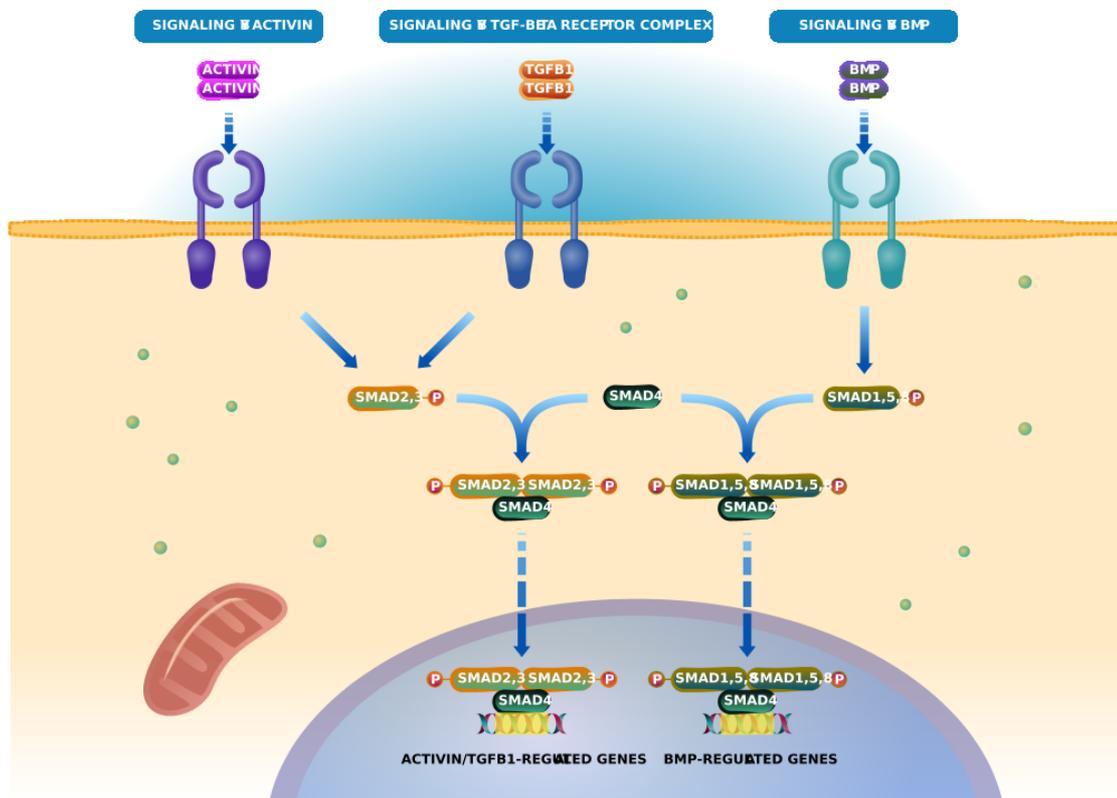


Signaling by TGFB family members



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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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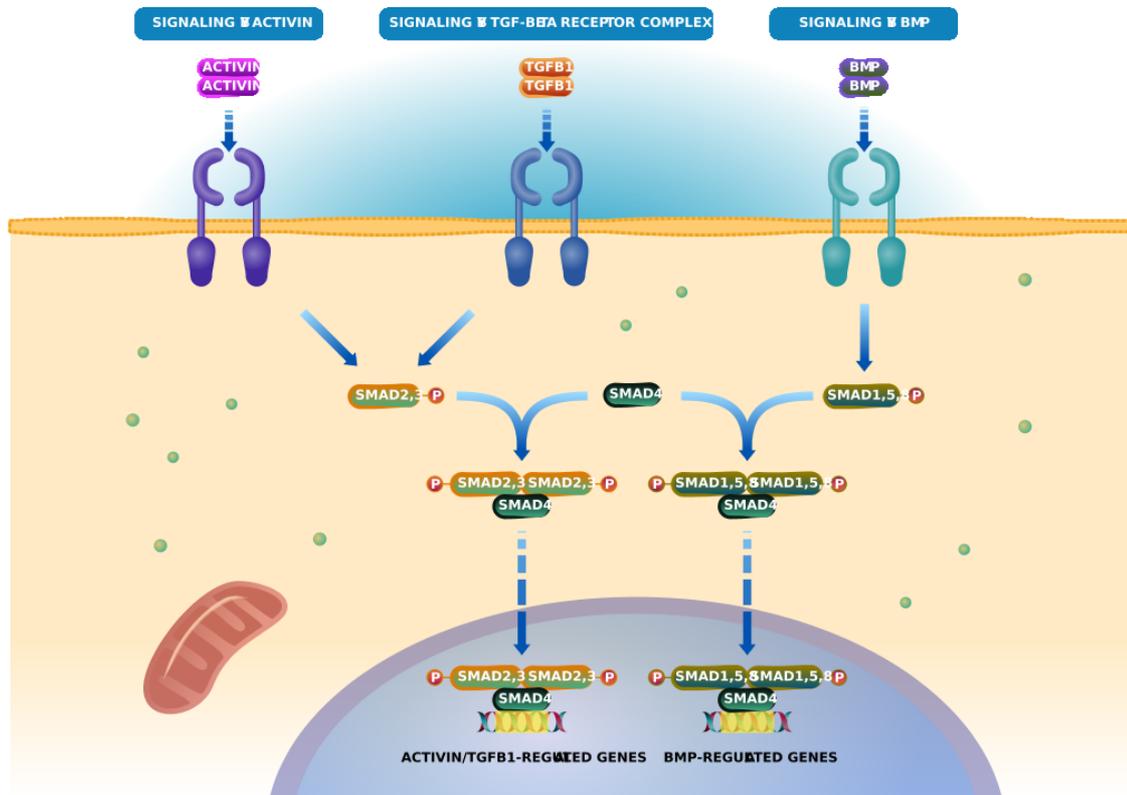
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Reactome database release: 75

