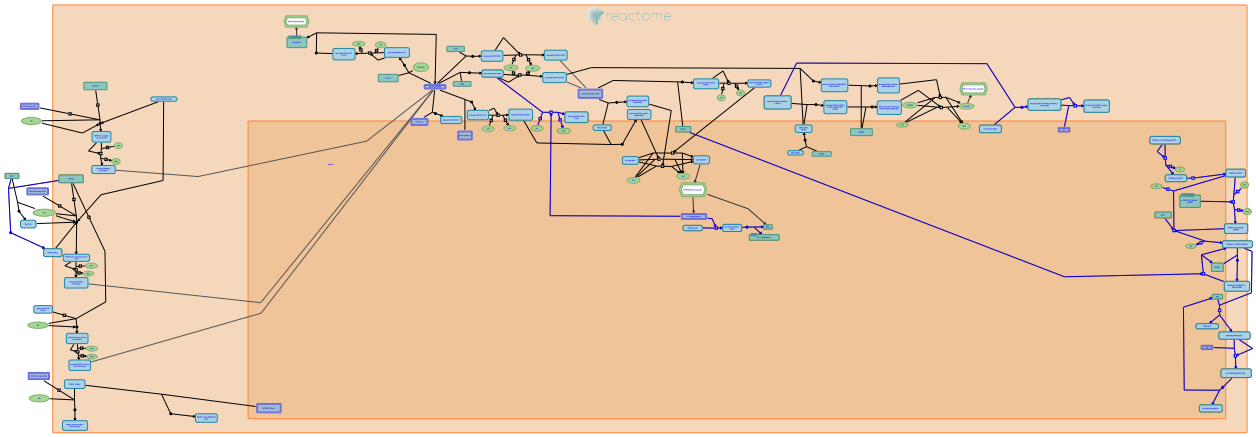
Negative regulation of FGFR1 signaling



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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.
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. ↗

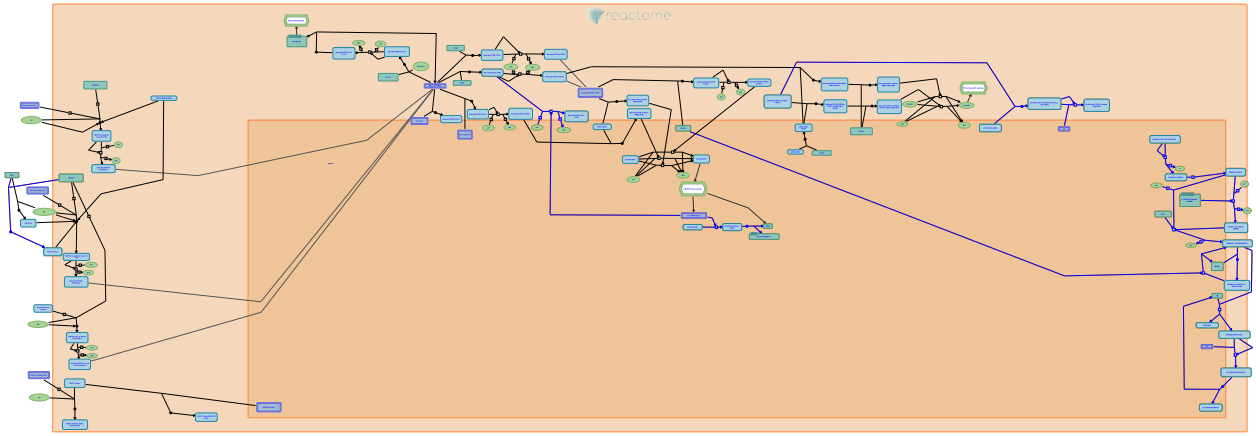
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Negative regulation of FGFR1 signaling ↗

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

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Yusoff, P., Fong, CW., Wong, ES., Lim, J., Leong, HF., 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. ↗

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.
2016-01-06	Reviewed	Grose, RP.

