elastic** fibers to limit the extent of stretching and prevent the tissue from tearing
- 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 type
    - **Lysine and alanine**–rich hydrophilic domains
    - Hydrophobic domains that are rich in **valine, proline, and glycine**



- The **hydrophobic** effect is the primary force that allows this **stretched structure to reform**
- Elastin contains some hydroxyproline, but **no** hydroxylysine so 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

♦ Keratin

- Collagen & elastin present in the ECM
- Keratin is a major component of intermediate filaments which exist inside the cell and can also present in the ECM
- **α-keratin** is the major proteins of hair, fingernails and animal skin
  - α-keratin has an unusually **high content of cysteine**
- Intermediate filaments are formed by:
  - 2 helical α-keratin molecules form a coiled-**dimer**
  - 2 dimers twist together to form a **tetramer** (protofilaments)
    - ✓ Tetramers associate head-to-tail
  - Two protofilaments twist together to form a protofibril
  - 4 protofibrils combine to make 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



Cross-links in keratin is **disulfide cross links** between cysteine residues

- **More disulfide bonds = more strength and hardness**
  - Keratin in fingernails contain more disulfide bonds and more Cys residues than keratin in the hair

- **Temporary wave of hair:** 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

Past papers

1. The following is NOT important in packing collagen fibrils and fibers:

A. Lysine
B. Proline
C. Allysine
D. Hydroxyproline
E. Hydroxylysine

2. Elastin fibers tend to aggregate back together after stretching due to

A. The lysine crosslinks
B. The hydroxyproline residues

C. The proline residues
D. The attached carbohydrates
E. Their hydrophobic nature

3. The following residue of collagen is important in intracellular signaling

A. Allysine
B. Glycine
C. Hydroxylysine
D. Proline
E. Hydroxyproline

4. Temporary hair styling involves

A. Dihydroxylation of amino acid residues
B. Reformation of non-covalent interactions
C. Synthesis of more alpha keratins
D. Reformation of covalent linkages
E. Removal of sugar attachments

5. Elastin is:

A. Part of globular proteins
B. Part of fibrous proteins
C. Hard & dry
D. For movement & transport
E. Part of salts in ECM

6. Which of the following bonds is not found in fibrous protein:

A. Hydrogen Bonds
B. Phosphodiester Bonds
C. Disulfide Brides
D. Aldol Cross-links
E. Hydrophobic Interactions

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