TGF-beta receptor signaling activates SMADs

Blagotinšek Cokan, K., Chen, YG., Contreras, O., Heldin, CH., Huang, T., Huminiecki, L., Jassal, B., Jupe, S., May, B., Moustakas, A., Muiznieks, LD., Orlic-Milacic, M.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

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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.

11/11/2022
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 16 reactions (see Table of Contents)

https://reactome.org
TGF-beta receptor signaling activates SMADs

Stable identifier: R-HSA-2173789

Binding of transforming growth factor beta 1 (TGF beta 1, i.e. TGFB1) to TGF beta receptor type 2 (TGFBR2) activates TGF beta receptor signaling cascade. TGFB1 is posttranslationally processed by furin (Dubois et al. 1995) to form a homodimer and secreted to the extracellular space as part of the large latent complex (LLC). After the LLC disassembles in the extracellular space, dimeric TGFB1 becomes capable of binding to TGFBR2 (Annes et al. 2003, Keski Oja et al. 2004). Formation of TGFB1:TGFBR2 complex creates a binding pocket for TGF-beta receptor type-1 (TGFBR1) and TGFBR1 is recruited to the complex by binding to both TGFB1 and TGFBR2. This results in an active heterotetrameric TGF-beta receptor complex that consists of TGFB1 homodimer bound to two heterodimers of TGFBR1 and TGFBR2 (Wrana et al. 1992, Moustakas et al. 1993, Franzen et al. 1993). TGF-beta signaling can also occur through a single heterodimer of TGFBR1 and TGFBR2, although with decreased efficiency (Huang et al. 2011). TGFBR1 and TGFBR2 interact through their extracellular domains, which brings their cytoplasmic domains together. Ligand binding to extracellular receptor domains is cooperative, but no conformational change is seen from crystal structures of either TGFB1- or TGFB3-bound heterotetrameric receptor complexes (Groppe et al. 2008, Radaev et al. 2010).

Activation of TGFBR1 by TGFBR2 in the absence of ligand is prevented by FKBP1A (FKBP12), a peptidyl-prolyl cis-trans isomerase. FKBP1A forms a complex with inactive TGFBR1 and dissociates from it only after TGFB1 is recruited by TGFB1-bound TGFBR2 (Chen et al. 1997).

Both TGFBR1 and TGFBR2 are receptor serine/threonine kinases. Formation of the hetero-tetrameric TGF-beta receptor complex (TGFBR) in response to TGFB1 binding induces receptor rotation, so that TGFBR2 and TGFBR1 cytoplasmic kinase domains face each other in a catalytically favourable configuration. TGFBR2 trans-phosphorylates serine residues at the conserved Gly-Ser-rich juxtapositioned domain (GS domain) of TGFBR1 (Wrana et al. 1994, Souchelnytskyi et al. 1996), activating TGFBR1.
In addition to phosphorylation, TGFBR1 may also be sumoylated in response to TGF-beta stimulation. Sumoylation enhances TGFBR1 kinase activity (Kang et al. 2008).

The activated TGFBR complex is internalized by clathrin-mediated endocytosis into early endosomes. With the assistance of SARA, an early endosome membrane protein, phosphorylated TGFBR1 within TGFBR complex recruits SMAD2 and/or SMAD3, i.e. R-SMADs (Tsukazaki et al. 1998). TGFBR1 phosphoylates recruited SMAD2/3 on two C-terminal serine residues (Souchelnytskyi et al. 2001). The phosphorylation changes the conformation of SMAD2/3 MH2 domain, promoting dissociation of SMAD2/3 from SARA and TGFBR1 (Souchelnytskyi et al. 1997, Macias-Silva et al. 1996, Nakao et al. 1997) and formation of SMAD2/3 trimers (Chacko et al. 2004). The phosphorylated C-terminal tail of SMAD2/3 has high affinity for SMAD4 (Co-SMAD), inducing formation of SMAD2/3:SMAD4 heterotrimers, composed of two phosphorylated R-SMADs (SMAD2 and/or SMAD3) and SMAD4 (Co-SMAD). SMAD2/3:SMAD4 heterotrimers are energetically favored over R-SMAD trimers (Nakao et al. 1997, Qin et al. 2001, Kawabata et al. 1998, Chacko et al. 2004).

