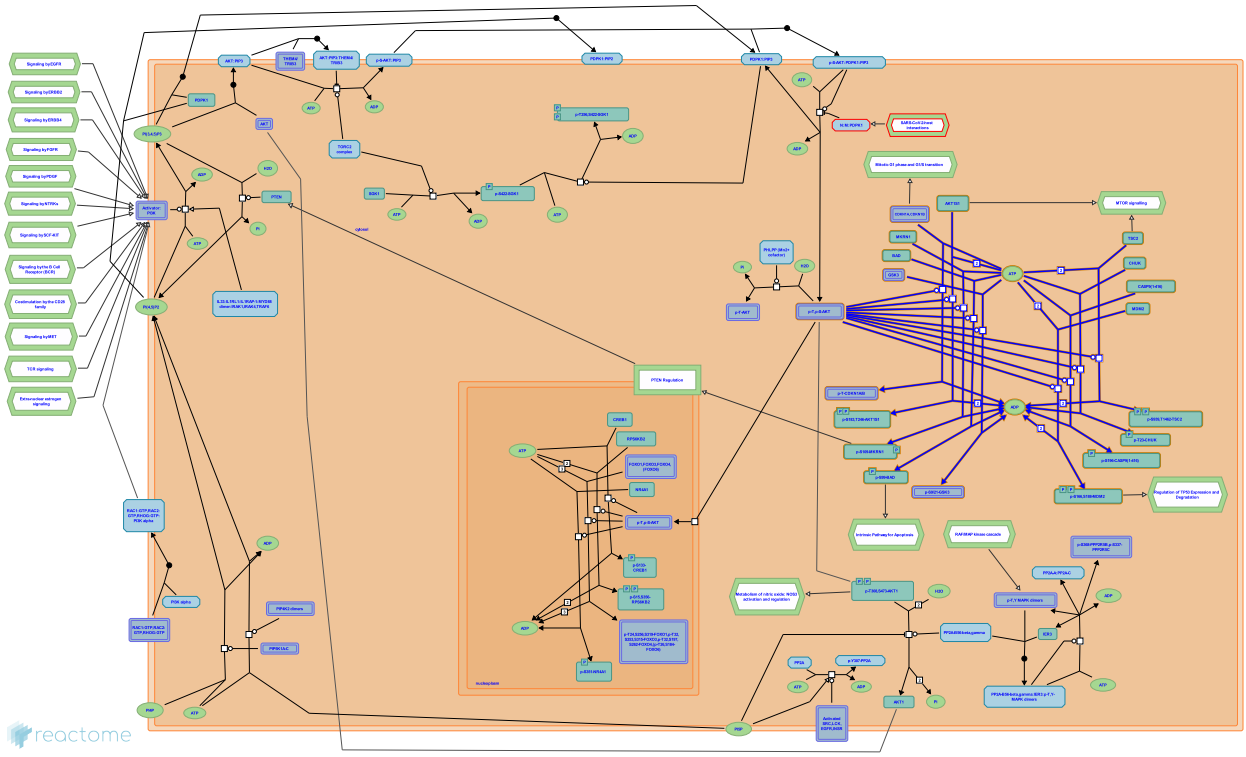
AKT phosphorylates targets in the cytosol



Annibali, D., Carracedo, A., Greene, LA., Inga, A., Jassal, B., Nasi, S., Orlic-Milacic, M., Salmena, L., Zaccara, S.

