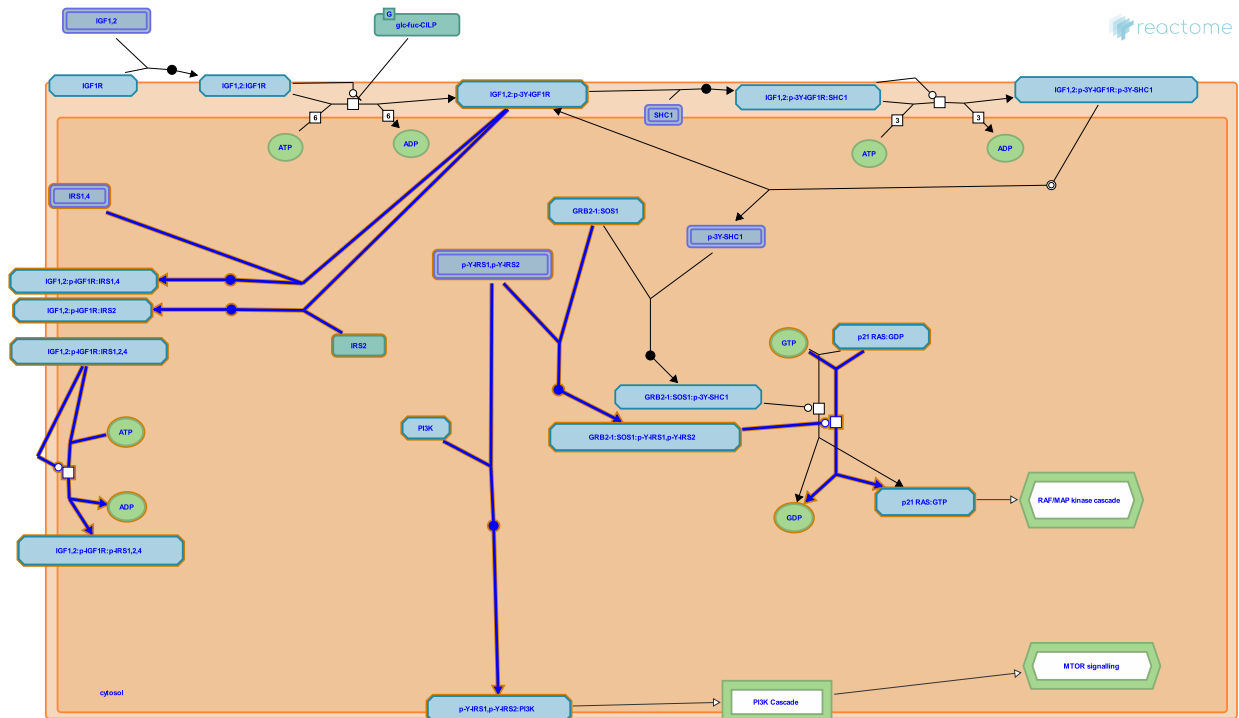


IRS-related events triggered by IGF1R



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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](#).

06/05/2024

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.

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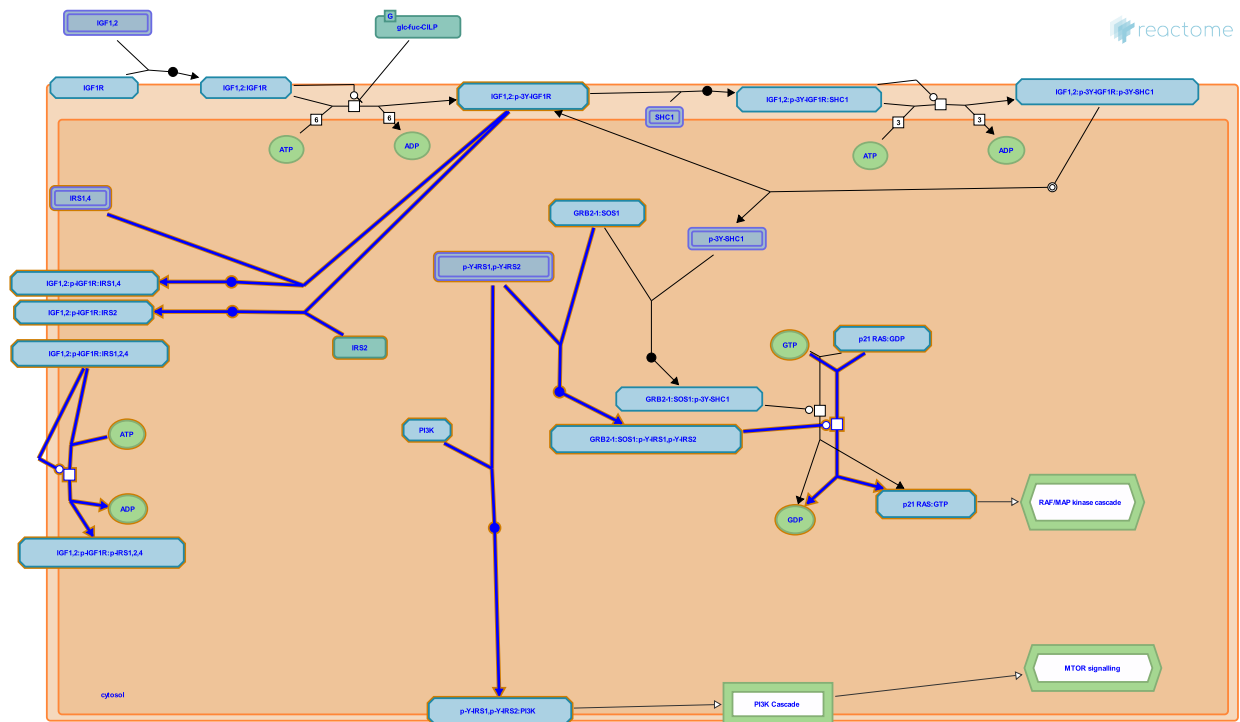
Reactome database release: 88

