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Role of matrix metalloproteinases in bone regeneration: Narrative review

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ABSTRACT

Background: Matrix metalloproteinases (MMPs) not only work as enzymes but also as degrading enzymes that have been shown to play an important function in extracellular matrix (ECM) regeneration, including bone regeneration. To generate new bone tissue, bone regeneration or repair relies on a series of regulated processes in which MMPs play an important role. Bone cells express the MMPs in an active state, and these MMPs are assumed to have a crucial role, not only for the viability and functionality of osteoclasts, osteoblasts, and osteocytes but also for the formation and development of chondrocytes.

Objective: This study aimed to review and present the roles of matrix metalloproteinases in bone regeneration.

Methods: An analysis of the scientific literature on the topics of matrix metalloproteinases in bone regeneration was done on PubMed and Google Scholar. Search results were screened for articles that described or investigated the impacts matrix metalloproteinases have on bones in relation to dentistry. The journals' cited papers were also assessed for relevance and included if they complied with the criteria for inclusion. Accessibility to the full document was one of the prerequisites for admission.

Result: Bone regeneration are intricate ongoing processes involving numerous MMPs, especially MMP 2, 9 and 13. MMP-2 appears to alter bone growth through influencing osteoclast and osteoblast activity and proliferation, MMP-9-deficient animals have abnormal bone formation exclusively during endochondral ossification, MMP 13 is responsible for osteoclast receptor activation, has been linked to the breakdown bone resorption.

Conclusions: MMP 2, 9, and 13 play a major protective role in osteogenesis and bone regeneration.

1. Introduction

One of the most frequent dental treatments is tooth extraction. This treatment may result in gingival recession near the extraction site and resorption of the alveolar bone. Different molecules, including inflammation mediators, integrins, growth factors, and matrix metalloproteinases (MMPs), have an impact on the healing of wounds. By altering the wound matrix, MMPs play a role in each stage of wound healing and facilitate cell migration, which is crucial to the remodeling process.[1]

Matrix metalloproteinases, or MMPs, are a type of zinc-dependent extracellular matrix (ECM) enzyme that can degrade enzymes that have been shown to play an important function in ECM regeneration. They are the proteins that cleave the ECM's structural components, like collagen and gelatin, allowing the ECM to breakdown and regenerate. Under physiological and pathological conditions, bone cells express the MMPs in an active state, and these MMPs are assumed to have a crucial role, not only for the viability and functionality of osteoclasts, osteoblasts, and osteocytes, but also for the formation and development of chondrocytes, which are all affected by bone matrix degradation.[2,3]

MMPs are crucial bone physiology mediators. Due to the dynamic nature of bone tissue and the need for a variety of enzymes that can break down the organic component of the bone matrix, the action of MMPs and their inhibitors has physiological significance. When certain molecules, including MMP-9, MT1-MMP (MMP-14), or MMP-13, are not present during skeletal development, serious defects in the long bone plates arise, impeding normal bone production.[4] The mechanisms of intramembranous ossification and endochondral ossification are responsible for bone production during bone development and regeneration. Intramembranous ossification is a mechanism in which mesenchymal cells fuse together within a membrane and are directly differentiated into bone to produce the majority of the craniofacial skeleton. Endochondral ossification, on the other hand, is a bone growth process in cartilage that serves as a form of bone morphogenesis. The formation of most bones, particularly the long bones, is governed by endochondral ossification. Mesenchymal cells condense, and after that, they develop into chondrocytes. In this process, the cells proliferate and hypertrophy before dying. Blood vessels and bone regeneration cells like

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osteoprogenitor cells can invade these cavities. After that, ossification appears along the structure of the cartilage, progressively replacing it with bone. A cartilage model that is mechanically stable but can be damaged to facilitate mineral deposition during ossification and eventually bone formation is required for successful bone growth. The MMPs in bones are critical for bone repair during osteogenesis. Other tissues' remodeling, such as the skin and blood vessels, has been shown to take part in a variety of physiological processes, like wound healing and angiogenesis.[5,6]

