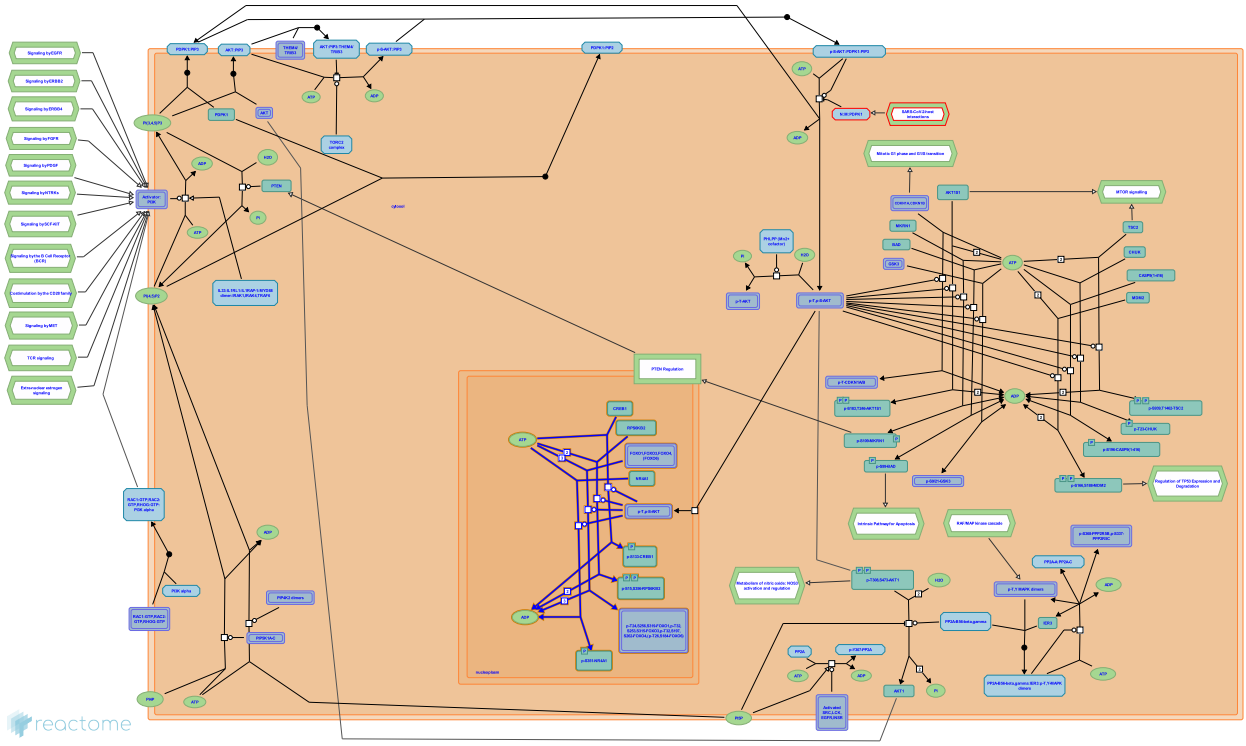
AKT phosphorylates targets in the nucleus



Annibali, D., Bertaggia, E., Donlon, T., Greene, LA., Nasi, S., Orlic-Milacic, M.

