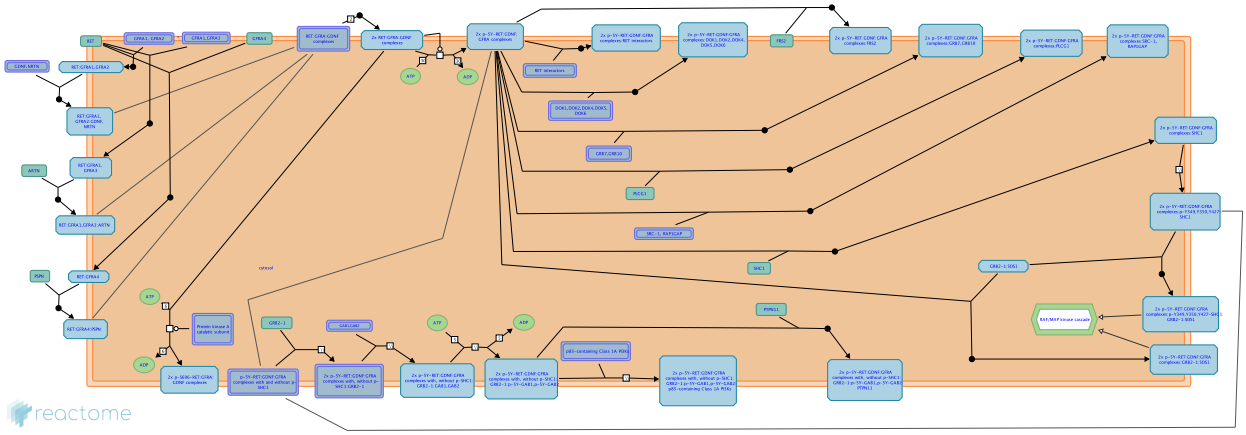
RET signaling



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07/09/2021

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. ↗

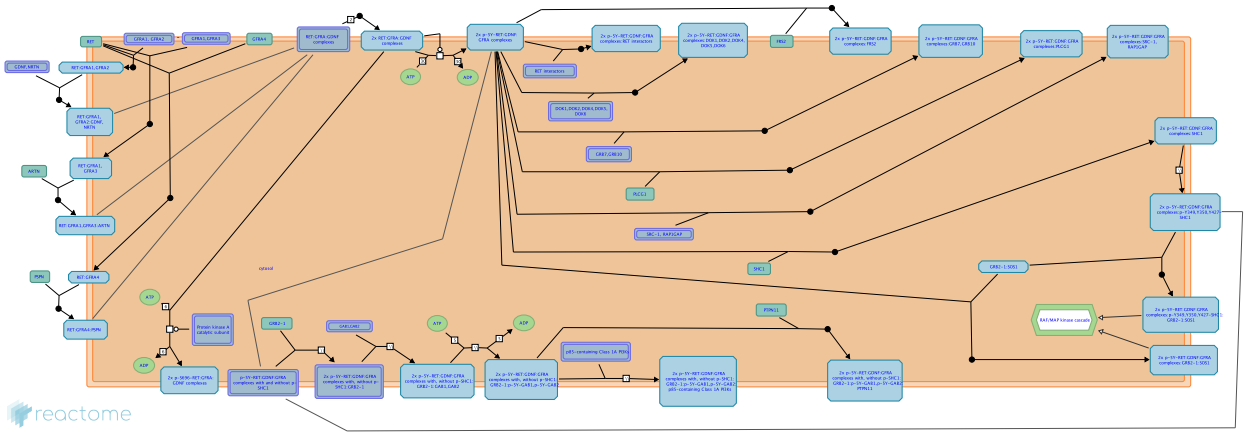
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

RET signaling ↗

Stable identifier: R-HSA-8853659



The RET proto-oncogene encodes a receptor tyrosine kinase expressed primarily in urogenital precursor cells, spermatogonocytes, dopaminergic neurons, motor neurons and neural crest progenitors and derived cells. . It is essential for kidney genesis, spermatogonial self-renewal and survivial, specification, migration, axonal growth and axon guidance of developing enteric neurons, motor neurons, parasympathetic neurons and somatosensory neurons (Schuchardt et al. 1994, Enomoto et al. 2001, Naughton et al. 2006, Kramer et al. 2006, Luo et al. 2006, 2009). RET was identified as the causative gene for human papillary thyroid carcinoma (Grieco et al. 1990), multiple endocrine neoplasia (MEN) type 2A (Mulligan et al. 1993), type 2B (Hofstra et al. 1994, Carlson et al. 1994), and Hirschsprung's disease (Romeo et al. 1994, Edery et al. 1994).

RET contains a cadherin-related motif and a cysteine-rich domain in the extracellular domain (Takahashi et al. 1988). It is the receptor for members of the glial cell-derived neurotrophic factor (GDNF) family of ligands, GDNF (Lin et al. 1993), neurturin (NRTN) (Kotzbauer et al. 1996), artemin (ARTN) (Baloh et al. 1998), and persephin (PSPN) (Milbrandt et al. 1998), which form a family of neurotrophic factors. To stimulate RET, these ligands need a glycosylphosphatidylinositol (GPI)-anchored co-receptor, collectively termed GDNF family receptor-alpha (GFRA) (Treanor et al. 1996, Jing et al. 1996). The four members of this family have different, overlapping ligand preferences. GFRA1, GFRA2, GFRA3, and GFRA4 preferentially bind GDNF, NRTN, ARTN and PSPN, respectively (Jing et al. 1996, 1997, Creedon et al. 1997, Baloh et al. 1997, 1998, Masure et al. 2000). The GFRA co-receptor can come from the same cell as RET, or from a different cell. When the co-receptor is produced by the same cell as RET, it is termed cis signaling. When the co-receptor is produced by another cell, it is termed trans signaling. Cis and trans activation has been proposed to diversify RET signaling, either by recruiting different downstream effectors or by changing the kinetics or efficacy of kinase activation (Tansey et al. 2000, Paratcha et al. 2001). Whether cis and trans signaling has significant differences in vivo is unresolved (Fleming et al. 2015). Different GDNF family members could activate similar downstream signaling pathways since all GFRAs bind to and activate the same tyrosine kinase and induce coordinated phosphorylation of the same four RET tyrosines (Tyr905, Tyr1015, Tyr1062, and Tyr1096) with similar kinetics (Coulpier et al. 2002). However the exact RET signaling pathways in different types of cells and neurons remain to be determined.

Literature references

Murakumo, Y., Jijiwa, M., Asai, N., Ichihara, M., Takahashi, M. (2006). RET and neuroendocrine tumors. *Pituitary, 9*, 179-92. ↗

Ichihara, M., Murakumo, Y., Takahashi, M. (2004). RET and neuroendocrine tumors. *Cancer Lett., 204*, 197-211. ↗

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2016-05-17	Reviewed	Luo, W.

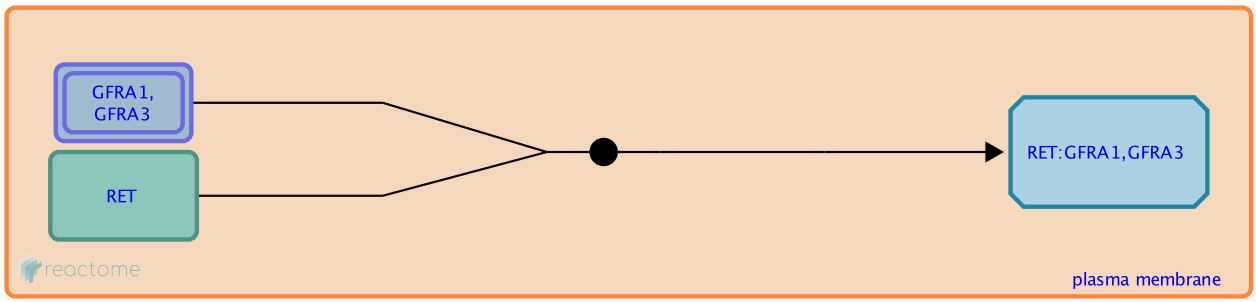
RET binds GFRA1,GFRA3 ↗

Location: RET signaling

Stable identifier: R-HSA-8853745

Type: binding

Compartments: plasma membrane



RET is a receptor tyrosine kinase with a cadherin-related motif and a cysteine-rich domain in the extracellular domain (Takahashi et al. 1988). It is the receptor for members of the glial cell-derived neurotrophic factor (GDNF) family of ligands (Lin et al. 1993, Kotzbauer et al. 1996, Baloh et al. 1998, Milbrandt et al. 1998). RET can only bind these ligands in the presence of a co-receptor from the family of glycosylphosphatidylinositol (GPI)-anchored co-receptors collectively termed GDNF family receptor-alpha (GFRA) (Treanor et al. 1996, Jing et al. 1996, Plaza-Menacho et al. 2006). Early models proposed that GDNF formed a complex with GFRA1 and subsequently recruited RET (Massagué et al. 1996). Current models suggest that GFRA and RET pre-associate before ligand binding, based on binding and site-directed mutagenesis studies (Eketjäll et al. 1999, Cik et al. 2000). An alternative model suggests that GPI-anchored GFRA recruits RET to lipid rafts after GDNF stimulation (Tansey et al. 2000). The stoichiometry as well as the kinetics of ligand-receptor complex formation are not well understood. It is believed that all GDNF family members interact with their cognate co-receptor and activate RET in a similar manner to GDNF (Airaksinen & Saarma 2002).

Followed by: ARTN binds RET:GFRA1,GFRA3

Literature references

Jing, S., Wen, D., Yu, Y., Holst, PL., Luo, Y., Fang, M. et al. (1996). GDNF-induced activation of the ret protein tyrosine kinase is mediated by GDNFR-alpha, a novel receptor for GDNF. *Cell, 85*, 1113-24. ↗

Baloh, RH., Tansey, MG., Lampe, PA., Fahrner, TJ., Enomoto, H., Simburger, KS. et al. (1998). Artemin, a novel member of the GDNF ligand family, supports peripheral and central neurons and signals through the GFRalpha3-RET receptor complex. *Neuron, 21*, 1291-302. ↗

Creedon, DJ., Tansey, MG., Baloh, RH., Osborne, PA., Lampe, PA., Fahrner, TJ. et al. (1997). Neurturin shares receptors and signal transduction pathways with glial cell line-derived neurotrophic factor in sympathetic neurons. *Proc. Natl. Acad. Sci. U.S.A., 94*, 7018-23. ↗

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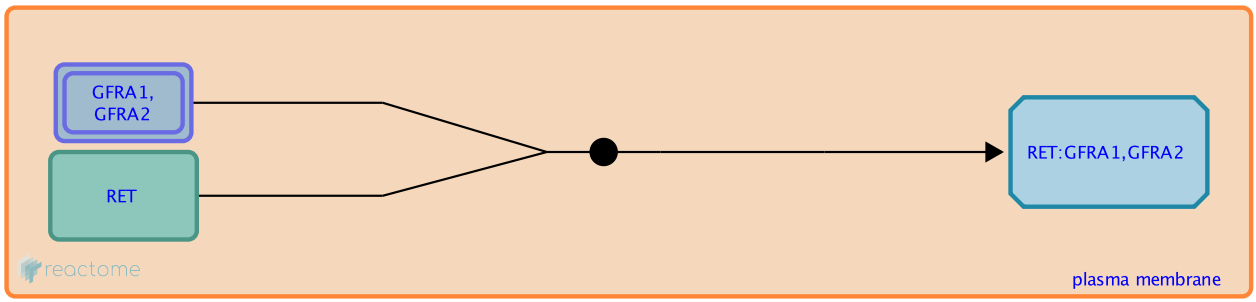
RET binds GFRA1,GFRA2 ↗

Location: RET signaling

Stable identifier: R-HSA-8871226

Type: binding

Compartments: plasma membrane



RET is a receptor tyrosine kinase with a cadherin-related motif and a cysteine-rich domain in the extracellular domain (Takahashi et al. 1988). It is the receptor for members of the glial cell-derived neurotrophic factor (GDNF) family of ligands (Lin et al. 1993, Kotzbauer et al. 1996, Baloh et al. 1998, Milbrandt et al. 1998). RET can only bind these ligands in the presence of a co-receptor from the family of glycosylphosphatidylinositol (GPI)-anchored co-receptors collectively termed GDNF family receptor-alpha (GFRA) (Treanor et al. 1996, Jing et al. 1996, Plaza-Menacho et al. 2006). Earlier models proposed that GDNF formed a complex with GFRA1 and subsequently recruited RET (Massagué et al. 1996). Current models suggest that GFRA and RET preassociate before ligand binding, based on binding and site-directed mutagenesis studies (Eketjäll et al. 1999, Cik et al. 2000). An alternative model suggests that GPI-anchored GFRA recruits RET to lipid rafts after GDNF stimulation (Tansey et al. 2000). The stoichiometry as well as the kinetics of ligand-receptor complex formation are not well understood. It is believed that all GDNF family members interact with their cognate co-receptor and activate RET in a similar manner to GDNF (Airaksinen & Saarma 2002).

