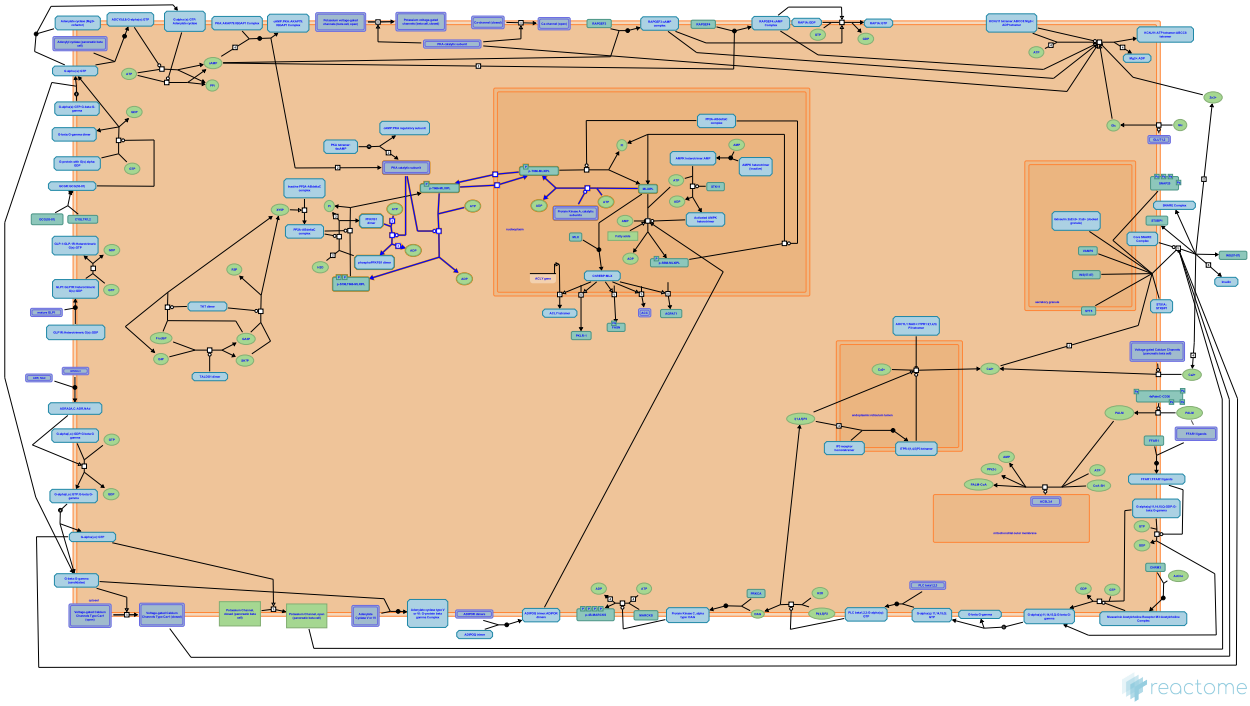
# PKA-mediated phosphorylation of key metabolic factors



Gopinathrao, G.

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



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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.

