BONE MORPHOGENETIC PROTEIN-3 FAMILY MEMBERS AND THEIR BIOLOGICAL FUNCTIONS

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1. ABSTRACT

Bone morphogenetic protein-3 and 3b (BMP-3 and BMP-3b) together represent a unique subgroup of the BMP family. BMP-3b shares 82% amino acid identity with BMP-3 in the mature region (ligand domain), but only 37% in the pro-region (pro-domain). In osteoblasts, BMP-3 and 3b have similar antagonistic activity against BMP-2, but they are differentially regulated. In developing embryos, BMP-3 and 3b have different dorsalizing activities. BMP-3b triggers secondary head formation in an autonomous manner, whereas BMP-3 induces aberrant tail formation. Loss-of-function analysis demonstrates that coordinated activity of xBMP-3b and cerberus, a head inducer, are required for head formation in Xenopus embryos. At the molecular level, BMP-3b antagonizes both nodal-like proteins (Xnr1 and derrière) and ventralizing BMPs (BMP-2 and ADMP), whereas BMP-3 only antagonizes ventralizing BMPs. Moreover, BMP-3b, but not BMP-3, associates with the monomeric form of Xnr1, a nodal-like protein. These molecular features of BMP-3 and 3b are due to their distinct pro-regions. These findings suggest that the processing of precursor regions and assembly of BMP-3 and 3b are important in various developmental processes and organogenesis.

2. INTRODUCTION

Bone morphogenetic proteins (BMPs) constitute a subgroup of proteins which belong to the transforming growth factor-ß (TGF-ß) superfamily. BMPs were originally identified as proteins that induce endochondral bone formation in adult mammals (1). Today, over 15 members of the BMP family have been isolated (2). They are expressed in a variety of tissues and have diverse effects on different cell types during embryogenesis and in adult life (3-5). BMPs are synthesized as large precursor proteins that are cleaved at a characteristic R-X-X-R consensus site to release mature domains containing a characteristic motif of seven conserved cysteine residues (4). The biologically active proteins are homo- or heterodimers of the mature domains (3-5). BMPs bind BMP receptors (types I and II) and signal through Smad proteins (6).

Several antagonists of the BMP family, discovered in Xenopus embryos, act as dorsalizing factors and neural inducers (7). One such antagonist, cerberus, is secreted from the organizer to induce head formation (8). This effect is due to its specific inhibition to BMP-4, nodal and Wnt family proteins (9). BMPs and their antagonists regulate the axial patterning of vertebrate embryos (10).

BMP-3 (also called osteogenin) and 3b (also called GDF-10) are structurally different members of the BMP family (1, 11-13). Studies of BMP-3 and 3b have frequently been contradictory and their precise biological activity remains obscure. BMP-3b was originally isolated from the rat femur, and BMP-3 was co-purified with BMP-2, a molecule that induces bone formation in adult animals (1, 11). Neither recombinant BMP-3 nor BMP-3b, has osteogenic activity, although native BMP-3 (osteogenin) purified from bovine bone has osteogenic activity (11, 13). Recently, it has been reported that BMP-3 and 3b are antagonists of BMP-2 (14, 15). Furthermore, we have
Biological activity of BMP-3 and BMP-3b

Figure 1. Structural characterization of BMP-3 and 3b. (A) Schematic representation of human BMP-3 and 3b. The amino-acid sequences are represented by bars. Percent identity in each domain is indicated. Potential glycosylation sites (Y) and proteolytic cleavage sites (triangle) are indicated. The seven cysteine residues conserved within the TGF-ß superfamily are indicated by (c).

(B) BMP-3 and 3b in the BMP family (adapted from 15). The complete precursor amino-acid sequences were aligned by the UPGMA method (GENETYX program, SDC Ltd, Japan). The underlined proteins were used in this paper. h, human; x, Xenopus; z, zebrafish.

demonstrated that BMP-3b, but not BMP-3, is essential for head formation in Xenopus embryos, and that regulation of the processing of BMP-3/3b precursor and assembly plays an important role in embryonic patterning (15). In this review, we will discuss the unique functions, characteristics, and regulation of BMP-3 and 3b.

