SVOA Dentistry

ISSN:2753-9172

ScienceVolks Open Access

Review

Dental Tissues Remodeling by Matrix Metalloproteinases (MMPS) and Tissues Inhibitors of MMPS (TIMPS)

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***Received:** August 09, 2022 **Published:** August 23, 2022*

Abstract

MMPs are proteolytic enzymes that degrade matrix and non-matrix proteins (serine proteases, furin, plasmin). Catalytic enzymes constitute a family of proteases calcium-dependent and zinc-containing endopeptidases, implicated in the remodeling of dental tissues. Others enzymes involved in extracellular matrix (ECM) degradation are the disintegrins and MMPs (ADAMs) and disintegrins with thrombospontin motifs (ADAMTs) playing role in the destruction of ECM and shedding of membranes-bound receptor molecules. MMPs are organized in 6 groups (collagenases, gelatinases, stromelysins, matrilysins, metalloelastase, and membrane-type MMPs) and non-classified MMPs (such as enamelysin, also named MMP20). TIMPs -1 to -4 are specific endogenous tissue inhibitors of metalloproteinases. Emmprin hydrolyses active cell surface and extracellular matrix proteins. Meprin α and meprin β, discovered as procollagen proteinases cleaving the globular C- and N-terminal procollagen implicates collagenases, degrading the triple-helical fibrillary collagen into distinctive ¾ and ¼ fragments. In addition to the initial signaling peptide, the propeptide domain is based on the substrate specificity, the catalytic domain and the hemopexin-like C-terminal domain linked to the catalytic domain by a flexible hinge region. Synthetized in the latent form of zymogen and secreted as proenzyme, they are activated by organomercurials and other proteases. Located in the forming and maturing enamel, in sound and carious dentin, and during the alveolar bone regeneration, MMPs, active at neutral pH, are implicated in the early mineralization of dental tissues, in prevention and development of the carious lesion and in dental tissues erosion. Degradonomic constitutes the functional roles of MMPs and TIMPs in survival, migration, and morphogenesis, the key processes in remodeling and dental development.

***Keywords:** Metalloproteinases (MMPs), tissue inhibitors of MMPs (TIMPs), collagenases, gelatinases, matrilysins, stromelysins, membrane-type MMPs, extracellular matrix cleavage, dentin, enamel, morphogenesis, carious lesions, and prevention*

1. Introduction

Matrix metalloproteinases (MMPs), also called matrixins, constitute a family of human proteolytic enzymes, calcium dependent and zinc-containing endopeptidases. MMPs are members of a large family of proteases named the metzincin superfamily. They are involved in the cleavage of cell surface receptors, the release of apoptotic ligands (such as FAS ligand) and chemokine/cytokine inactivation.

Cleavage of Type I collagen produces the characteristic ¾ and ¼ fragments. Others catalytic enzymes are 1) The Disintegrin and Metalloproteinases (ADAMs) and 2) A Distintegrin and Metalloproteinases with Thrombospondin motif (ADAMTS), 3) The bacterial serralysins, and proteases such as the astracins (including meprins).

All of them are zinc-dependent endopeptidases that play critical role in the remodeling of extracellular matrix proteins and the shedding of membrane-bound receptor molecules. MMPs (23 distinct proteases in human; and 24 in mouse) affect fundamental cellular processes such as development, survival, migration, remodeling, and morphogenesis that are the key processes of development. They degrade matrix and non-matrix proteins, playing a central role in the morphogenesis, wound healing, and tissue repair in response to injury.

Distinct domains of MMPs form 6 groups: collagenases (including MMP-1, -8, and -13), gelatinases (MMP-2, MMP-9), stromelysins, (MMP-3, -MMP-10 and 11), matrilysins, (MMP-7), metallo-elastase (MMP-12), membrane-type MMPs and other non-classified MMPs (such as enamelysin also named MMP20), endometase (PMMP-26), and epilysin (MMP-28), and the membrane-anchored MMPs (MMP-14, -15, -16, - 17, -24, and -25).

They are multi-domain proteins, regulated in normal cellular environment by tissue synthetic and natural inhibitors of metalloproteinase (TIMP-1 toTIMP-4). TIMP-1 is a small protein 28,5kDa, rich in mannose. In humans, the gene is located on chromosome 11. TIMP-2 is a small protein (21,5kDa with a gene located on chromosome 17). TIMP-3 is a non-glycosylated protein, 27kDa, (with a gene located on chromosome 22) and TIMP-4 which is a 22kDa protein (Vu & Werb, 2000, Hijova, 2005, Malemud 2019). They play a major role in cell proliferation, angiogenesis, apoptosis and host defense (Nagase and Woessner, 1999, Visse and Nagase 2003, Nagase et al., 2006, Jablonska-Trypud et al., 2016). The MMPs are inhibited by specific endogenous tissue inhibitors of metallo-proteinases and specific endogenous tissue inhibitors (TIMPs) (Klein and Bischoff, 2011).

Emmprin is localized on specific membranes or extracellular spaces. They can hydrolyze biologically active peptides, cytokines, extracellular matrix (ECM) proteins and cell-surface glycoproteins. The expression of MMPs is attenuated through the expression of relaxins, integrins and extracellular MMP inducer (Emmprin/CD147) (Norman et al. 2003). The potential contributions of Emmprin to the degradation and activation of proteins is crucial. They localize to specific membranes at the cell surface and in extracellular compartments. They can hydrolyze biologically active peptides, cytokines, extracellular matrix (ECM) proteins and cell-surface proteins (Sterchi et al., 2008). Emmprin/CD147 deficiency disturbs ameloblast-odontoblast cross talk and delays enamel mineralization. (MMPs 1, -8, -9, -13 and -18) (Khaddar et al. 2014; Proxy et al., 2015). The gelatinases have as substrate type IV collagen and gelatin (MMPs-2, and -9). Stromelysins (MMPs- 3, -10, and -11) constitute another group of MMPs, and include all the 6 membrane-type MMPs.

