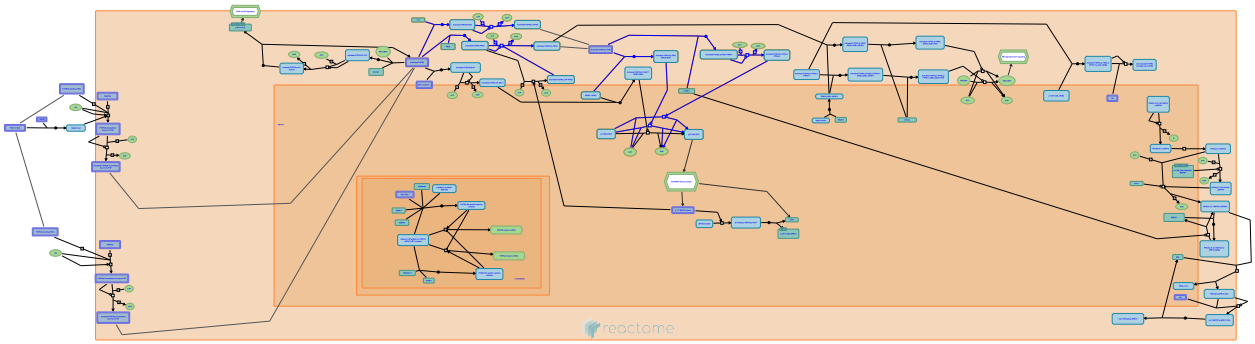
FRS-mediated FGFR2 signaling



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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. ↗

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. ↗

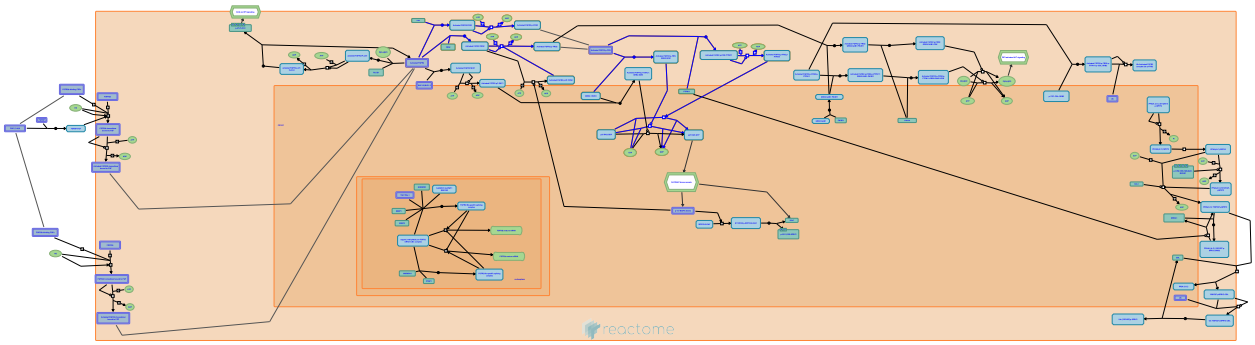
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 70

This document contains 1 pathway and 9 reactions (see Table of Contents)

FRS-mediated FGFR2 signaling ↗

Stable identifier: R-HSA-5654700



The FRS family of scaffolding adaptor proteins has two members, FRS2 (also known as FRS2 alpha) and FRS3 (also known as FRS2beta or SNT-2). Activation of FGFR tyrosine kinase allows FRS proteins to become phosphorylated on tyrosine residues and then bind to the adaptor GRB2 and the tyrosine phosphatase PPTN11/SHP2. Subsequently, PPTN11 activates the RAS-MAP kinase pathway and GRB2 activates the RAS-MAP kinase , PI-3-kinase and ubiquitinations/degradation pathways by binding to SOS, GAB1 and CBL, respectively, via the SH3 domains of GRB2. FRS2 acts as a central mediator in FGF signaling mainly because it induces sustained levels of activation of ERK with ubiquitous expression.

