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Collagen: A review article

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Abstract
Collagen is the main protein of connective tissue and is the most abundant protein in human body, making up about one quarter i.e 25% to 35% of the whole-body weight and helps to maintain the integrity of tissues. It is a large family of triple helical proteins present throughout the body. It is the principal tensile element of tissues in vertebrates, and is also main component of ligaments and tendons. Protein comprises roughly 20% of body mass out of which 25-35% is composed of collagen. Out of this 90% is type I collagen and rest is of other types. Hence an adult of 70 kg contains more than 1 x 10 type I collagen monomers.

Keywords: Collagen, glysine, proline, tropocollagen

1. Introduction

Types of Collagen

Collagen occurs in many places throughout the body. So far, 29 types of collagen have been identified and described. These are distinguishable by their molecular compositions, morphological characteristics, distribution and function. However maximum % is of type I, II, III, and IV collagen.

A. LC Junqueira classified collagen on the basis of their structure and functions into 4 groups:

a. Collagens forming long fibrils:-include types I, II, III, V and XI. Their molecules aggregate to form fibrils visible in electron microscope.
b. Fibril- associated collagens: - include collagen types IX, XII and XIV. These are short structures that bind collagen fibrils to one another and to other components of the extra cellular matrix.
c. Collagens forming networks: - include type IV collagen their molecules assemble in a meshwork that constitutes the structural components of basal lamina.
d. Collagens forming anchoring fibrils: -these include type VII collagen these bind collagen fibres to the basal lamina.

(B) Vertebrate collagens can also be classified according to function into

a. Fibril-Forming Collagens

These are the principal source of tensile strength in animal tissue and occur as 67-nm *D*-periodic fibrils [4]. These fibrils are indeterminate in length and range in diameter from 12 nm to >500 nm, depending on the stage of development and tissue. The periodic structure of the fibrils is due to regular staggering of triple helical collagen molecules. Mammals have 11 fibrillar collagen genes, which cluster phylogenetically into three distinct subclasses [5]. The Gly-X-Y domain of fibril forming collagens contains approx. 1000 residues and is uninterrupted, with the exception of collagen XXIV and collagen XXVII.

b. Fibril-Associated Collagens with Interrupted Triple Helices (Facits)

FACITs are relatively short collagens, having interruptions in the triple helical domain and can be found at the surfaces of collagen fibrils. Collagen IX is the archetypal FACIT; it is covalently cross linked to collagen II [6], and is post-transnationally modified to carry a glycosaminoglycan side chain.

c. Network-Forming Collagens

Collagen IV is the prototypical network forming collagen. It forms an interlaced network in basement membranes, where it has an important molecular filtration function. The network is

Generated by head-to-head interactions of two trimeric NC1 domains. The resultant hexamer is stabilised by covalent Met-Lys cross links [7]. N-to-N interactions between four collagen IV molecules establish the cross linked '7S domain', which is an important interaction node in the extended network. Collagen VIII is a major component of Descemet's membrane, the basement membrane separating corneal endothelial cells from corneal stroma, vascular subendothelial matrices and in association with medial elastic fibres. The structurally related collagen X occurs in the hypertrophic zone of growth plate cartilage and is thought to form a network similar to that of collagen VIII [8].

d. Transmembrane Collagens

These include collagens XIII and XXV, which have cell adhesive properties and occur on numerous cell types, including malignant cells. A growing number of collagen-like trans membrane proteins that have triple-helical ecto domains are being identified in vertebrates and invertebrates. These have not been assigned to a specific class but have important roles in neural function and neural tube dorsalisation, eye development, modulation of growth factor activity, and have cell adhesive functions. These un-adopted collagens include ectodysplasin, gliomedin and other members of the colmedin subfamily of transmembrane collagens [9].

e. Endostatin-Producing Collagens

Collagen XV is found bridging adjacent collagen fibrils near basement membranes and can form a variety of oligomeric assemblies [10]. Collagen XVIII is found in some basement membranes. Cleavage of part of the NC1 domains of collagens XV and XVIII releases endostatins, which are inhibitors of endothelial cell migration and angiogenesis, reduce tumour growth in animals [11].

f. Anchoring Fibrils

Collagen VII is the major component of the anchoring fibrils beneath the lamina densa of epithelium.

