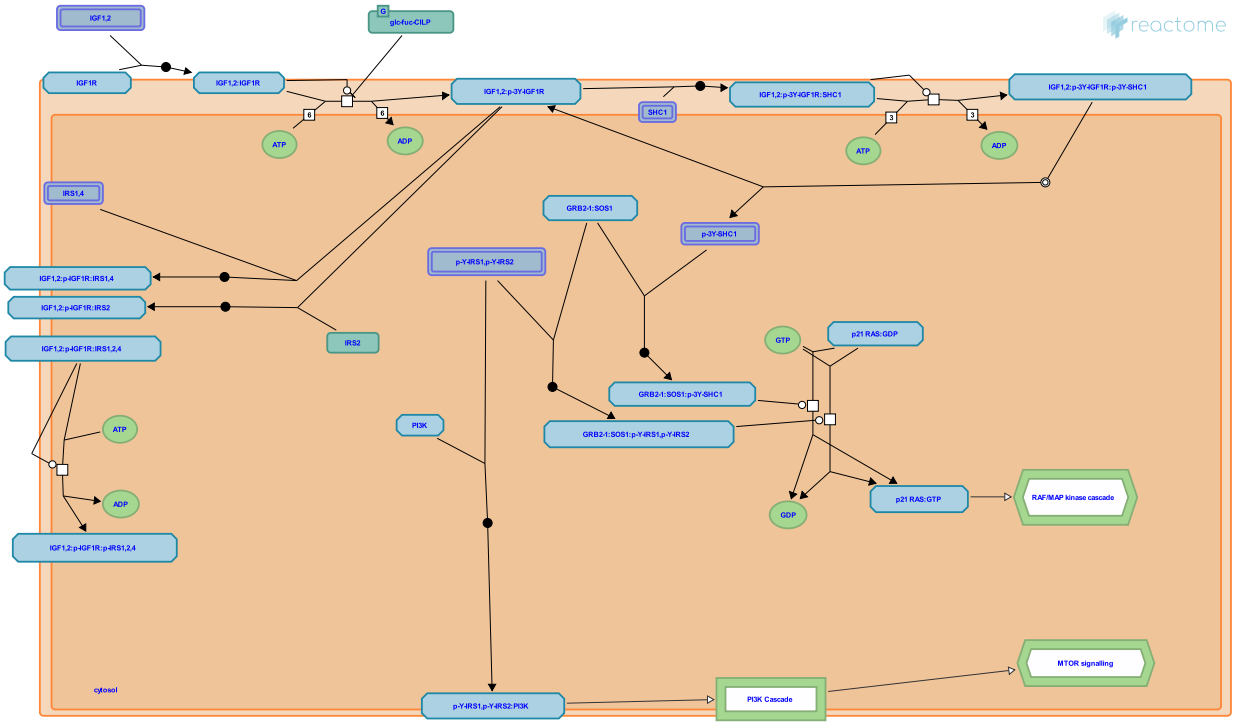
Signaling by Type 1 Insulin-like Growth Factor 1 Receptor (IGF1R)



Holzenberger, M., May, B.

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.

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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. ↗

