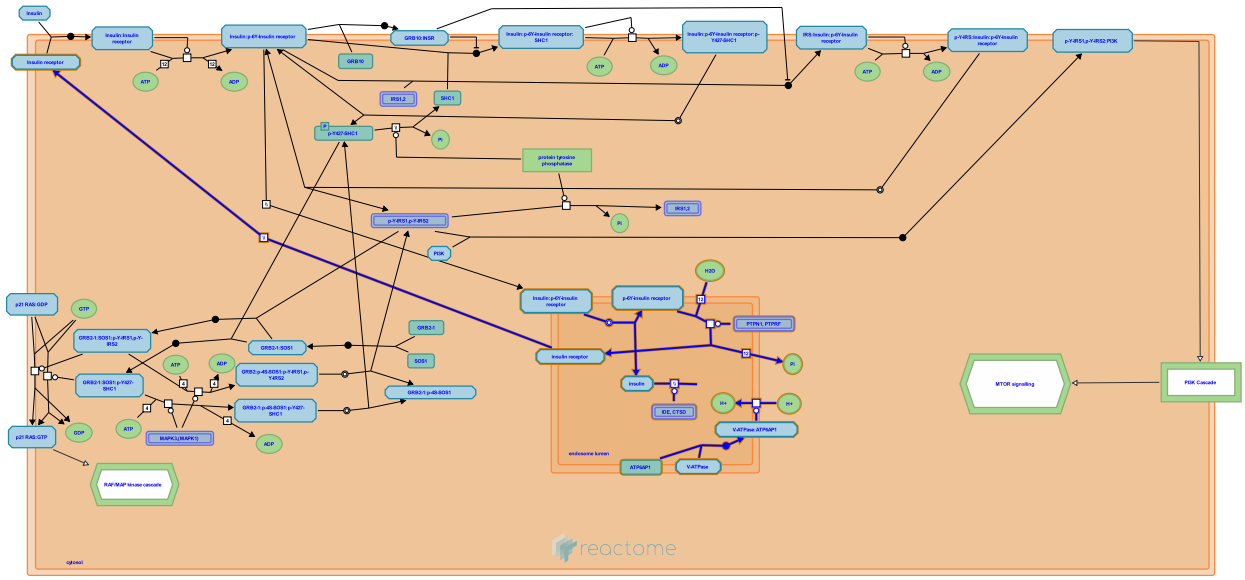
Insulin receptor recycling



Bevan, AP., D'Eustachio, P., He, L., Jassal, B.

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

27/04/2024

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. ↗

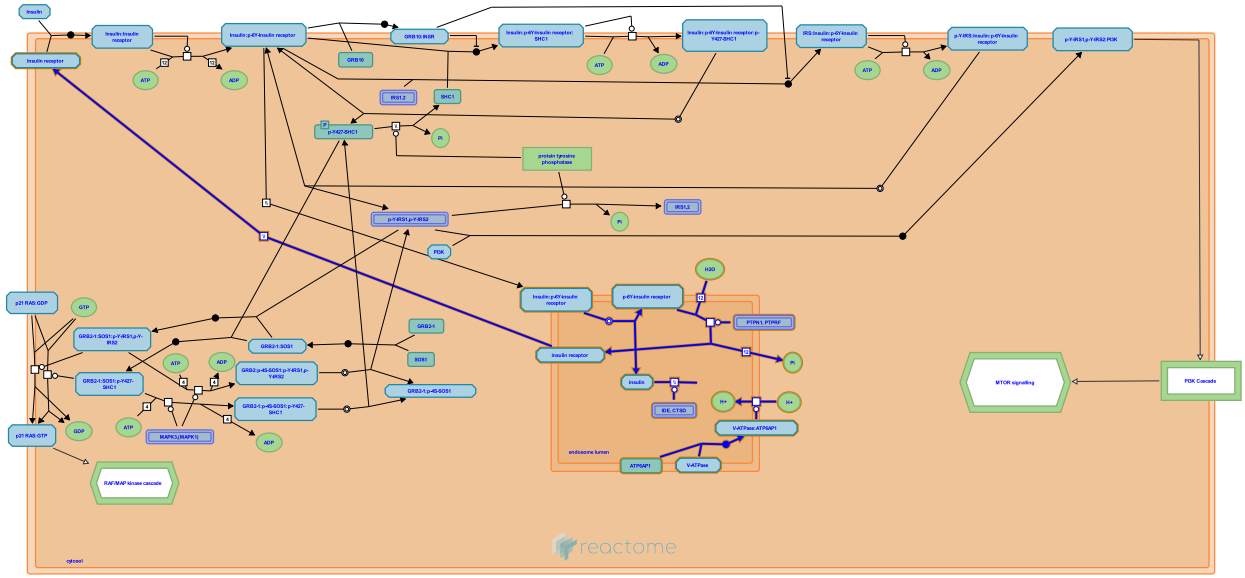
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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 recycling ↗