Structure of MMPs: the different domains

The MMPs have a common domain structure: the propeptide, the catalytic domain and the hemopexin-like C-terminal domain linked to the catalytic domain by a flexible hinge region (Weiss et al., 2007).

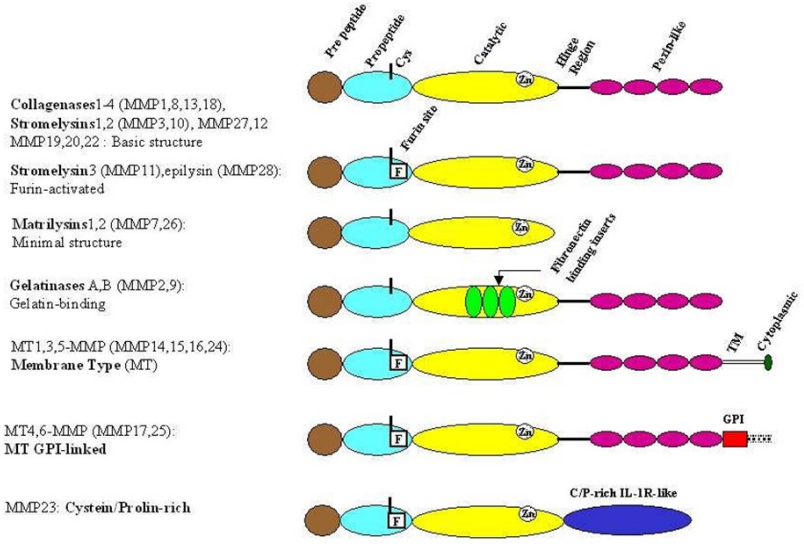

Figure 1: *MMPs general domain structure* (Reprint from Weiss et al., 2007).

Initially isolated in 1962 (Gross & Lapierrre, 1962) the MMPs are synthetized as inactive zymogens. It includes a small signaling peptide (~20 amino acids). The pro-peptide domain (~80 aa) that has to be removed before the enzyme becomes active. The catalytic domain (~165 aa) is connected to the C-terminal domain by a flexible hinge or linker region, formed by 75 amino acids, without a determined structure. The C-terminal domain has structural similarities to the serum protein hemopexin (~200 aa).

The signaling peptide (pre-domain), the propeptide domain, some MMPs are cleaved by foiling consensus site is based on the substrate specificity of the MMPs and on the cellular location,. The MMPs groups are the collagenases, gelatinases (degradation of type IV collagen and gelatin) positioned immediately before the zinc-binding motif (gelatinase 2 and 9), stromelysins, and 6 membrane-type MMPs, displaying a furin cleavage site. Synthetized in the latent form of zymogen, secreted as proenzyme, they are activated by organomercurials, chaotropic agents and other proteases (Malemud 2006).

Catalytic mechanism

As a member of the neurodegenerative family, MMPs play roles in Alzheimer, Parkinson, Japanese Encephalitis, and Glaucoma Diseases (Singh et al., 2015). Some mutation studies suggested a role in the folding and stability of metzincins.

Based mainly on studies on the distantly related MMPs, thermolysin and carboxypeptidase A, as well as on a number of MMP complexes. A single-step catalytic mechanism of action was suggested for MMPs. This mechanism comprises the nucleophilic attack of a catalytic solvent molecule, polarized by the general base/acid glutamate and the catalytic zinc ion, on the scissile peptide bond at close-to-neutral pH values.

MMPs and TIMPs functionality

Inhibited by specific endogenous tissue inhibitors of MMPs (TIMPs), they comprise a family of four protease inhibitors: TIMP-1, TIMP-2, TIMP-3, and TIMP-4. In addition to embryo development, morphogenesis and tissue remodeling, MMPs are synthetized and secreted as proenzymes. Activation mechanisms of MMPs plays important roles in the turnover of extracellular matrix components (ECM) (Nagase and Woessner, 1999). Tumor cells acquire the ability to change shape, detach and easily move through spaces disorganizing the normal tissue architecture. This property is due to changes in expression levels of adhesion molecules and/or due to elevated levels of secreted proteolytic enzymes, Matrix Metalloproteinases (MMPs) degrade the ECM and prepare the path for tumor cells to migrate, invade and spread to distant secondary areas, where they form metastasis. Tissue Inhibitors of Metalloproteinases (TIMPs) control MMP activities and, therefore, minimize matrix degradation. Both MMPs and TIMPs are involved in tissue remodeling and regulate tumor cell progression including tumor angiogenesis. (Bourboulia & Stetler-Stevenson, 2010).

The activation mechanisms of pro-maxtrixins, the cell surface activation of progelatinase and procollagenase 3, implicate intracellular activation of prostromelysin 3 and pro-membrane-type-1 MMP. The main characteristics of MMPs are

1. They are secreted or released in latent forms as zymogens and they are activated by proteinases or by organomercurials (due to loss of a prodomain) and allow cell migration.
2. The catalytic mechanism depends on zinc in the active site.
3. Their activity is inhibited by TIMPs.
4. The MMPs cleave one or more of the components of the extracellular matrix.
5. They have structural and sequence similarities that include the prodomain cysteine switch sequence and the zinc-binding sequence (Woessner, 1991, 1994, Vu and Werb, 2000).

Table 1- The MMPs Genes, location and substrate targets.

