Review Article

Role of matrix metalloproteinases (MMPS) in periodontitis and its management

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ABSTRACT

Matrix metalloproteinases (MMPs) are a family of proteolytic enzymes that mediate the degradation of extracellular matrix (ECM) macromolecules. The activity of MMPs is seen not only during normal organogenesis and wound healing, but also in pathological condition like inflammatory diseases. MMP synthesis and functions are regulated by transcriptional activation, post-transcriptional processing and by a family of endogenous inhibitors collectively known as tissue inhibitors of metalloproteinases (TIMPs). The balance of MMPs to TIMPs therefore determines matrix turnover, where either an excess of MMPs or a deficit of TIMPs may result in excess ECM degradation. This review describes the role of MMPs in periodontitis and its management.

Key words: Matrix metalloproteinases, tissue inhibitors of metalloproteinases, extracellular matrix, chemically modified tetracyclines, low-dose doxycycline, chronic periodontitis

INTRODUCTION

Extracellular matrix (ECM) macromolecules play a key role in development and morphogenesis. Matrix metalloproteinases (MMPs), also called matrixins, are an important family of metal-dependent endopeptidases responsible for the degradation of ECM components. Expression of the 28 matrixins genes in humans is transcriptionally controlled by inflammatorycytokines, growth factors, hormones, and cell-cell and cell-matrix interactions. Matrixin activities are also regulated by activation of the precursor zymogens and inhibition by endogenous inhibitors, tissue inhibitors of metalloproteinases (TIMPs). Thus, the balance between MMPs and TIMPs are critical for the eventual ECM remodeling.

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The MMP family

The following are the MMPs grouped according to their substrate specificity.[1]

Collagenases

MMP-1 (collagenase-1, interstitial collagenase), MMP-8 (collagenase-2, neutrophil collagenase), and MMP-13 (collagenase-3).

Gelatinases

MMP-2 (gelatinase A, 72kDa gelatinase), MMP-9 (gelatinase B, 92kDa gelatinase).

Stromelysins

MMP-3 (stromelysin-1), MMP-10 (stromelysin-2), MMP-11 (stromelysin-3), and MMP-12 (metalloelastase).

Matrilysins

MMP-7 (matrilysin, PUMP-1) and MMP-26 (matrilysin-2).

MT-MMPs (membrane type)

MMP-14 (MT1-MMP), MMP-15 (MT2-MMP), MMP-16 (MT3-MMP), MMP-17 (MT4-MMP), MMP-24 (MT5-MMP), and MMP-25 (MT6-MMP).

Other MMPs

MMP-18, MMP-19, MMP-20 (enamelysin), MMP-21, MMP-23, MMP-27, and MMP-28 (epilysin).

Regulation of MMP activity

The activity of MMP against ECM substrates is regulated at four "gates":[2]

1. Transcriptional regulation of MMP genes;
   a. Growth factors and cytokines-like interleukin (IL)-1alpha, tumor necrosis factor (TNF)-alpha, transforming growth factor (TGF)-alpha and beta, epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and basic fibroblast growth factor (B-FGF) induce MMPs
   b. Hormonal regulation
   c. Cell shape and cell substrate adhesion
   d. Second messenger signaling.
2. Precursor activation;
3. Differences in substrate specificity; and
4. MMP inhibitors.