g. Beaded-Filament-Forming Collagen

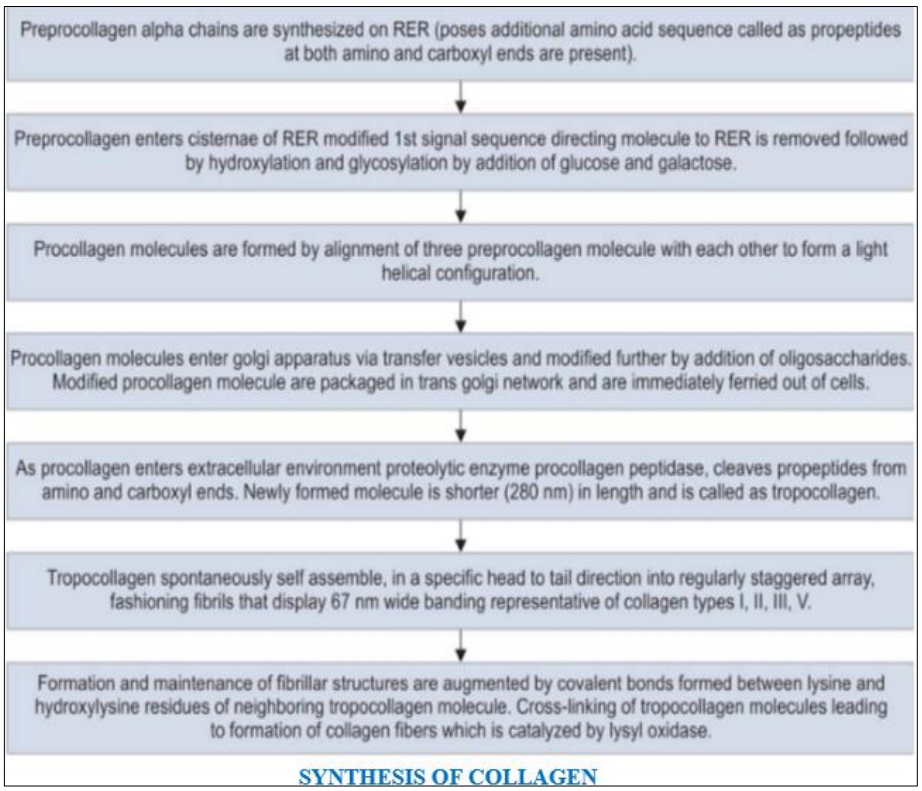
Collagen VI is the archetypal beaded filament- forming collagen. It is found in most tissues where it forms structural links with cells. Collagen VI monomers crosslink into tetramers that assemble into long molecular chains known as microfibrils, which have a beaded repeat of 105 nm [12].

2. Synthesis of Collagen

Mesenchymal cells and their derivatives (fibroblasts, osteoblast, odontoblast, chondroblasts and cementoblasts) arethe chief producers of collagen. Other cell types synthesizing collagen are epithelial, endothelial, muscle and Schwann cells [13]

Fibroblast

Fibroblast is the most common cell of connective tissue that produces and maintains the extracellular matrix. Fibroblasts provide a structural framework for many tissues and play animperative role in wound healing. The key function of fibroblasts is to maintain the structural integrity of connective tissues by continuously secreting precursors of the extracellular matrix, primarily the ground substance and a variety of fibers. They are recognized by their association with collagen fibers bundles. The quiescent fibroblast or fibrocyte s smaller than the active fibroblast and is usually spindle-shaped. It has fewer processes; a smaller, darker, elongated nucleus; and more acidophilic cytoplasm with much less rough endoplasmic reticulum. They have a branched cytoplasm surrounding an elliptical, speckled nucleus having one or two nucleoli. Active fibroblasts can be recognized by their oval, pale- staining nucleus and greater amount of cytoplasm, abundant rough endoplasmic reticulum, golgi apparatus, secretory vesicles and mitochondria. Fibroblasts exhibit contractility and motility which are important during connective tissue remodeling and formation and during wound repair. In certain tissues, fibroblasts have significant contractile properties and are called as myofibroblasts [14, 15].



SYNTHESIS OF COLLAGEN

3. Structure of Collagen

Molecular Structure

Collagen that makes up the matrix of most connective tissue in mammals consists of inter-woven fibres of the protein collagen.

