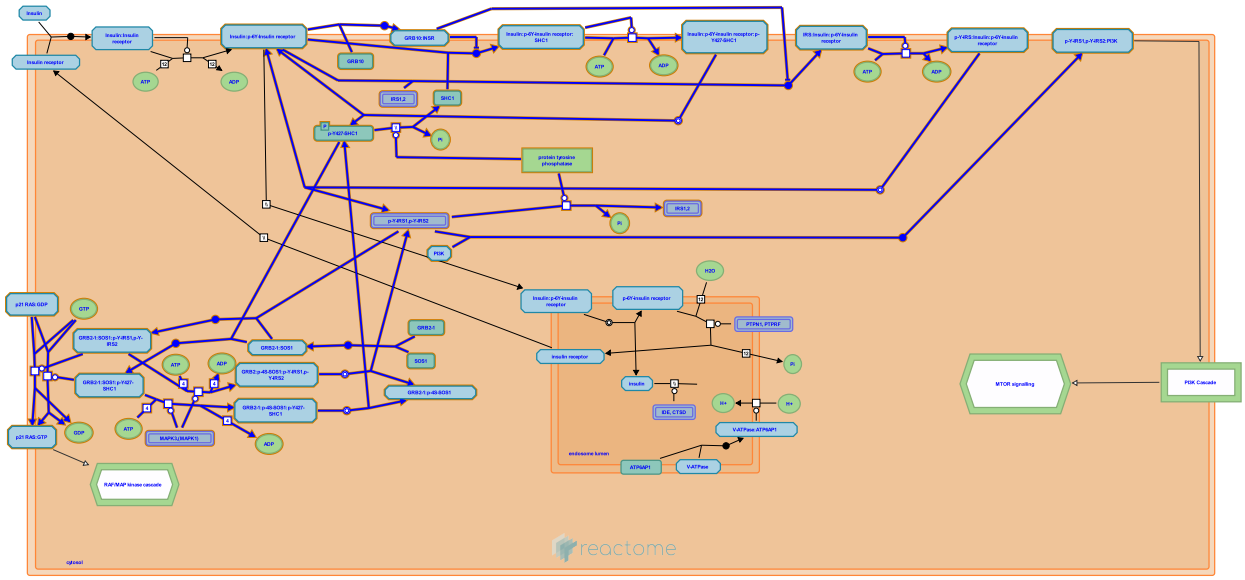
Insulin receptor signalling cascade



Bevan, AP., Charalambous, M., Greene, LA., Heldin, CH., Orlic-Milacic, M., Schmidt, EE.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

15/11/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

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

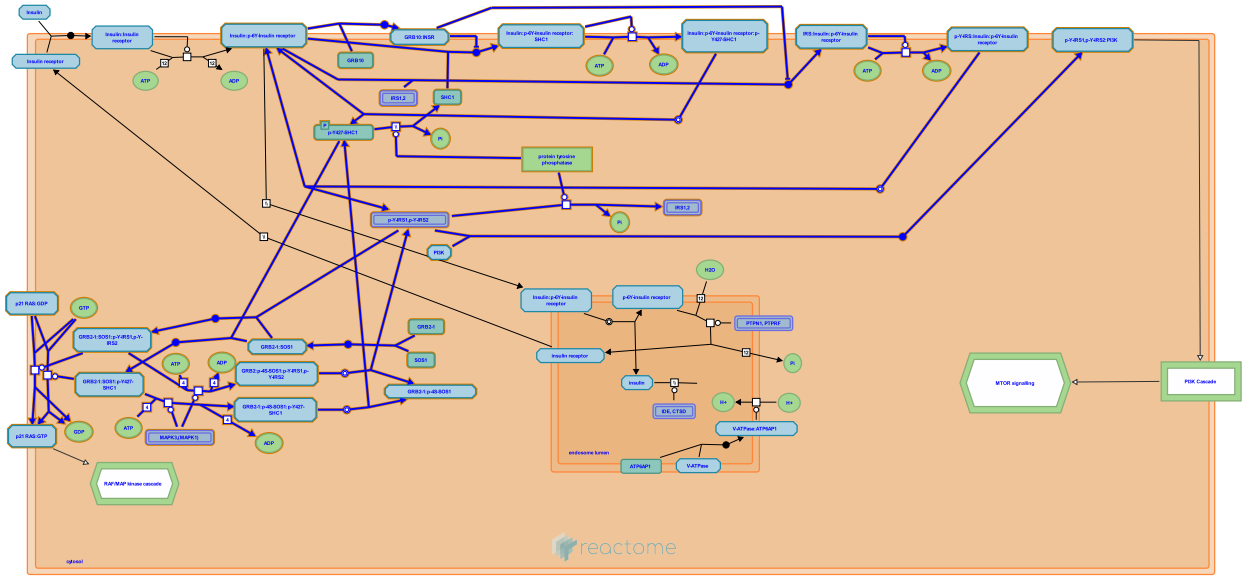
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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

