

## Recent Advances in Role of Matrix metalloproteinases in Some Dental Diseases

Review Article

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## Abstract

The common types of dental diseases are caries, periapical, pulpitis, gingivitis, oral infectious diseases and hereditary lesions. These chronic diseases are supposed to be due to interaction between the bacteria in oral cavity and the host. The progression of these diseases needs some major changes in the biochemistry and physiology of connective tissues where different types of collagens are present. In dental diseases the specific collagen is degenerated/lost in connective tissue probably due to matrix metalloproteinases (MMPs), reactive oxygen species (ROS), apoptosis and antioxidants. In this short review we discussed only the role MMPs in dental caries and periodontitis.

**Keywords:** Dental Caries, Periodontitis, MMP.

## Introduction

Dental health is not only essential but also an integral part of systemic health throughout the human life. Dental diseases are varied and may be of soft tissue origin (gingivitis) or may be of hard tissue (caries or periodontitis). Dental diseases may be simple like caries (cavitation) or complex one such as tumors and cyst of dental origin and may also cause more dangerous and life threatening problems [24, 41]. Dentition (teeth) plays an important role in mastication (chewing), speech (pronunciation of certain consonants and facial expression), cheek fullness (avoiding aged appearance) and also maintains facial height. The dental diseases may affect any of the above said functions of teeth [26]. The common types of human's dental diseases are caries, periapical and pulpal inflammation (pulpitis), gingival (gingivitis), periodontal (gum-periodontics) problems, oral infectious diseases, trauma from injuries, and hereditary lesions [41]. The inflammatory process is often associated with free radical damage and oxidative stress [39], [24, 29]. These diseases are considered as chronic problems and are supposed to be due to interaction between the bacteria in oral cavity (oral flora) and the host. The progression of these diseases

needs some major changes in the biochemistry and physiology of connective tissues because these tissues hold cells together to make tissues and organs in the body [42]. One of the important proteins in the connective tissue is the collagen, which is of different types and depends upon the tissues where it is present [19]. It is observed and suggested that in dental diseases the specific collagen is degenerated or lost in connective tissue probably due to matrix metalloproteinases (MMPs), reactive oxygen species (ROS), apoptosis and antioxidants. In this short review we discussed only the role MMPs in dental caries and periodontitis.

## Matrix Metalloproteinases (MMPs)

These endopeptidases enzymes belong to the M10A subfamily of metalloproteinases, which contain zinc methionine in their active site [1, 28]. They cut the extracellular matrix (ECM)/core matrix proteins into various small peptides by hydrolyzing inner peptide bonds. Their activity depends upon Ca<sup>++</sup> ions. MMPs are different from other endopeptidases because they do not function in the absence of metal ions [37]. These enzymes not only degrade collagens and ECM proteins but can also regulate

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the activity of many bioactive molecules, like cell surface receptors, the release of apoptotic ligands (FAS ligand) and cytokine/chemokine inactivation [16, 35]. Thus MMPs are also called as hydrolyse components of the ECM because they have the tendency/activity to break matrix components. These MMPs modulate the activity of the above-mentioned factors either by direct cleavage, or release them from ECM bound stocks, like buffers [5]. These enzymes are also supposed to play a major role in cell behaviors during critical events (physiological or pathological) of life such as cell migration, proliferation (dispersion/adhesion), differentiation, development, embryogenesis, angiogenesis, apoptosis, cell defense, as well as wound healing [1]. In this way they coordinate remodelling of extracellular matrix by accurate synthesis and depletion of proteins like collagens and others in ECM which is promoted and controlled by various proteases [28]. These include aspartic protease, cysteine protease, MMPs and serine protease [19]. Up till now the researchers have identified 24 MMP genes in humans and 26 members have been listed for these MMPs [23]. These MMP enzymes have been classified in to 6 major groups namely collagenases, gelatinases, matrilysins, membrane type MMPs, other MMPs and stromelysins [9]. All six MMPs contain furin cleavage site in the pro-peptide.

