Matrix GLA protein- its emerging role in periodontal tissue homeostasis: A review

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***Abstract*: Matrix Gla protein [MGP] is an extracellular matrix protein that inhibits the calcification of arteries and cartilage. Nevertheless, MGP is synthesized in many tissues, and it is particularly abundant in embryonic tissues. Matricellular proteins are secreted into the extracellular environment. They are not fundamental structural proteins; instead, they modulate the functions of cells by interacting with cell-surface receptors, proteases, hormones, and other effector molecules as well as with structural matrix proteins such as collagens. MGP is one such protein that inhibits calcification in the body. This review focuses on the role of MGP development and maintenance of dental and periodontal tissues**

***Index Terms*: Matrix Gla-protein, vitamin-k, periodontal ligament, bone morphogenic proteins, matricellular proteins**

I. INTRODUCTION:

Regeneration and healing of diseased tissues in periodontitis and periodontal deformities occur by intracellular and extracellular matrix interactions, with complex components present in the matrix playing a significant role. As a result, maintaining the normal structure and function of tissues requires the integrity of the extracellular matrix. During wound healing, the PDL around teeth provides an excellent mechanism for dynamically encasing the proteins and complex molecules of the extracellular matrix.

A variety of signals from the surrounding microenvironment, including the extracellular matrix, influence the behaviour of individual cells [ECM]. Previously thought to be a static scaffold for cell/tissue organization, the ECM is now recognized as a crucial niche in the regulation of cellular survival, proliferation, and migration. This understanding has put the ECM at the focus of normal physiological processes like development, tissue homeostasis, and tissue remodelling.

In contrast to the structural functions of "traditional" ECM proteins such as collagen and fibronectin, the dynamic nature of ECM signaling is governed by a secreted group of non-structural matricellular proteins [MCPs]. [1]

VKDPs [vitamin K–dependent proteins] are classified into two categories: hepatic VKDPs and extrahepatic VKDPs.21 Hepatic VKDPs are primarily engaged in blood coagulation. Because their Gla residues have a high affinity for calcium, extrahepatic VKDPs serve a variety of activities.. [1]

Currently, studies have discovered 17 different varieties of VKDPs in humans. Seven of them rely on vitamin K1 to perform their functions in the liver [coagulation factor II, VII, IX, X, and anticoagulant proteins C, S, Z]. Six of them were altered by vitamin K following transcription and were implicated in a variety of physiological and pathological processes in extrahepatic tissues. They are as follows: Osteocalcin, Matrix Gla Protein, Gas6, Gla Rich Protein, periostin, and periostin-like factors. [2]

Members of the Gla protein family have vitamin K-dependent g-carboxyglutamic acid residues with a high affinity for calcium ions, which play crucial roles in coagulation and bone homeostasis.

MGP belongs to a family of vitamin K-dependent proteins, also known as Gla proteins [g-carboxyglutamate], which plays an important role in limiting calcification in the body. MGP is a 14 kDa secretory protein expressed in a variety of tissues, including heart, lung, kidney, skin, and the arterial vessel wall, where it is synthesized by chondrocytes, vascular smooth muscle cells [VSMCs], endothelial cells [ECs], and fibroblasts[3]

The present review focuses on the role of MGP in dental and periodontal tissues.

II. MATRIX GLA PROTEIN:

Matrix Gla protein [MGP] is a 14 kDa secreted protein that belongs to a family of -carboxylated glutamic acid [Gla]-containing proteins and was first discovered in the demineralized bovine bone matrix.[4]

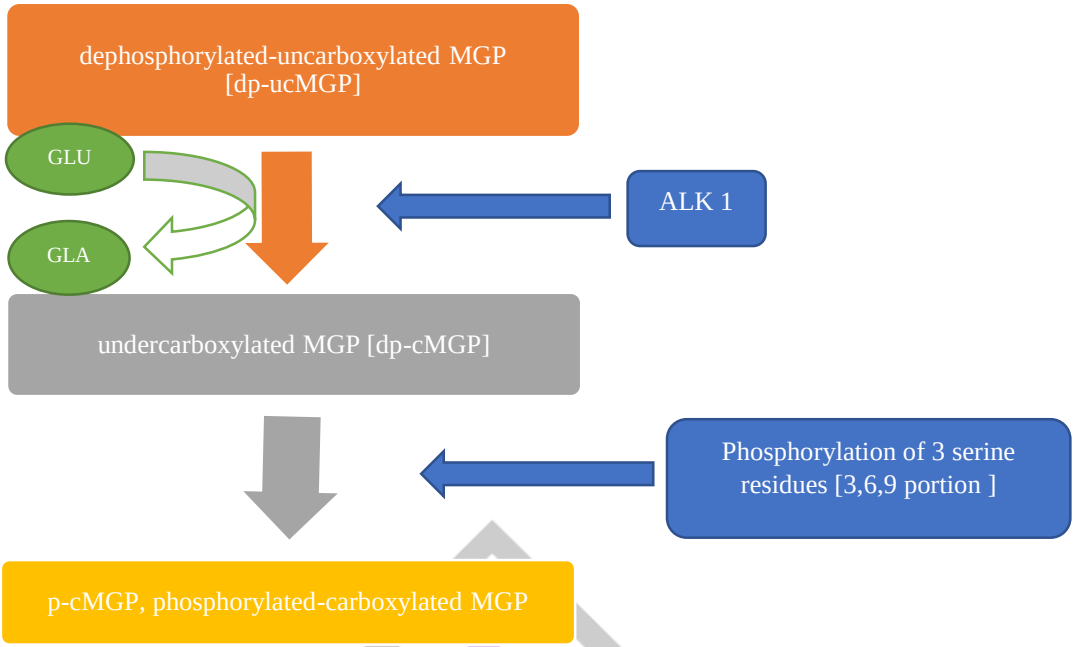
It is produced in many tissues, including the heart, lung, kidney, skin, and the arterial vessel wall, where it is secreted by chondrocytes, vascular smooth muscle cells [VSMCs], endothelial cells [ECs], and fibroblasts. [5].