Insulin receptor signalling cascade ↗

Stable identifier: R-HSA-74751

Compartments: cytosol



Autophosphorylation of the insulin receptor triggers a series of signalling events, mediated by SHC or IRS, and resulting in activation of the Ras/RAF and MAP kinase cascades. A second effect of the autophosphorylation of the insulin receptor is its internalisation into an endosome, which downregulates its signalling activity.

Literature references

Bevan, P. (2001). Insulin signalling. *J Cell Sci, 114*, 1429-30. ↗

Shepherd, PR., Siddle, K., Withers, DJ. (1998). Phosphoinositide 3-kinase: the key switch mechanism in insulin signalling. *Biochem J, 333*, 471-90. ↗

Editions

2003-07-31	Authored	Bevan, AP.

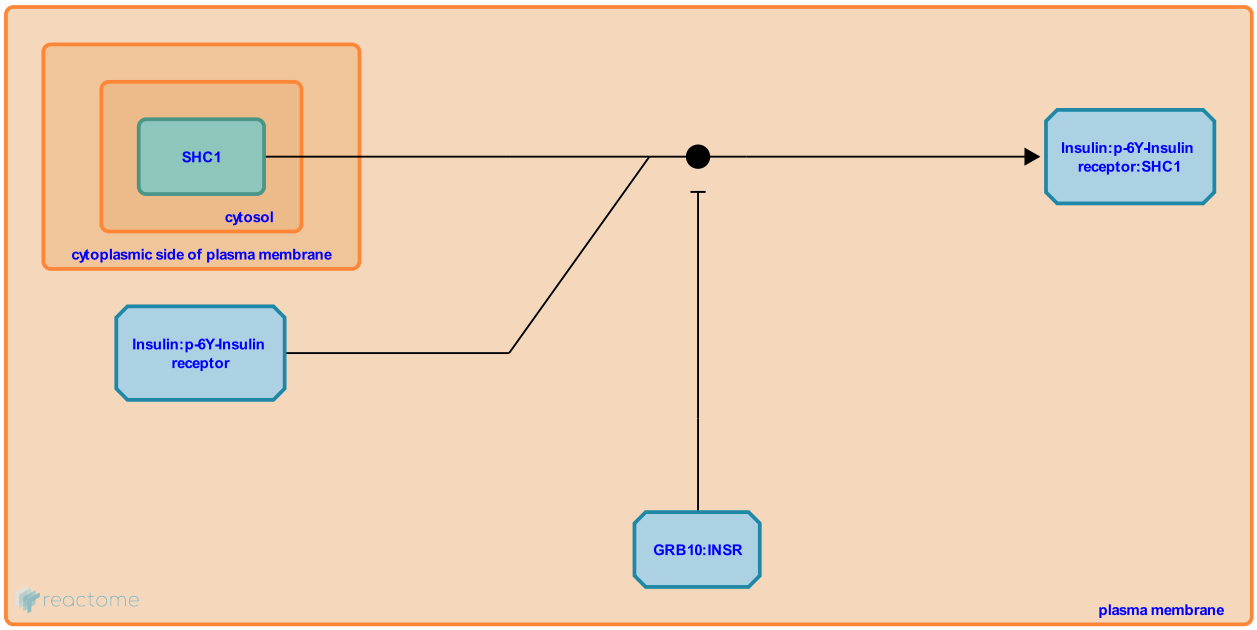
Binding of SHC1 to insulin receptor ↗

Location: Insulin receptor signalling cascade

Stable identifier: R-HSA-74740

Type: binding

Compartments: plasma membrane, cytosol



SHC1 interacts via its SH2 domain with the carboxyterminal phosphorylated tyrosines of the insulin receptor. As a result, SHC1 is tyrosine phosphorylated by the insulin receptor, later falling away from the receptor (Liang et al.1999, Sasaoka et al.1996).