Stable identifier: R-HSA-77387



Triggered by acidification of the endosome, insulin dissociates from the receptor and is degraded. The receptor is dephosphorylated and re-integrated into the plasma membrane, ready to be activated again by the binding of insulin molecules.

Editions

2003-07-31	Authored	Bevan, AP.

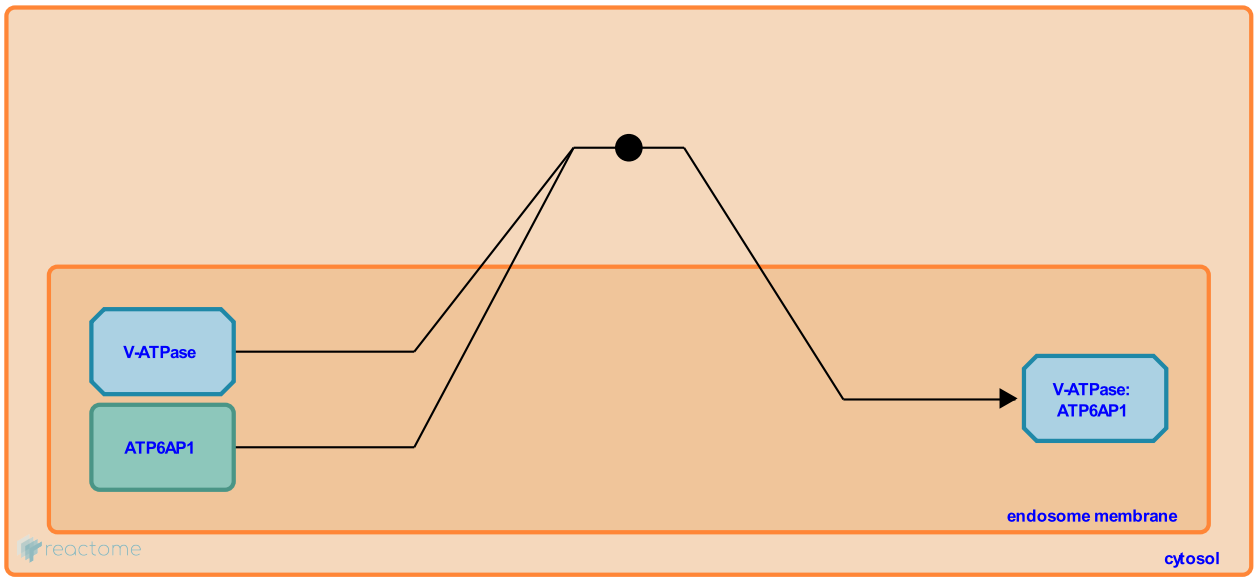
ATP6AP1 binds V-ATPase ↗

Location: Insulin receptor recycling

Stable identifier: R-HSA-5252133

Type: binding

Compartments: cytosol, early endosome membrane



Vacuolar-type H+-ATPases (V-ATPases) are proton pumps that acidify intracellular cargos and deliver protons across the plasma membrane of many specialised cells. V-type proton ATPase subunit S1 (ATP6AP1) is thought to function as an accessory subunit of the V0 subcomplex of V-ATPase, facilitating acidification (Supek et al. 1994). Experiments with the mouse orthologue reveals a role for Atp6ap1 in osteoclast formation and function (Qin et al. 2011).