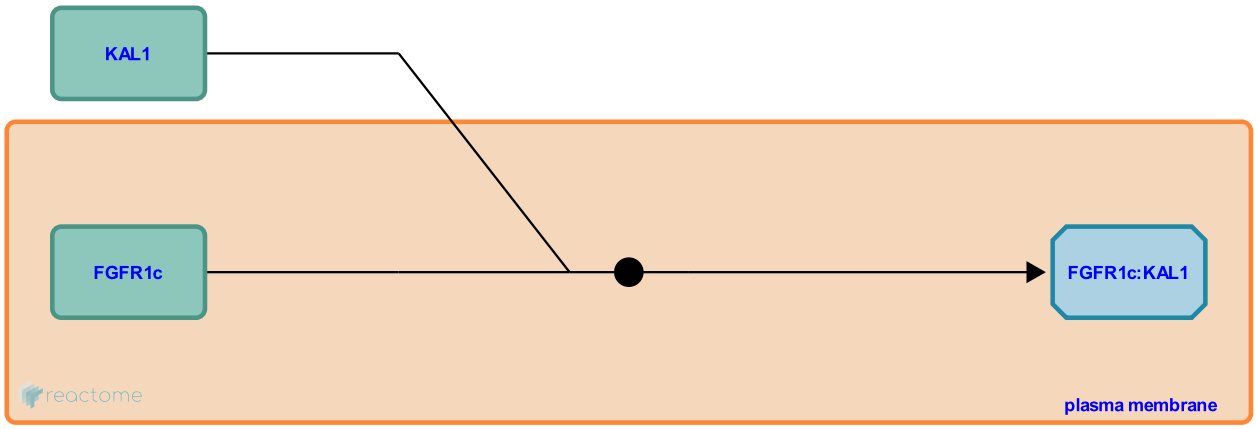
KAL1 binds FGFR1c ↗

Location: Negative regulation of FGFR1 signaling

Stable identifier: R-HSA-5654514

Type: binding

Compartments: plasma membrane



KAL1 is an extracellular matrix-associated protein that modulates signaling by FGFR1c. Mutations in the KAL1 gene are associated with Kallman syndrome, a genetic disorder characterized by olfactory bulb dysgenesis and hypogonadotrophic hypogonadism (Dode et al, 2003; Pitteloud et al, 2006; reviewed in Hu 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).
KAL1 consists of an N-terminal cysteine rich domain, a whey acidic protein-like (WAP) domain, four fibronectin III (FnIII) repeats and a C-terminal histidine rich region. The N-terminal cysteine rich region, the WAP domain and the first FnIII domain contribute to the interaction with the D2 and D3 Ig-like domains of FGFR1c. D1 and the acid box of the receptor inhibit the interaction with KAL1 in a manner analogous to the inhibition of FGF binding (Hu et al, 2009). Consistent with this, missense mutations in D1 and the acid box that affect the interaction with KAL1 have been identified in patients with Kallmann syndrome (Dode and Hardelin, 2009). Similarly, loss-of function mutations in the FnIII domain of KAL1 that disrupt the interaction with FGFR1c have also been characterized (Hu et al, 2009; Robertson et al, 2001; Gonzalez-Martinez et al 2004; Oliviera et al, 2001).

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. ↗

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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. ↗

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Kim, SH., Guimond, S., Vannelli, GB., González-Martínez, D., Hu, Y., Winyard, P. et al. (2004). Anosmin-1 modulates fibroblast growth factor receptor 1 signaling in human gonadotropin-releasing hormone olfactory neuroblasts through a heparan sulfate-dependent mechanism. *J. Neurosci., 24*, 10384-92. ↗

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.

