Dentin matrix degradation by host matrix metalloproteinases: inhibition and clinical perspectives toward regeneration

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Bacterial enzymes have long been considered solely accountable for the degradation of the dentin matrix during the carious process. However, the emerging literature suggests that host-derived enzymes, and in particular the matrix metalloproteinases (MMPs) contained in dentin and saliva can play a major role in this process by their ability to degrade the dentin matrix from within. These findings are important since they open new therapeutic options for caries prevention and treatment. The possibility of using MMP inhibitors to interfere with dentin caries progression is discussed. Furthermore, the potential release of bioactive peptides by the enzymatic cleavage of dentin matrix proteins by MMPs during the carious process is discussed. These peptides, once identified, may constitute promising therapeutic tools for tooth and bone regeneration.

Keywords: dentin, carious process, matrix degradation, MMPs, SIBLINGs, MMP inhibitors, biopeptides, regeneration

INTRODUCTION

Enamel is the hardest structure of the organism, containing about 96% of mineral but only traces of organic matrix (less than 1%). The enamel carious process involves physicochemical reactions, where the mineral is dissolved by acids liberated by cariogenic bacteria. In contrast, the dentin is less mineralized and contains an abundant organic material (19–20%), mainly composed of type I collagen. Therefore, the dentin carious process strongly differs from the enamel carious process. First, the bacterial acids dissolve the dentin mineral, which progressively uncovers the organic dentin extracellular matrix (ECM). Second, proteases degrade the ECM components allowing the progression of cariogenic bacteria toward pulp tissues. Such progression is facilitated by the tubular nature of the circumpulpal dentin. It has long been assumed that dentin organic matrix is degraded by proteases secreted by cariogenic bacteria. However, bacterial collagenases have been shown to be highly pH sensitive and not able to resist the acidic fall (pH 4.3) during the demineralization phase of a pH cycling model (Kawasaki and Featherstone, 1997), suggesting that this enzyme’s contribution to dentin matrix degradation may be limited. Therefore, the potential role of host-derived proteases and in particular MMPs, in dentin matrix degradation has been introduced. MMPs form a mammalian family of ECM proteinases involved in normal and pathological events in almost all tissues of the organism including the tooth. MMPs present specific properties and characteristics (Brinckerhoff and Matrisian, 2002), including their ability to cleave matrix components, their dependence on a zinc ion for activity, the requirement that the enzymes be activated by the cleavage of a prodomain, the conservation of specific amino acid sequences between family members, and inhibition of their enzymatic activity by endogenous tissue inhibitors of metalloproteinases (TIMPs) (Visse and Nagase, 2003). Numerous studies have demonstrated endogenous proteolytic enzyme activity within the dentin, including matrix metalloproteinases MMP-2, MMP-9 and MMP-3 (Tjaderhane et al., 1998; Mazzoni et al., 2007) which were shown to be required for normal dentin formation. Once the neofomed dentin matrix mineralizes, some of these enzymes remain trapped in the calcified matrix, either under active or proenzyme forms (Palosaari et al., 2003). It can be hypothesized that the cariogenic demineralization process not only re-exposes these enzymes but also potentially induces their activation. In addition, the saliva, which bathes the dentin carious lesion, contains several proteases that can also participate in the organic matrix degradation (Tjaderhane et al., 1998; Van Strijp et al., 2003). The aim of the present article is to review the role of the host metalloproteinases (MMPs) in the dentin carious process. The ability of MMPs to liberate bioactive peptides and degrade dentin matrix proteins as well as the potential use of protease inhibitors to block their activity in the treatment of caries will be discussed.