Human MGP contains five Gla residues that are -carboxylated [four in mice]. Although there is strong evidence that MGP may have a role in bone metabolism and osteogenesis regulation, the precise mechanism of action remains unknown. [6,7]

The maturation of MGP involves two modification steps:

Dephosphorylated uncarboxylated MGP [dp ucMGP] is initially transformed into undercarboxylated MGP [dp cMGP]. This mechanism converts five glutamate residues into -carboxylated glutamate residues known as Gla residues, which serve as binding sites for apoptotic bodies, calcium ions, and matrix vesicles.

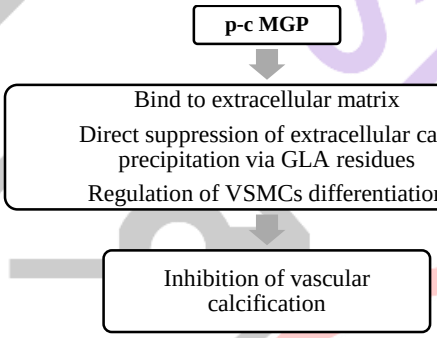
The second phase is modification phase. in this phase, dp-cMGP is transformed into phosphorylated carboxylated MGP [p cMGP]. Three serine residues are involved in this mechanism [9]. Although the function of serine phosphorylation is unknown, recent data suggest that it regulates protein secretion into the extracellular environment to some extent. This is supported by the discovery that phosphorylated MGP exits VSMCs via the secretory pathway, whereas non-phosphorylated MGP is only partially secreted and appears in the cytosol.



Maturation of mgp

[*ALK 1- activin receptor-like kinase 1; Glu-glutamic acid; Gla- γ-carboxylated glutamic acid]*

III. THE CELLULAR AND MOLECULAR MECHANISMS BY WHICH MGP PREVENTS ECTOPIC CALCIUM DEPOSITION:[3]



IV. FUNCTIONS OF MGP:

- MGP suppresses vascular calcification by acting as an inhibitor of calcium deposition and crystallisation in the blood vessel wall.
- MGP plays a vital role in tissue calcium homeostasis.
- Play a vital role in bone organisation

V. EFFECT ON DEVELOPMENT:

Keutel syndrome, an autosomal recessive genetic condition characterised by cartilage calcification, multiple peripheral pulmonary stenoses, and severe midfacial hypoplasia with class III malocclusion, as well as short stature and brachytelephalangia has been shown to be associated MGP gene mutations in humans [8]

Hearing loss, brain and tracheal calcifications, and aortic aneurysms are also symptoms of this syndrome. Subsequent research on Keutel syndrome patients revealed persistent skin rashes, thyroid papillary microcarcinoma, asthma, extensive bullous pulmonary emphysema, severe systemic arterial hypertension, and short-term memory loss. [9]

The Mgp knockout mouse mimics the characteristics of Keutel syndrome, including midface hypoplasia. [10].