3. IDENTIFICATION AND STRUCTURAL FEATURES OF BMP-3 AND BMP-3B

3.1. Comparison at the protein level

Bone morphogenetic protein-3b (BMP-3b) was isolated from rat and human femur by RT-PCR (11, 16). While purifying and identifying known BMPs (BMP-2, 3, 6 and 7) from demineralized bovine bone matrix, we noticed the presence of a novel BMP-3-related protein (unpublished data). Cunningham et al. have also cloned by RT-PCR the murine orthologue of BMP-3b (which they named GDF-10) from brain and lung (12).

BMP-3 has been co-purified with BMP-1 and BMP-2 from bovine bone using the rat ectopic bone formation assay (1, 13). After that, orthologues of both molecules were identified in other species (15, 17). Like other TGF-ß family members, both proteins are biologically and structurally well conserved throughout vertebrate evolution (18, 19); for example, rat BMP-3 and 3b have the same activities as their Xenopus orthologues (15).

BMP-3b shares 82% amino-acid sequence identity in the mature region with BMP-3, with which it constitutes a unique subgroup in TGF-ß superfamily (Figure 1). However, the proteins are only 37% similar in their pro-regions, a unique feature among TGF-ß superfamily members. Most TGF-ß subgroups are much more highly homologous; for example, BMP-2, 4, 5, 6, and 7 share 62% homology in their pro-regions (18). Importantly, the pro-region of BMP-3b contains a segment which is required for head-forming activity (Figure 1A). This segment is relatively conserved between Xenopus and rat, and is divergent from that of BMP-3. This feature is unique for BMP-3b since the activity of other BMP family members is normally determined by the mature region of the protein.

Both BMP-3 and 3b have two cleavage sites. One is a consensus tetra-basic (RXXR) site, and the other is an alternative tribasic site that was discovered by protein purification and N-terminal sequence analysis (Figure 1A); these sites give rise to two different sizes of ligand protein upon over-expression of the precursor in CHO cells (15). Some other TGF-ß family members have multiple cleavage sites (20-22) that are known to be important for their activities (23, 24). Further analysis is required to examine how these two cleavage sites control the activity of BMP-3 and 3b.
Biological activity of BMP-3 and BMP-3b

3.2. Comparison at the genomic level

The human BMP-3 and 3b genes are composed of three exons, and, for both genes, each splice junction is located at the same position (16, unpublished data); this genomic structure is well conserved between humans and mice. In the human TGF-β superfamily, the genes for the TGF-β subfamily (-β1, -β2 and -β3) and BMP-7 subfamily (-5, -6, -7/OP-1 and -8/OP-2) contain seven exons and similar splice junction locations (21, 25 and unpublished data). On the other hand, the genes for BMP-2 and BMP-4 contain only two exons that cover the entire coding region, with each splice junction located in an identical position (26, 27). These findings suggest that both genes are derived from a common ancestor. The human BMP-3 and 3b genes mapped to chromosome 4p14-q21 and 10q11.2-q21.1, respectively (data not shown and ref. 28). At present, these chromosomal regions have not been directly linked to any other genetic disorders.

4. EXPRESSION PATTERNS OF BMP-3 AND BMP-3B

4.1. Mammalian tissues

Several studies have described the mRNA expression of BMP-3 and 3b (11, 16, 12, 29-33). By Northern blotting analysis in rat and human tissues, both BMP-3 and 3b were shown to be expressed in bone (Figure 2A, ref. 16). The expression level of BMP-3b in the neonatal femur and calvaria is higher than in the adult, whereas the BMP-3 mRNA level in the femur is lower during neonatal stages. BMP-3b, but not BMP-3, is expressed highly in costicartilage. In other tissues, BMP-3b mRNA is most abundant in the cerebellum, followed by the aorta, and is expressed at a lower level in the ovary and testis. In the embryonic cerebellum (18 dpc), expression of BMP-3b is weak, but it increases immediately after birth and remains high up to and throughout adulthood (11). In contrast, BMP-3 is expressed at a high level in the ovaries and lungs, but at a low level in the kidneys and aorta. Cunningham et al. reported that BMP-3b (GDF-10) is highly expressed in the mouse uterus and adipose tissue (12). They subsequently examined BMP-3b expression during mouse embryogenesis, showing that BMP-3b mRNA can be detected at 8.5 dpc, and is expressed in developing skeletal structures at 12.5 and 14.5 dpc (31). Examination of BMP-3 mRNA in rat embryos revealed wide-spread expression in regions including the hair, teeth, and kidneys (29). In the rat ovary, strong expression of BMP-3b was observed during folliculogenesis, but BMP-3 expression was relatively weak (32). In the human