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. ↗

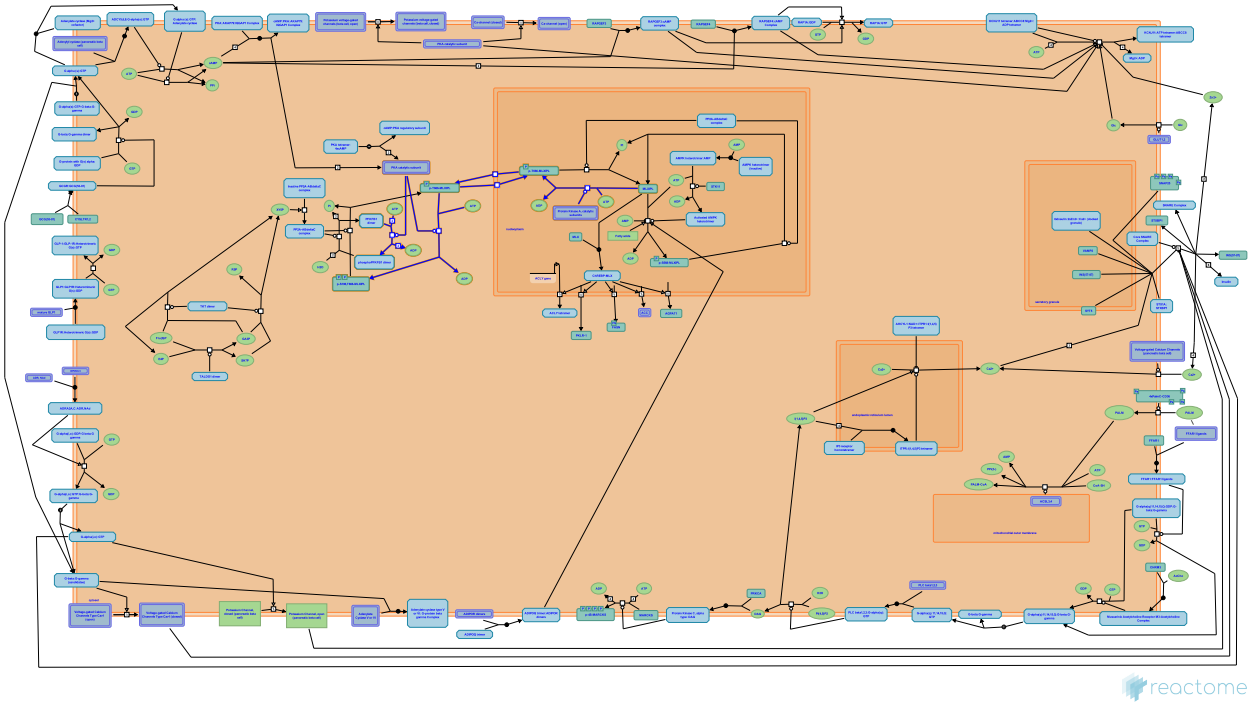
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

## PKA-mediated phosphorylation of key metabolic factors ↗

**Stable identifier:** R-HSA-163358

**Compartments:** nucleoplasm, cytosol



Upon dissociation of protein kinase A (PKA) tetramers in the presence of cAMP, the released PKA catalytic monomers phosphorylate specific serine and threonine residues of several metabolic enzymes. These target enzymes include glycogen phosphorylase kinase, glycogen synthase and PF2K-Pase. PKA also phosphorylates ChREBP (Carbohydrate Response Element Binding Protein), preventing its movement into the nucleus and thus its function as a positive transcription factor for genes involved in glycolytic and lipogenic reactions.

## Literature references


Veech, RL. (2003). A humble hexose monophosphate pathway metabolite regulates short- and long-term control of lipogenesis. *Proc Natl Acad Sci U S A, 100*, 5578-80. ↗


## Editions

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| 2005-05-13 | Authored | Gopinathrao, G. |

## Phosphorylation of ChREBP at Thr(666) by PKA ↗

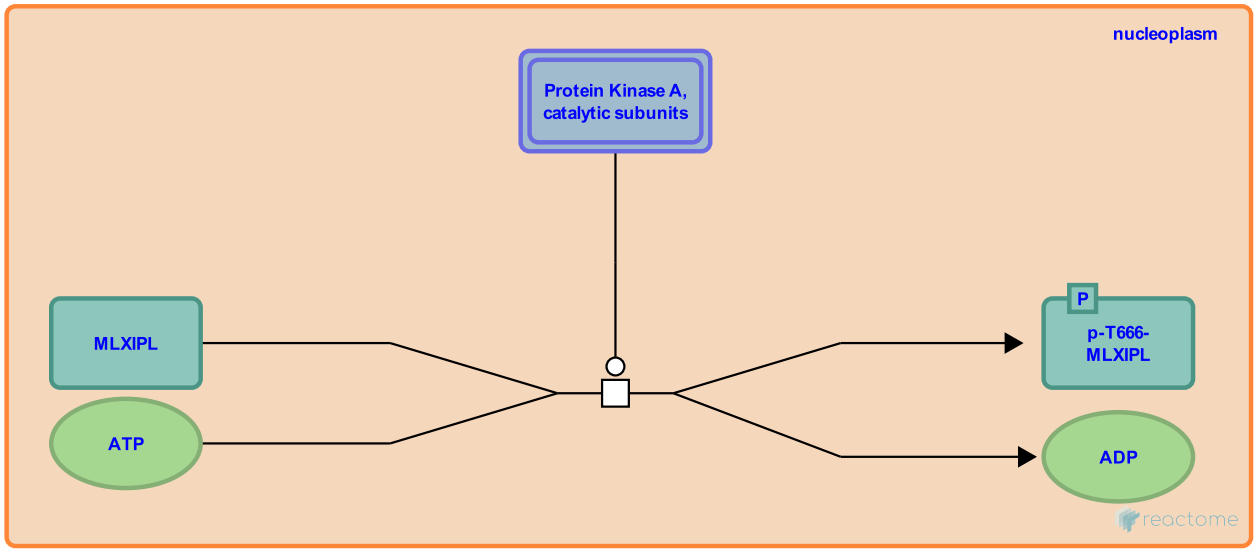
**Location:** PKA-mediated phosphorylation of key metabolic factors

