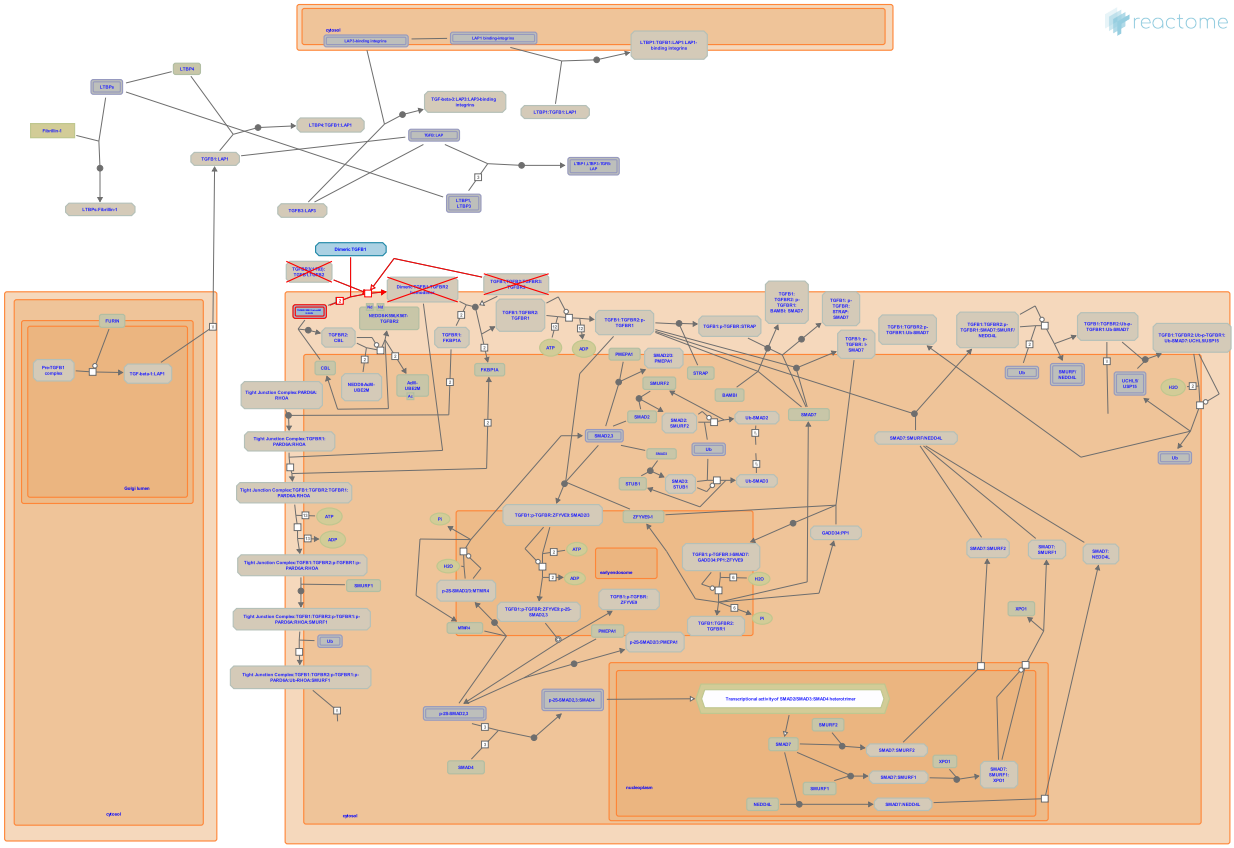
TGFBR2 MSI Frameshift Mutants in Cancer



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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.