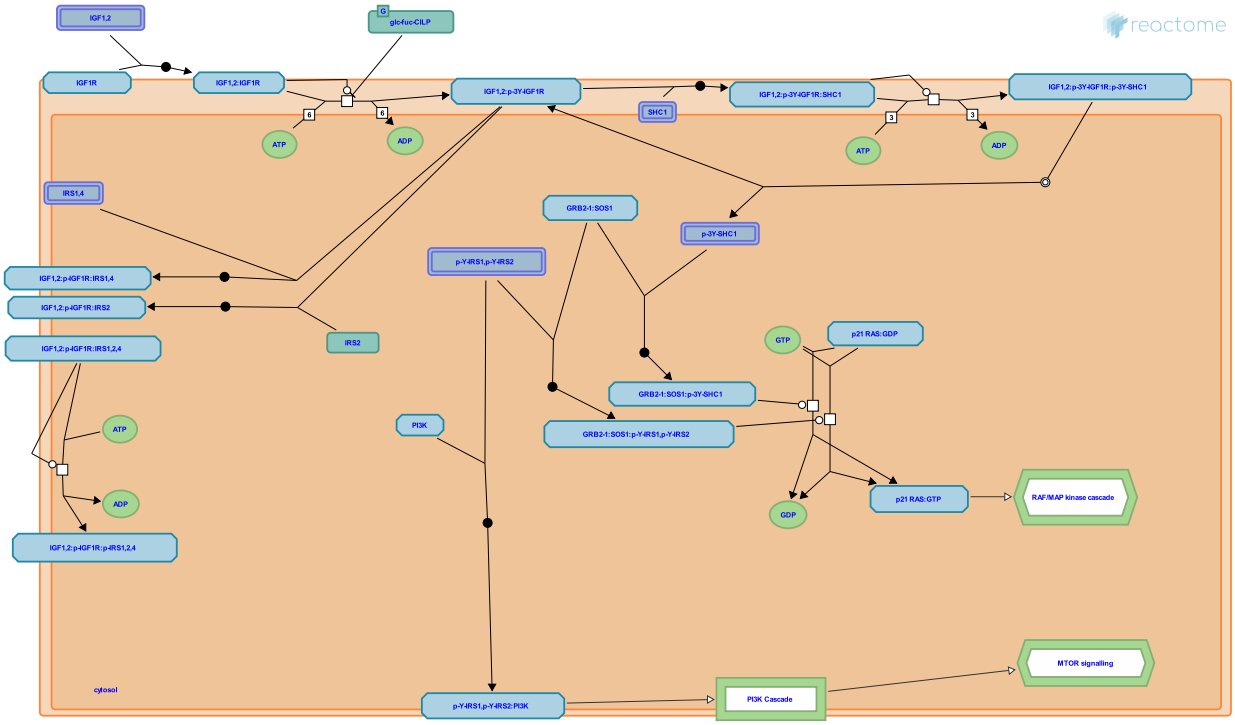
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Signaling by Type 1 Insulin-like Growth Factor 1 Receptor (IGF1R) ↗

Stable identifier: R-HSA-2404192

Compartments: plasma membrane, cytosol, extracellular region



Binding of IGF1 (IGF-I) or IGF2 (IGF-II) to the extracellular alpha peptides of the type 1 insulin-like growth factor receptor (IGF1R) triggers the activation of two major signaling pathways: the SOS-RAS-RAF-MAPK (ERK) pathway and the PI3K-PKB (AKT) pathway (recently reviewed in Pavelic et al. 2007, Chitnis et al. 2008, Maki et al. 2010, Parella et al. 2010, Annunziata et al. 2011, Siddle et al. 2012, Holzenberger 2012).

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. ↗

Longo, VD., Parrella, E. (2010). Insulin/IGF-I and related signaling pathways regulate aging in nondividing cells: from yeast to the mammalian brain. *ScientificWorldJournal, 10*, 161-77. ↗

Maki, RG. (2010). Small is beautiful: insulin-like growth factors and their role in growth, development, and cancer. *J. Clin. Oncol., 28*, 4985-95. ↗

Holzenberger, M. (2011). Igf-I signaling and effects on longevity. *Nestle Nutr Workshop Ser Pediatr Program, 68*, 237-45; discussion 246-9. ↗

Knezević, J., Matijević, T., Pavelić, J. (2007). Biological & physiological aspects of action of insulin-like growth factor peptide family. *Indian J. Med. Res., 125*, 511-22. ↗

