FGFR2 alternative splicing

Grose, RP., Rothfels, K.

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.

07/12/2019
**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**


Reactome database release: 70

This document contains 1 pathway and 4 reactions (see Table of Contents)
Alternative splicing of the FGFR2 nascent mRNA generates an epithelial specific isoform (FGFR2 IIIb) and a mesenchymal specific isoform (FGFR2 IIIc). The inclusion of exon 8 in FGFR2 IIIb or exon 9 in FGFR2 IIIc alters the C-terminal half of the D3 loop of the receptor and is responsible for the different ligand-binding specificities of the two isoforms (reviewed in Eswarakumar et al, 2005). In recent years, a number of cis- and trans-acting elements have been identified that regulate the alternative splicing event. Exon IIIb repression is mediated by the presence of weak splice sites flanking the exon, an exonic silencing sequence (ESS) within the IIIb exon and both intronic silencing sequences (ISS) upstream and downstream (Carstens et al, 2000; Del Gatto and Breathnach, 1995; Del Gatto et al, 1996; Wagner et al 2005; Wagner and Garcia-Blanco, 2001). Binding of hnRNPA1, PTB1, SR family proteins and other factors to these elements represses the IIIb exon and promotes FGFR2 IIIc expression in mesenchymal cells (Del Gatto-Konczak et al, 1999; Carstens et al, 2000; Wagner et al, 2005; Wagner and Garcia-Blanco, 2001; Wagner and Garcia-Blanco, 2002). In epithelial cells, recruitment of epithelial specific factors shifts the splicing events to favour inclusion of exon 8. ESPN1 and ESPN2 are epithelial-specific factors that bind to an ISE/ISS-3 (intronic splicing enhancer/intronic splicing silencer-3) region within intron 8 to promote FGFR2 IIIb-specific splicing (Warzecha et al, 2009). A complex of RBFOX2, hnRNPH1 and hnRNPF also contribute to epithelial-specific splicing by competing for binding to a site that is occupied by the SR proteins ASF/SF2 in mesenchymal cells (Baraniak et al, 2006; Mauger et al, 2008). Other proteins and sequences have also been identified that appear to contribute to the regulated expression of FGFR2b and FGFR2c, but the full details of the alternative splicing event remain to be worked out (Muh et al, 2002; Newman et al, 2006; Del Gatto et al, 2000; Hovhannisyan and Carstens, 2007).

Literature references

Hovhannisyan, RH., Carstens, RP. (2007). Heterogeneous ribonucleoprotein m is a splicing regulatory protein that can enhance or silence splicing of alternatively spliced exons. *J. Biol. Chem.*, 282, 36265-74.


## Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-10-06</td>
<td>Authored, Edited</td>
<td>Rothfels, K.</td>
</tr>
<tr>
<td>2016-01-06</td>
<td>Reviewed</td>
<td>Grose, RP.</td>
</tr>
</tbody>
</table>
PTB and hnRNPA1 bind FGFR2 pre-mRNA to repress IIIb splicing and promote formation of FGFR2c mRNA

Location: FGFR2 alternative splicing

Stable identifier: R-HSA-6803523

Type: binding

Compartments: nucleoplasm

Repression of FGFR2 exon IIIb splicing in mesenchymal cells depends on intronic splicing silencer (ISS) sequences upstream of exon IIIb as well as an exonic splicing element (ESE) within exon IIIb. These elements are bound by PTB1 and hnRNPA1, respectively, as part of a larger splicing complex, promoting the formation and expression of mature FGFR2c mRNA in mesenchymal cells (Carstens et al, 2000; Gil et al, 1991; Del Gatto et al, 1997; Del Gatto et al, 1999). For more detailed information on splicing and pre-mRNA maturation, please see the mRNA splicing pathway.

