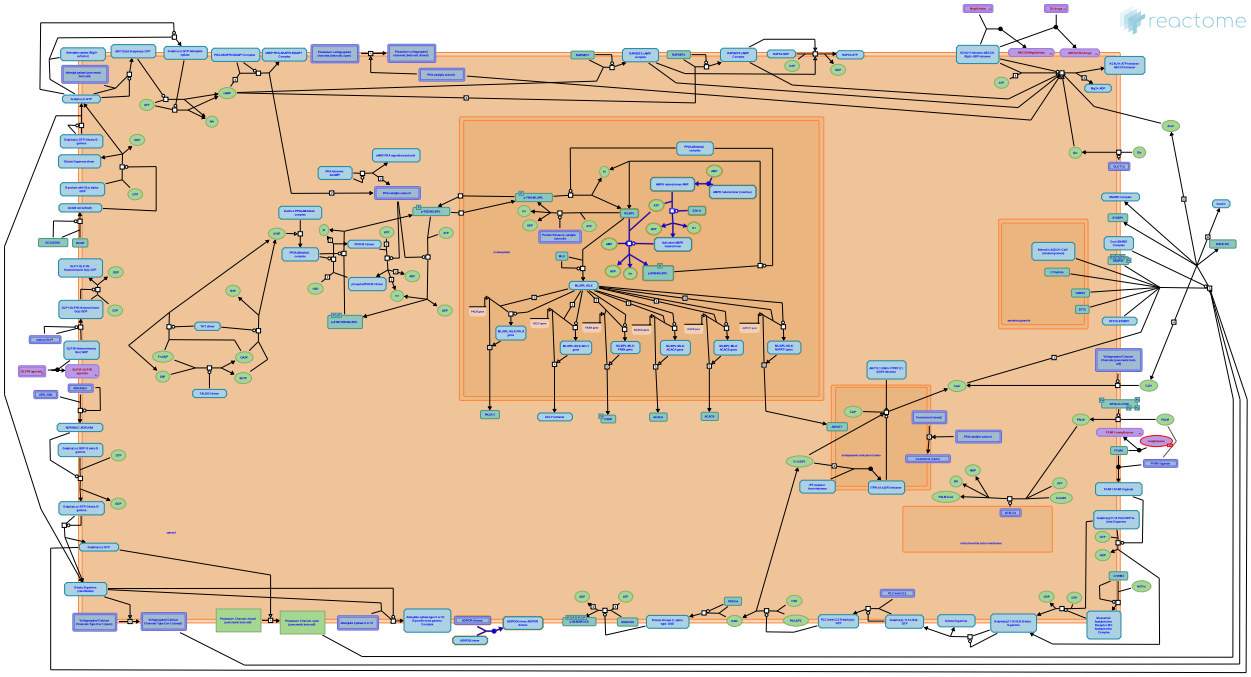
AMPK inhibits chREBP transcriptional activation activity