Followed by: GDNF,NRTN bind RET:GFRA1,GFRA2

Literature references

Jing, S., Wen, D., Yu, Y., Holst, PL., Luo, Y., Fang, M. et al. (1996). GDNF-induced activation of the ret protein tyrosine kinase is mediated by GDNFR-alpha, a novel receptor for GDNF. *Cell, 85*, 1113-24. ↗

Baloh, RH., Tansey, MG., Lampe, PA., Fahrner, TJ., Enomoto, H., Simburger, KS. et al. (1998). Artemin, a novel member of the GDNF ligand family, supports peripheral and central neurons and signals through the GFRalpha3-RET receptor complex. *Neuron, 21*, 1291-302. ↗

Creedon, DJ., Tansey, MG., Baloh, RH., Osborne, PA., Lampe, PA., Fahrner, TJ. et al. (1997). Neurturin shares receptors and signal transduction pathways with glial cell line-derived neurotrophic factor in sympathetic neurons. *Proc. Natl. Acad. Sci. U.S.A., 94*, 7018-23. ↗

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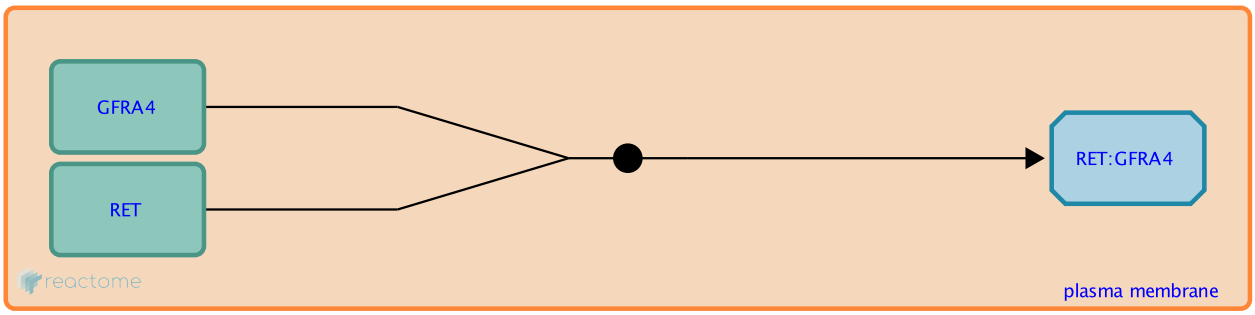
RET binds GFRA4 ↗

Location: RET signaling

Stable identifier: R-HSA-8871227

Type: binding

Compartments: plasma membrane



RET is a receptor tyrosine kinase with a cadherin-related motif and a cysteine-rich domain in the extracellular domain (Takahashi et al. 1988). It is the receptor for members of the glial cell-derived neurotrophic factor (GDNF) family of ligands (Lin et al. 1993, Kotzbauer et al. 1996, Baloh et al. 1998, Milbrandt et al. 1998). RET can only bind these ligands in the presence of a co-receptor from the family of glycosylphosphatidylinositol (GPI)-anchored co-receptors collectively termed GDNF family receptor-alpha (GFRA) (Treanor et al. 1996, Jing et al. 1996, Plaza-Menacho et al. 2006). Early models proposed that GDNF formed a complex with GFRA1 and subsequently recruited RET (Massagué et al. 1996). Current models suggest that GFRA and RET preassociate before ligand binding, based on binding and site-directed mutagenesis studies (Eketjäll et al. 1999, Cik et al. 2000). An alternative model suggests that GPI-anchored GFRA recruits RET to lipid rafts after GDNF stimulation (Tansey et al. 2000). The stoichiometry as well as the kinetics of ligand-receptor complex formation are not well understood. It is believed that all GDNF family members interact with their cognate co-receptor and activate RET in a similar manner to GDNF (Airaksinen & Saarma 2002).

Followed by: PSPN binds RET:GFRA4

Literature references

Milbrandt, J., de Sauvage, FJ., Fahrner, TJ., Baloh, RH., Leitner, ML., Tansey, MG. et al. (1998). Persephin, a novel neurotrophic factor related to GDNF and neurturin. *Neuron, 20*, 245-53. ↗

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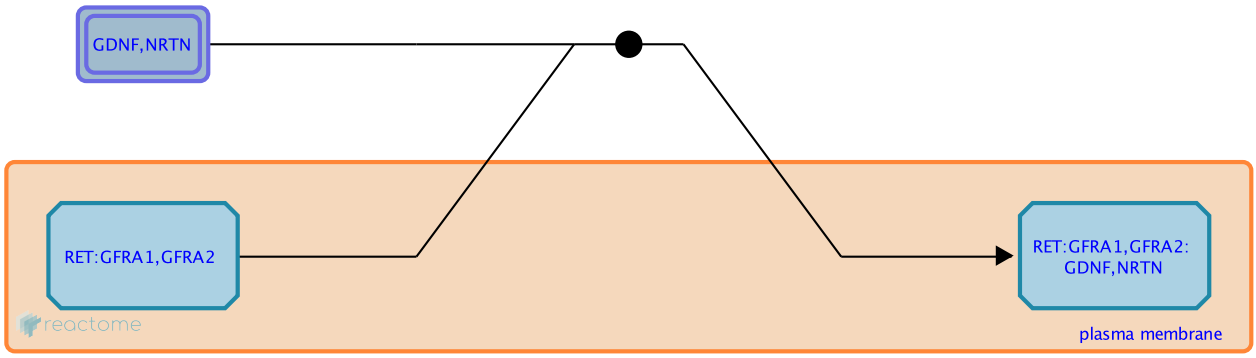
GDNF,NRTN bind RET:GFRA1,GFRA2 ↗

Location: RET signaling

Stable identifier: R-HSA-8853789

Type: binding

Compartments: extracellular region, plasma membrane



Glial cell-derived neurotrophic factor (GDNF) (Lin et al. 1993) and neurturin (NRTN) (Kotzbauer et al. 1996) are ligands for GDNF family receptor-alpha (GFRA) 1 and 2 (Jing et al. 1996, 1997, Creedon et al. 1997, Baloh et al. 1997). Despite the cross activation in vitro, GDNF preferentially acts through RET:GFRA1 (Schuchardt et al. 1994, Moore et al. 1996, Pichel et al. 1996, Sanchez et al. 1996, Calcano et al. 1998, Endomoto et al. 1998, whereas NRTN preferentially acts through RET: GFRA2 (Heuckeroth et al. 1999, Rossi et al. 1999, Luo et al. 2004, 2009, Lindfors et al. 2006) in vivo.

Preceded by: RET binds GFRA1,GFRA2

Followed by: RET dimerizes

Literature references

Jing, S., Wen, D., Yu, Y., Holst, PL., Luo, Y., Fang, M. et al. (1996). GDNF-induced activation of the ret protein tyrosine kinase is mediated by GDNFR-alpha, a novel receptor for GDNF. *Cell, 85*, 1113-24. ↗

Jing, S., Yu, Y., Fang, M., Hu, Z., Holst, PL., Boone, T. et al. (1997). GFRalpha-2 and GFRalpha-3 are two new receptors for ligands of the GDNF family. *J. Biol. Chem., 272*, 33111-7. ↗

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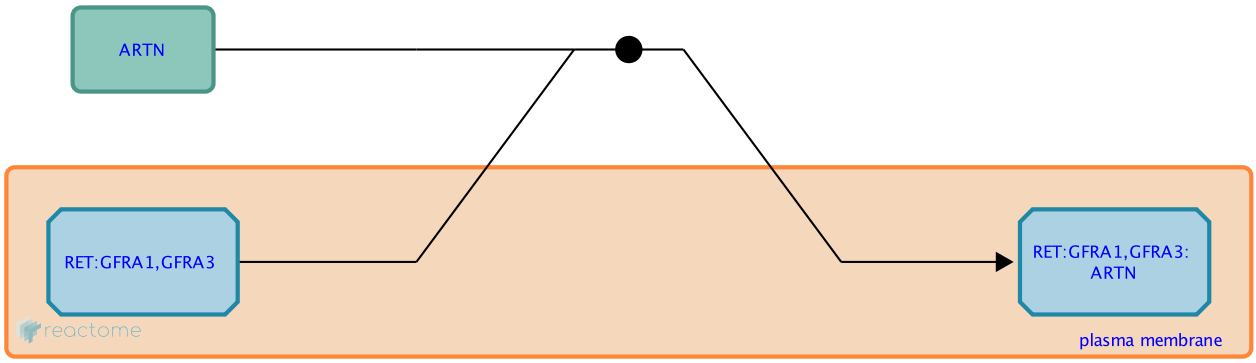
ARTN binds RET:GFRA1,GFRA3 ↗

Location: RET signaling

Stable identifier: R-HSA-8853800

Type: binding

Compartments: extracellular region, plasma membrane



Artemin (ARTN) is a ligand for GDNF family receptor-alpha (GFRA) 1 and 3, preferentially binding GFRA3 (Baloh et al. 1998).

Preceded by: RET binds GFRA1,GFRA3

Followed by: RET dimerizes

Literature references

Baloh, RH., Tansey, MG., Lampe, PA., Fahrner, TJ., Enomoto, H., Simburger, KS. et al. (1998). Artemin, a novel member of the GDNF ligand family, supports peripheral and central neurons and signals through the GFRalpha3-RET receptor complex. *Neuron, 21*, 1291-302. ↗

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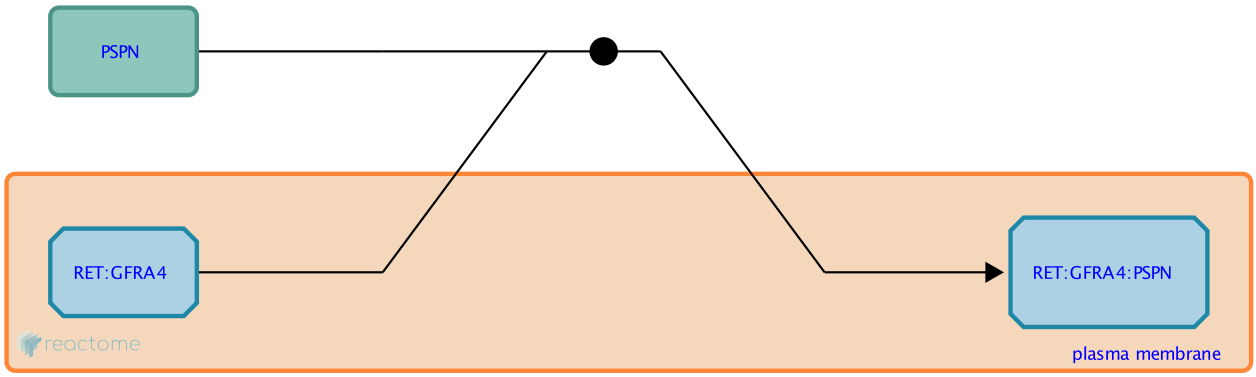
PSPN binds RET:GFRA4 ↗

Location: RET signaling

Stable identifier: R-HSA-8853801

Type: binding

Compartments: extracellular region, plasma membrane



Persephin (PSPN) is a ligand for GDNF family receptor-alpha (GFRA) 4 (Milbrandt et al. 1998, Masure et al. 2000).