The extracellular environment is finely regulated by proteinases, and it has a significant impact on cellular behaviors important in biological processes, including stem cell maintenance, embryogenesis, cellular metabolism, cellular proliferation, apoptosis, and tissue formation. Bone remodeling is mediated by two intertwined mechanisms: bone resorption and bone creation, which are regulated by osteoclasts and osteoblasts. After a fracture or a bone lesion, this process begins bone healing, resulting in bone repair or regeneration. Osteoporosis and other metabolic bone disorders can result from a misalignment of bone formation. To generate new tissue and bone function, bone regeneration or repair relies on a series of regulated processes, including ECM remodeling. Optimal ECM remodeling is necessary in all situations, and MMPs appear to be critical.[7,8] This study aimed to review and present the roles of matrix metalloproteinases in bone regeneration. This is due to bone cells expressing the MMPs in the active state, and these MMPs are assumed to have a crucial role in the viability and functionality of osteoclasts, osteoblasts, and osteocytes, highlighting the role of MMPs 2, 9, and 13 in the maintenance of composition and mechanical characteristics in bone regeneration.

2. Methods

An analysis of the scientific literature on the topics of matrix metalloproteinases in bone regeneration was done on PubMed and Google Scholar. Search results were screened for articles that described or investigated the impacts matrix metalloproteinases have on bones in relation to dentistry. The journals' cited papers were also assessed for relevance and included if they complied with the criteria for inclusion. Accessibility to the full document was one of the prerequisites for admission (Table 1).

A total of 53 published papers (original research articles and review article) were selected for the current review.

2.1. Role of Mmp-2 on osteogenesis during bone regeneration

Periodontal ligament cells express MMP 2 as pro-MMP-2, which is one of a number of MMPs for cellular remodeling and homeostasis. Controlling the rate or process of MMP 2 activation is considered an important regulatory step in maintaining periodontal tissue. Intracellular proteinase inhibitors, such as tissue antagonists of MMPs, can be used to prevent autolytic MMP activation and restrict extracellular MMP activity (TIMPs). The equilibrium between MT1 MMP and TIMP-2 is required for MMP-2's proteolytic activity to be regulated. Excessive tissue deterioration linked to inflammatory disorders can occur if this balance is disrupted.[9–11]

Table 1
Research method and criteria for choosing studies.

	Research Method and Criteria for Choosing Studies
A	A literature search was performed on PubMed and Google Scholar for studies related to Matrix metalloproteinases and bone regeneration. The combinations were used as search methods. ("name of Matrix metalloproteinases" + "Bone Regeneration") of the terms: "MMP 2", "MMP 9", "MMP 13", combined with "bone regeneration", "alveolar bone", "bone healing or repair". The papers were reviewed between January 1, 1998, and April 30, 2023, in English, in accordance with the inclusion requirements.
B	- Language: English; publishing period: January 1, 1998–April 30, 2023. Reviews, book chapters, original research articles, in vitro studies, in vivo animal or human studies, clinical studies, and meta-analyses were all included in the publications. - Case studies, letters, editorials, papers with irrelevant or useless data, articles without complete texts, and articles written in languages other than English were excluded.

MMP-2 knockout mice had a direct effect on osteopontin and sialoprotein expression. Osteopontin has been demonstrated to promote osteoclast activity, and bone sialoprotein has been proven to promote osteoblast development and activity. As a result, differences in the varied bones have different levels of expression of these two proteins. might lead to enhanced bone reabsorption or bone growth. Finally, MMP 2 appears to alter bone growth by influencing osteoclast and osteoblast activity and proliferation.[12,13] Furthermore, various animal models of osteolytic bone metastasis have shown that a considerable quantity of TGF- is loosened from the matrix of the damaged bone, and MMPs play a role in alveolar bone. particularly MMP2, and that this rise in TGF comes from osteolytic wounds following metastatic destruction. Excessive TGF signaling promotes osteolytic bone degradation by stimulating PTHrP and IL-11, which are released by tumor cells. TGF regulates bone remodeling and bone mass maintenance through its dual effects on osteoblasts. By stimulating Runx2, which is essential for the onset of osteoblast proliferation and the suppression of the late development of osteoblasts, it enhances early differentiation of osteoblast precursors is aided by the recruitment of mesenchymal stem cells.[14,15]

