REVIEW ARTICLE

THE ROLE OF BONE MORPHOGENETIC PROTEIN ON BONE TISSUE REPAIR

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SUMMARY

This literature review study addresses the progresses of the use of the bone morphogenetic protein (BMP) for repairing the bone tissue and its mechanisms of action in the injured tissue. The BMPs are pleiotropic molecules that are involved in the chemotaxis, mitosis and differentiation of mesenchymal cells in the bone tissue.

Keywords: *bone regeneration; growth factors; bone morphogenetic protein*

INTRODUCTION

The objective of this study is to review literature addressing the advancements in the use of bone morphogenetic protein (BMP) on bone tissue repair and its mechanisms of action in the injured tissue.

BMPs are glycoproteins accounting for the recruitment of osteoprogenitor cells to sites of bone formation[1].

For Bowers and Reddi[2] BMPs are proteins found in high amounts in bone tissues and are considered as responsible for inductive and regenerative abilities of demineralized bone grafts used in periodontal therapy.

DEVELOPMENT

The first inquiries about processes determining bone neoformation, in sites deprived of bone tissue, were based on Urist's finding. For him, a central factor could be responsible for that effect. That factor was reported as a substance inducing bone formation, present at bone matrix. Inductor cells and inducted cells were provided by host and those inductor cells would be descendants of histiocytes and perivascular conjunctive tissue cells. The term osteoinduction was designated to an essential principle of bone regeneration triggered by the action of bone morphogenetic proteins[3,4].

From an aminoacids sequence with a highly purified extract, Wozney et al.[5] obtained DNA clones containing each protein's code. At total, they obtained 8 proteins - 7 of them are named as BMPs and present similar structural characteristics. By purifying the BMP present in bovine bone, details were revealed about the identification and molecular cloning of factors with BMP activity. By isolating many polypeptides, the authors determined the sequence of many aminoacids and synthesized an oligonucleotide probe. Thus, 2-9 BMPs (BM-2 to BMP-9) cloning was possible, which are members of the family of the transformer growth factor beta (TGF-€). The members of this superfamily may exert an inhibiting or stimulating effect on cells, depending on the stage of cellular differentiation in which they come to act[6].

According to Wozney[7], the osteoinductive activity of bone morphogenetic proteins added to its presence in bone tissue suggest that they are important regulators in bone repair process and may be involved in such tissues' maintenance. They are part of the family of the transformer growth factor beta (TGF-€) and includes a subfamily based in its aminoacid sequences, and reported that the BMPs may present themselves in two forms: a) bone morphogenetic proteins derived from the bone; b) recombining human bone morphogenetic proteins (rhBMP).

Kawai and Urist[8] analyzed proteins extracted from bovine dental tissues regarding osteoinductive activity and suggested that those proteins were comparable to bovine bone morphogenetic proteins.

Wang et al.[9] and Wozney et al.[10], stated that the pure recombining human bone morphogenetic protein - two (rhBMP-2), when implanted in high doses, can induce bone formation.

The BMP effect on repairing dentine formation was examined by Nakashima when he implanted such mentioned bone morphogenetic proteins over dental pulps amputated from animals. The author verified that those proteins stimulated the mitosis of mesenchymal cells and induced the differentiation of osteodentinocytes. The resulting osteodentine may play a role on osteoblasts differentiation[11].

Lyons et al.[12] suggested that the BMP-2 plays multiple functions in the morphogenesis and pattern of vertebrate embryos. By using in situ hybridization, they showed that BMP-2's RNA manifest itself in a number of embryonary tissues, such as: epithelial, mesenchymal, and from skeletal system. Thus, BMP-2's RNA was found in organs, such as: heart, pilary follicles, dental button, craniofacial mesenchyma, and other sites.

Bowers et al.[13] compared the use of osteogenia (BMP-3) associated to dry and frozen demineralized graft (DFDBA) with bone matrix (DFDBA), with bovine tendon alone and with bovine tendon combined with osteogenin in the increase of periodontal regenerative processes in human infrabone defects. They concluded that osteogenin combined with DFDBA significantly increases the regeneration of the display of a new insertion and tissue components, such as: cement, alveolar bone, and periodontal ligament.

For Toriumi and Robertson[14],one of the most important factors that can determine the success or the failure of inductor bone grafts in reconstructive surgeries is the carrier material efficiency. The ideal carrier should increase the exposure of host's tissues to the growth substance and assure a uniform distribution, not allowing the implanted material to exceed site boundaries. The carrier should be absorbed as bone formation occurs. Additionally, it must be safe, biodegradable, and formulated to allow appropriate sizes and shapes to the graft.

