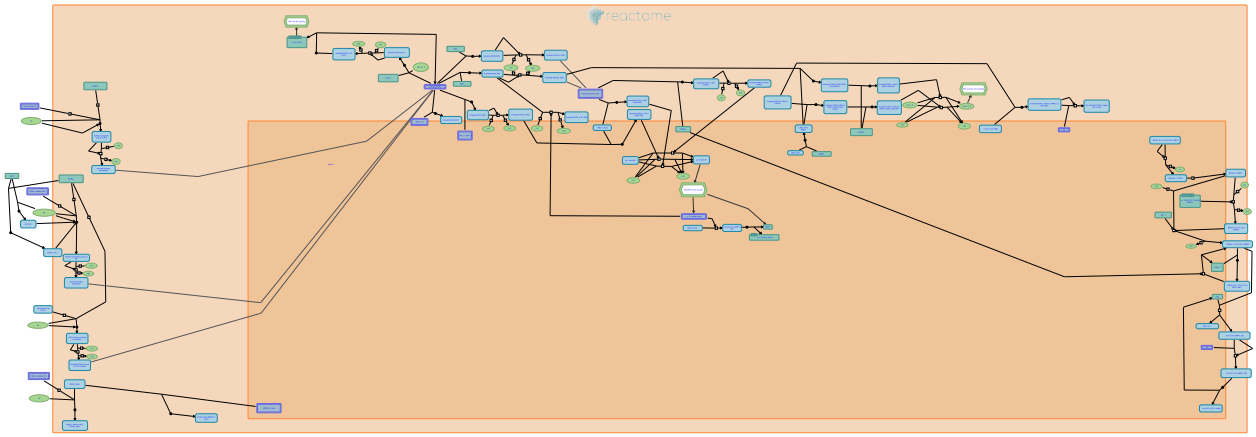
Signaling by FGFR1



D'Eustachio, P., Gotoh, N., Grose, RP., Jupe, S., Mohammadi, M., Nishimura, T., Rothfels, K., de Bono, B.

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

04/09/2021

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. ↗

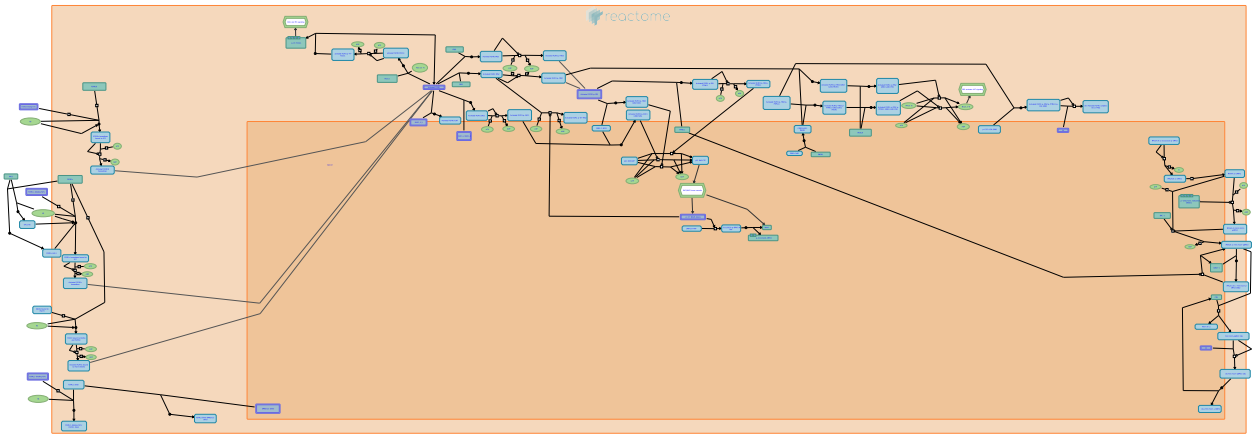
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Signaling by FGFR1 ↗

Stable identifier: R-HSA-5654736



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

Lemmon, MA., Schlessinger, J. (2010). Cell signaling by receptor tyrosine kinases. *Cell, 141*, 1117-34. ↗