DENTIN MATRIX PROTEINS

Dentin ECM consists of a 3D scaffold that is mainly formed of type I collagen fibrils (90%). Types III and V collagens were also identified in this scaffold but at lower levels (1–3%) (Goldberg...
and Smith, 2004; Opsahl Vital et al., 2012). Thin collagen fibrils are secreted at the apical pole of the odontoblast body to form the predentin (which is equivalent to the osteoid matrix in bone). Collagen fibrils undergo fibrillogenesis along the predentin by processes of self-assembly and cross-linking to form a template which can be efficiently mineralized. Non-collagenous proteins (NCPs), which have been the focus of intense studies in the last decade because of their potential roles in the regulation of bone and dentin mineralization, constitute the remaining 10% of the ECM scaffold. It has been suggested that some NCPs are associated with specific sites on collagen fibrils to regulate the nucleation and growth of hydroxyapatite (HAP) crystals. For example, the glycosaminoglycans (GAG) part of the proteoglycans (PG) was shown to be important for the collagen fibril maturation by delaying apatite crystals deposition to allow the fibrils to reach a diameter sufficient to achieve proper mineralization (Embery et al., 2001). The importance of NCPs in the mineralization process has been well demonstrated by mutation studies and by experimental suppression of NCP genes. These experiments have highlighted the importance in the mineralization process of SIBLINGs (Small Integrin Binding Ligand N-linked Glycoproteins), a phosphoprotein family in which mutations are associated with abnormal phenotypes in the mineralization of bone and/or dentin (Qin et al., 2004; Opsahl Vital et al., 2012). This family includes dentin sialophosphoprotein (DSPP), dentin matrix protein 1 (DMP1), bone sialoprotein (BSP), matrix extracellular phosphorylated glycoprotein (MEPE), and osteopontin (OPN). It appears that the associations of these highly phosphorylated and acidic NCPs with specific sites on collagen molecules are essential in promoting the nucleation and growth of apatite crystals. All SIBLINGs were identified in dentin and bone ECM, but a high rate of DSPP expression was shown to be specific to dentin. The SIBLING members carry an arginine-glycine-aspartate (RGD) cell adhesion domain and a highly conserved acidic serine and aspartate-rich motif (ASARM) (Rowe et al., 2000; Fisher and Fedarko, 2003). Noteworthy, the function of ASARM domain in bone and teeth mineralization (apatite crystals nucleator or inhibitor) is at present debated by the scientific community, in particular its implication in pathological processes such as inherited rickets (Addison and Mckee, 2004; Palosaari et al., 2003). The expression inhibitors were also detected but at a lower level of expression (Goldberg et al., 2008; Mazzoni et al., 2009, 2011). TIMPs, their endogenous inhibitors were also detected but at a lower level of expression (Goldberg et al., 2003b; Palosaari et al., 2003). The expression of MMP-2, the predominant MMP in sound dentin, was shown to increase gradually from the onset of dentinogenesis to reach maximal expression at day 6–7 post-natal (Bourd-Boittin et al., 2005). MMP-2 is thought to play a key role in basement membrane degradation which allows a direct epithelio-mesenchymal contact, a prerequisite for odontoblasts and ameloblasts terminal cytodifferentiation (Sahlberg et al., 1992; Heikinheimo and Salo, 1995; Sahlberg et al., 1999). At the more advanced stages of dentinogenesis, MMP-2 and MMP-9 were shown to be located near the dentino-enamel junction (Goldberg et al., 2002, 2003b), and a strong gelatinase activity was detected by in situ zymography along the mantle dentin (Pessoa et al., 2013). MMP-2 was shown to cooperate with MMP-20 in the processing of dental ECM components, and particularly in that of DSPP (Bourd-Boittin et al., 2004; Yamakoshi et al., 2006), or in the self-processing mechanism of DSPP (Godovikova and Ritchie, 2007). Importantly, MMP-2 was isolated from mature human mineralized dentin matrix (Martin-De Las Heras et al., 2000) and zymographically identified in demineralized dentin (Van Strijp et al., 2003; Mazzoni et al., 2007), suggesting a potential role in dentin ECM degradation during the carious process (Tjaderhane et al., 1998; Chaussain-Miller et al., 2006). Recent

