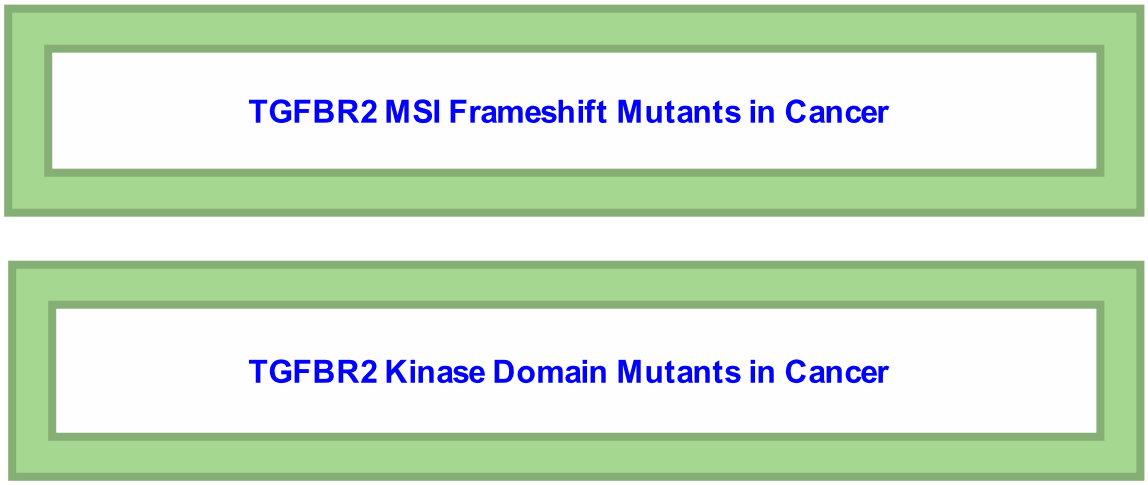
Loss of Function of TGFBR2 in Cancer



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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.
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

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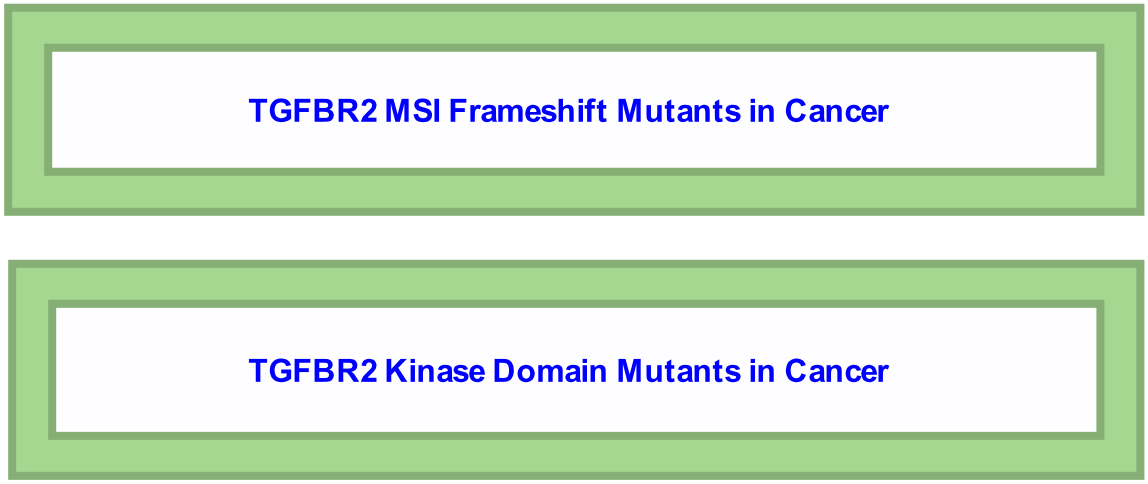
Reactome database release: 88

This document contains 3 pathways (see Table of Contents)

Loss of Function of TGFBR2 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).