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. ↗

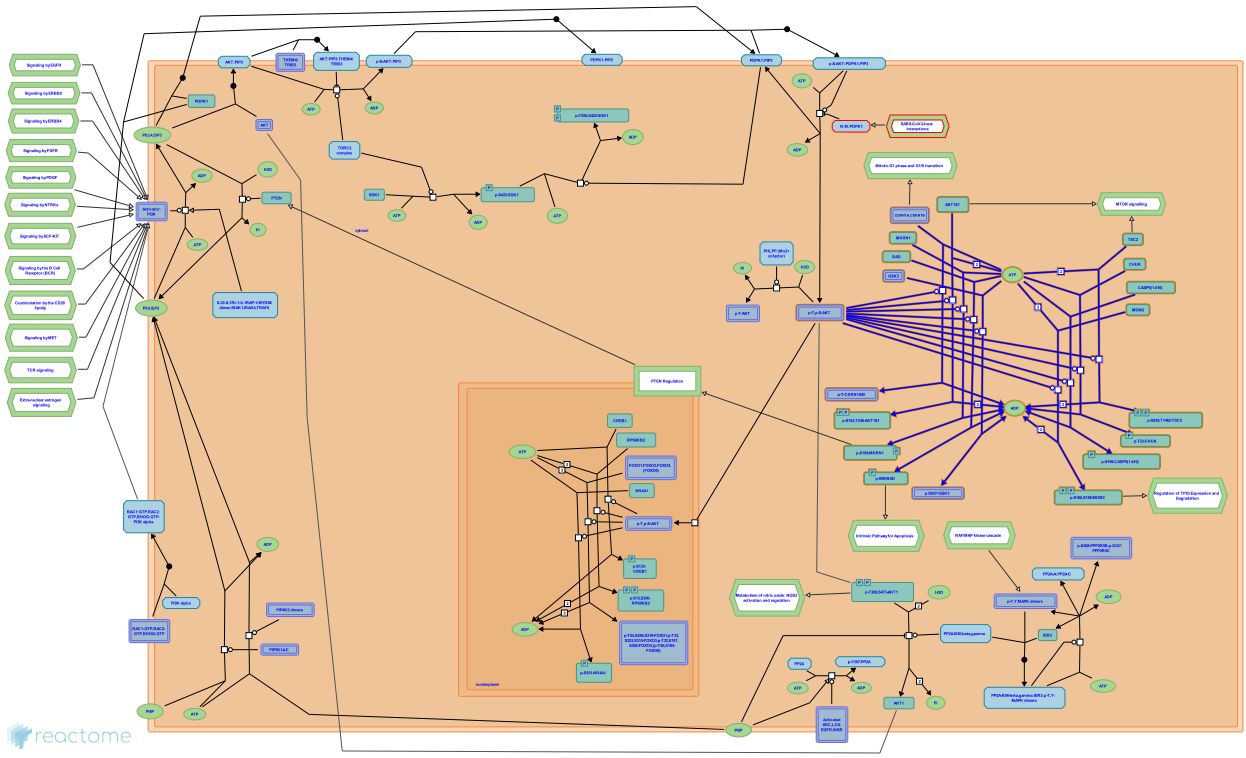
Reactome database release: 88

This document contains 1 pathway and 9 reactions (see Table of Contents)

AKT phosphorylates targets in the cytosol ↗

Stable identifier: R-HSA-198323

Compartments: cytosol



Following activation, AKT can phosphorylate an array of target proteins in the cytoplasm, many of which are involved in cell survival control. Phosphorylation of TSC2 feeds positively to the TOR kinase, which, in turn, contributes to AKT activation (positive feedback loop).

Editions

2006-10-10	Authored	Annibali, D., Nasi, S.
2007-11-08	Reviewed	Greene, LA.
2011-05-11	Edited	Jassal, B.

AKT phosphorylates BAD ↗

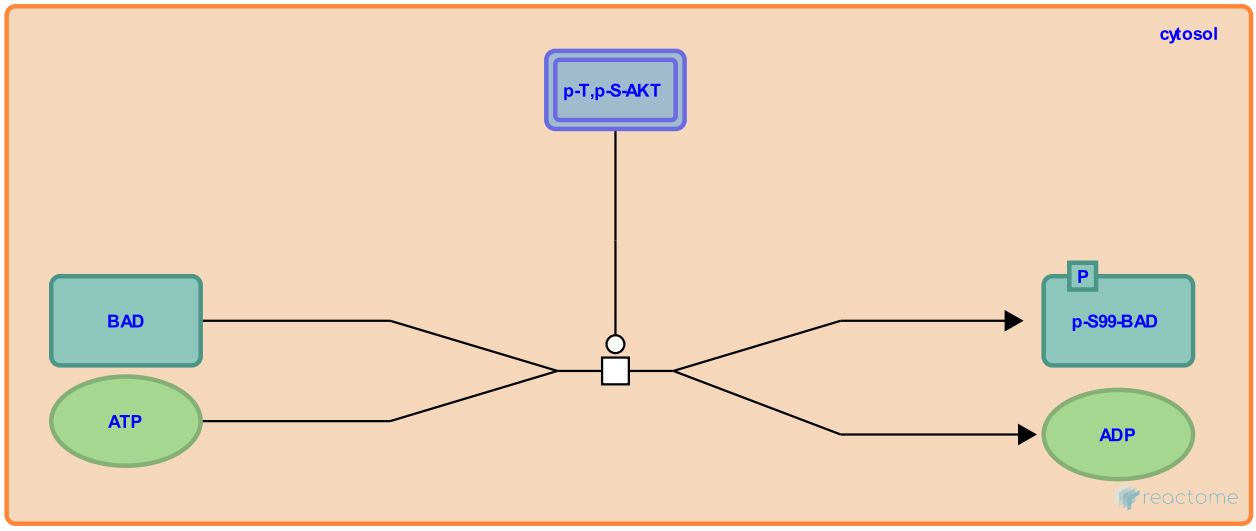
Location: AKT phosphorylates targets in the cytosol

Stable identifier: R-HSA-198347

Type: transition

Compartments: cytosol

Inferred from: AKT phosphorylates Bad (Homo sapiens)



Activated AKT phosphorylates the BCL-2 family member BAD at serine 99 (corresponds to serine residue S136 of mouse Bad), blocking the BAD-induced cell death (Datta et al. 1997, del Peso et al. 1997, Khor et al. 2004).