Eswarakumar, VP., Lax, I., Schlessinger, J. (2005). Cellular signaling by fibroblast growth factor receptors. *Cytokine Growth Factor Rev, 16*, 139-49. ↗

Williams, EJ., Furness, J., Walsh, FS., Doherty, P. (1994). Activation of the FGF receptor underlies neurite outgrowth stimulated by L1, N-CAM, and N-cadherin. *Neuron, 13*, 583-94. ↗

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

Ornitz, DM., Marie, PJ. (2002). FGF signaling pathways in endochondral and intramembranous bone development and human genetic disease. *Genes Dev, 16*, 1446-65. ↗

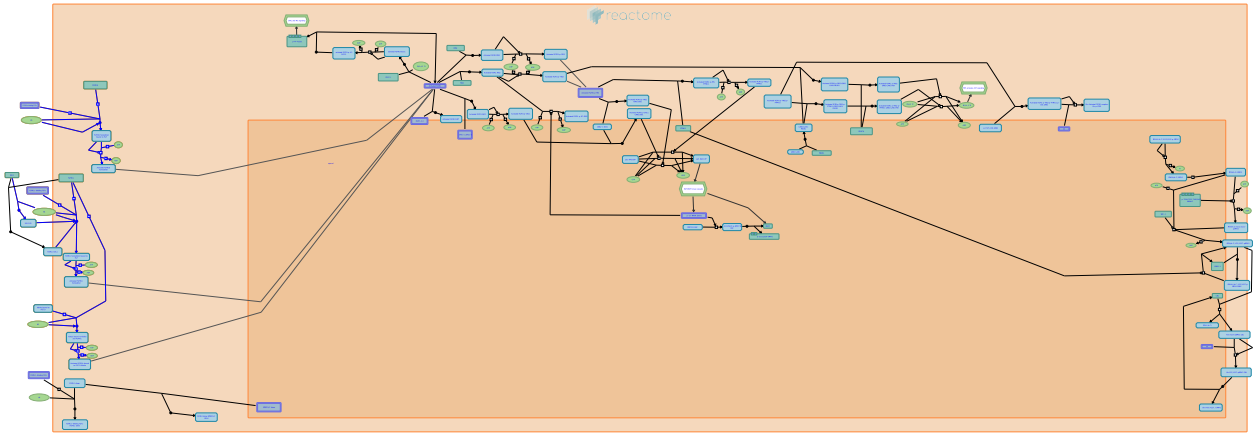
Editions

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.
2016-01-25	Reviewed	Grose, RP.

FGFR1 ligand binding and activation ↗

Location: Signaling by FGFR1

Stable identifier: R-HSA-190242



The vertebrate fibroblast growth factor receptor 1 (FGFR1) is alternatively spliced generating multiple variants that are differentially expressed during embryo development and in the adult body. The restricted expression patterns of FGFR1 isoforms, together with differential expression and binding of specific ligands, leads to activation of common FGFR1 signal transduction pathways, but may result in distinctively different biological responses as a result of differences in cellular context. FGFR1 isoforms are also present in the nucleus in complex with various fibroblast growth factors where they function to regulate transcription of target genes.

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

Groth, C., Lardelli, M. (2002). The structure and function of vertebrate fibroblast growth factor receptor 1. *Int J Dev Biol, 46*, 393-400. ↗

Kiselyov, VV., Skladchikova, G., Hinsby, AM., Jensen, PH., Kulahin, N., Soroka, V. et al. (2003). Structural basis for a direct interaction between FGFR1 and NCAM and evidence for a regulatory role of ATP. *Structure, 11*, 691-701. ↗

Kiselyov, VV., Soroka, V., Berezin, V., Bock, E. (2005). Structural biology of NCAM homophilic binding and activation of FGFR. *J Neurochem, 94*, 1169-79. ↗