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<th>Tissue</th>
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Figure 2. Expression patterns of BMP-3 and 3b in various tissues, and developmental embryos. (A) Expression levels of both genes in rat tissues were analysed by Northern blot (adapted from 11). Expression level was quantified and ranked from + to ++++. -, no signal (B-K) Embryonic expression of Xenopus BMP-3b and BMP-3 by whole-mount in situ hybridization (adapted from 15). (B) Dorsal view of stage 11. Anterior region faces top. (C) Solid line indicates level of section. (D) Sagittal section of embryo. Anterior faces left. BMP-3b expression is intense in ectoderm and faint in mesoderm and endoderm. Arrows highlight BMP-3b expression in the prechordal plate. (H) Dorsal faces top. (I) Anterior faces left.
ovary, BMP-3 mRNA is expressed in granulosa cells (33). Taken together, expression of BMP-3 and 3b in mammalian tissues is distinct; this temporal expression pattern of BMP-3 and 3b may be important for their functions.

4.2. Xenopus embryos

Figures 2B-K show whole-mount in situ analysis of BMP-3 and 3b in Xenopus embryos (adapted from 15). Expression of xBMP-3b is initially detected on the dorsal-lateral ectoderm (Figure 2B) and is enhanced in the neural fold from the rostral to the caudal regions (Figure 2C). xBMP-3b mRNA is detected in the prechordal plate and endoderm (Figure 2D). At the hatching stage, xBMP-3b is enriched in the region from the dorsal mesenchyme to the optic cup as well as posterior to the stomodeum (Figure 2E). BMP-3b expression is transient in the ventricular chamber (Figure 2E). BMP-3b is also detected in the spinal cord and the somite (Figure 2F). At the swimming stage, BMP-3b is expressed in the head mesoderm (Figure 2G). xBMP-3 is initially detected in the ectoderm and mesoderm (Figure 2H), but its expression is eventually restricted to the prechordal and chordal mesoderm (Figure 2I). At hatching, xBMP-3 is expressed in cranial neural-crest derivatives and in the cement gland (Figure 2J), whereas expression of xBMP-3 is restricted to the notochord (Figure 2K).

In summary, BMP-3 and 3b are expressed in a variety of embryonic tissues of Xenopus, but tend to mark the dorsal ectoderm and mesodermal cells.

5. REGULATION OF BMP-3 AND BMP-3B EXPRESSION IN OSTEOBLASTS

Expression of BMP-3 and 3b was analyzed in primary calvarial osteoblasts, in which both genes are highly expressed (Figure 3). BMP-2, which induces ectopic bone formation, increases alkaline phosphatase (ALPase) activity and regulates expression of BMP-3 and 3b in these cells, as shown by the time courses in Figure 3A. There was a dramatic, time-dependent increase in BMP-3b transcription beginning within 6 h after treatment and exhibiting a maximum 6.9-fold increase. In contrast, the BMP-3 mRNA level was decreased by BMP-2, especially during the early phase. Chen et al. (34) reported that BMP-3 expression in a similar osteoblastic cell system was enhanced by long-term treatment with BMP-2, for 5-to-17 days after treatment. Figure 3B shows the effects of TGF-β, bFGF, and retinoic acid on expression of BMP-3 and 3b in these cells. Among these growth factors, TGF-β completely and retinoic acid partially inhibited BMP-3b expression and bFGF had weak suppressive effect. Further analysis of the effect of TGF-β on BMP-3b expression in these cells showed that TGF-β causes a dramatic, rapid decrease in BMP-3b transcription, by nearly 50% after 3 h of incubation and almost 100% after 6 h (35). TGF-β acts as an inhibitor of osteoblastic differentiation in these cells; therefore, these data suggest that BMP-3b mRNA level decreases with dedifferentiation of osteoblasts. On the other hand, BMP-3 expression was inhibited by bFGF and enhanced by retinoic acid.

These results demonstrate that the regulation of BMP-3b differs from that of BMP-3, and that BMP-3b expression is regulated during osteoblast differentiation, indicating that BMP-3b functions in highly differentiated osteoblasts.