SMAD2/3:SMAD4 heterotrimers translocate to the nucleus where they act as transcriptional regulators.

**Literature references**


**Editions**

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https://reactome.org
In the Golgi apparatus, TGF-beta-1 (TGFβ1) is activated by furin protease cleavage of the N-terminal pro-peptide portion. This leads to the formation of the N-terminal disulphide-linked dimeric pro-peptides, also known as latency-associated proteins (LAPs) and the C-terminal mature disulphide-linked dimeric TGF-beta-1 (Dubois et al. 1995, Dubois et al. 2001, Leitlein et al. 2001). However, the N- and C-terminal polypeptides do not physically separate. Rather they stay in one complex. In addition, the LAP forms disulphide links with separate secreted proteins, the Latent TGF-beta binding proteins (LTBPs). LTBPs-linked to LAP and the non-covalently linked mature TGF-beta-1 remain together and form the large latent complex (LLC) (Annes et al. 2003).

Followed by: Secretion and activation of the latent large complex of TGF-beta-1

Literature references


Secretion and activation of the latent large complex of TGF-beta-1

Location: TGF-beta receptor signaling activates SMADs

Stable identifier: R-HSA-177107

Type: omitted

Compartments: Golgi lumen, extracellular region

The large latent complex (LLC) of TGF-beta-1 (TGFB1) is secreted by exocytosis to the extracellular region. TGF-beta-1 in the LLC (called small latent TGF-beta complex (SCL)) cannot interact with the receptors and for this reason we say that it requires "activation". This means release from the LLC. This release is achieved by many mechanisms: proteolytic cleavage of the LTBP5, thrombospondin-1 binding to the LLC, integrin alphaV-beta6 binding to the LLC, reactive oxygen species, plasmin or other proteases and low pH. The release of mature dimeric TGF-beta-1 is essentially a mechanical process that demands cleavage and opening of the LLC structure so that the caged mature C-terminal TGF-beta-1 polypeptide is released to reach the receptor (Annes et al. 2003, Keski-Oja et al. 2004).

Preceded by: Latent TGF-beta-1 is cleaved by FURIN

Literature references


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https://reactome.org
Transforming growth factor beta (TGF-beta) is a family of three cytokine 'isoforms' (encoded by three separate human genes) that control proliferation, cellular differentiation and other functions. TGF-beta originally referred to the founding member TGF-beta-1, now it is often used as a collective term for all three. TGF-beta is secreted from cells in latent form as part of a complex that includes two other proteins: the cleaved propeptide of TGF beta, known as latency associated peptide (LAP), and a member of the latent TGF beta binding protein (LTBP) family. LTBPs are members of the fibrillin/LTBP superfamily, characterised by the presence of unique TGF-binding protein (TB) domains, also known as 8 cys domains as they contain eight characteristic cysteines (Ramirez & Sakai 2010). LTBPs are microfibril-associated proteins that tether latent complexes of TGF-beta to microfibrils in the ECM (Taipale et al. 1996, Dallas et al. 2000, Isogai et al. 2003, Hyytiainen et al. 2004, Ono et al. 2009, Munger & Sheppard 2011). This allows TGF-beta to be targeted to the ECM where it is maintained in an inactive, latent state (Robertson et al. 2011).

LTBP1 and LTBP3 bind all three isoforms of latent TGF-beta, while LTBP4 only weakly binds TGF-beta1 (Saharinen & Keski-Oja 2000). LTBP2 does not bind TGF-beta and is a structural component of fibrillin microfibrils. The carboxyl termini of LTBP1 and LTBP4 binds to fibrillin. The incorporation of LTBP1 and LTBP4 into the ECM is abolished in fibrillin-1 null mice (Ono et al. 2009). The amino terminus of LTBPs binds ECM components such as collagen (Taipale et al. 1996) and fibronectin (Kantola et al. 2008). Fibulins compete for the LTBP sites in fibrillin (Ono et al. 2009).