It is approximately 300 nm long and 1.5 nm in diameter, made up of three polypeptide strands (called alpha chains), each possessing the conformation of a left-handed helix. These three left-handed helices are twisted together into a right-handed coiled coil, a triple helix or "super helix", a cooperative quaternary structure stabilized by numerous hydrogen bonds.

With type I collagen and possibly all fibrillar collagens, each triple-helix associates into a right-handed super-coil that is referred to as the collagen microfibre. Each micro fibril interdigitates with its neighbouring micro fibril. (Fig. 1) There is regular arrangement of amino acids in each of the alpha chains of the collagen sub-units. The sequence generally follows the pattern Gly-X-Y, where Gly stands for glycine, and X and Y for any amino acid residues. Most of the times, X is for proline and Y is for hydroxyproline. This inordinate number of Gly residue allows tight coiling of each of the alpha chain subunits of tropocollagen, where there is a rise per turn of just 0.3 nm as opposed to the 0.36 nm of a regular Alpha helical coil. Hydroxyl sine and hydroxyproline play important roles in the stabilisation of the tropocollagen globular structure as well as the final fibre shaped structure by forming covalent bonds. The resulting structure is called a collagen helix.

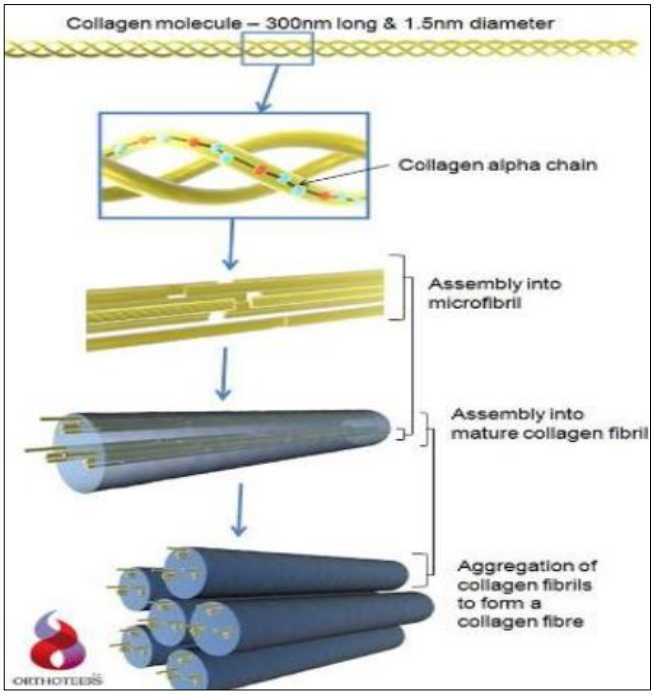


Fig 1 Schematic view of some of the hierarchical features of collagen, ranging from the amino acid sequence level at nanoscale up to the scale of collagen fibers with lengths on the order of 10 μm. Here we focus on the mechanical properties of collagen fibrils consisting of a staggered array of TC molecules [16].

4. Collagen in Health

Collagen in Health Collagen is sometimes referred to as the body's cement that holds everything in place. Collagen is important to health because it dictates the structure of skin, connective tissues, tendons, bones and cartilage.

1. Wound healing: Collagen is a key protein in connective tissue and play an imperative role in wound healing by repair and formation of scar. Collagen deposition and remodeling contribute to the increased tensile strength of the wound, which is approximately 20% of normal by 3 weeks after injury gradually reaching a maximum of 70% of that of normal skin. Collagen overproduction can form abnormal scars, which impede wound healing. A chronic wound burden among the elderly has been documented and much of this age-related, delayed wound healing is caused by impaired collagen synthesis and increased degradation. Increase in fibroblasts and collagen during healing suggested that a correlation might exist between number of fibroblasts, quantity of collagen and tensile strength of a scar [17].

2. Bone: Bone is a complex and dynamic tissue that provides structural support for the body, protection of internal organs and acts as levers to which muscles are attached, allowing movement. The combination of hard mineral and flexible collagen makes bone harder than cartilage without being brittle. Combination of collagen mesh and water forms a strong and slippery pad in the joint that cushions the ends of the bones in the joint during muscle movement [18, 19].

