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REVIEW ARTICLE

Collagen: A Brief Analysis

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ABSTRACT

Collagen is the most abounding structural protein in a human body representing 30% of its dry weight and is significant to health because it designates the structure of skin, connective tissues, bones, tendons, and cartilage. Much advancement has been made in demonstrating the structure of collagen triple helices and the physicochemical premise for their stability. Collagen is the protein molecule which produces the major part of the extracellular matrix. Artificial collagen fibrils that exhibit some characteristics of natural collagen fibrils are now congregated using chemical synthesis and self-aggregation. The indigenous collagen fibrils lead further development of artificial collagenous materials for nanotechnology and biomedicine.

Keywords: Collagen, Structure of Collagen, Diagnostic Importance, Collagen Disorders.

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INTRODUCTION

Collagen is the unique, triple helical protein molecule which organizes the major part of the extracellular matrix.[1] The word collagen was procured from the Greek word "kolla" which estates "glue producer". Previously the collagen of tendons and bones was accustomed in the industry to manufacture glue. Also in organism collagen is a kind of glue.[2] Collagen is a kind of biological macromolecule which constructs a greatly organized, three-dimensional architecture and can transfer any component due to its network-like organizational nature. It is used as a biomaterial because of its extensive applicability in diverse fields. Its adaptable role is due to its immense properties such as biocompatibility, biodegradability and easy availability.[1]

They are centrally involved in the constructions of basement membranes along with diverse structures of the extracellular matrix, fibrillar and microfibrillar networks of the extracellular matrix. It establishes their fundamental fractional monetary unit and identifies crucial steps in the biosynthesis and supramolecular preparing of fibrillar collagens.[3] They are the most abundant structural component of the connective tissue and are present in all multicellular organisms. In the light microscope, collagen fibers typically appear as the wavy structure of variable width and intermediate length.

They stain readily with eosin and other acidic dyes. When examined with a transmission electron microscope (TEM), collagen fibers appear as bundles of fine thread-like subunits. These subunits are collagen fibrils. Within individual fibers, the collagen fibrils are relatively uniform in diameter. In different locations and at different stages of development, however, the fibrils differ in size. In developing or immature tissues, the fibrils may be as small as 15 or 20 nm in diameter. In dense regular connective tissue of tendons or other tissues that are subject to considerable stress, they may measure up to 300 nm in diameter. Collagens are also known to form highly ordered aggregates. The periodicity in these macromolecular structures makes them suitable for investigation by means of X-ray diffraction.[4-6] However, collagen attracts attention not only for commercial motives. Also from a clinical perspective, there is much mesmerized in collagens because many diverse diseases are concomitant to disarray in collagen. Genetic disorders of collagen metabolism customarily influence tissues in which the proper advancement and integrity of connective tissue are of preponderant importance. Thus, a better understanding of the spatial structure will give us more insight into collagen-related disorder diseases.[1,7]

Structure and Types of Collagen

It consists of 3 helically coiled linear chains, each of about 1,000 amino acids. Two of these chains (α1) are identical while the third (α2) has a different amino acid composition. The amino acid composition of collagen is:

- 25% Glycine
- 25% Proline
- Hydroxyproline

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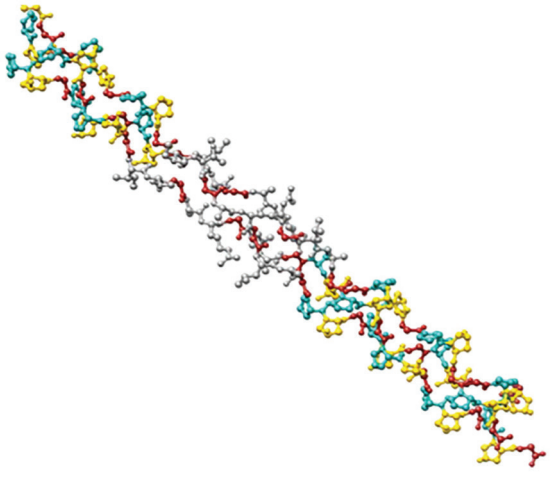

