REVIEW

The involvement of metalloproteinases and their tissular inhibitors in the processes of periodontal orthodontic remodeling

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Abstract

The orthodontic treatment uses forces that produce structural and biochemical changes in the periodontal space breaking the balance between the synthesis and the breakdown of the collagen in the periodontium. Matrix metalloproteinases (MMP) plays a central role in the normal tissular remodeling processes, those in the tissular morphogenesis and the tissular repair (including the remodeling of the periodontal space of the periodontal ligament, during the dental orthodontic translations). The inter-relation between the molecular mechanism of orthodontic remodeling and MMPs is still unclear.

***Keywords*:** orthodontic force, matrix metalloproteinases, MMP, TIMP, periodontal ligament, periodontology.

Introduction

The application of an orthodontic force on a tooth produces structural and biochemical changes in the periodontal space breaking the balance between the synthesis and the breakdown of the collagen in the periodontium. Matrix metalloproteinases (MMP) plays a central role in the normal tissular remodeling processes, those in the tissular morphogenesis and the tissular repair (including the remodeling of the periodontal space of the periodontal ligament, during the dental orthodontic translations) [1]. The inter-relation between the molecular mechanism of orthodontic remodeling and MMPs is still unclear.

MMPs and periodontal remodeling in orthodontics

The mechanical stress induces the production of MMP-1 in the cells of the periodontal ligament, of human nature, *in vivo* [2]. Collagenase-1 (MMP-1) and collagenase-2 (MMP-8) are able to break the native triple helix molecules of interstitial collagen, initiating cell remodeling [3, 4]. MMP-8 degranulation from the polymorphonuclear neutrophils represents one of the key factors of the pathologic breakdown of the collagen in the periodontal diseases [5, 6].

The levels, molecular forms and the degree of activation of MMP-1 and MMP-8 were less studied in humans. Apajalahti S *et al.* [2] noticed the existence of a significantly statistically increased of MMP-8 in the gingival fluid, in the initial stages of the orthodontic treatment (at 4–8 hours form the application of an orthodontic fixed device), but not the level of MMP-1 (a fact that suggests its contribution to the initiation of the PDL remodeling after the initial dental orthodontic translations). The aforementioned authors showed that also the self-activation of the MMP-8 is very rapidly produced, only one hour after the application of the orthodontic force. Mäntylä P *et al.* [7] *in vivo* studies upon patients with fixed orthodontic devices, sustain also that the level's increase and the partial activation of the many species of PMN and fibroblasts type MMP-8 reflect the periodontal remodeling processes during the orthodontic dental translations.

Increase of MMP-1 levels was seen *in vitro* on human fibroblasts repeatedly elongated, after four days [8]. Bolcato-Bellemin AL *et al.* [9] registered increase of mRNA MMP-1 levels after 12 hours of mechanical stimulation. As a response to the continuous orthodontic forces, the monocytes in the periodontal ligament are stimulated to produce osteoclasts, and they are seen at 30–40 hours from the onset of the forces' application, in the flattened periodontal ligament of young persons. This delay in the osseous response might suggest [2] that an increase in the MMP-1 activity is produced only in the next stages of the orthodontic treatment. The molecular forms of the MMP-8 in the gingival fluid of the orthodontic patients might have

multiple cellular sources, as the leucocytes infiltration, neutrophils, monocytes/macrophage [10], gingival fibroblasts, epithelial cells of the gingival sulcus or the osseous cells [11].

Furthermore studies, like those of Cantarella G *et al.* [12], upon the same patients with fixed orthodontic devices, shown that the orthodontic forces influences both the MMP-1 levels and the MMP-2 in the compression/tension areas, the changes being conditioned by the time factor: at one hour there is an increase of the MMP-1 level, but returns to normal in three hours; in the tension areas there is a significant increase the MMP-1 level at one hour; MMP-2 level is significantly increased after eight hours in the compression areas, and after one hour in the tension area, specifying that at this level the MMP-2 returns to the basal level in eight hours .