6. BIOLOGICAL ACTIVITY OF BMP-3 AND BMP-3B IN OSTEOBLASTS

BMP-3b was discovered in bone, and BMP-3 was isolated from a highly purified osteoinductive fraction of bone extracts (11, 1, 13). Native BMP-3 (ostegenin) purified from bone is osteoinductive (13). Furthermore, several groups found that a large amount of BMP-3 exists in bone (1, 13, 36 and unpublished data) and that BMP-3, as well as BMP-3b, is highly expressed in bone (11, 12, 16). Therefore, BMP-3 and 3b were thought to have osteogenic activity, like BMP-2. However, recombinant BMP-3 and 3b produced by CHO cells did not induce ectopic bone formation (11). To resolve these conflicting functions of BMP-3 and 3b in osteoblasts, we transfected...
Biological activity of BMP-3 and BMP-3b

Figure 4. BMP-3 and 3b activities in osteoblast MC3T3-E1 cells. BMP-3 and 3b expression plasmids were transfected into MC3T3-E1 cells. ALPase activities were determined as described (Figure 3, ref. 35).

Figure 5. Functions of BMP-3 and 3b during embryonic development (adapted from 15). (A-C) Differentiation of ventral marginal zone explants (VMZs) injected with BMP-3 or 3b mRNA. (A) VMZs injected with BMP-3b generated head-like structures consisting of an eye and cement glands. (B) VMZs injected with BMP-3 elongated and formed melanocytes. (C) Control VMZs developed into a cylindrical structure. (D-E) Rescue of UV-ventralized embryos by BMP-3b. (D) Injection of BMP-3b rescued the anterior structure of ventralized embryos. Cells expressing BMP-3b were localized in the head region. (E) Control embryos. (F-H) Loss-of-function analyses using morpholino antisense oligonucleotides (MO). (F) Simultaneous injection of xBMP-3b and cerberus MOs led to loss of head and dorsal structures, (G) whereas injection of xBMP-3 and cerberus MOs did not. (H) Control embryos.

BMP-3 and 3b expression plasmids in osteoblasts and found that BMP-3 and 3b inhibit ALPase activity over 50%, whereas BMP-2 increased ALPase activity more than two-fold. These results indicate that BMP-3 and 3b have opposite effect to BMP-2 (Figure 4). This finding agrees with that of Daluiski et al., who reported that BMP-3 antagonizes BMP-2 signaling (14). Collectively, these results confirmed the role of BMP-3 and 3b as negative regulators of osteogenesis.

7. FUNCTIONS OF BMP-3 AND BMP-3B IN XENOPUS EMBRYONIC DEVELOPMENT

7.1. Dorsalizing activities of BMP-3 and BMP-3b in Xenopus embryos

BMPs and their antagonists are involved in the axial patterning of vertebrate embryos (10). Moreover, we showed that BMP-3 and 3b are antagonists of BMP-2 in osteoblasts (Figure 4 and ref.14). Therefore, we examined the biological activity of BMP-3 and 3b in Xenopus embryos. BMP-3b injected into Xenopus embryos triggered secondary head formation, whereas BMP-3 induced aberrant tail formation (15). When injected into the ventral marginal zone (VMZ), BMP-3b generated head-like structures, leading to secondary head formation (Figure 5A). These effects of BMP-3b in embryos are comparable to those of cerberus, a known head inducer (8). In contrast, when the VMZ was injected with BMP-3, it elongated and formed melanocytes (Figure 5B). The effect of BMP-3 is similar to that of the dominant-negative forms of BMP-2, 4, and 7 (23). These results reveal that while both BMP-3 and 3b are dorsalizing factors, they act distinctly in Xenopus embryos.

7.2. The involvement of BMP-3b in head formation

To further examine the effect of BMP-3b on head formation, we first performed rescue and lineage tracing of UV-ventralized embryos (Figure 5D). Injection of BMP-3b mRNA generated a head structure with cyclopia and a cement gland; cells expressing BMP-3b were found in the head region. These observations indicate that BMP-3b triggers head formation through an intrinsic developmental pathway. Next, we performed loss-of-function analyses in Xenopus embryos using antisense morpholino oligonucleotides (MO) against BMP-3, 3b, and cerberus. MO injection alone did not obviously perturb the Xenopus embryos, suggesting that the molecules they inhibit have some functional redundancies (15). Although BMP-3b and cerberus are structurally different, they both trigger secondary head formation in Xenopus embryos. Moreover, both proteins are expressed concurrently with the differentiation of the organizer cells (Figure 2, ref.15). We therefore co-injected either BMP-3 or BMP-3b MO together with cerberus MO into embryos. Figures 5F-G show that co-injection of cerberus MO with BMP-3b MO, but not BMP-3 MO, generated headless and malformed dorsal axial structures. Histological analysis revealed that depletion of BMP-3 and cerberus affects the size of the somite (15). These results were confirmed by a rescue experiment (15), suggesting the BMP-3b cooperates with cerberus in Xenopus larval head formation.

