Journal of Orthopaedic Translation (2016) 4, 28—34

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://ees.elsevier.com/jot

REVIEW ARTICLE

Bone morphogenetic protein-7: Review of signalling and efficacy in fracture healing

Steven Cecchi [a,*], Simon J Bennet [a], Manit Arora [a,b,c]

[a] *Faculty of Medicine, University of Queensland, Brisbane, Queensland, Australia*
[b] *St George & Sutherland Clinical School, University of New South Wales, Kogarah, New South Wales, Australia*
[c] *Faculty of Medicine, Bond University, Robina, Queensland, Australia*

Received 18 April 2015; received in revised form 8 July 2015; accepted 3 August 2015
Available online 28 August 2015

KEYWORDS
autograft;
BMP-7;
fracture healing;
nonunion;
osteogenesis

Summary Bone morphogenetic proteins (BMPs) are a group of signalling molecules that belong to the transforming growth factor-β superfamily of proteins. Initially identified for their ability to induce bone formation, recent advances in the understanding of cellular and molecular mechanisms regarding BMPs have led to the use of the growth factor to accelerate bone healing. Recent clinical trials have demonstrated that BMPs, BMP-7 in particular, may present an alternative line of treatment other than the gold standard, autogenous bone grafting, in the treatment of fracture nonunion. We performed a literature search in September 2014 of PubMed and Embase using search terms, including "bone morphogenetic proteins", "BMP-7", "non-union", "fracture healing" and "cost-effectiveness", reviewing the efficacy, safety, and cost of treatment of nonunions with BMP-7. The authors further canvassed the reference lists of selected articles and used online search tools, such as Google Scholar. BMP-7 uses both the canonical and noncanonical signalling pathways. The treatment of fracture nonunion with recombinant human BMP-7 (rhBMP-7) has a comparable efficacy with that of autogenous bone grafting with an average union rate of 87% compared with 93% for bone grafting. Furthermore, fewer complications have been described with the use of rhBMP-7 compared with traditional bone grafting. We describe the signalling pathways that BMP-7 uses to exert its effect on bone. In nonunions, rhBMP-7 has been shown to have a similar efficacy to bone grafting with fewer complications.

* Corresponding author. Faculty of Medicine, University of Queensland, 6 Seventh Avenue, Windsor, 4030, Brisbane, Queensland, Australia.
E-mail address: steven.cecchi@uqconnect.edu.au (S. Cecchi).

http://dx.doi.org/10.1016/j.jot.2015.08.001

Introduction

In 1965, Urist [1] demonstrated that the demineralised, lyophilised segments of a bone were capable of a new bone formation when implanted into ectopic sites in rabbits. Subsequent research in the 1980s led to the dissociation of the bone-inducing component from the demineralised bone matrix into a soluble component using acid and chaotropic agents [2]. Following a biochemical analysis of the extract, proteins were cloned and tested for *in vivo* activity. An analysis of these clones indicated that the bone-inductive extract consisted of a highly conserved family of related proteins, named bone morphogenetic proteins (BMPs) [3]. This family consists of dimeric molecules belonging to the transforming growth factor-β (TGF-β) superfamily, containing a highly conserved seven-cysteine TGF-β domain in their C-termini [4]. To date, approximately 20 BMP family members have been identified and characterised [5] (Table 1).

Further evidence that BMPs were responsible for the bone-inductive activity in bone matrix was found in the recombinant expression of each of these proteins. By the use of molecular-biology techniques and sequence information from the bovine molecular clones, the human homologues of each BMP coding sequence were obtained. Mammalian cells were engineered to express the protein by inserting a vector encoding human BMP into the mammalian cell host of choice, resulting in the production of a single BMP molecule on amplification [6]. Early studies utilising this method focused on the function of BMP-7 [6]. Researchers were able to demonstrate that implantation of recombinant human BMP-7 (rhBMP-7) was capable of inducing a new bone formation. Numerous subsequent studies have proven the potency of rhBMP-7 using critical-size long-bone defects. These defects are defined by not being able to heal without therapeutic intervention and the application of exogenous stimuli. The implantation of BMP-7 into surgically created critical-size diaphyseal segmental defects led to the regeneration of a new bone that was fully functional both biologically and biomechanically [7,8]. The therapeutic potential of BMP-7 has been widely studied in both animal studies and human clinical trials [9,10]. Given the potential of BMPs in orthopaedic applications, this has resulted in the commercialisation of rhBMP-7.

Due to the supportive preclinical and clinical data, and approval from the Food and Drug Administration, rhBMP-7 (also known as osteogenic protein-1) is now commercially available. BMP-7 is now widely used in a variety of complex orthopaedic conditions either as an adjunct or as an alternative. It is particularly useful in the nonunion of bone as an alternative to conventional autogenous bone grafting (ABG), where the use of ABG alone is not feasible and/or other alternative treatments have failed. Recent studies have shown the efficacy of rhBMP-7 in inducing bone formation in nonunions to be equivalent to ABG. However, the avoidance of considerable issues, including donor-site morbidity, volume constraints, and infection commonly associated with ABG, has made rhBMP-7 an attractive alternative in the stimulation of bone formation [10,11]. The aim of this review is to discuss recent advances in the molecular mechanism of BMP-7, as well as clinical studies regarding the efficacy of rhBMP-7, in treating fracture nonunion.

Table 1 Bone morphogenetic proteins with musculoskeletal function (modified from (5)).

Identification	Description
BMP-2	Bone and cartilage morphogenesis, osteoinduction, osteoblast differentiation, apoptosis
BMP-3	Negative regulator of bone morphogenesis
BMP-3b	Negative regulator of bone morphogenesis
BMP-4	Cartilage, teeth and bone morphogenesis
BMP-5	Limb development, cartilage and bone morphogenesis
BMP-6	Osteoblast differentiation, chondrogenesis
BMP-7	Cartilage and bone morphogenesis
BMP-8	Bone and cartilage morphogenesis
BMP-9	Bone morphogenesis
BMP-11	Axial-skeleton patterning
BMP-12	Ligament and tendon development
BMP-13	Cartilage development
BMP-14	Chondrogenesis, angiogenesis

BMP = bone morphogenetic protein.

Methods

A literature search was performed (September 2014) of PubMed and Embase using various combinations of the keyword terms "bone morphogenetic protein", "BMP", "BMP-7", "non-union", "cost-effectiveness" and "signalling", and their associated synonyms. The inclusion criteria were papers written in English, peer-reviewed journals, randomised controlled trials, and prospective and retrospective case series. The exclusion criteria were abstracts, case reports, and reviews. For the "signalling" and "complications" sections, reviews were included. The authors further searched the reference lists of selected articles and online search engines, such as Google Scholar.

BMP signalling

The BMP family belongs to the TGF-β superfamily of growth factors, which are involved in vast cellular processes of fundamental importance. For example, TGF-β has been demonstrated to be central to embryogenesis in mammals, controlling the formation of neural tube, limbs, cartilage, and bone [12,13]. BMPs comprise a large group of phylogenetically conserved growth factors of which 20 members have been identified. In bone, BMPs are produced by osteoprogenitor cells, osteoblasts, chondrocytes, and platelets [14]. BMPs are potent osteoblast-differentiation factors, inducing the differentiation of multipotent mesenchymal cells into both osteochondrogenic lineage cells and osteoblast precursor cells [15,16]. The molecular basis of their action has been the subject of intensive research in recent years, leading to a growing understanding of their fundamental action at a cellular level. Initially, all BMPs are synthesised as precursor proteins with an N-terminal signal peptide, a prodomain for folding and secretion, and a C-terminal mature peptide. Precursors are