Preceded by: RET binds GFRA4

Followed by: RET dimerizes

Literature references

Milbrandt, J., de Sauvage, FJ., Fahrner, TJ., Baloh, RH., Leitner, ML., Tansey, MG. et al. (1998). Persephin, a novel neurotrophic factor related to GDNF and neurturin. *Neuron, 20*, 245-53. ↗

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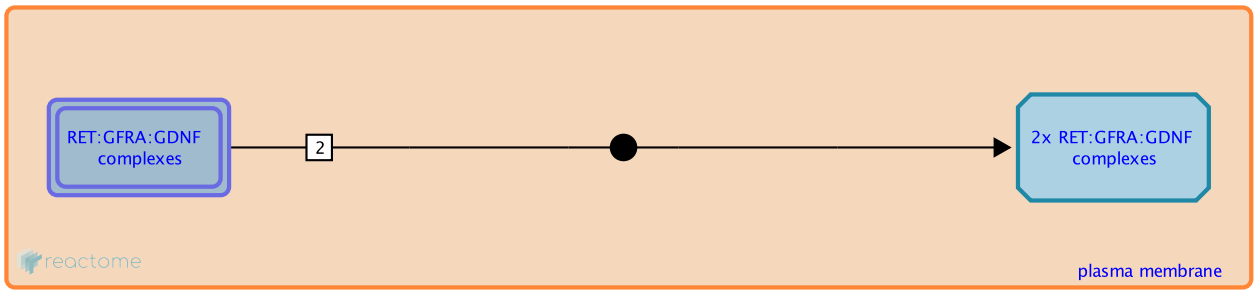
RET dimerizes ↗

Location: RET signaling

Stable identifier: R-HSA-8853762

Type: binding

Compartments: plasma membrane, extracellular region



It is widely accepted that RET undergoes dimerization and transphosphorylation following Glial cell line-derived neurotrophic factor (GDNF) binding to the GDNF-family receptor:RET complex. Transphosphorylation of specific tyrosine residues is a prerequisite for activation of RET tyrosine kinase activity and downstream signaling (Santoro et al. 1995, Airaksinen et al. 1999, Takeda et al. 2001, Leppänen et al. 2004). However, self-association of RET in the absence of GDNF has been reported and may contribute to the mechanism of RET activation (Kjaer et al. 2006). The stoichiometry and kinetics of ligand-receptor complex formation are not well understood. It is assumed that all GDNF family of ligands (GFL) members interact with their cognate co-receptor and activate RET in a similar manner to GDNF (Airaksinen & Saarma 2002).

Preceded by: ARTN binds RET:GFRA1,GFRA3, GDNF,NRTN bind RET:GFRA1,GFRA2, PSPN binds RET:GFRA4

Followed by: PKA phosphorylates RET:GDNF:GFRA dimer, RET tyrosine phosphorylation

Literature references

Leppänen, VM., Bespalov, MM., Runeberg-Roos, P., Puurand, U., Merits, A., Saarma, M. et al. (2004). The structure of GFRalpha1 domain 3 reveals new insights into GDNF binding and RET activation. *EMBO J., 23*, 1452-62. ↗

Takeda, K., Kato, M., Wu, J., Iwashita, T., Suzuki, H., Takahashi, M. et al. (2001). Osmotic stress-mediated activation of RET kinases involves intracellular disulfide-bonded dimer formation. *Antioxid. Redox Signal., 3*, 473-82. ↗

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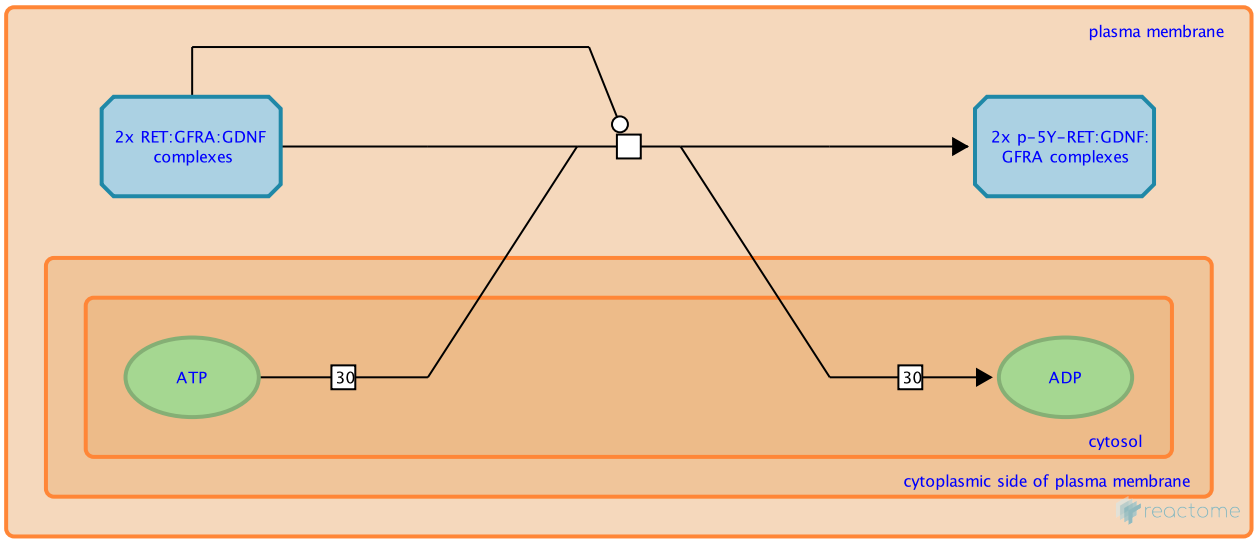
RET tyrosine phosphorylation ↗

Location: RET signaling

Stable identifier: R-HSA-8853792

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



RET undergoes trans-autophosphorylation on specific tyrosine (Y) residues. The short and medium-length isoforms of RET contain 16 tyrosine residues; 10 in the kinase domain, 2 in the juxtamembrane domain, 1 in the kinase insert and 3 in the carboxy-terminal tail. The long RET isoform has 2 additional tyrosines in the carboxy-terminal tail. Phosphorylation of Y905 stabilizes the active conformation of the kinase and facilitates the autophosphorylation of Y residues mainly located in the C-terminal tail (Iwashita et al. 1996, Kawamoto et 2004). Y905, 1015, 1062 and 1096 are binding sites for GRB7/GRB10, phospholipase Cgamma (PLCG1), SHC1 and GRB2, respectively (Ichihara et al. 2004, Murakumo et al. 2006). Y1096 is present only in the long isoform. Phosphorylated Y981 is reported to bind SRC (Encinas et al. 2004).

RET can activate various signaling pathways including RAS-RAF-ERK (van Weering et al. 1995, Ohiwa et al. 1997, van Weering & Bos 1997, Trupp et al. 1999, Hayashi et al. 2000), phosphatidylinositol 3-kinase (PI3K)/AKT (Murakami et al. 1999a, Murakami et al. 1999b, Trupp et al. 1999, Soler et al. 1999, Segouffin-Cariou & Billaud 2000, Hayashi et al. 2000), p38 mitogen-activated protein kinase (MAPK) (Worby et al. 1996, Feng et al. 1999) and c-Jun N-terminal kinase (JNK) pathways (Xing et al. 1998, Chiariello et al. 1998). All these pathways are activated mainly through Y1062 (Hayashi et al. 2000). Point mutations at Y1062 result in a severe loss-of-function phenotype (Ibáñez 2013). SHC1 further associates with GRB2 and GAB1/GAB2, all of which become tyrosine phosphorylated. Tyrosine-phosphorylated GAB1/2 associates with the p85 subunit of PI3K, resulting in PI3K and AKT activation (Murakami et al. 1999b, Hayashi et al. 2000, Besset et al. 2000). GRB2-GAB1/2 can also assemble directly onto phosphorylated Y1096, an alternative route to PI3K activation (Besset et al. 2000). SHC1 can also form a complex with GRB2:SOS leading to activation of the RAS-RAF-ERK pathway (Hayashi et al. 2000). However, mutation of Y1062 did not completely abolish activation of the RAS-RAF-ERK and PI3K-AKT pathways suggesting alternative signaling pathways (Ichihara et al. 2004). The adaptor protein FRS2 can bind phosphorylated Y1062 (Kurokawa et al. 2001, Melillo et al. 2001), competing with SHC1 (Lundgren et al. 2006). Differential signaling may be mediated by different compartments in the plasma membrane, as RET has been shown to interact with FRS2 in lipid rafts, but with SHC1 outside lipid rafts (Paratcha et al. 2001).

Many other proteins have been shown to bind and/or become activated via Y1062. Docking protein 1 (DOK1), 2, 4, 5, and 6 adaptor proteins all interact with phosphorylated Y1062 (Grimm et al. 2001; Crowder et al. 2004; Kurotsuchi et al. 2010). Other suggested RET interactors include Mitogen-activated protein kinase 7 (MAPK7, BMK1) (Hayashi et al. 2001), SH3 and multiple ankyrin repeat domains protein 3 (SHANK3) (Schuetz et al. 2004), Insulin receptor substrate-2 (IRS2) (Hennige et al. 2000), SHC-transforming protein 3 (SHC3) (Pelicci et al. 2002), Protein kinase C alpha (PKCA) (Andreozzi et al. 2003) and PDZ and LIM domain protein 7 (Enigma, PDLIM7) (Durick et al. 1996). PDLIM7 and SHANK3 bind Y1062 regardless of its phosphorylation state.

Rap1GAP can bind phosphorylated Y981 to suppress GDNF-induced activation of ERK and neurite outgrowth (Jiao et al. 2011).

Tyrosine-protein phosphatase non-receptor type 11 (PTPN11, SHP2) binds to phosphorylated Y687 and components of the Y1062 associated signaling complex, contributing to activation of PI3K/AKT and promoting survival and neurite outgrowth in primary neurons (Besset et al. 2000, Perrinjaquet et al. 2010).

It is unclear how RET activates the p38MAPK, JNK, and ERK5 signaling pathways (Ichihara et al. 2004). To simplify the representation of RET signaling, all RET tyrosines known to be involved in signalling are phosphorylated in this event.

Preceded by: RET dimerizes

Followed by: 2x p-5Y-RET:GDNF:GFRA complexes bind GRB7,10, 2x p-5Y-RET:GDNF:GFRA complexes bind PLCgamma1, 2x p-5Y-RET:GDNF:GFRA complexes bind RET interactors, 2x p-5Y-RET:GDNF:GFRA complexes bind FRS2, 2x p-5Y-RET:GDNF:GFRA complexes binds DOK1,DOK2,DOK4,DOK5,DOK6, 2x p-5Y-RET:GDNF:GFRA complexes bind SRC1, RAP1GAP, 2x p-5Y-RET:GDNF:GFRA complexes bind SHC1, 2x p-5Y-RET:GDNF:GFRA complexes bind GRB2-1:SOS1, p-5Y-RET complexes bind GRB2

Literature references

Iwashita, T., Asai, N., Murakami, H., Matsuyama, M., Takahashi, M. (1996). Identification of tyrosine residues that are essential for transforming activity of the ret proto-oncogene with MEN2A or MEN2B mutation. *Oncogene, 12,* 481-7. ↗

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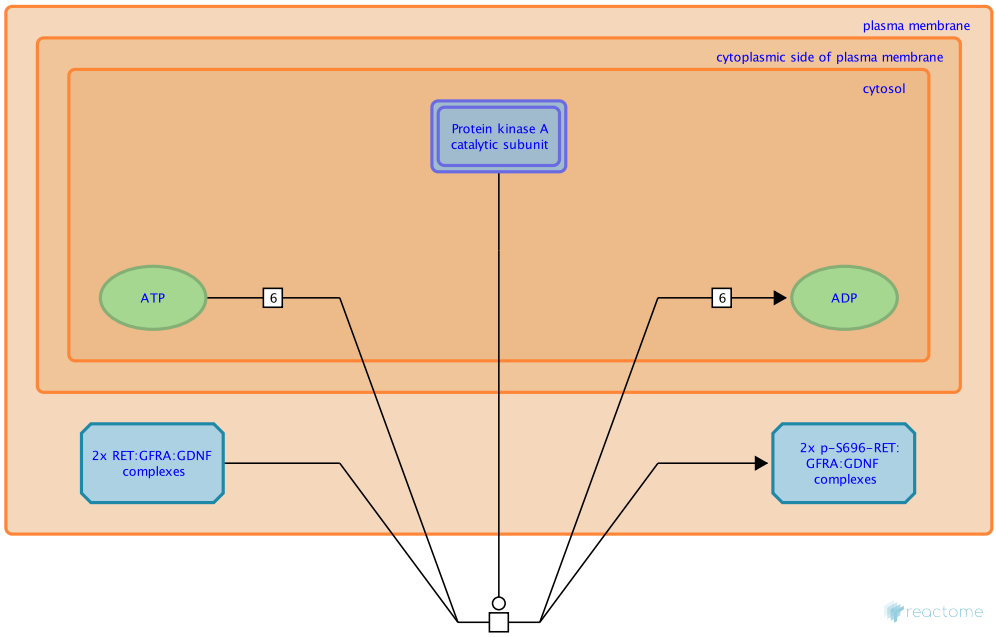
PKA phosphorylates RET:GDNF:GFRA dimer ↗

Location: RET signaling

Stable identifier: R-HSA-8854908

Type: transition

Compartments: extracellular region, plasma membrane, cytosol



Serine (S) 696 in RET is phosphorylated by protein kinase A. Mutation of this serine almost completely inhibits the ability of RET to activate the small GTPase Rac1 and stimulate formation of cell lamellipodia (Fukuda et al. 2002). Homozygous knock-in mice carrying this mutation lacked enteric neurons in the distal colon, resulting from a migration defect of enteric neural crest cells (Asai et al. 2006). The effects of the S696 RET mutant could be alleviated by simultaneous mutation of Tyrosine-687 (Fukuda et al. 2002). Activation of PKA by forskolin was found to impair the recruitment of SHP2 to RET and negatively affect ligand-mediated neurite outgrowth (Perrinjaquet et al. 2010). Mutation of S696 enhanced SHP2 binding and eliminated the effect of forskolin on ligand-induced neurite outgrowth.