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30/09/2024

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. ↗

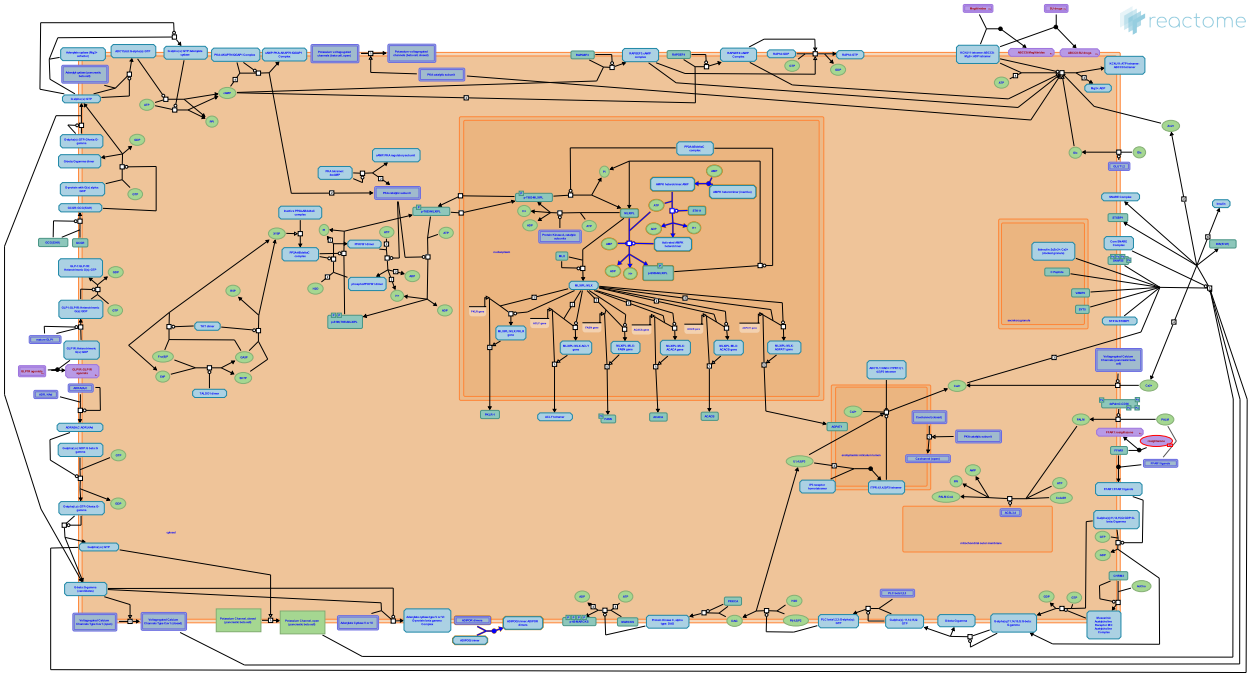
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

AMPK inhibits chREBP transcriptional activation activity ↗

Stable identifier: R-HSA-163680

Compartments: nucleoplasm



AMP-activated protein kinase (AMPK) is a sensor of cellular energy levels. A high cellular ratio of AMP:ATP triggers the phosphorylation and activation of AMPK. Activated AMPK in turn phosphorylates a wide array of target proteins, as shown in the figure below (reproduced from (Hardie et al. 2003), with the permission of D.G. Hardie). These targets include ChREBP (Carbohydrate Response Element Binding Protein), whose inactivation by phosphorylation reduces transcription of key enzymes of the glycolytic and lipogenic pathways.

Literature references

Hudson, ER., Scott, JW., Pan, DA., Hardie, DG. (2003). Management of cellular energy by the AMP-activated protein kinase system. *FEBS Lett, 546*, 113-20. ↗

Uyeda, K., Osatomi, K., Yamashita, H., Kabashima, T., Kawaguchi, T. (2002). Mechanism for fatty acid sparing effect on glucose-induced transcription: regulation of carbohydrate-responsive element-binding protein by AMP-activated protein kinase. *J Biol Chem, 277*, 3829-35. ↗

Hardie, DG. (2004). The AMP-activated protein kinase pathway--new players upstream and downstream. *J Cell Sci, 117*, 5479-87. ↗

Carling, D., Davies, SP., Salt, IP., Cheung, PC., Hardie, DG. (2000). Characterization of AMP-activated protein kinase gamma-subunit isoforms and their role in AMP binding. *Biochem J, 346*, 659-69. ↗

Editions

2005-05-13	Authored	Gopinathrao, G.