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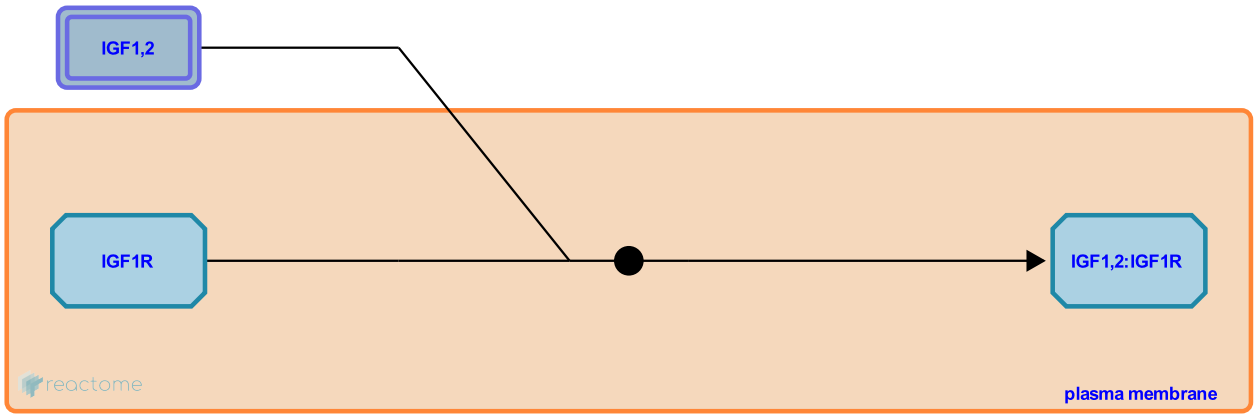
IGF1,2 binds IGF1R ↗

Location: Signaling by Type 1 Insulin-like Growth Factor 1 Receptor (IGF1R)

Stable identifier: R-HSA-2404200

Type: binding

Compartments: plasma membrane, extracellular region



Either IGF1 (IGF-I) or IGF2 (IGF-II) can bind the type 1 insulin-like growth factor receptor (IGF1R) (Casella et al. 1986, LeBon et al. 1986, Maly and Luthi 1986, Cacieri et al. 1988, Steele-Perkins et al. 1988, Burgisser et al. 1991, Germain-Lee et al. 1992, Keyhanfar et al. 2007, Alvino et al. 2009, Alvino et al. 2011). IGF1R has similar affinities for IGF1 and IGF2 (Casella et al. 1986, Steele-Perkins et al. 1988). The binding sites for IGF1 and IGF2 are in a similar location on the alpha peptide of IGF1R but there are some differences in which residues of IGF1R interact with IGF1 vs. IGF2 (Keyhanfar et al. 2007, Alvino et al. 2009, Alvino et al. 2011).

Followed by: IGF1,2:IGF1R autophosphorylates

Literature references

Humbel, RE., Lüthi, C., Weigl, S., Giger, R., Zarn, J., Bürgisser, DM. et al. (1991). Mutants of human insulin-like growth factor II with altered affinities for the type 1 and type 2 insulin-like growth factor receptor. *J. Biol. Chem., 266*, 1029-33. ↗

Forbes, BE., Booker, GW., Whittaker, J., Keyhanfar, M., Wallace, JC. (2007). Precise mapping of an IGF-I-binding site on the IGF-1R. *Biochem. J., 401*, 269-77. ↗

Forbes, BE., Delaine, C., Booker, GW., Whittaker, J., Wallace, JC., Alvino, CL. et al. (2009). A novel approach to identify two distinct receptor binding surfaces of insulin-like growth factor II. *J. Biol. Chem., 284*, 7656-64. ↗

Janicot, M., Lammers, R., Germain-Lee, EL., Ullrich, A., Casella, SJ. (1992). Expression of a type I insulin-like growth factor receptor with low affinity for insulin-like growth factor II. *Biochem. J., 281*, 413-7. ↗

Forbes, BE., Delaine, C., Booker, GW., Wallace, JC., Alvino, CL., Ong, SC. et al. (2011). Understanding the mechanism of insulin and insulin-like growth factor (IGF) receptor activation by IGF-II. *PLoS ONE, 6*, e27488. ↗