**Stable identifier:** R-HSA-163672

**Type:** transition

**Compartments:** nucleoplasm

**Inferred from:** Phosphorylation of mChREBP at Thr (666) residue by mPKA (Mus musculus)




In its active (unphosphorylated) form, ChREBP (Carbohydrate Response Element Binding Protein) binds so-called ChRE (Carbohydrate Response Element) DNA sequence motifs found upstream of several genes involved in glucose utilization and lipid synthesis, activating transcription of these genes. Phosphorylation of ChREBP at threonine residue 666 by PKA (protein kinase A) blocks this binding activity, and thus has the effect of down-regulating expression of the target genes. ChREBP phosphorylation can be reversed by the action of protein phosphatase 2A (PP2A).

**Followed by:** PhosphoChREBP (Thr 666) is exported to cytosol

### Editions

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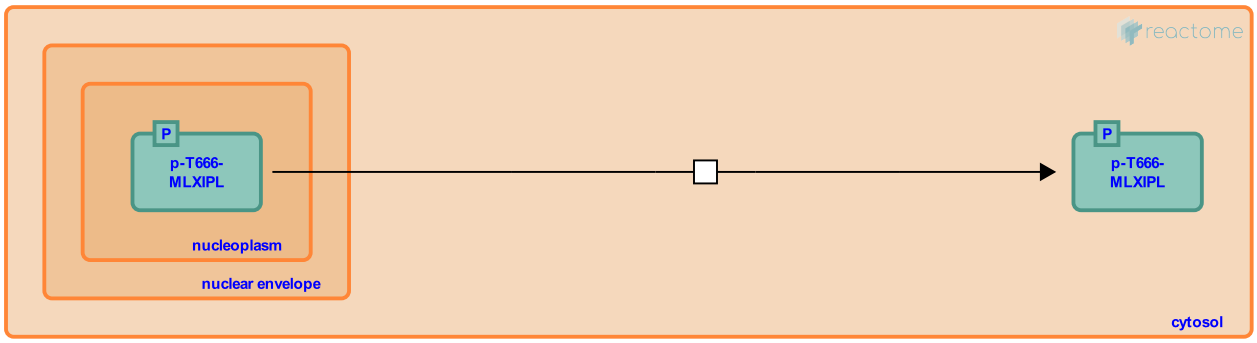
## PhosphoChREBP (Thr 666) is exported to cytosol ↗

**Location:** PKA-mediated phosphorylation of key metabolic factors

**Stable identifier:** R-HSA-164423

**Type:** transition

**Compartments:** cytosol, nucleoplasm




ChREBP (Carbohydrate Response Element Binding Protein) doubly phosphorylated at threonine 666 and serine 196 is inactive and is localized to the cytosol. Removal of the phosphate residue at serine 196 allows ChREBP to translocate between the cytosol and the nucleoplasm (Sakiyama et al. 2008).

**Preceded by:** Phosphorylation of ChREBP at Thr(666) by PKA

**Followed by:** Phosphorylation of pChREBP (Thr 666) at Ser(196) by PKA

## Literature references

Sakiyama, H., Wynn, RM., Lee, WR., Fukasawa, M., Mizuguchi, H., Gardner, KH. et al. (2008). Regulation of nuclear import/export of carbohydrate response element-binding protein (ChREBP): interaction of an alpha-helix of ChREBP with the 14-3-3 proteins and regulation by phosphorylation. *J. Biol. Chem., 283*, 24899-908. ↗

## Editions

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## Phosphorylation of pChREBP (Thr 666) at Ser(196) by PKA ↗