MMPs IN NON-CARIOUS DENTIN

MMPs are believed to play an important role in the matrix remodeling that takes place during dentinogenesis. The main MMPs identified in pulp, odontoblasts and in the predentin/dentin compartments are the collagenase MMP-8, the gelatinaises MMP-2 and MMP-9, stromelysin-1 (MMP-3 or proteoglycanase), the MMP-2 activator MMP-14 (MT1-MMP), MMP-13, and enamelysin (MMP-20) (Palosaari et al., 2002; Sulkala et al., 2002, 2004, 2007; Goldberg et al., 2003b; Bourd-Boittin et al., 2004; Boukessi et al., 2008; Mazzoni et al., 2009, 2011). TIMPs, their endogenous inhibitors were also detected but at a lower level of expression (Goldberg et al., 2003b; Palosaari et al., 2003). The expression of MMP-2, the predominant MMP in sound dentin, was shown to increase gradually from the onset of dentinogenesis to reach maximal expression at day 6–7 post-natal (Bourd-Boittin et al., 2005). MMP-2 is thought to play a key role in basement membrane degradation which allows a direct epithelio-mesenchymal contact, a prerequisite for odontoblasts and ameloblasts terminal cytodifferentiation (Sahlberg et al., 1992; Heikinheimo and Salo, 1995; Sahlberg et al., 1999). At the more advanced stages of dentinogenesis, MMP-2 and MMP-9 were shown to be located near the dentino-enamel junction (Goldberg et al., 2002, 2003b), and a strong gelatinase activity was detected by in situ zymography along the mantle dentin (Pessoa et al., 2013). MMP-2 was shown to cooperate with MMP-20 in the processing of dental ECM components, and particularly in that of DSPP (Bourd-Boittin et al., 2004; Yamakoshi et al., 2006), or in the self-processing mechanism of DSPP (Godovikova and Ritchie, 2007). Importantly, MMP-2 was isolated from mature human mineralized dentin matrix (Martin-De Las Heras et al., 2000) and zymographically identified in demineralized dentin (Van Strijp et al., 2003; Mazzoni et al., 2007), suggesting a potential role in dentin ECM degradation during the carious process (Tjaderhane et al., 1998; Chaussain-Miller et al., 2006). Recent
studies described a differential profile of localization and activity of the gelatinases in the different layers of human sound dentin (Boushell et al., 2011; Niu et al., 2011). High levels of MMP-2 were observed in odontoblasts where it was co-localized with TIMP-2. It was also observed in the deep dentine and at the dentinoenamel junction (Goldberg et al., 2003b). MMP-9, which colocalized with TIMP-1, was also shown to decrease from the deep to the superficial dentine layer (Niu et al., 2011). This gelatinase gradient may determine the rate of collagen degradation in pathological conditions, depending on the depth of the affected dentine.

Stromelysin-1 (MMP-3) has been identified in predentin, where it was proposed to participate in the mineralization process by degrading CS/DS (PG) (Hall et al., 1999) and in dentin where it was shown localized within the intertubular dentine, along the collagen fibrils (Mazzoni et al., 2011). Our own studies have shown that this enzyme is present in demineralized dentin in its active form, implying that it has the potential to degrade and disorganize the dentin matrix. Indeed, we have shown that when active, MMP-3 is able to cleave from the collagen scaffold several matrix proteins such as decorin, biglycan as well as four members of the SIBLING family: DSP, matrix extra-cellular phosphoglycoprotein (MEPE), bone sialoprotein (BSP) and osteopontin (OPN) (Boukpessi et al., 2008). The release by MMP-3 of (PG), such as decorin, could result in a subsequent release of the sequestered cytokines which in turn may activate other MMPs, thus potentiating the degradation of the demineralized matrix (Imai et al., 1997; Suppa et al., 2006).