Preceded by: RET dimerizes

Literature references

Fukuda, T., Kiuchi, K., Takahashi, M. (2002). Novel mechanism of regulation of Rac activity and lamellipodia formation by RET tyrosine kinase. *J. Biol. Chem., 277*, 19114-21. ↗

Editions

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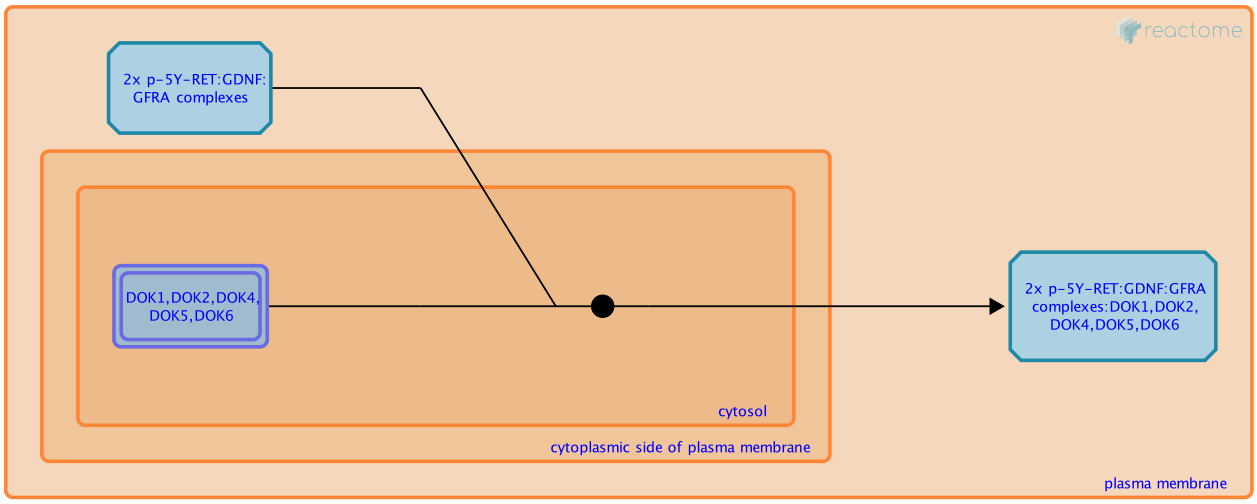
2x p-5Y-RET:GDNF:GFRA complexes binds DOK1,DOK2,DOK4,DOK5,DOK6 ↗

Location: RET signaling

Stable identifier: R-HSA-8855617

Type: binding

Compartments: cytosol, extracellular region, plasma membrane



Docking protein 1 (DOK 1), 2, 4, 5, and 6 adaptor proteins all interact with RET at phosphorylated tyrosine-1062 (Y1062) (Grimm et al. 2001, Crowder et al. 2004, Kurotsuchi et al. 2010).

DOKs are adaptor proteins that can inhibit mitogen-activated protein kinase (MAPK) signaling, cell proliferation, and cellular transformation. DOK1 and 2 may exert their inhibitory effects by recruiting Ras GTPase-activating protein 1 (RASA1, RasGAP), which is a negative regulator of Ras signaling, but DOK2 can attenuate EGF receptor-induced MAP kinase activation without RASA1. DOK3 negatively regulates signaling by recruiting INPP5D and CSK (Grimm et al. 2001).

RET promotes neurite outgrowth of the rat pheochromocytoma cell line PC12 via Y1062. RET-DOK4/5 fusion proteins induced ligand-dependent axonal outgrowth of PC12 cells, while RET-DOK2 fusions did not. DOK4/5 do not associate with RASA1 or NCK, and enhance RET-dependent activation of MAPK (Grimm et al. 2001).

Preceded by: RET tyrosine phosphorylation

Literature references

Grimm, J., Sachs, M., Britsch, S., Di Cesare, S., Schwarz-Romond, T., Alitalo, K. et al. (2001). Novel p62dok family members, dok-4 and dok-5, are substrates of the c-Ret receptor tyrosine kinase and mediate neuronal differentiation. *J. Cell Biol., 154*, 345-54. ↗

Crowder, RJ., Enomoto, H., Yang, M., Johnson, EM., Milbrandt, J. (2004). Dok-6, a Novel p62 Dok family member, promotes Ret-mediated neurite outgrowth. *J. Biol. Chem., 279*, 42072-81. ↗

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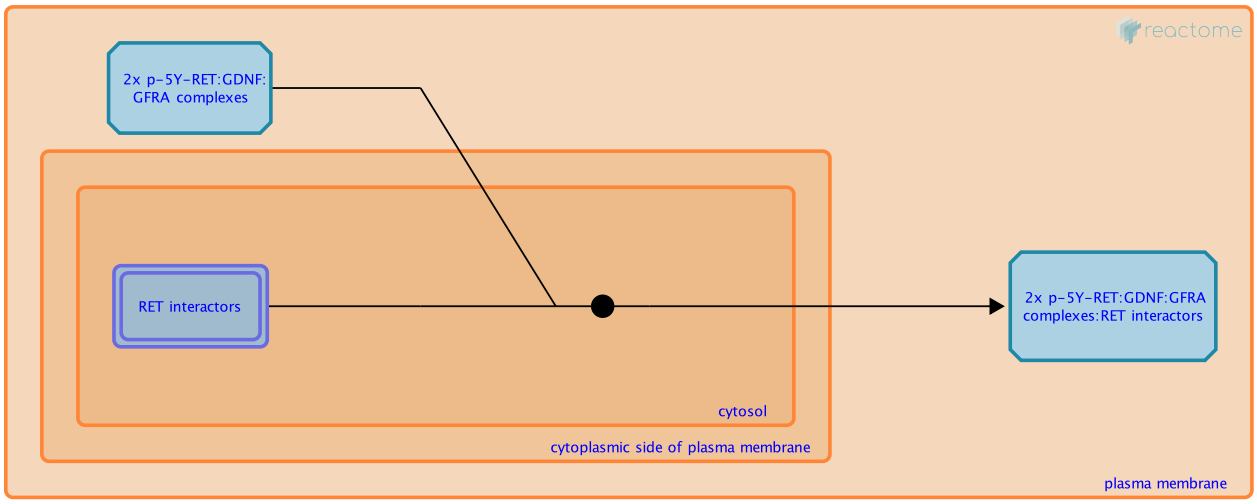
2x p-5Y-RET:GDNF:GFRA complexes bind RET interactors ↗

Location: RET signaling

Stable identifier: R-HSA-8855915

Type: binding

Compartments: cytosol, extracellular region, plasma membrane



Other RET interactors that may have a role in RET signaling include Mitogen-activated protein kinase 7 (MAPK7, BMK1) (Hayashi et al. 2001), SH3 and multiple ankyrin repeat domains protein 3 (SHANK3) (Schuetz et al. 2004), Insulin receptor substrate-2 (IRS2) (Hennige et al. 2000), SHC-transforming protein 3 (SHC3) (Pelicci et al. 2002), Protein kinase C alpha (PKCA) (Andreozzi et al. 2003) and PDZ and LIM domain protein 7 (Enigma, PDLIM7) (Durick et al. 1996). PDLIM7 and SHANK3 bind Tyrosine-1062 regardless of its phosphorylation state.

Preceded by: RET tyrosine phosphorylation

Literature references

Hayashi, Y., Iwashita, T., Murakamai, H., Kato, Y., Kawai, K., Kurokawa, K. et al. (2001). Activation of BMK1 via tyrosine 1062 in RET by GDNF and MEN2A mutation. *Biochem. Biophys. Res. Commun., 281*, 682-9. ↗

Schuetz, G., Rosário, M., Grimm, J., Boeckers, TM., Gundelfinger, ED., Birchmeier, W. (2004). The neuronal scaffold protein Shank3 mediates signaling and biological function of the receptor tyrosine kinase Ret in epithelial cells. *J. Cell Biol., 167*, 945-52. ↗

Hennige, AM., Lammers, R., Arlt, D., Höppner, W., Strack, V., Niederfellner, G. et al. (2000). Ret oncogene signal transduction via a IRS-2/PI 3-kinase/PKB and a SHC/Grb-2 dependent pathway: possible implication for transforming activity in NIH3T3 cells. *Mol. Cell. Endocrinol., 167*, 69-76. ↗

Pelicci, G., Troglio, F., Bodini, A., Melillo, RM., Pettirossi, V., Coda, L. et al. (2002). The neuron-specific Rai (ShcC) adaptor protein inhibits apoptosis by coupling Ret to the phosphatidylinositol 3-kinase/Akt signaling pathway. *Mol. Cell. Biol., 22*, 7351-63. ↗

Andreozzi, F., Melillo, RM., Carlomagno, F., Oriente, F., Miele, C., Fiory, F. et al. (2003). Protein kinase Calpha activation by RET: evidence for a negative feedback mechanism controlling RET tyrosine kinase. *Oncogene, 22*, 2942-9. ↗

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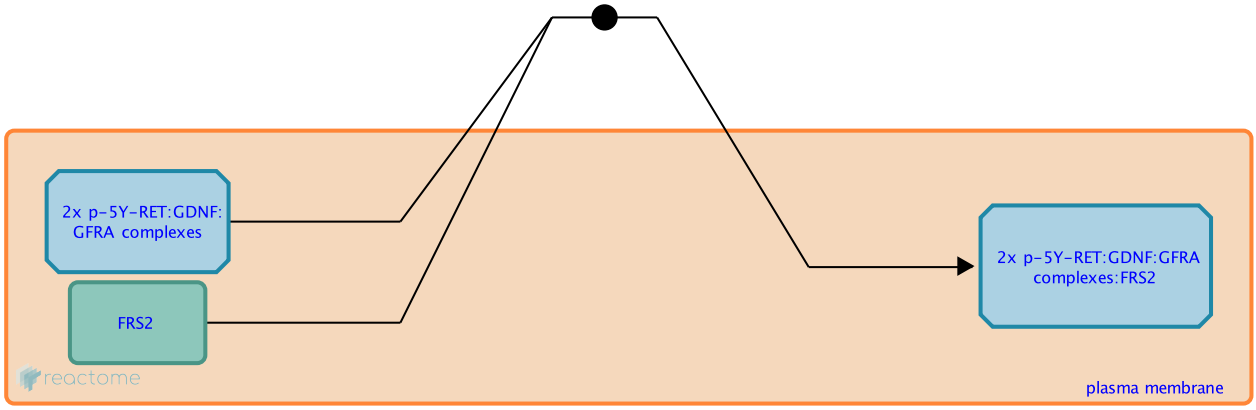
2x p-5Y-RET:GDNF:GFRA complexes bind FRS2 ↗

Location: RET signaling

Stable identifier: R-HSA-8855564

Type: binding

Compartments: extracellular region, plasma membrane



RET can bind FRS2, via phosphotyrosine-1062 (p-Y1062) (Kurokawa et al. 2001, Meillo et al. 2001). FRS2 competes with SHC1 for p-Y1062 binding (Lundgren et al. 2006). RET has been reported to associate with FRS2, instead of SHC1, when associated with lipid rafts (Paratcha et al. 2001).

