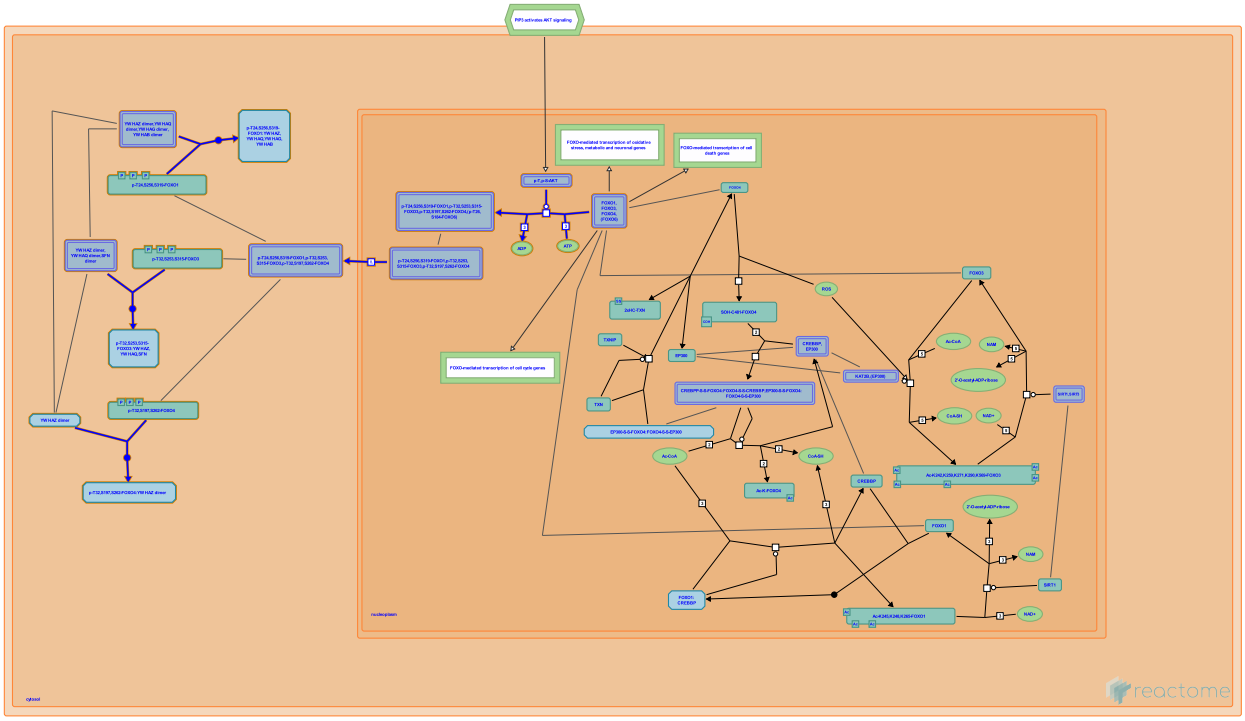
Regulation of localization of FOXO transcription factors



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

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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. ↗