Literature references

Khor, TO., Ithnin, H., Gul, YA., Seow, HF. (2004). Positive correlation between overexpression of phospho-BAD with phosphorylated Akt at serine 15183529. *Cancer Lett, 210*, 139-50. ↗

Fu, H., Tao, X., Masters, S., Dudek, H., Gotoh, Y., Datta, SR. et al. (1997). Akt phosphorylation of BAD couples survival signals to the cell-intrinsic death machinery. *Cell, 91*, 231-41. ↗

Page, CP., Nunez, G., Gonzalez-Garcia, M., Herrera, R., del Peso, L. (1997). Interleukin-3-induced phosphorylation of BAD through the protein kinase Akt. *Science, 278*, 687-9. ↗

Editions

2006-10-10	Authored	Annibali, D., Nasi, S.
2007-11-08	Reviewed	Greene, LA.
2013-02-13	Edited	Orlic-Milacic, M.

AKT phosphorylates GSK3 ↗

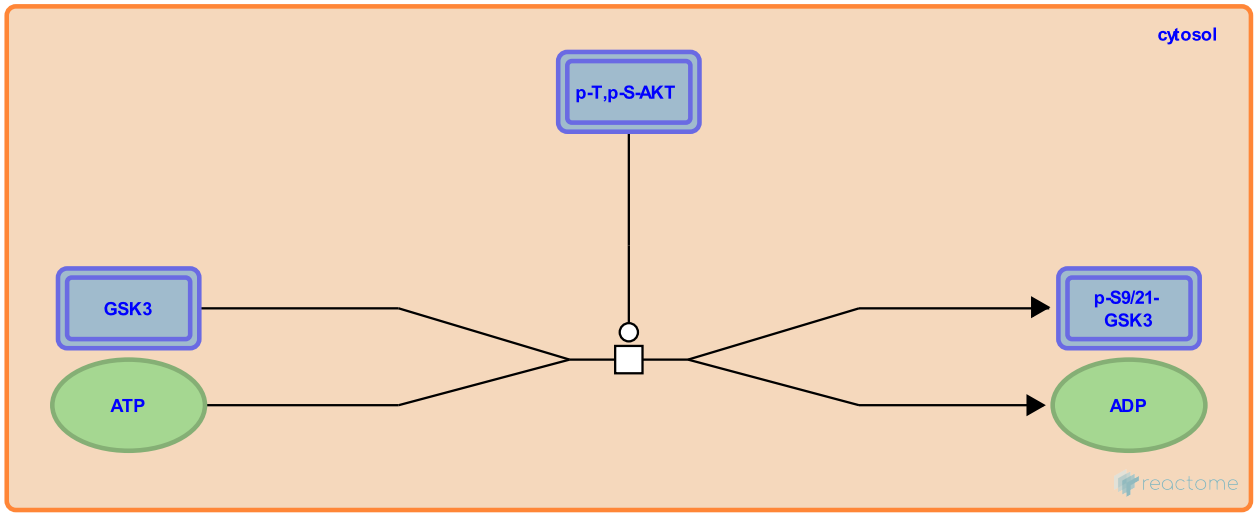
Location: AKT phosphorylates targets in the cytosol

Stable identifier: R-HSA-198371

Type: transition

Compartments: cytosol

Inferred from: Akt1 phosphorylates GSK3 (Rattus norvegicus)



GSK3 (glycogen synthase kinase-3) participates in the Wnt signaling pathway. It is implicated in the hormonal control of several regulatory proteins including glycogen synthase, and the transcription factors MYB and JUN. GSK3 phosphorylates JUN at sites proximal to its DNA-binding domain, thereby reducing its affinity for DNA. GSK3 is inhibited when phosphorylated by AKT1.