Table 1: Role of matrix metalloproteinases (MMPs) in periodontal diseases

Author and year	Method	Key conclusion
Soell *et al*., 2002[5]	A total of 16 subjects, 11 with advanced periodontitis, 5 healthy subjects. GCF MMPs -1, -2, -3, -9, and TIMP-1 and -2 levels analyzed	Increase in MMP-1, 2, 3, 9 with significant decrease in TIMP-1, 2 and catheps in level in tissue extract supernatants and GCF samples of periodontitis affected patients. Cathepsin C activity significantly lower in diseased than healthy samples
Tuter *et al*., 2002[6]	A total of 20 subjects, 10 healthy controls, 10 with chronic periodontitis. GCF MMP-1 and TIMP-1level analyzed before and after phase I periodontal therapy	Level of GCF MMP-1 decreased and TIMP-1 level increased after phase I periodontal therapy. The ratio of MMP-1 to TIMP-1 after phase I therapy in patients were closer to the controls
Smith *et al*., 2004[7]	Gingival tissue biopsy from 9 adult patients (35-65years) with advanced periodontitis, 4 healthy controls. Activity of MMP-9 was evaluated in gingival epithelium	Level of MMP-9 higher in inflammed junctional and pocket epithelium, indicating MMP-9 mediated gingival epithelial response to periodontal infection
Tuter *et al*., 2005[8]	A total of 40 subjects, 20 with chronic periodontitis (CP), 20 periodontally healthy controls. GCF (MMP-3andTIMP-1) analyzed before and after phase I periodontal treatment treatment	After phase I periodontal therapy, MMP-3level reduced and TIMP-1 level increased from pretreatment levels
Pozo *et al*., 2005[9]	GCF samples in 13 patients with CP, MMP-9 and -8, TIMP-1 and -2 levels analyzed from 60 sites at baseline, 3 and 6 months after scaling and root planing	Reduction in MMP-8 and increase inTIMP-1 and -2 level after phase I therapy
Emingil *et al*., 2006[10]	A total of 80 subjects, 20 with generalized aggressive periodontitis, 20 with CP, 20 with gingivitis, 20 healthy subjects. GCF MMP-7, TIMP-1, and EMMPRIN levels were analyzed	Increased MMP-7, EMMPRIN, and TIMP-1 levels in GCF are associated with the enhanced severity of periodontal inflammation
Maeso *et al*., 2007[11]	A total of 59 subjects, 16 healthy, 18 with gingivitis, 25 with periodontitis. GCF MMP-2 and-9, and TIMP-1 analyzed before and 1 month after basic periodontal therapy	Higher MMP-2 and -9, lower TIMP-1 level in CP patients were observed which reversed after treatment
Rai *et al*., 2008[12]	A total of 53 subjects, 15 healthy gingiva, 18 with gingivitis, 20 with periodontitis. GCF MMP-2 and -9 and salivary MMP-8 levels analyzed	Salivary MMP-8 andGCF MMP-2 and -9 levels were significantly higher in periodontitis patients
Goncalves *et al*., 2008[13]	A total of 38 gingival samples were collected10 with gingivitis, 10 with advanced CP, 8 with generalized aggressive periodontitis and 10 healthy individuals. MMP-1, -2, -9, -13 and TIMP-1 and -2 levels analyzed.	Higher MMP-2 and -9 gelatinase activities in the inflammed samples
Dong *et al*., 2009[14]	A total of42 subjects, 15 with CP, 15 with aggressive periodontitis, 12 periodontally healthy. Gingival biopsies were collected and mRNA of EMMPRIN, MMP-1 and -2 were analyzed	Periodontitis group had a significantly higher mRNA expression of EMMPRINMMP-1and -2 compared with the healthy subjects
Goncalves *et al*., 2009[15]	A total of 16 subjects, 8 healthy, 8 with CP. Salivary MMP-2 and -9 levels were analyzed before and after nonsurgical treatment	No significant difference in MMP-2 and -9 levels in saliva, suggesting salivary levels as a poor indicator of periodontal disease activity
Rai *et al*., 2010[16]	A total of 20 subjects, 10 periodontally healthy patients, 10 with periodontitis patients. GCF MMP-8 and-9 levels analyzed	Higher GCF MMP-8 and -9 levels in periodontitis and can aid as biomarkers of periodontal disease
Hernandez *et al*., 2010[17]	GCF samples collected from active (n = 25) and inactive (n = 25) sites of subjects with periodontitis. GCF MMP-8 and -14, myeloperoxidase (MPO), andTIMP-1 levels analyzed at baseline and after periodontal therapy	High MMP-8 and MPO levels were found in active and inactive sites at baseline which reduced posttreatment
Bosca *et al*., 2012[18]	A total of 21 subjects, 11 with CP, 10 healthy controls. MMP-8 salivary levels were measured	Salivary MMP-8 level were higher in CP patients and can be considered as a biomarker of periodontitis
Kyung *et al*., 2013[19]	Gingival tissues taken from 13 periodontitis patients. Correlation between activity and expression ofMMP-9 and -2 were analyzed	MMP-9 was highly expressed in all gingival tissue samples, whereas, MMP-2 was under expressed compared with MMP-9

