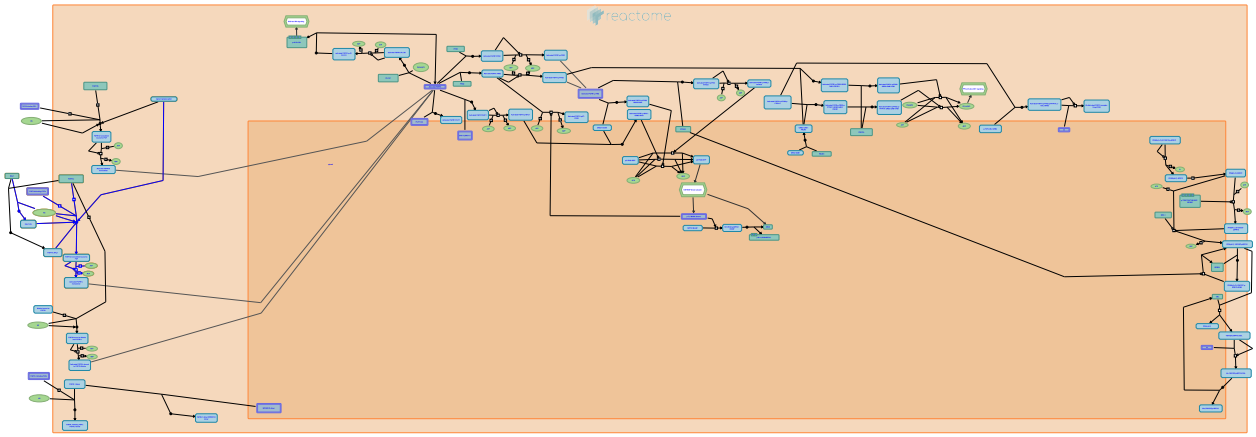
FGFR1c ligand binding and activation



Gotoh, N., Grose, RP., 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.

29/04/2024

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. ↗

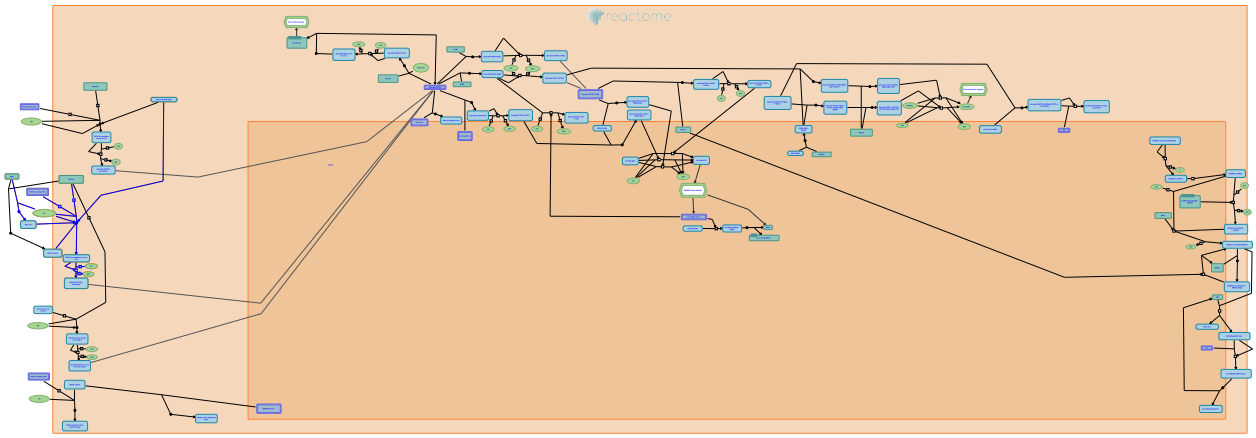
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

FGFR1c ligand binding and activation ↗

Stable identifier: R-HSA-190373



This pathway depicts the binding of an experimentally-verified range of ligands to FGFR1c. While binding affinities may vary considerably within this set, the ligands listed have been established to bring about receptor activation at their reported physiological concentrations.