3. Skin health: Collagen plays an important role in skin health. Type I and III collagen are formed in human skin in a higher proportion relative to other types and are maintained in a fixed proportion relative to one another in normal skin tissue. Collagen type I constitutes approximately 70% of collagen in the skin, with type III being 10% and trace amounts of collagen types IV, V, VI and VII. In formation of scar tissue as a result of age or injury, there is change in the abundance of types I and III collagen as well as their proportion to one another. Type III collagen synthesis decreases with age resulting in changes in skin tension, elasticity and healing [20].

4. Muscles: In muscle tissue, it serves as a major component of the endomysium. Collagen constitutes 1 to 2% of muscle tissue, and accounts for 6% of the weight of strong, tendinous muscles [13].

5. Cartilage, tendon, ligaments: Collagen, in the form of elongated fibrils, is predominantly found in fibrous tissues such as tendon and ligament. It is a flexible and stretchy protein that is used by the body to support tissues and thus it plays a vital role in the maintenance of the cartilage, tendons and ligaments. Normal tendon consists of soft and fibrous connective tissue that is composed of densely packed collagen fibers bundles aligned parallel to the longitudinal tendon axis and surrounded by a tendon sheath also consisting of extracellular matrix components [13, 15].

6. Dental tissues

a. Dentin: The mature dentin is made up of approximately 70% inorganic material, 20% organic material and 10% water by weight. The organic phase is about 30% collagen (mainly type I with small amounts of types III and V) with fractional inclusions of lipids and non-collagenous matrix proteins. Collagen type I acts as a scaffold that accommodates a large proportion (estimated at 56%) of the mineral in the holes and pores of fibrils [21].

b. Pulp: The extracellular compartment of the pulp or matrix consists of collagen fibers and ground substance. The fibers

are principally types I and III collagen. The overall collagen content of the pulp increases with age, the ratio between types I and III remains stable and the increased amount of extracellular collagen organizes into fiber bundles [22].

c. Cementum: Predominant collagen present in cementum is type I collagen (forms 90% of the organic matrix). Other collagens associated with cementum include type III, a less cross linked collagen found in high concentrations during development and repair and regeneration of mineralized tissues and type XII that binds to type I collagen and also to non-collagenous matrix proteins. Collagens found in trace amount in cementum are types V, VI and XIV [23].

d. Periodontal ligament: periodontal ligament is composed of collagen fibers bundles connecting cemented and alveolar bone proper. The predominant collagens of the periodontal ligament are types I, III and XII, with individual fibrils having a relatively smaller average diameter than tendon collagen fibrils. The vast majority of collagen fibrils in the periodontal ligament are arranged in definite and distinct fiber bundles and these are termed as principal fibers. The periodontal ligament has also the capacity to adapt to functional changes. When the functional demand increases, the width of the periodontal ligament can increase by as much as 50 % and the fiber bundles also increase markedly in thickness [23].

7. Basement membrane: the epithelial basement membrane and adjacent area is termed the epithelial basement membrane zone. The lamina densa consisting of type IV collagen that is coated by heparan sulfate, a glycosaminoglycan and anchoring fibrils, that are composed of type VII collagen and extend from the lamina densa to the connective tissue [24].

5. Collagen Disorders

a. Ehlers-Dalnos syndrome: Ehlers-Danlos syndrome (EDS) is a clinically and genetically heterogeneous connective tissue disorder characterized by hyper extensibility of the skin, hypermobility of joints and tissue fragility. In some clinical forms of EDS a mutation in COL1A1 and COL1A2 genes is reported which results in interferences with conversion of procollagen to collagen. Presence of dystrophic scars and a tendency to excessive bleeding manifested by bruises, ecchymoses and hematomas is noticed in EDS. The oral manifestations of EDS include the ability of 50% of these patients to touch the tip of their nose with their tongue (Gorlin sign), a feat that can be achieved by less than 10% of normal people. The gingiva is fragile and hemorrhage may be difficult to control during surgical procedures. Early onset generalized periodontitis is one of the most noteworthy oral manifestations of the syndrome resulting in the premature loss of deciduous and permanent teeth [25, 26].

