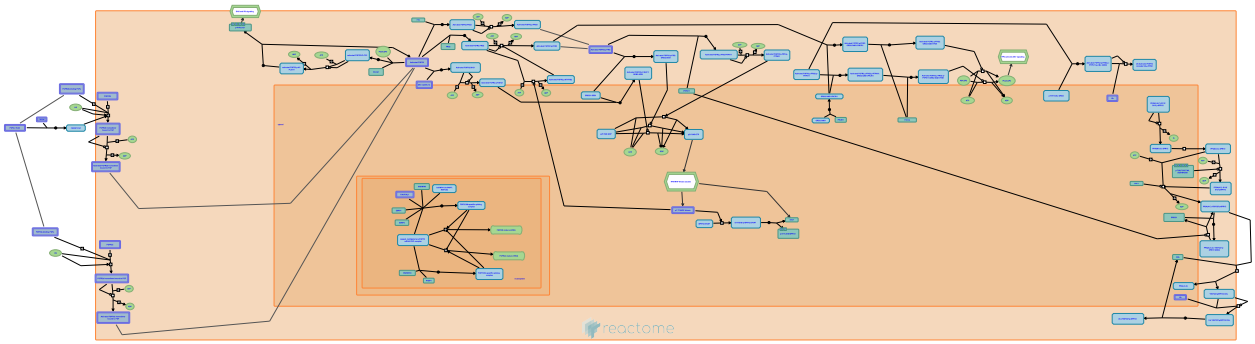
Signaling by FGFR2



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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

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

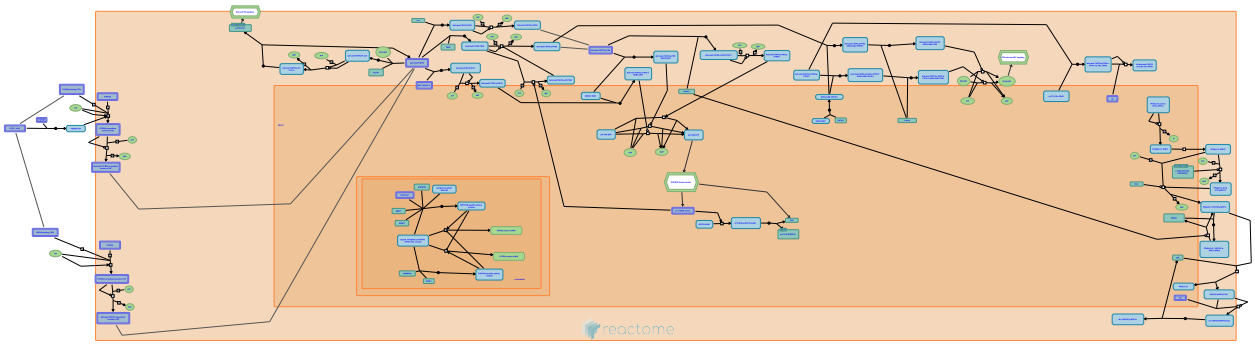
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 5 pathways (see Table of Contents)

Signaling by FGFR2 ↗

Stable identifier: R-HSA-5654738



The 22 members of the fibroblast growth factor (FGF) family of growth factors mediate their cellular responses by binding to and activating the different isoforms encoded by the four receptor tyrosine kinases (RTKs) designated FGFR1, FGFR2, FGFR3 and FGFR4. These receptors are key regulators of several developmental processes in which cell fate and differentiation to various tissue lineages are determined. Unlike other growth factors, FGFs act in concert with heparin or heparan sulfate proteoglycan (HSPG) to activate FGFRs and to induce the pleiotropic responses that lead to the variety of cellular responses induced by this large family of growth factors. An alternative, FGF-independent, source of FGFR activation originates from the interaction with cell adhesion molecules, typically in the context of interactions on neural cell membranes and is crucial for neuronal survival and development.

Upon ligand binding, receptor dimers are formed and their intrinsic tyrosine kinase is activated causing phosphorylation of multiple tyrosine residues on the receptors. These then serve as docking sites for the recruitment of SH2 (src homology-2) or PTB (phosphotyrosine binding) domains of adaptors, docking proteins or signaling enzymes. Signaling complexes are assembled and recruited to the active receptors resulting in a cascade of phosphorylation events.

