REVIEW
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Collagen Degradation in Periodontal Health and Disease: A Brief Review

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Abstract

The objective of this short review is to revisit the collagen destruction mechanisms associated with periodontal health and disease. It is important to differentiate between physiologic remodeling and bacterial enzymatic degradation in diseased periodontal tissues in order to understand the contribution of various factors assisting periodontal therapy.

Keywords: Bacterial enzymatic degradation, collagen, physiological remodeling

INTRODUCTION

Collagen is a heterogeneous group of protein that contains at least 1 triple-helical domain. Several sub-families exist, with fibrillar collagen being the most abundant extracellular component of the periodontium, and its metabolism requires to be accurately controlled by the balance between synthesis and degradation.[1]

Collagen degradation is an essential physiologic process responsible for wound repair and tissue remodeling. It is primarily mediated by collagenases and several other enzymes. This is reported to occur through 2 mechanisms, namely, i*ntracellular pathway and extracellular pathway.*

Intracellular pathway is primarily responsible for the physiologic turnover of collagen in periodontal ligament through the selective ingestion of collagen fibrils by fibroblasts. It is identified as a slow process and is crucial for maintaining collagen homeostasis. And the extracellular pathway is primarily in use during pathological conditions characterized by rapid collagen destruction. Collagenase is responsible for large-scale indiscriminate removal of collagen fibers during inflammation in periodontal disease.[2] Both pathways, play separately or in combination, enable the cells to degrade different types of collagens throughout the body. Fibroblasts secrete the activators and the inhibitors that allow these cells to participate in regulating collagen degradation. The role of cytokines like IL-1α has been addressed in collagenolysis and their episodic nature results in bursts of attachment loss ("burst hypothesis"). During the phases of healing, other cytokines like tumor growth factor-beta (TGF-β) have been shown to restore a state of equilibrium.[3] *Later compensatory mechanisms were proposed to participate a complementary role in intracellular and pericellular collagen degradation.*[4]

There are various types of collagens derived from different sources with varied resorption time periods.[5] *The activity of bacteria and their enzymes were identified to contribute to the rapid degradation.*[6] So knowledge about the mechanisms of collagen degradation is vital.

Hence, in the present study, an attempt was made to review various collagen degradation mechanisms in health and disease to understand the contribution of various factors assisting in periodontal therapy.

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SCOPE AND PURPOSE

The purpose of the review was to better understand the importance of collagen degradation mechanisms associated with periodontal health and disease in order to differentiate between physiologic remodeling and bacterial enzymatic degradation. This might give scope for identifying futuristic strategies to consider and manipulate these mechanisms allowing us to establish a possible control over this process.

REVIEW

Collagen turnover is attributed to various functions that include facilitation of the physical expansion of tissue, liberation of latent growth factors embedded within extracellular matrix, enables vascular development, suppression of the cellular proliferation by the extracellular matrix, and direct regulation of cellular differentiation.[7-9]

In the physiological and pathological tissue-remodeling process, 3 molecular pathways have been proposed for the turnover of collagen. The best-learned pathways involved a group of membrane-associated matrix metalloproteinases (collagenases) that directly cleave collagens within the pericellular or extracellular environment.[10,11]

Secondly, cathepsin K-mediated pathway that occurs in the acidic microenvironment represents specific osteoclast-mediated bone resorption created between the ruffled border of the osteoclast and the bone interface.[12,13]

Third pathway involves the binding of collagen fibrils to specific cell surface receptors intracellularly followed by cellular uptake, lysosomal delivery, and proteolytic degradation.[14-17]

Collagen turnover takes place during both physiological and pathological conditions. Previous studies believed that intracellular pathway of collagen degradation is likely to occur in physiology, *whereas* extracellular pathway takes place during pathological conditions.[2,3] *According to literature, several functionally different pathways have been proposed for extracellular and intracellular degradation by a wide range of specialized cell types. Wagenaar-Miller RA et al (2007)*[4] *proposed complementary roles of intracellular and pericellular collagen degradation pathways as compensatory mechanisms.*[4,18]

INTRACELLULAR PATHWAY OF COLLAGEN DEGRADATION

The mean turnover rates and the proportions of collagen degradation intracellularly vary widely between tissues. The collagen turnover in periodontal tissues may be much more rapid than originally believed, and therefore, changes in degradation might be important in collagen homeostasis(Bartold). Intracellular degradation of collagen can occur by any of the following mechanisms:[16,19-21] (i) phagocytosis, (ii) macropinocytosis, (iii) endocytosis, and (iv) autophagocytosis (Figure 1).

