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Review

Strategies for delivering bone morphogenetic protein for bone healing

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ABSTRACT

Bone morphogenetic proteins (BMPs) are the most significant growth factors that belong to the Transforming Growth Factor Beta (TGF-β) super-family. Though more than twenty members of this family have been identified so far in humans, Food and Drug Administration (FDA) approved two growth factors: BMP-2 and BMP-7 for treatments of spinal fusion and long-bone fractures with collagen carriers. Currently BMPs are clinically used in spinal fusion, oral and maxillofacial surgery and also in the repair of long bone defects. The efficiency of BMPs depends a lot on the selection of suitable carriers. At present, different types of carrier materials are used: natural and synthetic polymers, calcium phosphate and ceramic-polymer composite materials. Number of research articles has been published on the minute intricacies of the loading process and release kinetics of BMPs. Despite the significant evidence of its potential for bone healing demonstrated in animal models, future clinical investigations are needed to define dose, scaffold and route of administration. The efficacy and application of BMPs in various levels with a proper carrier and dose is yet to be established. The present article collates various aspects of success and limitation and identifies the prospects and challenges associated with the use of BMPs in orthopaedic surgery.

Contents

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1. Introduction

Bone shows the inherent capacity for regeneration as part of the repair process in response to injury and at the time of skeletal development or continuous remodeling throughout adult life. Bone regeneration is comprised of a well-organized series of biological process of bone induction and conduction, involving a number of cell types and intracellular and extracellular molecular signaling pathways, through a definite temporal and spatial sequence, in an effort for optimization of skeletal repair and restoration of skeletal function [1]. Bone formation depends on the cooperation of different aspects, such as: (i) specific cell types like mesenchymal stem cells (MSCs) and osteoclasts (ii) the scaffold (calcium hydroxyapatite, extracellular matrix molecules, etc.); (iii) expression of soluble molecules (cytokines, growth factors, hormones, ions, vitamins) and (iv) various mechanical stimuli [2,3].

The signaling molecules can be categorized into three groups: (i) the pro-inflammatory cytokines, (ii) the TGF-β superfamily and other growth factors, and (iii) the angiogenic factors [4,5]. Interleukin-1 (IL-1), Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) have an imperative role in initiating the repair cascade. Cytokines also regulate the endochondral bone formation and remodeling. TNF-α promotes the recruitment of MSCs, induces apoptosis of hypertrophic chondrocytes at the time of endochondral ossification and offers osteoclastic function [6]. The TGF super-family includes BMPs 1–8, GDF-1, 5, 8, 10, TGF-β1, -β2, -β3 promote the various stages of intramembranous and endochondral bone ossification during fracture healing.

2. Bone morphogenetic protein – overview

BMPs are the most vital growth factors in bone formation and healing [6]. The osteoinductive capacity of demineralized bone matrix was discovered by Urist in 1965 [7]. Several types of BMP have been isolated through molecular cloning and recombinant BMP have been synthesized. BMPs are produced during fracture repair from mesenchymal cells, osteoblasts, and chondrocytes. Different BMPs work independently or in combination with each other and other members of the TGF super-family, to trigger a cascade of events that endorse the development of bone and cartilage [8].

BMP is a dimeric molecule consisting of two polypeptide chains held together by a single disulphide bond [9]. The alignment of amino acid sequences shows that a significant amino acid sequence identity exists among all the BMPs in the carboxy-terminal region of the protein [10]. Osteogenic protein-1 (OP-1) and BMP-2 crystal holds "hand shaped structure" consisting of two fingers of anti parallel beta strand and an alpha helical region at the heel of the palm [9]. Depending on the similarity of the primary amino acid sequences, BMPs are typically classified into four groups BMP2/4, BMP5/6/7/8a/8b, BMP9/10, and BMP12/13/14 [11].