Preceded by: RET tyrosine phosphorylation

Literature references

Kurokawa, K., Iwashita, T., Murakami, H., Hayashi, H., Kawai, K., Takahashi, M. (2001). Identification of SNT/FRS2 docking site on RET receptor tyrosine kinase and its role for signal transduction. *Oncogene, 20*, 1929-38. ↗

Melillo, RM., Santoro, M., Ong, SH., Billaud, M., Fusco, A., Hadari, YR. et al. (2001). Docking protein FRS2 links the protein tyrosine kinase RET and its oncogenic forms with the mitogen-activated protein kinase signaling cascade. *Mol. Cell. Biol., 21*, 4177-87. ↗

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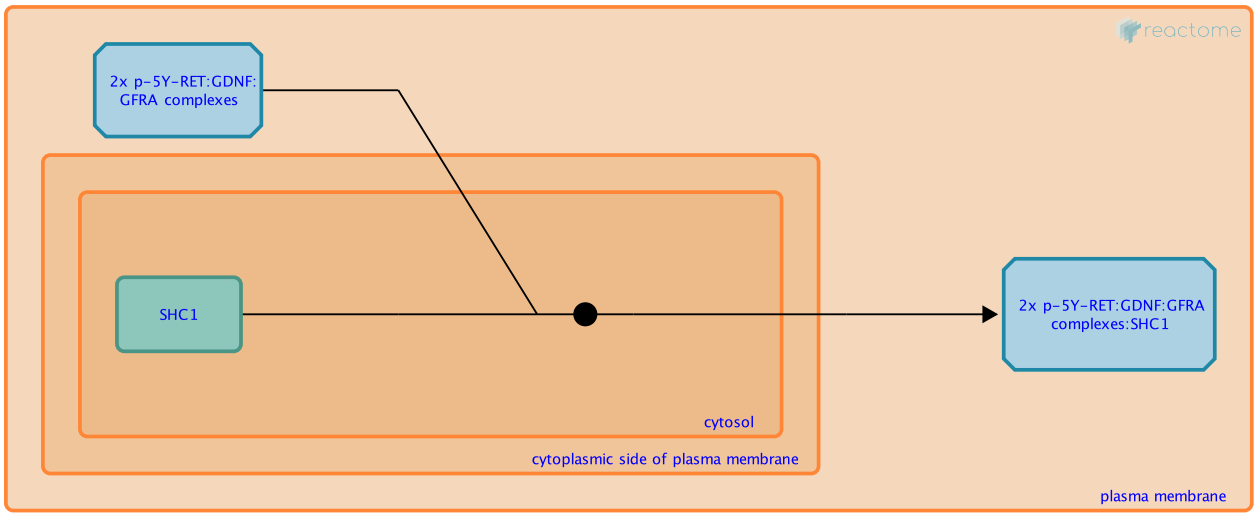
2x p-5Y-RET:GDNF:GFRA complexes bind SHC1 ↗

Location: RET signaling

Stable identifier: R-HSA-8853737

Type: binding

Compartments: cytosol, extracellular region, plasma membrane



GDNF stimulation of neuronal cells induces the assembly of a large protein complex containing RET, GRB2 and tyrosine-phosphorylated SHC1, p85 subunit of (PI3K), GAB2 (GAB1 in Hayashi et al. 2000) and Tyrosine-protein phosphatase non-receptor type 11 (PTPN11, SHP-2) (Besset et al. 2000). RET binds SHC1 via phosphorylated tyrosine-1062 (Asai et al. 1996, Arighi et al. 1997).

Preceded by: RET tyrosine phosphorylation

Followed by: SHC1 in the RET complex is phosphorylated

Literature references

Ohiwa, M., Murakami, H., Iwashita, T., Asai, N., Iwata, Y., Imai, T. et al. (1997). Characterization of Ret-Shc-Grb2 complex induced by GDNF, MEN 2A, and MEN 2B mutations. *Biochem. Biophys. Res. Commun., 237*, 747-51. ↗

Asai, N., Murakami, H., Iwashita, T., Takahashi, M. (1996). A mutation at tyrosine 1062 in MEN2A-Ret and MEN2B-Ret impairs their transforming activity and association with shc adaptor proteins. *J. Biol. Chem., 271*, 17644-9. ↗

Arighi, E., Alberti, L., Torriti, F., Ghizzoni, S., Rizzetti, MG., Pelicci, G. et al. (1997). Identification of Shc docking site on Ret tyrosine kinase. *Oncogene, 14*, 773-82. ↗

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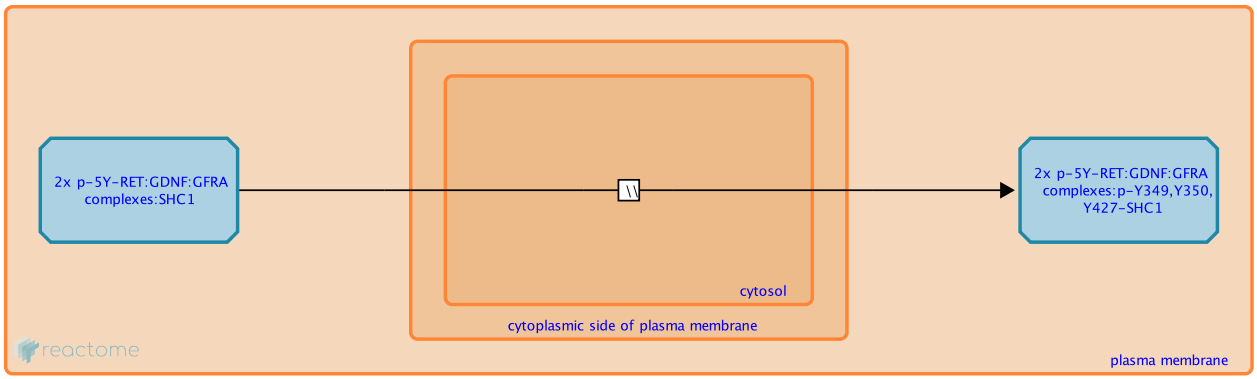
SHC1 in the RET complex is phosphorylated ↗

Location: RET signaling

Stable identifier: R-HSA-8854981

Type: omitted

Compartments: cytosol, extracellular region, plasma membrane



GDNF stimulation of neuronal cells induces the assembly of a large protein complex containing RET, GRB2 and tyrosine-phosphorylated SHC1, p85 subunit of (PI3K), GAB2 (GAB1 in Hayashi et al. 2000), and Tyrosine-protein phosphatase non-receptor type 11 (PTPN11, SHP-2) (Besset et al. 2000). Based on the mechanism of SHC1 activation in other receptor systems (Gu et al. 2000) it is likely that SHC1 tyrosine (Y) phosphorylation occurs as a consequence of RET binding and is required for subsequent events. GRB2 binding to SHC1 requires phosphorylation of Y349, Y350 and/or Y427 (Gu et al. 2000). Mutation of RET Y1062, which binds SHC1 to initiate recruitment of GRB2-GAB-p85, did not completely abolish the activation of RAS-RAF-ERK and PI3K-AKT (Besset et al. 2000), suggesting there are alternative pathways that do not utilize SHC1. RET has been shown to bind GRB2 directly, via Y1096 (Alberti et al. 1998, Besset et al. 2000).

It has not been established whether SHC1 associates with RET in phosphorylated form or is phosphorylated after binding, and the identity of the kinase is unknown, hence this is represented as an uncertain event.

Preceded by: 2x p-5Y-RET:GDNF:GFRA complexes bind SHC1

Followed by: p-5Y-RET complexes bind GRB2, 2x p-5Y-RET:GDNF:GFRA complexes:p-Y349,Y350,Y427-SHC1 binds GRB2-1:SOS1

Literature references

Besset, V., Scott, RP., Ibáñez, CF. (2000). Signaling complexes and protein-protein interactions involved in the activation of the Ras and phosphatidylinositol 3-kinase pathways by the c-Ret receptor tyrosine kinase. *J. Biol. Chem., 275*, 39159-66. ↗

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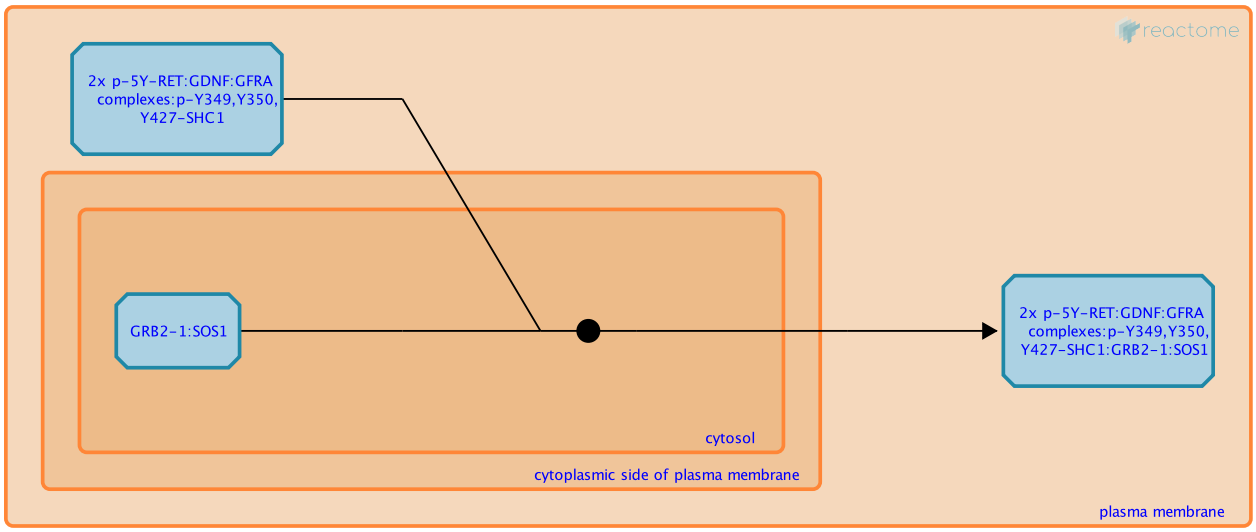
2x p-5Y-RET:GDNF:GFRA complexes:p-Y349,Y350,Y427-SHC1 binds GRB2-1:SOS1 ↗

Location: RET signaling

Stable identifier: R-HSA-8853734

Type: binding

Compartments: cytosol, extracellular region, plasma membrane



RET has been shown to bind GRB2 indirectly via SHC (Ohiwa et al. 1997). GRB2 is found in a complex with SOS1 in unstimulated cells (Hayashi et al. 2000).

GDNF stimulation of neuronal cells induces the assembly of a large protein complex containing RET, GRB2 and tyrosine-phosphorylated SHC, p85 subunit of (PI3K), GAB2 (GAB1 in Hayashi et al. 2000) and Tyrosine-protein phosphatase non-receptor type 11 (PTPN11, SHP-2) (Besset et al. 2000). This suggests that at least two distinct RET-SHC protein complexes can assemble via phosphorylated Tyrosine (Y) 1062, one involving GRB2:SOS1 leads to activation of the Ras/Erk pathway, another involving GRB1/2, GAB2 and PI3K leads to the PI3K/Akt pathway. This latter complex can also assemble directly onto phosphorylated Y1096 (Besset et al. 2000).

RET can activate the RAS-RAF-ERK signaling pathway (van Weering et al. 1995, Ohiwa et al. 1997, van Weering & Bos 1997, Trupp et al. 1999, Hayashi et al. 2000). RAS signaling is markedly impaired by mutations of RET Y1062 (Hayashi et al. 2000). RET RAS signaling and the effect of the Y1062 mutation are believed to be mediated by RET complexes involving GRB2:SOS, well known as mediators of signaling to RAS in other receptor systems (Ravichandran 2001).