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. ↗

Editions

2007-01-10	Authored	de Bono, B.
2007-02-07	Reviewed	Mohammadi, M.
2016-01-06	Reviewed	Grose, RP.

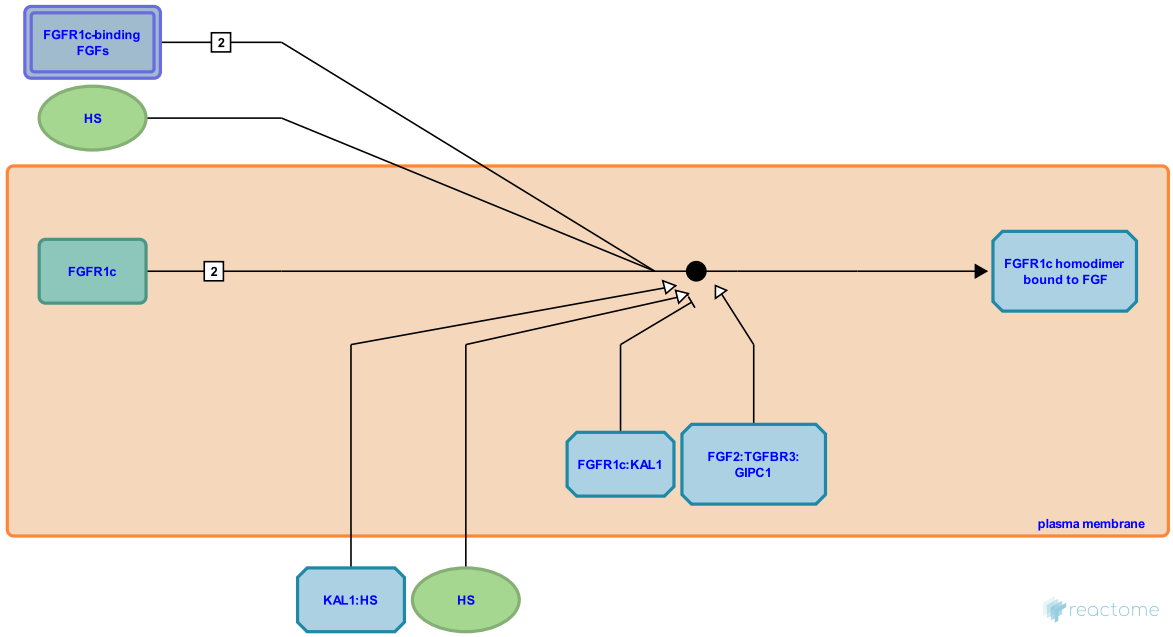
FGFR1c binds to FGF ↗

Location: FGFR1c ligand binding and activation

Stable identifier: R-HSA-190256

Type: binding

Compartments: plasma membrane, extracellular region



In this reaction, FGF receptor in the plasma membrane binds an associating extracellular ligand, a requisite step for subsequent activation. The resulting complex consists of dimerized receptor, two ligand molecules, and heparan sulfate. Also, TGFBR3 (beta-glycan) facilitates the binding of FGF2 with its receptor FGFR1 by binding with FGF2 itself and bringing more ligands into receptor proximity (Andres et al. 1992, Knelson et al. 2013).

Followed by: Autocatalytic phosphorylation of FGFR1c

Literature references

Olsen, SK., Mohammadi, M., Ibrahimi, OA. (2005). Structural basis for fibroblast growth factor receptor activation. *Cytokine Growth Factor Rev, 16*, 107-37. ↗

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.
2011-08-16	Revised	Rothfels, K.

