



Review Article

Bone morphogenetic protein-induced heterotopic bone formation: What have we learned from the history of a half century?



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Summary Bone morphogenetic protein (BMP) was originally discovered by Marshall Urist a half century ago following the observation of a unique activity that induced heterotopic bone formation in skeletal muscle tissue. The molecular mechanisms underlying the induction of heterotopic bone formation in skeletal muscle by BMPs were elucidated through the purification and molecular cloning of BMPs and identification of their functional receptors and downstream effectors, as well as from genetic disorders related to BMP activity. BMPs are important regulators of not only skeletal development and regeneration but also the homeostasis of normal skeletal muscle mass. There is still much to learn about the physiology and pathology at the interface of BMPs and skeletal muscle.

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1. Introduction

Today we know that bone morphogenetic proteins (BMPs) are multifunctional growth factors that control cell proliferation, differentiation and death in various tissues of vertebrates and invertebrates [1,2]. The original biological activity of BMP was reported by Marshall Urist in 1965 (Fig. 1) [3]. He prepared a demineralized bone matrix from various vertebrates, including the mouse, rat, rabbit, calf and human, by treatment with hydrochloric acid [3]. The demineralized bone matrix was then implanted into the skeletal muscle tissue of other host vertebrates, including the mouse, rat, Guinea pig, rabbit, dog and human. Urist [3] found that “living” bone tissue that included bone marrow was induced in the “dead” bone matrix within several weeks. The bone-inducing activity observed in the demineralized bone matrix was found not only in skeletal muscle but also in bone defects [3]. His findings suggest that the bone matrix contains unknown bone-inducing activity and that skeletal muscle tissues contain one or more responding cells able to differentiate into bone-forming cells. A similar bone-inducing activity was also found in demineralized teeth [4].

2. BMP was discovered via bone inducing activity

2.1. Extraction and bioassay of BMP

The bone-inducing activity in the demineralized bone matrix was resistant to collagenase but sensitive to trypsin, suggesting that the bioactive molecule is a non-collagenous protein; it was therefore named “bone morphogenetic protein” [5,6]. Moreover, new bone formation was induced outside diffusion chambers containing demineralized bone powders, suggesting that the bone-inducing activity diffuses through the membrane [7]. Extraction of the bioactive molecules with bone-inducing activity using protein denaturing reagents, such as 8M urea or 4M guanidine hydrochloride, attenuated the activity of the bone matrix residues as well as that of the dentins [8,9]. However, reconstituting the extracts and the residue restored the activity, and activity was found in fractions of the extracts with molecular weights below 50 k [8].

The biological activity of BMP was quantified using several in vivo and in vitro bioassay systems. The alkaline phosphatase (ALP) activity, Ca^{45} incorporation and Ca content of in vivo implants were measured as markers of heterotopic bone formation [8]. Because BMP induces heterotopic bone tissue via endochondral ossification, the levels of cartilage and bone tissue induced were scored from histological sections of the implants to estimate the level of bone-inducing activity [10]. An assay system was developed to examine chondrogenesis in vitro from minced muscle cells cultured on a demineralized bone matrix [11,12]. Chondrogenesis within the minced muscle cells was also induced in agarose-gel cultures in the presence of bone-inducing extracts of a demineralized bone matrix [13].

2.2. Molecular cloning of BMPs

After reduction, the highly purified BMP fraction at approximately 30 kDa was found to consist of several peptides, suggesting that BMP is not a single protein [10,14–16]. Indeed, amino acid sequences of the peptides indicate the presence of distinct but related molecules, including BMP-1, BMP-2/BMP-2A, BMP-3/osteogenin, BMP-4/BMP-2B, BMP-5, BMP-6/Vgr-1 and BMP-7/OP-1 [10,15–17]. Among these compounds, only BMP-1 has a distinct structure and belongs to the metalloproteinase family [14]. The other BMPs are related to each other and can be classified into multiple subclasses of the transforming growth factor- β (TGF- β) family, which contains several other members in both vertebrate and invertebrate species [14,15,17,18]. Importantly, each of the recombinant proteins, including BMP-2, BMP-4 and BMP-7, has been shown to induce heterotopic bone formation in vivo, confirming the presence of original “BMP” activity [14,19,20]. It was also shown that the bone-inducing activity of the extracts of demineralized bone and dentin could be attributed to several BMPs. Two recombinant *Drosophila* BMP homologs, Dpp and 60A, also induced heterotopic bone formation in rodents, suggesting that the signal transduction mechanisms are conserved across vertebrate and invertebrate species [21,22]. To date, genes encoding more than 20 members of the BMP and related growth and differentiation factor (GDF) families have been found in the human genome. Several BMPs and GDFs have been shown to induce the formation of bone and/or cartilage tissue not only through the implantation of recombinant proteins but also through the

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