Followed by: Endosome acidification

Literature references

Lin, Z., Dai, KR., Pavlos, NJ., Cheng, TS., Xu, J., Zheng, MH. et al. (2011). Versatile roles of V-ATPases accessory subunit Ac45 in osteoclast formation and function. *PLoS ONE, 6*, e27155. ↗

Mandiyan, S., Nelson, H., Supek, F., Nelson, N., Supekova, L., Pan, YC. (1994). A novel accessory subunit for vacuolar H(+)-ATPase from chromaffin granules. *J. Biol. Chem., 269*, 24102-6. ↗

Editions

2014-02-05	Authored, Edited	Jassal, B.
2015-02-11	Reviewed	D'Eustachio, P.

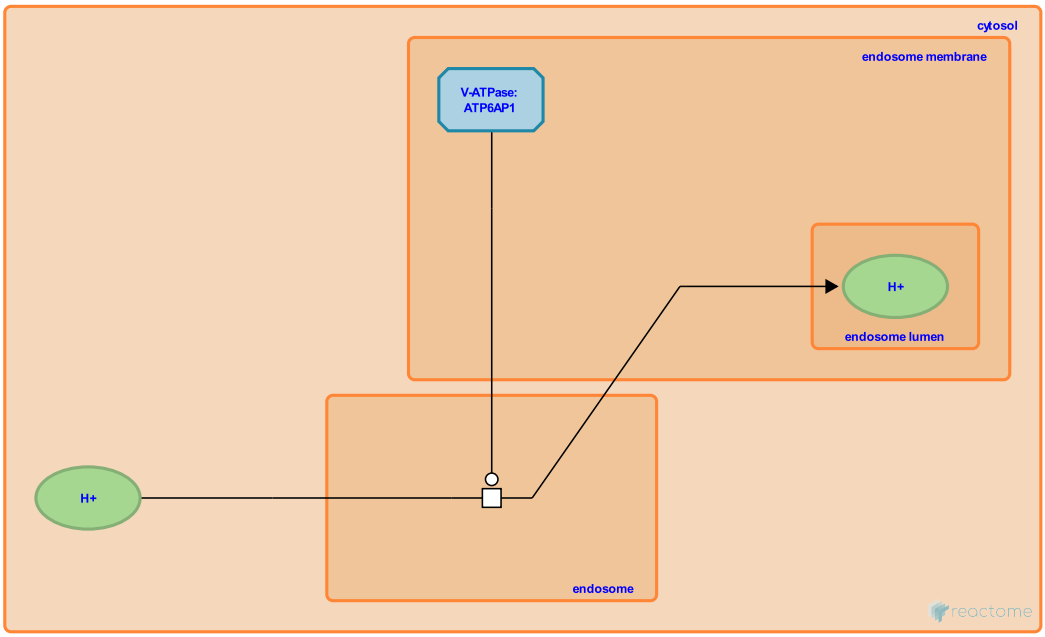
Endosome acidification ↗

Location: Insulin receptor recycling

Stable identifier: R-HSA-74723

Type: transition

Compartments: endosome



The effect of the proton pump is to allow entry of [H+] ions into the lumen of the endosome. The net effect of this is to lower the pH of the lumen from pH 7.4 (the pH at the plasma membrane) to pH 6.0 (documented with studies using FITC-labeled insulin - a pH dependent fluorescence marker).

