Signaling by BMP

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21/02/2020
Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references


Reactome database release: 71

This document contains 1 pathway and 17 reactions (see Table of Contents)
Bone morphogenetic proteins (BMPs) have many biological activities in various tissues, including bone, cartilage, blood vessels, heart, kidney, neurons, liver and lung. They are members of the Transforming growth factor-Beta (TGFβ) family. They bind to type II and type I serine-threonine kinase receptors, which transduce signals through SMAD and non-SMAD signalling pathways. BMP signalling is linked to a wide variety of clinical disorders, including vascular diseases, skeletal diseases and cancer. BMPs typically activate BMP type I receptors and signal via SMAD1, 5 and 8. They can be classified into several subgroups, including the BMP2/4 group, the BMP5-8 osteogenic protein-1 (OP1) group, the growth and differentiation factor (GDF) 5-7 group and the BMP9/10 group. Most of the proteins of the BMP2/4, OP1 and BMP9/10 groups induce formation of bone and cartilage tissues in vivo, while the GDF5-7 group induce cartilage and tendon-like, but not bone-like, tissues (Miyazono et al. 2010). Members of the TGFβ family bind to two types of serine-threonine kinase receptors, type I and type II (Massagué 2012). BMPs can bind type I receptors in the absence of type II receptors, but both types are required for signal transduction. The presence of both types dramatically increases binding affinity (Rozenweig et al. 1995). The type II receptor kinase transphosphorylates the type I receptor, which transmits specific intracellular signals. Type I and type II receptors share similar structural properties, comprised of a relatively short extracellular domain, a single membrane-spanning domain and an intracellular domain containing a serine-threonine kinase domain. Seven receptors, collectively referred to as the Activin receptor-like kinases (ALK), have been identified as type I receptors for the TGFβ family in mammals. ALKs are classified into three groups based on their structure and function, the BMP/RI group (Bone morphogenetic protein receptor type-1A, ALK3, BMPRIA and Bone morphogenetic protein receptor type-1B, ALK6, BMPRI1B), the ALK1 group (Serine/threonine-protein kinase receptor R3, ALK1, ACVR1L1 and Activin receptor type-1, ALK2, ACVR1) and the TBetaR1 group (Activin receptor type-1B, ALK4, ACVR1B and TGF-beta receptor type-1, ALK5, TGFBR1 and Activin receptor type-1C, ALK7, ACVR1C) (Kawabata et al. 1998). ALK1 group and BMPRI group activate SMAD1/5/8 and transduce similar intracellular signals. The TBetaR1 group activate SMAD2/3. BMPRI1A and ACVR1 are widely expressed. BMPRI1B shows a more restricted expression profile. ACVR1L1 is limited to endothelial cells and a few other cell types. The binding specificities of BMPs to type I receptors is affected by the type II receptors that are present (Yu et al. 2005). Typically, BMP2 and BMP4 bind to BMPRI1A and BMPRI1B (ten Dijke et al. 1994). BMP6 and BMP7 bind strongly to ACVR1 and weakly to BMPRI1B. Growth/differentiation factor 5 (BMP14, GDF5) preferentially binds to
BMPR1B, but not to other type I receptors (Nishitoh et al. 1995). BMP9 and BMP10 bind to ACVRL1 and ACVRL (Scharpfenecker et al. 2007). BMP type I receptors are shared by other members of the TGFB family. Three receptors, Bone morphogenetic protein receptor type-2 (BMPR2), Activin receptor type-2A (ACVR2A) and Activin receptor type-2B (ACVR2B) are the type II receptors for mammalian BMPs. They are widely expressed in various tissues. BMPR2 is specific for BMPs, whereas ACVR2A and ACVR2B are shared with activins and myostatin. BMP binding and signalling can be affected by coreceptors. Glycosylphosphatidylinositol (GPI)-anchored proteins of the repulsive guidance molecule (RGM) family, including RGMA, RGMB (DRAGON) and Hemojuvelin (HFE2, RGMC) are coreceptors for BMP2 and BMP4, enhancing signaling (Samad et al. 2005, Babitt et al. 2005, 2006). They interact with BMP type I and/or type II receptors and bind BMP2 and BMP4, but not BMP7 or TGFB1. BMP2/4 signalling normally involves BMPR2, not ACVR2A or ACVR2B. Cells transfected with RGMA use both BMPR2 and ACVR2A for BMP-2/4 signalling, suggesting that RGMA facilitates the use of ACVR2A by BMP2/4 (Xia et al. 2007). Endoglin (ENG) is a transmembrane protein expressed in proliferating endothelial cells. It binds various ligands including TGFB1/3, Activin-A and BMP2/7 (Barbara et al. 1999). It inhibits TGFB-induced responses and enhances BMP7-induced responses (Scherner et al. 2007). Mutations in ENG result in hereditary haemorrhagic telangiectasia (HHT1), also known as OslerWeberRendu disease, while mutations in ACVRL1 lead to HHT2, suggesting that they act in a common signalling pathway (McAllister et al. 1994, Johnson et al. 1996). BMP2 is a dimeric protein, having two receptor-binding motifs. One is a high-affinity binding site for BMPR1A, the other is a low-affinity binding site for BMPR2 (Kirsch et al. 2000). In the absence of ligand stimulation, small fractions of type II and type I receptors are present as preexisting homodimers and heterodimers on the cell surface. Ligand-binding increases oligomerization. The intracellular domains of type I receptors have a characteristic GS domain (glycine and serine-rich domain) located N-terminal to the serine-threonine kinase domains. Type II receptor kinases are constitutively active in the absence of ligand. Upon ligand binding, the type II receptor kinase phosphorylates the GS domain of the type I receptor, a critical event in signal transduction by the serine/threonine kinase receptors (Miyazono et al. 2010). Activation of the TGFBR1 receptor has been studied in detail. The inactive conformation is maintained by interaction between the GS domain, the N-terminal lobe and the activation loop of the kinase (Huse et al. 1999). When the GS domain is phosphorylated by the type II receptor kinase, the TGFBR1 kinase is converted to an active conformation. Mutations of Thr-204 in TGFBR1 and the corresponding Gln in BMP type I receptors lead to their constitutive activation. The L45 loop, in the kinase domain of type I receptors, specifically interacts with receptor-regulated Smads (R-Smads). Neurotrophic tyrosine kinase receptor type 3 (NT-3 growth factor receptor, TrkC, NTRK3) directly binds BMPR2, interfering with its interaction with BMPR1A, which inhibits downstream signalling (Jin et al. 2007). Tyrosine-protein kinase transmembrane receptor ROR2 and BMPR1B form a heteromeric complex in a ligand independent fashion that modulatesGDF5-BMPR1B signalling by inhibition of Smad1/5 signalling (Sammar et al. 2004). Type I receptor kinases activated by the type II receptor kinases, phosphorylate R-Smads. R-Smads then form a complex with common-partner Smad (co-Smad) and translocate to the nucleus. The oligomeric Smad complexes regulate the transcription of target genes through interaction with various transcription factors and transcriptional coactivators or corepressors. Inhibitory Smads (I-Smads) negatively regulate the action of R-Smads and/or co-Smads. Eight different Smads have been identified in mammals. Smad1, Smad5 and Smad8 are R-Smads in BMP signalling pathways (BMP-specific R-Smads). Smad2 and Smad3 are R-Smads in TGFbeta/activin signalling pathways. BMP receptors can phosphorylate Smad2 in certain types of cells (Murakami et al. 2009). Smad1, Smad5 and Smad8 are structurally highly similar to each other. The functional differences between them are largely unknown. Smad4 is the only co-Smad in mammals, shared by both BMP and TGFbeta/activin signalling pathways. Smad6 and Smad7 are I-Smads.
Literature references