Following experiments in mice, upon the production of MMP in the periodontal ligament during the orthodontic dental displacements, Takahashi I *et al.* [13] noticed that the MMP-8 is produced by the superficial cells of the cementum and in the bone's osteocytes but not in any other cell of the periodontal ligament. In the tension areas, there is an increased production of MMP-1 and MMP-13, by the superficial cells of the alveolar bone starting from the 4th day. MMP-8 is produced by the osteocytes in the alveolar bone, in the tension areas, in days 4–7. The production of both MMP returns to normal after 14 days. In the compression areas, MMP-8 is transiently produced in the cells surrounding the hyalinized tissue and in fibroblasts, from days 2–7. MMP-13 is transiently produced in days 2–4, but it is not produced by the cells included in the degenerated hyalinized tissue. In the compression areas the production of MMP-3 from the ostecytes is increased in the days 2–4. In the compression areas, the cells of the PDL (periodontal ligament) and the cells lined on the osseous resorption surface produce MMP-13 from the 4th day. The production of MMP-8 and MMP-13 usually returns to normal in the 14th day. The level of mRNA MMP-13 increases significantly after the application of an orthodontic force. Through immunodetection techniques of collagenase-3 (MMP-13), it was noticed an increase first in the compression areas, and then both in the compression areas and in the tension ones. The increase is detected both in PDL and in alveolar bone, showing that MMP-13 plays an important role during the orthodontic dental translations. Holliday LS *et al.* [14] sustain that the MMP are involved in the regulation of bone remodeling. The aforementioned authors sustain the hypothesis that the TIMPs (Tissue-Inhibitors of Metallo-Proteinases) might be useful to limit dental orthodontic translations, the process implying the alteration of the bone remodeling. Generally, TIMPs limit the bone resorption on medullar bone cultures stimulated with calcitriol, parathormone and basic fibroblast growth factor. The covering of the predentine slices with short peptides of arginine–glycine of the aspartic acid (RGD), but without any control of the arginine–glycine–glutamic acid (RGE), reestablishes the bone resorption in the presence of the TIMPs. The orthodontic displacements could be inhibited using TIMPs fact that suggests a mechanical link between the MMPs activity and the peptide production of RGD. During the bone remodeling, the components of the external cellular matrix, and so the collagen, are destroyed and removed and new components are synthesized and deposited [15].

Surprisingly, the cells submitted to tension, following a force application does not synthesized preferentially structural proteins. The mechanical deformity leads to the stimulation of enzyme synthesis like MMPs, collagenase, stromelysin, responsible of their specific hydrolysis and the production of TIMPs [16]. This fact suggests the hypothesis that the destruction of the extracellular matrix is stimulated by the fibroblasts submitted to a continuous tension. The functional importance of such an answer is not clear, but it seems that this increase in the turnover of the matrix is necessary to facilitate the cell division and accommodation to the increase of cellular population. Garlet TP *et al.* [17], confronting the changes in the production of pro- and anti-inflammatory cytokines, in the areas of tension and compression of the PDL emerged after the application of an orthodontic force, concluded that in the compression areas there is an increase production of TNF-alfa receptor activator of nuclear factor kappaB ligand (RANKL) and MMP-1, in the same time in the tension areas being observed an increase production of IL-10, IMP-1, collagen-1, osteoprotegerin (OPG), and osteocalcin (OCN). The production of TGF-beta is similar in both types of area.

Meikle MC [16] proposes also a hypothetic model of periodontal remodeling in the areas with tensions. According to it, the fibroblasts from the periodontal ligament submitted to stress synthesize cytokines as IL-1, IL-6 [1]. IL-1 and IL-6 stimulates the MMPs and inhibits TIMPS by the PDL cells through autocrine and paracrine mechanisms [2]. The vascular endothelial growth factor produced by the activated fibroblasts initiate the angiogenesis [3]. The breakdown of the extracellular matrix by the MMPs, facilitate the cell proliferation and the development of the capillaries. The PDL cells [4], osteoblasts and the osseous cells in the bone surface [5] enter in a biosynthesis of structural molecules and other matrix molecules (Figure 1).

In what concerns the answer of the osteoclasts from PDL to compression forces, Kanzaki H *et al.* [18] showed that the fibroblasts stimulate the osteoclastic genesis in the cultures of peripheral blood mononuclear and that the production of mRNA is highly regulated in this cells. The production of osteointegrin remains unchanged. This fact suggests that the PDL plays a central role in the differentiation and function of the osteoclasts during the dental orthodontic translations. He Y *et al.* [19] also showed that the PDL's cells submitted to tensile stress can perceive two different forms of mechanical stimuli and respond differently with extracellular synthesis of matrix (collagen-1, fibronectin) and destruction (MMP-2, TIMP-2).

In addition, Meikle MC [16] proposes a hypothetic model of periodontal remodeling in the compression

areas. The PDL cells submitted to compression synthesize IL-1 and IL-6 [1]. IL-1 and IL-6 regulate RANKL in an autocrine and paracrine manner [2] the production of MMP-3 by the PDL cells and osteoblasts. The MMPs derived from osteoblasts breakdown the non-mineralized surface of the bone, while the MMPs produced by the PDL cells breakdown their extracellular matrix [4]. RANKL stimulates the formation of osteoclasts from the mononuclear precursor cells and their function, acceding to the bone surface and breaking down the mineralized matrix. The deformation of the alveolar bone regulates the production of MMPs from the osteocytes adjacent to bone surface [5] (Figure 2).

