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Opinion

Structure, Function, and Targeting of Bone Morphogenetic Protein Receptors

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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

In a revolutionary investigation, Urist discovered that demineralized bone extracts contained bone starting components, which he dubbed bone morphogenetic proteins. BMPs were isolated to homogeneity from demineralized bone extracts using a time-consuming ectopic bone growth experiment in animals. Following that, amino acid sequencing of peptide fragments enabled PCR-based cloning of cDNAs encoding BMPs. According to the predicted primary amino acid sequence, they are related to Transforming Growth Factor- (TGF-) and activin. BMP proteins, which are TGF family members, are made and released as large precursor proteins that are then proteolytically degraded to release their bioactive region at the carboxy-terminus. BMPs have been linked to a variety of biological functions since their discovery. BMPs, like other TGF family members, are versatile proteins with context-dependent functions. They function as morphogens throughout early development, driving organ formation and regulating tissue homeostasis. As a result, it's no surprise that BMP deficiency causes severe developmental defects as well as a variety of clinical disorders. To identify transmembrane BMP receptors, researchers utilised affinity labelling experiments with radiolabeled BMP ligands on cells overexpressing ActR2-related proteins. Type I receptors (sometimes called activin receptor-like kinases) and type II receptors are two distinct receptor subfamilies.

BMP receptor signalling

BMPs are homo- or heterodimers that bind with two type I and two heteromeric type II receptor complexes BMPs bind poorly to type I and type II receptors, but their affinity rises when they engage with the type I-type II heteromeric complex. The general design of the extracellular domains is fairly constant among receptor complexes, with the tetramer having a 2-fold symmetry axis. Type II domains form an intermolecular disulfide bridge at the tetramer interface, whereas type I receptors have specialised 'binding loops.' Minor sequence changes can affect the conformation of this loop, and therefore the affinity of the type I-type II interaction. Specific 'hot spots' on the tetramer's binding surface alter the tetramer's interaction with BMP ligands, allowing for alterations in ligand and receptor complex selectivity. BMP dimers bind to heteromeric complexes with varying degrees of affinity. 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, however BMP6 can also bind ALK3 and ALK6; and BMP2 and BMP4 have the strongest connections with ALK3 and ALK6. BMPs have the ability to form heteromeric complexes with several type I receptors. The availability of ligand to signalling receptors is controlled by binding to ECM components and soluble ligand binding proteins. BMP ligands interact with signalling receptors through auxiliary accessory receptors, sometimes known as "co-receptors." Endoglin is a transmembrane receptor that lacks an enzymatic motif and has a brief intracellular domain.

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Such co-receptors include Repulsive Guidance Molecules (RGMs) A, B, and C (also known as hemojuvelin), which are coupled to the plasma membrane by a Glycosylphosphatidylinositol (GPI)-anchor.

The BMP/SMAD pathway appears to be simple: ligand activates BMP receptors, and SMADs transmit the activation signal from the plasma membrane to the nucleus. There are no intracellular enzymatic amplification stages, unlike tyrosine kinase receptors. As a result, in accordance with its morphogen function, the amount of active BMP ligand determines the degree of activated SMAD. Activated BMPRIs, such as ALK1, 2, 3, and 6, promote phosphorylation of SMAD1, SMAD5, and SMAD8. TRI/ALK5 and the activin type I receptor ALK4 phosphorylate SMAD2 and SMAD3, respectively.

CONCLUSION

To exert their physiological effects, 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. The structurally related 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 BMP ligand subgroups. Within each class, there is a lot of overlap in receptor binding specificity. BMPs are found in many tissues and govern the development and function of many distinct cell types, with the amplitude and length of the BMP signal being crucial. Each stage of the BMP pathway is regulated in a complicated way by extracellular and intracellular inputs. The function of BMP receptors is also controlled in a variety of ways. BMP stimulation produces inhibitory members of the SMAD family (SMAD6 and -7), which work in a feedback process to mediate BMPR ubiquitination and promote proteasomal degradation.