Editions

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

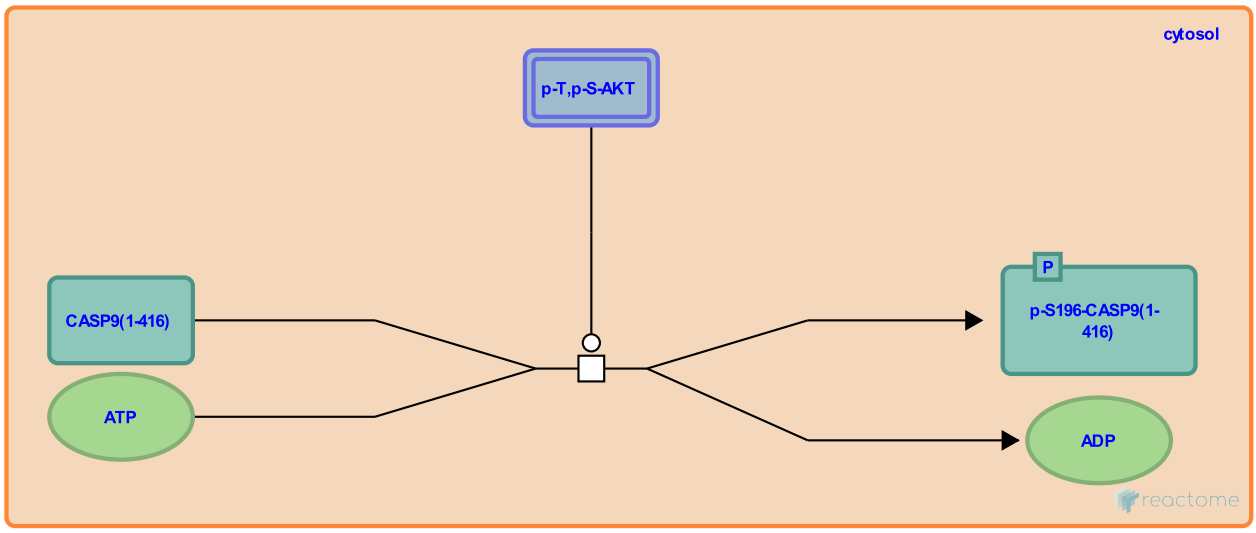
AKT phosphorylates caspase-9 ↗

Location: AKT phosphorylates targets in the cytosol

Stable identifier: R-HSA-198621

Type: transition

Compartments: cytosol



AKT can phosphorylate the apoptotic protease caspase-9, inhibiting it.

Literature references

Stennicke, HR., Stanbridge, E., Franke, TF., Roy, N., Reed, JC., Salvesen, GS. et al. (1998). Regulation of cell death protease caspase-9 by phosphorylation. *Science, 282*, 1318-21. ↗

Editions

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

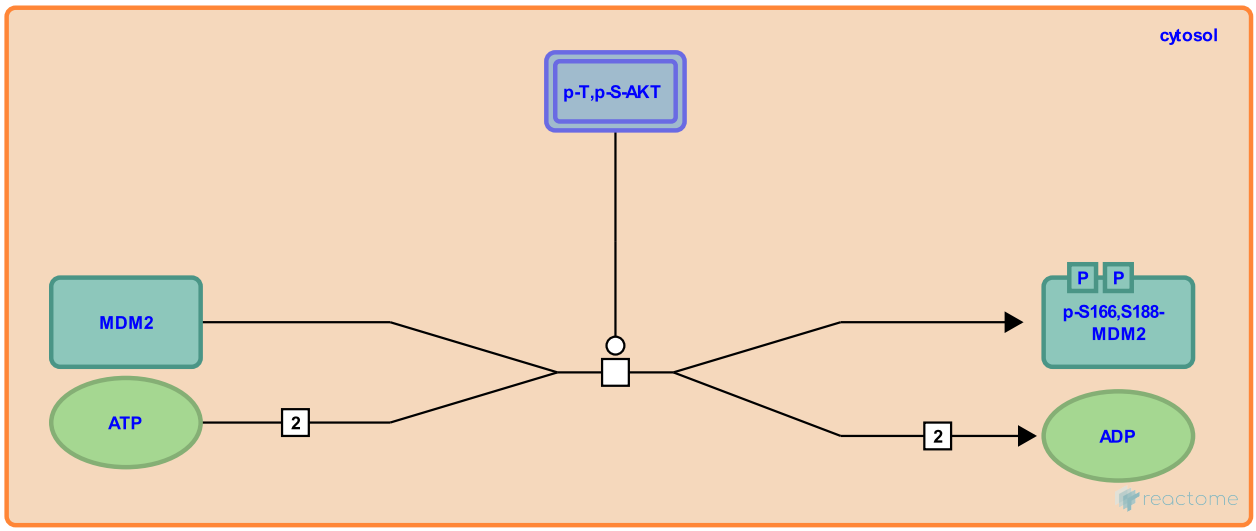
AKT phosphorylates MDM2 ↗

Location: AKT phosphorylates targets in the cytosol

Stable identifier: R-HSA-198599

Type: transition

Compartments: cytosol



AKT phosphorylates MDM2 on two serine residues, at positions 166 and 188 (Mayo and Donner 2001, Feng et al. 2004, Milne et al. 2004). AKT-mediated phosphorylation of the E3 ubiquitin-protein ligase MDM2 promotes nuclear localization and interferes with the interaction between MDM2 and p14-ARF, thereby decreasing p53 stability. This leads to a decreased expression of p53 target genes, such as BAX, that promote apoptosis (Zhou et al. 2001, Mayo and Donner 2001).