Preceded by: SHC1 in the RET complex is phosphorylated

Literature references

Ohiwa, M., Murakami, H., Iwashita, T., Asai, N., Iwata, Y., Imai, T. et al. (1997). Characterization of Ret-Shc-Grb2 complex induced by GDNF, MEN 2A, and MEN 2B mutations. *Biochem. Biophys. Res. Commun., 237*, 747-51. ↗

Besset, V., Scott, RP., Ibáñez, CF. (2000). Signaling complexes and protein-protein interactions involved in the activation of the Ras and phosphatidylinositol 3-kinase pathways by the c-Ret receptor tyrosine kinase. *J. Biol. Chem., 275*, 39159-66. ↗

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2016-05-17	Reviewed	Luo, W.

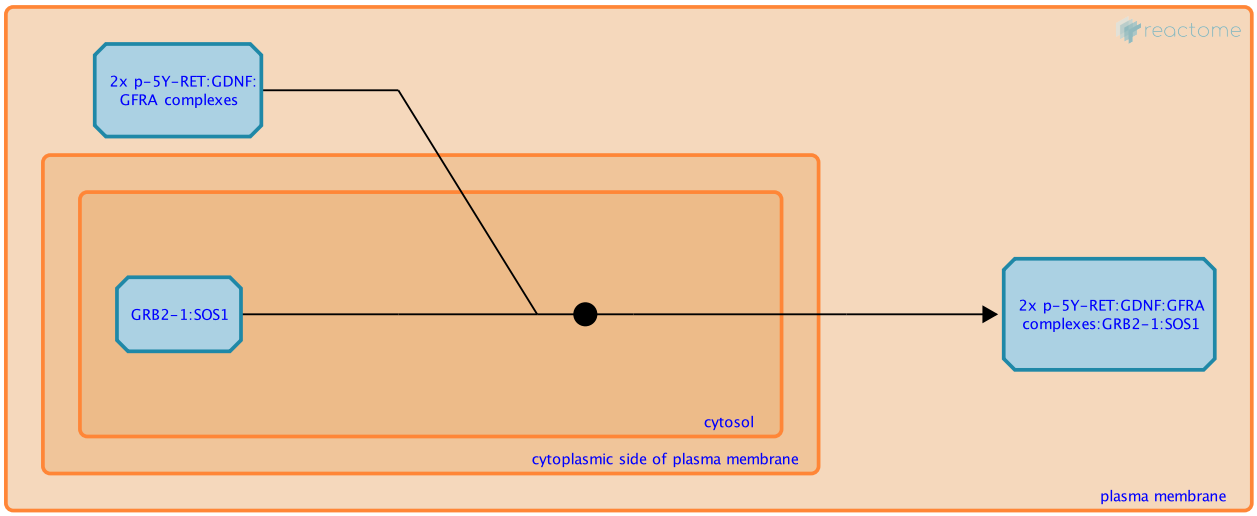
2x p-5Y-RET:GDNF:GFRA complexes bind GRB2-1:SOS1 ↗

Location: RET signaling

Stable identifier: R-HSA-8854899

Type: binding

Compartments: cytosol, extracellular region, plasma membrane



RET has been shown to bind GRB2 directly, via Tyrosine-1096 (Y1096) (Alberti et al. 1998, Besset et al. 2000). GRB2 is found in a complex with SOS1 in unstimulated cells (Hayashi et al. 2000).

GDNF stimulation of neuronal cells induces the assembly of a large protein complex containing RET, GRB2 and tyrosine-phosphorylated SHC1, p85 subunit of (PI3K), GAB2 (GAB1 in Hayashi et al. 2000) and Tyrosine-protein phosphatase non-receptor type 11 (PTPN11, SHP-2) (Besset et al. 2000). This suggests that at least two distinct RET-SHC1 protein complexes can assemble via phosphorylated Y1062, one involving GRB2 and SOS1 leads to activation of the RAS-RAF-ERK pathway, another involving GRB2, GAB2 and p85 leads to the PI3K-AKT pathway. This latter complex can also assemble directly onto phosphorylated Y1096 (Besset et al. 2000).

RET can activate the RAS-RAF-ERK signaling pathway (van Weering et al. 1995, Ohiwa et al. 1997, van Weering & Bos 1997, Trupp et al. 1999, Hayashi et al. 2000). RAS signaling is markedly impaired by mutations of RET Y1062 (Hayashi et al. 2000). RET RAS signaling and the effect of the Y1062 mutation are believed to be mediated by RET complexes involving GRB2:SOS1, well known as mediators of signaling to RAS in other receptor systems (Ravichandran 2001).

Preceded by: RET tyrosine phosphorylation

Literature references

Alberti, L., Borrello, MG., Ghizzoni, S., Torriti, F., Rizzetti, MG., Pierotti, MA. (1998). Grb2 binding to the different isoforms of Ret tyrosine kinase. *Oncogene, 17*, 1079-87. ↗

Besset, V., Scott, RP., Ibáñez, CF. (2000). Signaling complexes and protein-protein interactions involved in the activation of the Ras and phosphatidylinositol 3-kinase pathways by the c-Ret receptor tyrosine kinase. *J. Biol. Chem., 275*, 39159-66. ↗

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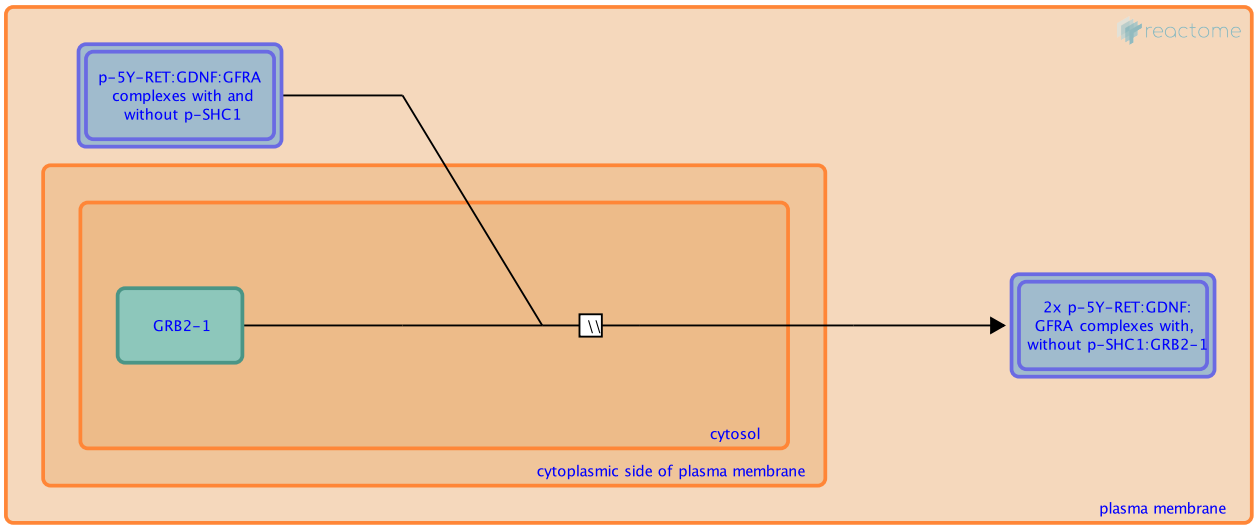
p-5Y-RET complexes bind GRB2 ↗

Location: RET signaling

Stable identifier: R-HSA-8853793

Type: omitted

Compartments: cytosol, plasma membrane



GDNF stimulation of neuronal cells induces the assembly of a large protein complex containing RET, GRB2 and tyrosine-phosphorylated SHC1, p85 subunit of (PI3K), GAB2 (GAB1 in Hayashi et al. 2000), and Tyrosine-protein phosphatase non-receptor type 11 (PTPN11, SHP-2) (Besset et al. 2000). GAB1 was found in complexes with GRB2 only after GDNF treatment (Hayashi et al. 2000). This contrasts with reports in other systems where GAB2-GRB2 were reported to constitutively associate (Gu et al. 1998). The likely order of recruitment to RET is SHC1, GRB2, GAB1/2, similar to the signaling mechanism of the Interleukin-3 receptor (Gu et al. 2000) and many others (Adams et al. 2012).

Preceded by: SHC1 in the RET complex is phosphorylated, RET tyrosine phosphorylation

Followed by: p-5Y-RET-GRB2-containing complexes bind GAB1,GAB2

Literature references

Hayashi, H., Ichihara, M., Iwashita, T., Murakami, H., Shimono, Y., Kawai, K. et al. (2000). Characterization of intracellular signals via tyrosine 1062 in RET activated by glial cell line-derived neurotrophic factor. *Oncogene, 19*, 4469-75. ↗

Besset, V., Scott, RP., Ibáñez, CF. (2000). Signaling complexes and protein-protein interactions involved in the activation of the Ras and phosphatidylinositol 3-kinase pathways by the c-Ret receptor tyrosine kinase. *J. Biol. Chem., 275*, 39159-66. ↗

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2016-01-25	Authored	Jupe, S.
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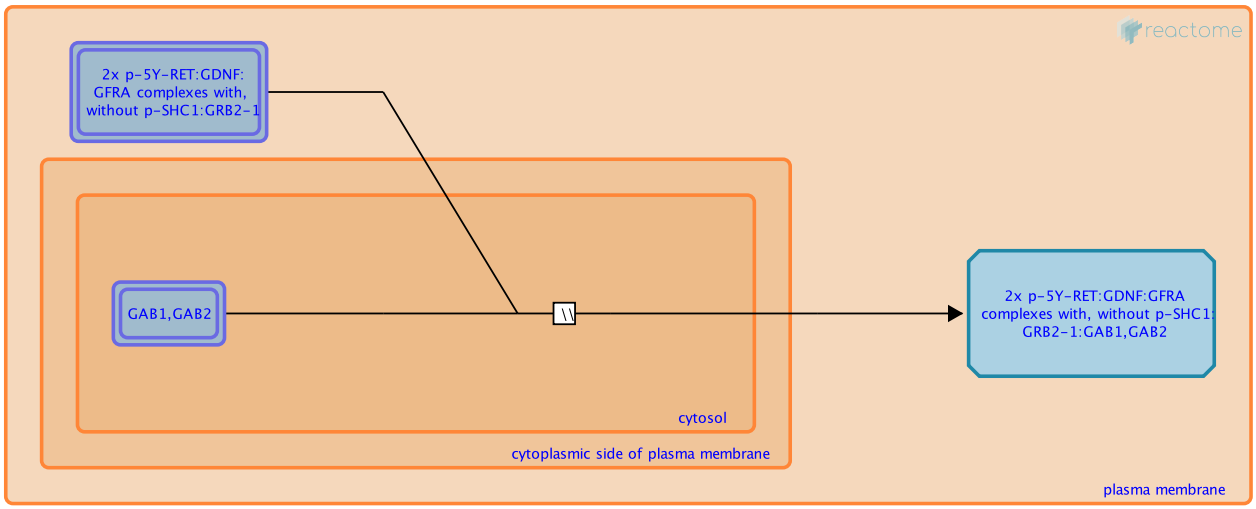
p-5Y-RET-GRB2-containing complexes bind GAB1,GAB2 ↗

Location: RET signaling

Stable identifier: R-HSA-8854897

Type: omitted

Compartments: cytosol, extracellular region, plasma membrane



Grb-associated binder (GAB) proteins are a family of docking proteins that transduce cellular signals between receptors and intracellular downstream effectors (Ding et al. 2015). When phosphorylated by protein-tyrosine kinases, GABs can recruit several Src homology-2 (SH2) domain-containing proteins, including Tyrosine-protein phosphatase non-receptor type 11 (PTPN11, SHP2), the p85 subunit of phosphoinositide-3 kinase (p85-PI3K), phospholipase C-gamma 1 (PLCG1), CRK and GAB-associated Cdc42/Rac GTPase-activating protein (ARHGAP32, GC-GAP). These interactions lead to various downstream signals involved in cell growth, differentiation, migration and apoptosis.

GDNF stimulation of neuronal cells induces the assembly of a large protein complex containing RET, GRB2 and tyrosine-phosphorylated SHC1, p85-PI3K, GAB2 (GAB1 in Hayashi et al. 2000) and PTPN11 (Besset et al. 2000). GAB1 was found in complexes with GRB2 only after GDNF treatment (Hayashi et al. 2000). This contrasts with reports that GAB2 constitutively associates with GRB2 (Gu et al. 1998).