In pre-dentine (odontoblasts) and dentin, another class of MMPs are present called as collagenase MMP-1, the gelatinases MMP-2 and MMP-9, MMP-3 (stromelysin-1), the MMP-2 activator MT1-MMP, and enamelysin (MMP-20) [9].

The collagenases are of different types depending upon their site of action and product formation. They degrade triple-helical fibrillar structure of collagens into various specific fragments and are the major components dentin (and cartilage and bone as well).

The different types of gelatinases mainly act on type-IV collagen and gelatin. The stromelysins act on proteins but unable to cleave the triple-helical fibrillar collagens [23].

It is known that all these MMPs are synthesized and secreted by the tissue cells as inactive form known as Zymogen (pro-enzymes) and then are activated by complex extracellular modulators [13]. As mentioned by Pardo, et al., (2016)[28], these MMPs are activated mostly in ECM or at the cell surface by molecules like  $\alpha$ 2-macroglobulin and the membrane-associated reversion-inducing Cys-rich protein with Kazal motifs (RECK). However, some of them can also be activated in side the intracellular organelles, including nuclear localization where they act on intracellular substrates, or may function as transcription factors [22]. These enzymes in turn are controlled by endogenous tissue inhibitors of (called as TIMPS) that inhibit the activity of MMPs and keep them at physiological desired levels (by the processes of homeostasis). At present the family of TIMPS consists of TIMP-1, TIMP-2, TIMP-3 and TIMP-4 [23, 38]. This remodelling of ECM is quite complex because these MMPs and their modulators are strongly regulated at multiple levels. Some are controlled at gene expression (transcriptional regulation), other by growth factors, cytokines, hormones, and cell-ECM, and some by cell-cell interactions. The stability of their mRNA, efficiency of protein translational and role played by microRNAs are thought to involve as post-transcriptional regulatory processes [13, 28]. Imbalance in the homeostasis of MMP and TIMP is responsible for the development of pathological conditions [1, 6, 28, 33]. Thus it is the dis-regulation of the balance between MMPs and TIMPs

that leads to many chronic systemic as well as dental diseases. It is observed that some nonspecific endogenous inhibitors can regulate the activity of MMP [9]. Similarly the search of exogenous modulators for these MMPs or TIMP can be used as drugs to treat various diseases of ECM including dental in origin. Most of the synthetic inhibitors have a chelating group that binds very strongly (like irreversible inhibitor) with the zinc atom at the active site of the MMP. The most common compounds in this category are hydroxamates, thiol, carboxylates and phosphinyls. Hydroxamates are particularly potent inhibitors of MMPs and other zinc-dependent enzymes, due to their bidentate chelation of the zinc atom. Other substituents of these inhibitors are usually designed to interact with various binding pockets on the MMP of interest, making the inhibitor more or less specific for given MMPs. Clinical trials for many of these agents showed poor pharmacokinetic and lack of specificity as anticancer or for cardiovascular diseases. Thus they showed many undesired side effects [2, 7, 27, 40]. The implication of MMPs and TIMPs in the dental disorders is vast and promising but due to complicated types very little is known the physiology of each of the MMPs. Therefore the understanding of the physiology & Biochemistry of these enzymes from the molecular, to the cellular and tissue levels, where these molecular complexes operate, will be necessary for the development of newtherapeutic agents [14].