**POTENTIAL MECHANISM(S) OF MMP ACTIVATION IN CARIOUS DENTIN**

MMPs are secreted to the ECM as inactive proenzymes and then require activation in order to be able to degrade matrix components. During the caries process, the acidic environment created by the release of bacterial acids can favor the activation of endogenous MMPs. Low pH was suggested to cause a conformational change within the propeptide domain of the enzyme that facilitates the cysteine switch, a critical step in the activation process (Tjaderhane et al., 1998). However, although the activated MMPs are stable in acidic pH, they can only be functional in neutral pH. Neutralization of the acids can be achieved by the dential buffering mechanisms (Camps and Pasley, 2000; Haapasalo et al., 2007) through the saliva buffering systems, thus allowing the pH-activated MMPs to cleave matrix components (Tjaderhane et al., 1998). In addition, the phosphorylated proteins released from the collagen scaffold by bacterial acids could interact with TIMP-inhibited MMPs within the carious lesion and re-activate them, enhancing the degradation process (Fedarko et al., 2004). Another enzyme family, the cysteine cathepsins, was identified in dentin (Tersariol et al., 2010) and in saliva of patients with periodontal conditions. They have also been reported in human carious dentin (Van Strijp et al., 2003) and it was suggested that these enzymes, when active, can in turn activate latent MMPs (Van Strijp et al., 2003). Along this line, a recent study reported a stronger immunostaining of cathepsins B in carious dentin, observed in dentin tubules and in odontoblasts, when compared with sound dentin (Nascimento et al., 2011). In addition, carious dentin displayed increased cysteine cathepsin activity, which was even greater in deep lesions with pulp exposure. Interestingly, it was also shown in this study that MMP activity in the saliva was higher in patients with active compared to chronic carious lesions, while salivary cathepsins did not show respective correlation. The reason may be that saliva is rich in cystatins (Dickinson, 2002), potent cysteine peptidase inhibitors. On the other hand, cathepsin activity increases with increasing depth of the lesion, indicating the role of pulp tissue-derived enzymes (Nascimento et al., 2011). Taken together, these studies suggest that cysteine cathepsins may participate in the carious process at least partly by activating latent MMPs.

**DENTIN MATRIX DEGRADATION DURING THE CARIOUS PROCESS**

Host MMPs derived from dentin or saliva have been shown to be able to degrade the dentin matrix which has been previously demineralized by bacterial acids (Tjaderhane et al., 1999; Chaussain-Miller et al., 2006) (Figure 1). Saliva contains several MMPs including collagens and gelatinases derived from either the gingival crevicular fluid or the secretion of salivary glands, MMP-9 being the most abundant as it is derived from both sources (Van Strijp et al., 2003). Indeed, the incubation of demineralized dentin slabs with acid-pretreated saliva resulted in the degradation of the organic matrix (Van Strijp et al., 2003). As saliva bathes the carious lesions, it is not surprising that the active form of MMP-9 was systematically detected by zymography performed on dentin extracts from several carious teeth (Tjaderhane et al., 1998). Together these studies indicate that salivary MMPs may have a strong contribution to dentin matrix degradation during the caries process. Carious lesions were also found to contain both latent and active forms of MMP-3, MMP-2 and MMP-8 (Tjaderhane et al., 1998; Mazzoni et al., 2007; Sulkala et al., 2007; Boukpessi et al., 2008). Along this line, dentin protein extracts obtained from the different dentin layers of decayed teeth were shown to have their gelatinase activity gradually increased from healthy dentin extracts to soft infected dentin extracts (superficial soft carious lesion, inner soft carious lesion, affected dentin, sound dentin) (Charadram et al., 2012). These observations confirm that endogenous MMP-2 contained within the sound dentin is activated during the carious process (Figure 2). It has also been suggested by immunohistochemical observations that the endogenous MMP-2 level may be increased through the induction of MMP-2 synthesis by the presence of caries (Toledano et al., 2010). This was supported by a study showing that MMP-2 and TIMP-2 gene expressions were significantly up-regulated in odontoblasts adjacent to the carious lesion (Charadram et al., 2012). Interestingly, several studies have reported that in the cancer context, MMP expression by tumor cells was up-regulated by an acidic extracellular pH (Kato et al., 2005; Rofstad et al., 2006). This can suggest that acidic pH during the carious process may both induce MMP expression by the odontoblasts and favor their activation, potentiating MMP proteolytic capacity. In addition, the expression of MT1-MMP, a potent activator of MMP-2 and MMP-20 (Palosaa et al., 2002), was also dramatically increased in these cells, enhancing dentin matrix degradation. In addition, MMP-2, MMP-20 and...