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01/12/2022

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. ↗

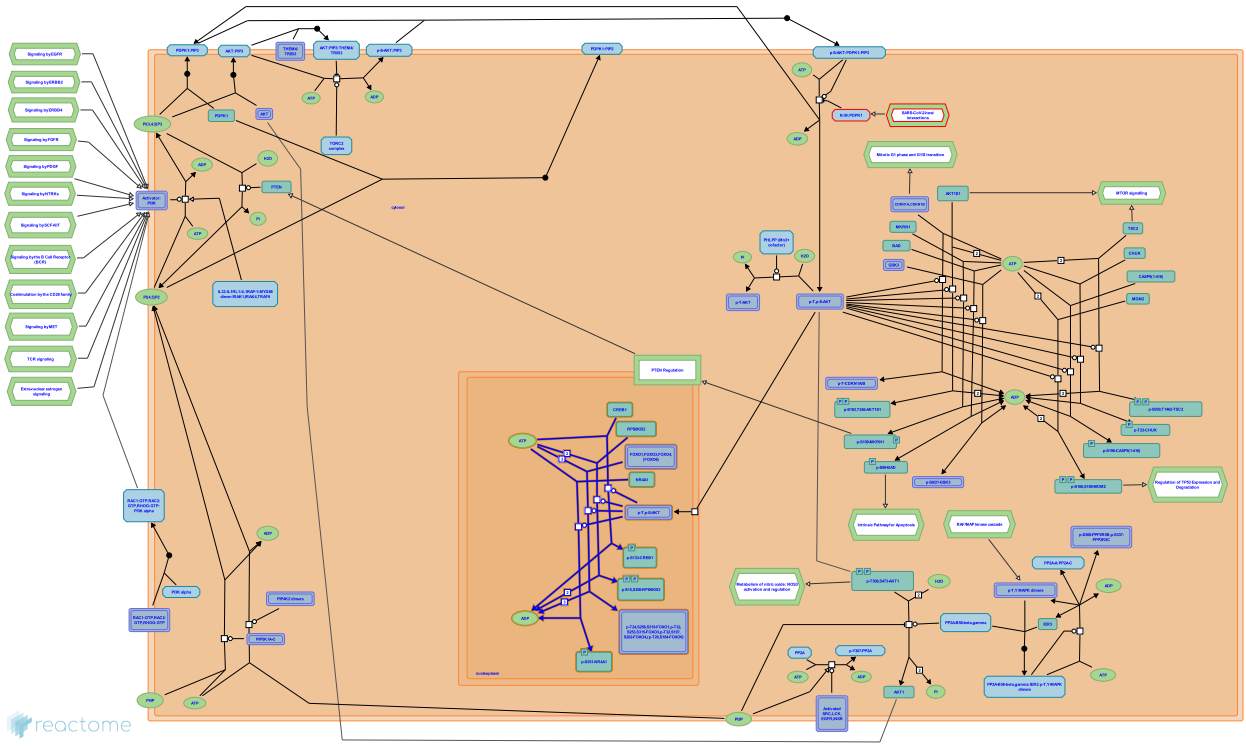
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

AKT phosphorylates targets in the nucleus ↗

Stable identifier: R-HSA-198693

Compartments: nucleoplasm



After translocation into the nucleus, AKT can phosphorylate a number of targets there such as CREB, forkhead transcription factors, SRK and NUR77.

Editions

2006-10-10	Authored	Annibali, D., Nasi, S.
2007-11-08	Reviewed	Greene, LA.