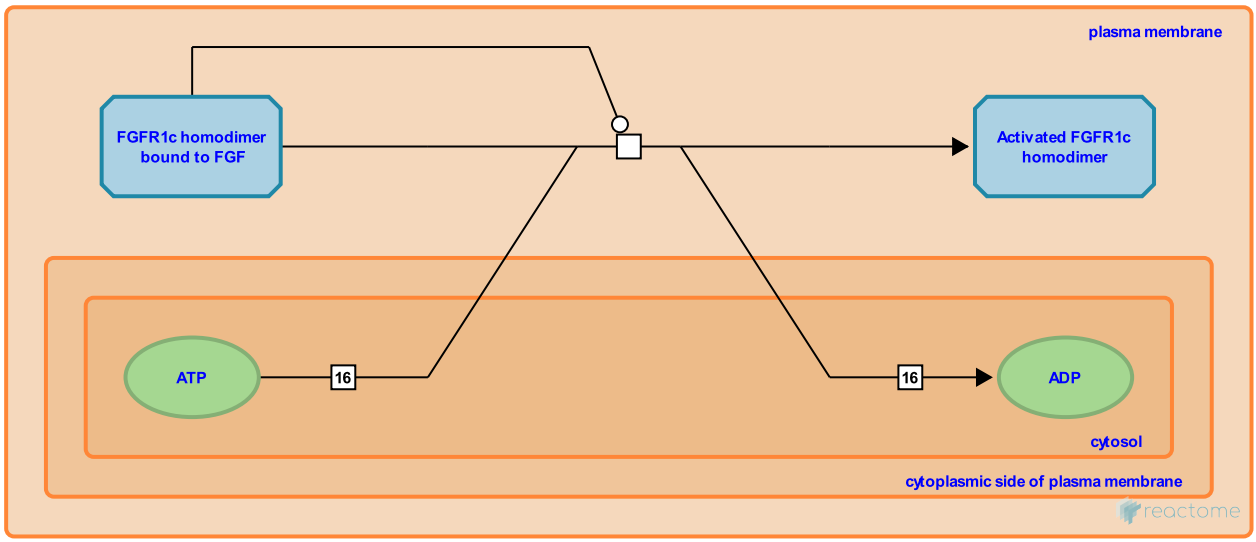
Autocatalytic phosphorylation of FGFR1c ↗

Location: FGFR1c ligand binding and activation

Stable identifier: R-HSA-190429

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Studies have mapped 8 tyrosine residues in the cytoplasmic domain of FGFR1 that are important for signaling. Autophosphorylation of residues 653 and 654, located in the activation loop of the kinase, is necessary to maintain the receptor in the active state. Phosphorylation of other tyrosine residues by the intrinsic protein tyrosine kinase activity of the activated receptor creates binding sites on its cytoplasmic tail for membrane bound docking proteins to gather intracellular signaling mediators.

Preceded by: FGFR1c binds to FGF

Literature references

Burgess, WH., Jaye, M., Schlessinger, J., Sorokin, A., Dikic, I., Mohammadi, M. (1996). Identification of six novel autophosphorylation sites on fibroblast growth factor receptor 1 and elucidation of their importance in receptor activation and signal transduction. *Mol Cell Biol, 16*, 977-89. ↗

Schlessinger, J., Furdui, CM., Anderson, KS., Lew, ED. (2006). Autophosphorylation of FGFR1 kinase is mediated by a sequential and precisely ordered reaction. *Mol Cell, 21*, 711-7. ↗

Dionne, CA., Jaye, M., Li, N., Schlessinger, J., Honegger, AM., Mohammadi, M. et al. (1992). Point mutation in FGF receptor eliminates phosphatidylinositol hydrolysis without affecting mitogenesis. *Nature, 358*, 681-4. ↗

Hubbard, SR., Schlessinger, J., Yeh, BK., Mohammadi, M., Tang, C., Sun, L. et al. (1997). Structures of the tyrosine kinase domain of fibroblast growth factor receptor in complex with inhibitors. *Science, 276*, 955-60. ↗

Donoghue, DJ., Hart, KC., Robertson, SC. (2001). Identification of tyrosine residues in constitutively activated fibroblast growth factor receptor 3 involved in mitogenesis, Stat activation, and phosphatidylinositol 3-kinase activation. *Mol Biol Cell, 12*, 931-42. ↗

Editions

2007-01-10	Authored	de Bono, B.
2007-02-07	Reviewed	Mohammadi, M.
2011-08-16	Revised	Rothfels, K.