7.3. The divergent activity of BMP-3 and BMP-3b

The molecular characteristics of BMP-3 and 3b were analyzed by Western blotting and by interference assay (15). These results are summarized in Figure 6. First,
Biological activity of BMP-3 and BMP-3b

<table>
<thead>
<tr>
<th>Precursor cleavage</th>
<th>Interaction with members of the TGF-β family</th>
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<tr>
<td>BMP-3b</td>
<td>xBMP-2 antagonistic ADMP antagonistic Derrière heterodimer Xnr1 association</td>
<td>ALPase in osteoblast neural inducing dorsalizing head forming</td>
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<td>BMP-3</td>
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Figure 6. Molecular characteristics and biological activities of BMP-3 and 3b (adapted from 15). The results of biochemical analyses and interference assay between both proteins and TGF-β members are summarised with their activities. Incomplete processing of BMP-3b, controlled by the pro-domain, generates precursor BMP-3b, which might be responsible for its unique activity. Both BMP-3 and 3b inhibit BMP-2 and ADMP. BMP-3b also blocks derrière and Xnr1. Heterodimers of precursor BMP-3b might reduce the activity of derrière and complex formation between BMP-3b and Xnr1 might alter Xnr1 function. These different types of BMP-3b antagonism result in ectopic head formation.

we analyzed the biosynthesis of BMP-3 and 3b. BMP-3b precursor is processed incompletely in *Xenopus* embryos and in CHO cells, whereas the BMP-3 precursor is processed completely. These results are consistent with chimeric protein analyses, showing that the BMP-3b pro-region interferes with the maturation of the mature region, whereas the BMP-3 pro-region promotes the maturation of the mature region (15). Furthermore, these analyses showed that the region required for head formation for BMP-3b is located in the pro-region, and that the BMP-3b mature region has the same activity as that of BMP-3.

Next, we carried out an interference assay in an animal cap, because the inhibition of BMP-2, nodal and ADMP activities are involved in head formation in *Xenopus* embryos. We found that BMP-3b antagonizes ventralizing BMPs (BMP-2 and ADMP) and nodal-like proteins (derrière and Xnr1), whereas BMP-3 antagonizes only ventralizing BMPs (Figure 6, ref.15). These patterns of inhibition are in agreement with the finding that BMP-3b, but not BMP-3, causes head formation.

Finally, we showed that the interaction between BMP-3 or BMP-3b and other TGF-β family members is direct. BMP-3b forms heterodimers with BMP-2, ADMP, and derrière and forms non-covalent complexes with monomeric Xnr1, whereas BMP-3 only forms heterodimers with BMP-2, ADMP, and derrière. These features are essentially consistent with a suppressive effect of BMP-3 or 3b on other TGF-β family members. Heterodimers of precursor BMP-3b and derrière might inhibit derrière activity and BMP-3b/Xnr1 complex formation might change Xnr1 function. In this regard, Xnr1 may interact with the region of BMP-3b that is required for head formation.

7.4. The role of BMP-3b in head formation

We showed that *Xenopus* BMP-3b indeed participates in embryonic head formation by coordinating with cerberus. Figure 7 shows a model of head formation by BMP-3b and cerberus. Initially, cerberus secreted from anterior endo-mesodermal cells in the organizer protects neighboring cells against nodal and ventralizing factors such as BMP-2, ADMP, and Wnt proteins, although nodal is essential for induction of mesodermal cells and for *cerberus* expression. As gastrulation proceeds, BMP-3b accumulates in the anterior mesodermal cells and forms a non-covalent complex with nodal, altering its function. When cerberus and BMP-3b successively block nodal and ventralizing factors from interacting with the anterior mesodermal cells, transcription factors such as Otx2 in the cells could proceed with expression of downstream genes and complete their self-differentiation as “head-organizing cells”.
These biological functions are consistent with their expression pattern (15). Our biochemical analyses demonstrate that BMP-3 and 3b form heterodimers with BMP-2 and thus trigger NCAM signaling through an activin receptor pathway (ALK-4 and ActRII) (14). However, we show that dorsalizing BMPs, unlike activin, do not induce mesoderm in animal caps (15). Therefore, BMP-3 binds activin receptors, but the downstream signaling molecules may be different from those used by activin. Alternatively, dorsalizing BMPs may also bind a specific receptor in Xenopus embryos and transduce their signals through unknown molecules or inhibitory Smads (Smad 6, 7 and 8).