Literature references

Kampanis, P., Campbell, DG., Nicol, S., Milne, D., Meek, D., Fuller-Pace, F. et al. (2004). A novel site of AKT-mediated phosphorylation in the human MDM2 onco-protein. *FEBS Lett., 577*, 270-6. ↗

Yang, Z., Hess, D., Tamaskovic, R., Merlo, A., Feng, J., Brazil, DP. et al. (2004). Stabilization of Mdm2 via decreased ubiquitination is mediated by protein kinase B/Akt-dependent phosphorylation. *J. Biol. Chem., 279*, 35510-7. ↗

Mayo, LD., Donner, DB. (2001). A phosphatidylinositol 3-kinase/Akt pathway promotes translocation of Mdm2 from the cytoplasm to the nucleus. *Proc. Natl. Acad. Sci. U.S.A., 98*, 11598-603. ↗

Zou, Y., Xia, W., Zhou, BP., Hung, MC., Spohn, B., Liao, Y. (2001). HER-2/neu induces p53 ubiquitination via Akt-mediated MDM2 phosphorylation. *Nat Cell Biol, 3*, 973-82. ↗

Editions

2006-10-10	Authored	Annibali, D., Nasi, S.
2007-11-08	Reviewed	Greene, LA.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

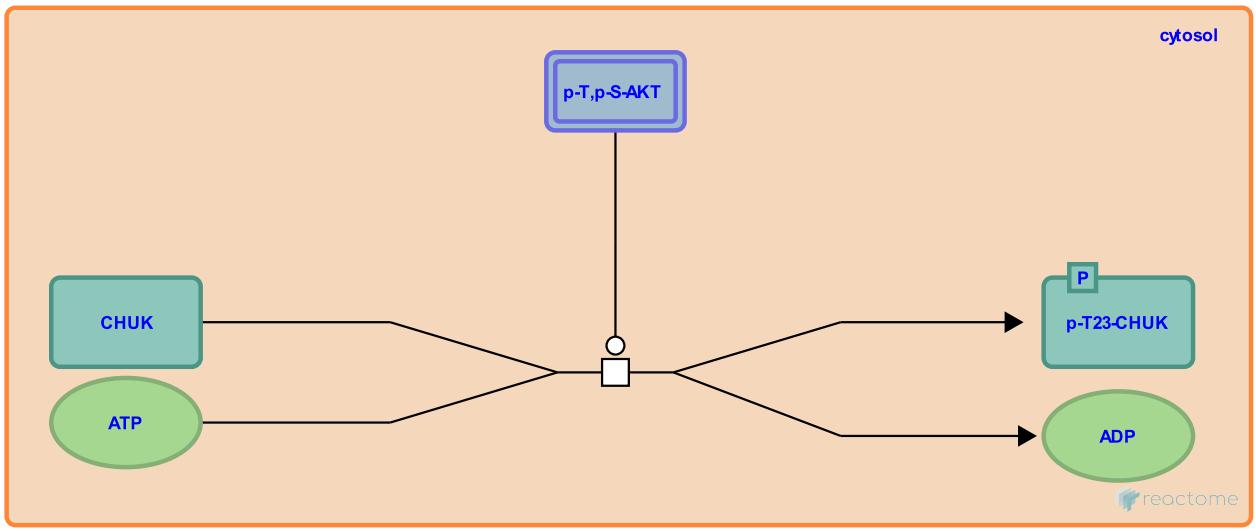
AKT phosphorylates IKKalpha ↗

Location: AKT phosphorylates targets in the cytosol

Stable identifier: R-HSA-198611

Type: transition

Compartments: cytosol



AKT mediates IKKalpha (Inhibitor of nuclear factor kappa B kinase subunit alpha) phosphorylation at threonine 23, which is required for NF-kB activation. NF-kB promoted gene transcription enhances neuronal survival.