Followed by: Phosphorylation of SHC1

Literature references

Imamura, T., Sawa, T., Sasaoka, T., Usui, I., Takata, Y., Ishihara, H. et al. (1996). Functional importance of amino-terminal domain of Shc for interaction with insulin and epidermal growth factor receptors in phosphorylation-independent manner. *J. Biol. Chem., 271*, 20082-7. ↗

Zhou, T., Frank, SJ., Gustafson, TA., Liang, L., Jiang, J., Pierce, JH. (1999). Insulin receptor substrate-1 enhances growth hormone-induced proliferation. *Endocrinology, 140*, 1972-83. ↗

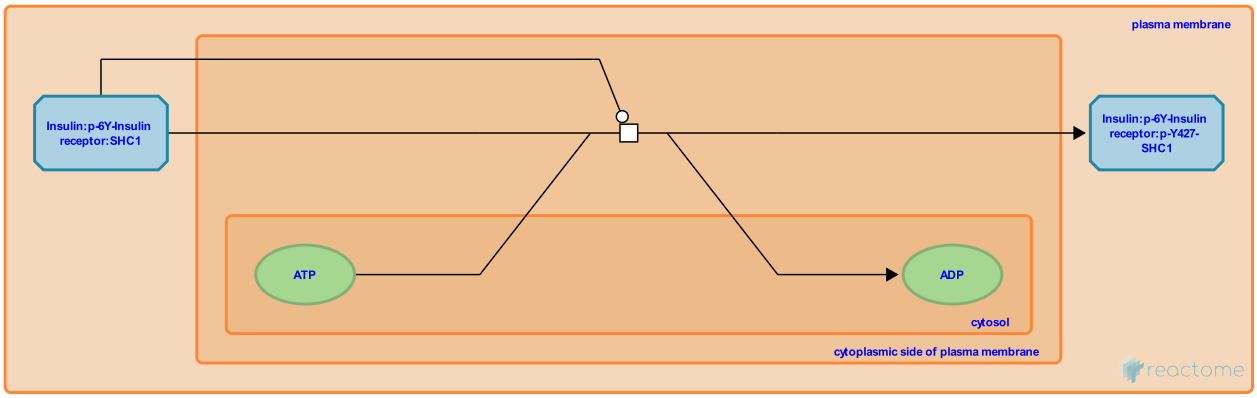
Phosphorylation of SHC1 ↗

Location: Insulin receptor signalling cascade

Stable identifier: R-HSA-74742

Type: transition

Compartments: cytoplasmic side of plasma membrane



SHC1 is tyrosine phosphorylated at Tyr-427 by the insulin receptor, later falling away from the receptor. Phosphorylation of SHC1 allows the SH2 domain of GRB2 to bind it (Sasaoka et al. 2000).

Preceded by: Binding of SHC1 to insulin receptor

Followed by: Dissociation of p-Y427-SHC1 from insulin receptor

Literature references

Sasaoka, T., Kobayashi, M. (2000). The functional significance of Shc in insulin signaling as a substrate of the insulin receptor. *Endocr. J., 47*, 373-81. ↗

Imamura, T., Sawa, T., Sasaoka, T., Usui, I., Takata, Y., Ishihara, H. et al. (1996). Functional importance of amino-terminal domain of Shc for interaction with insulin and epidermal growth factor receptors in phosphorylation-independent manner. *J. Biol. Chem., 271*, 20082-7. ↗

