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Review Article

Role of MMPs in connective tissue breakdown and periodontal disease: A Review

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ABSTRACT

Matrix metalloproteinases (MMPs) are a group of zinc-dependent enzymes that play a critical role in the degradation of extracellular matrix components, including collagen, elastin, and proteoglycans, making them central to tissue remodeling processes. In the context of periodontal disease, MMPs are key mediators of connective tissue breakdown and alveolar bone destruction, driven by chronic inflammation. This review focuses on the role of MMPs in periodontal disease, highlighting their regulation, activation mechanisms, and the interplay with inflammatory cytokines such as interleukins and tumor necrosis factor-alpha (TNF-α). Furthermore, the review discusses the contribution of specific MMPs, including MMP-1, MMP-8, and MMP-9, in periodontal tissue degradation and explores potential therapeutic approaches to inhibit MMP activity to prevent periodontal disease progression. By understanding the molecular basis of MMP involvement in periodontal pathology, this review aims to provide insights into novel therapeutic strategies aimed at mitigating connective tissue breakdown in periodontal disease.

1. Introduction

Periodontal diseases, such as gingivitis and periodontitis, are chronic inflammatory conditions that result in the destruction of the tooth-supporting structures, including the gingiva, periodontal ligament, cementum, and alveolar bone. A hallmark of periodontal disease is the breakdown of connective tissues, which occurs due to an imbalance between tissue degradation and repair processes. Matrix metalloproteinases (MMPs) are a family of zinc-dependent proteolytic enzymes that play a key role in this breakdown.[1,2] These enzymes are capable of degrading extracellular matrix (ECM) components such as collagen, elastin, gelatin, and proteoglycans, contributing significantly to tissue destruction in periodontal diseases. Understanding the role of MMPs in the pathogenesis of periodontal diseases and exploring potential therapeutic strategies to inhibit their activity is crucial for the management and treatment of these conditions.

1.1. Overview of MMPs

Matrix metalloproteinases (MMPs) are a group of enzymes that are involved in the degradation of various components of the extracellular matrix (ECM). They are produced by several cell types, including fibroblasts, keratinocytes, macrophages, neutrophils, and osteoclasts. MMPs are synthesized as inactive proenzymes and require activation to become functional. The family of MMPs includes collagenases (MMP-1, MMP-8, MMP-13), gelatinases (MMP-2, MMP-9), stromelysins (MMP-3, MMP-10), and others. MMPs play a physiological role in normal tissue

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remodeling, but their dysregulation leads to excessive tissue breakdown, contributing to pathological conditions, including periodontitis.[3,4]

1.2. Mechanism of MMP action in tissue breakdown and periodontal diseases

In periodontal diseases, MMPs are overexpressed in response to bacterial infection and inflammation. Oral bacteria, particularly Porphyromonas gingivalis and other periodontopathogens, release lipopolysaccharides (LPS) and other virulence factors that stimulate immune cells to release pro-inflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and prostaglandins.[5] These cytokines trigger the production of MMPs by resident and immune cells in the periodontal tissues.

Once activated, MMPs degrade the collagen-rich extracellular matrix of the gingiva, periodontal ligament, and alveolar bone, leading to loss of tissue integrity and attachment. The breakdown of collagen types I and III by collagenases (MMP-1 and MMP-8) and the degradation of basement membrane components by gelatinases (MMP-2 and MMP-9) are critical events in the progression of periodontal disease. MMP activity is normally regulated by endogenous tissue inhibitors of metalloproteinases (TIMPs), but during periodontal disease, the balance between MMPs and TIMPs is disrupted, favoring tissue destruction.[2]

1.3. Temporal relationship of gingival matrix metalloproteinase activity and alveolar bone loss

The progression of periodontal disease involves a temporal relationship between the activity of gingival MMPs and alveolar bone loss. In the early stages of periodontal disease, elevated MMP levels are detected in the gingival crevicular fluid (GCF), where they contribute to the degradation of soft tissue. As the disease progresses, MMPs continue to break down the extracellular matrix, eventually affecting the underlying alveolar bone.[6] Bone-resorbing osteoclasts are stimulated by MMPs, resulting in alveolar bone loss. The increased activity of MMP-9, in particular, has been associated with advanced stages of periodontitis, where it plays a key role in bone matrix degradation (Table 1).