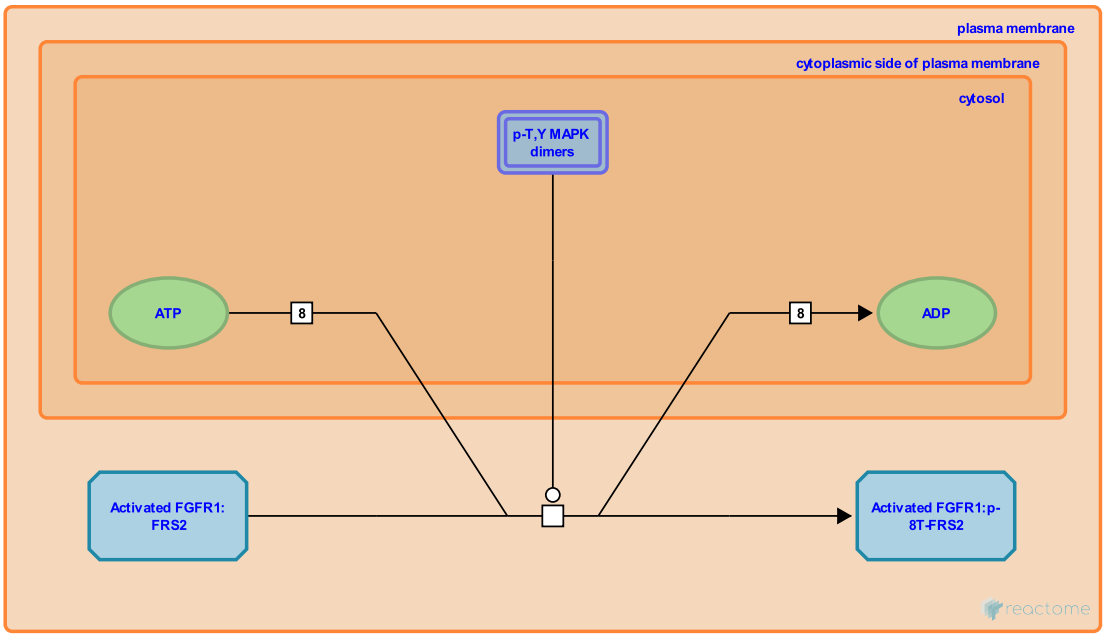
Activated ERK1/2 threonine-phosphorylates FGFR1-associated FRS2. ↗

Location: Negative regulation of FGFR1 signaling

Stable identifier: R-HSA-5654560

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



FRS2 has 8 canonical MAPK phosphorylation sites which are phosphorylated by activated ERK1/2 after FGF stimulation. Phosphorylation of these 8 threonine residues counteracts the activating effect of tyrosine phosphorylation of FRS2, although the exact mechanism for this negative regulation is not known. Expression of a version of FRS2 in which the 8 threonine residues are mutated to valine results in enhanced tyrosine phosphorylation of FRS2, enhanced GRB2-SOS1 recruitment and a more sustained MAPK response. The 8 threonine residues are not conserved in FRS3; as a result, signaling through FRS3 complexes do not appear to be subject to this downregulation.

Literature references

Frost, A., Wong, A., Hawes, J., Lee, A., Lamothe, B., Schlessinger, J. et al. (2002). The docking protein FRS2alpha controls a MAP kinase-mediated negative feedback mechanism for signaling by FGF receptors. *Mol Cell, 10*, 709-19. ↗

Chen, Z., Ullrich, A., Wu, Y. (2003). EGFR and FGFR signaling through FRS2 is subject to negative feedback control by ERK1/2. *Biol Chem, 384*, 1215-26. ↗

Chen, Z., Zhou, W., Zhang, Z., Benge, J., Feng, X., Wu, Y. (2009). FGF-receptor substrate 2 functions as a molecular sensor integrating external regulatory signals into the FGF pathway. *Cell Res, 19*, 1165-77. ↗

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.

