Collagen—The Skeleton of the Periodontium: A Review

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ABSTRACT

Aim and objective: The fibers of the periodontal ligament are a structurally integrated unit of fibrous components mainly collagenous in nature and similar to the other supportive connective tissues. Collagen is the foremost abundant protein in mammals. Within the extracellular matrix, they form supramolecular assemblies with a minimum of one triple-helical domain.

Background: The collagen family comprises 28 members. The fibers of the periodontium play a role in the structural organization of the tissues, and contribute to its mechanical properties, by accommodating intensive forces from mastication and tooth eruption. They interact with cells via several receptor families and regulate their proliferation, migration, and differentiation. Certain collagens have a restricted tissue distribution and hence specific biological functions.

Review results: This review brings to light the synthesis, mineralization, and degradation of various types of collagen.

Conclusion: Collagen serves immense functions related to the structural integrity as well in the tooth-eruption mechanism. It presents with a rapid turnover rate which along with its biochemical composition would thereby help in determining a pathological involvement causing periodontal destruction.

Keywords: Biochemistry, Collagen, Crimping, Degradation, Mechanical support, Mineralization, Sharpey's fibers.

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INTRODUCTION

The fibrous elements of the periodontium support it by providing tensile strength, whereas the ground substance dissipates the compressional forces. These components, seen in the electron microscope as an insoluble fibrillar network surrounded by a thixotropic gel, meet the functional requirements of tooth support and eruption. Collagen is the most abundant and is often presumed to be the most important in terms of tooth support. Collagen is a protein composed of various amino acids; mainly glycine, proline, hydroxylysine, and hydroxyproline. The collagen content in a tissue can be determined by its hydroxyproline content. The collagen is formed by packing together of individual tropocollagen molecules of approximately 5 µm in diameter and termed as principal fibers, with the bulk being type I collagen.¹

CLASSIFICATION OF COLLAGEN TYPES

Olsen² divided it into main groups Fibril collagen and FACIT Collagens.

Fibril collagens include collagen type I, III, and V.²

FACIT collagens are fibrils-associated collagens with interrupted triple helices, but it does not directly associate with the major band collagen fibrils (Vonder Mark et al., 1984).³

According to Kielty and Grant,⁴ 25 different gene sequences have been discovered encoding for collagenous polypeptides giving rise to 13 distinct collagen types, which can be divided into three groups:

The first, most abundant group is the fibrous collagens. These are in the form of uninterrupted helices that are highly conservative and are mainly I, II, III, V, and XI. The second group is the high molecular weight collagen, comprising of numerous intervening non-helical sequences, in association with the basement membrane. Types IV and VII. The third group is a short-chain, non-helical domain, and consists of types VI, VIII, IX, X, XII, and XIII.⁵⁻⁷

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The main types of collagen in the periodontal ligament are type I and type III (Table 1).

Type I Collagen

It is the major protein component of most connective tissues. The biosynthesis and fibrillogenesis of type I collagen within PDL could be determined by studying its posttranslational modifications.⁸ It comprises two identical α1 chains and a α2 chain which is low in hydroxylysine and glycosylated hydroxylysine. Collagen type II is a short-chain molecule that has only recently been located in the PDL (Romanos et al.)^{1,5}

Type III Collagen

The periodontal ligament is rich in type III collagen (about 20%) which is covalently linked to type I collagen relatively high in hydroxyproline and cysteine whereas low in hydroxylysine. It is found in the periphery of Sharpey's fiber attachments into the alveolar bone and around nerves and blood vessels, the function, however, is unknown. A higher proportion of collagen type III is present in fetal tissue (Berkowitz)⁵ and follows a similar distribution pattern with the major fibrils throughout the tissue.

Table 1: Classification of collagen

<i>Class</i>	<i>Type</i>	<i>Distribution</i>
Fibril-forming (fibrillar)	I	Bone, skin, cornea, ligaments, tendon
	II	Cartilage, vitreous humor in the eye
	III	Skin, blood vessels
	V	Bone, dermis, co-distribution with type I
	XI	Cartilage, intervertebral discs, co-distribution with type II
	XXIV	Bone, cornea
	XXVII	Cartilage
Fibril-associated collagens with interrupted triple helices (FACIT)	VII	Bladder, dermis
	IX	Cartilage, cornea
	XII	Tendon, dermis
	XIV	Bone, dermis, cartilage
	XVI	Kidney, dermis
	XIX	Basement membrane
	XX	Cornea of chick
	XXI	Kidney, stomach
	XXII	Tissue junctions
	XXVI	Ovary, testis
Networking associated	IV	Basement membrane
	VI	Muscle, dermis, cornea, cartilage
	VIII	Brain, skin, kidney, heart
	X	Cartilage
	XXVII	Dermis, Sciatic nerve
Membrane-associated collagens with interrupted triple helices (MACIT)	XIII	Dermis, eyes, endothelial cells
	XVII	Hemidesmosomes in epithelia
	XXIII	Heart and retina
	XXV	Heart, testis brain
Multiple triple helix domains and interruptions (MULTIPLEXINs)	XV	Capillaries, testis, heart, kidney
	XVIII	Liver and basement membrane