Literature references

Muñoz, NM., Madison, BB., Washington, MK., Moses, HL., Pozzi, A., Chytil, A. et al. (2006). Transforming growth factor beta receptor type II inactivation induces the malignant transformation of intestinal neoplasms initiated by Apc mutation. *Cancer Res., 66*, 9837-44. ↗

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Editions

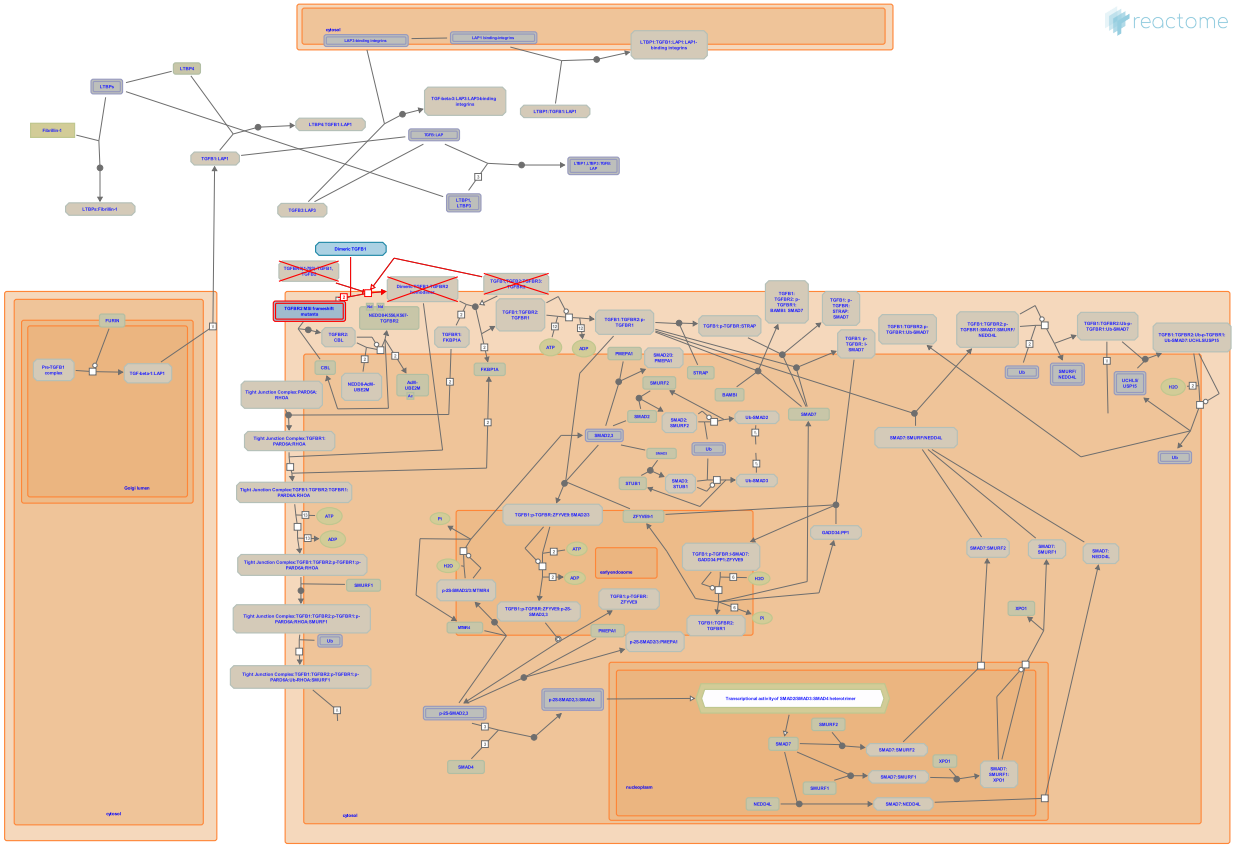
2013-08-08	Authored, Reviewed	Akhurst, RJ.
2013-08-08	Authored, Reviewed	Meyer, S.
2013-08-08	Authored, Edited	Orlic-Milacic, M.

TGFBR2 MSI Frameshift Mutants in Cancer ↗

Location: Loss of Function of TGFBR2 in Cancer

Stable identifier: R-HSA-3642279

Diseases: cancer



The short adenine repeat in the coding sequence of TGF-beta receptor II (TGFBR2) gene is frequently targeted by loss-of-function frameshift mutations in colon cancers with microsatellite instability (MSI). The 1- or 2-bp deletions in the adenine stretch of TGFBR2 cDNA introduce a premature stop codon that leads to degradation of the majority of mutant transcripts through nonsense-mediated decay or to production of a truncated TGFBR2 that cannot be presented on the cell surface. Cells that harbor TGFBR2 MSI frameshift mutations are resistant to TGF-beta (TGFB1)-mediated growth inhibition.