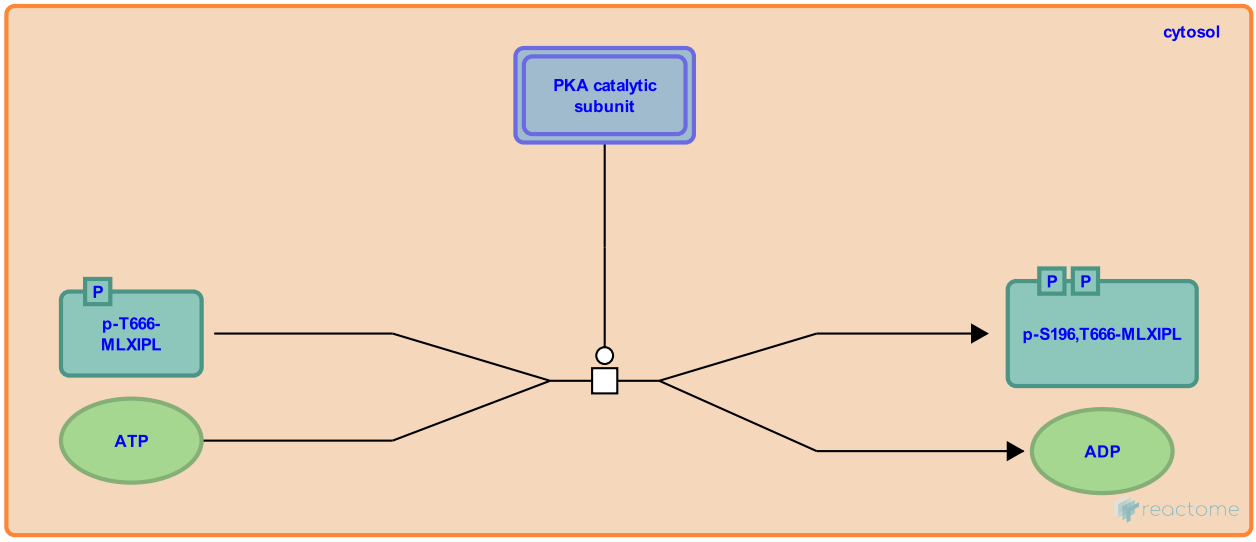
**Location:** PKA-mediated phosphorylation of key metabolic factors

**Stable identifier:** R-HSA-163676

**Type:** transition

**Compartments:** cytosol

**Inferred from:** Phosphorylation of mpChREBP (Thr 666) at Ser(196) by mPKA (Mus musculus)




Phosphorylation of ChREBP (Carbohydrate Response Element Binding Protein) at serine 196 by PKA inhibits its nuclear translocation. This reaction has been studied in detail using mouse proteins (Kawaguchi et al. 2001); the human version of the reaction is inferred from these studies.

**Preceded by:** PhosphoChREBP (Thr 666) is exported to cytosol

## Editions

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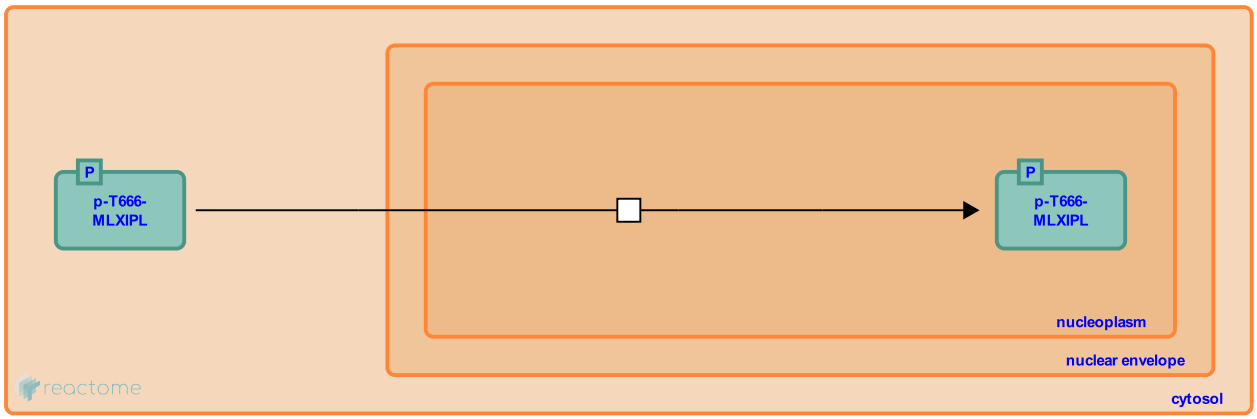
## Nuclear transport of pChREBP (Thr 666) protein ↗