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Saller and Kolb[15], after a review of relevant success of bone morphogenetic proteins in buccomaxillofacial and orthopaedic surgeries, demonstrated the efficiency of the purificate, that is, of the BMPs concentrate in bone induction in areas with apparently lost implants.

Graves and Cochran[16] described the family of the five growth factors having potential to induce periodontal regeneration when in contact with osteoblasts and periodontal ligament cells in vitro and in vivo. In this case, they included the platelet-derived growth factor (PDGF), the fibroblasts growth factor (FGF), the transforming growth factor beta (TGF-€), the insulin-like growth factor (IGF) and the bone morphogenetic proteins. The authors also reported the existence of the following BMPs: BMP-4, BMP-5, BMP-6, and BMP-7. From BMP-2 to BMP-7, the presence of molecular structures of members of the transforming growth factor beta (TGF-€) family occurs.

Ripamonti and Reddi[17] stated that, additionally to their functions on post-fetal osteogenesis, the BMPs may play multiple roles in embryogenic and organogenic development, including skeletogenesis, craniofacial and dental tissues development.

Hughes et al.[18] demonstrated through in vitro tests with rats' osteoprogenitor cells that the BMP-6, BMP-4 and BMP-2 can stimulate osteoblasts differentiation. They suggested that an early osteoprogenitor cell is an important cell for BMPs action during bone induction.

Nevins et al.[19] analyzed the efficacy, safety, and technical ease in inducing bone formation in dogs' bone defects, and maxillary sinus' membrane lifting with the use of an absorbable collagen sponge impregnated with rhBMP-2. Results suggested substantial bone formation and, in 68% of treated bone defects, a new bone was formed.

Lee[20] reviewed the biological basis of bone morphogenetic proteins and their implications on oral reconstruction. He reported that the materials used as bone grafts could offer osteoconduction in the presence of a physical or support matrix, thereby occurring a new bone deposing. He defined osteoinduction as the act or process of stimulating osteogenesis, thus the osteoblast would help the bone matrix.

Ripamonti and Duneas[21] conducted a review on tissue morphogenesis and on the regeneration promoted by bone morphogenetic proteins. The authors postulated that the post-birth tissue regeneration mimics events occurring during the usual course of development and tissue regeneration, similarly regulated by a distinct family of morphogenesis. Thus, we would have all BMPs acting on the development of tissues and organs, some of them with a higher number of specific proteins, such as in kidney (BMP-3 and BMP-7), in central and peripheral nervous system, liver (BMP-9), lungs (BMP-3 and BMP-4), heart, teeth, gonads, skin and liver (BMP-9).

Lynch et al.[22,23] said that an occurrence of slow release of rhBMP-2, with fast systemic washout, associated to other pharmacokinetic studies, such as absorption, distribution, metabolism and excretion confirmed he absence of toxic effects for rhBMP-2. BMPs ability to induce bone formation through endochondral or intramembranous process is not clear yet. They suggested that a number of factors involved, such as applied BMP dose, implantation site, responses of cells at implant site, vascularization and nature of the carrier material would be the responsible factors for determining the kind of ossification.

Ripamonti and Tasker[24], stated that tissue regeneration engineering has been rapidly increasing in the field of cell and molecular biology. The great recent processes in elucidating molecular biology of the BMPs and their receptors helped on the promotion and understanding of a wide field for future use of BMPs.

Minamide et al.[25], evaluated two carry systems for BMPs. The first was a porous structure called true bone ceramics and the other was the type-I collagen. Results showed that the first presented its porous structure filled with bone and was more efficient than the type-I collagen, which promoted a fast growth with strong bone formation.

CONCLUSION

BMPs present many possibilities of application in odontology, orthopaedics and in other knowledge areas involving cell differentiation due to the fact that they represent a distinct group of inducing factors, able to stimulate source-mesenchymal cells differentiation in specialized cells, inducing bone neoformation and bone tissue repair.

The indications for BMPs use are mainly associated to great bone losses, resulting from development abnormalities, as well as bone defects caused by some trauma in bone structures, infectious and inflammatory diseases.

A definitive evaluation on the clinical use of BMPs will only be possible after all those different factors influencing tissue repair are elucidated, along with the development of an appropriate carrier system, which should assure a more adequate treatment protocol.

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