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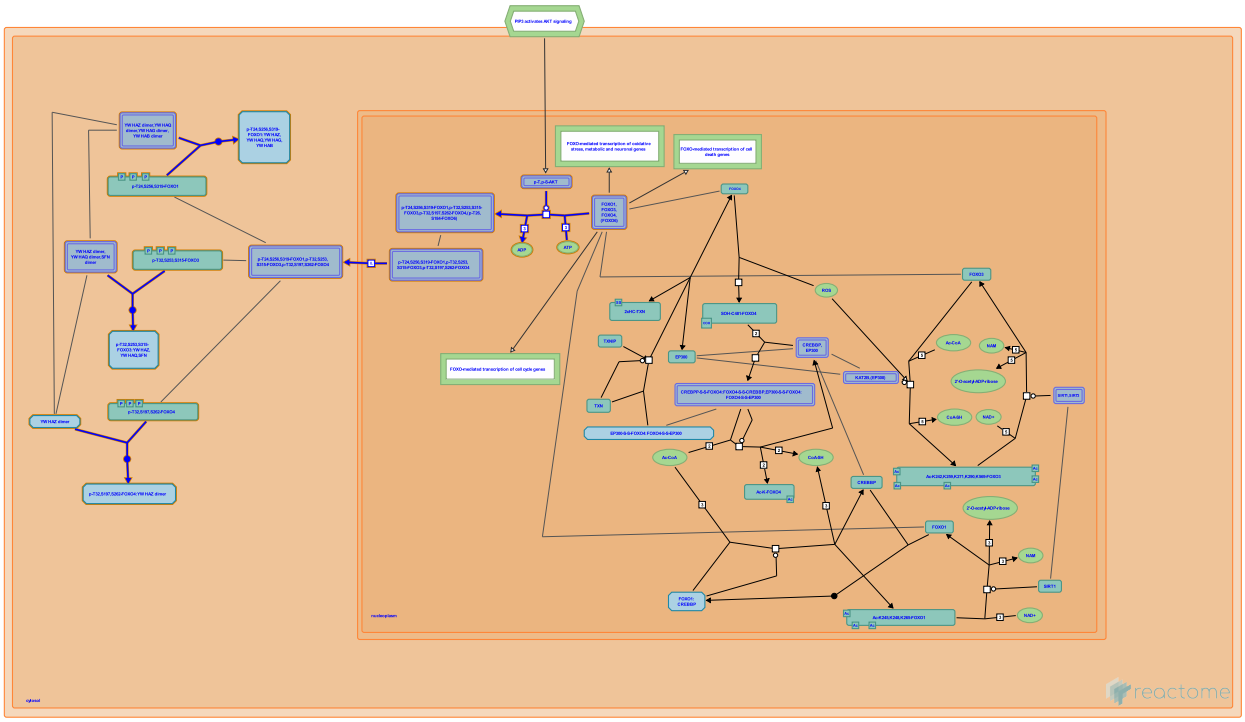
Regulation of localization of FOXO transcription factors

Stable identifier: R-HSA-9614399



Localization of FOXO transcription factors FOXO1, FOXO3 and FOXO4 is regulated by AKT-mediated phosphorylation. In the absence of PI3K/AKT signaling, FOXO1, FOXO3 and FOXO4 localize to the nucleus. AKT-mediated phosphorylation induces a conformational change that exposes a nuclear export signal (NES) and promotes translocation of FOXO1, FOXO3 and FOXO4 to the cytosol (Rena et al. 1999, Brunet et al. 1999, Kops et al. 1999). AKT-phosphorylated FOXO1, FOXO3 and FOXO4 bind to 14-3-3 proteins, which contributes to their retention in the cytosol (Rena et al. 2001, Brunet et al. 1999, Arimoto Ishida et al. 2004, Obsilova et al. 2005, Boura et al. 2007, Silhan et al. 2009). FOXO6 lacks the NES sequence and is exclusively nuclear, but phosphorylation in response to PI3K/AKT signaling affects the transcriptional activity of FOXO6 (Jacobs et al. 2003, van der Heide et al. 2005).

Literature references

Sulc, M., Silhan, J., Obsil, T., Obsilova, V., Vecer, J., Strnadova, P. et al. (2009). 14-3-3 protein masks the DNA binding interface of forkhead transcription factor FOXO4. *J. Biol. Chem., 284*, 19349-60.

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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.

Sulc, M., Silhan, J., Boura, E., Obsil, T., Obsilova, V., Vecer, J. et al. (2007). Both the N-terminal loop and wing W2 of the forkhead domain of transcription factor Foxo4 are important for DNA binding. *J. Biol. Chem., 282*, 8265-75.

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.