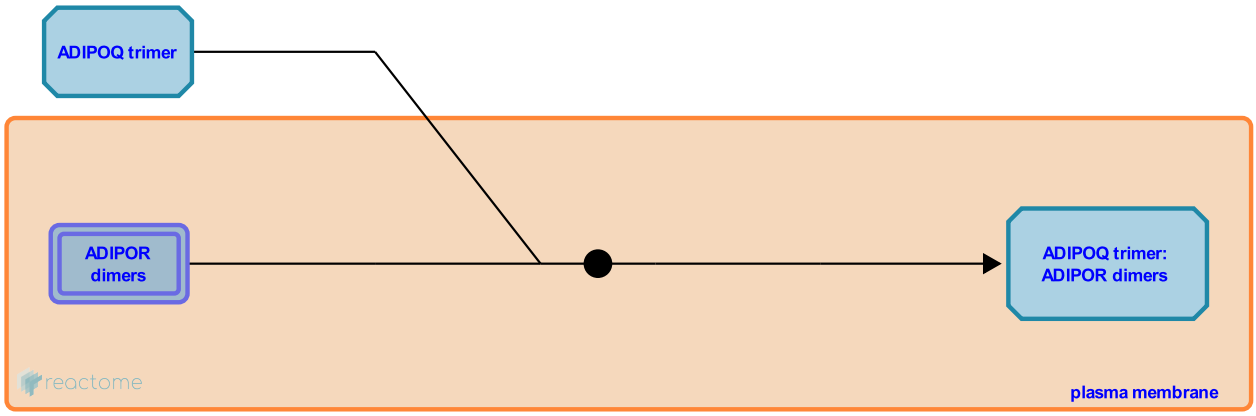
ADIPOQ trimer binds ADIPOR dimers ↗

Location: AMPK inhibits chREBP transcriptional activation activity

Stable identifier: R-HSA-8848663

Type: binding

Compartments: plasma membrane, extracellular region



Adipokines are a group of over 600 bioactive molecules produced by adipose tissue that acts as paracrine and endocrine hormones. These molecules are important in the regulation of diverse processes including appetite control, fat distribution, inflammation, blood pressure, hemostasis and endothelial function. Adipokines may present anti and proinflammatory effects. Cardiovascular diseases (CVDs) can be one of the most important causes of death in diabetics and diabetes can in turn increase the risk of cardiovascular events. Obesity is a chronic condition. It is associated with overproduction of inflammatory adipokines by adipose tissue, which may link obesity to CVD and diabetes (Freitas Lima et al. 2015).

Adiponectin (ADIPOQ, also known as 30-kDa adipocyte complement-related protein ACRP30) is an adipocyte-derived hormone that acts as an antidiabetic and anti-atherogenic adipokine. ADIPOQ blood levels are decreased under conditions of obesity, insulin resistance and type 2 diabetes. ADIPOQ can form a wide range of multimers from trimers to high molecular weight (HMW) multimers (Waki et al. 2003). The trimeric form is shown here. Through binding adiponectin receptor proteins 1 and 2 (ADIPOR1 and 2), ADIPOQ trimer stimulates AMPK phosphorylation and activation in the liver and the skeletal muscle, enhancing glucose and fatty-acid utilisation. ADIPOR1 is abundantly expressed in skeletal muscle, whereas ADIPOR2 is predominantly expressed in the liver (Yamauchi et al. 2003). ADIPORs are thought to function as homo- or hetero-multimers. For simplicity, the combinations annotated here are shown as homodimers. Although ADIPOR1 and 2 are predicted to contain seven transmembrane domains, they are structurally, topologically and functionally distinct from GPCRs.

Literature references

Kamon, J., Yamauchi, T., Waki, H., Ito, Y., Nagai, R., Kita, S. et al. (2003). Impaired multimerization of human adiponectin mutants associated with diabetes. Molecular structure and multimer formation of adiponectin. *J. Biol. Chem., 278*, 40352-63. ↗

Kamon, J., Tsuchida, A., Ohteki, T., Tsuno, NH., Yamauchi, T., Waki, H. et al. (2003). Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. *Nature, 423*, 762-9. ↗

Braga, VA., Sousa Santos, SH., Cruz, JC., Balarini, CM., Freitas Lima, LC., de Oliveira Monteiro, MM. et al. (2015). Adipokines, diabetes and atherosclerosis: an inflammatory association. *Front Physiol, 6*, 304. ↗

Editions

2015-12-10	Authored, Edited	Jassal, B.
2016-04-05	Reviewed	D'Eustachio, P.

