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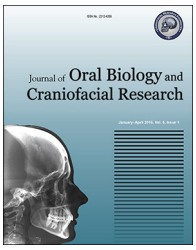

Review Article

Role of matrix metalloproteinases in dental caries, pulp and periapical inflammation: An overview

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ABSTRACT

Matrix metalloproteinases (MMPs) are a group of more than 25 secreted and membrane bound enzymes that represent class of enzymes responsible for degradation of pericellular substrates. They have been isolated from dentine, odontoblasts, pulp and periapical tissue. They play an important role in dentine matrix formation, modulating caries progression and secondary dentine formation. Earlier microbial proteolytic enzymes were believed to be responsible for degradation of dentine organic matrix, but lately the accumulated body of evidence suggests that MMPs have an important role in the process. During normal tissue modelling, differentiation during development, in modulating the cell behaviour, maintaining homeostasis and in numerous extracellular pathologic conditions, MMPs tends to be an equally important participant. Odontoblasts secrete some of the essential MMPs for both physiologic and pathologic conditions. MMPs also appear to be a participant in the process of reversible and irreversible pulpitis. Although they tend to have low expression and activity in adult tissues but at the onset of any destructive pathologic process, their production shoots up. They appear to have a significant presence during times of inflammation in the periapical region as well. We take a look at the various factors and evidence pointing towards the role of MMPs in the progression of caries, pulpal and periapical inflammation.

1. Introduction

The regulation of extracellular matrix (ECM) in both physiologic and pathologic conditions is carried out by different protease systems, viz. cysteine proteinase, aspartic proteinase, serine proteinase and metalloproteinase. Amongst the metalloproteinases, which comprise of several superfamilies, metzincin superfamily is the most important. The hallmark of matrix metalloproteinases, which belong to metzincin superfamily being, binding to zinc at the catalytic site and have a conserved 'Met-turn' motif.[1,2]

Matrix metalloproteinases are a group of more than 25 secreted and membrane bound enzymes that represent, a class of enzymes, responsible for degradation of pericellular substrates, including proteinase, clotting factors, chemotactic molecules, latent growth factors, cell surface receptors, cell–cell adhesion molecules and almost all structural ECM

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proteins. As a consequence, they are an important player in normal tissue modelling, differentiation during development and in modulating the cell behaviour. They play an essential role in homeostasis and are also involved in numerous ECM pathologic conditions, viz. inflammation and degradation of bone, autoimmune disease and invasion, migration of cancer cells across the basement membrane as in tumour metastasis. Thus MMP family proteins elicit dual roles in the pathogenesis of inflammation, stimulating protective innate and/or adaptive immune functions, as well as tissue destruction.[3]

On the basis of their putative substrate specificity and internal homologies, MMPs are classified into five main classes – collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs and others (Table 1). Their role in tissue destructional pathological conditions is evident but still however not completely clear. Their expression is regulated by proinflammatory cytokines and growth factors, as well as ECM components. The collagenases include MMP-1 (collagenase-1), MMP-8 (collagenase-2) and MMP-13 (collagenase-3). The gelatinases (type IV collagenase) include MMP-2 (gelatinase A) and MMP-9 (gelatinase B). Collagenases and gelatinases, which tend to break collagens and laminins, are considered to be the key MMPs responsible for ECM and BM destruction in many pathological conditions.[4]

Although MMPs are activated extracellularly or at the cell surface, some of them can be activated intracellularly as well. The activity of MMPs is highly controlled so as to confine them to the specific area. Proteolysis of plasminogen initiates an activation cascade leading to cleaving pro MMPs, and every step is controlled by specific activator or inhibitor called tissue inhibitors of metalloproteinases (TIMPs). Any imbalance in the expression or activity of MMP can have grave consequences in disease. Controlled degradation of ECM is essential in various physiological situations, including developmental tissue remodelling, tissue repair, angiogenesis, bone remodelling, nerve growth, immune response, apoptosis, etc. On the contrary, their unregulated activity has been implicated in numerous disease processes.

MMPs have been isolated from dentine, pulp tissue and odontoblasts, where they play an important role in dentine matrix formation, modulating caries progression and secondary dentine formation. Several pieces of evidence support the fundamental role of MMPs during the development, remodelling and destruction of oral tissues.

Through a comprehensive literature review, this article aims to provide an overview of the role of MMPs in dental caries, pulp and periapical inflammation.

Table 1 – Classification of MMPs.

1. Collagenases
MMP-1 (collagenase-1, interstitial collagenase)
MMP-8 (collagenase-2, neutrophil collagenase)
MMP-13 (collagenase-3)
2. Gelatinases
MMP-2 (gelatinase A, 72-kDa gelatinase)
MMP-9 (gelatinase B, 92-kDa gelatinase)
3. Stromelysins
MMP-3 (stromelysin-1)
MMP-10 (stromelysin-2)
MMP-11 (stromelysin-3)
MMP-12 (metalloelastase)
4. Matrilysins
MMP-7 (matrilysin, PUMP-1)
MMP-26 (matrilysin-2)
5. MT-MMPs (Membrane type)
MMP-14 (MT1-MMP)
MMP-15 (MT2-MMP)
MMP-16 (MT3-MMP)
MMP-17 (MT4-MMP)
MMP-24 (MT5-MMP)
MMP-25 (MT6-MMP)
6. Other MMPs
MMP-18
MMP-19
MMP-20 (enamelysin)
MMP-21
MMP-23
MMP-27
MMP-28 (epilysin)

2. Search criteria

Inclusion criteria: The search was limited to experimental study articles, review articles and thesis. Restrictions were not placed regarding the study design and the language usage.

Exclusion criteria: Publications that did not meet the above inclusion criteria are excluded.

Search strategy: A literature review was performed in Pubmed Central, MEDLINE, the Cochrane Library, and the EBSCO host. The articles identified included those published between 1989 and December 2014 with the following Subject Headings terms and/or keywords in various combinations: Matrix metalloproteinase, dentine, dental caries, odontoblast, pulp inflammation and periapical inflammation. About 160 articles were found, out of which many were excluded based on the exclusion criteria mentioned above and 71 of the articles and 2 theses were used for this review.

3. Role of MMPs in dental caries

Dentine ECM is mainly constituted of Type I collagen fibrils (90%), Type III and V collagen fibrils (1–3%),[5,6] which undergo fibrillogenesis to form a template, which can be efficiently and effectively mineralized. Rest is made up of non-collagenous proteins.

ECM can be degraded by various different mechanisms. These mechanism comprise of – (i) release of enzymes by host and bacterial cells, (ii) phagocytosis of matrix components, (iii) release of reactive oxygen species and (iv) release of cytokines, inflammatory mediators and apoptotic proteins that influence enzymes connected with matrix components.

In dental caries, demineralization is caused by microbial acids, and degradation of dentinal organic matrix was thought to be carried out by microbial proteolytic enzymes. The proteases produced by the cariogenic bacteria, which were believed to be responsible for the degradation of dentine organic matrix, have been found to be highly pH sensitive. They are not able to resist the acidic pH fall (4.3) during the demineralization phase, thus suggesting their limited contribution to the