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

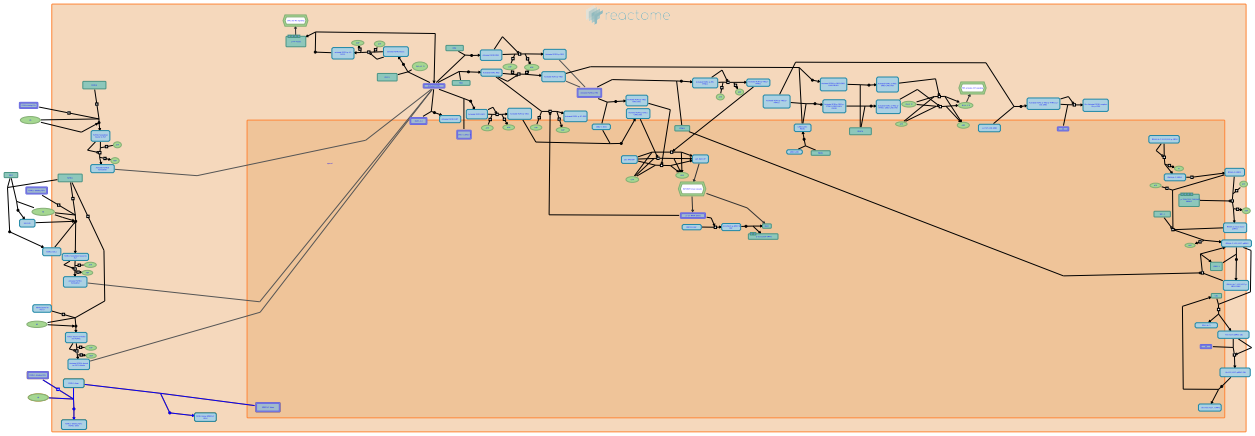
Editions

2007-01-10	Authored	de Bono, B.
2007-02-07	Reviewed	Mohammadi, M.
2007-02-11	Edited	de Bono, B., D'Eustachio, P.
2016-01-06	Reviewed	Grose, RP.

FGFRL1 modulation of FGFR1 signaling ↗

Location: Signaling by FGFR1

Stable identifier: R-HSA-5658623



FGFRL1 is a fifth member of the FGFR family of receptors. The extracellular region has 40% sequence similarity with FGFR1-4, but FGFRL1 lacks the internal kinase domain of the other FGF receptors and how it acts in FGFR signaling is unclear. Some models suggest FGFRL1 restricts canonical FGFR signaling by sequestering ligand away from kinase-active receptors, while other models suggest that FGFRL1 may promote canonical signaling by nucleating signaling complexes or enhancing ERK1/2 activation (reviewed in Trueb, 2011; Trueb et al, 2013).

Literature references

Trueb, B., Amann, R., Gerber, SD. (2013). Role of FGFRL1 and other FGF signaling proteins in early kidney development. *Cell. Mol. Life Sci., 70*, 2505-18. ↗

Trueb, B. (2011). Biology of FGFRL1, the fifth fibroblast growth factor receptor. *Cell. Mol. Life Sci., 68*, 951-64. ↗