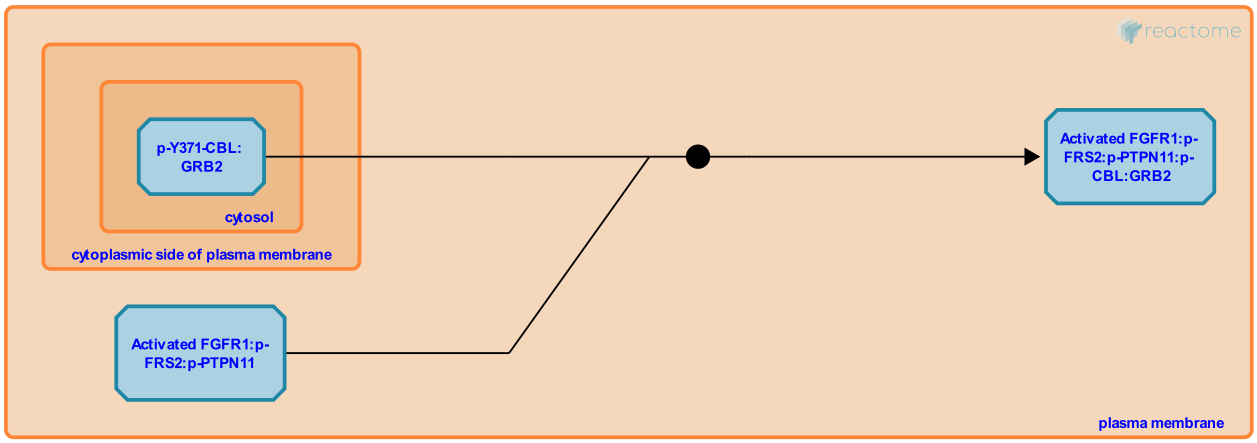
p-CBL:GRB2 binds p-FRS2:activated FGFR1

Location: Negative regulation of FGFR1 signaling

Stable identifier: R-HSA-5654673

Type: binding

Compartments: plasma membrane, extracellular region, cytosol



The ubiquitin ligase CBL exists in a complex with GRB2 and is recruited to tyrosine-phosphorylated FRS2 after FGF stimulation. In addition to promoting the ubiquitination, endocytosis, and degradation of the activated receptor complex, recruitment of the p-CBL:GRB2 complex seems to attenuate FGFR signaling by competing with GRB2:SOS1 for binding to the direct GRB2-binding sites on p-FRS2.

Followed by: CBL ubiquitinates FRS2 and FGFR1

Literature references

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.