This document contains 4 pathways ([see Table of Contents](#))

Signaling by TGFβ family members ↗

Stable identifier: R-HSA-9006936



The human genome encodes 33 TGF-beta family members, including TGF-beta itself, as well as bone morphogenetic protein (BMP), activin, nodal and growth and differentiation factors (GDFs). This super-family of ligands generally binds as dimers to hetero-tetrameric cell-surface receptor serine/threonine kinases to activate SMAD-dependent and SMAD-independent signaling (reviewed in Morikawa et al, 2016; Budi et al, 2017).

Signaling by the TGF-beta receptor complex is initiated by TGF-beta. TGF-beta (TGFB1), secreted as a homodimer, binds to TGF-beta receptor II (TGFB2R), inducing its dimerization and formation of a stable hetero-tetrameric complex with TGF-beta receptor I homodimer (TGFB1R). TGFB2R-mediated phosphorylation of TGFB1R triggers internalization of the heterotetrameric TGF beta receptor complex (TGFB) into clathrin coated endocytic vesicles and recruitment of cytosolic SMAD2 and SMAD3, which act as R-SMADs for TGF beta receptor complex. TGFB1R phosphorylates SMAD2 and SMAD3, promoting their association with SMAD4 (known as Co-SMAD). In the nucleus, the SMAD2/3:SMAD4 heterotrimer binds target DNA elements and, in cooperation with other transcription factors, regulates expression of genes involved in cell differentiation. For a review of TGF-beta receptor signaling, please refer to Kang et al. 2009.

Signaling by BMP is triggered by bone morphogenetic proteins (BMPs). BMPs can bind type I receptors in the absence of type II receptors, but the presence of both types dramatically increases binding affinity. The type II receptor kinase transphosphorylates the type I receptor, leading to recruitment and phosphorylation of SMAD1, SMAD5 and SMAD8, which function as R-SMADs in BMP signalling pathways. Phosphorylated SMAD1, SMAD5 and SMAD8 form heterotrimeric complexes with SMAD4, the only Co-SMAD in mammals. The SMAD1/5/8:SMAD4 heterotrimer regulates transcription of genes involved in development of many tissues, including bone, cartilage, blood vessels, heart, kidney, neurons, liver and lung. For review of BMP signaling, please refer to Miyazono et al. 2010.

Signaling by activin is triggered when an activin dimer (activin A, activin AB or activin B) binds the type II receptor (ACVR2A, ACVR2B). This complex then interacts with the type I receptor (ACVR1B, ACVR1C) and phosphorylates it. The phosphorylated type I receptor phosphorylates SMAD2 and SMAD3. Dimers of phosphorylated SMAD2/3 bind SMAD4 and the resulting ternary complex enters the nucleus and activates target genes. For a review of activin signaling, please refer to Chen et al. 2006.