This document contains 2 pathways and 3 reactions ([see Table of Contents](#))

IRS-related events triggered by IGF1R [↗](#)

Stable identifier: R-HSA-2428928

Compartments: cytosol, plasma membrane



The phosphorylated type 1 insulin-like growth factor receptor phosphorylates IRS1, IRS2, IRS4 and possibly other IRS/DOK family members (reviewed in Pavelic et al. 2007, Chitnis et al. 2008, Maki et al. 2010, Parrella et al. 2010, Siddle et al. 2012). The phosphorylated IRS proteins serve as scaffolds that bind the effector molecules PI3K and GRB2:SOS. PI3K then activates PKB (AKT) signaling while GRB2:SOS activates RAS-RAF-MAPK signaling.

Literature references

- Siddle, K. (2012). Molecular basis of signaling specificity of insulin and IGF receptors: neglected corners and recent advances. *Front Endocrinol (Lausanne)*, 3, 34. [↗](#)
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Editions

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2012-11-10	Reviewed	Holzenberger, M.

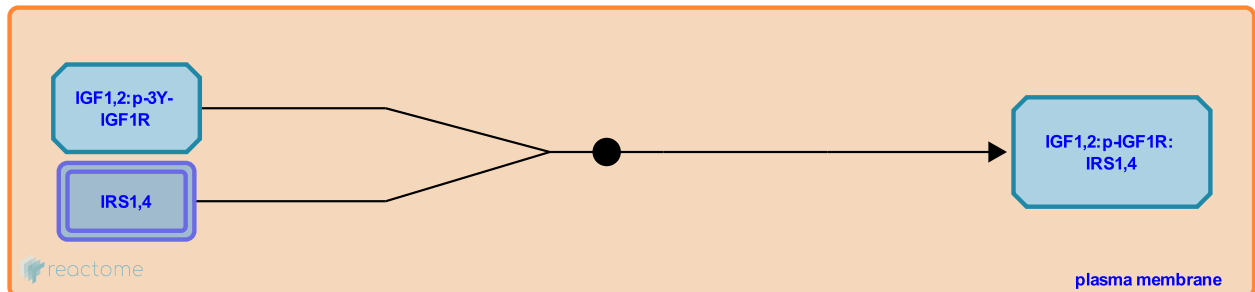
IGF1,2:p-Y1161,1165,1166-IGF1R binds IRS1,4 [↗](#)

Location: [IRS-related events triggered by IGF1R](#)

Stable identifier: R-HSA-2428930

Type: binding

Compartments: plasma membrane



IRS1 binds the NPEY-juxtamembrane motif of phosphorylated IGF1R (Craparo et al. 1995, He et al. 1995, Huang et al. 2001). IRS4 is also involved in signaling by IGF1R and is presumed to bind phosphorylated IGF1R in the same way as IRS1 (Qu et al. 1999, Cuevas et al. 2007). IRS1 and IRS4 are located at the plasma membrane (Karlsson et al. 2004, Fantin et al. 1998).