Phagocytosis involves internalization of intact collagen fibrils. Fibroblasts will recognize degradable collagen fibrils by β1-integrin receptors (α2β1, α10β1, and α11β1).[22] Activation of these receptors depends on GTPase Rap 1 and non-muscle myosin IIA (NMMIIA),[23,24] and their binding capacity to collagen fibrils is dictated by the presence of non-collagenous proteins such as proteoglycans and fibronectin. The surface of collagen fibril is usually covered with non-collagenous proteins. The binding of β1-integrins to the collagen fibrils is blocked due to the presence of these non-collagenous proteins on their surface.[25]

Recognized collagen fibrils get degraded to smaller fragments by gelatinase A (MMP-2), whereas initial cleavage of the fibrils requires membrane-bound MT1-MMP, which is the key regulatory agent for collagen phagocytosis, then fibroblasts form actin-rich pseudopods and these fragments get internalized leading to the formation of the phagolysosome.[26,27] Plasma membrane alkaline phosphatase has also been involved in promoting collagen phagocytosis through collagen binding.[28]

Macropinocytosis and endocytosis processes involve non-phagocytic internalization of precleaved collagen fragments. Macropinocytosis is a rapid and major pathway in collagen fibril internalization. Collagen fibril uptake is mediated by the presence of actin. After internalization, macropinosome is formed and fibrils in this macropinosome get degraded by cysteine proteases. During inflammation, phagocytosis gets replaced by this process leading to extensive tissue destruction.[18]

Receptor-mediated endocytosis includes urokinase plasminogen activator receptor-associated protein uPARAP/End o180-receptor, which is a C-type mannose receptor and clathrin-coated vesicles, expressed by various cells such as fibroblasts, macrophages, endothelial cells, chondrocytes, and bone-lining cells. Internalized collagen fibrils get degraded by cysteine proteases further leading to the formation of phagolysosome.[16,20]

In the phagolysosome, collagen fragments rapidly degrade by lysosomal enzymes. Lysosomal cysteine proteases such as cathepsins B and L cleave non-helical processes of collagen fibrils and cathepsin K can efficiently cleave multiple sites of triple helix in the presence of glycosaminoglycans.[29] Cathepsin K differs from collagenases of MMP family, as it lacks protein domains involved in the unfolding of collagen fibril. In a healthy state, osteoclasts mainly use cathepsin K to degrade the collagen in mineralized tissues such as bone, dentine, and cartilage. It also plays a prominent role in pathological tissue degradation.[18]

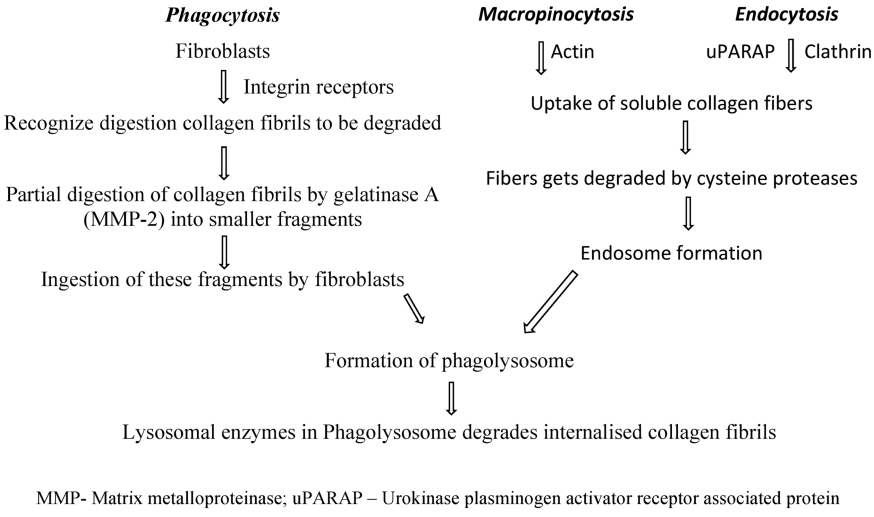

Figure 1. Intracellular pathway of collagen degradation.

Autophagocytosis is another distinct intracellular degradation pathway, where collagen fragments get enclosed by membranes derived from the endoplasmic reticulum leading to the formation of autophagosomes. When it gets fused with a lysosome, an autophagolysosome is formed and the collagen fragments are degraded by cysteine proteases.[18]

EXTRACELLULAR PATHWAY OF COLLAGEN DEGRADATION

In this process, the cells secrete a number of enzymes that sequentially degrade collagen (Figure 2). Matrix metalloproteinases are secreted as inactive precursors (proenzymes) and then proteolytically cleaved to become active. Membrane type-MMPs (MT-MMPs) are activated intracellularly before insertion into the membrane and activate MMPs such as gelatinase A (MMP2) and *stromelysin (MMP 3)*, in turn activate collagenases and other soluble MMPs. Before initiation of collagenase activity, stromelysin removes proteoglycans around collagen fibers and exposes them to collagenase and further degrades them into collagen peptides. Membrane type-MMP's can also directly degrade collagen fibrils. Lysosomal cysteine proteases also play a role in extracellular degradation of collagen.[2]