Followed by: Latent TGF-beta-1 binds integrins

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LTBP1 and 3 bind all three isoforms of latent TGF-beta, while LTBP4 only weakly binds TGF-beta1 (Saharinen & Keski Oja 2000). LTBP2 does not bind TGF-beta and is a structural component of fibrillin microfibrils. The carboxyl terminus of LTBP1 binds to fibrillin-1. LTBP1 and LTBP4 incorporation into the ECM is abolished in fibrillin-1 null mice (Ono et al. 2009). The amino terminus of LTBPs binds ECM components such as collagen (Taipale et al. 1996) and fibronectin (Kantola et al. 2008). Fibulins compete for the LTBP sites in fibrillin (Ono et al. 2009).

Literature references
Fibrillin-1 binds latent TGF-beta

**Location:** TGF-beta receptor signaling activates SMADs

**Stable identifier:** R-HSA-2328033

**Type:** binding

**Compartments:** extracellular region

TGF-beta is released from cells as a latent complex of three proteins: TGF-beta (which is encoded by three human genes), the processed TGF-beta propeptide (latency-associated peptide LAP), and a member of the latent TGF-beta binding protein (LTBP) family. LTBPs are microfibril (fibrillin)-associated proteins that bind LAP, tethering latent TGF-beta to microfibrils in the ECM (Taipale et al. 1996, Hyytiainen et al. 2004).

LTBP1 and LTBP4 incorporation into ECM requires fibrillin-1 (Ono et al. 2009). The protein–protein interaction sites between LTBPs and fibrillins have been determined using recombinant protein fragments and surface plasmon resonance (Ono et al. 2009). LTBP4 binds to the first hybrid domain of fibrillin-1 (Hyb1), whereas LTBP1 binds to a site involving both Hyb1 and adjacent EGF-like domains 2 and 3. Previous studies showed that the carboxyl terminus of LTBP1 binds to fibrillin-1, whereas the amino terminus of LTBPs is mainly responsible for binding ECM components made in cell culture generally, and fibronectin specifically (Kantola et al. 2008).

**Literature references**


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Latent TGF-beta-1 binds integrins

Location: TGF-beta receptor signaling activates SMADs

Stable identifier: R-HSA-2395320

Type: binding

Compartments: plasma membrane

The LAPs of TGF beta-1 and TGF beta-3 contain RGD sequences near the carboxyl termini that are bound by RGD binding integrins. The TGF beta-1 form of LAP (LAP1) binds the integrins alphaVBeta1 (Munger et al. 1998), alphaVBeta3 (Ludbrook et al. 2003), alphaVBeta5 (Munger et al. 1998), alphaVBeta6 (Munger et al. 1999, Araya et al. 2006), alphaVBeta8 (Mu et al. 2002, Araya et al. 2006) and alpha8Beta1 (Lu et al. 2002). Binding to integrins alphaVBeta6 and alphaVBeta8 leads to TGF beta activation.

Preceded by: LTBP1, LTBP3 bind TGF-Beta

Literature references


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https://reactome.org
Latent TGF-beta-3 binds integrins

Location: TGF-beta receptor signaling activates SMADs

Stable identifier: R-HSA-2396029

Type: binding

Compartments: plasma membrane

The LAPs of TGF-beta1 and TGF-beta3 contain RGD sequences near the carboxyl termini that are bound by RGD-binding integrins. LAP3 binds alphaVBeta1, 3, 5 and 6 (Ludbrook et al. 2003) and 8 (Kitamura et al. 2011). Binding to integrins alphaVBeta6 and alphaVBeta8 leads to TGF-beta activation.

Literature references


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Dimeric TGF-beta-1 binds to the receptor

Location: TGF-beta receptor signaling activates SMADs

Stable identifier: R-HSA-170861

Type: binding

Compartments: plasma membrane, extracellular region

The mature dimeric TGF-beta-1 (TGFβ1) binds with high affinity to its signaling receptor, the type II receptor serine/threonine kinase (TGFBR2) (Wrana et al. 1992, Moustakas et al. 1993, Franzen et al. 1993). While type II receptor can form dimeric complexes in the absence of TGFB1 when overexpressed, it predominantly exists as a monomer on the surface of unstimulated cells under physiological conditions, and dimerization of TGFBR2 is triggered by TGFB1 binding (Zhang et al. 2009).