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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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Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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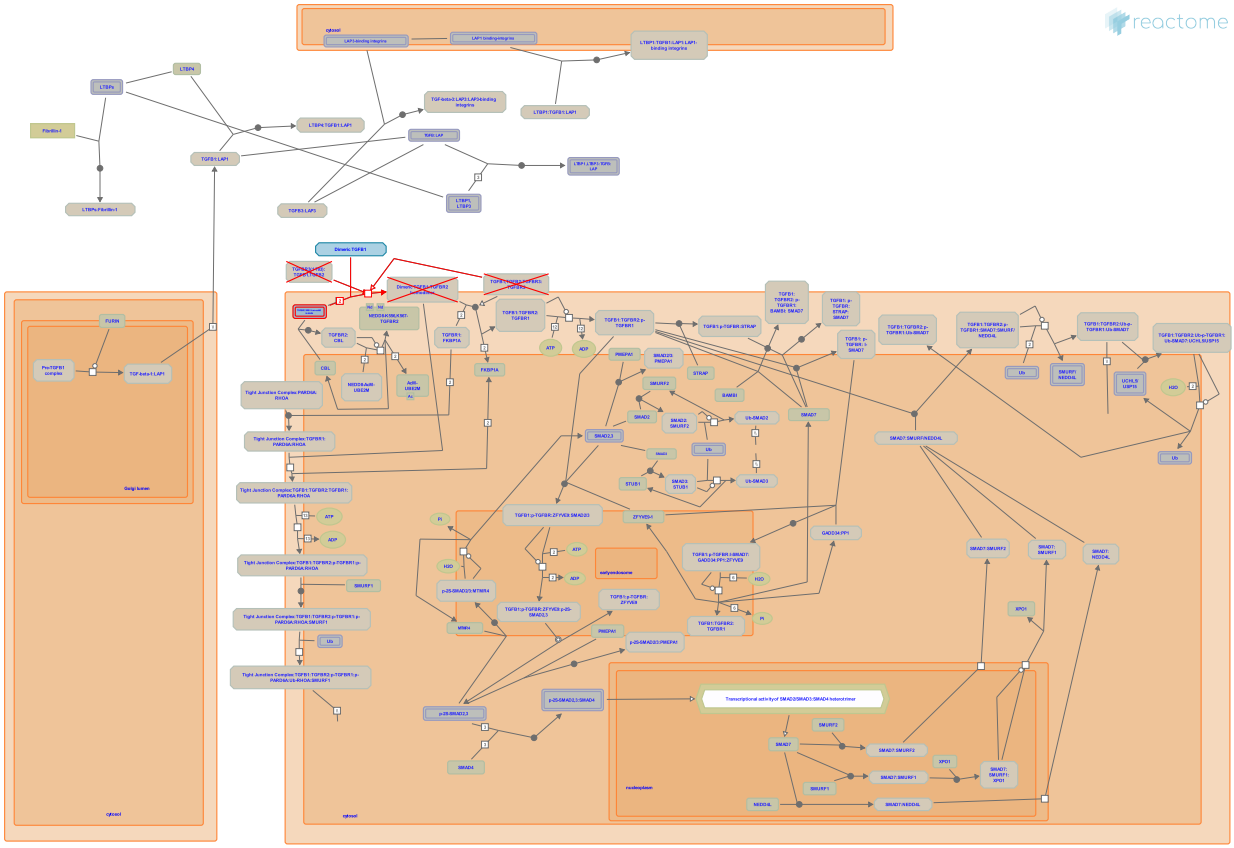
TGFBR2 MSI Frameshift Mutants in Cancer ↗

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. ↗

Sun, L., Willson, JK., Myeroff, L., Gentry, LE., Wang, J., Yang, J. et al. (1995). Demonstration that mutation of the type II transforming growth factor beta receptor inactivates its tumor suppressor activity in replication error-positive colon carcinoma cells. *J. Biol. Chem., 270*, 22044-9. ↗