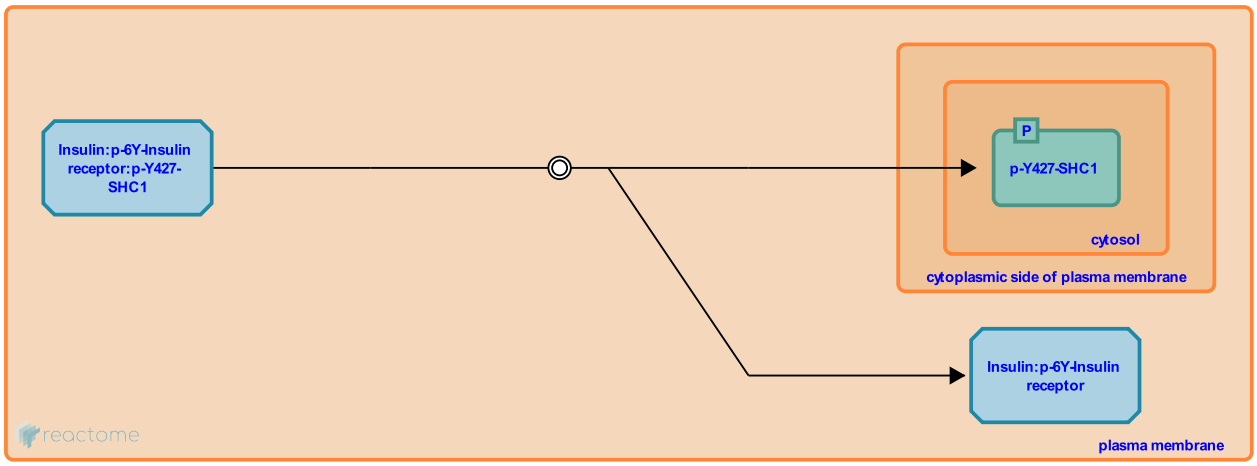
Dissociation of p-Y427-SHC1 from insulin receptor ↗

Location: Insulin receptor signalling cascade

Stable identifier: R-HSA-74743

Type: dissociation

Compartments: plasma membrane, cytosol



Release of tyrosine-phosphorylated SHC from the insulin receptor triggers a cascade of signalling events via SOS, RAF and the MAP kinases (Sasaoka et al. 1996, Kleiman et al.2011). This is a black box event since this dissociation is inferred from other reaction which show association and dissociation for this protein under EGF stimulation (Kleiman et al. 2011).

Preceded by: Phosphorylation of SHC1

Followed by: GRB2-1:SOS1 binds p-Y427-SHC1

Literature references

Sorger, PK., Kleiman, LB., Maiwald, T., Conzelmann, H., Lauffenburger, DA. (2011). Rapid phospho-turnover by receptor tyrosine kinases impacts downstream signaling and drug binding. *Mol. Cell, 43*, 723-37. ↗

Imamura, T., Sawa, T., Sasaoka, T., Usui, I., Takata, Y., Ishihara, H. et al. (1996). Functional importance of amino-terminal domain of Shc for interaction with insulin and epidermal growth factor receptors in phosphorylation-independent manner. *J. Biol. Chem., 271*, 20082-7. ↗

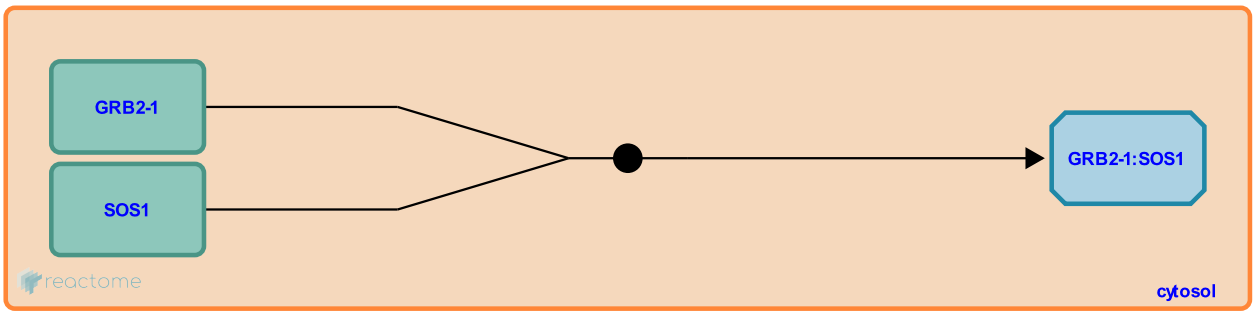
GRB2-1 binds SOS1 ↗

Location: Insulin receptor signalling cascade

Stable identifier: R-HSA-109813

Type: binding

Compartments: cytosol



In the cytoplasm of unstimulated cells, SOS1 is found in a complex with GRB2. The interaction occurs between the carboxy terminal domain of SOS1 and the Src homology 3 (SH3) domains of GRB2.