MMP 2 can affect angiogenesis in a variety of ways. MMP 2 allows pericytes to detach and endothelial cells to migrate by cleaving endothelium adhesions and damaging the vascular basement membrane and ECM. Second, MMP2's proteolytic action can increase bound angiogenic growth factors' secretion and stimulation of the ECM, such as VEGF, bFGF, and TGF-. In MMP2-deficient mice, the proangiogenic activity of MMP 2 was proven. In a previous study using an ischemia model, both artery capillary formation and growth were inhibited in MMP2-deficient animals, and the invading and multiplying properties of endothelial cells grown from mutant were significantly affected. Angiogenesis is a key requirement for tumor growth and bone creation. Consequently, despite having the same proangiogenic impact, MMP 2 overexpression indirectly promotes During bone metastasis, tumor cells develop and invade, whereas MMP 2 regulation directly hinders bone production as a result of osteogenesis and lowers blood supply.[16,17]

Recent research has added to our understanding of the link between MMP 2 and angiogenesis. Because of their ability to provide bone tissues with essential nutrients and release MMPs that control ECM and vessel formation, type-H vascular endothelial cells make closely connected bone modeling possible. MMP 9 and MMP 2 are involved in cartilage resorption and bone vasculature control, specifically. MMP2's role in osteoclast differentiation, in particular, is thought to facilitate the release of PDGF-BB, which stimulates the creation of type-H vasculature.[18,19] In cases of high osteoclastic bone resorption, osteopenia can occur during the formation of bones if osteoblastic bone synthesis is disrupted. Metabolism regulation is the most important element that regulates osteoblast bone formation, and metabolic illnesses like diabetes and anorexia can cause osteoblast malfunction and bone loss. MMP 2 deficiency has been linked to metabolic problems, placing individuals at risk for osteolysis and growth restriction. MMP 2 has a variety of intracellular roles, including degrading cytoplasmic proteins such as calcitonin and nuclear matrix proteins such as polymerase, in addition to its external proteolytic activity. As a result, MMP 2 mutations that cause loss of function may have an impact on osteoblasts' energy metabolism, limiting their ability to create bone during regeneration.[20,21]

In the study of Huang A et al. (2019), they evaluated whether EGCG's chemical alteration of gelatin resulted in increased bone growth through regulating MMP expression and finally described their results: the primary enzymes that break down gelatin are MMP-2 and -9. The early stages of wound healing are crucial for the function of gelatinases. The remaining gelatin served as an efficient scaffold for multipotent

progenitor cells and osteoblasts.[22]

2.2. Role of Mmp-9 on osteogenesis during bone regeneration

Non-ECM substances, including amyloid beta peptide and myelin basic protein, can also be cleaved by MMP-9. MMP-9 expression changes as a child grows. MMP-9 is expressed in trophoblasts and osteoclasts throughout early development, indicating that it is involved in bone implantation and resorption.[23,24]

A deficiency in endochondral ossification in long bones was the earliest stage of development abnormality documented in an MMP-knockout mouse. Because apoptosis is disrupted when MMP-9 is deleted, in the growth plate, a zone of hypertrophic chondrocytes expands. Galectin-3, an anti-apoptotic lectin that can be released and targeted to the ECM, appears to be a key MMP-9 substrate. Galectin-3 is cleaved and inactivated by MMP 9. When exogenously supplied to wild-type bone explants, uncleaved galectin-3 produces an enlargement of the growth plates; identically cleaved galectin-3 has no effect on the phenotype of MMP-9 mutants. MMP9 was significantly expressed during the healing process of a fractured bone, and MMP9 mutant animals mend their fractures more slowly than control mice. Exogenous VEGF corrects the abnormalities, suggesting that MMP9-mediated VEGF processing is limiting in bone regeneration. MMP-9 null animals recover from injuries with stable fractures via ossification, implying that a separate mechanism is utilized to cure the injury in the absence of MMP-9.[25–27]