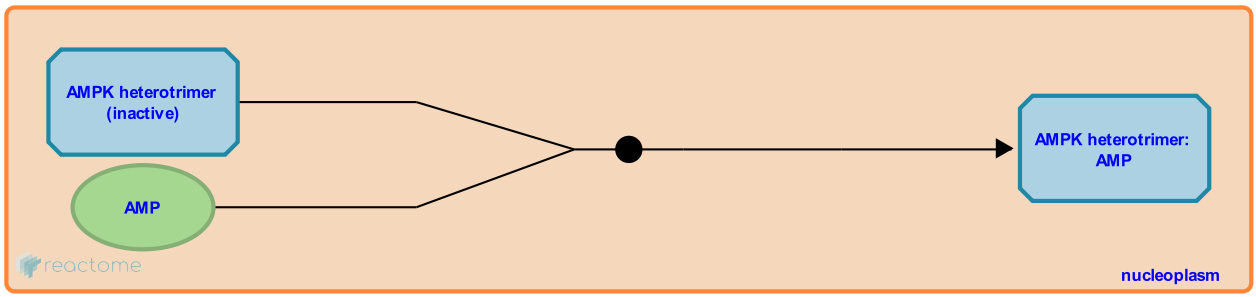
AMP binds to gamma subunit of AMP kinase heterotrimer ↗

Location: AMPK inhibits chREBP transcriptional activation activity

Stable identifier: R-HSA-163664

Type: binding

Compartments: nucleoplasm



At the beginning of this reaction, 1 molecule of 'AMPK heterotrimer (inactive)', and 1 molecule of 'AMP' are present. At the end of this reaction, 1 molecule of 'AMPK heterotrimer:AMP' is present.

This reaction takes place in the 'nucleus'.

Followed by: LKB1 phosphorylates the alpha subunit of AMPK heterotrimer

Literature references

Carling, D., Davies, SP., Salt, IP., Cheung, PC., Hardie, DG. (2000). Characterization of AMP-activated protein kinase gamma-subunit isoforms and their role in AMP binding. *Biochem J, 346*, 659-69. ↗

LKB1 phosphorylates the alpha subunit of AMPK heterotrimer ↗

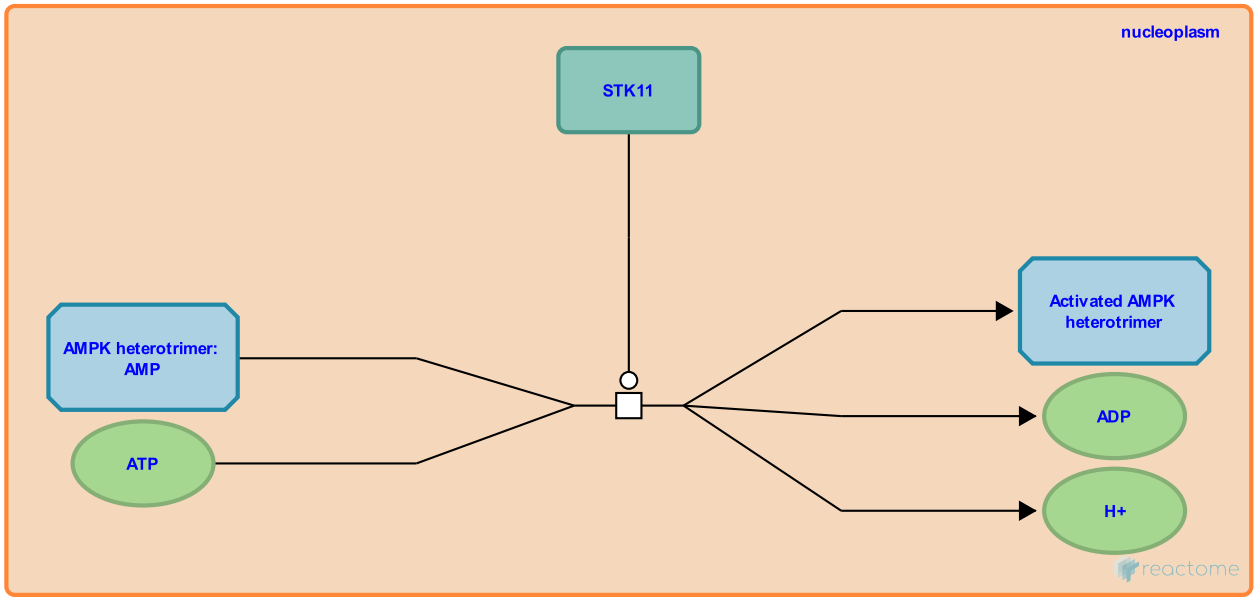
Location: AMPK inhibits chREBP transcriptional activation activity