Followed by: [IGF1,2;p-Y1161,1165,1166-IGF1R phosphorylates IRS1,2,4](#)

Literature references

- Cuevas, EP., Román, ID., Ramirez Rubio, S., Guijarro, LG., Escribano, O., Chiloeches, A. et al. (2007). Role of insulin receptor substrate-4 in IGF-I-stimulated HEPG2 proliferation. *J. Hepatol.*, 46, 1089-98. [↗](#)
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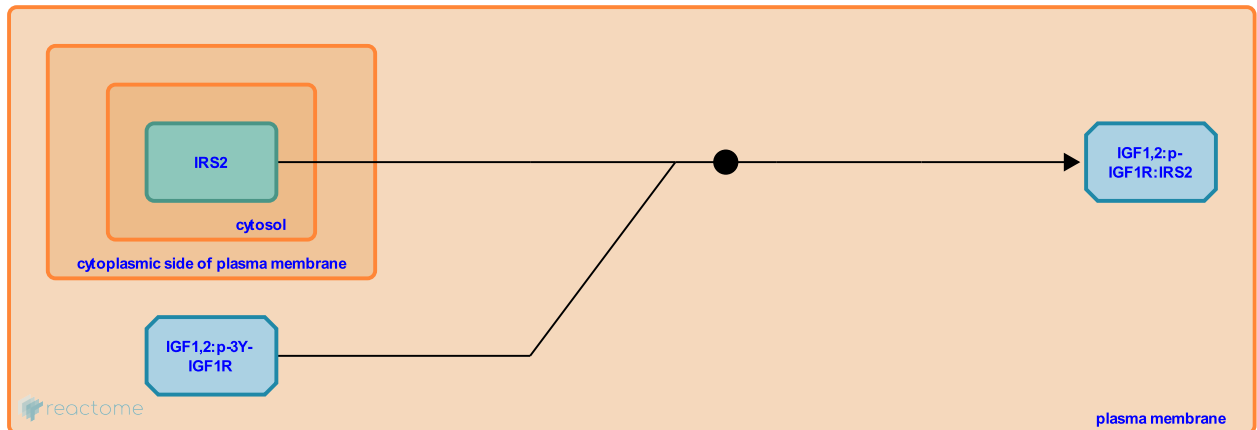
IGF1,2:p-Y1161,1165,1166-IGF1R binds IRS2 [↗](#)

Location: [IRS-related events triggered by IGF1R](#)

Stable identifier: R-HSA-2428922

Type: binding

Compartments: plasma membrane, cytosol



IRS2 binds the NPEY-juxtamembrane motif of phosphorylated IGF1R (He et al. 1996, Kim et al. 1998). IRS2 is cytosolic while IRS1 and IRS4 are located in the plasma membrane.

Followed by: [IGF1,2:p-Y1161,1165,1166-IGF1R phosphorylates IRS1,2,4](#)

Literature references

Feldman, EL., Cheng, HL., Margolis, B., Kim, B. (1998). Insulin receptor substrate 2 and Shc play different roles in insulin-like growth factor I signaling. *J. Biol. Chem.*, 273, 34543-50. [↗](#)

Zhu, Y., O'Neill, TJ., Gustafson, TA., Craparo, A., He, W., Pierce, JH. et al. (1996). Interaction of insulin receptor substrate-2 (IRS-2) with the insulin and insulin-like growth factor I receptors. Evidence for two distinct phosphotyrosine-dependent interaction domains within IRS-2. *J. Biol. Chem.*, 271, 11641-5. [↗](#)

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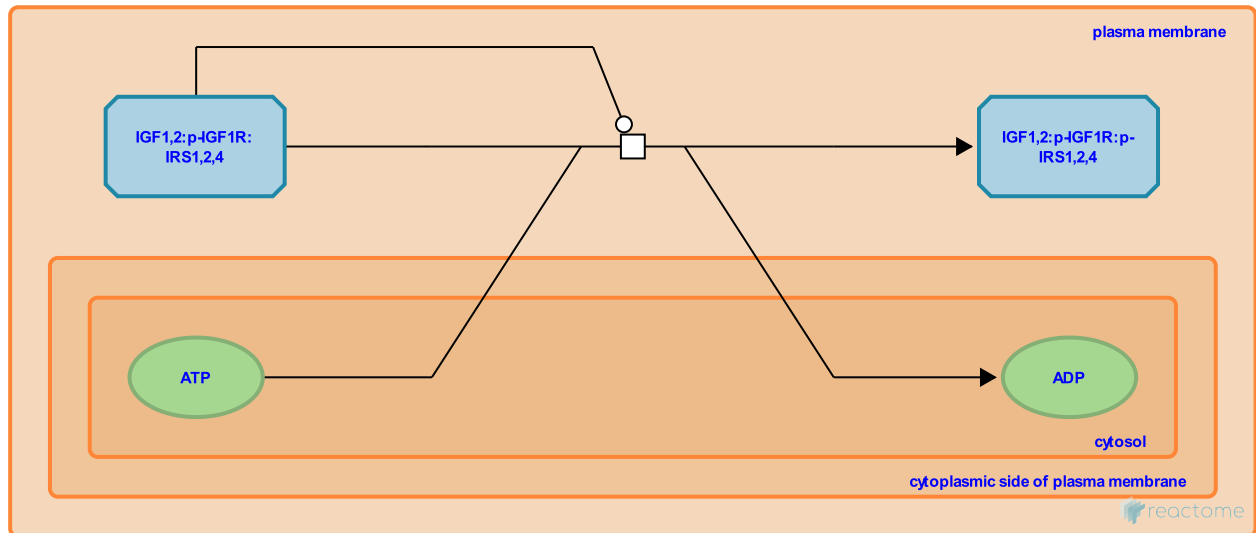
IGF1,2:p-Y1161,1165,1166-IGF1R phosphorylates IRS1,2,4 ↗