Fig. 1: Collagen Triple-helix Structure[3]

In α chain glycine is repeated every fourth residue. The triplets gly-pro-pro and gly-pro-hpro occur frequently. A protein consists of one or more polypeptide chains. Collagen consists of 3 polypeptide chains, each in the form of a left-handed helix. The explaining feature of collagen is a distinguished constructional motif in which three parallel polypeptide strands in a left-handed, polyproline type II helical conformation coil about each other with a one-residue stagger to organize a right-handed triple helix (Fig. 1).[3,4,6,8]

Until now, the molecule has been classified in 28 different types that are grouped into eight families depending on its structure, chain bonding, and position in the human body (Table 1).[4] Among the classifications, it can be found the fibril-forming, microfibrillar, anchoring fibrils, hexagonal network-forming, basement membrane, fibril-associated collagens with interrupted triple helix (FACIT), transmembrane, and multiplexins.

Microscopic Appearance

Collagen fibers of connective tissue are generally less than 10 µm in diameter and are colorless, when unstained. They appear as long, wavy, pink fibers bundles after staining with Hematoxylin and Eosin. These fibers are constructed from parallel aggregates of thinner fibrils 10 to 300 nm in diameter and numerous micrometers in length.[4]

In electron micrographs of negatively stained preparations, densely stained molecule fills the gap region, or holes between the ends of the adjacent collagen molecules and heavy metals display cross banding at regular intervals of 67 nm, a characteristic property of these fibers is seen. In hard tissues (bone, dentin, cementum), these holes are filled with mineral crystals. The banding pattern of the fibrils seen in thinly sectioned electron micrograph results from the differing amount of stain bound by a charged amino acid that is aligned in adjacent collagen molecules.[9,10]

Mechanism of collagen Formation and Degradation

Collagen Formation

The cells of the mesenchyme and their derivatives (fibroblasts, odontoblast, osteoblast, cementoblasts, and chondroblasts) are the active producers of collagen. Alternative cell types forming collagen are epithelial, endothelial, Schwann and muscle cells. As an excretory protein, fibrous collagen is manufactured as a proprotein (procollagen). Messenger RNA controls the assembly of distinct amino acids into polypeptide chains on ribosome related with the rough endoplasmic reticulum (RER). The primary polypeptide chains are around one and a half times lengthened than those in the consequent collagen molecule because they have N- and C-terminal distensions that are imperative for the aggregation of the triple helical molecule. As the chains are incorporated, they are transferred into the lumen of the rough endoplasmic reticulum, where considerable post-translational modification takes place.

The first conversion is innumerable hydroxylation of many of the lysine and proline by-products in the chain, which allows hydrogen bonding with the alongside chains as the triple helix is manufactured. The vitamin C reliant enzymes lysyl hydroxylase and prolyl hydroxylase are essential for this step. Through the effect of galactosyltransferase in the rough endoplasmic reticulum, some of the hydroxylysine remnants are glycosylated by the inclusion of galactose.

The three polypeptide chains are assembled into the triple helix. Proper alignment of the chains then is achieved by disulfide bonding at the C-terminal extension and then the three chains twist around themselves to "zip up" the helix. The assembled helix then is transported to the Golgi complex, where glycosylation is completed by the addition of glucose to the O-linked galactose residues. Secretary granules containing the procollagen molecule are formed at the Trans face of the Golgi complex and are released subsequently by the exocytosis by the cell surface. The formation and secretion of the collagen molecule take approximately 35 to 60 minutes.[4,9,10]

Fibroblast

It is the most common cell of connective tissue that forms and retains the extracellular matrix. They give a structural framework for numerous tissues and play an imperative role in wound healing. The essential function of fibroblasts is to preserve the structural integrity of connective tissues by repeatedly secreting precursors of the extracellular matrix, primarily the ground substance and diversity of fibers. They are identified by their interrelation with collagen fibers bundles. The quiescent

Table 1: Types of collagen[4]

