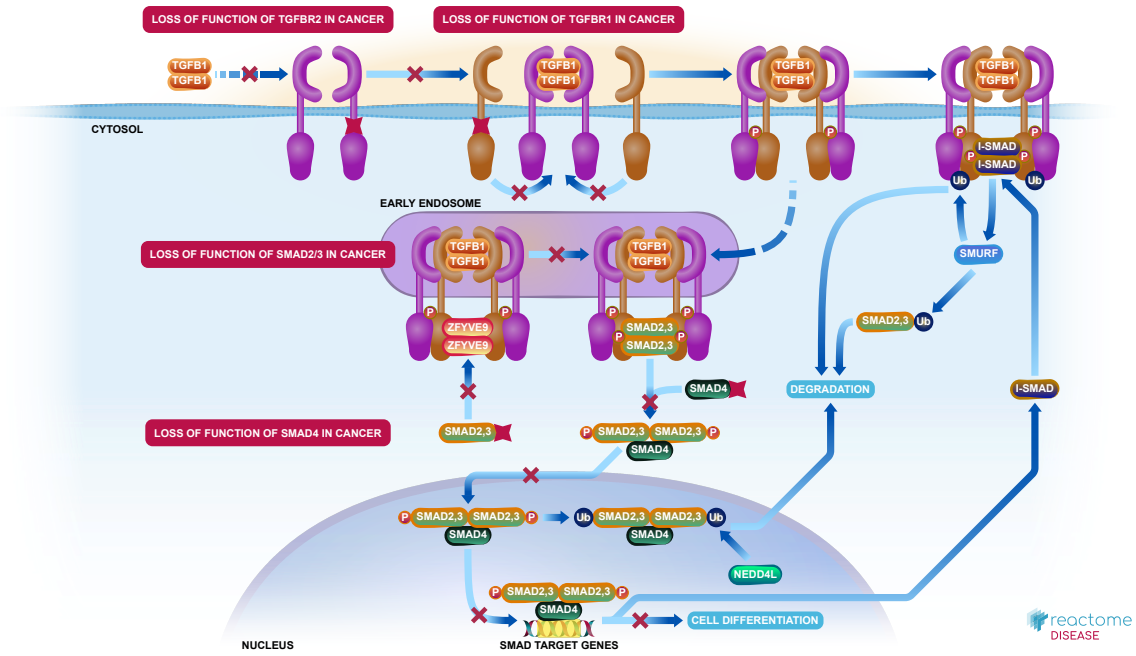
Signaling by TGF-beta Receptor Complex in Cancer



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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.

28/04/2024

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).

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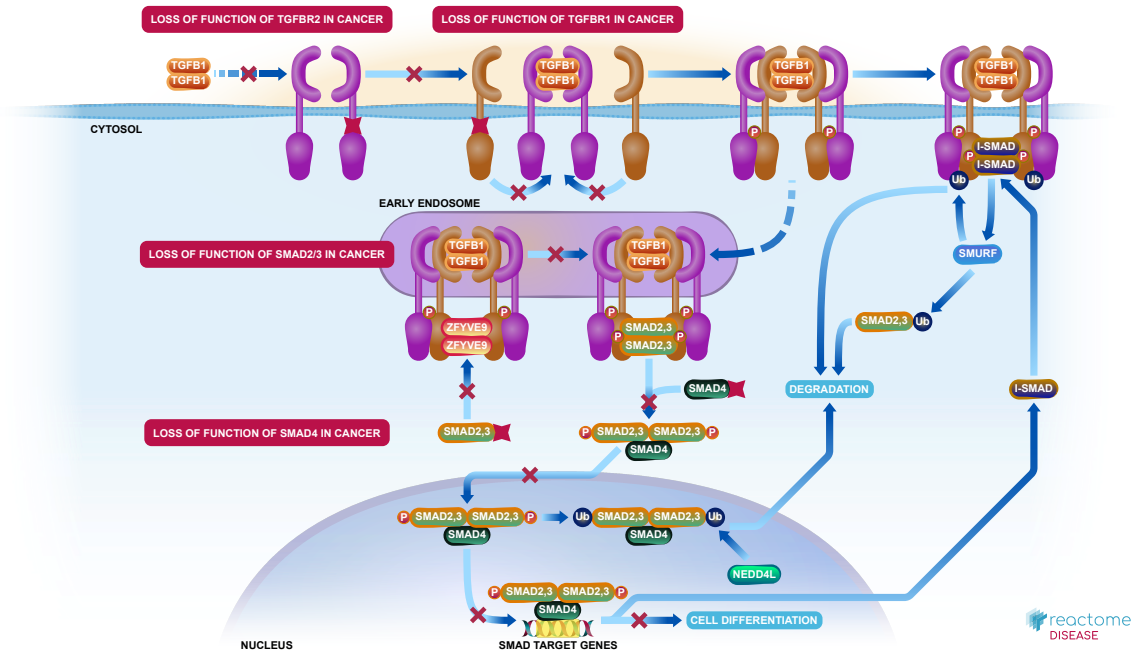
Reactome database release: 88