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The ligand trap binds the ligand BMP2, blocking BMP signalling

**Location:** Signaling by BMP

**Stable identifier:** R-HSA-201810

**Type:** binding

**Compartments:** extracellular region

BMP ligand traps are cystine-knot containing proteins which bind BMPs and antagonise their actions. They are active during organ development and morphogenesis. Different BMP ligand traps show specific spatio-temporal expression during development, and selective activity against specific BMP ligands.

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Formation of a heteromeric BMP receptor complex

Location: Signaling by BMP

Stable identifier: R-HSA-202604

Type: binding

Compartments: plasma membrane

BMP receptors, unlike TGF-beta receptors are known to form hetero-oligomeric complexes in the endoplasmic reticulum and are transported as oligomers to the plasma membrane where they bind ligand. However, evidence for ligand-induced heteromeric BMP receptor complexes on the cell surface has also been published, leading to a model where both pre-formed and ligand-induced receptor oligomers are encountered on the plasma membrane. Based on the latter, a theory has been formulated that suggests that the signaling outcome from pre-formed and ligand-induced BMP receptor complexes is different. The mechanism that might explain this theory must involve different ways of internalization and trafficking of the BMP receptor complexes.

Followed by: BMP2 binds to the receptor complex

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BMP2 binds to the receptor complex

Location: Signaling by BMP

Stable identifier: R-HSA-201457

Type: binding

Compartments: extracellular region, plasma membrane

The mature dimeric BMP2 binds with high affinity to its signalling receptor, the type II receptor serine/threonine kinase. The type II receptor is known to form dimeric complexes even in the absence of BMP2 (Rosenzweig et al.1995).

Preceded by: Formation of a heteromeric BMP receptor complex

Followed by: Type II receptor phosphorylates type I receptor

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Type II receptor phosphorylates type I receptor

Location: Signaling by BMP

Stable identifier: R-HSA-201443

Type: transition

Compartments: cytosol, plasma membrane

Formation of the hetero-tetrameric BMP2:receptor complex induces receptor rotation, so that their cytoplasmic kinase domains face each other in a catalytically favourable configuration. The constitutively active type II receptor kinase (which auto-phosphorylates in the absence of ligand), trans-phosphorylates specific serine residues at the conserved Gly-Ser-rich juxtapositioned domain of the type I receptor. It is not known if exactly 8 ATPs are required for the phosphorylation of type I receptor, there could be more or less than this number.

Preceded by: BMP2 binds to the receptor complex

Followed by: I-Smad binds to type I receptor, preventing Smad1/5/8 from being activated, An anchoring protein, Endofin, recruits R-Smad1/5/8

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Endofin is a FYVE domain-containing protein that strongly resembles SARA, the Smad anchor for receptor activation that facilitates TGF-beta signalling. Endofin acts in a similar manner as SARA, it binds to BMP-specific R-Smads, it localizes in early endosomes and it facilitates their phosphorylation, thus promoting signal transduction by the BMP receptors. However, it should be noted that endofin has also been reported to bind to the Co-Smad, Smad4, and to the TGF-beta type receptor, thus enhancing TGF-beta signalling. Since Smad4 is a common Smad that operates in the BMP-specific pathways, the latter observation might imply that endofin could regulate both TGF-beta and BMP signalling, a hypothesis still open for investigation.

**Preceded by:** Type II receptor phosphorylates type I receptor

**Followed by:** Activated type I receptor phosphorylates R-Smad1/5/8 directly

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Ubiquitin-dependent degradation controls basal levels of R-Smad1/5/8

Location: Signaling by BMP

Stable identifier: R-HSA-201445

Type: omitted

Compartments: cytosol

SMAD2 is polyubiquitinated by SMURF2 and targeted for proteasome-mediated degradation.

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I-Smad binds to type I receptor, preventing Smad1/5/8 from being activated

**Location:** Signaling by BMP

**Stable identifier:** R-HSA-201821

**Type:** binding

**Compartments:** cytoplasmic side of plasma membrane

Smad6 and Smad7, the two I-Smads, bind directly to the BMP type I receptors and recruit the ubiquitin ligase Smurf1. This reaction leads to competitive inhibition of R-Smad binding to the type I receptor and activating phosphorylation by the receptor, and also leads to BMP receptor ubiquitination and degradation.

**Preceded by:** Type II receptor phosphorylates type I receptor

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Activated type I receptor phosphorylates R-Smad1/5/8 directly

**Location:** Signaling by BMP

**Stable identifier:** R-HSA-201476

**Type:** transition

**Compartments:** plasma membrane

Activated type I receptor kinase directly phosphorylates two of the C-terminal serine residues of SMAD2 or SMAD3. Binding of these R-SMADs to the L45 loop of the type I receptor is critical for this event.