1.4. Matrix metalloproteinase inhibition by tetracycline analogues: Multiple mechanisms

Tetracycline and its analogues, particularly doxycycline, are known to inhibit MMP activity through multiple mechanisms. These mechanisms include chelation of the zinc ion at the MMP active site, inhibition of MMP gene expression, and direct binding to MMP enzymes. Tetracyclines also possess anti-inflammatory properties, reducing the production of pro-inflammatory cytokines that induce MMP expression. Sub-antimicrobial doses of doxycycline have been shown to inhibit MMP-8 and MMP-9, which are key enzymes in periodontal tissue breakdown(Table 2).[7]

Table 1: Matrix Metalloproteinase Inhibitors

Inhibitor	Mechanism of action	Clinical application
Tissue Inhibitors of Metalloproteinases (TIMPs)	Bind to active MMPs and prevent ECM degradation	Regulation of ECM turnover in normal tissues
Tetracycline analogues (e.g., doxycycline)	Inhibit MMP activity by binding to the zinc ion in the active site	Treatment of periodontitis and inflammation
Bisphosphonates	Inhibit bone resorption and MMP activity	Osteoporosis, potential application in periodontitis
Synthetic MMP inhibitors (e.g., Batimastat)	Prevent MMP activation or function	Experimental treatments in cancer, arthritis

Table 2: Mechanisms of inhibition of connective tissue breakdown by tetracyclines

Mechanism	Description
Zinc ion chelation	Binds to the catalytic zinc ion in the MMP active site, preventing MMP activity
Inhibition of MMP gene expression	Reduces the transcription of MMP genes in response to inflammatory stimuli
Anti-inflammatory effects	Decreases the release of cytokines (e.g., IL-1, TNF-α) that upregulate MMPs
Decreased osteoclast activity	Limits bone resorption by inhibiting MMP activity in osteoclasts

1.5. Exogenous matrix metalloproteinase inhibitors and their proposed role in the treatment of periodontitis

Exogenous MMP inhibitors, such as chemically modified tetracyclines (CMTs), bisphosphonates, and synthetic MMP inhibitors, have shown promise in the treatment of periodontitis. These agents target the excessive activity of MMPs in periodontal tissues, preventing further connective tissue and bone degradation. For example, sub-antimicrobial doses of doxycycline have been widely used as an adjunct to scaling and root planing in the management of periodontitis. Additionally, synthetic MMP inhibitors are being explored for their potential to limit tissue destruction and promote tissue regeneration in periodontal diseases.[2] (Table 3)

Table 3: Studies on the role of MMPs in periodontal diseases and use of MMP inhibitors

Study	Objective	MMP(s) studied	Key findings	MMP inhibitors used	Outcome
Golub et al., 1998 [8]	Investigated the effect of doxycycline on collagenase activity in periodontitis	MMP-8, MMP-9	Doxycycline significantly reduced MMP activity in gingival crevicular fluid (GCF)	Doxycycline (sub-antimicrobial dose)	Decreased collagenase activity, reduced gingival inflammation, improved periodontal attachment levels
Mäntylä et al., 2006 [9]	Evaluated MMP-8 as a biomarker for periodontitis severity	MMP-8	Elevated MMP-8 levels in GCF were strongly associated with advanced periodontitis	None (biomarker study)	Highlighted MMP-8 as a potential diagnostic biomarker for periodontitis severity
Checchi et al., 2012 [10]	Studied the role of MMPs in bone resorption during periodontitis	MMP-2, MMP-9	Increased MMP-2 and MMP-9 levels associated with alveolar bone loss during periodontal disease	None (mechanistic study)	Demonstrated the involvement of MMP-2 and MMP-9 in bone resorption in periodontitis
Sorsa et al., 2004 [11]	Reviewed the effectiveness of chemically modified tetracyclines (CMTs) in MMP inhibition	MMP-1, MMP-8, MMP-13	CMTs inhibited MMP-mediated tissue degradation without antimicrobial effects	Chemically modified tetracyclines (CMT-1, CMT-3)	Reduced gingival inflammation, prevented tissue and bone degradation in periodontitis
Gapski et al., 2009 [12]	Assessed MMP inhibition by bisphosphonates in periodontitis	MMP-9, MMP-13	Bisphosphonates decreased MMP activity and prevented alveolar bone loss	Bisphosphonates (alendronate)	Reduced MMP expression, decreased bone resorption in experimental periodontitis models
Van Wart & Birkedal-Hansen, [13] 1990	Explored the mechanism of MMP activation and ECM breakdown	MMP-1, MMP-3	Described MMP activation cascades and their role in connective tissue breakdown	None	Provided foundational knowledge on MMP activation in periodontal destruction
Ryan et al.2005, [14]	Studied the use of TIMPs in regulating MMP activity during periodontal inflammation	MMP-2, MMP-9	TIMPs balanced MMP activity to prevent excessive tissue breakdown	Endogenous TIMP-1, TIMP-2	Highlighted the therapeutic potential of enhancing TIMP activity in periodontal disease
Offenbacher et al., 2003 [15]	Investigated the role of MMPs in inflammatory response during periodontitis	MMP-1, MMP-8	Elevated MMP levels were linked to chronic inflammation and tissue destruction in periodontitis	None	Demonstrated the relationship between inflammation, MMP levels, and tissue breakdown in periodontal disease
Caton et al., 2000 [16]	Assessed sub-antimicrobial doxycycline in reducing periodontal tissue breakdown	MMP-8, MMP-9	Sub-antimicrobial doxycycline decreased MMP levels and stabilized periodontal attachment loss	Doxycycline (sub-antimicrobial dose)	Proved effective in reducing clinical parameters of periodontal disease, especially in patients with chronic periodontitis

2. Discussion

Matrix metalloproteinases (MMPs) have long been recognized as pivotal enzymes in the degradation of connective tissue, particularly in the context of periodontal disease. Recent studies have expanded our understanding of the molecular mechanisms underlying MMP activity, their regulation, and their role in the progression of periodontal diseases such as gingivitis and periodontitis.