Literature references

Donner, DB., Mayo, LD., Pfeffer, SR., Pfeffer, LM., Ozes, ON., Gustin, JA. (1999). NF-kappaB activation by tumour necrosis factor requires the Akt serine-threonine kinase. *Nature, 401*, 82-5. ↗

Editions

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

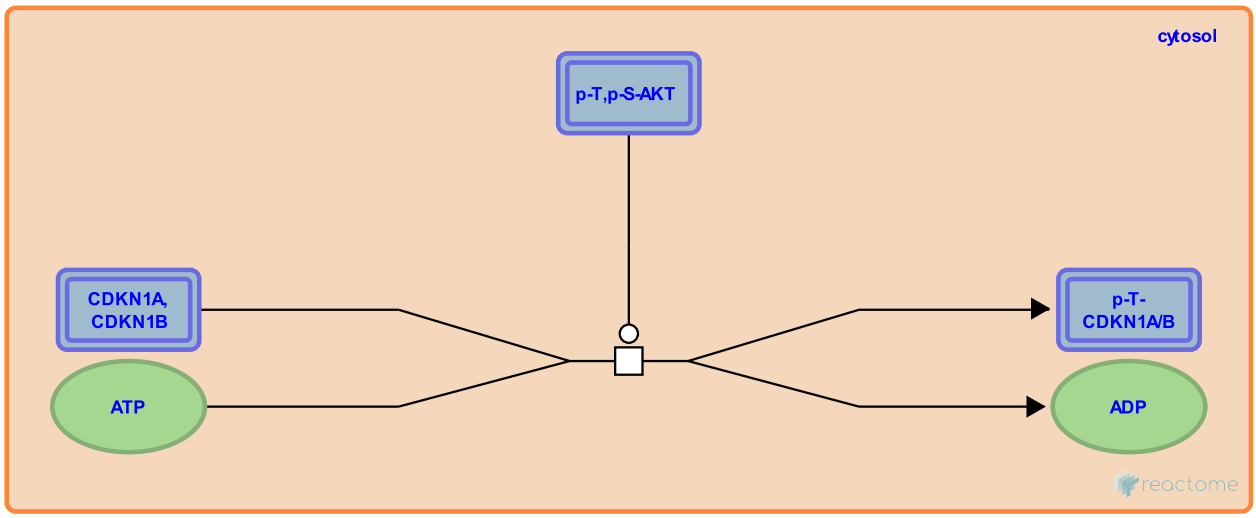
AKT phosphorylates p21Cip1 and p27Kip1 ↗

Location: AKT phosphorylates targets in the cytosol

Stable identifier: R-HSA-198613

Type: transition

Compartments: cytosol



Phosphorylation of p27Kip1 at T157 and of p21Cip1 at T145 by AKT leads to their retention in the cytoplasm, segregating these cyclin-dependent kinase (CDK) inhibitors from cyclin-CDK complexes.

Literature references

Xia, W., Liao, Y., Hung, MC., Zhou, BP., Lee, MH., Spohn, B. (2001). Cytoplasmic localization of p21Cip1/WAF1 by Akt-induced phosphorylation in HER-2/neu-overexpressing cells. *Nat. Cell Biol., 3*, 245-52. ↗

Tsichlis, P., Viglietto, G., Santoro, M., Bruni, P., Vinci, F., Motti, ML. et al. (2002). Cytoplasmic relocalization and inhibition of the cyclin-dependent kinase inhibitor p27(Kip1) by PKB/Akt-mediated phosphorylation in breast cancer. *Nat Med, 8*, 1136-44. ↗

Editions

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

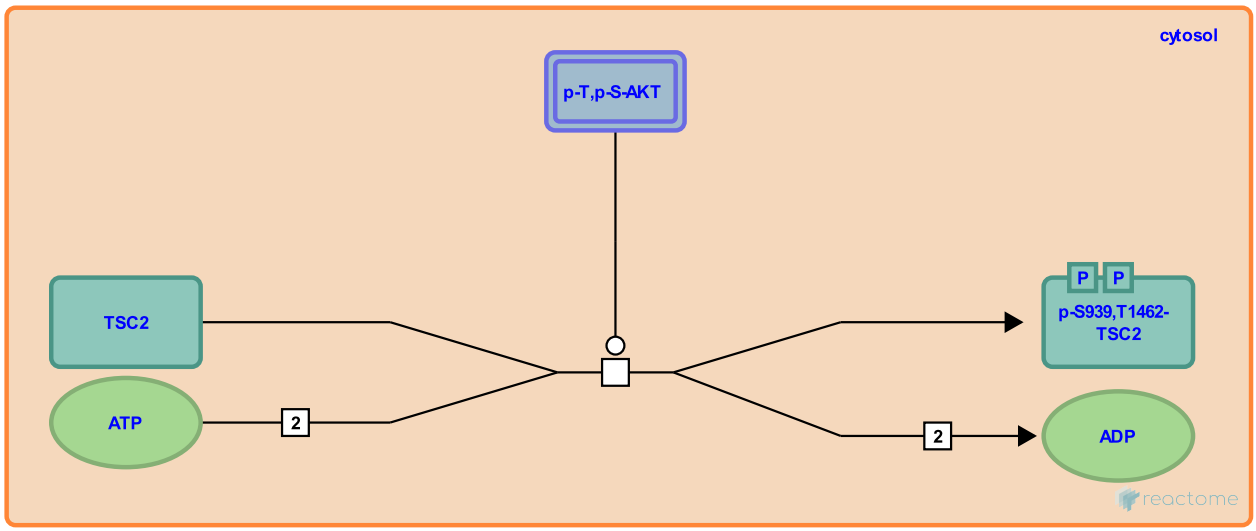
AKT phosphorylates TSC2, inhibiting it ↗