Preceded by: ATP6AP1 binds V-ATPase

Followed by: Dissociation of insulin from insulin receptor

Literature references

Duckworth, WC., Bennett, RG., Hamel, FG. (1998). Insulin degradation: progress and potential. *Endocr Rev, 19*, 608-24. ↗

Duckworth, WC. (1989). Insulin degradation: mechanisms, products, and significance. *Endocr Rev, 9*, 319-45. ↗

Bergeron, JJ., Authier, F., Posner, BI. (1996). Endosomal proteolysis of internalized proteins. *FEBS Lett, 389*, 55-60. ↗

Editions

2003-07-31	Authored	Bevan, AP.
2010-08-09	Reviewed	He, L.
2010-08-09	Edited	Jassal, B.

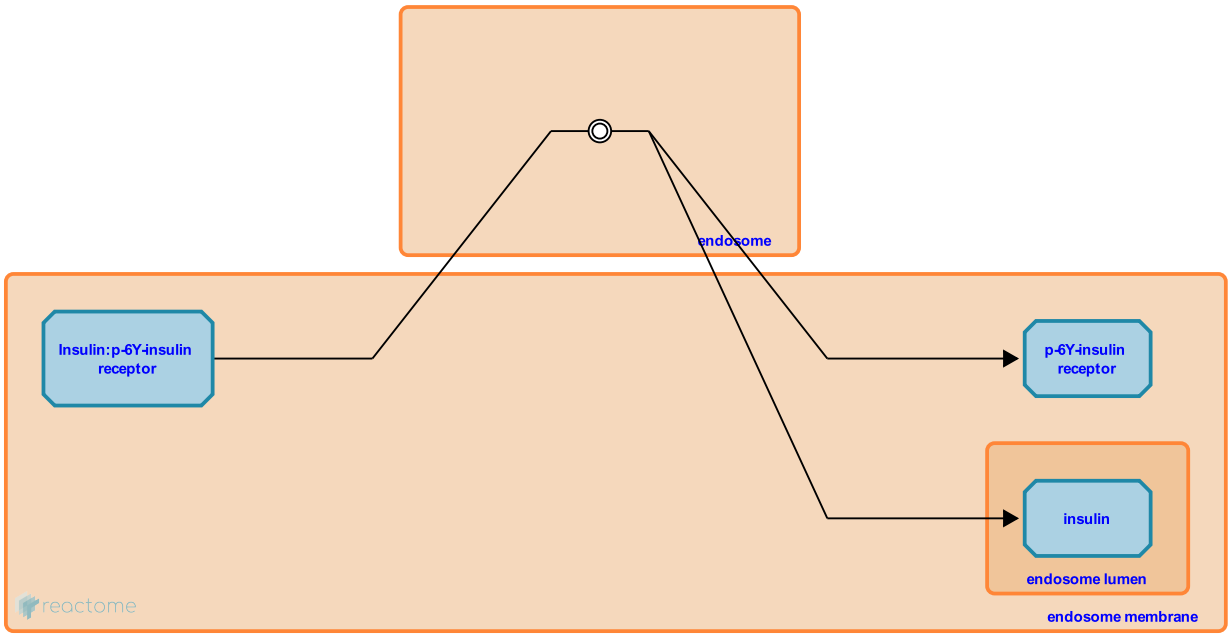
Dissociation of insulin from insulin receptor ↗

Location: Insulin receptor recycling

Stable identifier: R-HSA-74726

Type: dissociation

Compartments: endosome



As the endosomal lumen acidifies the insulin dissociates from the insulin receptor making it available for degradation by the insulin degrading activity (IDA) present in the endosomal membrane.

Preceded by: Endosome acidification

Followed by: Insulin degradation, Insulin receptor de-phosphorylation

Literature references

Duckworth, WC., Bennett, RG., Hamel, FG. (1998). Insulin degradation: progress and potential. *Endocr Rev, 19*, 608-24. ↗

Duckworth, WC. (1989). Insulin degradation: mechanisms, products, and significance. *Endocr Rev, 9*, 319-45. ↗

Bergeron, JJ., Authier, F., Posner, BI. (1996). Endosomal proteolysis of internalized proteins. *FEBS Lett, 389*, 55-60. ↗

Editions

2003-07-31	Authored	Bevan, AP.

