Insulin receptor signalling cascade

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22/03/2019
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


Reactome database release: 67

This document contains 4 pathways and 6 reactions (see Table of Contents)
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**


**Editions**

2003-07-31 Authored Bevan, AP.
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**


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**


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**


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**


**Editions**

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

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

Literature references


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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 (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


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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.
Table of Contents

Introduction 1

- Insulin receptor signalling cascade 2
  - Binding of SHC1 to insulin receptor 3
  - Phosphorylation of SHC1 4
  - Dissociation of p-Y427-SHC1 from insulin receptor 5
  - GRB2-1 binds SOS1 6
  - GRB2-1:SOS1 binds p-Y427-SHC1 7
  - GRB2:SOS:p-Y427-SHC1 mediated nucleotide exchange of RAS 8
  - IRS activation 9
  - IRS-mediated signalling 10
  - Signal attenuation 11

Table of Contents 12