Location: AKT phosphorylates targets in the cytosol

Stable identifier: R-HSA-198609

Type: transition

Compartments: cytosol



AKT phosphorylates and inhibits TSC2 (tuberin), a suppressor of the TOR kinase pathway, which senses nutrient levels in the environment. TSC2 forms a protein complex with TSC1 and this complex acts as a GAP (GTPase activating protein) for the RHEB G-protein. RHEB, in turn, activates the TOR kinase. Thus, an active AKT1 activates the TOR kinase, both of which are positive signals for cell growth (an increase in cell mass) and division.
The TOR kinase regulates two major processes: translation of selected mRNAs in the cell and autophagy. In the presence of high nutrient levels TOR is active and phosphorylates the 4EBP protein releasing the eukaryotic initiation factor 4E (eIF4E), which is essential for cap-dependent initiation of translation and promoting growth of the cell (PMID: 15314020). TOR also phosphorylates the S6 kinase, which is implicated in ribosome biogenesis as well as in the modification of the S6 ribosomal protein. AKT can also activate mTOR by another mechanism, involving phosphorylation of PRAS40, an inhibitor of mTOR activity.

Literature references

Inoki, K., Guan, KL., Li, Y., Wu, J., Zhu, T. (2002). TSC2 is phosphorylated and inhibited by Akt and suppresses mTOR signalling. *Nat Cell Biol, 4*, 648-57. ↗

Tee, AR., Logsdon, MN., Manning, BD., Blenis, J., Cantley, LC. (2002). Identification of the tuberous sclerosis complex-2 tumor suppressor gene product tuberin as a target of the phosphoinositide 3-kinase/akt pathway. *Mol Cell, 10*, 151-62. ↗

Editions

2006-10-10	Authored	Annibali, D., Nasi, S.
2007-11-08	Reviewed	Greene, LA.
2014-12-23	Edited	Orlic-Milacic, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