The likely order of recruitment to RET is SHC1, GRB2, GAB1/2, p85-PI3K, similar to the signaling mechanism of the Interleukin-3 receptor (Gu et al. 2000) and many others (Adams et al. 2012, Ding et al. 2015). As the order of RET complex formation is not firmly established, GAB binding is shown as an uncertain event.

Preceded by: p-5Y-RET complexes bind GRB2

Followed by: GAB in p-5Y-RET:GDNF:GFRA complexes is phosphorylated

Literature references

Besset, V., Scott, RP., Ibáñez, CF. (2000). Signaling complexes and protein-protein interactions involved in the activation of the Ras and phosphatidylinositol 3-kinase pathways by the c-Ret receptor tyrosine kinase. *J. Biol. Chem., 275*, 39159-66. ↗

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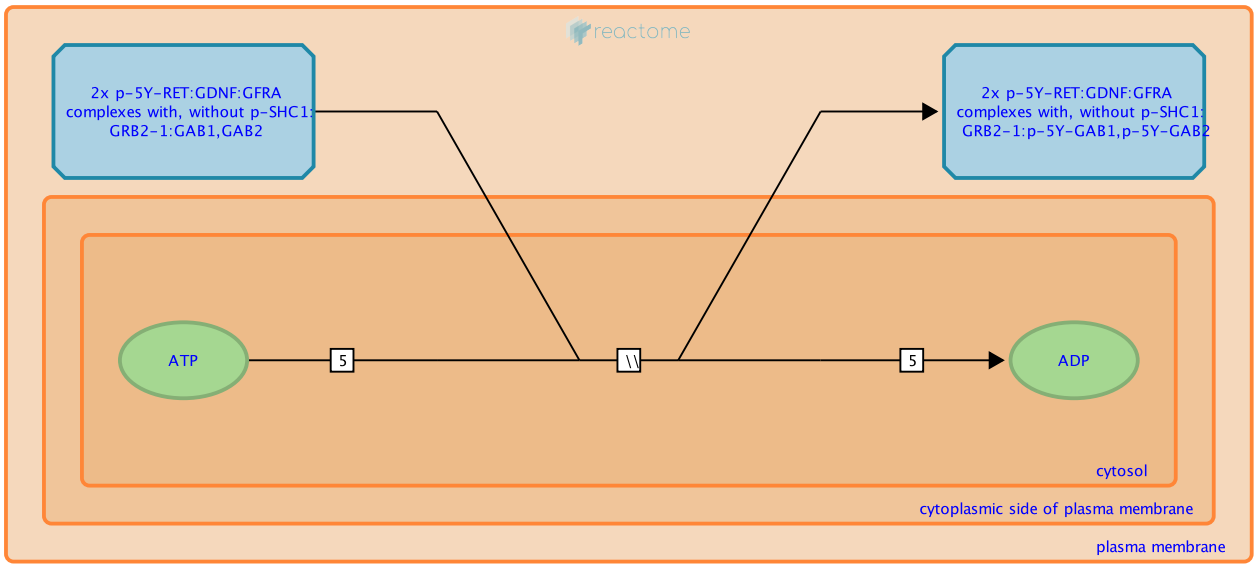
GAB in p-5Y-RET:GDNF:GFRA complexes is phosphorylated ↗

Location: RET signaling

Stable identifier: R-HSA-8853774

Type: omitted

Compartments: cytosol, extracellular region, plasma membrane



Grb2-associated-binder (GAB) family signaling is mediated by tyrosine phosphorylation. GAB1-3 all have an N-terminal pleckstrin homology (PH) domain, proline-rich motifs, and multiple potential tyrosyl and seryl/threonyl phosphorylation sites (Gu & Neel 2003, Liu & Rohrschneider 2002). GAB2 has several docking sites for SH2 domain-containing molecules, including tyrosine-protein phosphatase non-receptor type 11 (PTPN11, SHP-2) and the p85 subunit of phosphatidylinositol 3-kinase (p85-PI3K) (Ding et al. 2015). Similarly, GAB1 associates with PTPN11 and p85-PI3K; these interactions are considered essential for GAB1 activation of extracellular signal-regulated kinase (ERK)1/2 and PI3K-AKT, respectively (Wang et al. 2015).

GAB2 has three tyrosine (Y) residues, Y452, Y476 and Y584, that are binding sites for p85-PI3K (Crouin et al. 2001, Maus et al. 2009) and two more (Y614 and Y643) that interact with the SH2 domains of PTPN11 (Gu et al. 1998, Crouin et al. 2001, Arnaud et al. 2004). GAB1 also becomes tyrosine phosphorylated when transducing signals from receptor tyrosine kinases to p85 (Holgado-Madruga et al. 1997, Mattoon et al. 2004). There are three potential binding sites for p85 on GAB1 (Y447, Y472, and Y589) (Holgado-Madruga et al. 1997). GAB1 Y627 and Y659 appear to link it to PTPN11; GAB1 mutants that are unable to bind PTPN11 do not activate ERK (Schaeper et al. 2000, Cunnick et al. 2000, Sármay et al. 2006).

PI3K activation produces membrane-associated PI(3,4,5)P3, which facilitates membrane association of the PH domain of GAB, enhancing its recruitment (Zhang et al. 2009) in a positive feed-back loop. The kinases responsible for GAB phosphorylation are cell-type and receptor specific (Maus et al. 2009).

GDNF stimulation of neuronal cells induces the assembly of a complex containing RET, GRB2 and tyrosine-phosphorylated SHC, p85 subunit of (PI3K), GAB2 (GAB1 in Hayashi et al. 2000) and PTPN11 (SHP2) (Besset et al. 2000). GAB1 was found in complexes with GRB2 only after GDNF treatment (Hayashi et al. 2000). The likely order of recruitment to RET is SHC, GRB2, GAB1/2, p85 and/or PTPN11, similar to the signaling mechanism of the Interleukin-3 receptor (Gu et al. 2000) and others (Adams et al. 2012, Ding et al. 2015). It is likely, though not demonstrated, that GAB1/2 become tyrosine phosphorylated after binding GRB2 in the RET receptor complex. The kinase responsible is unclear. As the order of GAB binding

and phosphorylation, and the identity of the kinase responsible for GAB phosphorylation have not been demonstrated, GAB phosphorylation in the RET complex is shown as an uncertain event.

Preceded by: p-5Y-RET-GRB2-containing complexes bind GAB1,GAB2

Followed by: p-5Y-GAB in the RET-GRB2-GAB complexes binds p85-PI3K, p-5Y-GAB in RET-GRB2-GAB complexes binds PTPN11

Literature references

Besset, V., Scott, RP., Ibáñez, CF. (2000). Signaling complexes and protein-protein interactions involved in the activation of the Ras and phosphatidylinositol 3-kinase pathways by the c-Ret receptor tyrosine kinase. *J. Biol. Chem., 275*, 39159-66. ↗

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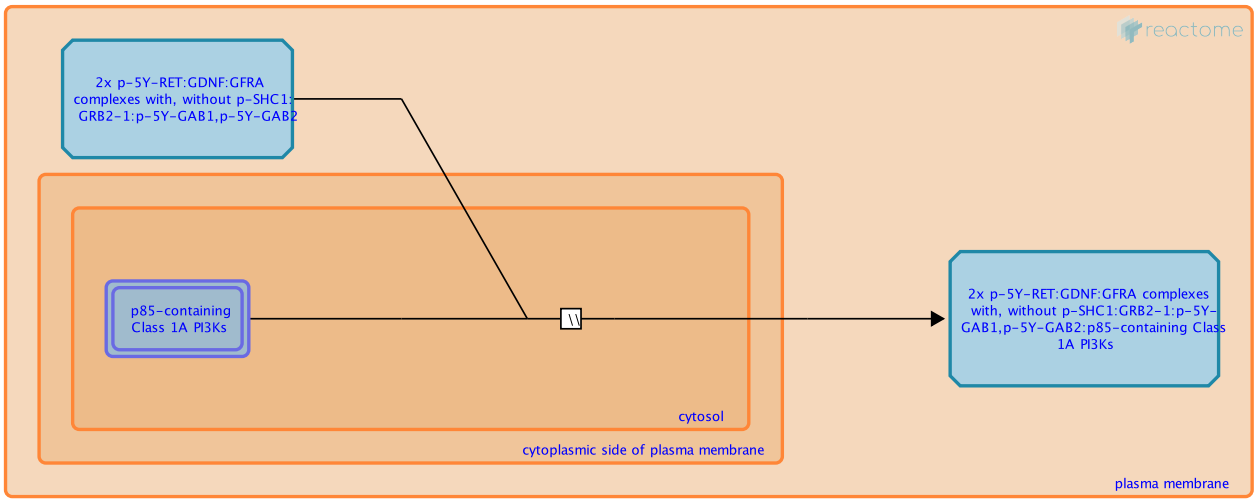
p-5Y-GAB in the RET-GRB2-GAB complexes binds p85-PI3K ↗

Location: RET signaling

Stable identifier: R-HSA-8854905

Type: omitted

Compartments: cytosol, extracellular region, plasma membrane



Following recruitment and phosphorylation of GAB1 or GAB2 to the RET complex, it binds the p85 subunit of p85-containing PI3 kinase (p85-PI3K), resulting in its activation (Murakami et al. 1999, Hayashi et al. 2000, Besset et al. 2000). p85-PI3K consists of a p85 adaptor subunit, which contains one Src homology 3 (SH3) and two Src homology 2 (SH2) domains, and a p110 subunit that has catalytic activity (Kapeller & Cantley 1994). These subunits are tightly associated (Carpenter et al. 1990). Though p85-PI3K can be phosphorylated, it is binding of the p85 SH2 domains that activates the enzyme (Rordorf-Nikolic et al. 1995).

GAB2 has three tyrosine residues, Y452, Y476 and Y584, which are involved in p85-PI3K binding (Crouin et al. 2001, Maus et al. 2009). GAB1 also becomes tyrosine phosphorylated and directly associates with p85 when transducing signals from receptor tyrosine kinases to p85 (Holgado-Madruga et al. 1997, Mattoon et al. 2004). There are three potential binding sites for p85 on GAB1 (Y447, Y472, and Y589) (Holgado-Madruga et al. 1997). Phosphorylation at these sites in GAB1 is represented in this reaction as a likely prerequisite for p85 binding, but this is not experimentally confirmed, hence this reaction is displayed as an uncertain event.

Preceded by: GAB in p-5Y-RET:GDNF:GFRA complexes is phosphorylated

Literature references

Murakami, H., Iwashita, T., Asai, N., Shimono, Y., Iwata, Y., Kawai, K. et al. (1999). Enhanced phosphatidylinositol 3-kinase activity and high phosphorylation state of its downstream signalling molecules mediated by ret with the MEN 2B mutation. *Biochem. Biophys. Res. Commun., 262*, 68-75. ↗

Hayashi, H., Ichihara, M., Iwashita, T., Murakami, H., Shimono, Y., Kawai, K. et al. (2000). Characterization of intracellular signals via tyrosine 1062 in RET activated by glial cell line-derived neurotrophic factor. *Oncogene, 19*, 4469-75. ↗

Besset, V., Scott, RP., Ibáñez, CF. (2000). Signaling complexes and protein-protein interactions involved in the activation of the Ras and phosphatidylinositol 3-kinase pathways by the c-Ret receptor tyrosine kinase. *J. Biol. Chem., 275*, 39159-66. ↗

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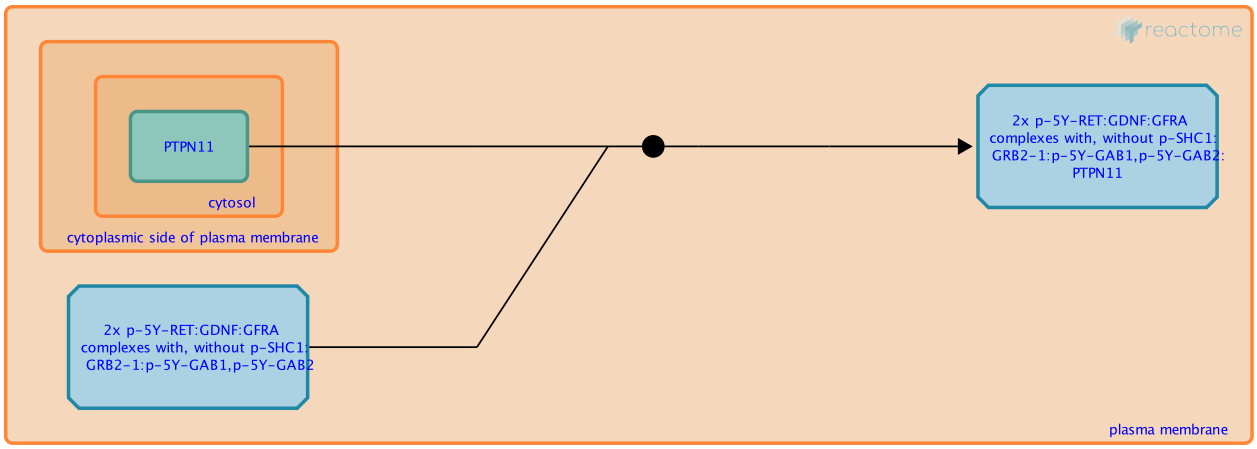
p-5Y-GAB in RET-GRB2-GAB complexes binds PTPN11 ↗

Location: RET signaling

Stable identifier: R-HSA-8855508

Type: binding

Compartments: plasma membrane, cytosol



GDNF stimulation of neuronal cells induces the assembly of a large protein complex containing RET, GRB2 and tyrosine-phosphorylated SHC1, p85 subunit of PI3K, GAB2 (GAB1 in Hayashi et al. 2000), and Tyrosine-protein phosphatase non-receptor type 11 (PTPN11, SHP-2) (Besset et al. 2000).