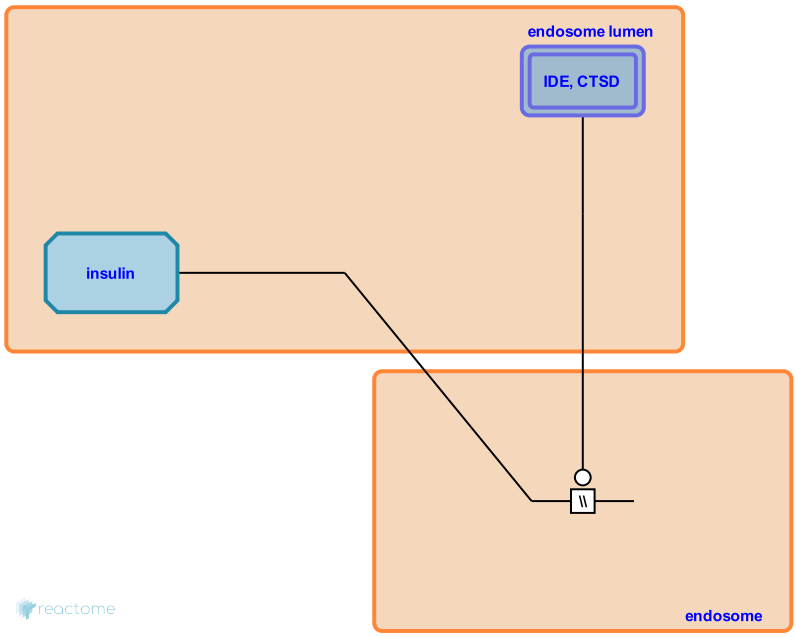
Insulin degradation ↗

Location: Insulin receptor recycling

Stable identifier: R-HSA-74730

Type: omitted

Compartments: endosome



IDE dimer in the endosome lumen catalyzes the processive degradation of insulin into multiple inactive fragments (Manolopoulou et al. 2009; Zhang et al. 2018) Insulin released into the endosome is rapidly degraded.

Two enzymes known to be present in liver parenchymal cells, insulin-degrading enzyme (IDE) and cathepsin D (CTSD) degrade insulin efficiently in vitro, and both are annotated as candidate catalysts of this reaction. The identity of the enzyme or enzymes mediating this degradation in vivo remains controversial, however. By a variety of immunological and enzymological criteria, catalytically active material from rat liver fractions exhibited properties distinct from those expected for insulin-degrading enzyme (IDE) (Authier et al. 1994), indistinguishable from those expected for cathepsin D (CTSD), and sufficient to account for the insulin-degrading activity in these fractions (Authier et al. 2002). Nevertheless, IDE deficiency in vivo is associated with abnormal insulin turnover, IDE is present at low levels in endosomes and biochemical studies indicate that IDE efficiently degrades insulin (Shen et al. 2006; Manopoulou et al. 2009; Zhang et al. 2018).

The active form of IDE is a dimer with one Zn++ bound to each protein subunit (Li et al. 2006).

Preceded by: Dissociation of insulin from insulin receptor

Literature references

Posner, BI., Bergeron, JJ., Rachubinski, RA., Authier, F. (1994). Endosomal proteolysis of insulin by an acidic thiol metalloprotease unrelated to insulin degrading enzyme. *J Biol Chem, 269*, 3010-6. ↗

Fabrega, S., Métioui, M., Authier, F., Briand, G., Kouach, M. (2002). Endosomal proteolysis of internalized insulin at the C-terminal region of the B chain by cathepsin D. *J Biol Chem, 277*, 9437-46. ↗