## Dental Caries

It is one of the most common infectious diseases worldwide [29]. As quoted by the WHO (2012), “worldwide, 60–90% of school children and nearly 100% of adults have dental cavities, often leading to pain and discomfort”. It is an irreversible disease caused mostly by *Streptococcus mutans*, *Streptococcus sobrinus* and *Lactobacillus* species of the oral cavity (oral flora). These bacteria form a complex community, which adheres on surfaces of tooth in a gelatinous mat, or biofilm, or dental plaque. These bacteria produce lactic acid (mostly) by degrading sugar component of diet. This acid then diffuses through dental calcified tissues and thus the pH at this point drops below 5.5. The acidic pH and probably heat activate “host” pro MMPs further from both dentin and saliva. This activation is supposed to be due to the conformational change of the propeptide and thus induce the cysteine switch, which is necessary for the activation process [9, 10]. It is suggested that although the MMPs are activated by the acidic pH but they cannot degrade components of organic matrix at this pH. As the pH drops the salivary buffer system neutralizes the acid and may increase in the pH towards 7.4 at the spot of demineralised dentin. This pH environment allows activated MMPs to degrade the organic matrix [9, 34]. The activated enzymes then dissolve mineral crystals in that local area and causes cavitation [8, 23]. It is known that dentin contains more organic material and water than enamel so this part of tooth acts, thus more preferable substrate for enzymatic degradation (due to host or bacterial proteinases). The organic components of dentine consist of type-I collagen (90%) and phosphorylated proteins called dentinphosphosialoprotein (DSPP) (10%). DSPP forms dentin sialoprotein (DSP) & dentin phosphoprotein (DPP) immediately after its secretion [23].

It is also observed that many Growth Factors (GFs) like Transforming GF-beta, fibroblast growth factor-2 (FGF-2) & Insulin like growth factor 1 and 2 (IGF-1 & 2) are also present in dentin. According to researchers as dental caries starts and ECM

degradation takes place, these GFs are then released and stimulate odontoblasts to form compensatory dentin materials [9, 12]. It is proposed that bacterial collagenases are the main “culprit” for the catabolism of organic matrix. However, now it has been found that MMPs derived from host have more important role to degrade organic matrix of dentin. These enzymes have been to be present both in dentin and saliva. It has been proposed that gingival crevicular fluid (GCF) is the main source of salivary MMPs [3, 9, 31].

## Biochemical Basis of Periodontitis

Periodontitis is an inflammatory condition of gingival tissue, due to which there is a loss of periodontal ligament that is attached with bones for functional support. To initiate and development of this disease, a plaque is observed at the affected areas. At the same time it is also believed that the physiological response of host to the pathogen is mainly responsible bone loss and breakdown of the respective connective. It is proposed that the MMPs, prostanooids (PGs) and cytokines originated from host are responsible for activation of the osteoclastic activity, which then destroys the periodontium tissue [36]. Due to exogenous and endogenous causative factors collagen degradation then starts in persons susceptible to this disease. Inflammatory process then extends laterally and apically and towards deeper connective tissues and bone as well [23]. Due to this inflammatory process, at the place of lesion, phagocytes and other defence cells are recruited (known as inflammatory cells). The macrophages secrete interleukins (ILs), PG-E2, MMPs and tumor necrosis factor alpha (TNF $\alpha$ ) [25, 36]. For this disease, initial hypothesis was that collagenases that initiate the process of this disease are secreted from infected or normal oral flora. However now it is believed that the host collagenases, especially MMP-1 (MMP- 1) cut collagens of the connective tissue at a single point and thus only two fragments are produced [11]. These are the best substrates for microbial proteolytic enzymes that produce different types of short peptides because they hydrolyse these fragmented collagens at multiple sites [32, 36]. In an experimental study, Makela et al., (1994) [20] have demonstrated that compared to normal tissues there were higher level of MMP-2 & MMP-9 gelatinases in periodontitis tissues. At the same time as the inflammatory process moves towards the apical side then the levels of ILs, PGs, and TNF $\alpha$  become more compared to normal tissues. This altered micro-environmental activates the osteoclasts that initiate the resorption of alveolar bone. It is also believed that MMP-2 plays vital role in bone remodelling while MMP-14 (present at border of osteoclasts) helps for the interaction between matrix and osteoclasts [17, 18]. The collagen remnants left over by osteoclasts in the lacunae of affected bones are cleared by MMP-13 already present in resorption lacunae [30].

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