Literature references

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

Manuvakhova, M., Thottassery, JV., Hays, S., Qu, Z., Rentz, SS., Westbrook, L. et al. (2006). Expression of the SNT-1/FRS2 phosphotyrosine binding domain inhibits activation of MAP kinase and PI3-kinase pathways and anti-estrogen resistant growth induced by FGF-1 in human breast carcinoma cells. *Oncogene, 25*, 6003-14. ↗

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

Hadari, YR., Gotoh, N., Kouhara, H., Lax, I., Schlessinger, J. (2001). Critical role for the docking-protein FRS2 alpha in FGF receptor-mediated signal transduction pathways. *Proc Natl Acad Sci U S A, 98*, 8578-83. ↗

Editions

2007-01-10	Authored	de Bono, B.
2007-02-06	Reviewed	Mohammadi, M.
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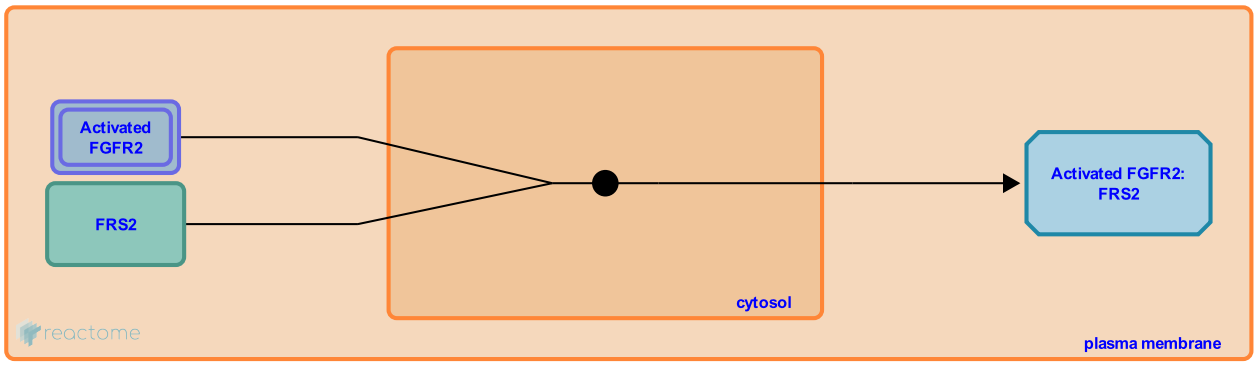
Activated FGFR2 binds FRS2 ↗

Location: FRS-mediated FGFR2 signaling

Stable identifier: R-HSA-5654399

Type: binding

Compartments: cytosol, extracellular region, plasma membrane



FRS2 (also known as FRS2alpha) is broadly expressed in adult and fetal tissues. Membrane-bound FRS2 interacts with FGFR as a first step in the phosphorylation of this docking protein. The juxtamembrane binding site for FRS2 does not contain tyrosine, so binding may be independent of receptor activation and/or constitutive. Activation of the FGFR receptor is required for FRS2 phosphorylation and subsequent recruitment of downstream effectors.

Followed by: Activated FGFR2 phosphorylates FRS2

Literature references

Ong, SH., Guy, GR., Hadari, YR., Laks, S., Gotoh, N., Schlessinger, J. et al. (2000). FRS2 proteins recruit intracellular signaling pathways by binding to diverse targets on fibroblast growth factor and nerve growth factor receptors. *Mol Cell Biol, 20*, 979-89. ↗

Xu, H., Lee, KW., Goldfarb, M. (1998). Novel recognition motif on fibroblast growth factor receptor mediates direct association and activation of SNT adapter proteins. *J Biol Chem, 273*, 17987-90. ↗

Ahmed, Z., Schüller, AC., Suhling, K., Tregidgo, C., Ladbury, JE. (2008). Extracellular point mutations in FGFR2 elicit unexpected changes in intracellular signalling. *Biochem J, 413*, 37-49. ↗

Editions

2011-08-15	Authored	Rothfels, K.
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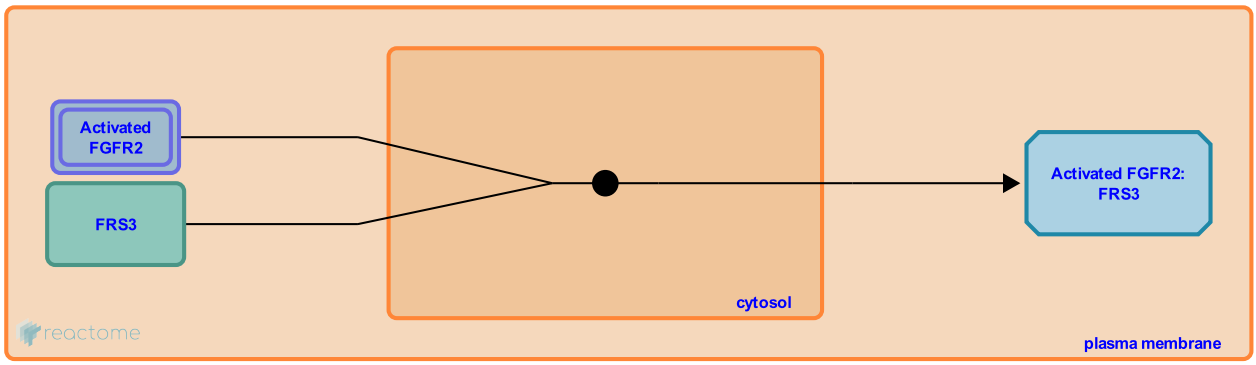
Activated FGFR2 binds FRS3 ↗