Tang, WJ., Kuo, WL., Rosner, MR., Li, P., Yousef, M. (2006). The C-terminal domain of human insulin degrading enzyme is required for dimerization and substrate recognition. *Biochem Biophys Res Commun, 343*, 1032-7. ↗

Manolopoulou, M., Tang, WJ., Schilling, AB., Guo, Q., Malito, E. (2009). Molecular basis of catalytic chamber-assisted unfolding and cleavage of human insulin by human insulin-degrading enzyme. *J Biol Chem, 284*, 14177-88. ↗

Tang, WJ., Rosner, MR., Joachimiak, A., Shen, Y. (2006). Structures of human insulin-degrading enzyme reveal a new substrate recognition mechanism. *Nature, 443*, 870-4. ↗

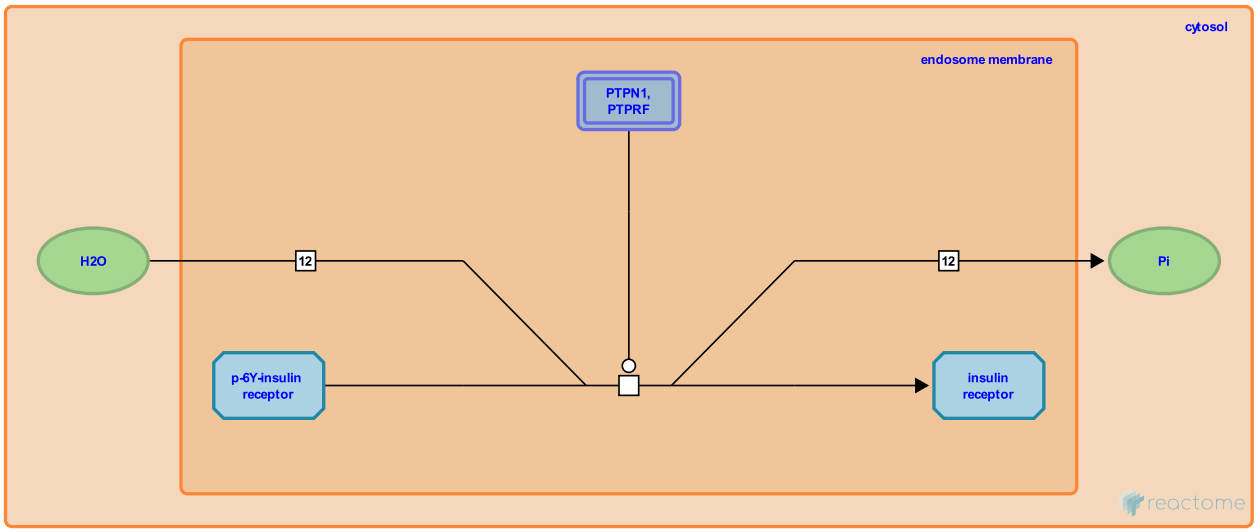
Insulin receptor de-phosphorylation ↗

Location: Insulin receptor recycling

Stable identifier: R-HSA-74733

Type: transition

Compartments: endosome membrane, cytosol



Endosomal protein tyrosine phosphatases (PTPs) dephosphorylate the insulin receptor, which cannot rephosphorylate itself as insulin is removed leaving the receptor in its inactive conformation (Bevan et al. 1996; Drake & Posner 1998). The identity of these PTPs is not definitively established, but structural studies and studies of cell lines and gene-knockout mice indicate that PTPRF / LAR (Ahmed & Goldstein 1997) and PTPN1 / PTP1B (Li et al. 2005) are each capable of mediating this reaction.

The dephosphorylated receptor recycles to the plasma membrane.