**Preceded by:** An anchoring protein, Endofin, recruits R-Smad1/5/8

**Followed by:** Phospho-R-Smad1/5/8 dissociates from the receptor complex

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Phospho-R-Smad1/5/8 dissociates from the receptor complex

Location: Signaling by BMP

Stable identifier: R-HSA-201453

Type: dissociation

Compartments: early endosome

Upon phosphorylation of the R-SMAD (SMAD2/3), the conformation of the C-terminal (MH2) domain of the R-SMAD changes, lowering its affinity for the type I receptor and ZFYVE9 (SARA). As a result, the phosphorylated R-SMAD dissociates from the activated receptor complex (TGFBR).

Preceded by: Activated type I receptor phosphorylates R-Smad1/5/8 directly

Followed by: I-Smad competes with Co-Smad for R-Smad1/5/8, Phospho-R-Smad1/5/8 forms a complex with Co-Smad

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I-Smad competes with Co-Smad for R-Smad1/5/8

Location: Signaling by BMP

Stable identifier: R-HSA-202626

Type: binding

Compartments: cytoplasmic side of plasma membrane

I-SMAD selectively antagonizes BMP-activated Smad1/5/9 by acting as a CO-SMAD decoy.

Preceded by: Phospho-R-Smad1/5/8 dissociates from the receptor complex

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Phospho-R-Smad1/5/8 forms a complex with Co-Smad

Location: Signaling by BMP

Stable identifier: R-HSA-201422

Type: binding

Compartments: cytosol

The phosphorylated C-terminal tail of R-SMAD induces a conformational change in the MH2 domain (Qin et al. 2001, Chacko et al. 2004), which now acquires high affinity towards Co-SMAD i.e. SMAD4 (common mediator of signal transduction in TGF-beta/BMP signaling). The R-SMAD:Co-SMAD complex (Nakao et al. 1997) most likely is a trimer of two R-SMADs with one Co-SMAD (Kawabata et al. 1998). It is important to note that the Co-SMAD itself cannot be phosphorylated as it lacks the C-terminal serine motif.

ZFYVE16 (endofin) promotes SMAD heterotrimer formation. ZFYVE16 can bind TGFBR1 and facilitate SMAD2 phosphorylation, and it can also bind SMAD4, but the exact mechanism of ZFYVE16 (endofin) action in the context of TGF-beta receptor signaling is not known (Chen et al. 2007).

Preceded by: Phospho-R-Smad1/5/8 dissociates from the receptor complex

Followed by: The phospho-R-Smad1/5/8:Co-Smad transfers to the nucleus

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The phospho-R-Smad1/5/8:Co-Smad transfers to the nucleus

Location: Signaling by BMP

Stable identifier: R-HSA-201472

Type: transition

Compartments: nuclear envelope

The phosphorylated-r-SMAD1/5/8:Co-SMAD complex rapidly translocates to the nucleus where it binds directly to DNA and interacts with a plethora of transcription co-factors. Regulation of target gene expression can be either positive or negative. A classic example of a target gene of the pathway are the genes encoding for i-SMADs. Thus, BMP2/SMAD signalling induces the expression of the negative regulators of the pathway (a negative feedback loop).

Preceded by: Phospho-R-Smad1/5/8 forms a complex with Co-Smad

Followed by: Ubiquitin-dependent degradation of the Smad complex terminates BMP2 signalling

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Ubiquitin-dependent degradation of the Smad complex terminates BMP2 signalling

**Location:** Signaling by BMP

**Stable identifier:** R-HSA-201425

**Type:** omitted

**Compartments:** nucleoplasm

The nuclear R-SMAD:Co-SMAD complex recruits ubiquitin conjugating enzymes, such as UBE2D1 and UBE2D3, that ubiquitinate the complex and eventually lead to its proteasomal degradation. This provides an end point to the signaling pathway.

**Preceded by:** The phospho-R-Smad1/5/8:Co-Smad transfers to the nucleus

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SKI complexes with the Smad complex, suppressing BMP2 signalling

**Location:** Signaling by BMP

**Stable identifier:** R-HSA-201423

**Type:** binding

**Compartments:** nucleoplasm

SKI and SKIL (SNO) are able to recruit NCOR and possibly other transcriptional repressors to SMAD2/3:SMAD4 complex, inhibiting SMAD2/3:SMAD4-mediated transcription (Sun et al. 1999, Luo et al. 1999, Strochein et al. 1999). Experimental findings suggest that SMAD2 and SMAD3 may target SKI and SKIL for degradation (Strochein et al. 1999, Sun et al. 1999 PNAS, Bonni et al. 2001), and that the ratio of SMAD2/3 and SKI/SKIL determines the outcome (inhibition of SMAD2/3:SMAD4-mediated transcription or degradation of SKI/SKIL). SKI and SKIL are overexpressed in various cancer types and their oncogenic effect is connected with their ability to inhibit signaling by TGF-beta receptor complex.