Location: FRS-mediated FGFR2 signaling

Stable identifier: R-HSA-5654603

Type: binding

Compartments: cytosol, extracellular region, plasma membrane



FRS3 (also known as FRS2beta) is predominantly expressed in the developing and adult neuroepithelium. As is the case for FRS2 (also known as FRS2alpha), binding of FRS3 to FGFR may be constitutive and/or independent of receptor activation. Elements of the downstream signaling mediated by the two FRS family members appear to be at least partially conserved, as FRS3 is phosphorylated upon FGF stimulation, binds PPTN11/SHP2 and GRB2 and results in ERK activation. Moreover, expression of FRS3 in FRS2-/- MEFs restores ERK activation.

Followed by: Activated FGFR2 phosphorylates FRS3

Literature references

Ong, SH., Guy, GR., Hadari, YR., Laks, S., Gotoh, N., Schlessinger, J. et al. (2000). FRS2 proteins recruit intracellular signaling pathways by binding to diverse targets on fibroblast growth factor and nerve growth factor receptors. *Mol Cell Biol, 20*, 979-89. ↗

Xu, H., Lee, KW., Goldfarb, M. (1998). Novel recognition motif on fibroblast growth factor receptor mediates direct association and activation of SNT adapter proteins. *J Biol Chem, 273*, 17987-90. ↗

Gotoh, N., Laks, S., Nakashima, M., Lax, I., Schlessinger, J. (2004). FRS2 family docking proteins with overlapping roles in activation of MAP kinase have distinct spatial-temporal patterns of expression of their transcripts. *FEBS Lett, 564*, 14-8. ↗

Minegishi, Y., Iwanari, H., Mochizuki, Y., Horii, T., Hoshino, T., Kodama, T. et al. (2009). Prominent expression of FRS2beta protein in neural cells and its association with intracellular vesicles. *FEBS Lett, 583*, 807-14. ↗

Editions

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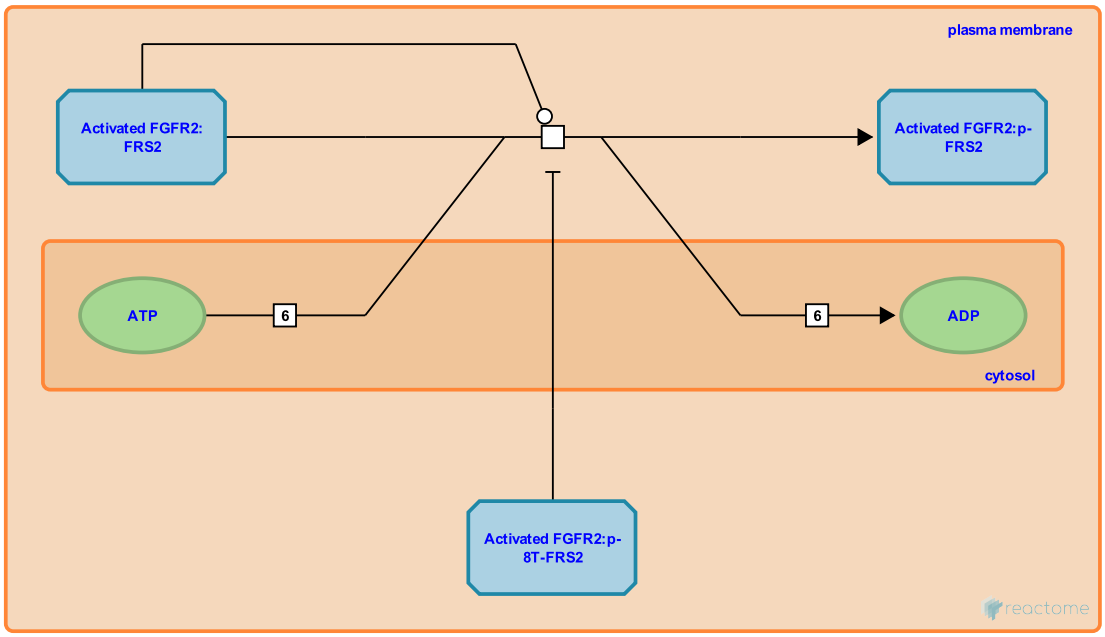
Activated FGFR2 phosphorylates FRS2