These proteins have been segregated from different mammal bone such as mouse, rats, bovine, monkey, man and also from clonal osteogenic sarcoma lines. Extracted purified BMP showed satisfactory bone induction activity but it takes longer producing time, high cost and very less quantity. It was revealed that a microgram of BMP was present in a kilogram of bone. Wozney et al. [12] cloned and acquired the cDNA of BMP and expressed in eukaryocyte and prokaryocyte but the cost was too high and the quantity was not also high. BMP was isolated from osteosarcoma cells and gave an idea for vast extraction through long time in vitro culture [13]. A substantial amount of BMP was extracted from mouse Dunn osteosarcoma tissue using 4 M guanidine hydrochloride solution [14,15]. Mizutani et al. [16] extracted BMP from bovine demineralized dentin matrix (DDM) and 3 mg of purified d-BMP was obtained from 100 g of DDM.

BMPs induces the formation of bone and cartilage in vivo. Various types of cells, including osteoblasts and chondroblasts, participate in the process of bone morphogenesis, and they are functionally regulated by BMPs [17]. They have multimodal action (i.e., chemotactic, metabolic, mitogenic, apoptotic effects, morphogenic, and their combination) depending on the concentration, exposure time and target cells [18–20].

3. Clinical application of BMPs

Till date number of clinical applications of BMPs are reported. The major application domains include spinal fusion, long bone fracture repair and oral and maxillofacial surgery. A brief review of each domain follows.

3.1. Spinal fusion

Spinal fusion using iliac crest bone graft may become a historical practice due to modern advances in bone morphogenetic proteins. Presently two specific BMPs (BMP-2 and BMP-7) with different carriers is being used to accomplish successful spinal fusion in pre-clinical and clinical studies [21]. Application of BMPs in spinal fusion and other fracture treatment has been summarized in Table 1. Kodera et al. [22] studied the effect of rhBMP-2 (recombinant human BMP-2) and ZA (Zoledronic acid) administered as a single systemic dose for spinal fusion and examined its feasibility for clinical application by using a rat spinal fusion model. This combination was efficient for increasing callus volume and reducing osteoclastic stimulation in spinal fusion although proper dose and an increase in fusion rate is unclear. Pelletier et al. [23] evaluated the lumbar spinal fusion using β-TCP (tri-calcium phosphate) granules and variable *Escherichia coli*-derived rhBMP-2 dose in sheep model. Their results confirmed improvement of new bone formation and fusion rate by using E-BMP-2 dose, while β-TCP alone was largely resorbed and did not attain fusion in the model at 12 weeks (Fig. 1).

Autologous growth factor has been used on 39 patients having lumber spinal fusion [24] with no impending pseudo-arthroses on radiographic assessment at last follow-up visit. Solid fusion was confirmed in three patients having routine hardware removal and in two patients having surgery at an adjacent level. The effect of Autologous Growth Factors (AGF) was tested on lumbar inter body fusion through specific attention paid to find out clinical and radiographic outcomes [25]. In another study, a high-fusion rate was achieved with BMP-2 (low dose 1.4 mg) and local bone graft for minimally invasive lumbar inter-body fusion [26].

Till date, the uses of BMPs have been demonstrated clinically in only one level fusion. Spinal fusion often requires multiple levels especially in cases where deformity-correction surgery is required. The efficacy and use of BMPs in multiple levels with an appropriate carrier and dose has still not been established. Comprehensive understanding in this needed domain has been yet to develop. The major challenges of the future are to further optimize the dose and the carrier material for the specific fusion application, i.e. anteriorly, posteriorly, for repair of pseudarthrosis, multi level surgeries and instrumented cases.

3.2. Long bone fracture

BMPs are reported to play a pertinent role in the long bone fracture healing. They aid the repair of critical-sized segmental bone defects in animals by stimulating the migration of mesenchymal stem cells from periosteum, muscle, endosteum, and bone marrow into the defect via proliferation and differentiation of the mesenchymal stem cells, and by the formation of bone through endochondral ossification [45].

Various studies have been carried out to explore the effect of BMPs on healing of bone - defects. The effect of BMP-7 on allograft integration in a long-bone critical-size defect sheep model has been studied with faster callus formation and bone remodeling [46]. Azad et al. [47] evaluated the effect of BMP-2 in a diabetic rat segmental defect model and found improvement of new bone formation, higher mechanical stability and rapid consolidation than control. The repair of long intercalated rib