Literature references

Fan, RS., Sun, L., Vogelstein, B., Myeroff, L., Wang, J., Kinzler, KW. et al. (1995). Inactivation of the type II TGF-beta receptor in colon cancer cells with microsatellite instability. *Science, 268*, 1336-8. ↗

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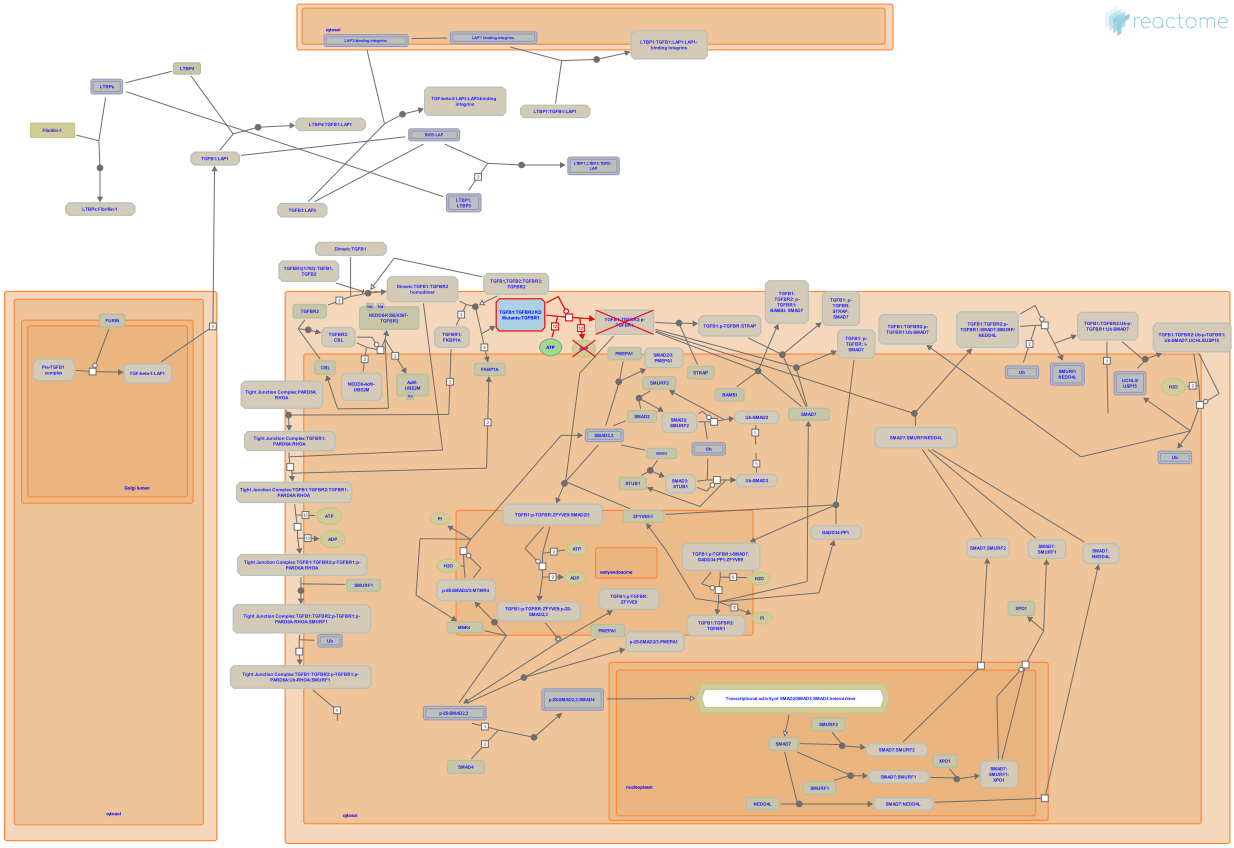
TGFBR2 Kinase Domain Mutants in Cancer ↗

Location: Loss of Function of TGFBR2 in Cancer

Stable identifier: R-HSA-3645790

Diseases: cancer



Missense mutations in the kinase domain (KD) of TGF-beta receptor II (TGFBR2) are found in ~20% of microsatellite stable (MSS) colon cancers and make affected tumors resistant to TGF-beta (TGFB1)-mediated growth inhibition (Grady et al. 1999). While both alleles of TGFBR2 are affected by inactivating mutations in MSS colorectal cancer (Grady et al. 1999), a study of MSS esophageal carcinoma indicates that TGFBR2 KD mutations may function in a dominant-negative way (Tanaka et al. 2000). KD mutations in TGFBR2 are rarely reported in microsatellite instable (MSI) colorectal cancer (Parsons et al. 1995, Takenoshita et al. 1997).

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