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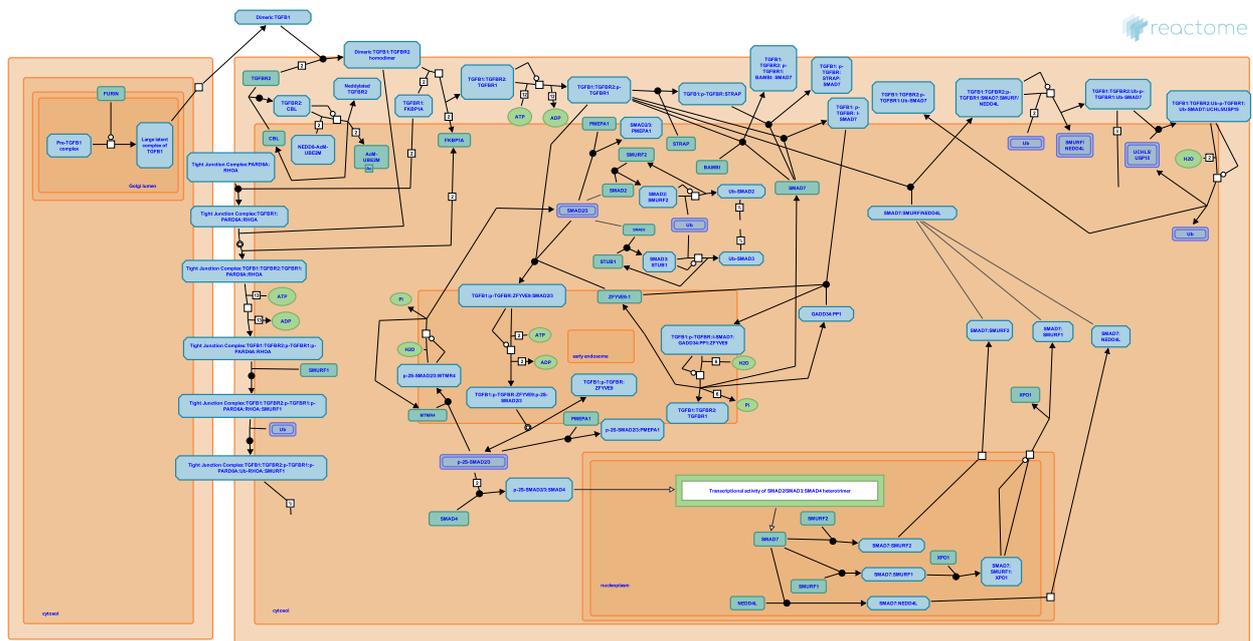
Editions

2017-05-24	Authored, Edited	Rothfels, K.
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Signaling by TGF-beta Receptor Complex ↗

Location: Signaling by TGFB family members

Stable identifier: R-HSA-170834



The TGF-beta/BMP pathway incorporates several signaling pathways that share most, but not all, components of a central signal transduction engine. The general signaling scheme is rather simple: upon binding of a ligand, an activated plasma membrane receptor complex is formed, which passes on the signal towards the nucleus through a phosphorylated receptor SMAD (R-SMAD). In the nucleus, the activated R-SMAD promotes transcription in complex with a closely related helper molecule termed Co-SMAD (SMAD4). However, this simple linear pathway expands into a network when various regulatory components and mechanisms are taken into account. The signaling pathway includes a great variety of different TGF-beta/BMP superfamily ligands and receptors, several types of the R-SMADs, and functionally critical negative feedback loops. The R-SMAD:Co-SMAD complex can interact with a great number of transcriptional co-activators/co-repressors to regulate positively or negatively effector genes, so that the interpretation of a signal depends on the cell-type and cross talk with other signaling pathways such as Notch, MAPK and Wnt. The pathway plays a number of different biological roles in the control of embryonic and adult cell proliferation and differentiation, and it is implicated in a great number of human diseases.

TGF beta (TGFB1) is secreted as a homodimer, and as such it binds to TGF beta receptor II (TGFBRII), inducing its dimerization. Binding of TGF beta enables TGFBRII to form a stable hetero-tetrameric complex with TGF beta receptor I homodimer (TGFBRI). TGFBRII acts as a serine/threonine kinase and phosphorylates serine and threonine residues within the short GS domain (glycine-serine rich domain) of TGFBRI.

The phosphorylated heterotetrameric TGF beta receptor complex (TGFBRI-TGFBRII) internalizes into clathrin coated endocytic vesicles where it associates with the endosomal membrane protein SARA. SARA facilitates the recruitment of cytosolic SMAD2 and SMAD3, which act as R-SMADs for TGF beta receptor complex. TGFBRII phosphorylates recruited SMAD2 and SMAD3, inducing a conformational change that promotes formation of R-SMAD trimers and dissociation of R-SMADs from the TGF beta receptor complex.