Location: FRS-mediated FGFR2 signaling

Stable identifier: R-HSA-5654397

Type: transition

Compartments: plasma membrane, cytosol, extracellular region



FRS2 (also known as FRS alpha is activated through tyrosine phosphorylation catalyzed by the protein kinase domain of the activated FGFR. FRS2 contains four binding sites for the adaptor protein GRB2 at residues Y196, Y306, Y349 and Y392, and two binding sites for the protein tyrosine phosphatase PPTN11/SHP2 at residues Y436 and Y471. Different FGFR isoforms may generate different phosphorylation patterns on FRS2 leading to alternate downstream signaling.

Preceded by: Activated FGFR2 binds FRS2

Followed by: Activated FGFR2:p-FRS bind to PPTN11, Activated FGFR2:pFRS binds GRB2:SOS1

Literature references

Ong, SH., Goh, KC., Lim, YP., Low, BC., Klint, P., Claesson-Welsh, L. et al. (1996). Suc1-associated neurotrophic factor target (SNT) protein is a major FGF-stimulated tyrosine phosphorylated 90-kDa protein which binds to the SH2 domain of GRB2. *Biochem Biophys Res Commun, 225*, 1021-6.

Kouhara, H., Hadari, YR., Spivak-Kroizman, T., Schilling, J., Bar-Sagi, D., Lax, I. et al. (1997). A lipid-anchored Grb2-binding protein that links FGF-receptor activation to the Ras/MAPK signaling pathway. *Cell, 89*, 693-702.

Hadari, YR., Kouhara, H., Lax, I., Schlessinger, J. (1998). Binding of Shp2 tyrosine phosphatase to FRS2 is essential for fibroblast growth factor-induced PC12 cell differentiation. *Mol Cell Biol, 18*, 3966-73.

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2007-01-10	Authored	de Bono, B.
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2011-08-16	Revised	Rothfels, K.
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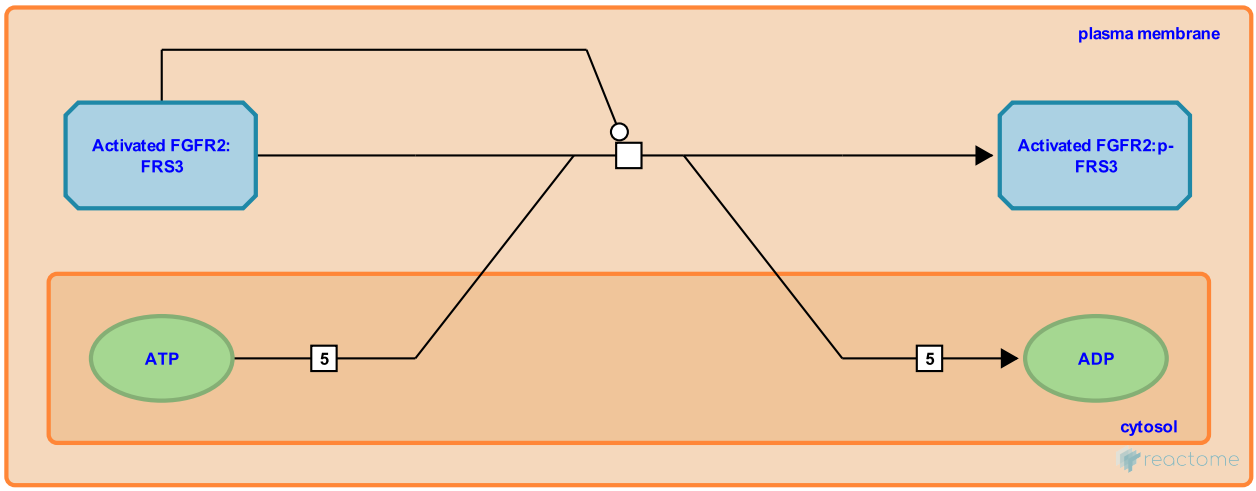
Activated FGFR2 phosphorylates FRS3

Location: FRS-mediated FGFR2 signaling

Stable identifier: R-HSA-5654605

Type: transition

Compartments: plasma membrane, cytosol, extracellular region



FRS3 (also known as FRS2 beta) is activated through tyrosine phosphorylation catalyzed by the protein kinase domain of the activated FGFR. By sequence comparison, FRS3 has the 2 PPTN11/SHP2-binding sites and has three of the four GRB2-binding sites.