This document contains 5 pathways (see Table of Contents)

Signaling by TGF-beta Receptor Complex in Cancer ↗

Stable identifier: R-HSA-3304351

Diseases: cancer



Signaling by the TGF-beta receptor complex is tumor suppressive, as it inhibits cell growth and promotes cell differentiation and apoptosis (Shipley et al. 1986, Hannon et al. 1994, Datto et al. 1995, Chen et al. 2002, Azar et al. 2009). TGF-beta signaling is frequently impaired in cancer, mostly through SMAD4 gene deletion or loss-of-function mutations (described in the pathway Loss of Function of SMAD4 in Cancer), which are especially frequent in pancreatic cancer (Hahn et al. 1996, Shi et al. 1997, Fleming et al. 2013). Signaling by TGF-beta receptor complex can also be disrupted by loss-of-function mutations in SMAD2 and SMAD3 (Fleming et al. 2013), as described in the pathway Loss of Function of SMAD2/SMAD3 in Cancer, or loss-of-function mutations in TGFBR2 (TGF-beta receptor II) (Markowitz et al. 1995, Garrigue-Antar et al. 1995, Parsons et al. 1995, Grady et al. 1999), as described in the pathway Loss of Function of TGFBR2 in Cancer, or TGFBR1 (TGF-beta receptor I) (Chen et al. 1998, Chen et al. 2001, Goudie et al. 2011), as described in the pathway Loss of Function of TGFBR1 in Cancer.

In advanced cancer, signaling by TGF-beta may be tumor promoting, as it induces epithelial-to-mesenchymal transition (EMT), thereby increasing invasiveness (Cui et al. 1996, Guasch et al. 2007, reviewed by Heldin et al. 2012).

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2013-05-03	Edited	Jassal, B.
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Loss of Function of SMAD4 in Cancer ↗

Location: Signaling by TGF-beta Receptor Complex in Cancer

Stable identifier: R-HSA-3304347

Diseases: cancer

SMAD4 was identified as a gene homozygously deleted in ~30% of pancreatic cancers and was named DPC4 (DPC stands for deleted in pancreatic cancer). SMAD4 maps to the chromosomal band 18q21.1, and about 90% of pancreatic carcinomas show allelic loss at chromosomal arm 18q (Hahn et al. 1996), while ~50% of pancreatic cancers show some alteration of the SMAD4 gene (reviewed by Schutte et al. 1999).

Based on COSMIC database (Catalogue Of Somatic Mutations In Cancer) (Forbes et al. 2011), mutations in the coding sequence of SMAD4 gene are frequently found in pancreatic cancer, biliary duct carcinoma and colorectal cancer (reviewed by Schutte et al. 1999). Germline SMAD4 mutations are the cause of juvenile polyposis, an autosomal dominant disease that predisposes affected individuals to hamartomatous polyps and gastrointestinal cancer (Howe et al. 1998). Homozygous Smad4 loss is embryonic lethal in mice (Takaku et al. 1998). Smad4 +/- heterozygotes appear normal but develop intestinal polyps between 6 and12 months of age and these polyps can progress to cancer. Loss of the remaining wild-type Smad4 allele is detectable only at later stages of tumor progression in Smad4+/- mice (Xu et al. 2000). Compound Apc+/-;Smad4+/- mice develop malignant tumors from intestinal polyps more rapidly than Apc+/- mice (Takaku et al. 1998).

SMAD4 coding sequence mutations are most frequently found in the MH2 domain and impair the formation of SMAD4 heterotrimers with phosphorylated SMAD2 and SMAD3 (Shi et al. 1997, Fleming et al. 2013), thereby impairing SMAD4:SMAD2/3 heterotrimer-mediated transcriptional regulation of TGF-beta responsive genes. MH2 domain is also involved in the formation of SMAD4 homotrimers which may play a role in SMAD4 protein stability (Shi et al. 1997).

Coding sequence mutations are also found in the MH1 domain of SMAD4. MH1 domain is involved in DNA binding (Dai et al. 1999) and it is also involved in the formation of SMAD4 homotrimers (Hata et al. 1997).

