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REVIEW ARTICLE

Bone Morphogenetic Protein (BMP) signaling in development and human diseases

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Abstract Bone Morphogenetic Proteins (BMPs) are a group of signaling molecules that belongs to the Transforming Growth Factor-β (TGF-β) superfamily of proteins. Initially discovered for their ability to induce bone formation, BMPs are now known to play crucial roles in all organ systems. BMPs are important in embryogenesis and development, and also in maintenance of adult tissue homeostasis. Mouse knockout models of various components of the BMP signaling pathway result in embryonic lethality or marked defects, highlighting the essential functions of BMPs. In this review, we first outline the basic aspects of BMP signaling and

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then focus on genetically manipulated mouse knockout models that have helped elucidate the role of BMPs in development. A significant portion of this review is devoted to the prominent human pathologies associated with dysregulated BMP signaling.

Introduction

The activity of Bone Morphogenetic Proteins (BMPs) was first observed in the mid-1960s when it was discovered they could induce ectopic bone formation.[1] It was not until the late 1980s, however, when the first BMPs were characterized and cloned, that individual BMPs could be studied biochemically.[2] Many studies have since demonstrated the ability of BMPs to induce mesenchymal stem cells to differentiate into bone, confirming their role in bone and cartilage formation. BMPs are part of the Transforming Growth Factor-β (TGF-β) superfamily of proteins (Fig. 1A), which includes TGF-βs, activins, inhibins, Growth Differentiation Factors (GDFs), Glial Derived Neurotrophic Factors (GDNFs), Nodal, Lefty, and anti-Müllerian hormone. Since their initial discovery, they have been shown to affect a wide variety of cell types and processes beyond bone and osteogenesis. They are important morphogens in embryogenesis and development, and also regulate the maintenance of adult tissue homeostasis.

Many processes in early development are dependent on BMP signaling for cell growth, apoptosis, and differentiation.[3–6] BMPs also play important roles in maintaining adult tissue homeostasis, such as the maintenance of joint integrity, the initiation of fracture repair, and vascular remodeling.[7–9] Because of these diverse functions in all organ systems, it has been suggested that BMPs deserve to be called body morphogenetic proteins.[10] Due to their ubiquitous expression and importance as regulators throughout the body, deficiency in BMP production or functionality usually leads to marked defects or severe pathologies (Fig. 2). Here, we review the mouse knockout models that have helped elucidate the role of BMPs in development and also emphasize some of the prominent human pathologies associated with deficiencies related to BMP signaling.

Bmp signaling: canonical and non-canonical pathways

BMPs are synthesized as precursor proteins with an N-terminal signal peptide, a prodomain for folding and secretion, and a C-terminal mature peptide.[11] Precursors are formed in the cytoplasm as dimeric pro-protein complexes, which are cleaved by pro-protein convertases to generate N- and C-terminal fragments. The C-terminal mature fragment is capable of binding to its receptor, with the non-covalently associated prodomain playing an important regulatory role.

BMPs can signal through both canonical and non-canonical pathways. In the canonical signaling pathway, they initiate the signal transduction cascade by binding to cell surface receptors and forming a heterotetrameric complex comprised of two dimers of type I and type II serine/threonine kinase receptors (Fig. 1B).[12] Both receptor types have a short extracellular domain, a single transmembrane domain, and an intracellular domain with serine/threonine kinase activity. There are a total of seven type I receptors (ALK1-7) for the TGF-β family of ligands, three of which bind BMPs: type 1A BMP receptor (BMPR-1A or ALK3), type 1B BMP receptor (BMPR-1B or ALK6), and type 1A activin receptor (ActR-1A or ALK2).[13] There are a total of four type II receptors for the TGF-β family, three of which are known to interact with BMPs: type 2 BMP receptor (BMPR-2), type 2 activin receptor (ActR-2A), and type 2B activin receptor (ActR-2B). While BMPR-1A, BMPR-1B, and BMPR-2 are specific to BMPs, ActR-1A, ActR-2A, and ActR-2B can function as receptors for activins, which are also members of the TGF-β superfamily. The mechanism of the heterotetrameric signaling complex formation can vary. For example, BMP6 and BMP7 interact with type II receptors and recruit type I receptors, whereas BMP2 and BMP4 preferentially bind type I receptors and recruit type II receptors.[14] The existence of preformed oligomeric complexes adds an additional layer of intricacy; indeed, binding to preformed receptor complexes versus BMP-induced receptor recruitment can activate different pathways.[15]

Upon formation of a heterotetrameric complex, the constitutively active type II receptor transphosphorylates the type I receptor at a glycine—serine rich motif known as the GS domain. This activates the type I receptor and allows phosphorylation of the immediately downstream substrate proteins known as the receptor-regulated Smads (R-Smads) at a C-terminal SSXS motif.[13] The R-Smads involved in BMP signaling are Smad1, Smad5, and Smad8 (Smad1/5/8). R-Smads then associate with the co-mediator Smad (co-Smad) Smad4, and this complex translocates to the nucleus where it functions as a transcription factor with coactivators and corepressors to regulate gene expression. Inhibitory Smads (I-Smads), Smad6 and Smad7 (Smad6/7), are involved in feedback inhibition of the signaling pathway.[16]

Several non-canonical, Smad-independent signaling pathways for BMPs have been identified. BMP4, for example, was found to activate TAK-1, a serine—threonine kinase of the MAPKKK family.[17,18] In addition to the MAPK pathway, BMP signaling has been found to affect PI3K/Akt, P/kc, Rho-GTPases, and others.[19] Interestingly, BMPs can have temporal regulation of signaling via the canonical Smad pathway or non-canonical pathways.[20] The specific