Location: IRS-related events triggered by IGF1R

Stable identifier: R-HSA-2428926

Type: transition

Compartments: plasma membrane, cytosol



Phosphorylated IGF1R phosphorylates IRS1 (Siemeister et al. 1995, Xu et al. 1995, Takahashi et al. 1997, Rakatzi et al. 2006), IRS2 (Kim et al. 1998, Kim et al. 2004), and IRS4 (Fantin et al. 1998, Karas et al. 2001, Cuevas et al. 2007) on numerous tyrosine residues. IRS4 is phosphorylated by IGF1R in HEK cells but not in primary muscle cells (Fantin et al. 1998, Schreyer et al. 2003). The phosphotyrosine residues create binding sites for downstream effectors such as GRB2:SOS and PI3K.

Preceded by: IGF1,2:p-Y1161,1165,1166-IGF1R binds IRS2, IGF1,2:p-Y1161,1165,1166-IGF1R binds IRS1,4

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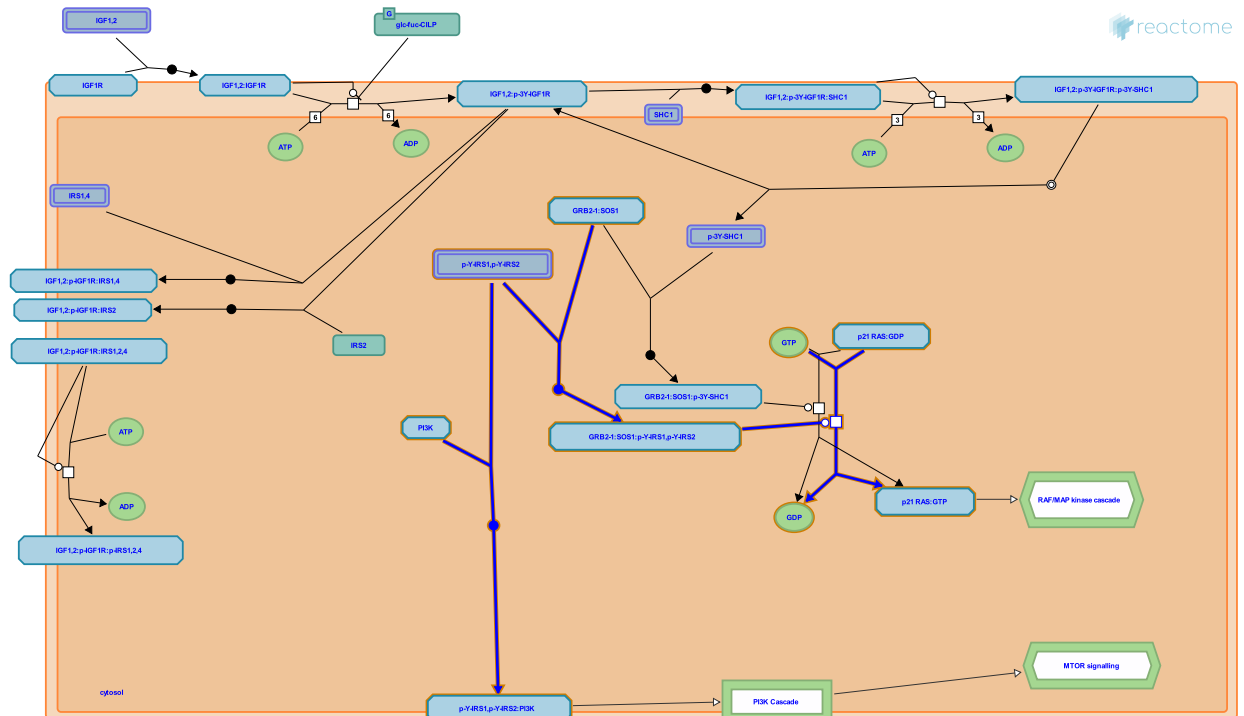
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IRS-mediated signalling ↗

Location: IRS-related events triggered by IGF1R

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.

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