In the cytosol, phosphorylated SMAD2 and SMAD3 associate with SMAD4 (known as Co-SMAD), forming a heterotrimer which is more stable than the R-SMAD homotrimers. R-SMAD:Co-SMAD heterotrimer translocates to the nucleus where it directly binds DNA and, in cooperation with other transcription

factors, regulates expression of genes involved in cell differentiation, in a context-dependent manner.

The intracellular level of SMAD2 and SMAD3 is regulated by SMURF ubiquitin ligases, which target R-SMADs for degradation. In addition, nuclear R-SMAD:Co-SMAD heterotrimer stimulates transcription of inhibitory SMADs (I-SMADs), forming a negative feedback loop. I-SMADs bind the phosphorylated TGF beta receptor complexes on caveolin coated vesicles, derived from the lipid rafts, and recruit SMURF ubiquitin ligases to TGF beta receptors, leading to ubiquitination and degradation of TGFBR1. Nuclear R-SMAD:Co-SMAD heterotrimers are targets of nuclear ubiquitin ligases which ubiquitinate SMAD2/3 and SMAD4, causing heterotrimer dissociation, translocation of ubiquitinated SMADs to the cytosol and their proteasome-mediated degradation. For a recent review of TGF-beta receptor signaling, please refer to Kang et al. 2009.

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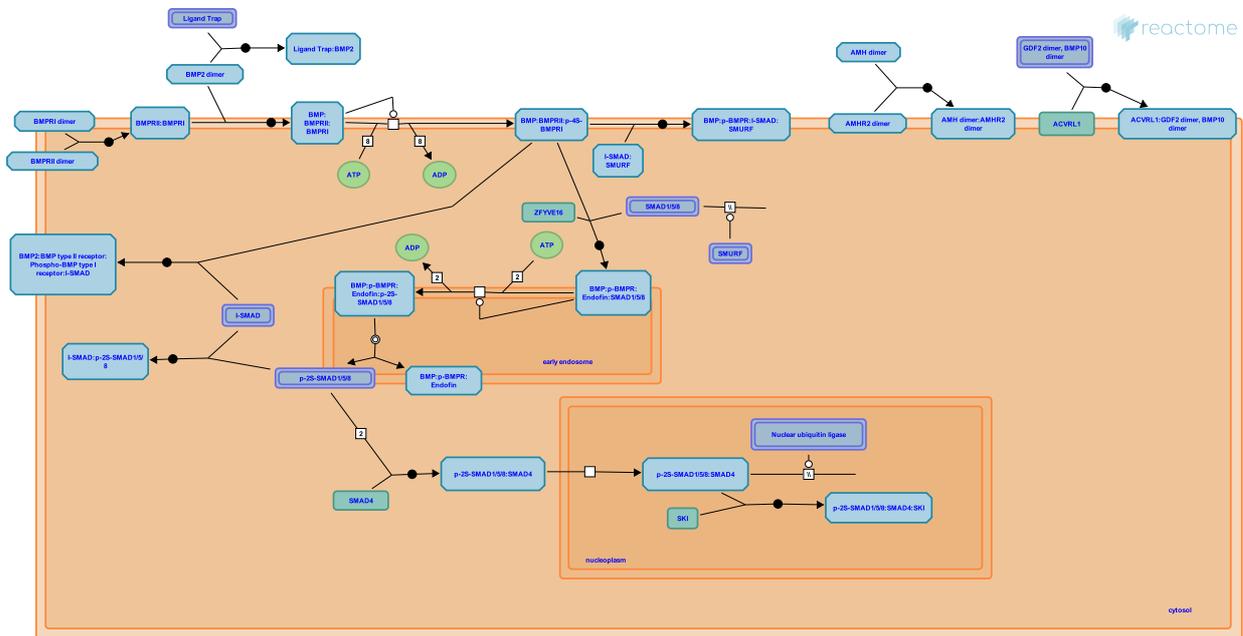
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2006-02-02	Authored	Jassal, B., Heldin, CH., Moustakas, A., Huminiecki, L.
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Signaling by BMP ↗

Location: Signaling by TGFB family members

Stable identifier: R-HSA-201451



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 (TGFB) 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 sub-groups, 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 TGFB 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 TGFB family in mammals. ALKs are classified into three groups based on their structure and function, the BMPRI group (Bone morphogenetic protein receptor type-1A, ALK3, BMPRI1A and Bone morphogenetic protein receptor type-1B, ALK6, BMPRI1B), the ALK1 group (Serine/threonine-protein kinase receptor R3, ALK1, ACVRL1 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. ACVRL1 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 BMPR1A and BMPR1B (ten Dijke et al. 1994). BMP6 and BMP7 bind strongly to ACVR1 and weakly to BMPR1B. 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 modulates GDF5-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 TGFB/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 TGFB/activin signalling pathways. Smad6 and Smad7 are I-Smads.