Molecule type	*Synthesizing cell*	*Function*	*Location in body*
1. Fibril-forming: most common of all collagens	Fibroblasts, Osteoblasts, Odontoblasts, Cementoblasts	Resists tension	Dermis, tendon, Ligaments, capsules of organs, bone, dentin, Cementum
2. Fibril-forming	Chondroblasts	Resists pressure	Hyaline and elastic cartilage
3. Fibril-forming; also known as reticular fibers. Highly glycosylated	Fibroblasts, reticular cells, smooth muscle cells, hepato-cytes	Forms structural framework of spleen, Liver, lymph nodes. smooth muscle, adipose tissue	The lymphatic system, spleen, liver, cardiovascular system, Lung. skin
4. Network-forming: do not display 67 nm periodicity and a -chains retain propeptides	Epithelial cells, muscle Cells, Schwann cells	Forms meshwork of the lamina densa of the basal lamina to provide support and filtration	Basal lamina
5. Fibril-forming	Fibroblasts, mesenchyme cells	Associated with type I collagen, also with placental ground substance	Dermis, tendon, ligaments, capsules of organs, bone, Cementum, placenta
6. Microfibre forming collagen	_	Bridging between cells and matrix (has binding properties for cells, proteoglycan, a type I collagen)	Ligaments, skin, cartilage
7. Network-forming: form dimers that assemble into anchoring fibrils	Epidermal cells	Forms anchoring fibrils that fasten lamina densa to underlying lamina reticularis	Junction of epidermis and dermis
8. Meshwork	_	Tissue support. porous meshwork, provide compressive strength	Basal laminae of endothelial cells and smooth muscle cells and Descemet's membrane of the cornea
9. Fibril-associated: decorate the surface of type II collagen fibers	Epithelial cells	Associates with type II Collagen fibers	Cartilage
10. Meshwork	_	Calcium binding	Hypertrophic zone of cartilage growth plate
11. Fibril collagen fibers	_	Forms core of type II fibers provides tensile strength	Cartilage and vitreous humor
12. Fibril-associated; decorate the surface of type I collagen fibers	Fibroblasts	Associated with type I collagen fibers	Tendons. ligaments and aponeuroses
13. Transmembrane protein	–	Cell-matrix and cell, adhesion	Cell surfaces, focal adhesion, and intercalated disks
14. FACIT	_	Modulates fibril interactions	
15. Endostatin forming collagen	Endothelial cells	Proteolytic release of antiangiogenic factor	Endothelial basement membrane
16. Cartilage and placenta	_	Unknown	Endothelial, perineural muscle and some epithelial basement membrane, cartilage, and placenta
17. Collagen-like protein: a transmembrane protein, formerly known as bullouspemphigoid antigen	Epithelial cells	Cell to matrix attachment	Hemidesmosomes
18. Collagen-like protein; cleavage of its C – terminal forms endostatin and	Endothelial cells	Proteolytic release of antiangiogenic factor	Endothelial basement membrane

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Molecule type	Synthesizing cell	Function	Location in body
19. FACIT	_	Unknown	Endothelial, perineural muscle and some epithelial basement membrane, cartilage, and placenta
20. FACIT	–	–	Cornea (chick)
21. FACIT	-	-	Stomach, kidney
22. FACIT	-	-	Tissue junctions
23. Membrane-associated collagen with interrupted triple helix	-	-	Heart, retina
24. Fibrillar	-	-	Bones, cornea
25. Membrane-associated collagen with interrupted triple helix	-	-	Brain, heart, testis
26. FACIT	-	-	Testis, ovary
27. Fibrillar	-	-	Cartilage
28. Microfiber forming collagen	-	-	Dermis, sciatic nerve

fibroblast or fibrocyte is minor than the active fibroblast and is commonly spindle-shaped. It has a minor, darker, elongated nucleus; fewer processes and higher acidophilic cytoplasm with the much less rough endoplasmic reticulum. They have a branched cytoplasm surrounding an elliptical, speckled nucleus having one or two nucleoli. Active fibroblasts can be identified by their oval, pale-staining nucleus and higher amount of cytoplasm, Golgi apparatus, abundant rough endoplasmic reticulum, secretory vesicles and mitochondria (Fig. 2). They exhibit motility and contractility which are crucial during connective tissue remodeling and generation and wound repair. In certain tissues, fibroblasts have significant contractile properties and are called as Myofibroblasts.[4]

