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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

16/11/2022
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.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 82

This document contains 2 pathways and 8 reactions (see Table of Contents)
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 (INHBA: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.

**Literature references**


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Activin A, AB, B binds Activin Receptor ACVR2A, B:ACVR1B

Location: Signaling by Activin

Stable identifier: R-HSA-1181153

Type: binding

Compartments: plasma membrane, extracellular region

Activin binds the Activin receptor composed of a type II receptor (ACVR2A/B) and a type I receptor, in this case ACVR1B (ALK4) (Attisano et al. 1996, Zhou et al. 2000). Activin appears to interact initially with the type II receptor component (Attisano et al. 1996). It is unclear if the type II and type I receptors are associated before binding Activin. Any of Activin A (INHBA:INHBA), Activin AB (INHBA:INHBB), and Activin B (INHBB:INHBB) can bind and signal via an activin receptor containing the ACVR1B (ALK4) type I receptor.

Followed by: ACVR2A, B (ActRIIA, B) phosphorylates ACVR1B (ActRIB, ALK4) in response to Activin

Literature references


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**Activin AB,B binds Activin Receptor ACVR2A,B:ACVR1C**

**Location:** Signaling by Activin

**Stable identifier:** R-HSA-2470483

**Type:** binding

**Compartments:** plasma membrane, extracellular region

**Inferred from:** Activin AB/B binds Activin Receptor Acvr2a:Acvr1c (Mus musculus)

As inferred from mouse, Activin binds the Activin receptor composed of a type II receptor (ACVR2A/B) and a type I receptor, in this case ACVR1C (ALK7). It is unclear if the type II receptor and the type I receptor are associated before binding Activin, Activin AB (INHBA:INHBB) and Activin B (INHBB:INHBB), but not Activin A (INHBA:INHBA) can bind and signal via an activin receptor containing the ACVR1C (ALK7) type I receptor.

**Followed by:** ACVR2A,B (ActRIIA,B) phosphorylates ACVR1C (ActRIC, ALK7) in response to Activin

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**ACVR2A,B (ActRIIA,B) phosphorylates ACVR1B (ActRIB, ALK4) in response to Activin**

**Location:** Signaling by Activin

**Stable identifier:** R-HSA-1181149

**Type:** transition

**Compartments:** plasma membrane, cytosol

Upon binding Activin A (INHBA:INHBA), Activin AB (INHBA:INHBB), or Activin B (INHBB:INHBB), the type II component of the activin receptor (ACVR2A or ACVR2B) phosphorylates the type I component ACVR1B (ALK4) at multiple serine and threonine residues within the GS domain (Attisano et al. 1996, Willis et al. 1996, Willis and Mathews 1997, Zhou et al. 2000).

**Preceded by:** Activin A,B,B binds Activin Receptor ACVR2A,B:ACVR1B

**Followed by:** Phosphorylation of SMAD2,3 by Activin:Activin Receptor

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ACVR2A,B (ActRIIA,B) phosphorylates ACVR1C (ActRIC, ALK7) in response to Activin

**Location:** Signaling by Activin

**Stable identifier:** R-HSA-2470508

**Type:** transition

**Compartments:** plasma membrane, cytosol

**Inferred from:** Acvr2a phosphorylates Acvr1c in response to Activin (Mus musculus)

As inferred from mouse, upon binding Activin AB (INHBA:INHBB) or Activin B (INHBB:INHBB), the type II component of the activin receptor (ACVR2A or ACVR2B) phosphorylates the type I component ACVR1C (ALK7) at multiple serine and threonine residues within the GS domain.

**Preceded by:** Activin AB,B binds Activin Receptor ACVR2A,B:ACVR1C

**Followed by:** Phosphorylation of SMAD2,3 by Activin:Activin Receptor

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Phosphorylation of SMAD2,3 by Activin:Activin Receptor

Location: Signaling by Activin

Stable identifier: R-HSA-1549526

Type: transition

Compartments: plasma membrane, cytosol

Activin receptors containing the type II receptors ACVR2A/B (ActRIIA, ActRIIB) and the type I receptors ACVR1B/C (ALK4, ALK7) signal through SMAD2 and SMAD3. The phosphorylated type I receptor (ACVR1B/C) phosphorylates SMAD2 or SMAD3. Homodimers or heterodimers of SMAD2 and SMAD3 bind the co-Smad SMAD4 and the ternary complex (SMAD2/3:SMAD3:SMAD4) enters the nucleus and activates expression of target genes.