Gene	Name	Aliases	Location	Description
MMP1	Interstitial collagenase	CLG, CLGN	secreted	Substrates include Col I, II, III, VII, VIII, X, gelatin
MMP2	Gelatinase-A, 72 kDa gelatinase		secreted	Substrates include Gelatin, Col I, II, III, IV, Vii, X
MMP3	Stromelysin 1	CHDS6, MMP-3, SL-1, STMY, STMY1, STR1	secreted	Substrates include Col II, IV, IX, X, XI, gelatin
MMP7	Matrilysin, PUMP 1	MMP-7, MPSL1, PUMP -1	secreted	membrane associated through binding to cholesterol sulfate in cell membranes, substrates include: fibronectin, laminin, Col IV, gelatin
MMP8	Neutrophil collagenase	CLG1, HNC, MMP-8, PMNL-CL	secreted	Substrates include Col I, II, III, VII, VIII, X, aggrecan, gelatin
MMP9	Gelatinase-B, 92 kDa gelatinase	CLG4B, GELB, MAND-P2, MMP-9	secreted	Substrates include Gelatin, Col IV, V
MMP10	Stromelysin 2	SL-2, STMY2	secreted	Substrates include Col IV, laminin, fibronectin, elastin

Table continued….

MMP11	Stromelysin 3	SL-3, ST3, STMY3	secreted	MMP-11 shows more similarity to the MT-MMPs, is convertase-activatable and is secreted therefore usually associated to convertase-activatable MMPs. Substrates include Col IV, fibronectin, laminin, aggrecan
MMP12	Macrophage metalloelastase	HME, ME, MME, MMP-12	secreted	Substrates include elastin, fibronectin, Col IV
MMP13	Collagenase 3	CLG3, MANDP1, MMP-13	secreted	Substrates include Col I, II, III, IV, IX, X, XIV, gelatin
MMP14	MT1-MMP	MMP-14, MMP-X1, MT-MMP, MT-MMP 1, MT1-MMP, MT1MMP, MTMMP1, WNCHRS	membrane-associated	type-I transmembrane MMP; substrates include gelatin, fibronectin, laminin
MMP15	MT2-MMP	MT2-MMP, MTMMP2, SMCP-2, MMP-15, MT2MMP	membrane-associated	type-I transmembrane MMP; substrates include gelatin, fibronectin, laminin
MMP16	MT3-MMP	C8orf57, MMP-X2, MT-MMP2, MT-MMP3, MT3-MMP	membrane-associated	type-I transmembrane MMP; substrates include gelatin, fibronectin, laminin
MMP17	MT4-MMP	MT4-MMP, MMP-17, MT4MMP, MTMMP4	membrane-associated	glycosyl phosphatidylinositol-attached; substrates include fibrino-
MMP18	Collagenase 4, xcol4, xenopus collagenase		–	No known human orthologue
MMP19	RASI-1, occasionally referred to as stromelysin-4	MMP18, RASI-1, CODA	–	
MMP20	Enamelysin	AI2A2, MMP-20	secreted	
MMP21	X-MMP	MMP-21, HTX7	secreted	
MMP23A	CA-MMP	MIFR, MIFR-1, MMP22, MMP23A	membrane-associated	type-II transmembrane cysteine array
MMP23B	MIFR, MIFR-1, MMP22,		membrane-associated	type-II transmembrane cysteine array
MMP24	MT5-MMP	MMP-24, MMP25, MT-MMP 5, MT-MMP5, MT5-MMP, MT5MMP, MTMMP5	membrane-associated	type-I transmembrane MMP
MMP25	MT6-MMP	MMP-25, MMP20, MMP20A, MMPL1, MT-MMP 6, MT-MMP6, MT6-MMP, MT6MMP,	membrane-associated	glycosyl phosphatidylinositol-attached
MMP26	Matrilysin-2, endometase		-	
MMP27	MMP-22, C-MMP	MMP-27	-	
MMP28	Epilysin	EPILYSIN, MM28, MMP-25, MMP-28, MMP25	Secreted	Discovered in 2001 and given its name due to have been discovered in human keratinocytes. Unlike other MMPs this enzyme is constitutivley expressed in many tissues. A threonine replaces proline in its cysteine switch (PRCGVTD).

2. Tooth germs and early alveolar bone mineralization.

MMP inhibition deregulated the molecular processing of two major dental matrix proteins, amelogenin and dentin sialoprotein (DSP). This coincided with their accumulation and the loss of their normal distribution within the extracellular matrix, resulting in a defective mineralization of dentin and enamel matrices (Goldberg et al., 2003, Bourd-Boittin et al., 2005). The increased thickness of the predentin layer and decreased mineralization of dentin were observed. Enamel formation had ceased at the highest concentration or in the presence or absence of Marimastat or CT (1166), a more selective inhibitor of gelatinases. The lack of enamel formation was possibly due to diffusion of amelogenin from its normal site of apposition. The protein was not retained at the surface of the non-mineralized dentin layer, and immunopositive amelogenin accumulated in the odontoblast compartment. The diffusion of enamel proteins and the accumulation revealed by immunolabeling of two small leucine-rich proteoglycans, decorin and biglycan, in the predentin may have contributed to impaired dentin mineralization (Fanchon et al., 2004).

Enamel:

The formation of enamel (secretory stage) involves a mixture of MMPs: amelogenin (AMEL), ameloblastin (AMBN); enamelin (ENAM) and enamelysin (MMP20 matrix metalloproteinase-20). Kallikrein 4 (KLK4) constitute a late protease. Enamelysin (MMP-20) is secreted by transition and maturation stage and is an ameloblast associated protease. At the end of the secretory stage, the thickness of the incisor enamel is about 120 mm. Enamel protein cleavage product: the generated dental enamel layer is harder, less porous and unstained by retained enamel proteins (Lu et al., 2008).