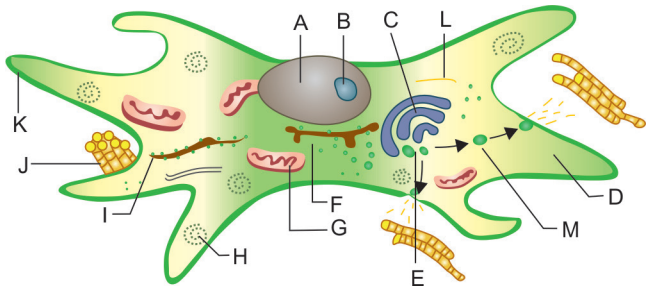

Fig. 2: Shape of fibroblast: A: Nucleus; B: Nucleolus; C: Golgi apparatus; D: Cytoplasm; E: Intermediate/transfer vesicles; F: Ribosomes; G: Mitochondria; H: Polyribosome; I: Rough endoplasmic reticulum; J: Collagen fibrils; K: Cell processes; L: Microtubules; M: Secretory granules.[4]

Degradation of Collagen

The C-terminal extensions and at least part of the N-terminal extensions are removed by the action of procollagen peptidases. These condensed molecules range as a 5 unit, quarter-overwhelmed microfibrils, which then aggregate in a collateral function, giving advancement to a well-organized series of holes or gaps inside the fibrils. These gaps are the regions of the primary deposits of mineral-related with the collagen fibrils in dentin, bones, and cementum. After the fibrils are assembled, the remaining portion of the N-terminal extension is removed by procollagen peptidase. The oxidization of some lysine and hydroxylysine residues by the extracellular enzyme lysyl oxidase, forming reactive aldehydes, results in intermolecular cross-links that further stabilize the fibrils.[4,9,10]

Factors involved in collagen degradation are:

- Highly strong to Proteolytic attack
- Collagenase 1, 2 and 3 degenerate types I, II, III, V collagen Collagenase 3 can degenerate type I, II, III, IV, IX, X, XI, fibronectin and another extracellular matrix component.[11]

Matrix metalloproteinases (MMP) is a great family of proteolytic enzymes that involves:

- Collagenases (MMP-1, 8, 13)
- Metalloelastases (MMP-12)
- Stromelysins (MMP-3, 10, 11)
- Matrilysin (MMP-7)
- Gelatinases (MMP-2, 9) [4]

Diagnostic Importance of Collagen in Various Conditions

Many histochemical stains have been accustomed to determine Collagen fibers which involve Weigert's Resorcin Fuchsin, Modified Movat's Stain, Goldner's Trichrome method, Van Gieson, Masson's Trichrome, etc, but the picrosirius red stain underneath the polarizing microscope is the most extensively used because of the inherent character of birefringence of collagen.[11]

Cysts

Collagen was considered playing an active role in the pathologic process and expansion of odontogenic cyst. Junqueira

et al. reported that under pathological conditions birefringence represents various patterns in contrast with collagen in general tissue and demonstrated that type I collagen was massive, greatly birefringent red fibers while type III collagen exposed as fine weakly birefringent green fibers.[12]

Tumor

In a tumor, there is an enhanced density of collagen in the initial phase, which stimulates tumor initiation and metastasis.[13]

Odontogenic Fibroma

In odontogenic fibromas, mature type I collagen fibers are present. These fibers ran roughly parallel to the inactive epithelial strands and foci of mineralization were surrounded by concentric thick type I collagen bundles.[12]

Ameloblastoma

The collagen fibers in the basement membranes of ameloblasts in ameloblastomas are found to be spatially organized with thick type I collagen passing perpendicularly through the basement membrane zone and merging with the collagen in the capsule and fibrous septa between the epithelial follicles.[12]

