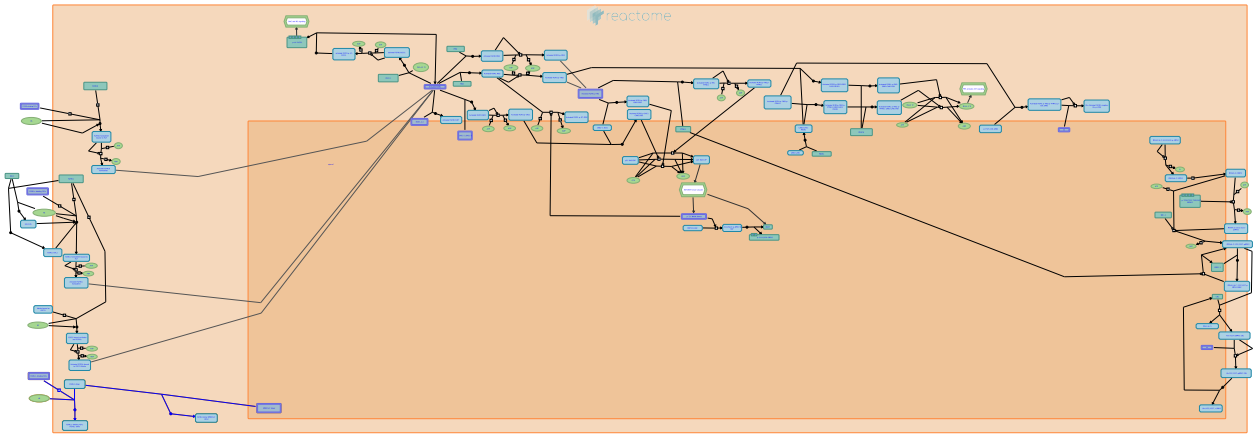
FGFRL1 modulation of FGFR1 signaling



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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.

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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. ↗

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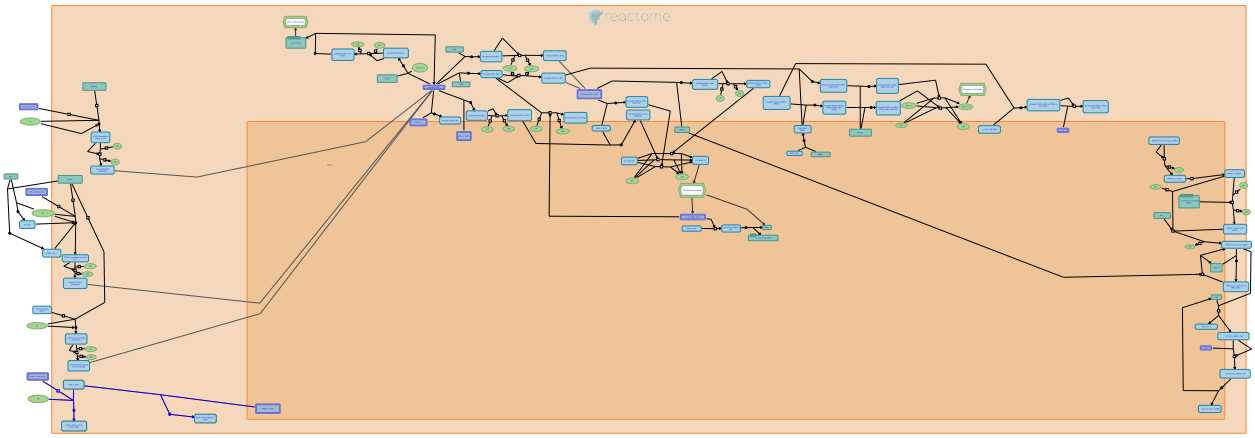
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

FGFRL1 modulation of FGFR1 signaling ↗

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

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. ↗

Editions

2014-12-12	Authored	Rothfels, K.
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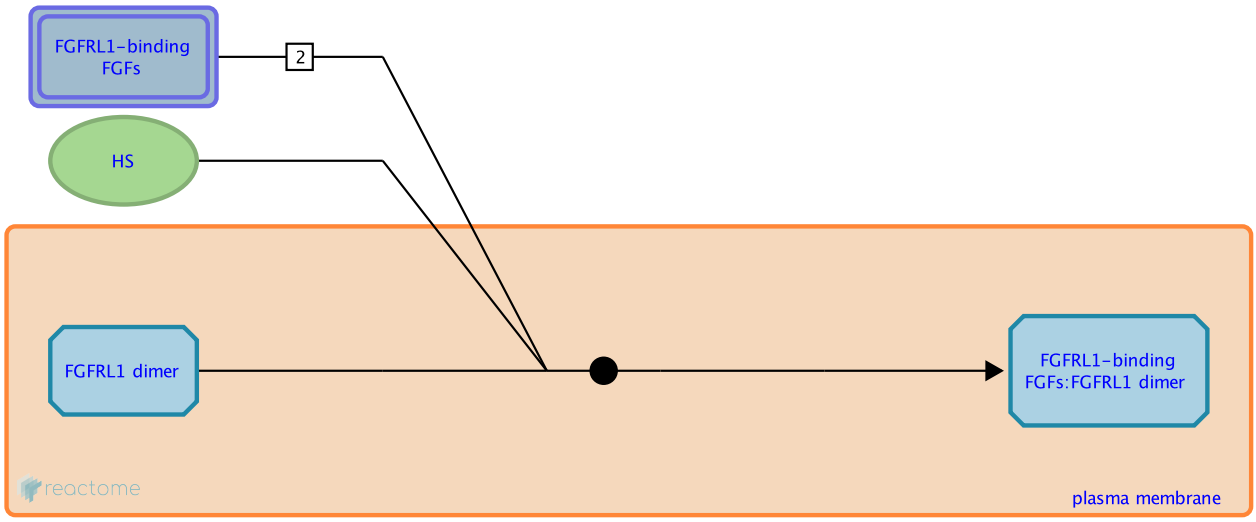
FGFRL1 dimer binds FGFs ↗