**MMP inhibitors for the treatment of carious dentin**

Considering the potential role of MMPs in dentin ECM degradation, it seems logical that, when associated with a thorough control of the caries (Selwitz et al., 2007), MMP inhibition would help to control dentin caries progression. This notion was supported by studies in rat caries models where dentin caries progression was delayed by intra-oral administration of chemical MMP inhibitors (Tjaderhane et al., 1999; Sulkala et al., 2001). Several effective MMP inhibitors have been described. Tetracyclines and their derivatives, doxycycline and minocycline are able to inhibit MMP activity independent of their antimicrobial action. They are commonly used as antibiotics in the treatment of periodontitis (Ryan et al., 1996) and have been shown both in vitro and in vivo to inhibit MMP-1, MMP-2, MMP-8 and MMP-12 (Golub et al., 1995; Lauhio et al., 1995). Another effective and safe MMP inhibitor is the non-antimicrobial chemically modified tetracyclines (CMTs), which can inhibit both the release and the activity of MMPs (Golub et al., 1998; Ramamurthy et al., 1998). Zoledronate is a third generation bisphosphonate which has the ability to inhibit MMP proteolytic activities (Teronen et al., 1997; Boissier et al., 2000). Sulkala et al. (2001) have shown that the systemic MMP inhibition with CMT-3 and zoledronate in vivo suppressed the progression of dental caries under fissures, indicating that systemic administration of MMP inhibitors could be effective in caries prevention (Sulkala et al., 2001). Indeed, the authors observed a reduction in the progression of caries in rats treated with these MMP inhibitors, though no synergistic potentiating effect of these two compounds could be demonstrated.

In humans, MMP inhibitors would preferably be administered locally to treat dental caries by either incorporating them in topical preparations for daily use or by applying them directly on the dentin surface, depending on the clinical situation. When treating coronal caries, especially in young patients with deep and active caries lesions, a solution containing MMP inhibitors may be applied directly to the lesion after the mechanical removal of the caries and before restoration. A second strategy would be to incorporate these inhibitors in mouth rinses or toothpastes to prevent root caries progression. Several synthetic MMP inhibitors are already used in the dental practice. The MMP inhibitory action of most of them is based on their zinc- and calcium-chelating groups, since MMPs require metal ions (calcium and zinc) for their catalytic activity (Gendron et al., 1999). Among them, Ethylenediaminetetraacetic acid (EDTA), which is an effective zinc and calcium chelator, was recently shown to inhibit the degradation by acid-activated endogenous MMPs of dentin beams treated for 1 min with 17% EDTA (Thompson et al., 2012). Chlorhexidine digluconate (CHX) has also potent MMP inhibitory effects that also involve a calcium-chelating mechanism (Gendron et al., 1999). These inhibitors have been shown to improve the integrity of the hybrid layers obtained by a simplified etch-and-rinse adhesive after dentin caries removal (Carrillo et al., 2007). The local application of 2% CHX for 1 min to the etched dentin surface just before applying the dentin bonding primer was able to inhibit the degradation of the hybrid layer by MMPs for at least 14 months. This clinical study highlights that CHX, a MMP inhibitor already used in dental practice, is able to impair dentin matrix degradation. Interestingly, Scaffa et al. demonstrated that CHX was also a potent inhibitor of the cysteine cathepsin enzymes (Scaffa et al., 2012), which were shown to be present and active in sound and carious dentin (Tersarioi et al., 2010; Nascimento et al., 2011).