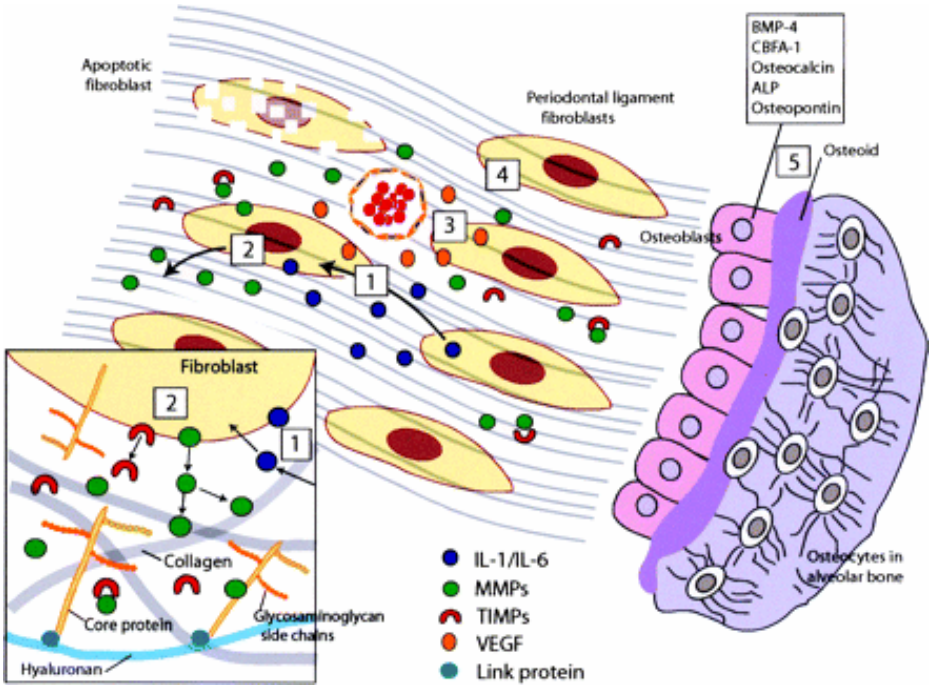

Figure 1 – ***Hypothetic model of periodontal remodeling in the areas with tensions [16].***

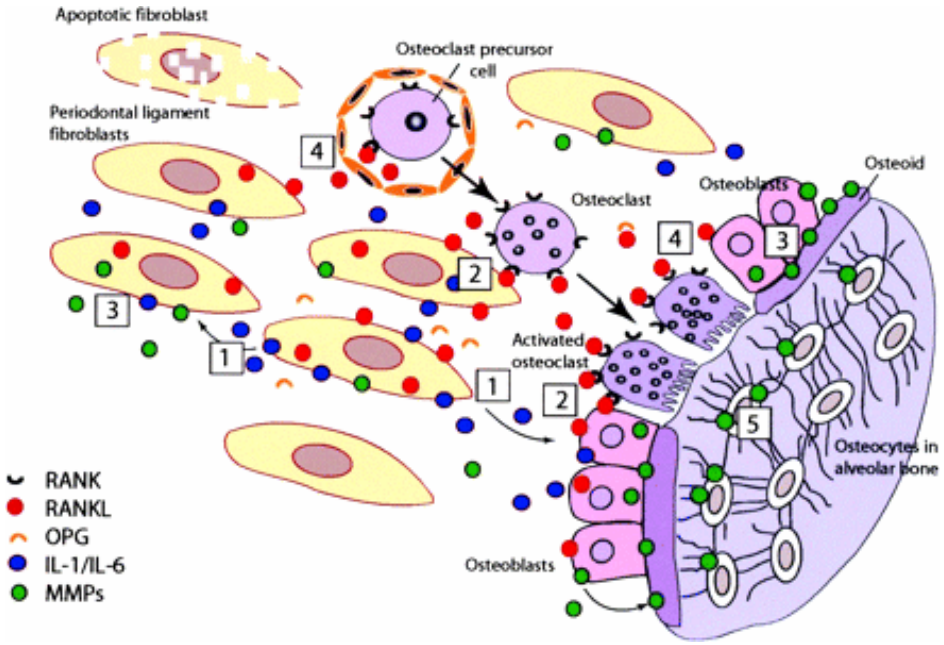

Figure 2 – ***Hypothetic model of periodontal remodeling in the compression areas [16].***

In conclusion, the remodeling of the connective tissue is mediated by a complex mechanism that co-interests the osteotropic cytokines synthesis as IL-1, IL-6, RANKL in cells as osteoblasts/fibroblasts. During orthodontic displacements, the TIMPs influences the osteoblasts and other cells involved in the dental orthodontic translations, aberrant remodeling of periodontal vessels might influence the efficiency of the orthodontic treatment.

The changes in activity and profile of the MMPs joined with the action of their natural TIMPs in the extracellular environment is important in the monitoring of the metabolic activity of the periodontal tissue and in the determination of the pathways leading to the emergence of connective tissue metabolic products in the gingival crevicular fluid [20]. The changes in the MMPs activity, very probable during orthodontic movements, following the imbalance between the

extracellular level of MMPs and TIMPs are considered as pathologic mechanisms important in the periodontal connective tissue breakdown [21].

Significant rises of the MMP-8 levels in the gingival fluid are produced in inflammatory periodontal conditions [7] The application of orthodontic fixed devices, rendering the hygiene difficult, especially in the area between the bracket and the gingival edge, creates those conditions and furthermore could lead to chronic gingival hyperplasia with deepening of the gingival sulcus and even loss of periodontal support. This type of gingival reactions may unleash a counter force after the tooth has reached its desired position. But, what is the role of MMPs and TIMPs in the onset of gingival overgrowth during orthodontic treatment? Is the bacterial plaque the only responsible for these changes? The subject remains in debate.

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