**Location:** PKA-mediated phosphorylation of key metabolic factors

**Stable identifier:** R-HSA-163670

**Type:** transition

**Compartments:** nucleoplasm, cytosol




ChREBP (Carbohydrate Response Element Binding Protein) doubly phosphorylated at threonine 666 and serine 196 is inactive and is localized to the cytosol. Removal of the phosphate residue at serine 196 allows ChREBP to translocate between the cytosol and the nucleoplasm (Sakiyama et al. 2008).

## Literature references

Sakiyama, H., Wynn, RM., Lee, WR., Fukasawa, M., Mizuguchi, H., Gardner, KH. et al. (2008). Regulation of nuclear import/export of carbohydrate response element-binding protein (ChREBP): interaction of an alpha-helix of ChREBP with the 14-3-3 proteins and regulation by phosphorylation. *J. Biol. Chem., 283*, 24899-908. ↗

## Phosphorylation of PF2K-Pase by PKA catalytic subunit ↗

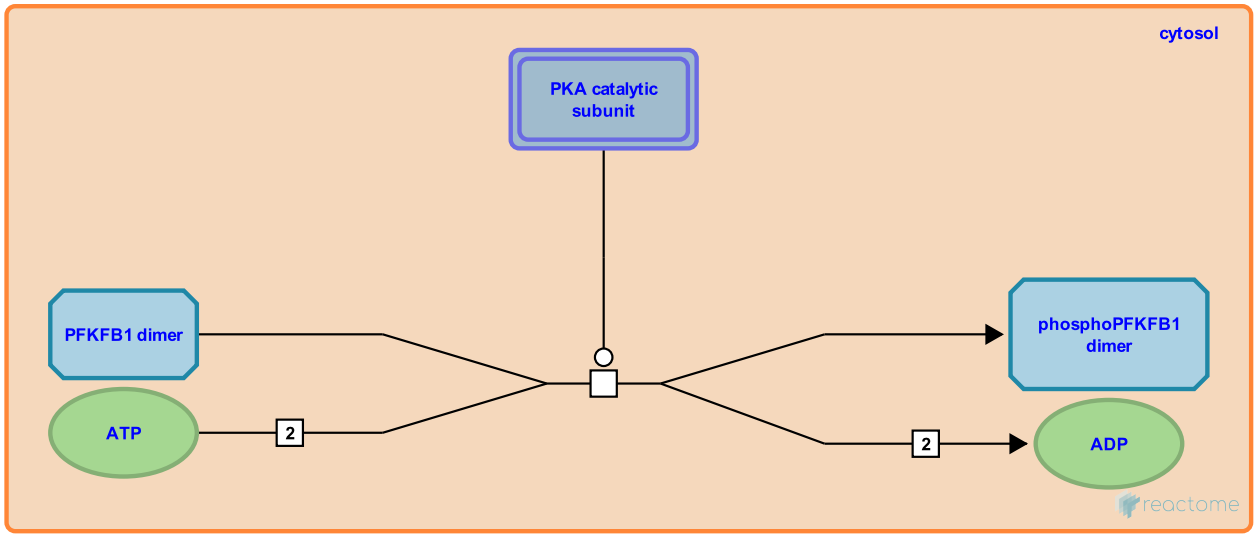
**Location:** PKA-mediated phosphorylation of key metabolic factors

**Stable identifier:** R-HSA-163773

**Type:** transition

**Compartments:** cytosol

**Inferred from:** Phosphorylation of rPF2K-Pase by rPKA (Rattus norvegicus)




Activated PKA (protein kinase A) phosphorylates serine 36 of the bifunctional 6-Phosphofructo-2-kinase /Fructose-2,6-bisphosphatase (PFKFB1) enzyme. This phosphorylation inhibits the enzyme's phosphofructokinase (PFK-2) activity while activating its phosphatase activity. As a result, cytosolic levels of Fructose-2,6-bisphosphate (F-2,6-P2) are reduced. F-2,6-P2 in turn is a key positive regulator of the committed step of glycolysis, so the net effect of this phosphorylation event is a reduced rate of glycolysis.

## Editions

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