

TGF beta signaling pathway

The **Transforming growth factor beta (TGF β) signaling pathway** is involved in many cellular processes in both the adult organism and the developing embryo including cell growth, cell differentiation, apoptosis, cellular homeostasis and other cellular functions. In spite of the wide range of cellular processes that the TGF β signaling pathway regulates, the process is relatively simple. TGF β superfamily ligands bind to a type II receptor, which recruits and phosphorylates a type I receptor. The type I receptor then phosphorylates receptor-regulated SMADs (R-SMADs) which can now bind the coSMAD SMAD4. R-SMAD/coSMAD complexes accumulate in the nucleus where they act as transcription factors and participate in the regulation of target gene expression.

Mechanism

Ligand Binding

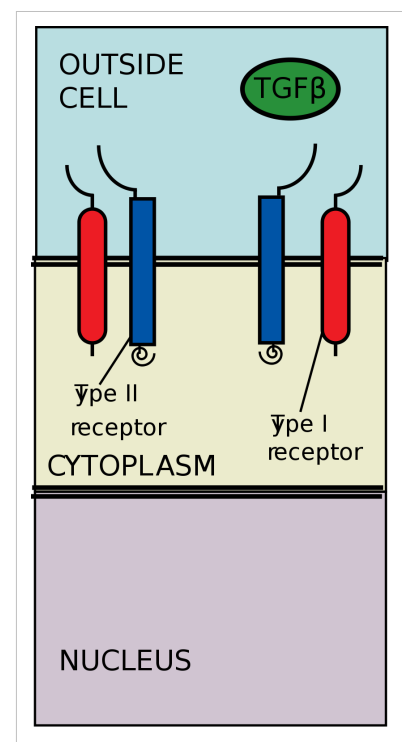
The TGF Beta superfamily of ligands include: Bone morphogenetic proteins (BMPs), Growth and differentiation factors (GDFs), Anti-müllerian hormone (AMH), Activin, Nodal and TGF β 's^[1]. Signalling begins with the binding of a TGF beta superfamily ligand to a TGF beta type II receptor. The type II receptor is a serine/threonine receptor kinase, which catalyses the phosphorylation of the Type I receptor. Each class of ligand binds to a specific type II receptor^[2]. In mammals there are seven known type I receptors and five type II receptors^[3].

There are three activins: Activin A, Activin B and Activin AB. Activins are involved in embryogenesis and osteogenesis. They also regulate many hormones including pituitary, gonadal and hypothalamic hormones as well as insulin. They are also nerve cell survival factors.

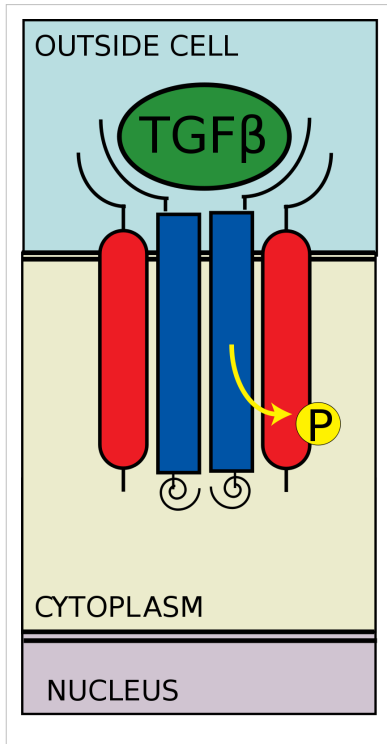
The BMPs bind to the Bone morphogenetic protein receptor type-2 (BMPR2). They are involved in a multitude of cellular functions including osteogenesis, cell differentiation, anterior/posterior axis specification, growth, and homeostasis.

The TGF beta family include: TGF β 1, TGF β 2, TGF β 3. Like the BMPs, TGF betas are involved in embryogenesis and cell differentiation, but they are also involved in apoptosis, as well as other functions. They bind to TGF-beta receptor type-2 (TGFB2R2).

Nodal binds to activin A receptor, type IIB ACVR2B. It can then either form a receptor complex with activin A receptor, type IB (ACVR1B) or with activin A receptor, type IC (ACVR1C)^[3].



Receptor recruitment and phosphorylation

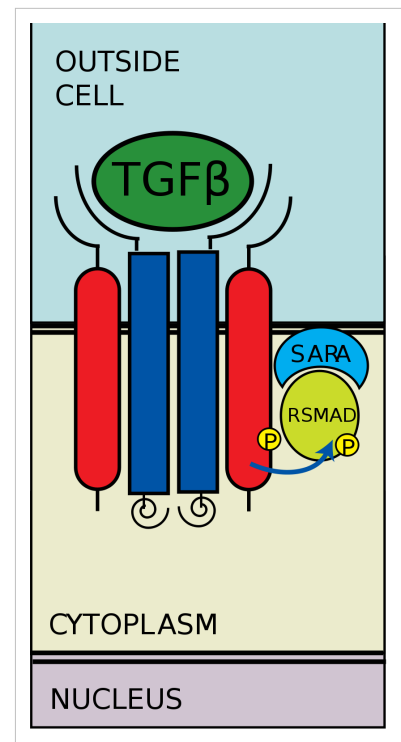


The TGF beta ligand binds to a type II receptor dimer, which recruits a type I receptor dimer forming a hetero-tetrameric complex with the ligand^[4]. These receptors are serine/threonine kinase receptors. They have a cysteine rich extracellular domain, a transmembrane domain and a cytoplasmic serine/threonine rich domain. The GS domain of the type I receptor consists of a series of about thirty serine-glycine repeats^[5]. The binding of a TGF beta family ligand causes the rotation of the receptors so that their cytoplasmic kinase domains are arranged in a catalytically favorable orientation. The Type II receptor phosphorylates serine residues of the Type I receptor, which activates the protein.