Dentin is a biological composite with collagen matrix embedded HAp mineral crystallites. Dentin also contains MMP activity, and at least the collagenase MMP-8, gelatinases (such as MMP-2 and MMP-9), and enamelysin (MMP-20) . All of them have been identified in mineralized human dentin. MMPs might be involved in several physiologic processes in dentin-pulp complex, including the organization of matrix before mineralization, control of mineralization, peritubular dentin formation, and matrix alterations during aging. It was also demonstrated that MMP-7 is an endogenous component of the human dentin fibrillar network (Mazzoni et al., 2016). Western blot analysis detected MMP-8 equally distributed in crown and root dentin.

With Marimastat a dose-dependent increase of thickness of the predentin layer, together with a decreased mineralization of dentin. Possibly MMP-2, 3, -9 and -20 play a role in the onset of dentin mineralization. Amelogenin was not retained at the surface and immmuno-positive protein diffused at the surface of non-mineralized dentin layer. Decorin and biglycan accumulate in predentin and contribute to impair dentin mineralization.

The lysosomal cysteine proteinases, cathepsins, can degrade extracellular matrix proteins such as collagen, laminin, fibronectin, and proteoglycans. This class of enzymes has been implicated in a variety of pathologic conditions, especially in diseases involving tissue remodeling states. Cathepsins B and L cleave non-helical telo-peptide extensions of collagens, and cathepsin K cleaves collagen in the triple helical region. Especially cathepsin K, but also B, H, L, and S, are expressed by osteoclasts and participate in bone resorption. Also, cathepsin B is linked to the acti-vation of procollagenase, prostromelysin, and pro-uPA, enzymes involved in proteolytic cascade observed in focal degradation of osteoid and tumor matrices.

Cysteine proteinases can also activate tartrate-resistant acid phosphatase, an important enzyme in dentin and bone matrix resorption (Van Strip et al., 2003; Tersariol et al., 2010).

Pulp and odontoblasts

The MMP-14 and MMP-12 were identified in human dental pulp and odontoblasts (Brodzikowska et al., 2019). Innate immune cells can secrete ILs such as IL-1, IL-6, IL-10, IL-12 and IL-18 with multiple roles; e.g., IL-1 induces macrophage and lymphocyte stimulation, while IL-6 activates B cells and IL-10 inhibits macrophages and dendritic cells' functions ILs and MMPs can act synergically in the pathogenesis of dental pulp inflammation. Elevated levels of IL can stimulate pulp cells to produce and secrete MMPs. MMPs can degrade the ECM present in dental pulp but also can destroy newly formatted predentin, which can lead to inhibition of dentinogenesis. MMP-8 is present in reversible and irreversible pulpitis (Aguirre-Lopez et al., 2020)

Salivary ¨inhibitors

Marked reduction in gelatinolytic activity of human salivary MMPs was observed with CMT-3. (Chemically Modified Tetracyclines) CMT-3 and zoledronate, both alone and in combination, also reduced dentin caries progression in the rats (Sukal et al., 2001).

Periodontal pathology

Periodontal pathologies involve collagenases and TIMPs inhibitors (MMP-2, MMP-8, MMP-9 and MMP-13). The LPS activate the release of potent cytokines such as interleukin-1, interleukin-8, tumor necrosis factor-α, prostaglandins and proteases (Ryan et al, 1996, Birkedal-Hansen 1993).

MMP-9 is mainly secreted by fibroblasts, osteoblasts, endothelial cells macrophages, neutrophils, lymphocytes, and polymorphonuclear leukocytes. They degrade type IV collagen present in gingival tissues (basement membrane remodeling). It has been reported that in vivo immune cell interactions in the presence of plasma proteins show that TC (tetracycline), doxy (doxycycline), and CMT-3 (chemically modified tetracycline-3) can reduce the production of pro-inflammatory mediators in periodontitis (Lin et al., 2008).

Alveolar bone regeneration

MMPs improve alveolar bone regeneration via activation of the PLC/PKC/MAPK pathway. (Yi, et al. 2022)

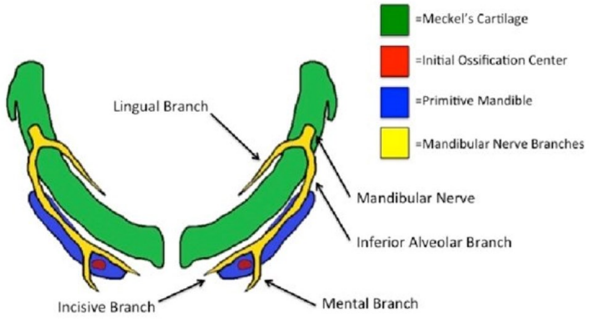

Figure 2: *Generation of tissues of the mandible. Some matrix metalloproteinases are implicated in the mandibular formation, degradation and regeneration.*

Sclérostine is a glycoprotein secreted primarily by osteocytes that acts as a negative regulator of bone formation by inhibiting canonical Wnt signaling. Sclérostine inhibition leads to increase canonical Wnt signaling in bone and increased bone formation. Dikkopf-1, a Wnt pathway inhibitor stimulates bone formation in younger animals and to a lesser extent in adult animals. They enhance fracture healing. Both were used to evaluate the effects of Slab (sclérostine antibody) and DKK1-Ab in humans for the treatment of bone loss and for bone repair.

The principal non-collagenous proteins of bone matrix are sialoprotein, osteonectin, osteopontin and osteocalcin. TGF β 1 or chemokines (cytokines IL-6, TNF-a and I1 b and growth factors (IGF-1, PDGF-BB, TGF -β and HGF. Growth factors, such as BMPs, VEGF, TGF-β, PDGF, IGF-1, and FGFs have frequently been included in scaffold.