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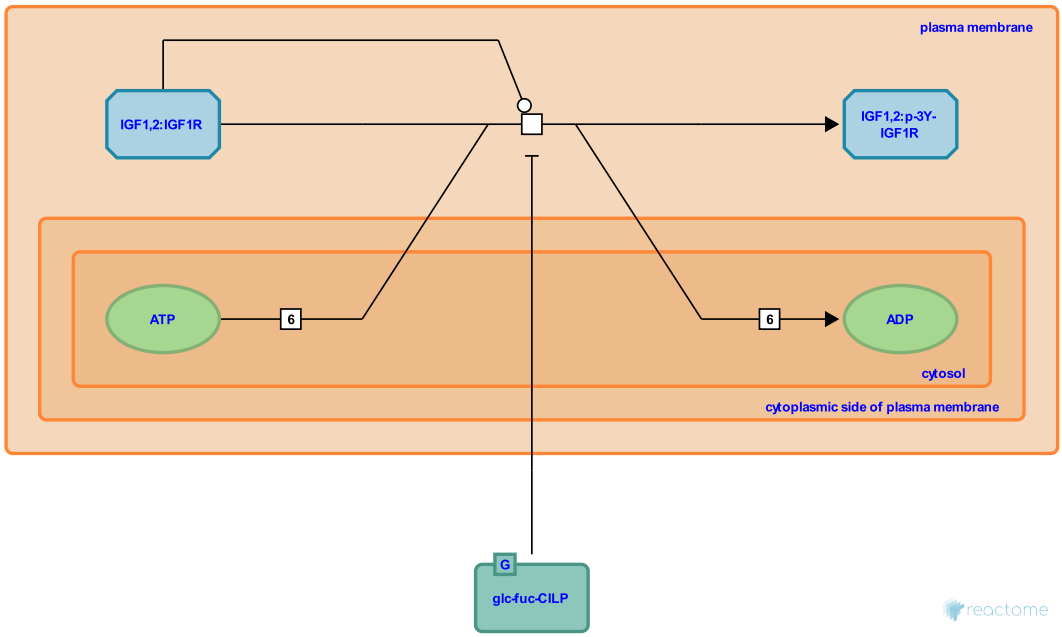
IGF1,2:IGF1R autophosphorylates ↗

Location: Signaling by Type 1 Insulin-like Growth Factor 1 Receptor (IGF1R)

Stable identifier: R-HSA-2404199

Type: transition

Compartments: plasma membrane, cytosol



CILP1 (CILP-1) inhibits ligand-induced autophosphorylation of IGF1R, the IGF-1 receptor (Johnson et al. 2003). CILP1 is expressed in chondrocytes and cultured knee meniscal cartilage cells where it blocks the ability of IGF1 to reduce extracellular pyrophosphate. Expression of CILP1 is commonly enhanced in aging and osteoarthritic cartilage.
The beta peptide of the type 1 insulin-like growth factor (IGF1R) spans the plasma membrane and trans-autophosphorylates tyrosine residues in response to binding of either IGF1 or IGF2 by the extracellular alpha peptide (LeBon et al. 1986, Yu et al. 1986, Doronio et al. 1990, Hernandez-Sanchez et al. 1995, Alvino et al. 2001).

Preceded by: IGF1,2 binds IGF1R

Literature references

Forbes, BE., Delaine, C., Booker, GW., Wallace, JC., Alvino, CL., Ong, SC. et al. (2011). Understanding the mechanism of insulin and insulin-like growth factor (IGF) receptor activation by IGF-II. *PLoS ONE, 6*, e27488. ↗

Yu, KT., Czech, MP., Peters, MA. (1986). Similar control mechanisms regulate the insulin and type I insulin-like growth factor receptor kinases. Affinity-purified insulin-like growth factor I receptor kinase is activated by tyrosine phosphorylation of its beta subunit. *J. Biol. Chem., 261*, 11341-9. ↗

Fujita-Yamaguchi, Y., LeBon, TR., Jacobs, S., Kathuria, S., Cuatrecasas, P. (1986). Purification of insulin-like growth factor I receptor from human placental membranes. *J. Biol. Chem., 261*, 7685-9. ↗

Kalebic, T., Blakesley, V., LeRoith, D., Hernández-Sánchez, C., Helman, L. (1995). The role of the tyrosine kinase domain of the insulin-like growth factor-I receptor in intracellular signaling, cellular proliferation, and tumorigenesis. *J. Biol. Chem., 270*, 29176-81. ↗

Duronio, V. (1990). Insulin receptor is phosphorylated in response to treatment of HepG2 cells with insulin-like growth factor I. *Biochem. J., 270*, 27-32. ↗