Editions

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

Dimeric TGFB1 does not bind TGFBR2 MSI frameshift mutants ↗

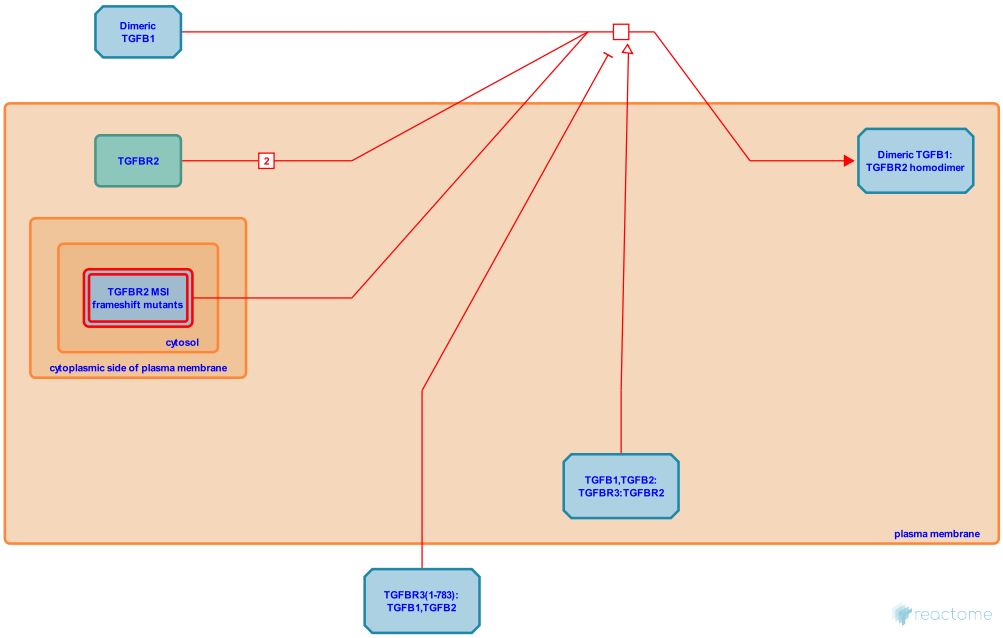
Location: TGFBR2 MSI Frameshift Mutants in Cancer

Stable identifier: R-HSA-3642203

Type: transition

Compartments: extracellular region, cytosol

Diseases: cancer



Inactivating mutations in TGF-beta receptor II (TGFBR2) are found in the majority of colorectal cancers with microsatellite instability (MSI). MSI is frequently observed in hereditary nonpolyposis colorectal cancers (HNPCC) caused by defects in mismatch repair genes, which leads to elevated gene mutation rates, especially within simple repeated sequences (Aaltonen et al. 1994, Fishel et al. 1993, Leach et al. 1993, Nicolaides et al. 1994, Bronner et al. 1994, Miyaki et al. 1997, Wu et al. 2001). As TGFBR2 cDNA contains a repeat sequence of 10 adenines at coding nucleotides 374-383 (nucleotides 756-765 of the reference TGFBR2 mRNA NM_003242.5), it is susceptible to the MSI-associated mutator mechanism. The majority of TGFBR2 mutations observed in MSI colorectal cancer tumors are deletions of 1 or 2 adenines within the 10 adenine repeat sequence, resulting in a frameshift that is prediced to produce truncated proteins of 161 (TGFBR2 K128Sfs*35) and 129 amino acids (TGFBR2 K128Afs*3), respectively. As these frameshift mutations produce a nonsense codon in the 5' half of the mRNA, the majority of mutant transcripts are degraded, likely through nonsense-mediated decay (Hagan et al. 1995), resulting in very low levels of mutant TGFBR2 mRNAs (Markowitz et al. 1995, Wang et al. 1995). Even if the mutant mRNA gets translated, the mutant proteins cannot be expressed at the cell surface, as the truncation is located upstream of the transmembrane domain of TGFBR2.

Cancer cells with MSI frameshift mutations in the TGFBR2 gene do not express any TGFBR2 on their cell surface and are resistant to TGF-beta 1 (TGFB1)-mediated growth inhibition (Markowitz et al. 1995, Wang et al. 1995). The responsiveness to TGFB1 can be restored by exogenous expression of the wild-type TGFBR2 (Wang et al. 1995), as long as the downstream effectors of TGF-beta receptor complex signaling are intact.

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Quan, Y., Hagan, KW., Ruiz-Echevarria, MJ., Peltz, SW. (1995). Characterization of cis-acting sequences and decay intermediates involved in nonsense-mediated mRNA turnover. *Mol. Cell. Biol., 15*, 809-23. ↗

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