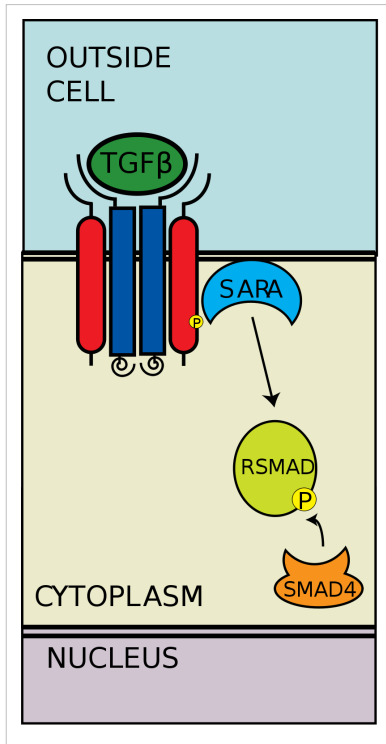
SMAD phosphorylation

There are five receptor regulated SMADs: SMAD1, SMAD2, SMAD3, SMAD5, and SMAD9 (sometimes referred to as SMAD8). There are essentially two intracellular pathways involving these R-SMADs. TGF beta's, Activins, Nodals and some GDFs are mediated by SMAD2 and SMAD3, while BMPs, AMH and a few GDFs are mediated by SMAD1, SMAD5 and SMAD9. The binding of the R-SMAD to the type I receptor is mediated by a zinc double finger FYVE domain containing protein. Two such proteins that mediate the TGF beta pathway include SARA (The SMAD anchor for receptor activation) and HGS (Hepatocyte growth factor-regulated tyrosine kinase substrate).

SARA is present in an early endosome which, by clathrin-mediated endocytosis, internalizes the receptor complex^[6]. SARA recruits an R-SMAD. SARA permits the binding of the R-SMAD to the L45 region of the Type I receptor^[7]. SARA orients the R-SMAD such that serine residue on its C-terminus faces the catalytic region of the Type I receptor. The Type I receptor phosphorylates the serine residue of the R-SMAD. Phosphorylation induces a conformational change in the MH2 domain of the R-SMAD and its subsequent dissociation from the receptor complex and SARA^[8].



CoSMAD binding



The phosphorylated RSMAD has a high affinity for a coSMAD (e.g. SMAD4) and forms a complex with one. The phosphate group does not act as a docking site for coSMAD, rather the phosphorylation opens up an amino acid stretch allowing interaction.

Transcription

The phosphorylated RSMAD/coSMAD complex enters the nucleus where it binds transcription promoters/cofactors and causes the transcription of DNA.

Bone morphogenetic proteins cause the transcription of mRNAs involved in osteogenesis, neurogenesis, and ventral mesoderm specification.

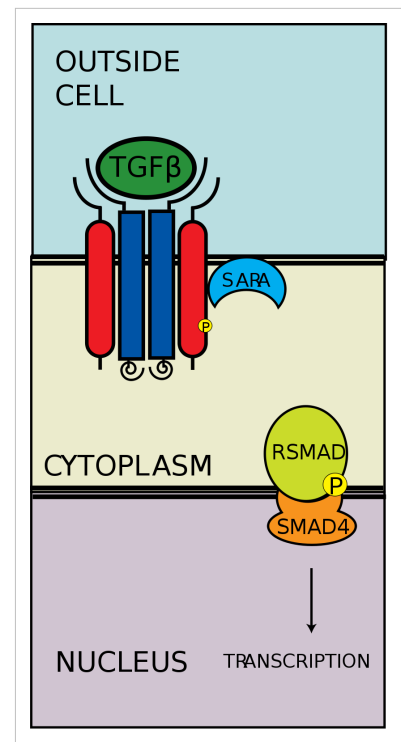
TGF betas cause the transcription of mRNAs involved in apoptosis, extracellular matrix neogenesis and immunosuppression. It is also involved in G1 arrest in the cell cycle.

Activin causes the transcription of mRNAs involved in gonadal growth, embryo differentiation and placenta formation.

Nodal causes the transcription of mRNAs involved in left and right axis specification, and mesoderm and endoderm induction.

Pathway regulation

The TGF beta signaling pathway is involved in a wide range of cellular process and subsequently is very heavily regulated. There are a variety of mechanisms that the pathway is modulated both positively and negatively: There are agonists for ligands and R-SMADs; there are decoy receptors; and R-SMADs and receptors are ubiquitinated.



