Loss of Function of TGFBR1 in Cancer

TGFBR1 LBD Mutants in Cancer

TGFBR1 KD Mutants in Cancer

Akhurst, RJ., Meyer, S., Orlic-Milacic, M.

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

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of Creative Commons Attribution 4.0 International (CC BY 4.0) License. For more information see our license.

11/10/2019
Introduction

Reactome is a 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: 70

This document contains 3 pathways (see Table of Contents)
Loss of Function of TGFBR1 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).

Literature references


<table>
<thead>
<tr>
<th>Date</th>
<th>Role</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-08</td>
<td>Authored, Reviewed</td>
<td>Akhurst, RJ.</td>
</tr>
<tr>
<td>2013-08-08</td>
<td>Authored, Reviewed</td>
<td>Meyer, S.</td>
</tr>
<tr>
<td>2013-08-08</td>
<td>Authored, Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
Mutations in the ligand-binding domain (LBD) of TGF-beta receptor 1 (TGFBR1) have been reported as germline mutations in Ferguson-Smith tumor (multiple self-healing squamous epithelioma - MSSE), an autosomal-dominant skin cancer condition (Ferguson-Smith et al. 1934, Ferguson-Smith et al. 1971), with tumors frequently showing loss of heterozygosity of the wild-type TGFBR1 allele (Goudie et al. 2011). Somatic mutations in the LBD of TGFBR1 have been reported in esophageal carcinoma (Dulak et al. 2013).

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Activity</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-08</td>
<td>Authored, Reviewed</td>
<td>Akhurst, RJ.</td>
</tr>
<tr>
<td>2013-08-08</td>
<td>Authored, Reviewed</td>
<td>Meyer, S.</td>
</tr>
<tr>
<td>2013-08-08</td>
<td>Authored, Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
Mutations in the kinase domain (KD) of TGF-beta receptor 1 (TGFBR1) have been found in Ferguson-Smith tumor i.e. multiple self-healing squamous epithelioma - MSSE (Goudie et al. 2011), breast cancer (Chen et al. 1998), ovarian cancer (Chen et al. 2001) and head-and-neck cancer (Chen et al. 2001). KD mutations reported in MSSE are nonsense and frameshift mutations that cause premature termination of TGFBR1 translation, resulting in truncated receptors that lack substantial portions of the kinase domain, or cause nonsense-mediated decay of mutant transcripts. A splice site KD mutation c.806-2A>C is predicted to result in the skipping of exon 5 and the absence of KD amino acid residues 269-324 from the mutant receptor. The splice site mutant is expressed at the cell surface but unresponsive to TGF-beta stimulation (Goudie et al. 2004).

TGFBR1 KD mutations reported in breast, ovarian and head-and-neck cancer are missense mutations, and it appears that these mutant proteins are partially functional but that their catalytic activity or protein stability is decreased (Chen et al. 1998, Chen et al. 2001a and b). These mutants are not shown.

**Literature references**


## Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Role</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-08-08</td>
<td>Authored, Reviewed</td>
<td>Akhurst, RJ.</td>
</tr>
<tr>
<td>2013-08-08</td>
<td>Authored, Reviewed</td>
<td>Meyer, S.</td>
</tr>
<tr>
<td>2013-08-08</td>
<td>Authored, Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
Table of Contents

Introduction 1

- Loss of Function of TGFBR1 in Cancer 2
  - TGFBR1 LBD Mutants in Cancer 4
  - TGFBR1 KD Mutants in Cancer 5

Table of Contents 7