Other Types of Collagen

Minute amounts of type IV, V, VI, and VII collagen have been found in the ligament. Type IV and VII collagen forms the major fraction of basal lamina protein of the blood vessels,⁹ the neurovascular bundles and epithelial rests of PDL. It does not form fibrils and helps maintain the structure and integrity of the PDL.¹⁰

Type V is believed to be associated with the cell surface and coats the type III and type I fibrils. Type VI is a component of oxytalan fibers though not directly associated with the major fibrils. It may play a role in maintaining the integrity and elasticity of the extracellular matrix (ECM).¹¹

Type XII collagen helps organize the ECM architecture of dense connective tissues¹² and occurs only when the ligament is fully functional.^{12,13} This type has an NC3 domain that carries glycosaminoglycan chains, and it interacts with matrix proteins such as decorin, cartilage oligomeric matrix protein, fibromodulin, and tenascin and could possibly be associated with the functional regeneration of the PDL¹⁴ (Table 2).

General Structure of Fibrous Collagens

All collagens are made up of three polypeptide chains organized into a triple-helical structure¹⁵ with a mean diameter of 45–55 nm and transverse striations with a characteristic periodicity of 64 nm. Each polypeptide chain contains 1,056 amino acid residues, in the form of the repeating tri-residue Motif (Gly-x-y), (where x is often

proline and y is often hydroxyproline) conferring its characteristic conformation.^{15–17}

General Biosynthesis of Fibrous Collagens

Fessler et al.¹⁸ found the precursor to be “procollagen” synthesized from fibroblasts of tissue explants *in vitro*. Pro collagens possess a relative molecular mass greater than tropocollagen. They comprise peptide extensions on the C and N termini referred to as propeptides. Cleavage of those propeptides may be a necessary prerequisite for fibrillogenesis within the ECM. Schofield and Prockop¹⁹ at the pretranslational level.

Synthesis of Procollagen

The ribosomes on the rough endoplasmic reticulum (RER) initiates the biosynthesis of procollagen involving extensive cotranslation and posttranslational modifications controlled by various enzymes.²⁰ Conversion from procollagen to collagen is a specific process.²¹ Peltonen et al. proposed that the cleavage of the carboxy-terminal propeptides of types I and III are differently affected by lysine.²²

Hydroxylation of Proline and Lysine

Hydroxylation of PRO and LYS residues is a cotranslational event occurring during chain elongation at the ribosome.²¹ Its cross-linking is based upon aldehyde formation from specific telopeptides, Knott and Bailey²³ catalyzed by three hydroxylase

Table 2: Ultrastructural distribution of collagen fibers

	<i>Tissue distribution</i>	<i>Supramolecular organization</i>	<i>Associations</i>
Collagen type I	Interstitial	Cross-banded fibers; diameters $\cong$ 30–35 nm; banding interval $\cong$ 64 nm	Basic structural component associated with collagen types III, V, VI, and fibronectin
Collagen type III	Interstitial	Beaded fibers; diameter $\cong$ 15–20 nm; beaded interval $\cong$ 40–64 nm	Associated with other interstitial collagens and fibronectin
Collagen type V	Interstitial	Thin filaments $\cong$ 10 nm	Associated with types I and III often extending to this interstitial aspect of vascular basement membranes
Collagen type VI	Interstitial	Thin filaments $\cong$ 10 nm	Associated with types I and III often extending to this interstitial aspect of basement membranes
Fibronectin	Interstitial and plasma	Thin filaments and glomerular aggregates diameter $\cong$ 10 nm	Associated with interstitial collagen
Laminin	Basement membranes both laminae but preferentially in the lamina rare	Not resolved	Associated with type IV collagen
Collagen type IV	Basement membrane both laminae but preferentially in the lamina densa	Not resolved	Associated with laminin

enzymes which require Fe^{2+} , α -ketoglutarate, O_2 , and ascorbic acid.^{19,20} This, however, ceases after triple-helix formation.