Followed by: GRB2-1:SOS1 binds p-Y427-SHC1

Literature references

Yajnik, V., Skolnik, E., Batzer, A., Daly, R., Li, N., Schlessinger, J. et al. (1993). Guanine-nucleotide-releasing factor hSos1 binds to Grb2 and links receptor tyrosine kinases to Ras signalling. *Nature, 363*, 85-8. ↗

Editions

2005-01-07	Authored	Charalambous, M.
2008-02-12	Reviewed	Heldin, CH.
2011-08-25	Edited	Orlic-Milacic, M.
2024-08-27	Edited	Schmidt, EE.

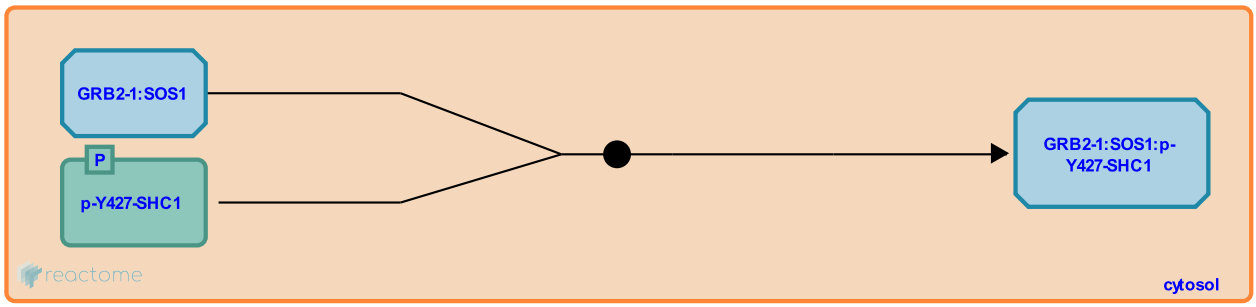
GRB2-1:SOS1 binds p-Y427-SHC1 ↗

Location: Insulin receptor signalling cascade

Stable identifier: R-HSA-74746

Type: binding

Compartments: cytosol



Tyrosine-phosphorylated SHC1 recruits the SH2 domain of the adaptor protein GRB2, which is complexed with SOS, an exchange factor for p21ras and RAC, through its SH3 domain. Besides SOS, the GRB2 SH3 domain can associate with other intracellular targets, including GAB1. Erk and Rsk mediated phosphorylation results in dissociation of the SOS-GRB2 complex. This may explain why Erk activation through Shc and SOS-GRB2 is transient. Inactive p21ras-GDP is found anchored to the plasma membrane by a farnesyl residue. As Shc is phosphorylated by the the stimulated receptor near to the plasma membrane, the SOS-GRB2:Shc interaction brings the SOS enzyme into close proximity to p21ras.

Preceded by: Dissociation of p-Y427-SHC1 from insulin receptor, GRB2-1 binds SOS1

Followed by: GRB2:SOS:p-Y427-SHC1 mediated nucleotide exchange of RAS

Literature references

Pessin, JE., Okada, S. (1996). Interactions between Src homology SH2/SH3 adapter proteins and the guanylnucleotide exchange factor SOS are differentially regulated by insulin and epidermal growth factor. *J Biol Chem, 271*, 25533-8 . ↗

Editions

2005-01-07	Authored	Charalambous, M.
2007-11-08	Reviewed	Greene, LA.
2024-08-27	Edited	Schmidt, EE.