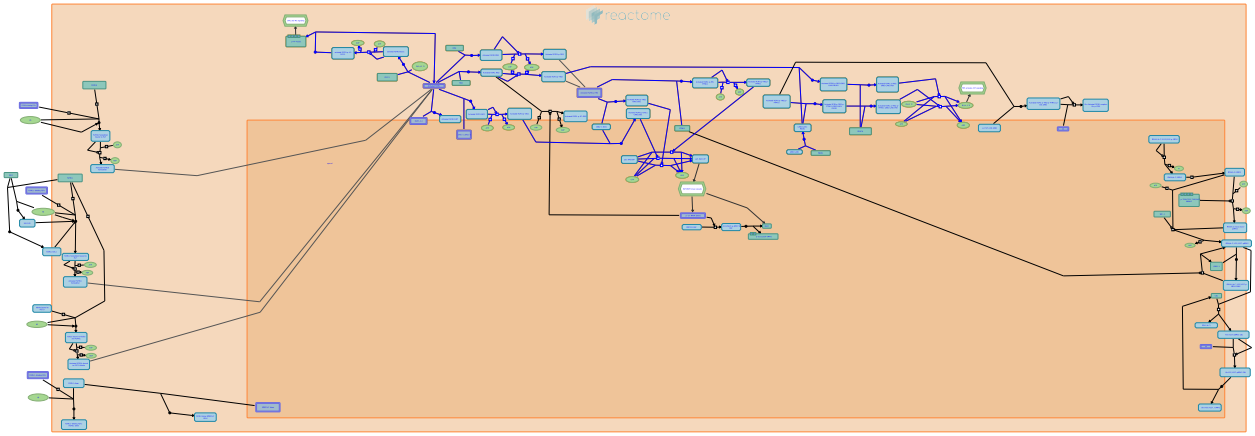
Editions

2014-12-12	Authored	Rothfels, K.
2015-01-14	Edited	Rothfels, K.
2016-01-06	Reviewed	Nishimura, T., Grose, RP.
2016-03-18	Reviewed	Gotoh, N.

Downstream signaling of activated FGFR1 ↗

Location: Signaling by FGFR1

Stable identifier: R-HSA-5654687



Signaling via FGFRs is mediated via direct recruitment of signaling proteins that bind to tyrosine autophosphorylation 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

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

Editions

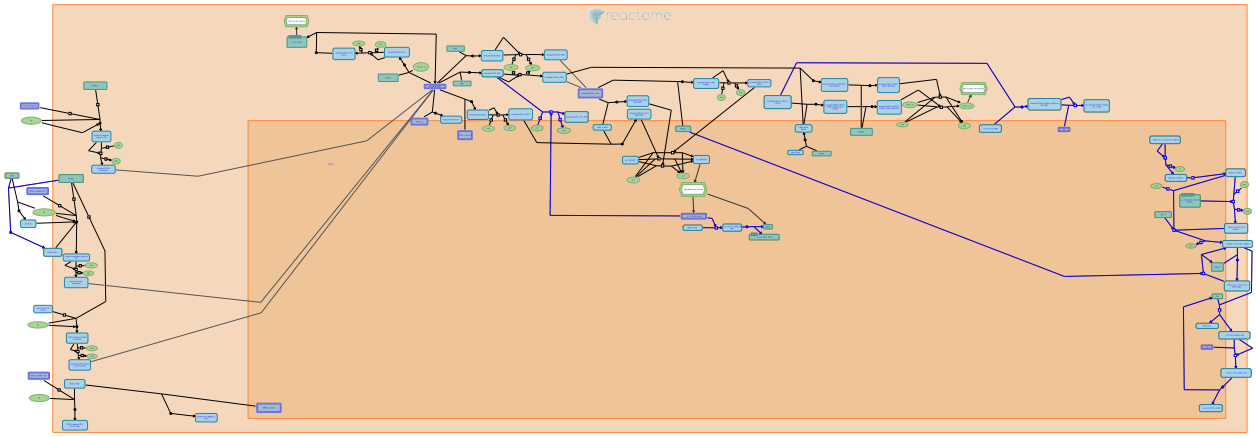
2007-01-10	Authored	de Bono, B.
2007-02-07	Reviewed	Mohammadi, M.
2010-02-03	Edited	Jupe, S.
2016-01-06	Reviewed	Grose, RP.

Negative regulation of FGFR1 signaling ↗

Location: Signaling by FGFR1

Stable identifier: R-HSA-5654726

Compartments: cytosol, extracellular region, plasma membrane



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

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

Itoh, N., Ornitz, DM. (2011). Fibroblast growth factors: from molecular evolution to roles in development, metabolism and disease. *J Biochem, 149*, 121-30. ↗

Wong, A., Lamothe, B., Lee, A., 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. ↗

Fong, CW., Leong, HF., Wong, ES., Lim, J., Yusoff, P., Guy, GR. (2003). Tyrosine phosphorylation of Sprouty2 enhances its interaction with c-Cbl and is crucial for its function. *J Biol Chem, 278*, 33456-64. ↗

Editions

2011-08-15	Authored	Rothfels, K.
2011-08-26	Reviewed	Gotoh, N.
2016-01-06	Reviewed	Grose, RP.

Table of Contents