Ligand agonists/antagonists

Both chordin and noggin are antagonists of BMP's. They bind BMP's preventing the binding of the ligand to the receptor. It has been demonstrated that Chordin and Noggin dorsalize mesoderm. They are both found in the dorsal lip of *Xenopus* and convert otherwise epidermis specified tissue into neural tissue (see neurulation). Noggin plays a key role in cartilage and bone patterning. Mice *Noggin*^{-/-} have excess cartilage and lacked joint formation^[9].

Members of the DAN family of proteins also antagonize TGF beta family members. They include Cerberus, DAN, and Gremlin. These proteins contain nine conserved cysteines which can form disulfide bridges. It is believed that DAN antagonizes GDF5, GDF6 and GDF7.

Follistatin inhibits Activin, which it binds. It directly affects follicle-stimulating hormone (FSH) secretion. Follistatin also is implicated in prostate cancers where mutations in its gene may preventing it from acting on activin which has anti-proliferative properties^[9].

Lefty is a regulator of TGF β and is involved in the axis patterning during embryogenesis. It is also a member of the TGF superfamily of proteins. It is asymmetrically expressed in the left side of murine embryos and subsequently plays a role in left-right specification. Lefty acts by preventing the phosphorylation of R-SMADs. It does so through a constitutively active TGF β type I receptor and through a process downstream of its activation^[10].

Drug-based antagonists have also been identified, such as SB431542^[11], which selectively inhibits ALK4, ALK5, and ALK7.

Receptor regulation

The Transforming growth factor receptor 3 (TGFR3) is the most abundant of the TGF- β receptors yet^[12], it has no known signaling domain^[13]. It however may serve to enhance the binding of TGF beta ligands to TGF beta type II receptors by binding TGF β and presenting it to TGFR2. One of the downstream targets of TGF β signaling, *GIPC*, binds to its PDZ domain, which prevents its proteosomal degradation, which subsequently increases TGF β activity. It may also serve as an inhibin coreceptor to ActivinRII^[9].

BMP and Activin membrane bound inhibitor (BAMBI), has a similar extracellular domain as type I receptors. It lacks an intracellular serine/threonine protein kinase domain and hence is a pseudoreceptor. It binds to the type I receptor preventing it from being activated. It serves as a negative regulator of TGF beta signaling and may limit tgf-beta expression during embryogenesis. It requires BMP signaling for its expression

FKBP12 binds the GS region of the type I receptor preventing phosphorylation of the receptor by the type II receptors. It is believed that FKBP12 and its homologs help to prevent type I receptor activation in the absence of a ligands, since ligand binding causes its dissociation.

R-SMAD regulation

Role of inhibitory SMADs

There are two other SMADs which complete the SMAD family, the inhibitory SMADs (I-SMADS), SMAD6 and SMAD7. They play a key role in the regulation of TGF beta signaling and are involved in negative feedback. Like other SMADs they have an MH1 and an MH2 domain. SMAD7 competes with other R-SMADs with the Type I receptor and prevents their phosphorylation^[9] ^[14]. It resides in the nucleus and upon TGF beta receptor activation translocates to the cytoplasm where it binds the type I receptor. SMAD6 binds SMAD4 preventing the binding of other R-SMADs with the coSMAD. The levels of I-SMAD increase with TGF beta signaling suggesting that they are downstream targets of TGF-beta signaling.

R-SMAD ubiquitination

The E3 ubiquitin-protein ligases SMURF1 and SMURF2 regulate the levels of SMADs. They accept ubiquitin from a E2 conjugating enzyme where they transfer ubiquitin to the RSMADs which causes their ubiquitination and subsequent proteosomal degradation. SMURF1 binds to SMAD1 and SMAD5 while SMURF2 binds SMAD1, SMAD2, SMAD3, SMAD6 and SMAD7. It enhances the inhibitory action of SMAD7 while reducing the transcriptional activities of SMAD2.

Summary table

TGF Beta superfamily ligand	Type II Receptor	Type I receptor	R-SMADs	coSMAD	Ligand inhibitors
Activin A	ACVR2A	ACVR1B (ALK4)	SMAD2 , SMAD3	SMAD4	Follistatin
GDF1	ACVR2A	ACVR1B (ALK4)	SMAD2 , SMAD3	SMAD4	
GDF11	ACVR2B	ACVR1B (ALK4), TGFβRI (ALK5)	SMAD2 , SMAD3	SMAD4	
Bone morphogenetic proteins	BMPR2	BMPR1A (ALK3), BMPR1B (ALK6)	SMAD1 SMAD5, SMAD9	SMAD4	Noggin, Chordin, DAN
Nodal	ACVR2B	ACVR1B (ALK4), ACVR1C (ALK7)	SMAD2 , SMAD3	SMAD4	Lefty
TGFβs	TGFβRII	TGFβRI (ALK5)	SMAD2 , SMAD3	SMAD4	LTBP1, THBS1, Decorin

External links

- Kyoto Encyclopedia of Genes and Genomes -TGF beta signaling pathway^[15] map
- Netpath - A curated resource of signal transduction pathways in humans

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