The role of hydroxyproline and hydroxylysine in helix stability and cross-linkage is of prime importance and a failure results in a range of pathologies²² such as scurvy, and Menkes' Kinky hair syndrome. The varied rates of PDL destruction amongst individuals speculate of distinctive lysine/hydroxylysine cross-linking variations in collagen.²³

Glycosylation of Hydroxylysine and Asparagine

Glycosylation reactions are catalyzed by hydroxylysyl galactosyltransferase and galactosyl hydroxylysyl glucosyltransferase and its amount varies with age and the type of tissue. Yamauchi and Sricholpech provided an overview on the enzymatic lysine modifications and subsequent cross-linking to form covalent intra- and inter-molecular cross-links.²⁴

Helix Formation

Triple helix formation is initiated via the association of the three C-terminal propeptides,²⁵ whereas chain alignment begins by non-covalent (hydrophobic) interactions at the C-terminal propeptide (Fessler et al.).¹⁸ The rate-determining step for helix formation is the stabilization of the alignment by disulfide bonds in the propeptides (Freedman)²⁶ catalyzed by disulfide isomerase (Freedman and Hillson).²⁷ Subsequently, the folding of the triple helix proceeds rapidly. The procollagen molecule is then exported via the Golgi apparatus in the classical secretory pathway, further processing occurs by endopeptidases to form tropocollagen aggregates. The elimination of the propeptidases is achieved by enzymes belonging to the class of matrix metalloproteinases.⁵

Collagen Crimping

Collagenous tissues exhibit a quantifiable periodicity of the structure of variable scale; ranging from submicroscopic to anatomical; sinusoidal waveform.^{28,29} This has been referred to as "crimp" (Diamant et al., Gathercole).^{30,31} It was suggested that the developing fibroblastic processes help fabricate the crimped structure, thus a prerequisite in tooth eruption (Gathercole and Keller).³¹

Crimping can be recognized by a regular banding of dark lines across a collagenous bundle in polarizing microscopes, biomechanical studies, and X-ray diffraction analysis (Keller and Gathercole and Keller).^{31,32} Crimping may either be due to the arrangement of collagen fibrils or due to the microanatomical organization of collagenous sheets and bundles (Gathercole and Keller).³¹ SEM observations demonstrate the intertwining of fibrils with one another and in the outer region.³³ Birefringence studies reported no evidence of fiber directional dispersions (Kolenda and Serwa et al., 2018).³⁴

Sharpey's Fibers

Sharpey's fibers (SF) are poorly mineralized fibers of the animal tissue, composed mostly of several sorts of collagen, elastin, or tenascin^{35–37} embedded into the cementum and alveolar bone and concentrated within the crestal region^{38,39} in various orientation.³⁷

Light microscopic observations suggest their continuity with the periodontal ligament of adjacent teeth. On the premise of ultrastructural and microradiographic observations, Selvig 1965 has reported that Sharpey's fibers have unmineralized cores and are separated by lamellar bone fibers which are either randomly arranged or are parallel to the mineral surface.⁴⁰ Immunohistochemistry reveals that Sharpey's fibers are enclosed within a sheath of collagen type III conferring elasticity and preventing remineralization.⁴¹ Scanning electron microscopy shows that the peripheral bone surrounding the Sharpey's fibers may be mineralized to a level slightly above or below the level of the bone surface and exhibit a stippled appearance that indicates that the mineralization occurs approximately at right angles to the axis of the fibers⁴² and this offers a mechanical advantage for transmitting axially directed forces and tensional forces.⁴³ The amount and ratio of collagenous protein in the Sharpey's fibers and adjacent alveolar bone, gets affected by the intensity and characteristics of the orthodontic movements.⁴⁴

Mineralization of Collagen

Collagen fibers are mineralized along their length and cores with hydroxyapatite crystals.⁴⁵ A well-defined interface is present between the mineralized and non-mineralized collagen within the PDL which implies a mechanism that retains the

width (approximately 200 pm within the case of human PDL) of unmineralized fibers. Sharpey's fibers represent an embedding of the PDL fibers by entrapment in the advancing mineral front.^{40,46}

Collagen mineralization may be mediated by restriction enzymes such as alkaline phosphatase located in the bulk of the tissue adjacent to the alveolar bone. Several causes may lead to the failure of the mineralization of the PDL fibers. Cross linkage of PDL fibrils could lead to restriction of access of minerals to its nucleation sites, thereby affecting the glycosylation of collagen, its assembly, and the proteoglycans.^{5,34,47}

General Features of Collagen Degradation

In the event of morphogenesis, the collagen undergoes breakdown thus maintaining a balance between its degradation and synthesis.