This leads to stimulation of intracellular signaling pathways that control cell proliferation, cell differentiation, cell migration, cell survival and cell shape, depending on the cell type or stage of maturation.

Literature references

Beenken, A., Mohammadi, M. (2009). The FGF family: biology, pathophysiology and therapy. *Nat Rev Drug Discov, 8*, 235-53. ↗

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Ornitz, DM., Umemori, H., Mohammadi, M., Olsen, SK., Ibrahimi, OA., Zhang, X. (2006). Receptor specificity of the fibroblast growth factor family. The complete mammalian FGF family. *J Biol Chem, 281*, 15694-700. ↗

Editions

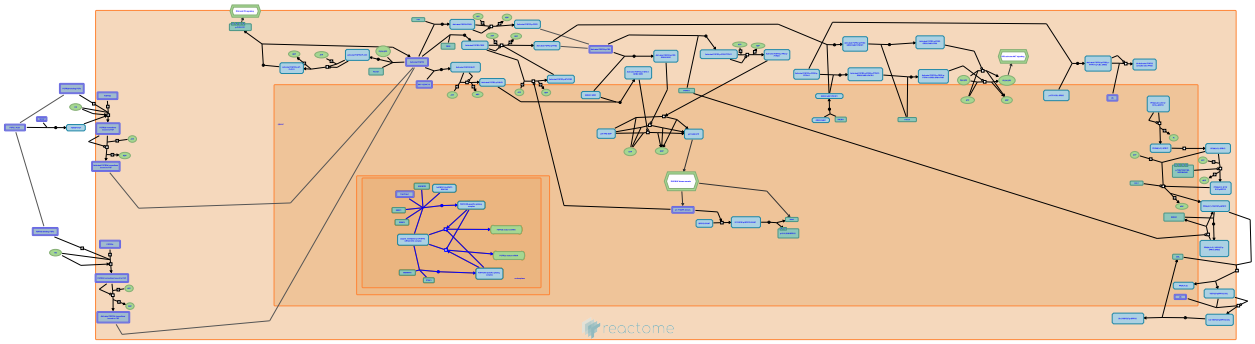
2007-01-10	Authored	de Bono, B.
2007-02-07	Reviewed	Mohammadi, M.
2007-02-11	Edited	de Bono, B., D'Eustachio, P.
2011-08-26	Reviewed	Gotoh, N.

FGFR2 alternative splicing ↗

Location: Signaling by FGFR2

Stable identifier: R-HSA-6803529

Compartments: nucleoplasm



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

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Garcia-Blanco, MA., Mauger, DM., Lin, C. (2008). hnRNP H and hnRNP F complex with Fox2 to silence fibroblast growth factor receptor 2 exon IIIc. *Mol. Cell. Biol., 28*, 5403-19. ↗

Garcia-Blanco, MA., Chen, JR., Baraniak, AP. (2006). Fox-2 mediates epithelial cell-specific fibroblast growth factor receptor 2 exon choice. *Mol. Cell. Biol., 26*, 1209-22. ↗

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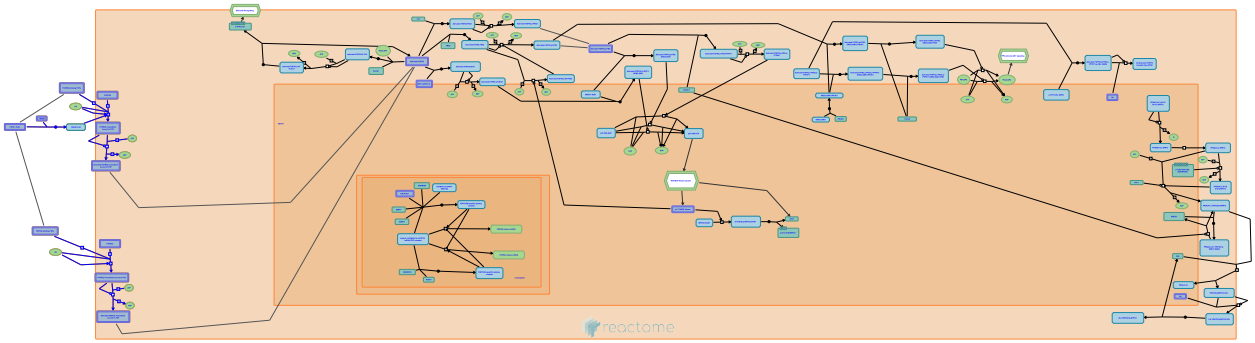
Editions

2015-10-07	Authored, Edited	Rothfels, K.
2016-01-06	Reviewed	Grose, RP.

