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Review

BMP signaling in skeletal development

Mei Wan, Xu Cao*

Department of Pathology, University of Alabama at Birmingham, Birmingham, AL 35294, USA

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Abstract

Development of the vertebrate skeleton, a complex biological event that includes diverse processes such as formation of mesenchymal condensations at the sites of future skeletal elements, osteoblast and chondrocyte differentiation, and three dimensional patterning, is regulated by many growth factors. Bone morphogenetic proteins (BMPs), members of the TGF-β superfamily, play a pivotal role in the signaling network and are involved in nearly all processes associated with skeletal morphogenesis. BMP signals are transduced from the plasma membrane receptors to the nucleus through both Smad pathway and non-Smad pathways, and regulated by many extracellular and intercellular proteins that interact with BMPs or components of the BMP signaling pathways. To gain a better understanding of the molecular mechanisms underlying the role of BMP in early skeletal development, it is necessary to elucidate the BMP signaling transduction pathways in chondrocytes and osteoblasts. The major objective of this review was to summarize BMP signaling pathways in the context of craniofacial, axial, and limb development. In particular, this discourse will focus on recent advances of the role of different ligands, receptors, Smads, and BMP regulators in osteoblast and chondrocyte differentiation during embryonic development.

Keywords: BMPs; BMP receptors; Smads; Skeleton development; Osteoblast differentiation; Chondrogenesis

The vertebrate skeleton, derived from different embryonic lineages, comprises two tissues: cartilage and bone. Distinct embryonic lineages from cranial neural crest cells, paraxial mesoderm, and lateral plate mesodermal cells proliferate and migrate into distinct mesenchymal condensations at the sites of future skeletal elements. The embryonic cells within these condensations differentiated into three cell types: chondrocytes in cartilage and ostoblasts and osteoclasts in bone, and eventually form the craniofacial, axial, and limb skeleton [1].

Cell differentiation into chondrocytes or osteoblast, subsequent cartilage and bone formation, and ultimately skeletal remodeling are processes governed by various growth factors and their intercellular signals [2,3]. The bone morphogenetic protein (BMP) family of proteins, through a cascade of downstream signals, regulates many aspects of skeletal development, including osteoblast and chondrocyte differentiation, cartilage and bone formation, mesoderm patterning, and craniofacial and limb development. In this review article, we discuss some recent progress in research on the role of BMP signaling in vertebrate development, focusing on how a wide variety of ligands, receptors, signal transducer Smads, and Smad regulators exert their effects on osteoblast and chondrocyte differentiation, cartilage and bone formation, and skeletal patterning during embryonic development.

The BMP signaling pathway

BMP ligands

BMPs, originally isolated as proteins that induce bone and cartilage formation, represent almost one-third of the transforming growth factor-β (TGF-β).

* Corresponding author. Fax: +1 205 934 1775.
E-mail address: cao@path.uab.edu (X. Cao).

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The BMP family is the largest within the TGF-β superfamily of growth factors, which also includes TGF-βs, activins, inhibins, myostatin, and others [4,5]. A common feature of the TGF-β superfamily is the presence of seven conserved cysteines, which are involved in folding the molecule into a cystine knot [6]. Members of the BMP family are distinguished from those of the TGF-β and activin families by having two extra conserved cysteines. BMPs are translated as large preproproteins composed of a signal peptide, prodomain, and mature domain. After removal of the signal peptide, the proproteins undergo dimerization after which the specific proteolytic enzymes cleave the dimerized proprotein to generate biologically active dimeric mature protein [7].

BMPs are potent osteoblast differentiation factors in vitro. Various BMPs, including BMP-2, BMP-4, and BMP-7, induce the differentiation of multipotential mesenchymal cells (e.g., C3H10T1/2 cells) into both osteochondrogenic lineage cells and osteoblast precursor cells [8–11]. BMPs also inhibit the differentiation of adipocytes from bone marrow stromal precursors [12]. In addition, BMPs regulate chondrocyte differentiation and chondrogenesis during skeletal development. BMPs induce mesenchymal cell chondrogenesis in mesenchymal cells and induce differentiation in isolated chondrocytes [13–17].