Oral Submucous Fibrosis

One of the most customary precancerous conditions which are broadly pervasive in the Indian subcontinent is oral submucous fibrosis (OSMF). In a very early stage, fine fibrillar collagen distributed with pronounced edema and sturdy fibroblastic response demonstrating plump young fibroblasts including profuse cytoplasm will be observed. In early and moderately advanced stage collagen is seen as thickened separate bundles and moderately hyalinised respectively.[14] Studies done in OSMF using picrosirius red stain and polarizing microscopy revealed that there was a gradual decrease in the greenish-yellow color of the fibers and a shift to orange-red color with increase in severity of the disease which appeared that the tight packing of collagen fibers in OSMF progressively increased as the disease progressed from early to advanced stages.[11]

In Drug Delivery Systems and Tissue Engineering

Collagen is a predominant biomaterial in medical utilization due to its particular characteristics, like weak antigenicity and biodegradability. In the biomedical application, the chief reason for the usefulness of collagen is the fabrication of fibers with supplemental vitality and stability through its self-assembly and cross-linking and the *in vivo* metabolism of collagen is supervised by the application of cross-linking agents, such as glutaraldehyde, formaldehyde, polyepoxy compounds, chromium tanning, acrylamide, and carbodiimides.[15]

A generalized view of collagen in the body

Collagens are a great family of triple helical proteins that are extensive throughout the body. They are crucial for a wide range of functions, involving cell migration, cancer, angiogenesis, tissue morphogenesis, tissue scaffolding, cell adhesion, and tissue repair. It is the main component of tissues such as fibrous tissue, bone, cartilage, valves of heart, cornea, and basement membrane etc.[1,4,6,16]

Collagen in Health

Collagen is seldom referred to as the body's cement that keeps everything in place. It is crucial to health because it dictates the designs of skin, connective tissues, tendon, bone, and cartilage.[16]

Skin Health

Collagen plays an important role in skin health. Dermis layer of the skin is a connective tissue layer made up of dense and stout collagen fibers, fibroblast, and histiocytes. Collagen type I constitute 70% of the collagen in the skin, with type III being 10% and a trace amount of collagen types IV, V, VI and VIII. Collagen conserves the toughness and elasticity of the skin. Collagen in the form of collagen hydrolysate keep skin hydrated. During the aging process, a lack of collagen becomes obvious as skin begins to sag and lines and wrinkles begin to form. In the development of scar tissue as a result of age or injury, there is variation in the abundance of types I and III collagen as well as their proportion to one another. Type III collagen synthesis reduces with age resulting in changes in skin tension, elasticity, and healing.[4]

Muscles

In muscle tissue, it serves as an utmost component of endomysium. In Smooth Muscle Cells (SMCs) collagen exist as a meshwork surrounding individual SMCs (type IV or basement membrane collagen) or as interstitial dense fibers that occupy a substantial volume of the tissue (type I and III fibrillar collagens).[17,18,19]

Wound Healing

Collagen plays an important role in wound healing by repair and formation of a scar. The tensile strength of the wound increases by its deposition and remodeling, which is nearly 20% of normal by 3 weeks after injury and gradually reaches an extreme of 70% of that of normal skin. Col-

lagen overproduction can produce an abnormal scar, which delays wound healing. A chronic wound burden between the elderly has been recorded and much of this age-related delayed wound healing is caused by diminished collagen synthesis and an advanced degradation. Increase in collagen and fibroblasts during healing proposed that a correlation might exist among a quantity of collagen, number of fibroblasts and tensile strength of a scar.[4,16]

Bone

Bone is a complex and dynamic tissue that renders structural support for the body, preservation of internal organs and acts as levers to which muscles are attached, allowing movement. In total, out of 22 to 25% of the organic component, the principal collagen type I is 94 to 98% along with other noncollagenous proteins and 2 to 5% are cells present in the bone tissue. The mixture of flexible collagen and hard mineral makes bone dense than cartilage without being brittle. A mixture of water and collagen mesh constructs a strong and slippery pad in the joint that shields the ends of the bones in the joint during muscle movement.