GRB2:SOS:p-Y427-SHC1 mediated nucleotide exchange of RAS ↗

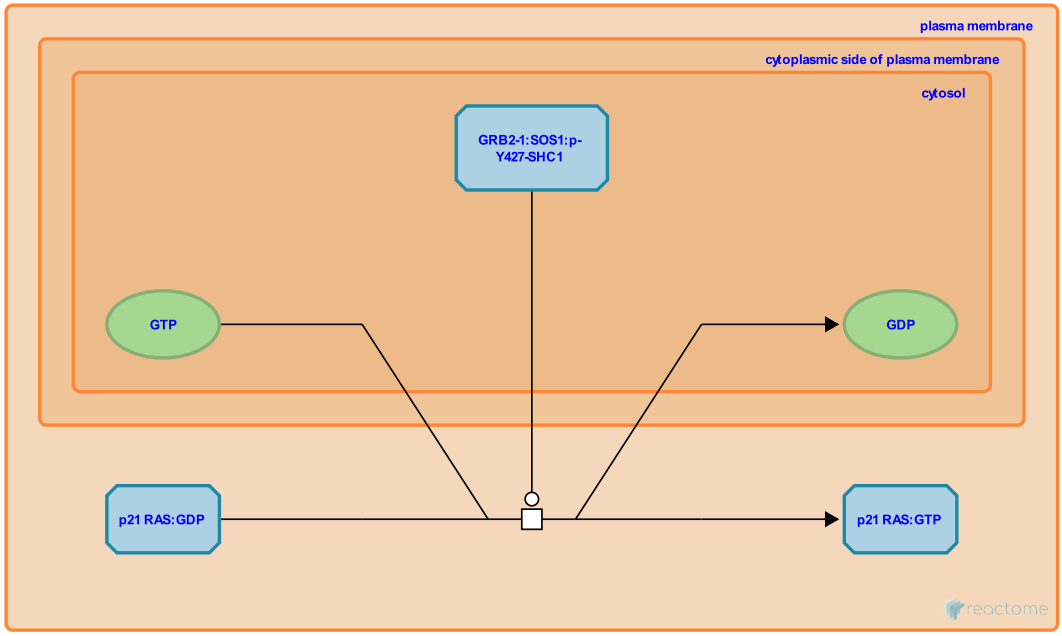
Location: Insulin receptor signalling cascade

Stable identifier: R-HSA-109807

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: SOS mediated nucleotide exchange of RAS (SHC) (Rattus norvegicus)



SOS promotes the formation of GTP-bound RAS, thus activating this protein. RAS activation results in activation of the protein kinases RAF1, B-Raf, and MAP-ERK kinase kinase (MEKK), and the catalytic subunit of PI3K, as well as of a series of RALGEFs. The activation cycle of RAS GTPases is regulated by their interaction with specific guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs). GEFs promote activation by inducing the release of GDP, whereas GAPs inactivate RAS-like proteins by stimulating their intrinsic GTPase activity. NGF-induced RAS activation via SHC-GRB2-SOS is maximal at 2 min but it is no longer detected after 5 min. Therefore, the transient activation of RAS obtained through SHC-GRB2-SOS is insufficient for the prolonged activation of ERKs found in NGF-treated cells.

Preceded by: GRB2-1:SOS1 binds p-Y427-SHC1

Literature references

Boriack-Sjodin, PA., Margarit, SM., Kuriyan, J., Bar-Sagi, D. (1998). The structural basis of the activation of Ras by Sos . *Nature, 394*, 337-43. ↗