Cathepsin K deficiency promote alveolar bone regeneration. Systemic Scl-Ab administration improved bone regeneration and tended to increase cementogenesis, while Scl-Ab delivered by MSs did not result in enhancements in bone or cementum repair compared to MSs alone or control. Systemic administration of Scl-Ab promotes bone and cementum regeneration while local, low dose delivery did not heal periodontal osseous defects (Yao et al., 2020).

Osteogenesis allows the use of autologous bone. Osteoinduction enables migrations and proliferations of connective undifferentiated cells in the site conditioned by the presence of GF on the site. Osteoconduction is the ability of a material to operate as a scaffold to guide the tissue regeneration.

Biologic /growth factors involved in the bone regeneration process: BMP-2, BMP-7, α FGF-1 GF-2; VEGF, SGF, Wnt signaling, Hh signaling, Bone Growth and Regeneration family of transcription factors, Dlx gene family, IGF, Runx transcription factor, SMAD transcription factors, and catenin/LEF/TCF transcription factors.

3. MMPs and the carious lesion

ECM can be degraded by various mechanisms 1) the 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 influencing enzymes connected with matrix components.

Results of human MMP-2; MMP-8, MMP-9, and MMP-13 identified in demineralized human dentin demonstrate the pH-dependent activation mechanism of MMPs, which may have a distinct role in different physiological and pathological conditions. They further demonstrate that host MMPs, activated by bacterial acids, have a crucial role in the destruction of dentin by caries (Tjaderhane et al., 1998) 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.

MMPs and cysteine cathepsins present in saliva, mineralized dentin, and/or dentinal fluid may affect the dentin caries process at the early phases of demineralization. Changes in collagen and no collagenous protein structure may participate in observed decreases in mechanical properties of caries-affected dentin and reduce the ability of caries-affected dentin to remineralize (Mazzoni et al., 2015).

Patients with phagocytic dysfunctions caused by neutropenia or ketoacidosis, as well as patients with high iron serum concentrations, are at high risk of developing zygomycosis. These underlying conditions can influence clinical presentation and outcome. The rhinocerebral presentation is the most frequently reported localized symptom followed by pulmonary, cutaneous, cerebral, gastrointestinal, and disseminated infections. In the rhinocerebral or pulmonary forms, patient death rates are reported to be as high as 60% because of delayed diagnosis or delayed therapeutic management. Treatment strategies are based on high doses of any lipid formulation of amphotericin B, associated with large surgical resections when possible.[6]

In this survey on mucormycosis 142 responses from private general and dental practitioners from various demographic areas in India were gathered it shows awareness of oral manifestations after post covid19 recovery. The study group comprised 92.3 % practitioners were aware of oral manifestations after post covid19 recovery 7.7 % practitioners were not aware of oral manifestations after post covid19 recovery.

73 practitioners (81.1%) responded that transmission of covid19 pathogen occurs while coughing/sneezing. 44(48.9 %) practitioners responded that transmission of covid19 pathogen occurs directly by catching infected persons moisture. 40 (44.4%) practitioners responded that transmission of covid19 pathogen occurs person to person contact. (2.2 %) practitioners were not aware about transmission of covid19 pathogen. 27.5% practitioners responded that they were infected with covid19 pathogen. (67.9 %) practitioners responded that their oral mucosa was not affected. (17.9 %) practitioners responded that transmission of covid19 pathogen occurs directly and affected their oral mucosa showing signs like dry mouth, oral ulcers, and superinfection by bacteria and fungi by catching infected persons moisture. 40 (44.4%) practitioners responded that transmission of covid19 pathogen occurs person to person contact. (2.2%) practitioners were not aware about transmission of covid 19 pathogen (90.8 %) practitioners responded that mucourmycosis is an Opportunistic infection seen in immunocompromised patients. (8%) practitioners responded that mucourmycosis is Bacterial infection. (2%) practitioners responded that mucourmycosis is Worm infection. (50.7%) practitioners responded that mucourmycosis is not seen only in postcovid patients, (28.9 %) responded it is seen only in postcovid patients. (90.1 %) people says that mucourmycosis is seen most commonly in diabetic, aged and patients taking corticosteroids. (5 %) patients with diabetes and on corticosteroids are on high risk. (69.3 %) practitioners responded that mucourmycosis is seen most commonly in sinumaxillary region, (26.4 %) patients have no idea about CAM associated with orthodontic treatment. (1.5 %) patients have gastrointestinal and pulmonary CAM.

(93.5 %) practitioners responded that mucourmycosis affects duration of orthodontic treatment. (6.5 %) practitioners responded that mucourmycosis does not affects duration of orthodontic treatment (80.4%) practitioners responded that orthodontic treatment depends on bone levels. (10.1%) practitioners responded that there is no need of orthodontic treatment in CAM. (9.4%) showing no correlation of orthodontic treatment and CAM graph showing type of mucosal lesion associated with CAM . multiple inraoral sinus with mobile teeth is associated with CAM (84.5%) practitioners noticed this. (7%) practitioners responded gingivitis is associated with CAM. (5.5%) practitioners responded mucocele is associated with CAM. (4.5%) practitioners responded radicular cyst is associated with CAM.