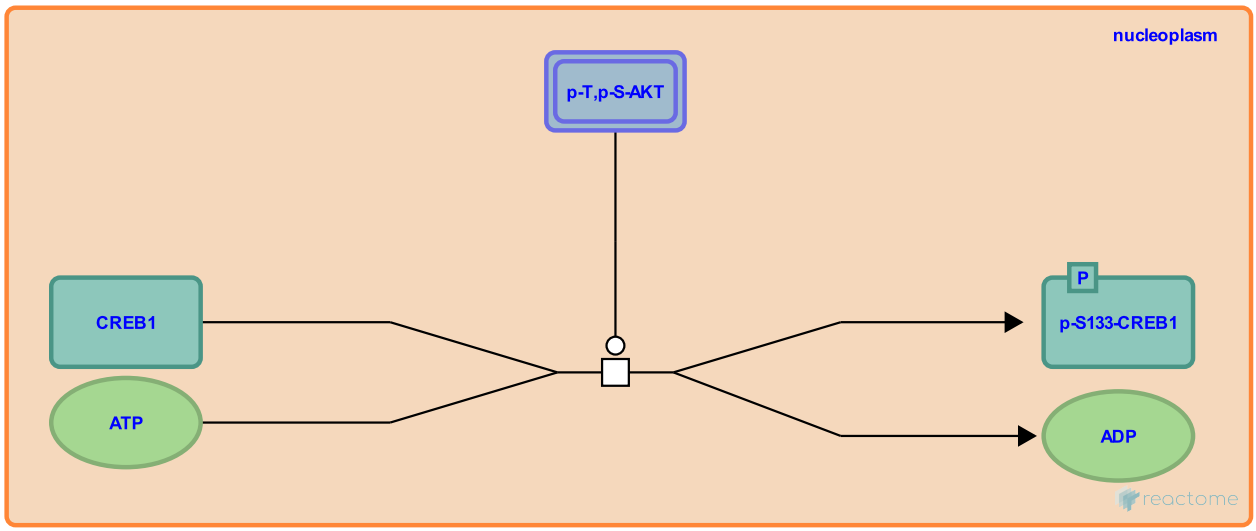
AKT phosphorylates CREB1 ↗

Location: AKT phosphorylates targets in the nucleus

Stable identifier: R-HSA-199298

Type: transition

Compartments: nucleoplasm



AKT phosphorylates CREB (cAMP response element-binding protein) at serine 133 and activates gene expression via a CREB-dependent mechanism, thus promoting cell survival.

Literature references

Du, K., Montminy, M. (1998). CREB is a regulatory target for the protein kinase Akt/PKB. *J Biol Chem, 273*, 32377-9. ↗

Editions

2006-10-10	Authored	Annibali, D., Nasi, S.
2007-11-08	Reviewed	Greene, LA.

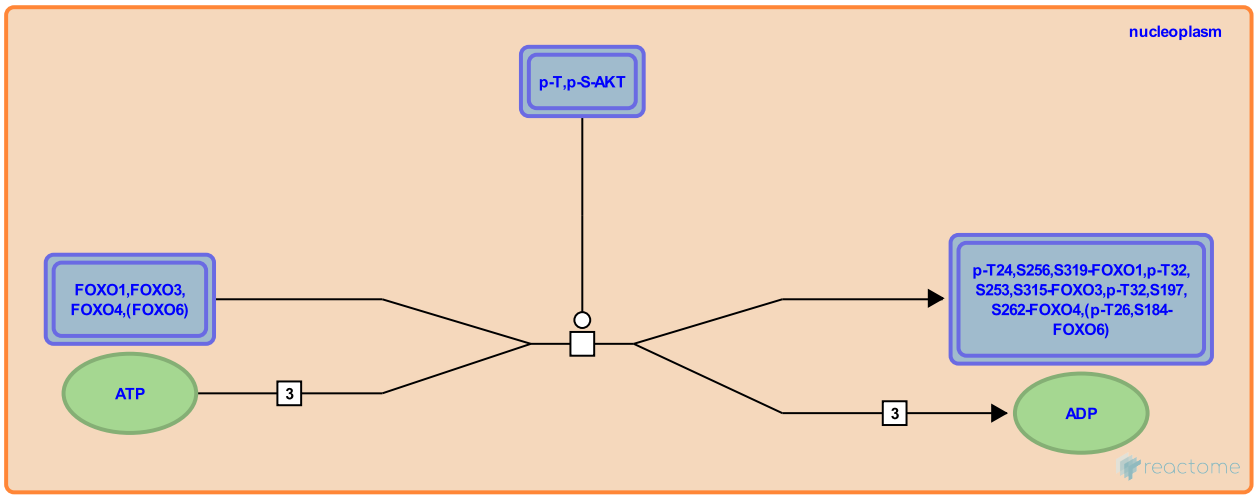
AKT phosphorylates FOXO transcription factors ↗

Location: AKT phosphorylates targets in the nucleus

Stable identifier: R-HSA-199299

Type: transition

Compartments: nucleoplasm



AKT-mediated phosphorylation of Forkhead box (FOX) transcription factors of the FOXO family, FOXO1 (FKHR), FOXO3 (FoxO3a, also known as FKHRL1) and FOXO4 (AFX) contributes to PI3K/AKT signaling-stimulated cell survival and growth. Activated AKT1 phosphorylates FOXO1 on threonine residue T24 and serine residues S256 and S319 (Rena et al. 1999), FOXO3 on threonine residue T32 and serine residues S253 and S315 (Brunet et al. 1999), and FOXO4 on threonine residue T32 and serine residues S197 and S262 (Kops et al. 1999).