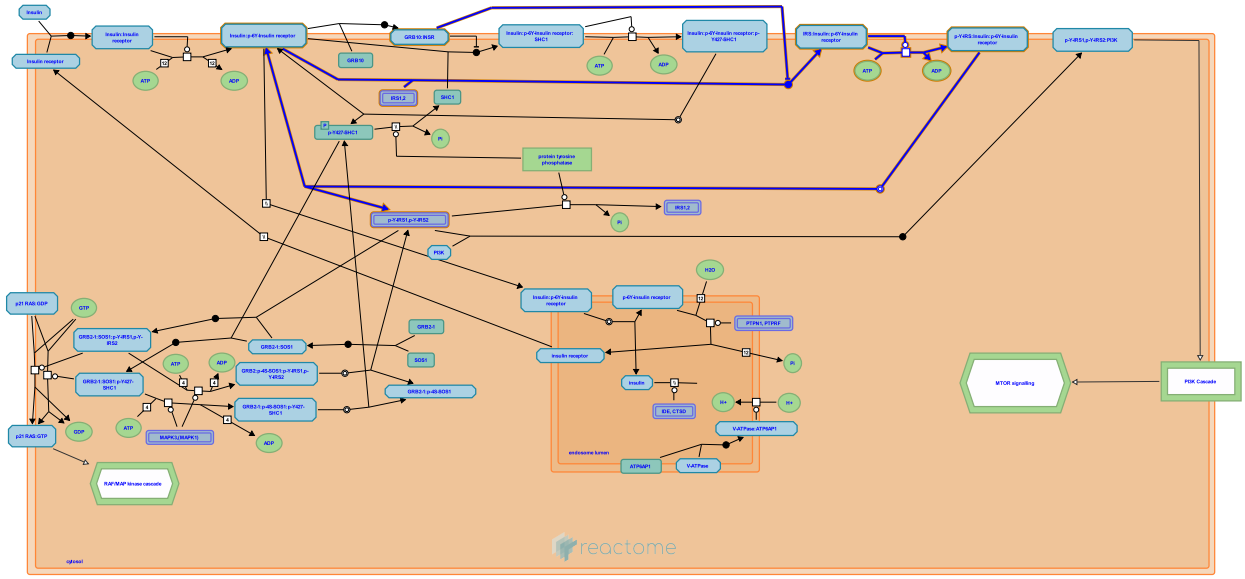
Editions

2005-01-07	Authored	Charalambous, M.
2007-11-08	Reviewed	Greene, LA.
2024-08-27	Edited	Schmidt, EE.

IRS activation ↗

Location: Insulin receptor signalling cascade

Stable identifier: R-HSA-74713



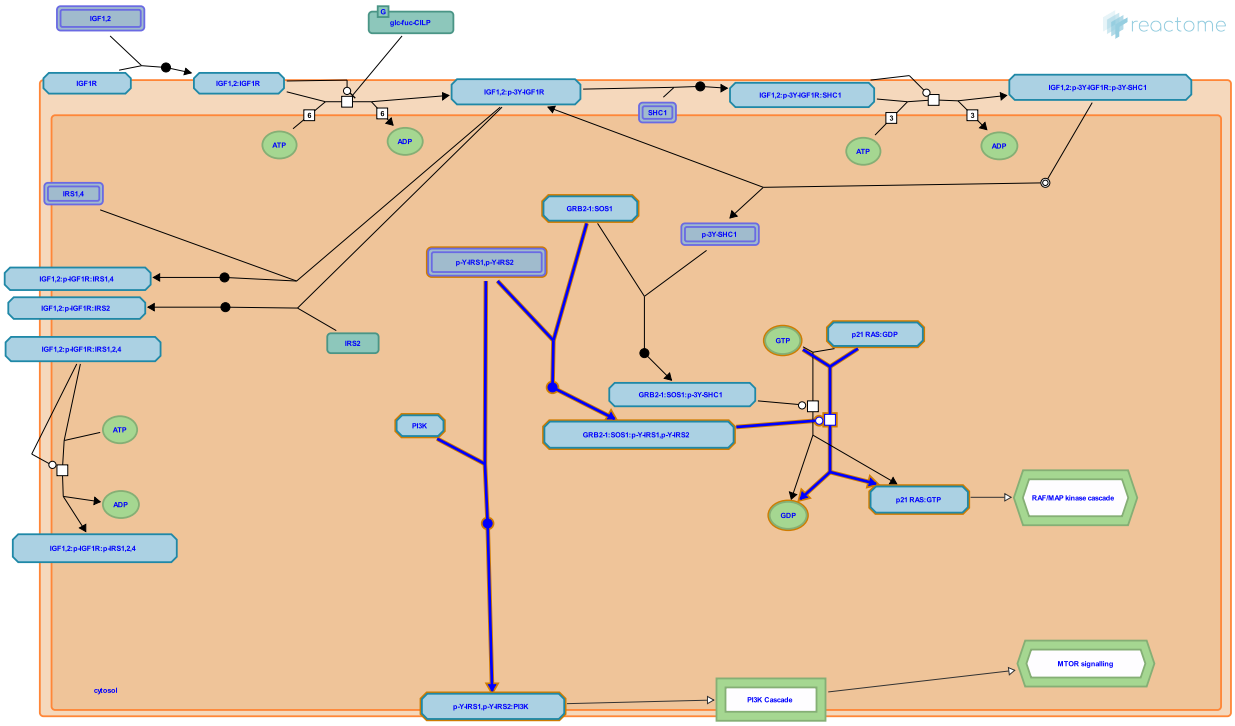
IRS is one of the mediators of insulin signalling events. It is activated by phosphorylation and triggers a cascade of events involving PI3K, SOS, RAF and the MAP kinases. The proteins mentioned under IRS are examples of IRS family members acting as indicated. More family members are to be confirmed and added in the future. Using receptor mutagenesis studies it is known that IRS1 via its PTB domain binds to the insulin receptor at the juxtamembrane region at tyrosine 972. The interaction is further stabilized by the PH domain of IRS1 which interacts with the phospholipids of the plasma membrane. This allows the receptor to phosphorylate IRS1 on up to 13 of its tyrosine residues. Once phosphorylated the IRS1 falls away from the receptor. Now in a tyrosine phosphorylated and hence activated state other proteins can interact with the IRS proteins.