(68.1%) practitioners responded that Patient who are undergoing orthodontic treatment experienced covid 19 associated oral mucosal lesions in the various form such as irregular ulcers, petechia, erythematous plaques, and large blisters. (18.1%) practitioners responded that Patient who are undergoing orthodontic treatment experienced CAM in the form of irregular ulcers. (10.1%) practitioners responded CAM lesions as petechia and (8%) in the form of erythematous plaque. (9.4%) associated with large blisters on mucosa. (84.5%) practitioners responded that CAM shows palatal ulceration secondary to CAM. (13.4%) practitioners responded that image shows oroantral fistula (69%) practitioners responded that Contrast enhanced CT PNS shows mucosal thickening, inflammation of nasal Turbinate, Bone Erosion, Fluid Filled Sinus, and Sequestered Bone. (16.2%) practitioners responded that Contrast enhanced CT PNS shows Fluid Filled Sinus. (14.8%) practitioners responded that Contrast enhanced CT PNS shows Bone Erosion,

(15.5%) practitioners responded that Contrast enhanced CT PNS shows mucosal thickening, and inflammation of nasal Turbinate, (10.6%) practitioners responded that Contrast enhanced CT PNS shows Sequestered Bone. graph shows what precautions to be followed in palatal perforation by CAM (38.7%) practitioners advised to Maintaing good oral hygiene. (28.2%) practitioners advised Palatal prosthesis to avoid trauma to commissure. (25.4%) practitioners advised to take Maxillary jaw impression using irreversible hydrochloride when required. (7.9%) practitioners advised to give 2mm of spacer in case of erupting teeth.

The survey gives idea about medical management of CAM. (62.4%) practitioners advised for strict glycemic control, amphotericin B, corticosteroids to relieve pain, debridement of necrotic ischar, excision and resection. Maintaing good oral hygiene. (20.6%) practitioners advised for strict glycemic control, amphotericin B. (12.1%) practitioners advised debridement of necrotic ischar, excision and resection. (2.5 %) practitioners advised for corticosteroids to relieve pain. (0.5 %) practitioners advised for more sucrose consumption. (59.9 %) practitioners says that periodontal disease associated bone loss with CAM due to presence of systemic conditions. (47.2 %) practitioners says that hyperglycaemic state leads to periodontal disease associated bone loss with CAM. (41.5%) practitioners says that avascular necrosis leads to periodontal disease associated bone loss with CAM.

The proteases produced by the cariogenic bacteria, 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. MMPs are involved in matrix remodeling during dentinogenesis. MMP-8, MMP-2, MMP-9, MMP-3, MMP-14 and MMP-20 are the main MMPs that have been identified in pulp, odontoblasts and predentin/dentin (Yi 2022, Nascimento 2011, Vidal 2014, Jain 2016)

Odontoblasts secrete at least gelatinase A (MMP-2), gelatinase B (MMP-9), collagenase 2 (MMP-8), collagenase-3 (MMP-13), enamelysin (MMP-20) and membrane type matrix metalloproteinase-1 (MT1-MMP). MMPs have been identified in carious dentin (Dayan et al., 1983, Chaussain et al,. 2006, 2013).

4. Prevention of caries arrestment (Sulkala, 2001) and dental erosion

Effects of iron (ferrous sulphate- $FeSO_4$) and/or epigallocatechin gallate- EGCG) on MMPs inhibition, caries arrestment and the prevention of dentin erosion are well documented (Imfeld 1996, Meurmann & TenCate 1996, Kato et al., 2010 a, 2010 b, Carrilho 2012, Shellis and Addy. 2014).

A statistically significant association between tooth erosion and expression of enamelin (ENAM) has been reported. There is no evidence of association between dental erosion and ameloblastin (AMBN), tuftelin 1 (TUFT1), and tuftelin 1 (TUFT1). Another interesting gene is msh homeobox 1 (MSX1), which is a part of a large family of homeobox genes.

Kallikrein-related peptidase 4 (KLK4) and matrix metalloproteinases 20 and 16 (MMP20, MMP16) degrade amelogenin. KLK4 gene variations are associated with both lower and higher caries experiences, while MMP20 and MMP16 are associated with higher caries experiences combined with poor oral health. Additionally, matrix metalloproteinases 2, 9, and 13 have also been investigated in correlation with caries susceptibility.

Several studies have demonstrated an association between dental caries, dental erosive wear, and genetic factors. The genes coding for enamel matrix proteins, i.e., amelogenin, enamelin, tuftelin, and tuftelin interaction protein 11, are associated with increased susceptibility to both dental erosion and caries. Enormous progress and interest in identifying the genetic factors influencing the development of erosion and caries is evident. Both diseases are still highly prevalent worldwide, and it has been more than a century of investigation of their pathogenesis. New strategies that can protect individuals at higher risk are warranted. Recently, studies have identified promising biomarkers that aim to help in personalizing treatment for individuals at higher risk to develop dental erosion and dental caries. Genetic studies aim to investigate the underlying susceptibility and reveal the risk prior to the disease/condition onset.

Recent evidence from in vitro and in situ studies has shown a protective role of MMP inhibitors against dentin erosion and erosion plus abrasion. Sodium fluoride inhibits MMP-2 and MMP-9 (Kato et al., 2014, Buzalaf et al., 2014). The inhibitors tested were green tea and its active epigallocatechin-gallate (EGCG), ferrous sulfate, and chlorhexidine. The use of MMP inhibitors has emerged as an important preventive tool against caries and dentin erosion (Kato et al., 2010; Buzalaf et al. 2012).

Conclusions

Degradonomic is a functional role of MMPs and TIMPs during development, survival, migration, remodeling and morphogenesis (Ashwini et al., 2020) They play a key role in the initial dental development, and also later during enamel maturation. MMPs are involved in tooth germs mineralization (enamel and dentin), in the prevention, and in the treatment of dental erosion. They were also identified in sound and carious dentin, in the pulp and saliva. Remodeling of dental tissues are also under the control of MMPs and TIMPs.

References

Vu TH, Werb Z. Matrix metalloproteinases: effectors of development and normal physiology. *Genes & Development* 2000; 14: 2123-2133

Hijova E. Matrix metalloproteinases: their biological functions and clinical implications Bratist Lek Listy 2005; 106(3): 127-132.