Stable identifier: R-HSA-164151

Type: transition

Compartments: nucleoplasm

Inferred from: rLkb-1 (Stk-11) activates AMPK by phosphorylation (Rattus norvegicus)



LKB1 phosphorylates threonine residue 172 of the alpha subunit of the AMPK heterotrimer, activating it. LKB1, a serine/threonine kinase, was first identified as the gene whose mutation is associated with the Peutz-Jeghers familial cancer syndrome. This disease phenotype is consistent with the hypothesis that the interaction between LKB1 and AMPK normally plays a key role in the negative regulation of cell growth (Hardie 2004).

Preceded by: AMP binds to gamma subunit of AMP kinase heterotrimer

Followed by: Phosphorylation of ChREBP at Serine 556 by AMPK

Editions

2005-05-13	Authored	Gopinathrao, G.
2024-02-12	Reviewed	Hill, DP.

Phosphorylation of ChREBP at Serine 556 by AMPK ↗

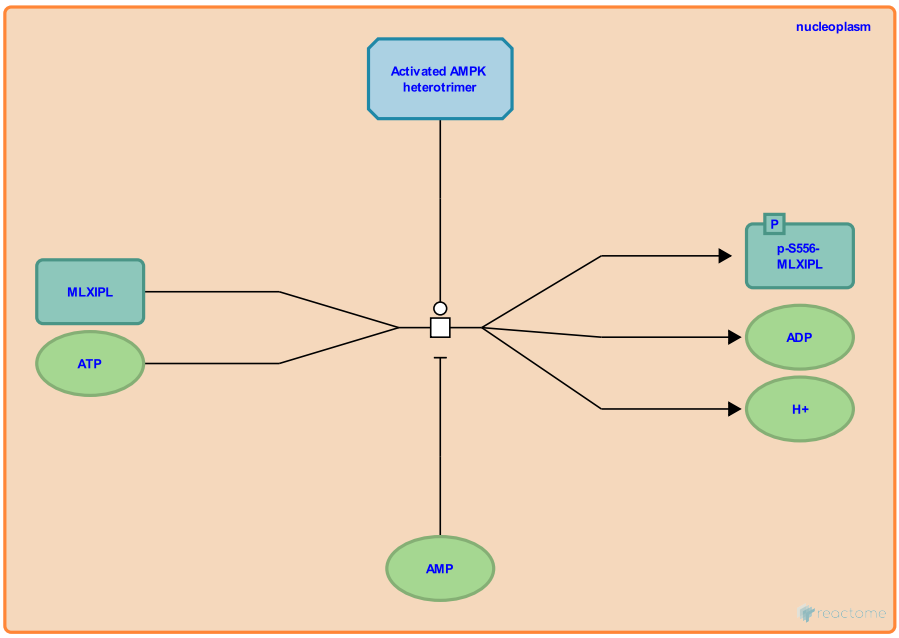
Location: AMPK inhibits chREBP transcriptional activation activity

Stable identifier: R-HSA-163691

Type: transition

Compartments: nucleoplasm

Inferred from: Phosphorylation of rChREBP(Ser 568) by rAMPK (Rattus norvegicus)



In the nucleus, activated AMPK phosphorylates serine residue 556 of ChREBP (Carbohydrate Response Element Binding Protein). Phosphorylated ChREBP does not bind to ChRE chromosomal DNA sequence elements and thus loses its ability to promote transcription of genes involved in glycolysis and lipogenesis.

Preceded by: LKB1 phosphorylates the alpha subunit of AMPK heterotrimer

Editions

2005-05-13	Authored	Gopinathrao, G.
2024-02-13	Reviewed	Hill, DP.
2024-03-04	Reviewed	D'Eustachio, P.

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