Murshed and colleagues discovered that overexpression of Mgp in bone results in minimal impairment of bone mineralization utilizing conditional knock-in and knockout mouse models. I On the contrary, increasing MGP serum levels had no effect on ECM mineralization, suggesting that ECM mineralization is controlled locally. [11]

However, researchers still do not understand exactly how MGP controls craniofacial development despite the craniofacial phenotype of Keutel syndrome patients and analogous mouse models. [7,10]

VI. EFFECT ON TOOTH MINERALISATION:

The evidence of the mineralization process begins at specific places within the ECM, manifesting as tiny mineralization foci [containing multiple apatitic crystallites] amid the collagen fibrils in the diverse bone and tooth ECMs. This suggests that even at high levels of inhibitory MGP, mineralization does not extend beyond these small foci once triggered. [12]

VII. EFFECT ON PERIODONTIUM:

EFFECT ON CEMENTUM:

Cell populations associated with PDLs [PDLCs] are heterogeneous cells capable of differentiating into adipocytes, neurons, osteoblasts, or cementoblasts and possessing mineralized nodules and osteoblastic markers in vitro. [13]

MGP mRNA signal was detected in rat acellular cementum, polygonal PDL cells at the interface between acellular cementum and uncalcified cellular cementum in the periodontium, implying that MGP expression in cells proximal to the cementum may be crucial in preventing hypercalcification.[14].

EFFECT ON PERIODONTAL LIGAMENT:

Physiologically PDL remains non-mineralized space although located between two hard tissues. Molecules that negatively regulate mineralization are thought to play key roles in maintaining the homeostasis of the PDL trapped between the cementum and the alveolar bone. It has been reported that MGP, asporin, msh homeobox 2 [Msx2] and twist-related protein 1 [Twist1] act as inhibitors of the mineralization of the Pdl. But the exact mechanism of MGP in maintaining the PDL space is still unclear. [15] [16] [17] [18,19]

MGP GENE, CHRONIC PERIODONTITIS AND TOOTH LOSS:

Researchers have found a link between CA-repeat variants in the MGP gene and the number of natural teeth left. Based on their findings, they speculate that variation/mutation in MGP gene may affect susceptibility to natural tooth loss, chronic periodontitis and bone metabolism.. Polymorphic microsatellites may be useful markers to track tooth loss/chronic periodontitis in high-risk populations when early therapeutic intervention is needed to prevent tooth loss/chronic periodontitis. [20]

EFFECT ON ALVEOLAR BONE:

It has been observed that MGP and BMP-2 are both expressed at both the mRNA and protein levels in hPDLCs. In hPDLCs, MGP and Bone Morphogenic Protein [BMP] -2 colocalize at the protein level and also show similar expression patterns. It can be hypothesized that MGP might contribute to osteogenic differentiation of hPDLCs via BMP-2. [21] Matrix Gla protein [MGP] modulates BMP effects by interacting with them and inhibiting their binding to their signalling receptors..[22] Understanding the underlying mechanisms of osteogenic differentiation of hPDLCs could provide new insights.

MGP [Matrix Gla Protein] is a potent inhibitor of mineralization [12]. When compared to dental pulp MSCs, periodontal Mesenchymal Stem Cells [MSCs] showed higher levels of Osteonectin [SPARC] and MGP [Matrix Gla Protein]. Periodontal fibroblasts produce more SPARC and MGP, as well as Osteocalcin [BGLAP] and Bone Sialophosphoprotein [BSP].[23]

The expression of MGP during tooth development was found. This is attributed to the odontoblastic and ameloblastic processes [24]

In vitro studies have shown that MGP acts as a distinct positive regulator of osteoblast proliferation, differentiation, and osteogenesis mainly associated with the Wnt/-catenin signalling pathway. Zhang J et al., [2019] reported an overexpression of MGP increased osteoblast proliferation, differentiation, and mineralization. Overexpression of MGP increased osteoblast proliferation, differentiation, and mineralization was in accordance with this sudy. They proposed that MGP might induce skeletal anabolic activities via a Wnt/-catenin signaling-related mechanism. MGP increased Wnt3a and -catenin expression, promoting cell proliferation, differentiation, and mineralization, and so osteogenesis.. [6]

VIII. EFFECT ON DENTAL PULP:

A microbial insult to pulpal tissue resulted in elevated MGP levels, possibly suggesting that the protein participates in the defence and/or repair process of the tissue. [25]

Despite the fact that these studies have shown the presence of MGP in the pulp, periodontal ligament, and alveolar bone, more evidence is needed to determine its significance and its role in the development, maintenance, and repair of human dental tissues.

IX. OTHER FUNCTIONS OF MGP:

In humans, MGP can inhibit the bone morphogenetic proteins [BMPs] 2 and 4, which have an antagonistic effect on vascular calcification. MGP can also influence the TGF* superfamily, including activation of TGF*1 receptors and inhibition of BMPs-2 and 4. [26,27]

Recent studies showed that MGP was incorporated into crosslinked multimers of fibronectin, which increased the attachment of cancer cells to fibronectin [28]

X. CONCLUSION:

We summarized the evidence gathered from in vitro, in vivo, and clinical studies here discussed the role that MGP in the development and maintenance of dental and periodontal tissues.

XI. FUTURE PERSPECTIVES:

It is possible to shed light on this matter through further genetic and functional studies of the entire MGP gene region and various clinical studies for the detection on periodontal tissues.

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