A different group of MMP inhibitors include those derived from natural sources. Green tea polyphenols, especially...
epigallocatechin gallate (EGCG), were found to have potent and distinct inhibitory activity against MT1-MMP, resulting in the decrease of MMP-2 activation. Furthermore, EGCG inhibits directly MMP-2 and MMP-9 (Demeule et al., 2000; Garbisa et al., 2001; Dell’aica et al., 2002), and was recently shown to inhibit dentinal erosion, along with other known MMP inhibitors (Kato et al., 2010). Grape seed extract (GSE) has been shown to suppress lipopolysaccharide-induced MMP secretion by macrophages and to inhibit MMP-1 and MMP-9 activity in periodontitis (La et al., 2009a). Recent in vitro studies demonstrated that GSE inhibited the demineralization and/or promoted the remineralization of artificial root carious lesions under dynamic pH-cycling conditions (Xie et al., 2008; Pavan et al., 2011). The MMP-inhibitory effects of these or other natural substances such as cranberry proanthocyanidins (La et al., 2009b) suggest that they could be effective in slowing down dentin caries progression. The fact that these molecules are devoid of undesirable side effects, when compared with those of synthetic drugs, makes them particularly attractive for the treatment of dentin caries, since they can be safely applied directly on the affected tooth or integrated in daily-used topical products.

GENERATION OF BIOACTIVE PEPTIDES FROM DENTIN MATRIX DEGRADATION

By cleaving large insoluble ECM components, MMPs are known to liberate bioactive fragments and cytokines (Mott and Werb, 2004). The release of active peptides by the enzymatic cleavage of dentin matrix proteins by MMPs during the carious process was also suggested (Chaussain-Miller et al., 2006). These peptides, which often retain the activity of the parent protein (Dean and Overall, 2007), or display a function different from those of the protein they are derived from, can affect several biological properties in terms of proliferation, angiogenesis, differentiation that may favor the pulp healing process (Dean et al., 2007; Smith et al., 2012a). In particular, the degradation of matrix (PG), which often bind and sequester growth factors, by proteases such as the MMP-3 would cause the release and activation of these factors within the carious lesion and can as a result impact pulp healing (Smith et al., 2012b). The gelatinase MMP-2 has been proposed to be able to release active TGF-β2 in the carious lesion, which can then stimulate diverse repair processes (Charadram et al., 2012).

Using an injured rat pulp model to test the biological properties of such cleavage products derived from the (ECM), we demonstrated that a polypeptide containing the C-terminal part of DMP1, and mimicking DMP1 cleavage product by MMP-2, was able to enhance pulp healing capacity when implanted in a rat pulp-injury model (Chaussain et al., 2009). A dense and continuous reparative dentin bridge was rapidly observed after implantation and the cells boarding the bridge presented a characteristic polarized odontoblastic phenotype, organized as a palisade and expressing the odontoblastic markers DSP and OPN (Charadram et al., 2012). The use of such ECM-derived bioactive peptides associated with restorative materials constitutes a promising therapeutic option for tooth repair (Goldberg et al., 2008). In addition, these peptides may also be used for bone regeneration, potentially associated with engineered scaffolds and mesenchymal stem cells (Mao et al., 2006), as dentin and bone are similar in several aspects, especially pertaining to the composition of the ECM (Opsahl Vital et al., 2012).

In conclusion, accumulating data have demonstrated that endogenous enzymes contained in dentin and saliva are involved in the dentin caries process. These findings are important, since they open new options for caries prevention and treatment. Slowing down or preventing the irreversible destruction of the organic matrix would allow for natural healing of the lesion by remineralization. MMP inhibitors may prove to be useful in the prevention of dentin caries progression. However, the outcomes of this approach will depend on the management of the caries risk, involving the control of caries risk factors such as cariogenic biofilm, diet, inadequate salivary flow rate and insufficient fluoride exposure (Selwitz et al., 2007).

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