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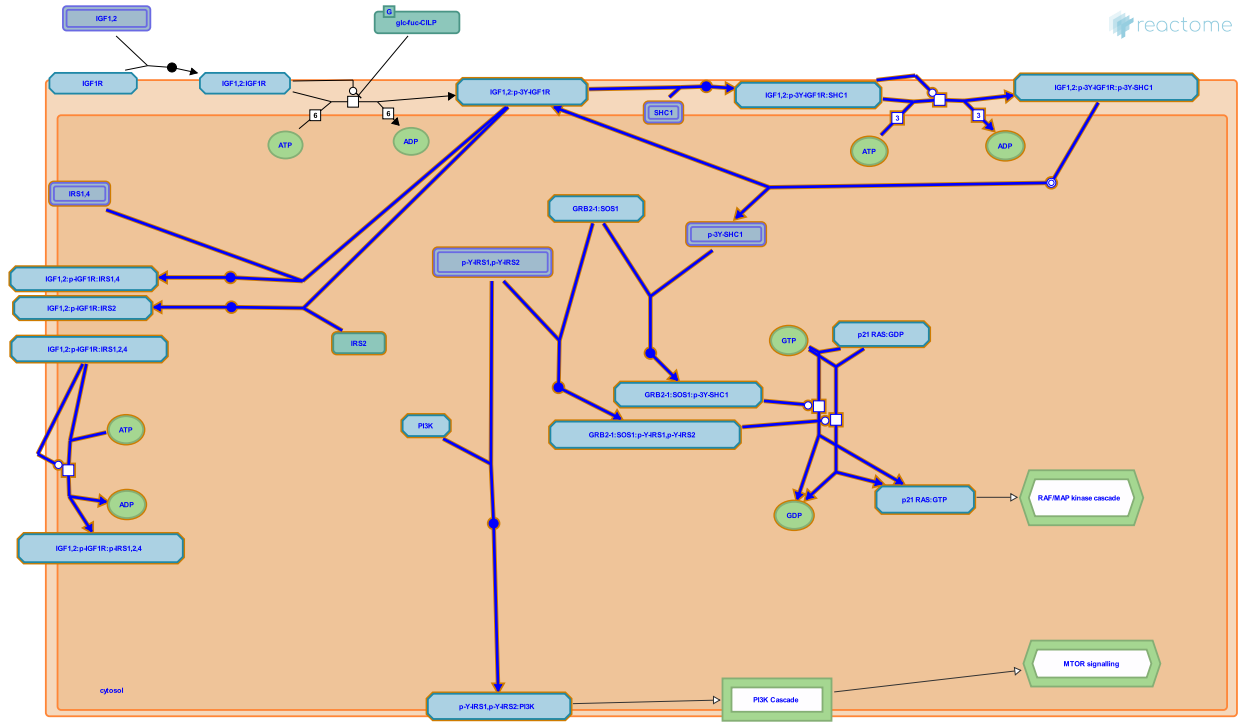
IGF1R signaling cascade ↗

Location: Signaling by Type 1 Insulin-like Growth Factor 1 Receptor (IGF1R)

Stable identifier: R-HSA-2428924

Compartments: plasma membrane, cytosol



After autophosphorylation the type 1 insulin-like growth factor receptor (IGF1R) binds and phosphorylates scaffold proteins, IRS1/2/4 and SHC1, which in turn bind effectors possessing enzymatic activity (recently reviewed in Pavelic et al. 2007, Chitnis et al. 2008, Maki et al. 2010, Parrella et al. 2010, and Siddle et al. 2012). IRS1/2/4 can bind both PI3K (via the p85 subunit of PI3K) and the GRB2:SOS complex. PI3K activates PKB (AKT, AKT1) signaling. GRB:SOS stimulates RAS to exchange GDP for GTP leading to activation of RAF and MAPK.

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. ↗

Longo, VD., Parrella, E. (2010). Insulin/IGF-I and related signaling pathways regulate aging in nondividing cells: from yeast to the mammalian brain. *ScientificWorldJournal, 10*, 161-77. ↗

Maki, RG. (2010). Small is beautiful: insulin-like growth factors and their role in growth, development, and cancer. *J. Clin. Oncol., 28*, 4985-95. ↗

Knezević, J., Matijević, T., Pavelić, J. (2007). Biological & physiological aspects of action of insulin-like growth factor peptide family. *Indian J. Med. Res., 125*, 511-22. ↗

Ghigo, E., Annunziata, M., Granata, R. (2011). The IGF system. *Acta Diabetol, 48*, 1-9. ↗

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