Based on studies with recombinant mouse Foxo6 expressed in the human embryonic kidney cell line HEK293, FOXO6 has two conserved AKT phosphorylation sites: T26 and S184. Mouse Foxo6 has a third predicted Akt phosphorylation site at the C-terminus, T338, which is not present in other Foxo family members and is not conserved in human FOXO6. T26 and S184 are phosphorylated in response to growth factors known to activate PI3K/AKT signaling, but AKT has not been explicitly identified as the responsible kinase. In contrast to other FOXO family members, FOXO6 remains predominantly nuclear irrespective of growth factor-induced signaling, and only a small portion of phosphorylated FOXO6 may shuttle to the cytosol. Phosphorylation of FOXO6 on putative AKT sites, however, may inhibit binding of FOXO6 to target DNA sites (Jacobs et al. 2003, van der Heide et al. 2005).

Protein phosphatase DUSP6 (MKP3) may act to dephosphorylate FOXO1 after AKT-mediated phosphorylation (Rodrigues et al. 2017).

Literature references

Hu, LS., Bonni, A., Brunet, A., Blenis, J., Zigmond, MJ., Anderson, MJ. et al. (1999). Akt promotes cell survival by phosphorylating and inhibiting a Forkhead transcription factor. *Cell, 96*, 857-68. ↗

Unterman, TG., Guo, S., Cichy, SC., Rena, G., Cohen, P. (1999). Phosphorylation of the transcription factor forkhead family member FKHR by protein kinase B. *J Biol Chem, 274*, 17179-83. ↗

van der Heide, LP., Hoekman, MF., Smidt, MP., Jacobs, FM., Burbach, JP. (2005). FoxO6 transcriptional activity is regulated by Thr26 and Ser184, independent of nucleo-cytoplasmic shuttling. *Biochem. J., 391*, 623-9. ↗

van der Heide, LP., Hoekman, MF., Smidt, MP., Wijchers, PJ., Jacobs, FM., Burbach, JP. (2003). FoxO6, a novel member of the FoxO class of transcription factors with distinct shuttling dynamics. *J. Biol. Chem., 278*, 35959-67. ↗

Editions

2006-10-10	Authored	Annibali, D., Nasi, S.
2018-10-17	Reviewed	Donlon, T.
2018-10-26	Reviewed	Bertaggia, E.
2018-10-31	Edited	Orlic-Milacic, M.