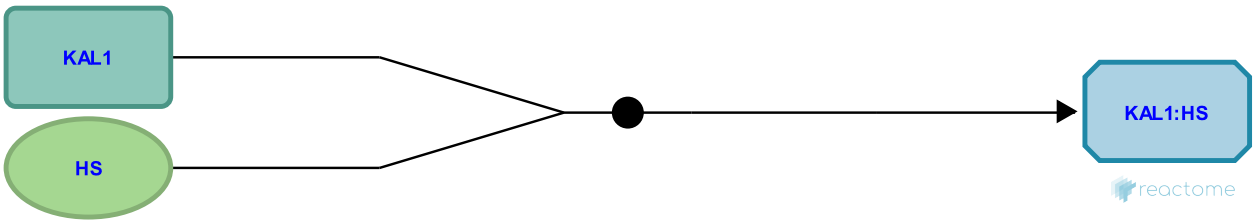
KAL1 binds HS ↗

Location: FGFR1c ligand binding and activation

Stable identifier: R-HSA-5654515

Type: binding

Compartments: extracellular region



KAL1 is an extracellular matrix-associated protein that modulates signaling by FGFR1c. Mutations in the KAL1 gene are associated with Kallmann syndrome, a genetic disorder characterized by olfactory bulb dysgenesis and hypogonadotrophic hypogonadism (Dode et al, 2003; Pitteloud et al, 2006; reviewed in Yu and Bouloux, 2010). KAL1 has been shown to interact with both FGFR1c and with heparan sulfate, with opposing effects on downstream signaling. Preformation of an FGFR1c:KAL1 complex inhibits the association of FGF ligand with the complex and subsequent receptor dimerization and in this way negatively regulates FGFR1c ligand-dependent signaling. In contrast, preformation of a KAL1:heparan sulfate complex promotes stable FGF ligand:receptor interaction thereby enhancing FGFR1c signal transduction (Hu et al, 2009; Hu et al, 2004; Soussi-Yanicostas et al, 1998).

Literature references

Cadman, S., Kim, SH., Hohenester, E., Travers, P., Guimond, SE., Turnbull, JE. et al. (2009). Novel mechanisms of fibroblast growth factor receptor 1 regulation by extracellular matrix protein anosmin-1. *J. Biol. Chem., 284*, 29905-20. ↗

Hu, Y., Bouloux, PM. (2010). Novel insights in FGFR1 regulation: lessons from Kallmann syndrome. *Trends Endocrinol. Metab., 21*, 385-93. ↗

Kim, SH., Bouloux, PM., González-Martínez, D., Hu, Y. (2004). Cross-talk of anosmin-1, the protein implicated in X-linked Kallmann's syndrome, with heparan sulphate and urokinase-type plasminogen activator. *Biochem. J., 384*, 495-505. ↗

Petit, C., Soussi-Yanicostas, N., Hardelin, JP., Goulet-Salmon, B., Delemarre-van de Waal, H., Delmaghani, S. et al. (2003). Loss-of-function mutations in FGFR1 cause autosomal dominant Kallmann syndrome. *Nat. Genet., 33*, 463-5. ↗

Dwyer, AA., Acierno, JS., Seminara, S., Fliers, E., Quinton, R., Ma, J. et al. (2006). Mutations in fibroblast growth factor receptor 1 cause Kallmann syndrome with a wide spectrum of reproductive phenotypes. *Mol. Cell. Endocrinol., 254*, 60-9. ↗

Editions

2014-12-02	Authored	Rothfels, K.
2015-01-14	Edited	Rothfels, K.
2016-01-06	Reviewed	Nishimura, T., Grose, RP.
2016-03-18	Reviewed	Gotoh, N.

Table of Contents