GCF: Gingival crevicular fluid; TIMP: Tissue inhibitors of metalloproteinase; EMMPRIN: Extracellular matrix metalloproteinase inducer

Alpha 2-macroglobulins

Active MMP are captured by alpha 2-macroglobulins by a unique venus-fly-trap mechanism activated by cleavage of a bond in the "bait region". This cleavage leads to hydrolysis of a labile internal thiol-ester bond and covalent cross-linking of a nascent glutamyl residue to lysyl side chains exposed on the surface of the attacking proteinase.[2]

TIMPs

The first TIMP was described in 1975 as a protein, in culture medium of human fibroblasts and in human serum, which was able to inhibit collagenase activity. The molecular weight of this protein was later shown to be 28.5 kDa. Since then, three new TIMPs have been discovered in different species, and have been designated TIMP-2, -3, and -4, respectively.[3]

Role of MMPS in periodontal diseases

In periodontal diseases, MMPs play key roles in the degradation of the ECM, basement membrane and protective serpins as well as in the modification of cytokine action and activation of osteoclasts. Both resident gingival and periodontal ligament fibroblasts produce collagenases that are thought to be involved in normal tissue turnover. Inflammatory cells such as neutrophils and macrophages produce MMPs, with neutrophils being the major source of collagenase and gelatinase in inflammatory diseases such as periodontitis. Epithelial cells can also produce elevated levels of these enzymes, which may facilitate the apical migration and lateral extension of the junctional epithelium and the subsequent loss of connective tissue attachment. Inflammatory cells, particularly neutrophils, are thought to play a particularly important role in the MMP-mediated periodontal destructive lesion.[4]

Osteoblasts express fibroblast collagenase (FIB-CL) when stimulated by bone-resorbing agents. Osteoclastic bone resorption is initiated by an osteoblast response to resorptive signals such as parathyroid hormone (PTH), which includes expression of FIB-CL and perhaps other MMPs, and result in dissolution of the unmineralized collagenous osteoid layer [Table 1].[4]

Exogenous (Synthetic) MMP inhibitors

Inhibiting MMPs can be an effective adjunctive treatment in the management of periodontitis as they are important mediators in the connective tissue breakdown in periodontitis.

Inhibitors of MMPs fall into three pharmacologic categories:[20]

1. Collagen peptidomimetics and nonpeptidomimetics,
   a. Peptidomimetic MMP inhibitors
   b. Batimastat
   c. Marimastat
   d. Nonpeptidic MMP inhibitors
   e. BAY 12-9566
   f. AG3340
   g. BMS-27529
   h. CGS-27023A
2. Tetracycline derivatives,
   a. Doxycycline
   b. Col-3 (metastat)
3. Bisphosphonates.
   a. In Table 2 and 3 related studies of exogenous inhibitors has been discussed

CONCLUSION

MMPs are important components in many biological and pathological processes because of their ability to degrade