Preceded by: Dissociation of insulin from insulin receptor

Followed by: Re-integration of insulin receptor into plasma membrane

Literature references

Ahmad, F., Goldstein, BJ. (1997). Functional association between the insulin receptor and the transmembrane protein-tyrosine phosphatase LAR in intact cells. *J Biol Chem, 272*, 448-57. ↗

Depetris, RS., Hubbard, SR., Li, S., Barford, D., Chernoff, J. (2005). Crystal structure of a complex between protein tyrosine phosphatase 1B and the insulin receptor tyrosine kinase. *Structure, 13*, 1643-51. ↗

Drake, PG., Posner, BI. (1999). Insulin receptor-associated protein tyrosine phosphatase(s): role in insulin action. *Mol Cell Biochem, 182*, 79-89. ↗

Bevan, AP., Drake, PG., Bergeron, JJ., Posner, BI. (1996). Intracellular Signal Transduction: The Role of Endosomes. *Trends in Endocrinology and Metabolism, 7*, 13-21. ↗

Editions

2003-07-31	Authored	Bevan, AP.

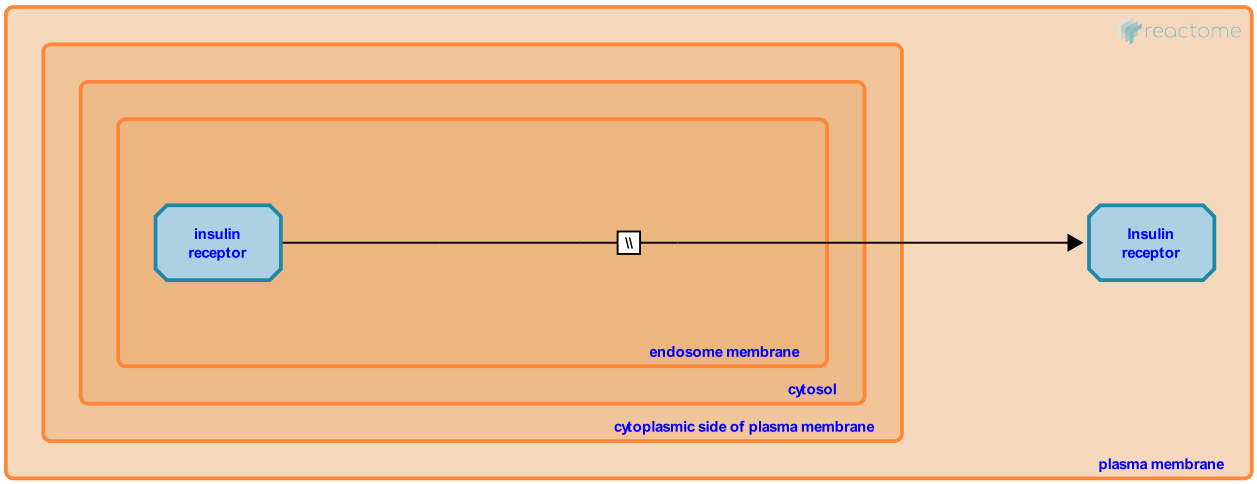
Re-integration of insulin receptor into plasma membrane ↗

Location: Insulin receptor recycling

Stable identifier: R-HSA-74734

Type: omitted

Compartments: endosome membrane, plasma membrane



The endosome fuses with the plasma membrane allowing the insulin receptor to re-integrate there. Any degraded insulin remnants which remained in the endosome are also expelled (The majority having been excreted into the cytoplasm and secreted out of the cell via other mechanisms).

The cycle is complete with the dephosphorylated receptor now back in the plasma membrane available to bind the next insulin molecule presented to it. There is some insulin receptor degradation over time when damaged insulin receptors are not recycled but fuse instead with the lysosomes where they are degraded. However the majority of insulin receptors are recycled back to the plasma membrane with greater than 95% efficiency.

Preceded by: Insulin receptor de-phosphorylation

Literature references

Cruz, J., Khan, MN., Bergeron, JJ., Posner, BI. (1985). Uptake of insulin and other ligands into receptor-rich endocytic components of target cells: the endosomal apparatus. *Annu Rev Physiol, 47*, 383-403. ↗

Editions

2003-07-31	Authored	Bevan, AP.

Table of Contents