PTPN11 is recruited to RET via a combination of direct interactions and indirect interactions with other components of the receptor complex such as FRS2A and GAB1/2 (Perrinjaquet et al. 2010, Willecke et al. 2011). Binding of PTPN11 SH2-domains induces a conversion of the closed inactive into an open active structure (Willecke et al. 2011).

GAB2 interacts with the SH2 domains of PTPN11 (Gu et al. 1998, Crouin et al. 2001, Arnaud et al. 2004), which binds GAB2 Tyrosine (Y) 614 and Y643 through its N- and C-terminal SH2 domains respectively. Mutation of Y614 is sufficient to prevent GAB2 from recruiting PTPN11. In the Interleukin-2 receptor system, this prevents ERK (extracellular-signal-regulated kinase) activation (Arnaud et al. 2004). Similarly, phosphorylated GAB1 binds PTPN11, PI3K, PLCgamma1 and SHC1 in activated B cells (Ingham et al. 1998). GAB1 Y627 and Y659 appear to link it to PTPN11; GAB1 mutants that are unable to bind PTPN11 do not activate ERK (Schaeper et al. 2000, Cunnick et al. 2000, Sármay et al. 2006).

Preceded by: GAB in p-5Y-RET:GDNF:GFRA complexes is phosphorylated

Literature references

Besset, V., Scott, RP., Ibáñez, CF. (2000). Signaling complexes and protein-protein interactions involved in the activation of the Ras and phosphatidylinositol 3-kinase pathways by the c-Ret receptor tyrosine kinase. *J. Biol. Chem., 275*, 39159-66. ↗

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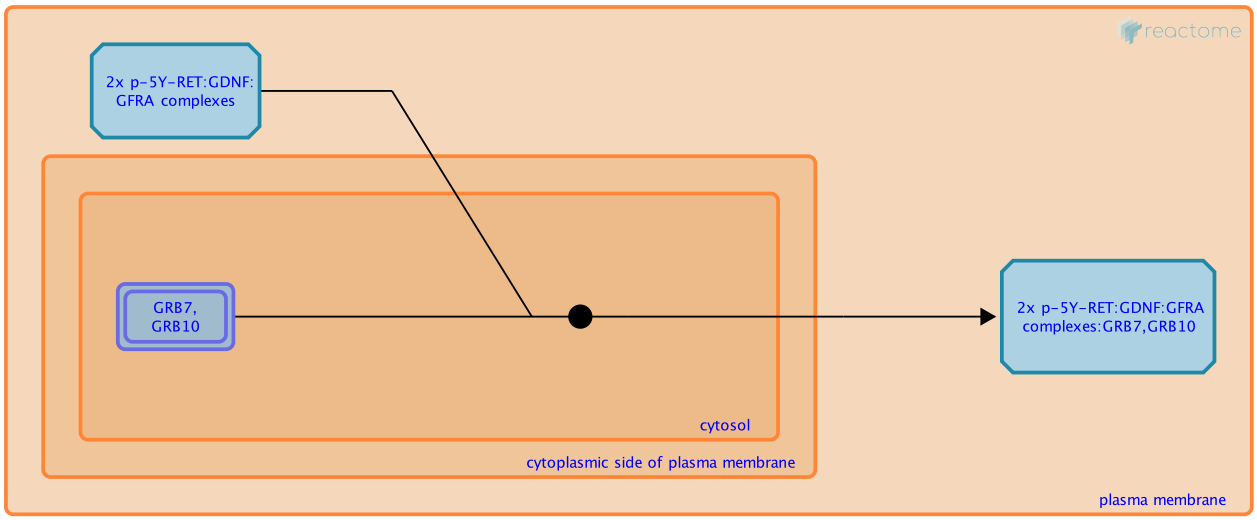
2x p-5Y-RET:GDNF:GFRA complexes bind GRB7,10

Location: RET signaling

Stable identifier: R-HSA-8853753

Type: binding

Compartments: cytosol, extracellular region, plasma membrane



Tyrosine-phosphorylated RET can bind GRB7 or GRB10 via tyrosine-905 (Pandey et al. 1995, 1996).

Preceded by: RET tyrosine phosphorylation

Literature references

Pandey, A., Duan, H., Di Fiore, PP., Dixit, VM. (1995). The Ret receptor protein tyrosine kinase associates with the SH2-containing adapter protein Grb10. *J. Biol. Chem., 270*, 21461-3.

Pandey, A., Liu, X., Dixon, JE., Di Fiore, PP., Dixit, VM. (1996). Direct association between the Ret receptor tyrosine kinase and the Src homology 2-containing adapter protein Grb7. *J. Biol. Chem., 271*, 10607-10.

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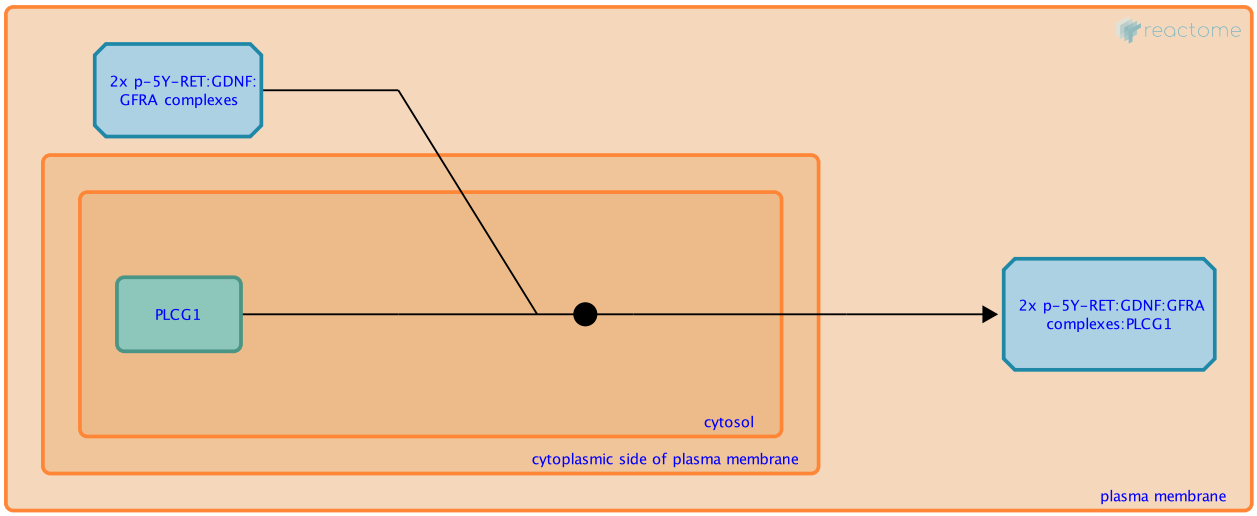
2x p-5Y-RET:GDNF:GFRA complexes bind PLCgamma1

Location: RET signaling

Stable identifier: R-HSA-8853755

Type: binding

Compartments: cytosol, plasma membrane, extracellular region



Phosphorylated RET binds Phospholipase C gamma 1 (PLCG1) via tyrosine 905 (Borello et al. 1996) and/or tyrosine-1015 (Lundgren et al. 2012).

Preceded by: RET tyrosine phosphorylation

Literature references

Borrello, MG., Alberti, L., Arighi, E., Bongarzone, I., Battistini, C., Bardelli, A. et al. (1996). The full oncogenic activity of Ret/ptc2 depends on tyrosine 539, a docking site for phospholipase Cgamma. *Mol. Cell. Biol., 16*, 2151-63.

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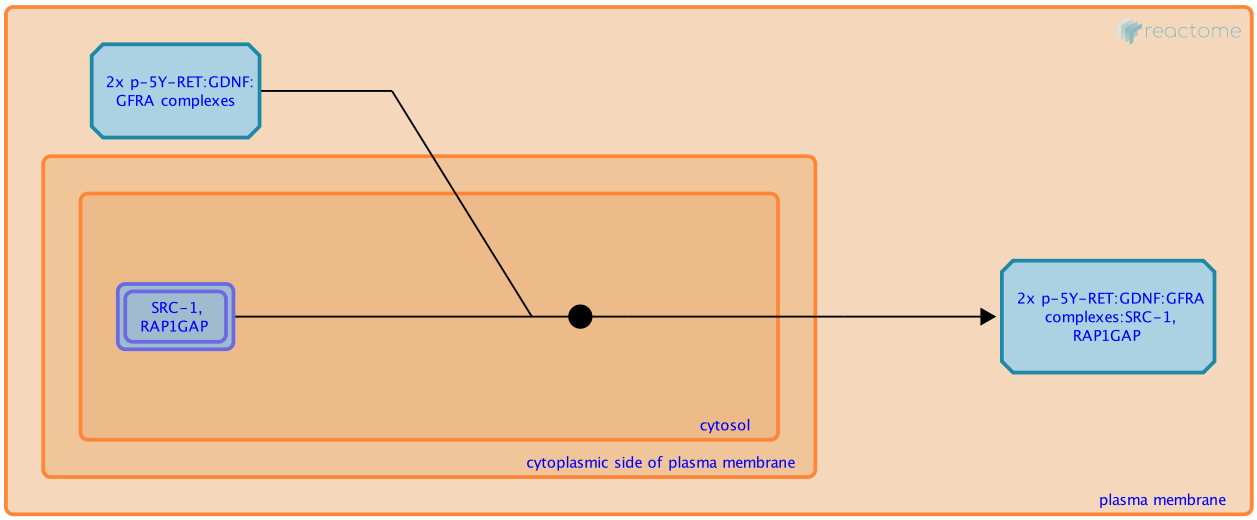
2x p-5Y-RET:GDNF:GFRA complexes bind SRC1, RAP1GAP ↗

Location: RET signaling

Stable identifier: R-HSA-8855747

Type: binding

Compartments: cytosol, extracellular region, plasma membrane



RET phospho-Tyr981 binds the cytoplasmic tyrosine kinase SRC (Encinas et al. 2004). Recently, a yeast-two-hybrid screen led to the identification of the GTPase-activating protein (GAP) for Rap1, RAP1GAP, as a novel RET-binding protein (Jiao et al. 2011). Like SRC, Rap1GAP was also found to require phosphorylation of Tyrosine-981 for RET binding and suppressed GDNF-induced activation of ERK and neurite outgrowth.

Preceded by: RET tyrosine phosphorylation

Literature references

Encinas, M., Crowder, RJ., Milbrandt, J., Johnson, EM. (2004). Tyrosine 981, a novel ret autophosphorylation site, binds c-Src to mediate neuronal survival. *J. Biol. Chem., 279,* 18262-9. ↗

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