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Opinion

Bone Morphogenetic Protein Receptors: Structure, Function, and Targeting

Joseph Walker*

Editorial office, Journal of Bone Research, Spain

ABSTRACT

BMPs (Bone Morphogenetic Proteins) are released cytokines that regulate cell destiny and function in a variety of cell types. They activate specific BMP type I and type II serine/threonine kinase receptors, such as BMPRIA and BMPRII, to cause cellular responses. Three type II and four type I receptors have been identified as Activin Receptor-Like Kinases (ALKs). The type II kinase, which is constitutively active, phosphorylates the type I receptor, which activates intracellular signalling by phosphorylating SMAD effectors. Auxiliary cell surface receptors such as Endoglin and Repulsive Guidance Molecules (RGM), which lack inherent enzymatic motifs, can fine-tune signalling by controlling the interaction of BMP ligands with BMPRs. The functional annotation of the BMPR producing genes has aided in the understanding of the underlying mechanisms of disorders caused by mutations in these genes. BMPRII, Endoglin, and RGMc loss of function mutations have been related to pulmonary arterial hypertension, hereditary hemorrhagic telangiectasia, and juvenile hemochromatosis, respectively.

Keywords: Kinase inhibitor; Pulmonary arterial; Hypertension; FOP; PAH

INTRODUCTION

Urist discovered that demineralized bone extracts included bone initiating components, which he called bone morphogenetic proteins, in a groundbreaking study. Using a time-consuming ectopic bone formation experiment in rodents, BMPs were then purified to homogeneity from demineralized bone extracts. Following that, PCR-based cloning of cDNAs encoding BMPs was possible thanks to amino acid sequencing of peptide fragments. They are related to Transforming Growth Factor- (TGF-) and activin, according to the projected primary amino acid sequence. BMP proteins, which are members of the TGF family, are produced and secreted as giant precursor proteins that are then proteolytically digested to release their bioactive area at the carboxy-terminus. Since their discovery, BMPs have been attributed to a wide range of biological roles. BMPs, like other members of the TGF family, are multifunctional proteins that work in a context-dependent manner. They act as morphogens in early development, drive organ creation, and mediate tissue homeostasis. As a result, it's no surprise that BMP dysfunction leads to severe developmental abnormalities and a wide range of human diseases. Affinity labelling experiments using radiolabeled BMP ligands on cells overexpressing ActR2-related proteins were used to identify transmembrane BMP receptors. Type I receptors (also known as activin receptor-like kinases) and type II receptors are two separate subfamilies of receptors.

BMP receptor signalling

BMPs are homo- or heterodimers that bind with two type I and two type II receptor heteromeric complexes. BMPs bind weakly to type I and type II receptors, but when they interact with the type I-type II heteromeric complex, the affinity increases. The extracellular domains' overall architecture is remarkably consistent among receptor complexes, with the tetramer exhibiting a 2-fold symmetry axis. At the tetramer interface, type II domains create an intermolecular disulfide bridge, whereas type I receptors have specialised 'binding loops'. The conformation of this loop, and hence the affinity of the type I-type II interaction, can be modulated by minor sequence alterations. Specific 'hot spots' on the binding surface of the tetramer modify the interaction of the tetramer with BMP ligands, allowing for changes in specificity between the ligand and receptor complex. Varying BMP dimers bind to heteromeric complexes with different affinities. When it comes to BMP subgroups and their interactions with type I receptors, BMP9 has the highest affinity for ALK1 and binds weakly to ALK2; BMP10 preferentially binds ALK1, over ALK3 and ALK6; BMP5, BMP6, and BMP7 signal through ALK2, though BMP6 can also bind ALK3 and ALK6; and BMP2 and BMP4 have the strongest interactions with ALK3 and ALK6. BMPs have the ability to attach to heteromeric complexes made up of different type I receptors. Binding to Extracellular Matrix (ECM) components and soluble ligand binding proteins regulates ligand availability to signalling receptors. Auxiliary accessory receptors, often known as "co-receptors," control how BMP ligands interact with signalling receptors. Endoglin, a transmembrane receptor with a short intracellular domain that lacks an enzymatic motif [48], and the

Correspondence to: Joseph Walker, Editorial office, Journal of Bone Research, Spain, E-mail: orthopedicsurgery@journalsoa.org

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Repulsive Guidance Molecules (RGMs) A, B, and C (also known as hemojuvelin), which are linked to the plasma membrane via a Glycosylphosphatidylinositol (GPI)-anchor, are examples of such co-receptors.

The BMP/SMAD pathway appears straightforward: ligand activates BMP receptors, and SMADs transport the receptor activation signal from the plasma membrane to the nucleus. Unlike tyrosine kinase receptors, there are no intracellular enzymatic amplification steps involved. As a result, the amount of active BMP ligand dictates the degree of activated SMAD, in accordance with its morphogen function. Activated BMPRIs, such as ALK1, 2, 3, and 6, cause SMAD1, SMAD5, and SMAD8 to become phosphorylated. SMAD2 and SMAD3 are phosphorylated by the TRI/ALK5 and the activin type I receptor ALK4, respectively.

CONCLUSION

More than ten dimeric isoforms of the BMP family bind to hetero-tetrameric complexes of type I and type II serine/threonine kinase receptors, of which there are four and three, respectively, to exercise their physiological effects. The BMP-2/-4 group, the BMP-5/-6/-7/-8 group, the BMP-9/-10 group, and the BMP-12/-13/-14 group are all structurally similar subgroups of BMP ligands. There is a lot of overlap in receptor binding specificity within each class. BMPs are found in a wide range of tissues and regulate the differentiation and function of a wide range of cell types, with the amplitude and duration of the BMP signal being extremely important. Extracellular and intracellular stimuli regulate each step of the BMP pathway in a complex fashion. BMP receptor function is also regulated in a variety of ways. Inhibitory members of the SMAD family (SMAD6 and -7) are produced by BMP stimulation and work in a feedback mechanism to mediate BMPR ubiquitination and promote proteasomal degradation.