Literature references

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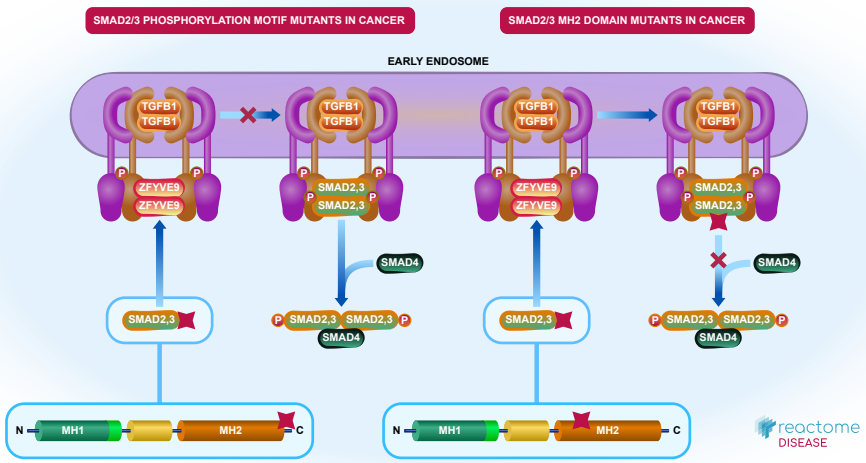
Loss of Function of SMAD2/3 in Cancer ↗

Location: Signaling by TGF-beta Receptor Complex in Cancer

Stable identifier: R-HSA-3304349

Diseases: cancer



Loss-of-function of SMAD2 and SMAD3 in cancer occurs less frequently than the loss of SMAD4 function and was studied in most detail in colorectal cancer (Fleming et al. 2013).

Similarly to SMAD4, coding sequence mutations in SMAD2 and SMAD3 in cancer cluster in the MH2 domain, involved in the formation of transcriptionally active heterotrimers with SMAD4. Another region of SMAD2 and SMAD3 that is frequently mutated in cancer is the phosphorylation motif Ser-Ser-X-Ser at the very C-terminus (Fleming et al. 2013). The phosphorylation of this conserved motif by the activated TGF-beta receptor complex is an essential step in SMAD2 and SMAD3 activation and a prerequisite for the formation of heterotrimers with SMAD4 (Chacko et al. 2001, Chacko et al. 2004).

Smad2 knockout mice die at embryonic day 8.5, with impaired visceral endoderm function and deficiency in mesoderm formation. Smad2+/- heterozygotes appear normal and are fertile (Hamamoto et al. 2002). While polyps of compound Smad2+/-;Apc+/- mice show no difference in the number, size or histopathology from the polyps of Apc+/- mice (Takaku et al. 2002, Hamamoto et al. 2002), Smad2+/-;Apc+/- mice develop extremely large intestinal tumors and multiple invasive cancers not observed in Apc+/- mice. Therefore, loss of Smad2 does not contribute to initiation of intestinal tumorigenesis, but accelerates malignant progression (Hamamoto et al. 2002). Smad3 knockout mice are viable and fertile but die between 4 and 6 months of age from colorectal adenocarcinoma (Zhu et al. 1998), indicating that the loss of Smad3 initiates intestinal tumorigenesis.

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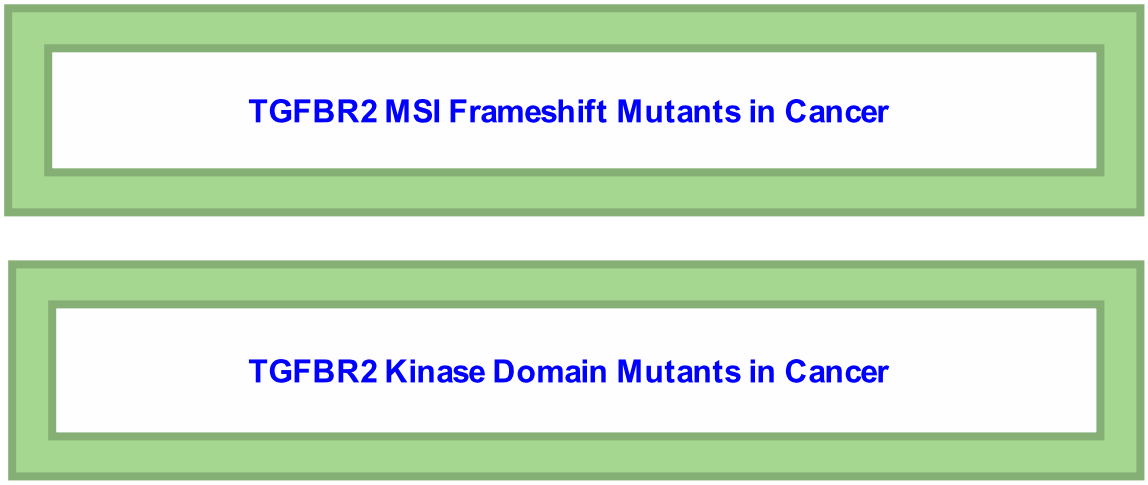
Loss of Function of TGFBR2 in Cancer ↗