MMP-9-deficient animals have abnormal bone formation exclusively during endochondral ossification. After birth, changes in the substitution of cartilage for bone have been reported, with altered chondrocyte differentiation affecting mechanisms of bone growth and angiogenesis as well as altering bone formation. This is caused by Hypertrophic chondrocyte death is delayed, and ossification is changed, resulting in In the growth plates, there is an increased hypertrophic zone and less vascularization. Furthermore, on the long bone in the center, it has been observed that enlarged chondrocytes die and that ossification occurs around them. This abnormal development of the skeleton is compensated for 4 weeks after birth, resulting in animals with a normal skeletal phenotype. MMP 13 expression was shown to be high in enlarged chondrocytes adjacent to the osseous interface of the growth plate in MMP 9 null animals, indicating this metalloproteinase is trying to make up for the lack of MMP 9. This phenotype could be triggered in two distinct ways: first, the absence of MMP 9 causes inefficient cartilage matrix proteolysis, resulting in limited VEGF bioavailability from the effects of the ECM on the recruitment of osteoclasts and endothelial cells into calcified cartilage; second, galectin 3 is abundant in the growth plates of MMP 9 deficient mice, whereas galectin 3 knockout mice have the opposite phenotype as MMP-9, indicating that MMP 9 cleavage of galectin 3 regulates hypertropic chondrocyte terminal differentiation.[9,28,29]

In the study, Li Y et al. (2021) describe their results, which indicate that MMPs play additional roles in angiogenesis and innervation in addition to influencing ECM remodeling. MMP 9 controls endothelial cell invasion. MMP 9 controls VEGF expression, and MMP9-deficient mice develop their long bones with aberrant growth plates and delayed angiogenesis. MMP-9 is involved in the release of growth factors from the extracellular matrix (ECM) and the recruitment of osteoclasts. It also participates in the cleavage of a number of proteins.[30]

2.3. Role of Mmp-13 on osteogenesis during bone regeneration

MMP 13 has a catalytic domain that is comparable to hemopexin, which is responsible for MMP-13's degrading capabilities. Although MMP-13's catalytic domain can destroy collagen, it isn't as effective as hemopexin's catalytic domain. MMP 13 is a critical metalloproteinase in the skeletal system's development and maturation of bones, as MMP-13's destruction of extracellular matrix proteins that were already present has been identified as an essential and significant phase prior to new angiogenesis and mineralization in bone development. MMP 13, which is responsible for osteoclast receptor activation, has been linked to the breakdown of bone resorption. Numerous factors have been described, including osteoclast secreted MMP 9 induction, which will absorb the hydrolyzed collagen from MMP 13 action; protease of galectin 3, a known antagonist of bone resorption present on osteoclasts, which will result in the abdication of its inhibition activity; and adjusting the RANKL/OPG axis, which will result in the abdication of MMP 13, which is implicated in osteoclast differentiation.[31]

The lifespan of MMP-13 knockout mice is normal, and they reproduce normally with no phenotypic defects. These mice's growth plates showed substantial abnormalities, including a hypertrophic chondrocyte zones expand, but chondrocyte proliferation remains normal, and endochondral ossification is delayed, notably at secondary ossification. The mice have more trabecular bone, but their bone spicules are uneven. This causes disruption of ECM remodeling and bone matrix arrangement in cartilage, resulting in a loss in both their long bones' strength and rupture resistance, although the mice's long bone development is otherwise unaffected. In hypertrophic chondrocytes, MMP 13 is a Cbfa1/Runx2 transcription factor that has a subsequent target, as Cbfa1 mutant animals do not MMP 13 is expressed throughout the developing fetus. C-maf deficiency significantly reduces collagen breakdown by MMP 13, resulting in aberrant chondrocyte terminal differentiation and extension of the hypertrophic state. As a result, MMP 13 was linked to the start of bone resorption. Despite Because these mice lack the aggrecan breakdown product, aggrecan degradation is unaffected in the MMP 13 knockouts, showing that additional mechanisms for aggrecan removal exist during cartilage-to-bone transitions. A recent investigation of a mouse strain with an aggrecan proteinase-sensitive interglobular domain found that the aggrecan proteinase-sensitive interglobular domain is resistant to MMPs. Missense mutations in MMP 13 cause spondyloepimetaphyseal dysplasia, a hereditary bone condition characterized by faulty growth and aberrant In childhood, the spine and long bones are sculpted, which cure as a result of adolescence. The late evacuation of chondrocytes from the development plate, despite appropriate differentiation, appears to be the origin of these temporary disease manifestations, according to data from knockout mouse models. More research into the involvement of MMP-13 in experimental arthritis mouse models, which plays a role in bone remodeling, will lead to a better understanding of the pathological process in human bone illnesses.[32–34]