Editions

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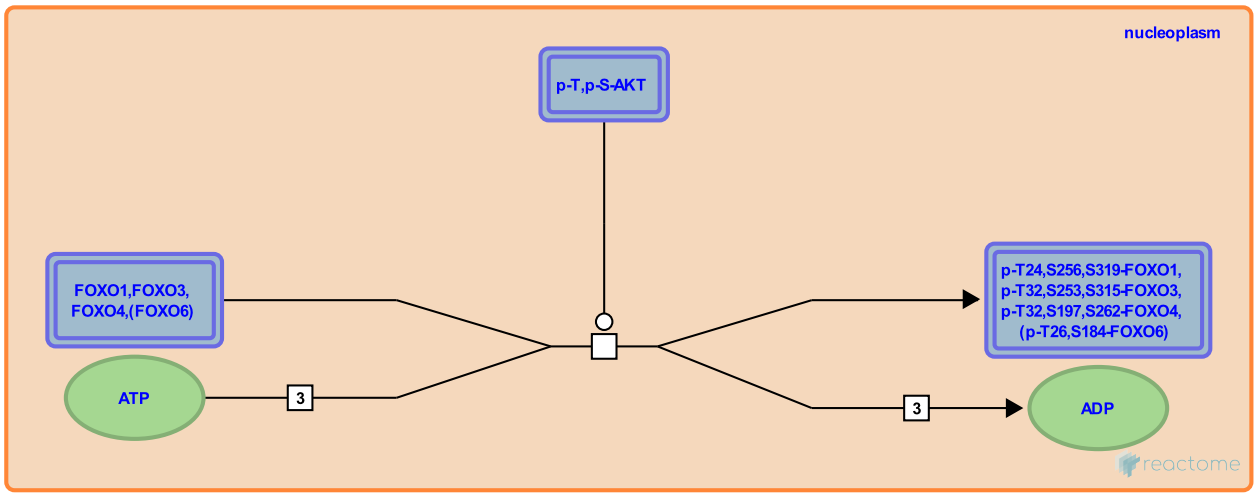
AKT phosphorylates FOXO transcription factors ↗

Location: Regulation of localization of FOXO transcription factors

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).

Followed by: AKT-phosphorylated FOXO1,FOXO3,FOXO4 translocate to the cytosol

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.
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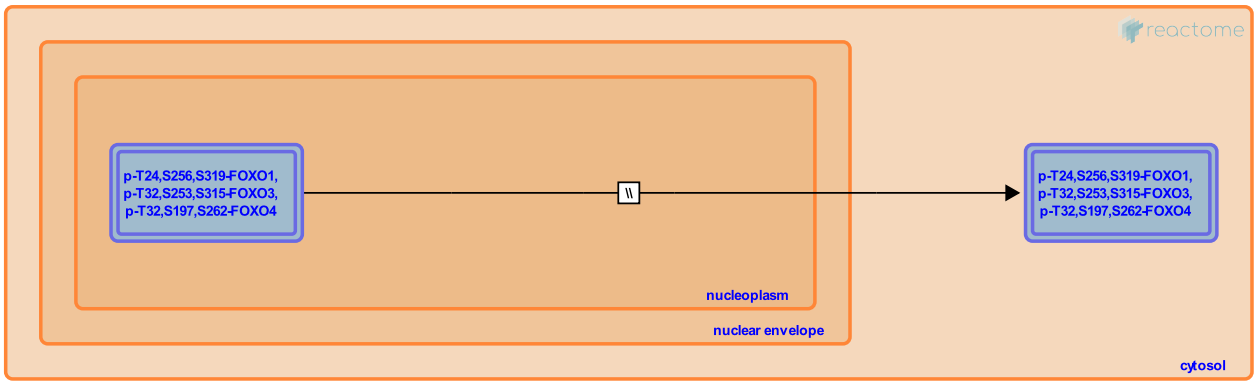
AKT-phosphorylated FOXO1,FOXO3,FOXO4 translocate to the cytosol ↗