Location: Signaling by TGF-beta Receptor Complex in Cancer

Stable identifier: R-HSA-3642278

Diseases: cancer



Loss-of-function of transforming growth factor-beta receptor II (TGFBR2) is most prevalent in colorectal cancer. Over 60% of colorectal cancers with microsatellite instability (MSI) harbor inactivating mutations in both alleles of TGFBR2, mostly 1 or 2 bp deletions in the 10 bp adenine repeat that codes for three lysine residues in the extracellular domain of TGFBR2. These small deletions result in a frameshift and a premature stop codon (Markowitz et al. 1995). TGFBR2 kinase domain (KD) mutations are found in ~20% of microsatellite stable (MSS) colorectal cancers and these are mostly missense mutations that results in substitution of conserved amino acids in the kinase domain (Grady et al. 1999), likely impairing the catalytic activity of TGFBR2 KD mutants. The silencing of TGFBR2 gene via promoter methylation has been reported in B-cell lymphoma (Chen et al. 2007). Knockout of murine Tgfbr2 in colonic epithelium promotes azoxymethane-induced colon cancer formation (Biswas et al. 2004) and increases the number of adenomas and adenocarcinomas in Apc+/- mice (Munoz et al. 2006).

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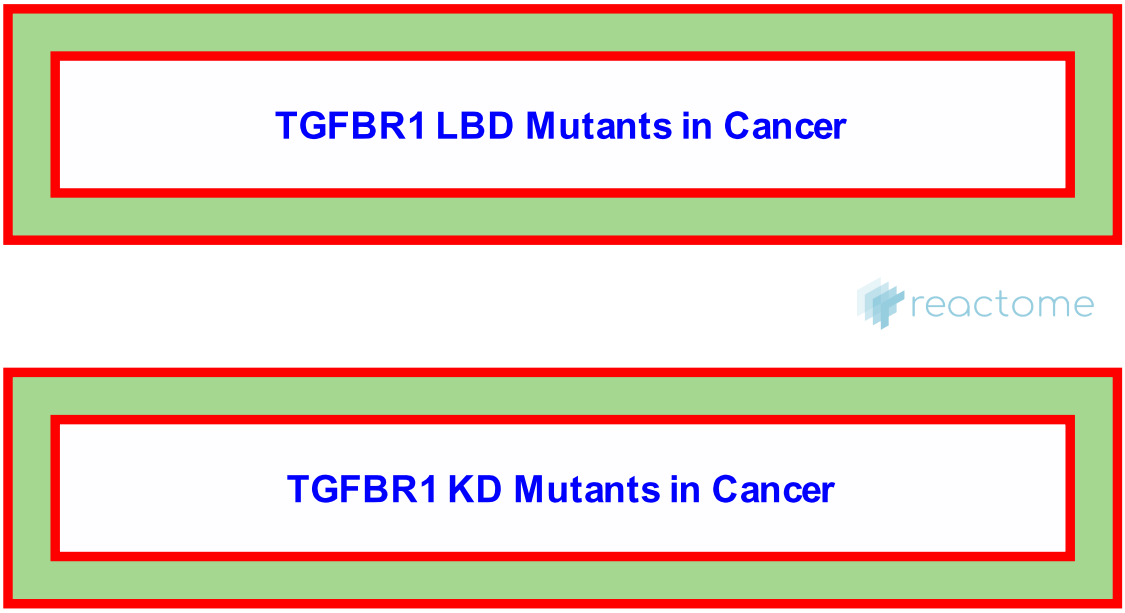
Loss of Function of TGFBR1 in Cancer ↗

Location: Signaling by TGF-beta Receptor Complex in Cancer

Stable identifier: R-HSA-3656534

Diseases: cancer



TGF-beta receptor 1 (TGFBR1) loss-of-function is a less frequent mechanism for inactivation of TGF-beta signaling in cancer compared to SMAD4 and TGFBR2 inactivation. Genomic deletion of TGFBR1 locus has been reported in pancreatic cancer (Goggins et al. 1998), biliary duct cancer (Goggins et al. 1998) and lymphoma (Schiemann et al. 1999), while loss-of-function mutations have been reported in breast (Chen et al. 1998) and ovarian cancer (Chen et al. 2001), metastatic head-and-neck cancer (Chen et al. 2001), and in Ferguson-Smith tumors (multiple self-healing squamous epithelioma - MSSE) (Goudie et al. 2011). Loss-of-function mutations mainly affect the ligand-binding extracellular domain of TGFBR1 and the kinase domain of TGFBR1 (Goudie et al. 2011). In the mouse model of colorectal cancer, Tgfbr1 haploinsufficiency cooperates with Apc haploinsufficiency in the development of intestinal tumors (Zeng et al. 2009).

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Table of Contents