Table 2: MMP inhibitors: *In vitro* studies

Author and year	Method	Key conclusion
Hanemaaijer *et al*., 1998[21]	Effects of doxycycline and chemically-modified tetracyclines (CMTs) on the MMP gene expression (MMP-2 and -9) in human endothelial cells	CMTs showed inhibition of both (MMP-2 and -9) similar to that of doxycycline, butless efficient
Makela *et al*., 1998[22]	Effects of chemically modified non-antimicrobial tetracycline derivatives (CMT-1, 3, 5, and 8) and other low molecular weight synthetic matrix metalloproteinase (MMP) inhibitors (batimastat, low molecular weight heterocyclic carbonate-derived compounds) onkeratinocyte migration andMMP-2 and-9 production	Batimastat was the most effective inhibitor of MMP-9 and -2. Overall, CMTs were found to be efficient in the inhibition of MMP-9 and -2 production and keratinocyte migration
Nakaya *et al*., 2000[23]	MMP-1 and -3 were assessed in cultured human periodontal ligament cells treated with a bisphosphonate (tiludronate) at various concentration	Tiludronate inhibits the activity of both MMP-1 and MMP-3 without altering either mRNA or protein levels for these enzymes
Ramamurthy *et al*., 2002[24]	Inhibitory effect of doxycycline (2 mg/day) and CMTs (CMT-1,-3,-4,-7, and -8) on MMP mediated periodontal bone loss in a rat model	All 6 tetracyclines (2 mg/day) inhibited the MMP in the following order of efficacy: CMT-8 > CMT-1 > CMT-3 > doxycycline > CMT-4 > CMT-7
Grenier *et al*., 2002[25]	The proteolytic activities of doxycycline and CMTs at various concentration and doxycycline on progelatinase-B (pro-MMP-9) activation by purified proteinases from *Porphyromonas gingivalis*and *Treponema denticola* and the effects of doxycycline and CMT-1, -3, and -5 on Arg- and Lys-gingipain activities of *P. gingivalis*as well as on trypsin- and chymotrypsin-like activities of *T. denticola*	Doxycycline and CMTs, except CMT-5 inhibited Arg- and Lys-gingipain activitiesas well as collagenolytic activity of *P. gingivalis*. Doxycycline and CMTs markedly affect the trypsin-like activity of *T. denticola*. Doxycycline prevent the latent to active conversion ofpro-MMP-9
Eralp *et al*., 2007[26]	The effects of doxycycline and alendronate on gingival tissue expression of MMP-8, -13, and -14; tissue inhibitors of MMP (TIMP)-1; and Ln-5 g2 chain in experimental periodontitis induced by *Escherichia coli* endotoxin (LPS) in rats	Alendronate and doxycycline inhibit MMP-8 expression significantly; particularly, their combined administration may provide beneficial effects

LPS: Lipopolysaccharides

Table 3: MMP inhibitors: Clinical studies

Author and year	Method	Key conclusion
Golub *et al*., 2001[27]	In a 36-week study of 66 patients undergoing a treatment regimen involving two episodes of SRP followed by 12 weeks of SDD or placebo and separated by a 12-week period of no drug	Statistically significant reductions in GCF collagenase levels were observed after treatment with SDD
Choi *et al*., 2004[28]	A total of 32 patients with chronic adult periodontitis were included: SRP + SDD group received SDD, 20 mg twice daily, SRP + placebo gingival crevicular fluid (GCF) MMP-8 levels, MMP-9, TIMP-1, and IL-6 levels from baseline to 120 days	MMP-8 level reduced in chronic adult periodontitis after the therapy.
Emingil *et al*., 2004[29]	The effectiveness of LDD in combination with nonsurgical periodontal therapy, compared to nonsurgical periodontal therapy alone, on GCFMMP-8 levels and clinical parameters over a 12-month period in patients with CP	Low-dose doxycycline (LDD) therapy in combination with scaling and root planing can reduce GCF MMP-8 levels and improve clinical periodontal parameters in patients with CP

SDD: Subantimicrobial-dose doxycycline; MMP: Matrix metalloproteinase; TIMP: Tissue inhibitors of metalloproteinase; IL: Interleukin

ECM components. ECM and basement membrane destruction are key events in the initiation and progression of periodontal disease. These processes involve the cooperative activities and cascades of both host and bacterial derived proteolytic enzymes. The role of MMPs in the destructive processes of periodontal disease has been proved, distinguishing them as a viable target for a chemotherapeutic approach. The use of MMP inhibitor as an adjunct to conventional periodontal treatment can enhance and make clinical therapeutic responses more predictable.

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