Preceded by: Activated FGFR2 binds FRS3

Followed by: Activated FGFR2:p-FRS bind to PPTN11, Activated FGFR2:pFRS binds GRB2:SOS1

Literature references

Kouhara, H., Hadari, YR., Spivak-Kroizman, T., Schilling, J., Bar-Sagi, D., Lax, I. et al. (1997). A lipid-anchored Grb2-binding protein that links FGF-receptor activation to the Ras/MAPK signaling pathway. *Cell, 89*, 693-702.

Lax, I., Wong, A., Lamothe, B., Lee, A., Frost, A., Hawes, 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.

Editions

2007-01-10	Authored	de Bono, B.
2007-02-06	Reviewed	Mohammadi, M.
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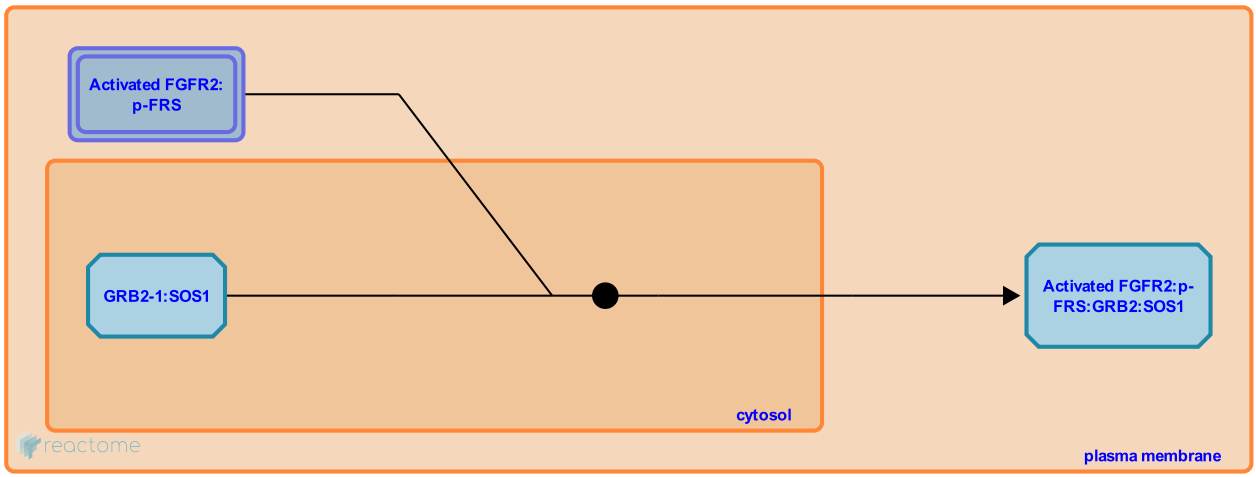
Activated FGFR2:pFRS binds GRB2:SOS1 ↗

Location: FRS-mediated FGFR2 signaling

Stable identifier: R-HSA-5654615

Type: binding

Compartments: cytosol, extracellular region, plasma membrane



Tyrosine phosphorylated FRS2 recruits GRB2:SOS1 complex by means of the SH3 domain of GRB2, leading to RAS-MAP kinase activation. The FRS2:GRB2-mediated pathway plays a minor role in the activation of RAS-MAP kinase pathway compared to that mediated by FRS2:PPTN11.

Preceded by: Activated FGFR2 phosphorylates FRS2, Activated FGFR2 phosphorylates FRS3

Followed by: Activated FGFR2:p-FRS2:GRB2:SOS1 activates RAS nucleotide exchange

Literature references

Kouhara, H., Hadari, YR., Spivak-Kroizman, T., Schilling, J., Bar-Sagi, D., Lax, I. et al. (1997). A lipid-anchored Grb2-binding protein that links FGF-receptor activation to the Ras/MAPK signaling pathway. *Cell, 89*, 693-702. ↗

Ong, SH., Hadari, YR., Gotoh, N., Guy, GR., Schlessinger, J., Lax, I. (2001). Stimulation of phosphatidylinositol 3-kinase by fibroblast growth factor receptors is mediated by coordinated recruitment of multiple docking proteins . *Proc Natl Acad Sci U S A, 98*, 6074-9. ↗

Ong, SH., Goh, KC., Lim, YP., Low, BC., Klint, P., Claesson-Welsh, L. et al. (1996). Suc1-associated neurotrophic factor target (SNT) protein is a major FGF-stimulated tyrosine phosphorylated 90-kDa protein which binds to the SH2 domain of GRB2. *Biochem Biophys Res Commun, 225*, 1021-6. ↗