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I-Smad competes with R-Smad1/5/8 for type I receptor

**Location:** Signaling by BMP

**Stable identifier:** R-HSA-201475

**Type:** binding

**Compartments:** plasma membrane, cytosol, extracellular region

I-SMADs reside in the nucleus presumably to be sequestered from the BMP2:receptor complex and thus avoid inappropriate silencing of the signalling pathway. Upon activation of the signalling pathway, I-SMADs exit the nucleus and are recruited to the signalling BMP2:receptor complex. I-SMADs directly bind to the so-called L45 loop of the type I receptor, the site of binding of R-SMADs. Thus, I-SMADs competitively inhibit the activation/phosphorylation of R-SMADs.

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Anti-Müllerian hormone (AMH), also known as Müllerian inhibiting substance (MIS), is a member of the Transforming growth factor Beta (TGFB) superfamily (Massagué 1998). It plays a crucial role during male sexual differentiation, inducing the regression of the Müllerian ducts in male fetuses (Nef & Parada 2000). Mutations in the AMH gene (Cate et al. 1986) cause Persistent Müllerian duct syndrome, a rare form of male pseudohermaphroditism (Belville et al. 1999, MacLaughlin & Donahoe 2004). As a member of the TGFB superfamily, it was expected that AMH signaling would resemble the signaling pathways defined for other family members (Visser 2003). TGFB family members signal through a heteromeric receptor complex consisting of two related serine/threonine kinase receptors, the type I and II receptors. The dimeric ligand initially binds to the type II receptor, which recruits and phosphorylates the type I receptor. This activates the type I receptor resulting in phosphorylation of Smad proteins.

Prior to secretion, AMH undergoes glycosylation and dimerization to produce a 144-kDa dimer composed of identical disulphide-linked 72-kDa monomer subunits; each monomer contains an N-terminal domain 'pro' region and a C-terminal domain 'mature' region. The type II receptor for AMH is AMHR2 (Baarends et al. 1994, di Clemente et al. 1994, Teixeira et al. 1996). AMH must be cleaved to bind AMHR2 but dissociation of the pro-region from the mature C-terminal dimer is not required for this initial interaction (di Clemente et al. 2010). The AMH:AMHR2 complex has been reported to recruit in a context specific manner two candidate type I receptors, Bone morphogenetic protein receptor type-1B (BMPR1A, ALK3) (Jamin et al. 2002), and Activin receptor type-1 (ACVR1, ALK2) (Clarke et al. 2001, Visser et al. 2001) leading to SMAD1/5/8 activation (Gouedard et al. 2000, Zhan et al. 2006).

**Literature references**

ACVRL1 binds BMP9,BMP10

**Location:** Signaling by BMP

**Stable identifier:** R-HSA-8858369

**Type:** binding

**Compartments:** extracellular region, plasma membrane

Growth/differentiation factor 2 (Bone morphogenic protein 9, BMP9, GDF2) and Bone morphogenetic protein 10 (BMP10) bind with sub-nanomolar affinities to both the type I receptor Serine/threonine-protein kinase receptor R3 (ACVRL1, Activin receptor-like kinase 1, ALK1) and the type II receptor Activin receptor type-2B (ActR-IIB, ACVR2B) (Scharpfenecker et al. 2007, Laurent et al. 2007, Townson et al. 2012). BMP9 also bind with high affinity the type II receptors Bone morphogenetic protein receptor type-2 (BMPR2) and Activin receptor type-2A (ACVR2A, ActRIIA) (Kuo et al. 2014; Kienast et al. 2016). BMP9 binding leads to phosphorylation of Mothers against decapentaplegic homolog 1 (SMAD1), SMAD5 and SMAD8 in microvascular endothelial cells (David et al. 2007).

ACVRL1 is an important regulator of normal blood vessel development as well as pathological tumor angiogenesis (Massague 1998).

**Literature references**


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