FGFR2 ligand binding and activation ↗

Location: Signaling by FGFR2

Stable identifier: R-HSA-190241



Dominant mutations in the fibroblast growth factor receptor 2 (FGFR2) gene have been identified as causes of four phenotypically distinct craniosynostosis syndromes, including Crouzon, Jackson- Weiss, Pfeiffer, and Apert syndromes. FGFR2 binds a number of different FGFs preferentially, as illustrated in this pathway.

FGFR is probably activated by NCAM very differently from the way by which it is activated by FGFs, reflecting the different conditions for NCAM-FGFR and FGF-FGFR interactions. The affinity of FGF for FGFR is approximately 10e6 times higher than that of NCAM for FGFR. Moreover, in the brain NCAM is constantly present on the cell surface at a much higher (micromolar) concentration than FGFs, which only appear transiently in the extracellular environment in the nanomolar range.

Literature references

Ornitz, DM., Umemori, H., Mohammadi, M., Olsen, SK., Ibrahimi, OA., Zhang, X. (2006). Receptor specificity of the fibroblast growth factor family. The complete mammalian FGF family. *J Biol Chem, 281*, 15694-700. ↗

Ethier, SP., Moffa, AB. (2007). Differential signal transduction of alternatively spliced FGFR2 variants expressed in human mammary epithelial cells. *J Cell Physiol, 210*, 720-31. ↗

Hatch, NE., Hudson, M., Cunningham, ML., Seto, ML., Bothwell, M. (2006). Intracellular retention, degradation, and signaling of glycosylation-deficient FGFR2 and craniosynostosis syndrome-associated FGFR2C278F. *J Biol Chem, 281*, 27292-305. ↗

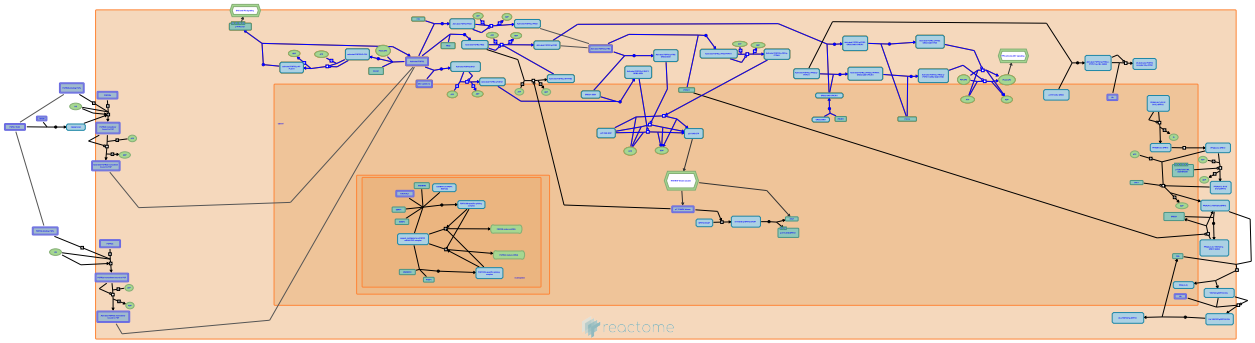
Editions

2007-01-10	Authored	de Bono, B.
2007-02-07	Reviewed	Mohammadi, M.
2007-02-11	Edited	de Bono, B., D'Eustachio, P.

Downstream signaling of activated FGFR2 ↗

Location: Signaling by FGFR2

Stable identifier: R-HSA-5654696



Signaling via FGFRs is mediated via direct recruitment of signaling proteins that bind to tyrosine auto-phosphorylation sites on the activated receptor and via closely linked docking proteins that become tyrosine phosphorylated in response to FGF-stimulation and form a complex with additional complement of signaling proteins.