BMP receptors

Like other TGF-β superfamily members, BMPs bind to two major types of membrane-bound serine/threonine kinase receptors, the type-I and type-II receptors [4,5]. BMPR-IA (ALK-3), BMPR-IB (ALK-6), and ActR-IA (ALK-2) are BMP type-I receptors [18–22]. Particular BMP ligands bind to different type-I receptors in different cell types. BMPR-II bind exclusively to BMP ligands, including BMP-2 [23], BMP-4 [24,25], BMP-6 [26], BMP-7 [23], GDF-5 [19], and GDF-9 [27]. ActR-II and ActR-IIB, originally identified as activin receptors, can also act as receptors for BMP-6 [26], BMP-7 [18], and GDF-5 [19]. BMP receptor oligomerization appears to be different from activin and TGF-β receptor oligomerization. For activin and TGF-β receptor, the ligands first bind to type-II receptors, which in turn, leads to the recruitment of the type-I receptors [4,5]. However, it has been demonstrated that BMPR-II and the type-I receptor form both homomeric and heteromeric complexes, even before ligand stimulation [28]. Binding of BMPs to preformed heteromeric receptor complexes results in activation of the Smad pathway, whereas formation of heteromeric receptor complexes induced by BMP results in activation of the MAPK pathway [28].

BMPR-IA is more widely expressed than BMPR-IB in various tissues [29], but BMPR-IB is the only receptor expressed within all types of cartilage [30]. Expression of dominant-negative BMPR-IB, but not dominant-negative BMPR-IA, blocks chondrogenesis and osteogenic differentiation [31,32]. ALK2 is expressed in isolated chick osteoblasts and chondrocytes, and overexpression of constitutively active ALK2 enhances chondrocyte maturation, suggesting that it is essential for normal chondrocyte maturation and skeletal development [33].

BMP intercellular signal transduction

Smad proteins play central roles in intracellular signaling by members of the TGF-β superfamily [34]. Upon binding of a BMP ligand, the type-II receptor transphosphorylates the type-I receptor at an intracellular juxtamembrane site termed the GS domain [35]. The phosphorylated type-I receptor, in turn, phosphorylates a set of intracellular substrate signaling proteins collectively known as Smads [4,5]. Smad proteins are classified into three subgroups, i.e., receptor-regulated Smads (R-Smads), a common-partner Smad (Co-Smad), and inhibitory Smads (I-Smads). The BMP-specific R-Smads, Smad1, 5, and 8, transiently and directly interact with activated BMPR-Is and become phosphorylated at SSXS motifs at their C termini. Smad1/5/8 then form heteromeric complexes with Co-Smad Smad4 and translocate into the nucleus where they regulate transcription of various target genes.

Smads play important roles in osteoblast differentiation. Smad1 and Smad5 have been shown to be the major signaling molecules for inducing differentiation of C2C12 cells into osteoblasts [36,37]. However, this differentiation is not as efficient as that induced by ligands or constitutively active BMP receptors. It is possible that other signaling pathways (e.g., p38 MAP kinase and JNK) independent of the Smads may be required for efficient induction of osteoblast differentiation [38,39]. Smad1 or Smad5, but not Smad8, synergizes with Smad4 to promote chondrocyte differentiation from chondroprogenitor cells. In contrast, Smad8 and Smad4 exhibit modest synergy in mesenchymal cells [15].

The Smad pathway is a well-characterized BMP signaling pathway. However, BMPs also initiate non-Smad interacellular signaling pathways. Several lines of evidence suggested that BMPs activate the MAPK family of signaling molecules, i.e., ERK1/2, p38, and stress-activated protein kinase/Jun N-terminal kinase [40–42]. It has been demonstrated that the activation of the p38 pathway by BMP-2 or BMP-4 is due to the activation of TAK1/TAB1 [43,44]. Activated MAPK molecules have been shown to activate alkaline phosphatase and osteocalcin expression in osteoblastic cells, providing evidences that these MAP kinases have distinct roles in regulating osteoblast differentiation [39]. In addition, the ability of the BMPs to promote chondrogenesis requires p38, and p38 inhibitors strongly suppress induction of type-II collagen and chondrogenesis [42]. BMPRII has also been demonstrated to directly interact