Collagen degradation is primarily associated with two mechanisms:

- Various cells (fibroblasts, PMNs, and macrophages) in the healthy or inflamed tissues secrete collagenases and other enzymes; (which degrade collagen and other matrix macromolecules into small peptides are called matrix metalloproteinases) destroy collagen extracellularly.
- Secondly, fibroblasts degrade collagen fibers by phagocytosis. Cytoplasmic processes of the fibroblasts extend to the ligament–cementum interface and thereby degrade the inserted collagen fibrils and the fibrils of the cementum matrix.^{1,5,6,7,48}

The collagen breakdown is mediated *via* matrix metalloproteinases—a group of zinc-containing endopeptidases characterized by their metal-binding properties, and secreted as inactive precursors, and inhibited by tissue inhibitor of metalloproteinases (TIMP).

MMPs are predominantly secreted by fibroblasts and also produced by some leukocytes (polymorphonuclear neutrophil leukocytes and macrophages). Six major matrix metalloproteinases are effective in collagen degradation. Matrix metalloproteinases are also known to be inducible enzymes, and the cytokines, particularly interleukin-1, seem to play an important role in the control of their expression.⁴⁹

The triple helix fibrillar collagen though resistant to proteolytic degradation⁵⁰ loses its conformation after cleavage, resulting in a denatured molecule exposed to less specific proteases. The regulation of MMP's is important for the maintenance of tissue morphostasis. The primary control is exerted by the production of the inhibitor molecule.⁵¹ Tissue inhibitor of metalloproteinases is a glycoprotein secreted by fibroblasts and macrophages. Tissue inhibitor of metalloproteinases forms an irreversible complex with the MMPs via non-covalent interactions. TGFB also increases TIMP production.

These can be further degraded by lysosomal enzymes (notably cysteine proteases), which operate at acidic pHs. In contrast to the extracellular degradation of collagen, is an intracellular pathway of collagen phagocytosis and subsequent breakdown does not appear to involve matrix metalloproteinases.^{52–55} Glucocorticoids and retinoids inhibit MMP production^{56–58} and simultaneously increase the production of TIMP (Table 3).

CONCLUSION

The major fibrous protein of the PDL is type I collagen, with type III collagen present in unusually high quantities (about 20% of collagen present). Types IV, V, VI, and XII have also been detected,

Table 3: Matrix metalloproteinases and collagen remodeling

Enzyme	MMP	Substrate	Other substrates
Collagenases			
Collagenase-1	MMP-1	I, II, III, VII, X (VIII, XI)	Gelatin
Collagenase-2	MMP-8	I, II, III (VII, VIII, X)	Aggrecan and gelatin
Collagenase-3	MMP-13	I, II, III (IV, VI, X, XIV)	Gelatin
Gelatinases			
Gelatinase-A	MMP-2	I, IV, V, VII, X (II, III, X)	Gelatin
Gelatinase-A	MMP-9	IV, V, XIV (XI)	Gelatin
Stromelysins			
Stromelysin-1	MMP-3	III, IV, XI, X (II, VII, XI)	Gelatin
Stromelysin-2	MMP-10	IV (III, V)	Laminin, fibronectin, elastin
Stromelysin-3	MMP-11	IV	Laminin, fibronectin, aggrecan
Matrilysins			
Matrilysin-1	MMP-7	IV (I)	Laminin, fibronectin, gelatin
Matrilysin-2	MMP-26	IV	Fibrinogen, fibronectin, gelatin
Membrane type MMPs			
MT1-MMP	MMP-14	I, II, III (and proMMP-2) general (and proMMP-2)	Laminin, fibronectin, gelatin
MT2-MMP	MMP-15	III	Laminin, fibronectin, gelatin
MT3-MMP	MMP-16		Laminin, fibronectin, gelatin
MT4-MMP	MMP-17		Fibrinogen, fibrin
MT5-MMP	MMP-24		Laminin, fibronectin, gelatin
MT6-MMP	MMP-25	IV	Gelatin
Others			
Macrophage metalloelastase	MMP-12	I, IV	Elastin, fibronectin
Enamelysin	MMP-19	IV	Aggrecan, elastin, fibrillin, gelatin
XMMP	MMP-20		Aggrecan
	MMP-21		Aggrecan
	MMP-23		Gelatin, casein, fibronectin
CMMP	MMP-27	Unknown	Unknown
Epilysin	MMP-28	Unknown	Unknown

albeit in much smaller amounts. Periodontal ligament collagen is unusual in its supermolecular arrangement, rapid assimilation into fibrils with an absence of non-reducible cross-links with age and as compared with other soft connective tissues.⁵⁹ This results in an extremely rapid rate of collagen turnover in the ligament. Collagen degradation is mediated by interstitial collagenase.

Whereas increased collagenase activity appears to be associated with chronic inflammatory periodontal disease and could be cytokine-mediated.

The biochemistry of the fibers of the collagen of the PDL suggests that this is an unusual connective tissue, with many fetal-like characteristics. This may be related to tissue function and may represent an important factor in the etiology of chronic inflammatory periodontal disease.

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