Followed by: TGFBR2 recruits TGFBR1

Literature references


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The protein complex of dimeric TGF-beta-1 with the type II receptor dimer (dimeric TGFβ1:TGFBR2 homodimer) recruits the low affinity receptor, type I receptor (TGFBR1), thus forming a hetero-tetrameric receptor bound to the dimeric ligand on the extracellular face of the plasma membrane (TGFβ1:TGFBR2:TGFBR1) (Wrana et al. 1992, Moustakas et al. 1993, Franzen et al. 1993). FKBP1A (FKBP12), a peptidyl-prolyl cis-trans isomerase, forms a complex with TGFBR1 and prevents phosphorylation of TGFBR1 by TGFBR2 in the absence of ligand. FKBP1A dissociates from TGFBR1 after it forms a complex with ligand-activated TGFBR2 (Chen et al. 1997). TGFBR1 can homodimerize in the absence of TGFβ1 when overexpressed, but under physiological conditions it exists as a monomer on the surface of unstimulated cells. TGFβ1-induced dimerization of TGFBR1 is TGFBR2-dependent (Zhang et al. 2010).

**Preceded by:** Dimeric TGF-beta-1 binds to the receptor

**Followed by:** TGFBR2 phosphorylates TGFBR1

**Literature references**


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TGFBR2 phosphorylates TGFBR1

**Location:** TGF-beta receptor signaling activates SMADs

**Stable identifier:** R-HSA-170843

**Type:** transition

**Compartments:** plasma membrane, cytosol

Formation of the hetero-tetrameric TGF-beta-1 receptor complex induces receptor rotation, so that TGFBR2 and TGFBR1 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 (GS domain) of the type I receptor (Wrana et al. 1994, Souchelnytskyi et al. 1996). In addition to phosphorylation, TGFBR1 may also be sumoylated in response to TGF-beta-1 stimulation. Sumoylation enhances TGFBR1 function by facilitating recruitment and phosphorylation of SMAD3 (Kang et al. 2008).

**Preceded by:** TGFBR2 recruits TGFBR1

**Followed by:** An anchoring protein, ZFYVE9 (SARA), recruits SMAD2/3

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An anchoring protein, ZFYVE9 (SARA), recruits SMAD2/3

Location: TGF-beta receptor signaling activates SMADs

Stable identifier: R-HSA-170835

Type: binding

Compartments: cytoplasmic side of plasma membrane

The activated TGF-beta receptor complex is internalized by clathrin-mediated endocytosis into early endosomes. ZFYVE9 (SARA) resides in the membrane of early endosomes. Crystallographic studies suggest that dimeric SARA in the early endosome coordinates two R-SMAD molecules (SMAD2 and/or SMAD3) per one receptor complex.

Preceded by: TGFBR2 phosphorylates TGFBR1

Followed by: Activated type I receptor phosphorylates SMAD2/3 directly

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Activated type I receptor phosphorylates SMAD2/3 directly

Location: TGF-beta receptor signaling activates SMADs

Stable identifier: R-HSA-170868

Type: transition

Compartments: early endosome membrane

Activated type I receptor kinase directly phosphorylates two of the C-terminal serine residues of SMAD1, SMAD5 or SMAD8. Binding of these R-SMADs to the L45 loop of the type I receptor is critical for this event.

Preceded by: An anchoring protein, ZFYVE9 (SARA), recruits SMAD2/3

Followed by: Phosphorylated SMAD2/3 dissociates from TGFBR

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Phosphorylated SMAD2/3 dissociates from TGFBR

Location: TGF-beta receptor signaling activates SMADs

Stable identifier: R-HSA-170850

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 SMAD2/3 directly

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:** TGF-beta receptor signaling activates SMADs

**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:** Phosphorylated SMAD2/3 dissociates from TGFBR

**Literature references**


## Editions

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Downregulation of TGF-beta receptor signaling

**Location:** TGF-beta receptor signaling activates SMADs

**Stable identifier:** R-HSA-2173788

TGF-beta receptor signaling is downregulated by proteasome and lysosome-mediated degradation of ubiquitinated TGFBR1, SMAD2 and SMAD3, as well as by dephosphorylation of TGFBR1, SMAD2 and SMAD3.