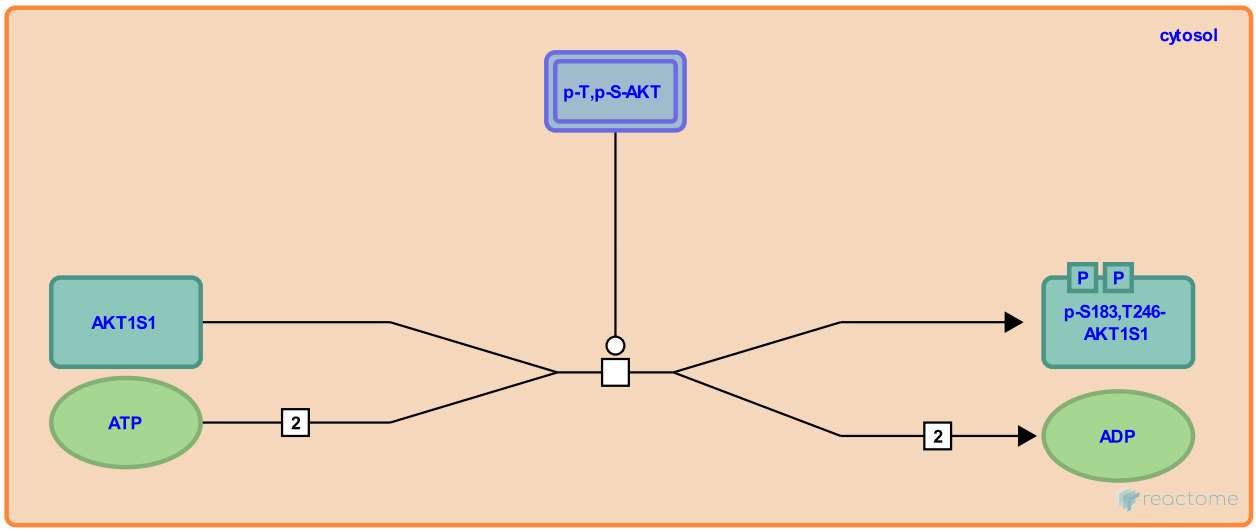
AKT phosphorylates AKT1S1 (PRAS40) ↗

Location: AKT phosphorylates targets in the cytosol

Stable identifier: R-HSA-200143

Type: transition

Compartments: cytosol



PRAS40 (proline-rich Akt/PKB substrate 40 kDa) is a substrate of AKT, the phosphorylation of which leads to the binding of this protein to 14-3-3. PRAS40 binds to mTOR complexes, mediating AKT signals to mTOR. Interaction of PRAS40 with the mTOR kinase domain is induced under conditions that inhibit mTOR signalling, such as growth factor deprivation. Binding of PRAS40 inhibits mTOR. PRAS40 phosphorylation by AKT and association with the cytosolic anchor protein 14-3-3, lead to mTOR stimulation (Vander Haar E, et al, 2007). Although it was originally identified in the context of insulin signalling, it was later shown that PRAS40 may also play a role in nerve growth factor-mediated neuroprotection (Saito A, et al, 2004).

Literature references

Kovacina, KS., Roth, RA., Schaefer, E., Birnbaum, MJ., Bae, SS., Park, GY. et al. (2003). Identification of a proline-rich Akt substrate as a 14-3-3 binding partner. *J Biol Chem, 278*, 10189-94. ↗

Editions

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

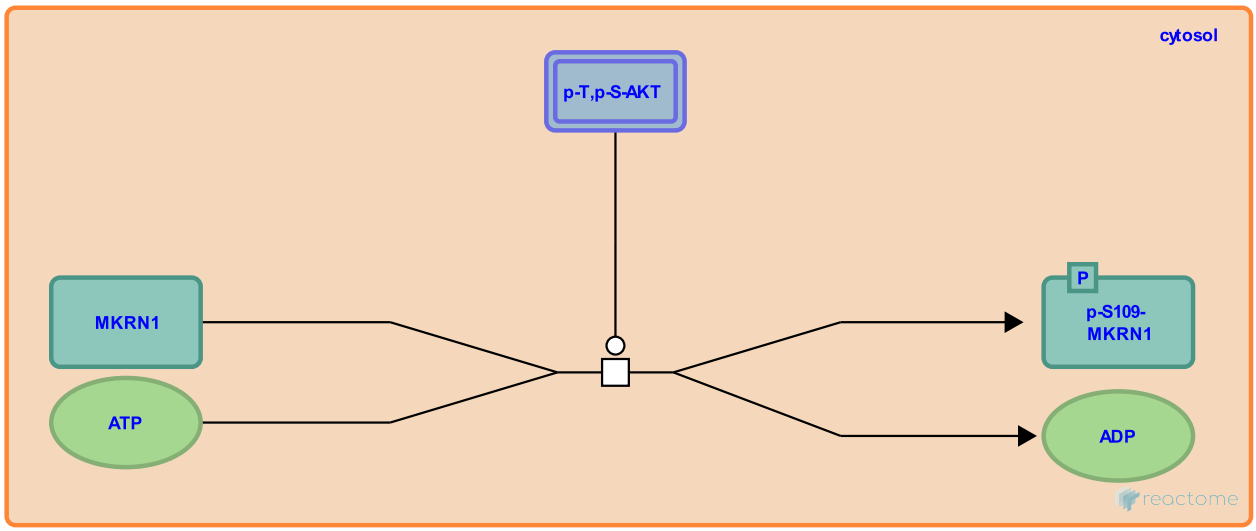
AKT phosphorylates MKRN1 ↗

Location: AKT phosphorylates targets in the cytosol

Stable identifier: R-HSA-8948757

Type: transition

Compartments: cytosol



AKT1 (and possibly AKT2 and AKT3), activated in response to EGF treatment, phosphorylates MKRN1, an E3 ubiquitin ligase, on serine residue S109. AKT-mediated phosphorylation results in stabilization of MKRN1, protecting it from ubiquitination and proteasome-mediated degradation (Lee et al. 2015).

Literature references

Hewitt, SM., Han, HJ., Lee, MS., Lee, C., Chung, JY., Kim, JH. et al. (2015). PI3K/AKT activation induces PTEN ubiquitination and destabilization accelerating tumourigenesis. *Nat Commun, 6*, 7769. ↗

Editions

2016-08-11	Authored	Carracedo, A., Salmena, L.
2016-11-16	Authored	Orlic-Milacic, M.
2017-05-09	Edited	Orlic-Milacic, M.

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