Klint, P., Kanda, S., Claesson-Welsh, L. (1995). Shc and a novel 89-kDa component couple to the Grb2-Sos complex in fibroblast growth factor-2-stimulated cells. *J Biol Chem, 270*, 23337-44. ↗

Hadari, YR., Gotoh, N., Kouhara, H., Lax, I., Schlessinger, J. (2001). Critical role for the docking-protein FRS2 alpha in FGF receptor-mediated signal transduction pathways. *Proc Natl Acad Sci U S A, 98*, 8578-83. ↗

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2011-08-15	Authored	Rothfels, K.
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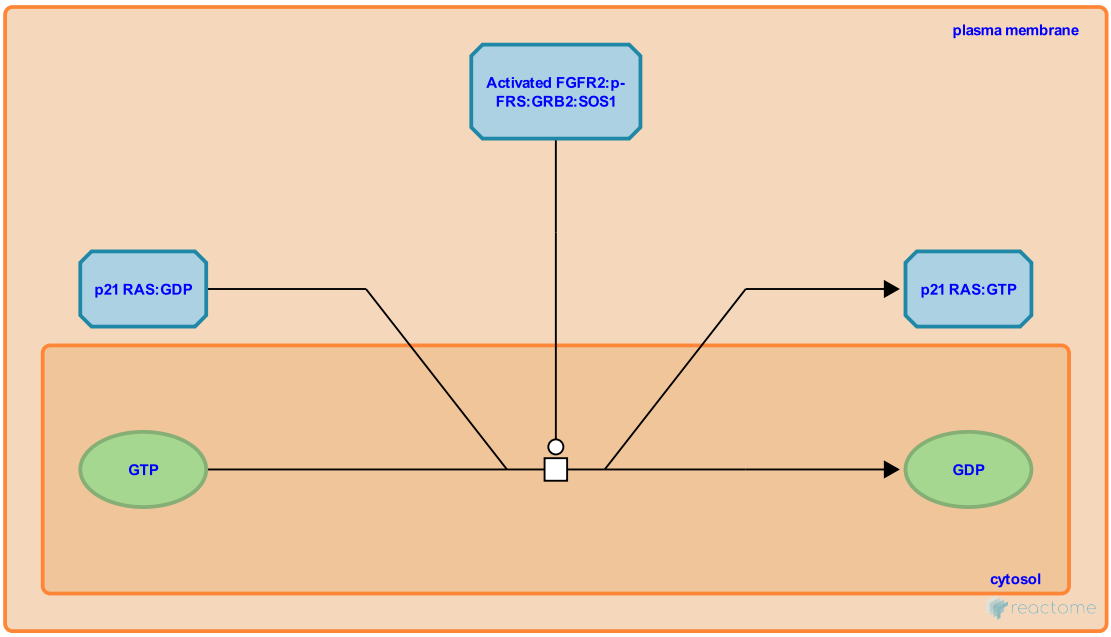
Activated FGFR2:p-FRS2:GRB2:SOS1 activates RAS nucleotide exchange ↗

Location: FRS-mediated FGFR2 signaling

Stable identifier: R-HSA-5654618

Type: transition

Compartments: cytosol, extracellular region, plasma membrane



SOS, recruited by GRB2:p-FRS2 to activated FGFR, activates RAS nucleotide exchange from the inactive GDP-bound to the active GTP-bound state.

Preceded by: Activated FGFR2:pFRS binds GRB2:SOS1

Literature references

Chardin, P., Camonis, JH., Gale, NW., Van Aelst, L., Schlessinger, J., Wigler, MH. et al. (1993). Human Sos1: a guanine nucleotide exchange factor for Ras that binds to GRB2. *Science, 260*, 1338-43. ↗

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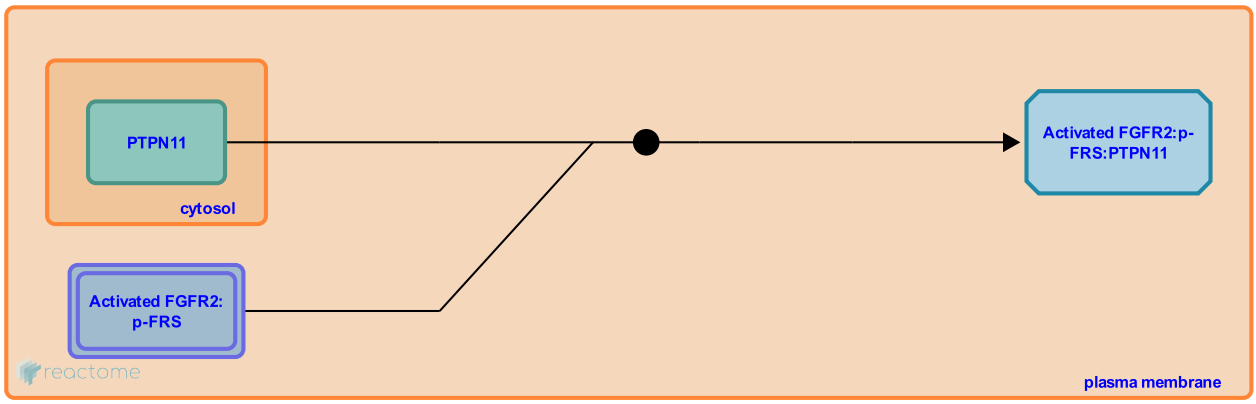
Activated FGFR2:p-FRS bind to PPTN11 ↗