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-10-05</td>
<td>Authored, Edited</td>
<td>Rothfels, K.</td>
</tr>
<tr>
<td>2016-01-06</td>
<td>Reviewed</td>
<td>Grose, RP.</td>
</tr>
</tbody>
</table>
ESRP1 and 2 bind FGFR2 pre-mRNA to promote FGFR2b maturation and expression

**Location:** FGFR2 alternative splicing

**Stable identifier:** R-HSA-6803527

**Type:** binding

**Compartments:** nucleoplasm

Expression of FGFR2 IIIb splice variant is characteristic of epithelial cells. A number of cis-acting elements have been identified in the FGFR2 pre-mRNA that are required for correct expression of the IIIb isoform and repression of the mesenchymal IIIc form (Muh et al, 2002; Hovhannisyan and Carstens, 2005; Hovhannisyan et al, 2006). These include the ISAR and ISE/ISS elements 1-3 in the region between exon 8 and exon 9 of the pre-mRNA. ESRP1 and ESRP2 are RNA-binding mRNA splicing factors that promote epithelial-specific IIIb splicing by binding to the ISE/ISS-3 sequence (Warzecha et al, 2009). A complex of RBFOX2, hnRNP1 and hnRNPF may cooperate with the ESRP proteins to stimulate IIIb-specific splicing by binding to adjacent exonic GGG motifs (Baraniak et al, 2006; Mauger et al, 2008). This RBFOX2-hnRNP complex appears to compete with the IIIc-promoting trans-acting factor ASF/SF2 for binding to these exonic sites (Mauger et al, 2008). Other factors that appear to contribute to IIIb-specific splicing include hnRNP-M, TIA1 and TIAL1, although their precise roles remain to be elucidated (Hovhannisyan and Carstens, 2007; Del Gatto-Konczak et al, 2000; Newman et al, 2006).

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-10-05</td>
<td>Authored, Edited</td>
<td>Rothfels, K.</td>
</tr>
<tr>
<td>2016-01-06</td>
<td>Reviewed</td>
<td>Grose, RP.</td>
</tr>
</tbody>
</table>
FGFR2b-specific alternative splicing produces FGFR2b transcript

**Location:** FGFR2 alternative splicing

**Stable identifier:** R-HSA-6803836

**Type:** omitted

**Compartments:** nucleoplasm

In epithelial cells, FGFR2 IIIb-specific alternative splicing is favoured by the binding of ESRP1 and 2, RB-FOX2, TIA1 and TIAL1 to the nascent transcript. These proteins, in conjunction with other splicing factors, activate exon IIIb-specific splicing and repress exon IIIc-specific splicing (Warzecha et al, 2009; Baraniak et al, 2006; Mauger et al, 2008; Hovhannisyan and Carstens, 2007; Del Gatto et al, 2000).

**Literature references**


Hovhannisyan, RH., Carstens, RP. (2007). Heterogeneous ribonucleoprotein m is a splicing regulatory protein that can enhance or silence splicing of alternatively spliced exons. *J. Biol. Chem.*, 282, 36265-74.


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Author/Editor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-10-06</td>
<td>Authored, Edited</td>
<td>Rothfels, K.</td>
</tr>
<tr>
<td>2016-01-06</td>
<td>Reviewed</td>
<td>Grose, RP.</td>
</tr>
</tbody>
</table>
FGFR2c-specific alternative splicing produces FGFR2c transcript

**Location:** FGFR2 alternative splicing

**Stable identifier:** R-HSA-6803838

**Type:** omitted

**Compartments:** nucleoplasm

In mesenchymal cells, FGFR2 IIIc exon splicing is favoured by the binding of PTB1 to intronic splice silencer (ISS) sequences 1 and 2 that flank the IIIb specific exon, and by the binding of hnRNPA1 to an exonic splicing silencer (ESS) within the IIIb specific exon (Del Gatto-Konczak et al, 1999; Carstens et al, 2000). Binding of these proteins to the nascent mRNA, which occurs in the context of a larger splicing complex, represses IIIb-specific alternative splicing and favours the formation of FGFR2 IIIc-specific mRNA.

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Type</th>
<th>Author/Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-10-06</td>
<td>Authored, Edited</td>
<td>Rothfels, K.</td>
</tr>
<tr>
<td>2016-01-06</td>
<td>Reviewed</td>
<td>Grose, RP.</td>
</tr>
</tbody>
</table>
# Table of Contents

- **Introduction**  
- **FGFR2 alternative splicing**  
  - PTB and hnRNPA1 bind FGFR2 pre-mRNA to repress IIIb splicing and promote formation of FGFR2c mRNA  
  - ESRP1 and 2 bind FGFR2 pre-mRNA to promote FGFR2b maturation and expression  
  - FGFR2b-specific alternative splicing produces FGFR2b transcript  
  - FGFR2c-specific alternative splicing produces FGFR2c transcript

---

https://reactome.org