The activation loop in the catalytic domain of FGFR maintains the PTK domain in an inactive or low activity state. The activation-loop of FGFR1, for instance, contains two tyrosine residues that must be autophosphorylated for maintaining the catalytic domain in an active state. In the autoinhibited configuration, a kinase invariant proline residue at the C-terminal end of the activation loop interferes with substrate binding while allowing access to ATP in the nucleotide binding site.
In addition to the catalytic PTK core, the cytoplasmic domain of FGFR contains several regulatory sequences. The juxtamembrane domain of FGFRs is considerably longer than that of other receptor tyrosine kinases. This region contains a highly conserved sequence that serves as a binding site for the phosphotyrosine binding (PTB) domain of FRS2. A variety of signaling proteins are phosphorylated in response to FGF stimulation, including Shc, phospholipase-C gamma and FRS2 leading to stimulation of intracellular signaling pathways that control cell proliferation, cell differentiation, cell migration, cell survival and cell shape.

Literature references

Hubbard, SR., Schlessinger, J., Mohammadi, M. (1996). Structure of the FGF receptor tyrosine kinase domain reveals a novel autoinhibitory mechanism. *Cell, 86*, 577-87. ↗

Editions

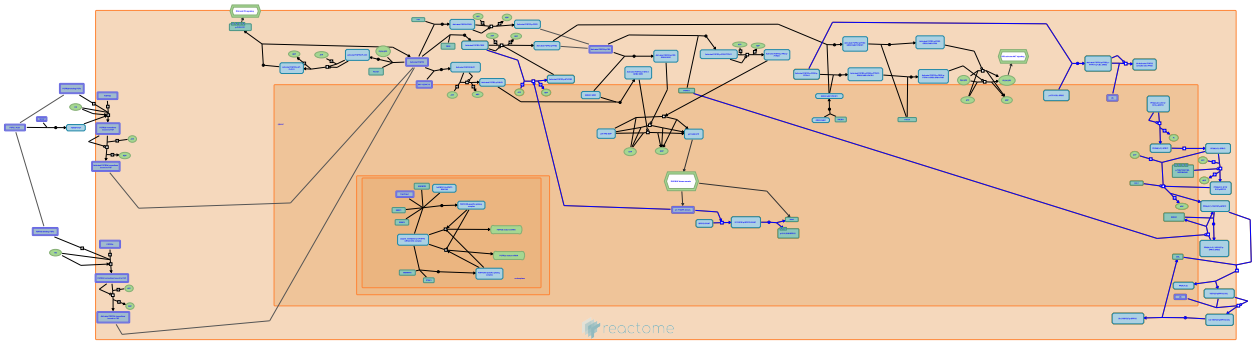
2007-01-10	Authored	de Bono, B.
2007-02-07	Reviewed	Mohammadi, M.
2010-02-03	Edited	Jupe, S.

Negative regulation of FGFR2 signaling ↗

Location: Signaling by FGFR2

Stable identifier: R-HSA-5654727

Compartments: plasma membrane, extracellular region, cytosol



Once activated, the FGFR signaling pathway is regulated by numerous negative feedback mechanisms. These include downregulation of receptors through CBL-mediated ubiquitination and endocytosis, ERK-mediated inhibition of FRS2-tyrosine phosphorylation and the attenuation of ERK signaling through the action of dual-specificity phosphatases, IL17RD/SEF, Sprouty and Spred proteins. A number of these inhibitors are themselves transcriptional targets of the activated FGFR pathway.

Literature references

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Wong, A., Lee, A., Lamothe, B., Schlessinger, J., Lax, I. (2002). FRS2 alpha attenuates FGF receptor signaling by Grb2-mediated recruitment of the ubiquitin ligase Cbl. *Proc Natl Acad Sci U S A, 99*, 6684-9. ↗

Gotoh, N. (2008). Regulation of growth factor signaling by FRS2 family docking/scaffold adaptor proteins. *Cancer Sci, 99*, 1319-25. ↗

Editions

2011-08-15	Authored	Rothfels, K.
2011-08-26	Reviewed	Gotoh, N.

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