Location: FRS-mediated FGFR2 signaling

Stable identifier: R-HSA-5654608

Type: binding

Compartments: plasma membrane, cytosol



p-FRS2 has two PPTN11/SHP2-binding sites at pY436 and pY471.

Preceded by: Activated FGFR2 phosphorylates FRS2, Activated FGFR2 phosphorylates FRS3

Followed by: Activated FGFR2 phosphorylates PPTN11

Literature references

Agazie, YM., Movilla, N., Ischenko, I., Hayman, MJ. (2003). The phosphotyrosine phosphatase SHP2 is a critical mediator of transformation induced by the oncogenic fibroblast growth factor receptor 3. *Oncogene, 22*, 6909-18. ↗

Hadari, YR., Kouhara, H., Lax, I., Schlessinger, J. (1998). Binding of Shp2 tyrosine phosphatase to FRS2 is essential for fibroblast growth factor-induced PC12 cell differentiation. *Mol Cell Biol, 18*, 3966-73. ↗

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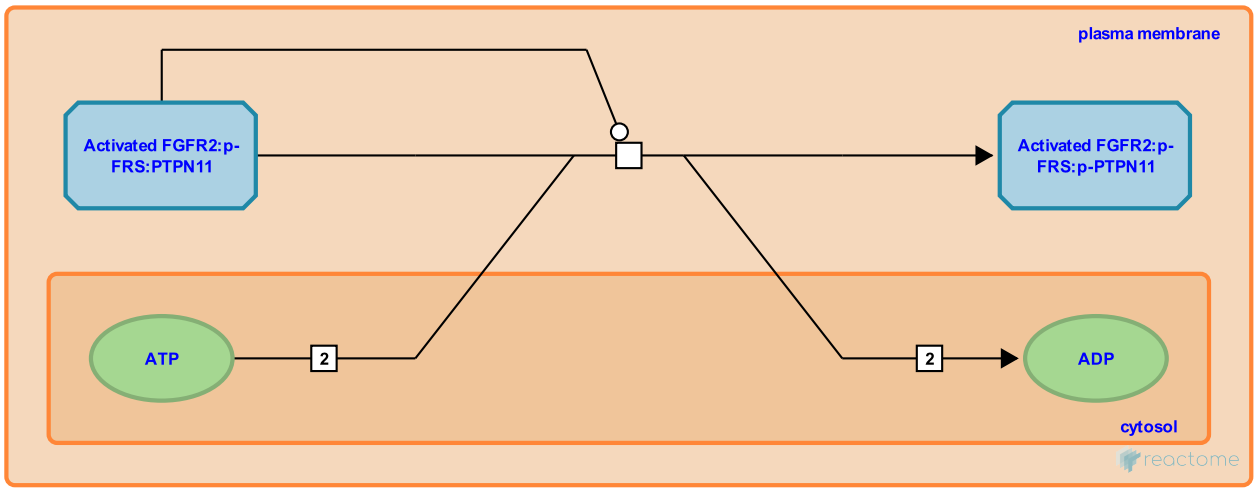
Activated FGFR2 phosphorylates PPTN11 ↗

Location: FRS-mediated FGFR2 signaling

Stable identifier: R-HSA-5654607

Type: transition

Compartments: plasma membrane, cytosol, extracellular region



Tyrosine phosphorylation of PPTN11/SHP2 by FGFR kinase is required for activation of the phosphatase activity of PPTN11 and for downstream signaling. Tyrosine phosphorylated PPTN11 plays a major role in the activation of RAS-MAP kinase pathway, although the precise role is not yet clear.