Preceded by: ACVR2A,B (ActRIIA,B) phosphorylates ACVR1B (ActRIB, ALK4) in response to Activin, ACVR2A,B (ActRIIA,B) phosphorylates ACVR1C (ActRIC, ALK7) in response to Activin

Followed by: Phosphorylated SMAD2 and SMAD3 form a complex with SMAD4

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Phosphorylated SMAD2 and SMAD3 form a complex with SMAD4

Location: Signaling by Activin

Stable identifier: R-HSA-170847

Type: transition

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).

SARS-CoV-1 nucleocapsid protein (N) associates with SMAD3 and this binding interferes with the complex formation between SMAD3 and SMAD4. By this mechanism N modulates TGF-beta signaling to block apoptosis of SARS-CoV-infected host cells (Zhao et al. 2008).

Preceded by: Phosphorylation of SMAD2,3 by Activin:Activin Receptor

Followed by: The SMAD2/3:SMAD4 complex transfers to the nucleus

Literature references

Lin, K., Correia, JJ., Chacko, BM., Lam, SS., Qin, BY., de Caestecker, MP. (2001). Structural basis of Smad1 activation by receptor kinase phosphorylation. Mol Cell, 8, 1303-12.


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The SMAD2/3:SMAD4 complex transfers to the nucleus

Location: Signaling by Activin

Stable identifier: R-HSA-173488

Type: omitted

Compartments: cytosol, nucleoplasm

The phosphorylated R-SMAD:CO-SMAD complex rapidly translocates to the nucleus (Xu et al. 2000, Kuri-saki et al. 2001, Xiao et al. 2003) where it binds directly to DNA and interacts with a plethora of transcription co-factors. Translocation of SMAD2 and SMAD3 to the nucleus is negatively regulated by ERK-mediated phosphorylation (Kretzschmar et al. 1999). 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, TGF-beta/SMAD signaling induces the expression of the negative regulators of the pathway (negative feedback loop).

Preceded by: Phosphorylated SMAD2 and SMAD3 form a complex with SMAD4

Followed by: Phospho R-SMAD(SMAD2,3):CO-SMAD(SMAD4):FOXH1 binds Activin Response Element

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Phospho R-SMAD(SMAD2,3):CO-SMAD(SMAD4):FOXH1 binds Activin Response Element

**Location:** Signaling by Activin

**Stable identifier:** R-HSA-1225919

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** p-Smad2,3:Smad4:Foxh1 binds Activin Response Element (Mus musculus)

As inferred from mouse, DRAP1 binds FOXH1 and inhibits activation of gene expression in response to NODAL signaling.

SMAD2 and SMAD3 do not bind DNA efficiently. They must interact with DNA-binding proteins to activate transcription. FOXH1 interacts with phospho-SMAD2 and phospho-SMAD3 complexed with CO-SMAD (SMAD4) at promoters containing the Activin Response Element (Zhou et al. 1998, Yanagisawa et al. 2000, inferred from Xenopus in Chen et al. 1996, Chen et al. 1997, Yeo et al. 1999). Follicle-stimulating hormone beta subunit (FSHB) and the Lim1 homeobox gene (LXH1) are examples of genes regulated by Activin.

**Preceded by:** The SMAD2/3:SMAD4 complex transfers to the nucleus

**Literature references**


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Both Follistatin (FST) and Follistatin-like-3 (FSTL3) irreversibly bind Activin dimers and prevent Activin from interacting with its receptor (reviewed in Schneyer et al. 2004, Xia and Schneyer 2009). Though functionally similar in vitro, FST and FSTL3 do not function identically in vivo. Mice lacking FST die shortly after birth due to defects in muscle and bone (Matzuk et al. 1995); mice lacking FSTL3 are viable but have altered glucose metabolism (Mukherjee et al. 2007).

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