9. THE PRO-REGION OF BMP-3B DETERMINES ITS ACTIVITY

In TGF-β family members, the pro-region simply modifies the activity of the mature region through control of its assembly, secretion, and turnover (37-41). Precursors of TGF-βs, synthesized in the cells, are cleaved by proteolytic processing, generating pro-regions and mature regions. Then, both regions are secreted as inactive high-molecular-weight complexes (42-44). In these complexes, the mature region of TGF-β is non-covalently associated with a pro-region of TGF-β, which covalently binds to the TGF-β binding protein. The TGF-β pro-region itself can act as a functional binding domain (45). Similar function of pro-region for Myostatin/GDF-8 has been described and GDF-8 also belongs to the TGF-β superfamily (46). Typically, the function of the TGF-β pro-region is simply to inhibit the activity of the mature region. In contrast, the BMP-3b pro-region alters the activity of the mature region through control of its precursor processing. In other words, the BMP-3b precursor has an additional activity different from that of its mature region, while the TGF-β precursor is an inactive form.

Our chimeric protein analyses demonstrate that the pro-region of BMP-3b contains the region that is required for head formation, and interferes with maturation of its mature region (15). In practice, BMP-3b precursor is secreted and forms heterodimers or complexes with other BMP family members. These unique characteristics of BMP-3b could result in autonomous head formation in Xenopus embryos. Our results show that the mature region of BMP-3b is secreted and has the same activity of BMP-3, namely dorsalizing activity and antagonism of ventralizing BMPs.

The activity of BMP-3 and 3b may be regulated at different levels: transcriptional and post-translational levels. In the case of transcription, we demonstrated the regulation of BMP-3 and 3b in osteoblasts (Figure 3) and their distribution in various tissues (Figure 2), indicating that regulation and distribution of BMP-3 and 3b are different from those of BMP-3. In the case of post-translational, BMP-3b has two different activities regulated by precursor processing and assembly in Xenopus embryos: dorsalizing activity identical to that of BMP-3, and head-forming activity. These regulatory mechanisms might determine correct spatial and temporal gradients of BMP-3 and 3b activity in various physiological systems. In embryonic development, processing and assembly of the BMP-3 and 3b precursors are crucial to anterior-posterior patterning, and the pro-region of BMP-3b is essential for the regulation of its activity. This post-translational
regulation is unique among TGF-ß family members, and further analysis of it may provide a clue to other salient, yet unidentified regulatory systems mediated by TGF-ß superfamily members in other tissues.

10. PERSPECTIVE

We have focused here on recent findings regarding the structure and function of two TGF-ß superfamily members, BMP-3 and 3b. The most striking feature is that despite their close relatedness, BMP-3 and 3b have apparently different activities in Xenopus embryos. These differences appear to be due to their respective pro-regions, which affect their precursor processing and assembly. Understanding the biological activities of BMP-3 and 3b is just beginning. Although BMP-3 and 3b are highly expressed in several adult tissues including brain, aorta, and ovary, their functions in these tissues are still unknown. In these tissues, other TGF-ß family members may interact with BMP-3 and 3b and BMP-3 and 3b may act as antagonists of these TGF-ß family members as they do in Xenopus embryos. It will be exciting to see how BMP-3 and 3b function and interact with other TGF-ß family members or BMP-binding proteins in the nervous, cardiovascular, and reproductive systems.

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Figure 3 from Takao, M., J. Hino, N. Takeshita, Y. Konno, T. Nishizawa, H. Matsuo & K. Kangawa: Identification of rat bone morphogenetic protein-3b (BMP-3b), a new member of BMP-3. Biochem Biophys Res Commun 219, 656-662 (1996)


Key Words: BMP-3, Osteogenin, BMP-3b, GDF-10, TGF-ß, Osteogenic activity, Osteoblast, ALPase, dorsalizing activity, Cerberus, Head formation, Neural inducer, Precursor processing, Embryos, Review

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