Preceded by: Activated FGFR2:p-FRS bind to PPTN11

Followed by: Activated FGFR2:p-FRS:p-PTPN11 activates RAS nucleotide exchange

Literature references

Agazie, YM., Movilla, N., Ischenko, I., Hayman, MJ. (2003). The phosphotyrosine phosphatase SHP2 is a critical mediator of transformation induced by the oncogenic fibroblast growth factor receptor 3. *Oncogene, 22*, 6909-18. ↗

Ahmed, Z., Schüller, AC., Suhling, K., Tregidgo, C., Ladbury, JE. (2008). Extracellular point mutations in FGFR2 elicit unexpected changes in intracellular signalling. *Biochem J, 413*, 37-49. ↗

Ong, SH., Lim, YP., Low, BC., Guy, GR. (1997). SHP2 associates directly with tyrosine phosphorylated p90 (SNT) protein in FGF-stimulated cells. *Biochem Biophys Res Commun, 238*, 261-6. ↗

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2007-01-10	Authored	de Bono, B.
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2011-08-26	Reviewed	Gotoh, N.

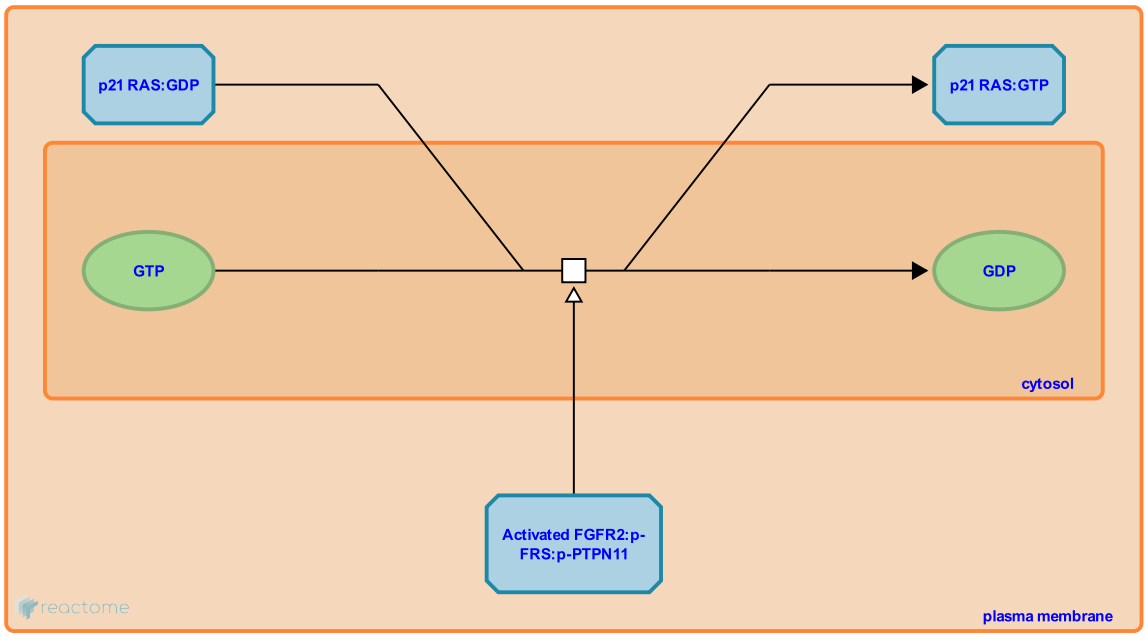
Activated FGFR2:p-FRS:p-PTPN11 activates RAS nucleotide exchange ↗

Location: FRS-mediated FGFR2 signaling

Stable identifier: R-HSA-8941618

Type: transition

Compartments: cytosol, extracellular region, plasma membrane



RAS nucleotide is stimulated downstream of activated FGFR2 in a p-PTPN11-dependent manner. The phosphatase activity of PTPN11 is required for activation of the RAS-MAP kinase pathway, although the mechanism for RAS pathway activation is not yet clear (Hadari et al, 1998; reviewed in Mohi et al, 2007; Gotoh et al, 2008).

Preceded by: Activated FGFR2 phosphorylates PPTN11

Literature references

Hadari, YR., Kouhara, H., Lax, I., Schlessinger, J. (1998). Binding of Shp2 tyrosine phosphatase to FRS2 is essential for fibroblast growth factor-induced PC12 cell differentiation. *Mol Cell Biol, 18*, 3966-73. ↗

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

Mohi, MG., Neel, BG. (2007). The role of Shp2 (PTPN11) in cancer. *Curr. Opin. Genet. Dev., 17*, 23-30. ↗

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2011-08-15	Authored	Rothfels, K.
2011-08-26	Reviewed	Gotoh, N.
2016-10-05	Edited	Rothfels, K.

Table of Contents