In the study of Damayanti MM and Rachmawati M (2022), they evaluated MMP-13 expression, indicated how adding HA as a scaffold to PRF as a growth factor affects how quickly wounds heal, and finally described their results. MMP-13 has demonstrated that it participates in every stage of wound healing by altering the wound matrix and facilitating cell migration, which is crucial to the remodeling process.[1]

3. Discussion

Tissue remodeling can be both normal and pathological and is aided by the MMP group of proteins. Matrix proteins, growth factors, and cytokines are all processed in this way. MMPs not only work as enzymes, but also for the formation and development of osteoclasts, osteoblasts, and osteocytes which are all affected by bone matrix degradation. MMPs play a role in each stage of wound healing and facilitate cell migration, which is crucial to the remodeling process.[1–3] MMP 2 has the ability to breakdown FGF receptors, collagen, elastin, and IGF-binding proteins, as well as activate MMP 9 and 13. Enhanced levels of MMP 2, retrieved from tissue that filled the gap in the parietal bone, improved during the first weeks, then reduced until 24 weeks, according to the study. MMP 2 and other MMPs were discovered to facilitate collagen cleavage, a key stage in the process of bone production and resorption. MMP 2 has been identified as a viable target for capillary calcification therapy in several investigations. MMP 2 may be involved in the alveolar ridge healing

process, according to this research.

The use of MMP-deficient animal models has revealed a relationship between MMPs and bone homeostasis, which is demonstrated by a number of bone defects, including delayed ossification and fracture repair, aberrant bone development, irregularly shaped bones, or decreased resistance to fracture. Seven days following surgery, there was no rise in microvessel density due to MMP inhibition.[35–38] In mice lacking MMP-13, only bone remodeling and endochondral ossification are affected. During the first four months of life, MMP 13 develops. Growth plate expansion causes aberrant skeletal development, with increased trabecular bone mass but uneven bone spicules, and increased hypertrophic chondrocytes that express VEGF, collagen X, and osteopontin. The growth plate's hypertrophic zone, as well as bone mass, recover to normal size after that. In hypertrophic chondrocytes, the fact that Cbfa1 fails to express MMP-13 throughout fetal development indicates that MMP-13 is a downstream target of PTHrP and the transcription factor Cbfa1/Runx2. The absence of c-maf, another transcriptional factor, resulted in a lengthening of the chondrocyte hypertrophic state and a significant reduction in MMP 13, implying that c-maf was involved in the initiation of terminal differentiation. Osteocyte and chondrocyte lacunae creation and osteocytic remodeling need MMP-13 to function properly.[9,38,39]