Editions

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

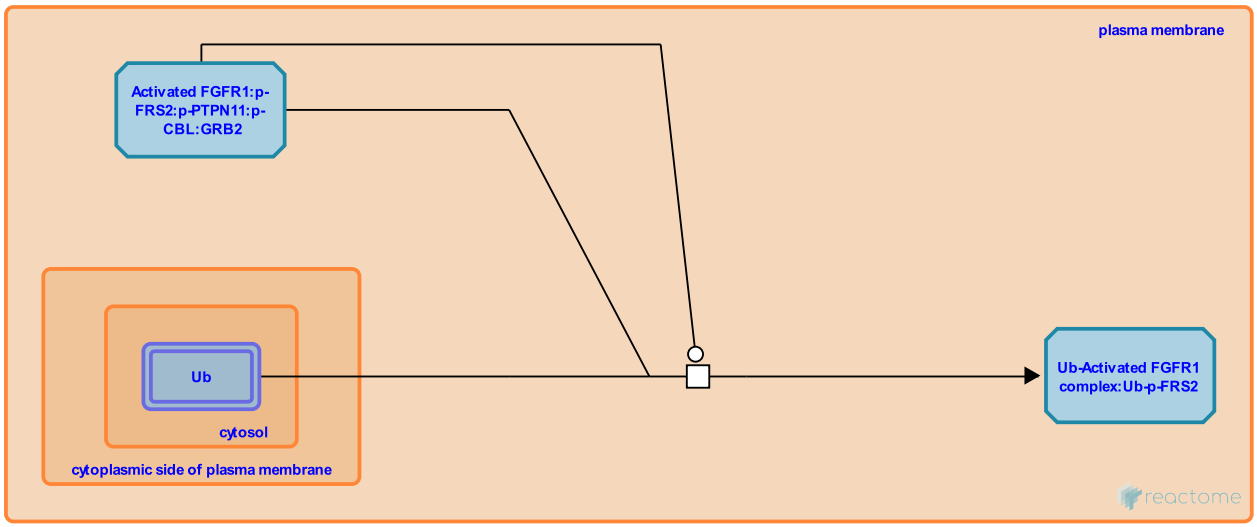
CBL ubiquitinates FRS2 and FGFR1 ↗

Location: Negative regulation of FGFR1 signaling

Stable identifier: R-HSA-5654672

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Grb2 bound to tyrosine phosphorylated FRS2 forms a ternary complex with Cbl through the binding of the SH3 domains of Grb2 to a proline rich region in Cbl. Grb2-mediated recruitment of Cbl results in ubiquitination of FGFR and FRS2. Cbl is a multidomain protein that posses an intrinsic ubiquitin ligase activity and also functions as a platform for recruitment of a variety of signaling proteins. Multiple mechanisms appear to be required for downregulation of FGFR, as internalization of the receptor is reduced but not abolished if recruitment of CBL to FRS2 is compromised by mutation of GRB2-binding sites.

Preceded by: p-CBL:GRB2 binds p-FRS2:activated FGFR1

Literature references

Yusoff, P., Fong, CW., Wong, ES., Lim, J., Leong, HF., 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. ↗

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. ↗

Editions

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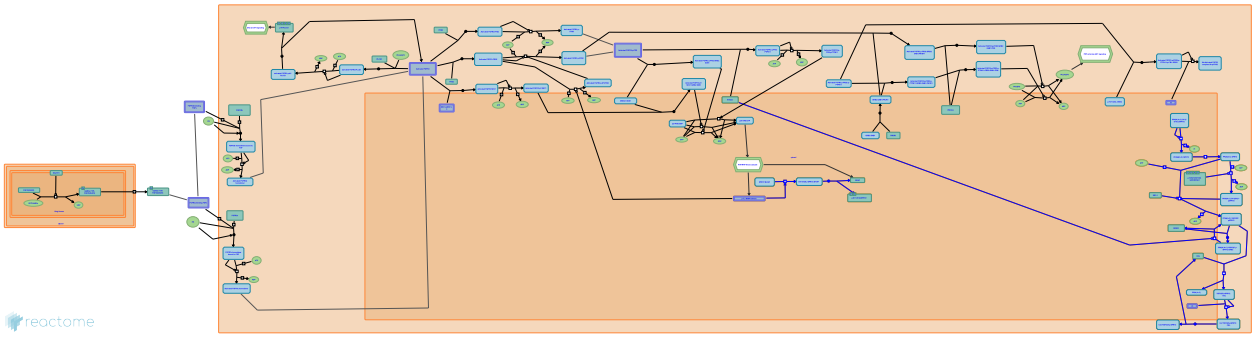
2011-08-26	Reviewed	Gotoh, N.

Spry regulation of FGF signaling ↗

Location: Negative regulation of FGFR1 signaling

Stable identifier: R-HSA-1295596

Compartments: plasma membrane, cytosol



Sprouty was initially characterized as a negative regulator of FGFR signaling in Drosophila. Human cells contain four genes encoding Sprouty proteins, of which Spry2 is the best studied and most widely expressed. Spry proteins modulate the duration and extent of signaling through the MAPK cascade after FGF stimulation, although the mechanism appears to depend on the particular biological context. Some studies have suggested that Sprouty binds to GRB2 and interferes with the recruitment of GRB2-SOS1 to the receptor, while others have shown that Sprouty interferes with the MAPK cascade at the level of RAF activation. In addition to modulating the MAPK pathway in response to FGF stimulation, Sprouty itself appears to be subject to complex post-translational modification that regulates its activity and stability.

Literature references

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Editions

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

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