Location: FGFRL1 modulation of FGFR1 signaling

Stable identifier: R-HSA-5654511

Type: binding

Compartments: plasma membrane



FGFRL1 is a fifth member of the FGFR family of receptors that shares 40% sequence similarity with the extracellular region of FGFR1-4, but FGFRL1 lacks the internal kinase domain required for typical downstream FGFR signaling. Instead, FGFRL1 has a short intracellular domain with a C-terminal histidine rich region that has been shown to interact with the MAP kinase regulator SPRED proteins (Sleeman et al, 2001; Zhuang et al, 2011; reviewed in Trueb et al, 2013). FGFRL1 forms constitutive dimers and has been shown to bind to a wide range of FGF ligands, including FGF3,4,8,10, 22 and with lower affinity to FGF2,5,17,18 and 23 (Reickman et al, 2008; Steinberg et al, 2010). FGFRL1 knockout mice die shortly after birth from lung and renal defects (Gerber et al, 2009; Gerber et al, 2012; Trueb et al, 2013). FGFRL1 has been postulated to act as a decoy receptor that sequesters ligand away from canonical FGF receptors; more recently, however, alternate roles for FGFRL1 in enhancing ERK1/2 activation or promoting FGFR1-mediated signaling have been suggested (Sleeman et al, 2001; Steinberg et al, 2010; Silva et al, 2013; Amann and Trueb, 2013). Further work will be required to elucidate the role(s) of FGFRL1.

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Sleeman, M., Fraser, J., McDonald, M., Yuan, S., White, D., Grandison, P. et al. (2001). Identification of a new fibroblast growth factor receptor, FGFR5. *Gene, 271*, 171-82. ↗

Zhuang, L., Villiger, P., Trueb, B. (2011). Interaction of the receptor FGFRL1 with the negative regulator Spred1. *Cell. Signal., 23*, 1496-504. ↗

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Rieckmann, T., Kotevic, I., Trueb, B. (2008). The cell surface receptor FGFRL1 forms constitutive dimers that promote cell adhesion. *Exp. Cell Res., 314*, 1071-81. ↗

Steinberg, F., Zhuang, L., Beyeler, M., Kälin, RE., Mullis, PE., Brändli, AW. et al. (2010). The FGFRL1 receptor is shed from cell membranes, binds fibroblast growth factors (FGFs), and antagonizes FGF signaling in Xenopus embryos. *J. Biol. Chem., 285*, 2193-202. ↗

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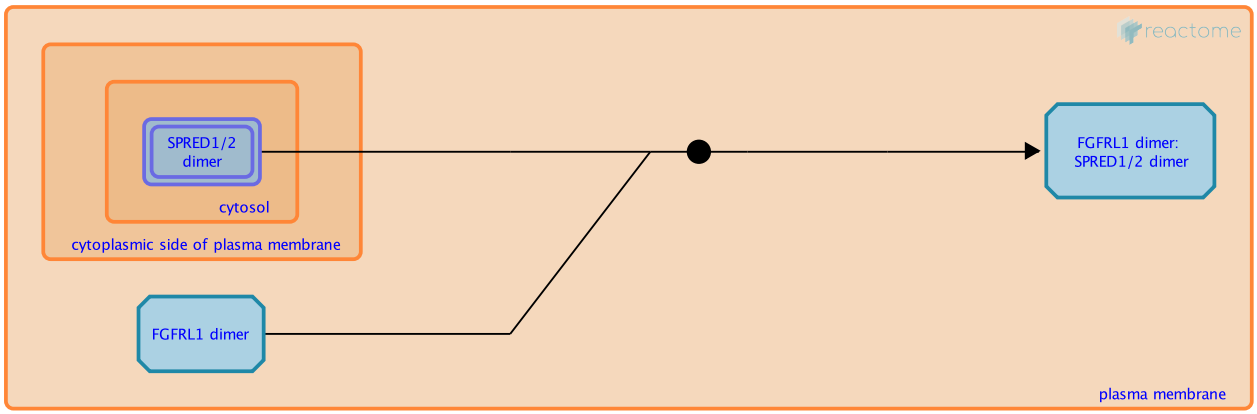
FGFRL1 binds SPRED1/2 ↗

Location: FGFRL1 modulation of FGFR1 signaling

Stable identifier: R-HSA-5654510

Type: binding

Compartments: plasma membrane



FGFRL1 binds to SPRED1 and 2 and Sprouty1 as assessed by co-immunoprecipitation, although the exact stoichiometry of the complex remains to be determined. The interaction requires the C-terminal residues of the short intracellular domain of FGFRL1 (Zhuang et al, 2011). The SPRED proteins are members of the Sprouty family, with established roles as negative regulators of the Ras/Raf/Erk signaling pathway (reviewed in McClatchey and Cichowski, 2012).

Literature references

Zhuang, L., Villiger, P., Trueb, B. (2011). Interaction of the receptor FGFRL1 with the negative regulator Spred1. *Cell. Signal., 23*, 1496-504. ↗

McClatchey, AI., Cichowski, K. (2012). SPRED proteins provide a NF-ty link to Ras suppression. *Genes Dev., 26*, 1515-9. ↗

Editions

2014-11-20	Authored	Rothfels, K.
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