IRS-mediated signalling ↗

Location: Insulin receptor signalling cascade

Stable identifier: R-HSA-112399

Compartments: plasma membrane, cytosol



Release of phospho-IRS from the insulin receptor triggers a cascade of signalling events via PI3K, SOS, RAF and the MAP kinases.

Editions

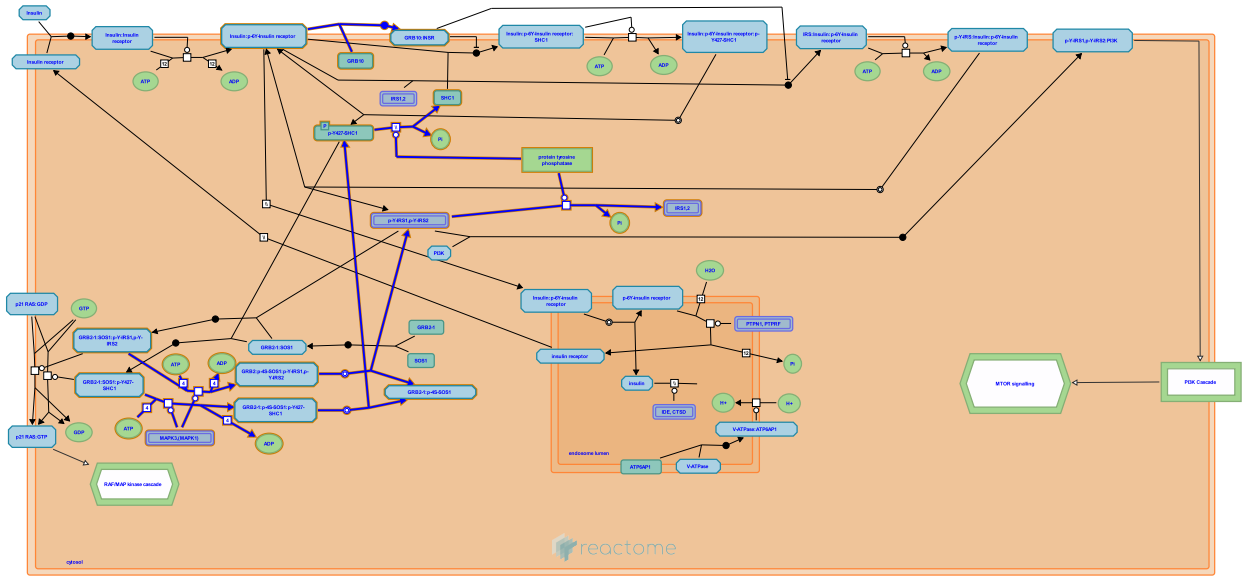
2004-04-29	Authored	Charalambous, M.

Signal attenuation ↗

Location: Insulin receptor signalling cascade

Stable identifier: R-HSA-74749

Compartments: cytosol



Now with the complete receptor-ligand dissociation and subsequent degradation of insulin in the endosomal lumen, the endosomally associated protein tyrosine phosphatases (PTPs) complete the receptor dephosphorylation. So too are all the receptor substrates dephosphorylated leading to the collapse of the signalling complexes and signal attenuation.

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