b. Osteogenesis imperfect: comprises a heterogeneous group of heritable disorders characterized by impairment of collagen maturation. The disease causes either a decrease in collagen synthesis or the production of structurally defective collagen, hence, all tissues rich in type I collagen may be affected. Except on rare occasions, the disorder arises from heterozygosity for mutations in one of two genes that guide the formation of type I collagen: The clinical features commonly observed in patients with osteogenesis imperfecta include abnormal bone formation, growth deficiency, bone fragility, blue sclerae, hearing loss, skin thinness, joint laxity and hypermobility and dentinogenesis imperfecta [27].

c. Stickler syndrome: It is a unique autosomal dominant syndrome of premature osteoarthritis, retinal degeneration, hearing loss and orofacial abnormalities described by Gunnar B Stickler in 1965. The disorder (hereditary arthro ophthalmopathy or Stickler syndrome) is known to be caused by mutations in the COL2A1, COL11A1 and COL11A2 procollagen genes of type 2 and 11 collagen [28].

d. Alport syndrome: Alport syndrome is a generalized inherited disorder of basement membranes, particularly those of glomeruli that involve type IV collagen. The mutations occur in the gene located on the X chromosome. It is characterized by renal impairment, loss of hearing and lens abnormalities, hypertension, hematuria and proteinuria. The damage of collagen IV due to mutations causes dysfunction of bound epithelium and results in organ damage [29].

E. Epidermolysis bullosa: hereditary epidermolysis bullosa is a group of rare genetically transmitted disorders that have several methods of inheritance with various degrees of severity and expression. It is a multiracial disorder that is characterized by the formation of vesicles and bullae on the skin and mucous membranes. The vesicles may arise spontaneously or from minor trauma. The four types of epidermolysis bullosa are simplex, dystrophic and junctional and hemidesmosomal. Specific mutations in the K5 or K14 genes and genes coding for the laminin has been responsible for dominant simplex type and junctional form respectively [30, 31].

f. Marfan syndrome: It is the most common inherited connective tissue disorder with a reported incidence of one in 10,000 individual and equal distributions between the sexes. It is caused by an autosomal dominant mutation in the gene encoding fibrillin (FBN1, chromosome 15q15–21.3), a glycoprotein that is an integral part of the connective tissue in the body (ligaments, blood vessel, eye lenses). It primarily involves the skeletal, ocular and cardiovascular systems [32].

6. Autoimmune Collagen Disorders

a. Systemic lupus erythematosus: Lupus erythematosus is a multifactorial autoimmune collagen vascular or connective tissue disease, which may affect the oral mucosa in either its cutaneous and systemic forms with varied prevalence. Common findings include fever, weight loss, arthritis, fatigue and general malaise. A characteristic rash, having the pattern of a butterfly, develops over the malar area and nose. Cardiac involvement is also common with pericarditis. Warty vegetations affecting the heart valves are also observed. Oral lesions include ulceration, pain, erythema and hyperkeratosis may be present. Other oral complaints are xerostomia, stomatodynia, candidiasis, periodontal disease and dysgeusia [30].

b. Systemic sclerosis: Progressive systemic sclerosis is a disorder of the connective tissue that illustrates fibrosis of the skin, blood vessels, visceral organs and mucosa. The pathological findings signify that fibroblasts are activated to produce excessive amounts of collagen and other components of the cellular matrix. Cutaneous manifestations include thickening of skin, starting with pitting edema and over several months pitting edema is replaced by tightening and hardening of skin. The oral manifestations include classic facial skin hardening and limited opening of the oral orifice with characteristic furrows radiating from the mouth resulting in a classic mask-like and appearance purse string appearance respectively. Bone resorption at the angle of the mandible is also a common feature [30].

c. Oral submucous fibrosis: It is a chronic, premalignant condition of the oral mucosa which was first described by

Schwartz 1952. Recently it is thought to be an autoimmune disease. The presence of various autoantibodies in varying titers is reported in several studies confirming autoimmune basis to the disease. This disease is considered to be a consequence of disturbances in the homeostatic equilibrium between synthesis and degradation of extracellular matrix, wherein collagen forms a major component, thus can be recognized as a collagen-metabolic disorder. It is characterized by a juxta epithelial inflammatory reaction followed by fibroelastic change in the lamina propria and associated epithelial atrophy. This leads to a restricted mouth opening, resulting in trismus leading to restriction of food consumption, difficulty in maintaining oral health, as well as impairs the ability to speak [33, 34].

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