In the nucleus, SMAD2/3:SMAD4 complex stimulates transcription of SMAD7, an inhibitory SMAD (I-SMAD). SMAD7 binds phosphorylated TGFBR1 and competes with the binding of SMAD2 and SMAD3 (Hayashi et al. 1997, Nakao et al. 1997). Binding of SMAD7 to TGBR1 can be stabilized by STRAP, a protein that simultaneously binds SMAD7 and TGFBR1 (Datta et al. 2000). BAMBI simultaneously binds SMAD7 and activated TGFBR1, leading to downregulation of TGF-beta receptor complex signaling (Onichtchouk et al. 1999, Yan et al. 2009).

In addition to competing with SMAD2/3 binding to TGFBR1, SMAD7 recruits protein phosphatase PP1 to phosphorylated TGFBR1, by binding to the PP1 regulatory subunit PPP1R15A (GADD34). PP1 dephosphorylates TGFBR1, preventing the activation of SMAD2/3 and propagation of TGF-beta signal (Shi et al. 2004).

SMAD7 associates with several ubiquitin ligases, SMURF1 (Ebisawa et al. 2001, Suzuki et al. 2002, Tajima et al. 2003, Chong et al. 2010), SMURF2 (Kavsak et al. 2000, Ogunjimi et al. 2005), and NEDD4L (Kuratomi et al. 2005), and recruits them to phosphorylated TGFBR1 within TGFBR complex. SMURF1, SMURF2 and NEDD4L ubiquitinate TGFBR1 (and SMAD7), targeting TGFBR complex for proteasome and lysosome-dependent degradation (Ebisawa et al. 2001, Kavsak et al. 2000, Kuratomi et al. 2005). The ubiquitination of TGFBR1 can be reversed by deubiquitinating enzymes, UCHL5 (UCH37) and USP15, which may be re-
cruited to ubiquitinated TGFBR1 by SMAD7 (Wicks et al. 2005, Eichhorn et al. 2012).

Basal levels of SMAD2 and SMAD3 are maintained by SMURF2 and STUB1 ubiquitin ligases. SMURF2 is able to bind and ubiquitinate SMAD2, leading to SMAD2 degradation (Zhang et al. 2001), but this has been questioned by a recent study of Smurf2 knockout mice (Tang et al. 2011). STUB1 (CHIP) binds and ubiquitinates SMAD3, leading to SMAD3 degradation (Li et al. 2004, Xin et al. 2005). PMEPA1 can bind and sequester unphosphorylated SMAD2 and SMAD3, preventing their activation in response to TGF-beta signaling. In addition, PMEPA1 can bind and sequester phosphorylated SMAD2 and SMAD3, preventing formation of SMAD2/3:SMAD4 heterotrimer complexes (Watanabe et al. 2010). A protein phosphatase MTMR4, residing in the membrane of early endosomes, can dephosphorylate activated SMAD2 and SMAD3, preventing formation of SMAD2/3:SMAD4 complexes (Yu et al. 2010).

**Literature references**


**Editions**

- **2012-04-05** Authored by Orlic-Milacic, M.
- **2012-04-10** Edited by Jassal, B.
- **2012-05-14** Reviewed by Huang, T.
The E3 ubiquitin ligase CBL binds the cytoplasmic tail of plasma membrane-bound TGFBR2 (TGF-beta receptor 2) but not TGFBR1 (TGF-beta receptor 1). The tyrosine kinase binding (TKB) domain of CBL is involved in this interaction (Zuo et al. 2013).

Followed by: CBL neddylates TGFBR2

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CBL neddylates TGFBR2

Location: TGF-beta receptor signaling activates SMADs

Stable identifier: R-HSA-4332236

Type: transition

Compartments: plasma membrane, cytosol

CBL neddylates TGFBR2 on lysine residues K556 and K567. The E3 ubiquitin ligase activity of CBL is necessary for this modification, and the kinase activity of TGFBR2 is also required. CBL-mediated neddylation prolongs the half-life of TGFBR2, thereby enhancing signaling by the TGF-beta receptor complex. CBLB, a CBL-related protein, may cooperate with CBL in TGFBR2 neddylation (Zuo et al. 2013).

Preceded by: CBL binds TGFBR2

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