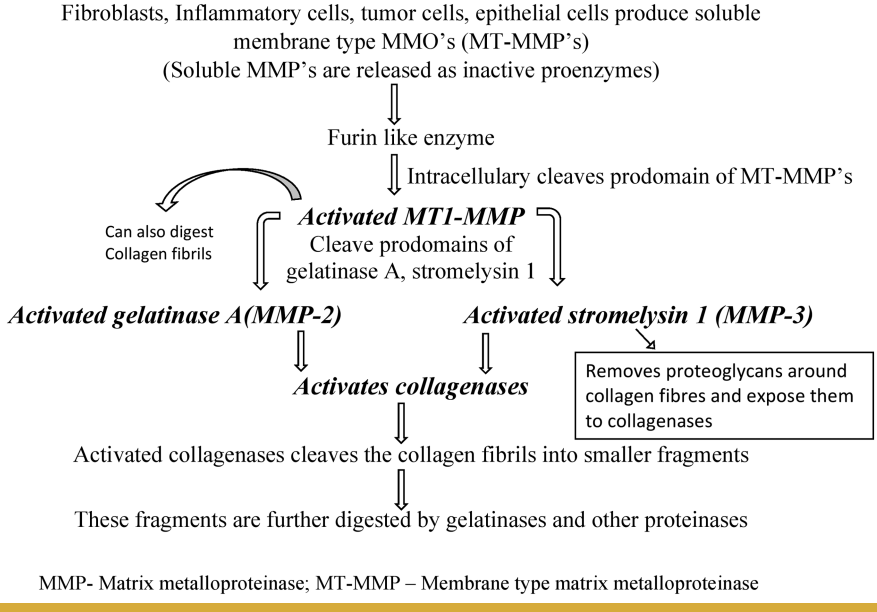

Figure 2. Extracellular pathway of collagen degradation.

RELATIONSHIP BETWEEN INTRACELLULAR AND EXTRACELLULAR PATHWAYS

The role of cytokines has been reported in the regulation of collagen degradation pathways. Cytokines like interleukin (IL)-1α and TGF-β have opposite effects and act as antagonists to each other. Interleukin-1α has the capacity to inhibit the intracellular pathway and promote extracellular pathway of collagen degradation by inducing the release of collagenases.[3]

It has been reported that these 2 pathways act simultaneously, first partial digestion of collagen fibrils by extracellular pathways followed by internalization of partially cleaved collagen fibrils.[18]

Functional defects in intracellular pathways could be compensated by extracellular pathways and vice versa, whereas combined defects in both pathways lead to impaired bone formation.[4,18] The inhibition of matrix degradation, therefore, has long been recognized as an attractive target for therapeutic intervention in a variety of human diseases.

During bone growth, collagen is rapidly removed in the endosteal regions and produced under the periosteum. According to Vaes,[30] collagenase-independent pathway takes place for alteration in collagen framework of mineralized tissues based on the release of lysosomal cathepsins through the ruffled border of osteoclasts.

Later, Baron et al[31] suggested that the zone between the osteoclast and the bone surface is functionally equivalent to an intracellular phagolysosome. In this mechanism of osteoclastic resorption, there will be the removal of the calcium hydroxyapatite through the production of acid by the Adenosine Triphosphate (ATP)-activated proton pump in the cells with a ruffled border initially. And then, the exposed collagen fibrils were degraded by lysosomal cathepsins contributing to the destruction of the organic matrix. Locally, elevated concentration of calcium has been identified to cause the breakdown of bone collagen carried out by osteoclasts in the presence of lysosomal enzymes and matrix collagenase. Various factors which influence collagen degradation are reported in Table 1.[31-33]

FACTORS INFLUENCING COLLAGEN DEGRADATION

Resorption Rate of Collagen and Regeneration of Periodontium

From the literature, it has been identified that the degradation time of collagen is proportional to the regeneration of periodontal tissues. The resorption rate of collagen is degraded through enzymes secreted by macrophages and polymorphonuclear leukocytes. Collagenase enzyme initiates resorption at a specific site of collagen membrane resulting in denaturized fragments, and become gelatine, that is further degraded to amino acids and other enzymes. This process of

Table 1. Factors in Collagen Degradation[32-34]