2.1. Role of MMPs in periodontal disease progression

MMPs are critical in both physiological tissue remodeling and pathological tissue destruction. In periodontal disease, an imbalance between MMPs and their natural inhibitors, tissue inhibitors of metalloproteinases (TIMPs), leads to excessive degradation of the extracellular matrix, particularly collagen, which is essential for the structural integrity of periodontal tissues. MMP-1 (collagenase-1) and MMP-8 (collagenase-2) are primarily involved in the breakdown of type I collagen, the most abundant protein in the periodontal ligament. Elevated levels of these MMPs have been consistently found in gingival crevicular fluid (GCF) of patients with periodontitis, correlating with disease severity.

Recent studies have highlighted the specific roles of various MMPs in periodontal pathology. A 2016 study by Timo Sorsa et al.,[17] demonstrated that MMP-8 levels in GCF could serve as a biomarker for early detection of periodontitis, indicating its diagnostic potential . Similarly, MMP-9 (gelatinase B), which degrades basement membrane components such as type IV collagen, has been linked to advanced stages of periodontal disease and tissue destruction . Moreover, recent research underscores that not only the levels but also the activation states of MMPs, particularly MMP-2 and MMP-9, are critical in determining the extent of periodontal tissue destruction.

2.2. Inflammatory mediators and MMP regulation

MMP activity is closely regulated by inflammatory mediators such as cytokines, including interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and prostaglandins. These cytokines upregulate MMP expression in periodontal tissues in response to bacterial infections, particularly by periodontal pathogens such as Porphyromonas gingivalis and Treponema denticola. Studies have shown that the interaction between host immune responses and bacterial virulence factors, such as lipopolysaccharides (LPS), triggers the release of MMPs, further promoting tissue destruction.

A 2021 review by Takaaki Tomofuji et al.,[18], examined the impact of oxidative stress on MMP regulation, suggesting that reactive oxygen species (ROS) generated during chronic inflammation also activate latent MMPs, exacerbating connective tissue breakdown in periodontal disease . This adds another layer of complexity to MMP regulation, as oxidative stress-induced MMP activation can potentiate periodontal damage, suggesting that targeting oxidative stress pathways may also mitigate MMP activity.

2.3. Therapeutic approaches targeting MMPs

Given the central role of MMPs in periodontal disease, several therapeutic strategies have been explored to inhibit their activity. Tetracyclines, particularly their non-antimicrobial forms like doxycycline, have been shown to inhibit MMPs directly and are commonly used as adjunctive therapies in periodontal treatment. A 20 randomized controlled trial by Dong-Hoon Choi et al.,[19] found that sub-antimicrobial dose doxycycline (SDD) significantly reduced MMP-8 and MMP-9 levels in GCF, improving clinical outcomes in periodontitis patients .

More recent approaches focus on the development of specific MMP inhibitors (MMPIs) that can selectively block the activity of pathogenic MMPs while sparing those required for normal physiological processes. However, clinical trials with synthetic MMP inhibitors have faced challenges due to off-target effects and toxicity.

Additionally, natural compounds such as curcumin, green tea polyphenols, and resveratrol have been investigated for their MMP-inhibitory properties. A review study found that curcumin effectively inhibited MMP-2 and MMP-9 in vitro, reducing inflammation and collagen degradation in experimental periodontitis . These natural compounds may offer safer alternatives to synthetic MMP inhibitors and could be integrated into non-surgical periodontal therapies.

2.4. Future directions

The ongoing research into the role of MMPs in periodontal disease highlights the need for more precise diagnostic and therapeutic approaches. Biomarkers such as MMP-8 and MMP-9 in GCF hold promise for early detection and monitoring of periodontal disease progression. In terms of treatment, a combined approach targeting both MMP activity and the inflammatory pathways that regulate them could offer more comprehensive management of periodontal disease.

Moreover, as research advances in the field of gene therapy and molecular biology, novel therapies aimed at selectively inhibiting or modulating MMP activity without disrupting normal tissue homeostasis could become a reality. The integration of personalized medicine, using specific MMP profiles to tailor treatments, is an exciting avenue for future periodontal disease management.

3. Conclusion

MMPs play a critical role in the pathogenesis of periodontal disease by mediating connective tissue breakdown.

Understanding the regulatory mechanisms of MMPs, their interaction with inflammatory mediators, and recent advancements in MMP-targeted therapies is essential for improving periodontal disease management. While therapeutic challenges remain, emerging treatments, particularly those focusing on selective MMP inhibition, hold potential for transforming the management of periodontal disease and preserving periodontal tissue integrity.

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5. Conflict of Interest

None.

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