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Editions

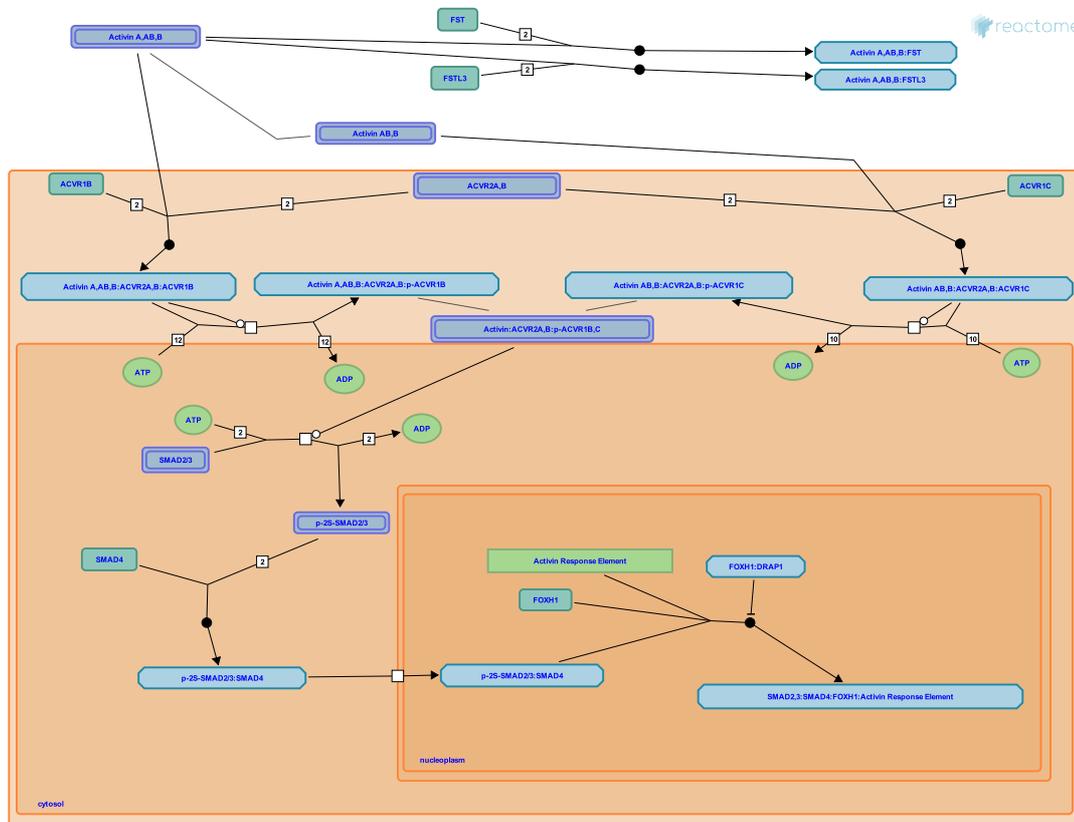
2007-11-07	Authored	Moustakas, A., Huminiecki, L.
2007-11-12	Reviewed	Heldin, CH.

Signaling by Activin ↗

Location: Signaling by TGFB family members

Stable identifier: R-HSA-1502540

Compartments: cytosol, extracellular region, plasma membrane



Activin was initially discovered as an activator of follicle stimulating hormone in the pituitary gland. It has since been shown to be an important participant in the differentiation of embryonic cells into mesodermal and endodermal layers. Activin binds the Activin receptor and triggers downstream events: phosphorylation of SMAD2 and SMAD3 followed by activation of gene expression (reviewed in Attisano et al. 1996, Willis et al. 1996, Chen et al. 2006, Hinck 2012). Activins are dimers comprising activin A (I-NHBA:INHBA), activin AB (INHBA:INHBB), and activin B (INHBB:INHBB). Activin first binds the type II receptor (ACVR2A, ACVR2B) and this complex then interacts with the type I receptor (ACVR1B, ACVR1C) (Attisano et al. 1996). The type II receptor phosphorylates the type I receptor and then the phosphorylated type I receptor phosphorylates SMAD2 and SMAD3. Dimers of phosphorylated SMAD2/3 bind SMAD4 and the resulting ternary complex enters the nucleus and activates target genes.

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