Cartilage, Tendon, Ligaments

In fibrous tissue, such as tendon and ligament, collagen in the form of elongated fibrils is predominantly present. It is a stretchy and flexible protein that is used by the body to support tissues and thus it plays an important role in the preservation of the cartilage, tendons, and ligaments. Normal tendon consists of soft and fibrous connective tissue that is consisted of densely packed collagen fibers bundles and surrounded by a tendon sheath also consisting of components of the extracellular matrix. Collagen comprises 75% of the dry tendon weight and functions principally to withstand and transfer large forces among muscle and bone. Collagen also constructs a great constituent of cartilages. Cartilage collagen fibrils composed of collagen II, the quantitatively few collagens IX and XI.

Dental Tissues

Dentin

The mature dentin is made up of nearly 20% organic material, 70% inorganic material and 10% water by weight. The organic phase is about 30% collagen (principally type I with few amounts of types III and V) with fractional inclusions of non-collagenous matrix proteins and lipids. Collagen type I serve as a scaffold that contains a great proportion (estimated at 56%) of the mineral in the pores and holes of fibrils.

Pulp

The extracellular compartment of the matrix or pulp made up of collagen fibers and ground substance. The fibers are mainly types I and III collagen. The general collagen content of the pulp advances with age, the ratio among types I and III remain steady and the increased amount of extracellular collagen constructs into fiber bundles.

Cementum

Type I collagen (forms 90% of the organic matrix) is predominant collagen present in cementum. Collagens found in trace amount in cementum are types V, VI, and XIV. Different collagens related with cementum include type III, less cross-linked collagen found in high concentrations during advancement and reconstruction and repair of mineralized tissues and type XII that binds to type I collagen and also to non-collagenous matrix proteins.

Periodontal ligament

The periodontal ligament is made up of collagen fibers bundles connecting cementum and alveolar bone proper. The chief collagens are types I, III and XII, with individual fibrils having an approximately minor average diameter than tendon collagen fibrils.

Principal fibers are the vast majority of collagen fibrils found in the periodontal ligament and are arranged in definite and distinct fiber bundles. The periodontal ligament has also the capability to adapt to functional changes. When the functional demand advances, the thickness of the periodontal ligament can advance by as much as 50 % and the fiber bundles also increase noticeably in thickness.

Basement membrane:

The epithelial basement membrane and neighboring area are termed the epithelial basement membrane zone. The lamina densa comprising of type IV collagen that is covered by heparin sulfate, a glycosaminoglycan and anchoring fibrils, that are made up of type VII collagen and widen from the lamina densa to the connective tissue.[4]

Collagen Disorders

These collagen disorders are classified as [20]

Heritable/Genetic Collagen Disorders:

- Ehlers-Danlos syndrome
- Osteogenesis Imperfecta
- Stickler Syndrome
- Alport Syndrome

- Epidermolysis Bullosa
- Marfan Syndrome

Collagen Vascular Disorders/Autoimmune Collagen Disorders:

- Systemic Lupus Erythematous
- Systemic Sclerosis
- Oral submucous fibrosis
- Sjogren's syndrome
- Scleroderma
- Rheumatoid Arthritis
- Ankylosis Spondylitis

Miscellaneous:

- Human Atherosclerotic Plaques
- Osteoporosis
- Scurvy

CONCLUSION

Collagen is the predominant structural material of the body and is the most bountiful mammalian protein accounting for about 20 to 30% of total body proteins. They are principal constituent of the extracellular matrix (ECM) that encourages the tissues. The ECM is defined as the diverse collection of proteins and sugars that surrounds cells in all solid tissues.

They have been classified by types that describe specific sets of polypeptide chains that can form homo- and heterotrimeric assemblies. Collagen plays an imperative role in the development of tissues and organs and is involved in diverse functional expressions of cells. It is a good surface-active agent and has the capability to penetrate a lipid-free interface.[4,5,6,21]

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