Malemud CJ, Inhibition of MMPs and ADAM/ADAMTS *Biochemical Pharmacology*. 2019; 165: 33-40.

Weiss A, Goldman S, and Shalev E. The matrix metalloproteinases (MMPs) in the deciduous and fetal membranes. *Frontiers in Bioscience* 2007;12; 649-659.

Nagase H, Woessner JF. Matrix metalloproteinases. *J Biol Chem* 1999; 274: 21491-21494.

Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. *Circ Res* 2003; 92: 827-839.

Nagase H, Visse R, Murphy G. Structure and function of Matrix metalloproteinases and TIMPs *Cardiovascular Research* 2006 ; 69(3) : 562-573.

Jablonska-Trypud A, Matejczyk M, Rosochacki S. Matrix metalloproteinases (MMPs), the main extracellular matrix (ECM) enzymes in collagen degradation, a target for anticancer drugs. *J Enzyme Inhib Med Chem* 2016; 31(1): 177-183.

Norman LP, Matters GL, Chrisman JM, Bond JS. Expression of meprins in health and disease in "*Current Topics in developmental Biology*" vol. 54; 2003; pp145-165

Khaddam M, Huet E, Vallée B, Bensidhoum M, Le Denmat D, , Filatova A et al., Emmprin/CD147 deficiency disturb ameloblast-odontoblast cross-talk and delays enamel mineralization *Bone* 2014 ; 66 : 256-266.

Prox J, Arnold P, Becker-Pauly C. Meprin and meprin procollagen proteinases in health and disease. *Matrix Biology* 2015; 44-46: 7-13.

Sterchi EE, Stöcker W, Bond JS. Meprins, membrane-bound and secreted astracin metalloproteinases *Mol. Aspects Med* .2008; 29(5): 309-328.

Gross, J., and Lapiere, C. M. Collagenolytic activity in amphibian tissues: a tissue culture assay. *Proc. Natl. Acad. Sci. U.S.A.* 1962; 48, 1014–1022.

Klein T, Bischoff R. Physiology and physiopathology of matrix metalloproteinases *Amino Acids* 2011; 41(2): 271-290.

Singh D, Srivastava SK, Chaudhuri TK, Upadhyay G. Multifaceted role of matrix metalloproteinases (MMPs) *Frontiers in Molecular Biosciences*. 2015; 2: Article 19

Bourboulia D, Stetler-Stevenson WG. Matrix Metalloproteinases (MMPs) and Tissue Inhibitors of MetalloProteinases: positive and negative regulators in tumoral cell adhesion. *Seminar in cancer biology* 2010; 20(3): 161-168.

Malemud CJ . Matrix metalloproteinases (MMPs) in health and disease: an overview. *Frontiers in Bioscience* 2006; 11: 1696-1701.

Woessner JF. Matrix metalloproteinases and their inhibitors in connective tissue remodeling FASEB J 1991; 5: 2145-2154

Woessner JF. The family of matrix metalloproteinases. In "*inhibiton of matrix metalloproteinases. Therapeutic potential*"l Greenwald RA, Golub LM, (eds). New York. The New York Academy of Sciences. 1994; pp11-21.

Sulkala M, Wahlgren J, Larmas M, Sorsa T, Teronen O, Salo T, *et al*. The effects of MMP inhibitors on human salivary MMP activity and caries progression in rats. *J Dent Res 2001;* 80:1545-1549.

Dayan D, Binderman I, Mechanic GL. A preliminary study of activation of collagenase in carious human dentine matrix. *Arch Oral Biol. 1983;28:185–187.*

Tjäderhanea L, Buzalaf MA, Carrilhod M, Chaussain C. Matrix Metalloproteinases and Other Matrix Proteinases in Relation to Cariology: The Era of 'Dentin Degradomics'. *Caries Res*. 2015;49:193–208.

Chaussain C, Boukpessi T, Khaddam M, Tjaderhane L, George A, Menashi S. Dentin matrix degradation by host matrix metalloproteinases: inhibition and clinical perspectives toward regeneration. *Front Physiol*. 2013; 4: 308.

Brodzikowska A, Gondek A, Rak B, Paskal W, Pełka K, Cudnoch-Jędrzejewska A, Włodarski P. Metalloproteinase 14 (MMP -14) and has-miR-410-3p expression in human inflamed dental pulp and odontoblasts. *Histochem Cell Biol* 2019; 152(5): 345-353.

Tjäderhane L, Lanjava H; Sorsa T, Uitto V-j, Larmas M, Salo T. The activation and function of host matrix metalloproteinases in Dentin Matrix Breakdown in caries lesions. *J Dent Res* 1998; 77(8): 1622-1629.

Bourd-Boittin K, Friedman R, Fanchon S, Septier D, Goldberg M, Menashi S. Matrix metalloproteinase inhibition impairs the processing, formation and mineralization of dental tissue during mouse molar development. *Exp Cell Res* 2005; 304 (2): 493-505.

Fanchon S, Bourd K, Septier D, Everts V, Beertsen W, Menashi S, Goldberg M. Involvement of matrix metalloproteinases in the onset of dentin mineralization. *Eur J Oral Sci* 2004 ; 112(2) : 171-176.

Goldberg M, Septier D, Bourd K, Hall R, George A, Goldberg H., Menashi S. Immunohistochemical localization of MMP-2, MMP-9, TIMP-1, and TIMP-2 in the forming rat incisor . *Connective Tissue Research* 2003; 44, issue 3-4: 143-153.

Lu Y, Papagerakis P, Yamakoshi Y, Hu J C-C, Bartlett JD, Simmer JP. Functions of KLK4 and MMP20 in dental enamel formation. *Biological chemistry* 2008; 389(6): 695-700.