Factors/Enzymes	Mechanism of Action	References
Cathepsins (S,L,N,K)	Degrade insoluble collagen in acidic microenvironments, intracellularly in the lysosome and extracellularly in local zones, between the invading osteoclast and the underlying surface of the bone	Baron et al[31]; Kafienah et al[32]
Collagenase group		Nagase et al[33]
1. Collagenase I/MMP-1/ fbroblast type collagenase	Produced by human epithelial cells and a variety of mesenchymal cells including keratinocytes, fibroblasts, and macrophages. Hydrolyses collagen type I-III,VII,VIII,X.	
2. Collagenase II/MMP-8/ PMN leukocyte collagenase	Found only in the specific granules of polymorphonuclear neutrophil cells. Hydrolyses collagen type I-III,VII,VIII,X, gelatin, fibronectin.	
Gelatinase group		
1. GelatinaseA/MMP-2 2. GelatinaseB/MMP-9	Hydrolyses gelatin, collagens (IV-VI), elastin, fibrillin, osteonectin.	
Stromelysin group		
1. Stromelysin-1/ MMP-3 2. Stromelysin-2/MMP-10 3. Stromelysin-3/MMP-11	Removes proteoglycans around collagen fibrils and expose them to collagenases. Hydrolyses laminin, aggregan, gelatin, fibronectin, elastin, collagen (III-V).	
Matrylysin group		
1. MMP-7 2. MMP-26	Hydrolyses collagen (I-IV), laminin, gelatin, fibronectin, proteoglycan, elastin, pro MMP-9, aggregan.	
Membrane type MMP's		
1. MT-MMP-1/ MMP-14 2. MT-MMP-2/ MMP-15 3. MT-MMP-3/ MMP-16 4. MT-MMP-4/ MMP-17 5. MT-MMP-5/ MMP-24	Hydrolyzes collagen (I-III), laminin, tenascin, fibronectin, aggregan, gelatin, fibrinogen, TNF precursor proteoglycans, activate gelatinase-A (MMP-2).	

MMP, matrix metalloproteinase; MT-MMP, membrane type-matrix metalloproteinase.

Table 2. Rate of Resorption of Collagen Membranes from Different Sources[5]

Commercial Name	Composition	Resorption Rate
Bovine Tendon	100% type I collagen; cross-linked with formaldehyde	6-8 weeks
Bovine Dermis	Types I and III collagen; cross-linked with glutaraldehyde	4-8 weeks
Calf Skin	96% type I collagen and 4% chondroitin-4-sulfate; cross-linked with diphenylphosphorylazide	4-8 weeks
Porcine Dermis	Types I and III non-cross-linked collagen	2- 4 weeks

collagen degradation is similar to the extracellular pathway of collagen degradation. Olaechea et al[34] have evaluated biodegradation of 3 collagen membranes from different sources and the evaluation of blood vessel penetration and collagen fiber penetration. They reported that degradation time should be sufficiently long to show better regeneration.

Cross-linked collagen membranes have slower resorption rates compared to non-cross-linked (Table 2) and are more favorable for regenerative periodontal therapy.[5]

The focus of research has shown the importance of the ability of periodontal bacteria to colonize and infect different types of membranes during the late 90s. Enzymatic degradation by periodontal pathogens has been reported to play an important role in collagenolysis. According to Sela et al.[6] 3 enzymes produced by *Porphyromonas gingivalis* (P. gingivalis)—Rgp, Kgp, Prolyl peptidases—are capable of hydrolyzing both cross-linked and non-cross-linked collagen membranes. *Treponema denticola* (*T. denticola*) produces proteases like chymotrypsin-like, and phenylalanine (PAP) and peptidases like arginine, proline, and anddentilisin that were found to hydrolyze type IV collagen. *T. denticola* PAP degraded collagen IV but not collagen I under denaturating conditions, whereas, at 37°C, PAP is able to degrade collagen types I and III.

Sela et al[35] studied the therapeutic effects of antibacterial agents on the degradation of collagen membranes and reported that all tested collagen membranes are prone to lysis by oral bacterial proteases. Cross-linked membranes are more resistant to proteolysis, and antibacterial agents significantly inhibit enzymatic breakdown of these membranes.

Other contributory factors influencing collagen degradation include aging and the circadian clock.

The influence of age is also reported to increase the rate of conversion of soluble to insoluble collagen, higher levels of lysosomal enzymes, and increased resistance to proteolytic enzymes despite a low rate of synthesis.[2] Therefore, the net loss of collagen observed in older periodontal ligament cells is caused by excessive resorption when compared to the production of new collagen.

The circadian clock regulates collagen homeostasis by means of synthesis and collagen degradation affecting newly synthesized collagen. Alteration in the circadian rhythm leads to abnormal collagen fibrils and collagen accumulation.[36]

CONCLUSION

Pathways for collagen degradation in the human periodontium in health and disease are complex in nature. It is essential to understand various factors affecting collagen destruction for the development of future therapeutic strategies.

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