The key enzymes for ECM remodeling are MMPs, a family of enzymes by finding similar substrates, make it possible to split all ECM components. MMPs have traditionally been associated with only one biological function: ECM breakdown and turnover. Studies in MMP gene knockout animals, as well as the discovery of overlapping functions, dubious roles, unexpected substrates, and tissue-specific expression, depending on the biological process involved, have changed the dogma surrounding MMP function, implying that these enzymes regulate key cell behavior and signaling pathways.[40,41] Bone remodeling is mediated by two intertwined mechanisms: bone resorption and bone creation, which are regulated by osteoclasts and osteoblasts. After a bone lesion, this process begins, resulting in bone formation or repair through bone healing. Metabolic bone diseases, such as osteoporosis, can result from bone resorption that is out of balance and creation. To generate bone function and regenerate new tissue, bone regeneration or repair relies on a series of coordinated processes, including ECM remodeling. Correct ECM remodeling is necessary in all situations, and MMPs appear to be critical. MMPs are involved in multiple stages throughout the repair of crucial bone defects and fractures and are important for the efficacy of bone repair, according to studies of MMP expression and MMP-knockout mouse models.[42,43]

Three separate phases were discovered to describe alveolar bone repair after tooth extraction in a well-established rat model for bone repair evaluation. RECK and gelatinases are present at all phases, but especially in osteoblasts that are forming new bone, connective tissue, and epithelial cells. This may be critical in the development, maturation, and remodeling of new bone, as well as the blood clot being replaced by connective tissue. MMPs have been proposed as biomarkers for the advancement of injury healing and bone regeneration after arthroscopic surgery.[44,45]

Due to significant bone loss, the bone repair system may fail. Scaffolds or biomaterials, which function by encouraging mesenchymal differentiation, resident cell migration, bone growth direction, and new bone formation by cells at the damaged location, have been used as an alternative to support this process in vivo. The implantation of bone repair biomaterials necessitates a coordinated and regulated remodeling of tissue and matrix. MMPs are released by macrophages in interaction with the graft for biomaterial or remodeling surrounding tissue in demineralized or inorganic bone implants. MMP 2 expression was enhanced during the restoration of sintered anorganic bone of critical lesions in rats, according to a recent study. Furthermore, calvarial remodeling occurred faster in the experimental group that used biomaterial within the crucial defect than in the control group in the same study. According to the scientists, increased expression of VEGF leads to bone growth and remodeling, as well as successful healing. The description of MMPs engaged in biomaterial-induced biological responses is important in this context in order to know their stability in the host.[46,47]

The ECM is important for maintaining the tissue's regeneration capability by controlling adult stem cells and their activity. Cleaving and degrading proteases, or reshaping the ECM, can influence the stem cell because it is a dynamic structure. Through modification of the accessibility of growth factors and cytokines bound to the ECM that regulate stem cell activity, MMPs can alter the extracellular setting that determines the bone marrow's myeloid cells. MMP-9 has a major role in this by releasing and mobilizing a kit ligand that is soluble and promotes HSC recruitment and differentiation. Additionally, this protease is implicated in the degradation of the CXCL12 and c-Kit receptors, two important molecules for HSC development. During hematopoietic differentiation, the mobilizing agent granulocyte-colony stimulating factor, which increases the proliferation of neutrophilic granulocytes and their degranulation in the bone marrow, causes ECM remodeling by proteases. Several proteases, including neutrophil MMP 8 and MMP 9, are released when these cells degranulate. In the HSC niche, these enzymes generate a proteolytic environment that encourages the release of cytokines, mobilizing factors, and the disruption of cell matrix connections, all of which promote HSC development. These events demonstrate not only the importance of cytokine and growth factor bioavailability in influencing stem cell function in this physiological condition. MMP-13 is released by bone lining cells to cause the osteoid to break down prior to osteoclast attachment and resorption. The only known MMP to be altered in response to parathyroid hormone-induced resorption signaling is MMP13. MMP-13 expression indicates that it participates in every stage of wound healing by altering the wound matrix and facilitating cell migration, which is crucial to the remodeling process.[1,48–53]

4. Conclusions and future outlook

MMP 2, 9, and 13 play a major protective role in osteogenesis and bone regeneration. MMPs are involved in a variety of cellular processes and are recognized as environmental-responsive triggers in the development of biomaterials. It presents a promising technique to use MMP in bone tissue engineering because the materials have been extensively shown in the literature to be helpful for bone regeneration. Dental implants and the rehabilitation of dentures are two areas that can benefit if the patient has healthy alveolar bones after tooth extraction.

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Declaration of competing interest

None.

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