Tersariol IL, Geraldeli S, Minciotti CL, Nascimento FD, PÄäkkönen V, Martins MT, Carrilho MR, Pashley DH, Tay FR, Salo T, Tjäderhane. Cystein Cathepsins in human dentin-Pulp Complex *J. Endod* 2010; 36: 475-481.

Mazzoni A, Maravic T, Tezvergil-Mutluay A, Tjäderhane L, Scaffa PMC, Seseoguilari-Dirhan R, Bavelioni A, Gobbi P, Pashley DH, Tay FR, Breschi L. Biochemical and immunohistochemical identification of MMP-7 in human dentin. *J. Dent* 2018; 79: 90-95.

Chaussain-Miller C, Fioretti F, Goldberg M, Menashi S. The role of matrix metalloproteinases (MMPs) in human caries *J Dent Res* 2006: 85(1): 22-32.

Van Strijp AJ, Jansen DC, Degroot J, TenCate JM, Everts V. Host-derived proteinases and degradation of dentine collagen in situ. *Caries Res.* 2003;37: 58–65.

Ashwini A, Dineshkumar T, Rameshkumar A, Swarnalakshmi R, Shahnaz A, Nagarathinam AE, Rajkumar K. Dentin degradonomics - The potential role of salivary MMP-8 in dentin caries *J Clin Exp Dent* 2020; 12(2) e-108-e-116.

Mazzoni A, Tjäderhane L, Checchi V, Lenarda R,D, Salo T, Tay FR, Pashley DH, Breschi L. Role of dentin MMPs in caries progression and bond stability. *J Dent Res*. 2015 ; 94(2) : 241-251.

Aguirre-Lopez EC Patino-Marin N, Martinez-Castabon GA, et al….Rosales-Garcia P. Levels of matrix metalloproteinase-8 and cold test in reversible and irreversible pulpitis, *Medicine* 2020, 24, 99(52): e23782.

Ryan ME, Ramamurthy S, Golub LM. Matrix metalloproteinases and their inhibition in periodontal treatment. *Current Opinion in Periodontology* 1996; 3: 85-96.

Birkedal-Hansen H. Role of matrix Metalloproteinases in human Periodontal Diseases. *J. Periodontology* 1993; 64(5S): 474-484.

Lin N-H, Gronthos S, Bartold. Stem cells and periodontal regeneration. *Australian Dental Journal* 2008; 53: 106-121.

Yi G, Zhang S, Ma Y, Yang X, Huo F, Chen Y, Yang B, Tian W Matrix vesicles from dental follicle cells improve alveolar bone regeneration via activation of the PLC/PKC/MAPK pathway. *Stem Cell Research & Therapy 2022; 13,41*,

Nascimento F.D., Miniciotti C.L., Tersariol I.L.S. Cysteine cathepsins in human carious dentin. *J Dent Res*. 2011;90(4):506–511.

Vidal C.M., Tjaderhane L., Saffa P.M. Abundance of MMPs and cysteine cathepsins in caries-affected dentin. *J Dent Res*. 2014;93:269–274.

Jain A, Bahuguna R Role of matrix metalloproteinases in dental caries, pulp and periapical inflammation: an overview *j oral Biology and Craniofacial Research* 2016; 5(3): 212-218.

Kato MT , Leite AL, Hannas AR, Oliveira RC, Pereira JC, Tjäderhane L, *et al*. Effect of iron on matrix metalloproteinase inhibition and on the prevention of dentine erosion. *Caries Res* 2010a; 44: 309- 316.

Kato MT, Leite AL, Hannas AR, Buzalaf MA. Gels containing MMP inhibitors prevent dental erosion *in situ*. *J Dent Res* 2010b ; 89:468- 472.

Carrilho MR. Can exogenous protease inhibitors control dentin matrix degradation? *J Dent. Res.* 2012; 91(12): 1099-1102.

Imfeld T. Dental erosion. Definition, classification and links*. Eur J Oral Sci* 1996; 104(2) : 151-155.

Meurman JH, ten Cate JM. Pathogenesis and modifying factors of dental erosion. *Eur J Oral Sci* 1996;104(2):199-206.

Shellis RP, Addy M. The interactions between attrition, abrasion and erosion in tooth wear. *Monogr Oral Sci* 2014; 25: 32 -45.

Yao Y, Kauffmann F, Maekawa S, Sarment LV, Sugai JV, Schmiedeler CA, Doherty EJ, Holdsworth G, Kostenuik Pj, Giannobile WV. Sclerostin antibody stimulates periodontal regeneration in large alveolar bone defects. *Scientific Reports* 2020; 16217

Kato MT, Bolanho A, Zarella BL, Sato T, Tadehane L, Buzalaf MA. Sodium fluoride inhibits MMP-2 and MMP-9 *J Dent Res* 2014; 93(1): 74-77.

Buzalaf MAR, Magalhäes AC, Wiegand A Alternatives to fluoride in the prevention and treatment of dental erosion. *Monogr Oral Sci* 2014; 25: 244-252.

Buzalaf MAR, Kato MT, Hannas AR. The role of matrix metalloproteinases in dental erosion. *Adv Dent Res* 2012; 24(2): 72 -76.

Kato MT, Leite AL, Hannas AR, Buzalaf MA. Gels containing MMP inhibitors prevent dental erosion in situ. *J Dent Res* 2010; 89(5): 468-472.

Citation: Goldberg M. "Dental Tissues Remodeling by Matrix Metalloproteinases (MMPS) and Tissues Inhibitors of MMPS (TIMPS)". *SVOA Dentistry* 2022, 3:4, 203-212.