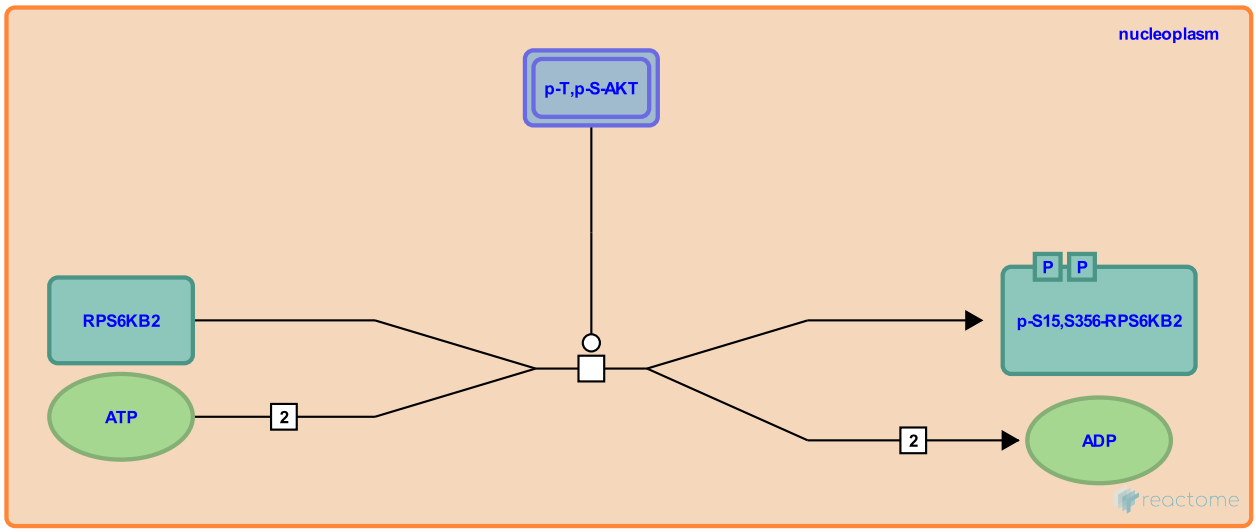
AKT can phosphorylate RSK ↗

Location: AKT phosphorylates targets in the nucleus

Stable identifier: R-HSA-199839

Type: transition

Compartments: nucleoplasm



Ribosomal protein S6 kinase beta-2 (RSK) activation is a highly conserved mitogenic response, and the activities of RSK are stimulated by multiple serine/threonine phosphorylations by different upstream kinases, one of which is AKT.

Literature references

Kim, JW., Kim, J., Lee, B., Chung, J., Koh, H., Kim, D. et al. (1999). Cloning and characterization of a nuclear S6 kinase, S6 kinase-related kinase (SRK); a novel nuclear target of Akt. *Oncogene, 18*, 5115-9. ↗

Editions

2006-10-10	Authored	Annibali, D., Nasi, S.
2007-11-08	Reviewed	Greene, LA.

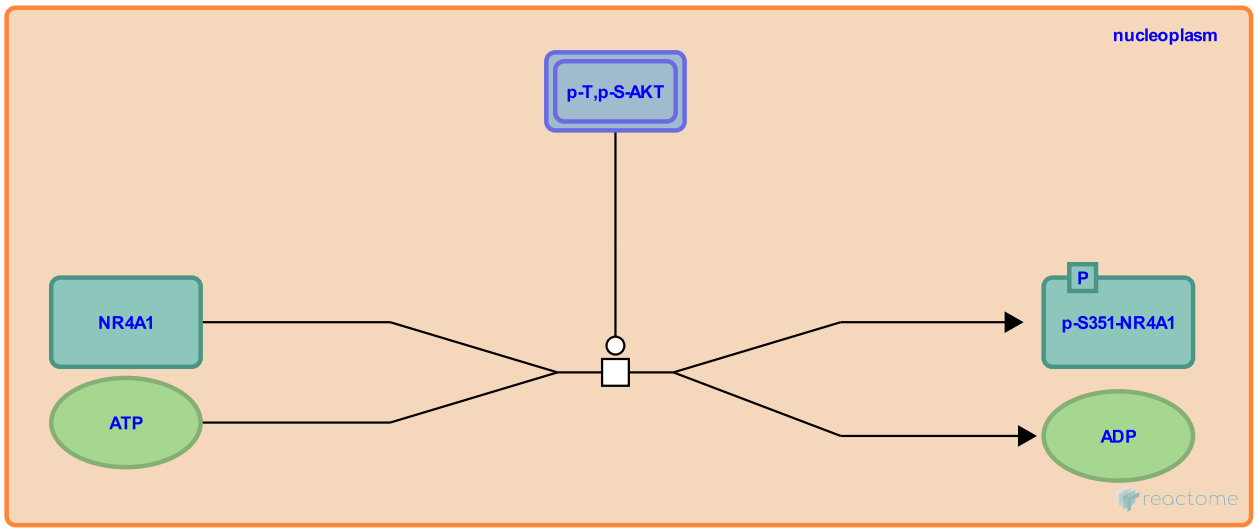
AKT can phosphorylate NR4A1 (NUR77) ↗

Location: AKT phosphorylates targets in the nucleus

Stable identifier: R-HSA-199863

Type: transition

Compartments: nucleoplasm



AKT inhibits DNA binding of NUR77 and inhibits its pro-apoptotic function (PMID 11438550). However, the relevance of AKT for NUR77 phosphorylation has recently been questioned: according to recent work, NUR77 is phosphorylated by RSK (and MSK) rather than by AKT (PMID 16223362).

Literature references

Bullrich, F., Pekarsky, Y., Bichi, R., Koval, A., Letofsky, J., Hallas, C. et al. (2001). Akt phosphorylates and regulates the orphan nuclear receptor Nur77. *Proc Natl Acad Sci U S A, 98*, 3690-4. ↗

Editions

2006-10-10	Authored	Annibali, D., Nasi, S.
2007-11-08	Reviewed	Greene, LA.

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