Location: Regulation of localization of FOXO transcription factors

Stable identifier: R-HSA-9614414

Type: omitted

Compartments: nucleoplasm, cytosol



AKT-mediated phosphorylation results in exclusion of FOXO1 (Rena et al. 2001), FOXO3 (Brunet et al. 1999) and FOXO4 (Obslova et al. 2005) from the nucleus. In the absence of PI3K/AKT signaling, FOXO1 (Rena et al. 2001), FOXO3 (Brunet et al. 1999) and FOXO4 (Matsuzaki et al. 2005) are mainly nuclear, but after activation of PI3K/AKT signaling, they become cytoplasmic. One of the conserved AKT phosphorylation sites is within the nuclear localization signal (NLS) of FOXO1, FOXO3 and FOXO4.
In contrast to other FOXO family members, FOXO6 remains predominantly nuclear irrespective of growth factor-induced signaling, and only a small portion of FOXO6 phosphorylated on putative AKT sites may shuttle to the nucleus (Jacobs et al. 2003, van der Heide et al. 2005).

Preceded by: AKT phosphorylates FOXO transcription factors

Followed by: 14-3-3 proteins bind AKT-phosphorylated FOXO4, 14-3-3 proteins bind AKT-phosphorylated FOXO1, 14-3-3 proteins bind AKT-phosphorylated FOXO3

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. ↗

Sulc, M., Boura, E., Obsil, T., Obsilova, V., Pabianova, A., Vecer, J. et al. (2005). 14-3-3 Protein interacts with nuclear localization sequence of forkhead transcription factor FoxO4. *Biochemistry, 44*, 11608-17. ↗

Kikkawa, U., Yamamoto, T., Hayashi, T., Ichino, A., Matsuzaki, H. (2005). Regulation of intracellular localization and transcriptional activity of FOXO4 by protein kinase B through phosphorylation at the motif sites conserved among the FOXO family. *J Biochem (Tokyo), 138*, 485-91. ↗

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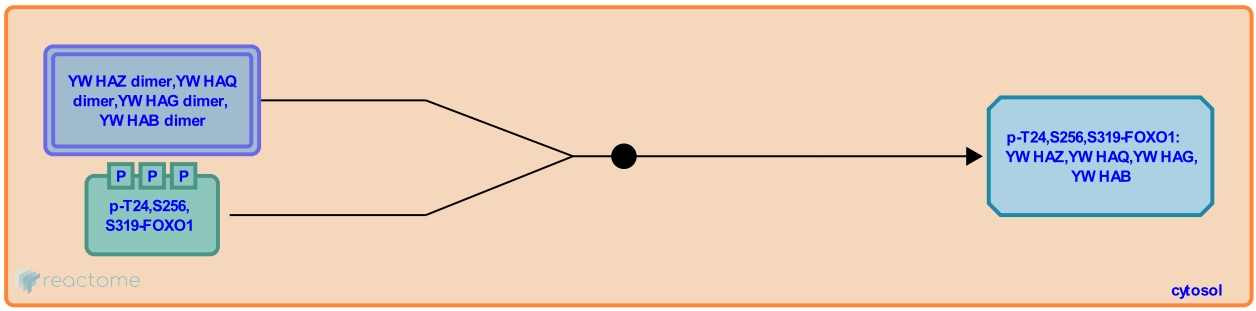
14-3-3 proteins bind AKT-phosphorylated FOXO1 ↗

Location: Regulation of localization of FOXO transcription factors

Stable identifier: R-HSA-9614423

Type: binding

Compartments: cytosol



Nuclear exclusion and cytoplasmic retention of AKT-phosphorylated FOXO1 is promoted by binding of FOXO1 to 14-3-3 proteins: YWHAZ (14-3-3 zeta), YWHAQ (14-3-3 theta), YWHAB (14-3-3 beta) and YWHAG (14-3-3 gamma) (Rena et al. 2001).

Preceded by: AKT-phosphorylated FOXO1,FOXO3,FOXO4 translocate to the cytosol

Literature references

Cohen, P., Guo, S., Prescott, AR., Rena, G., Unterman, TG. (2001). Roles of the forkhead in rhabdomyosarcoma (FKHR) phosphorylation sites in regulating 14-3-3 binding, transactivation and nuclear targetting. *Biochem. J., 354*, 605-12. ↗

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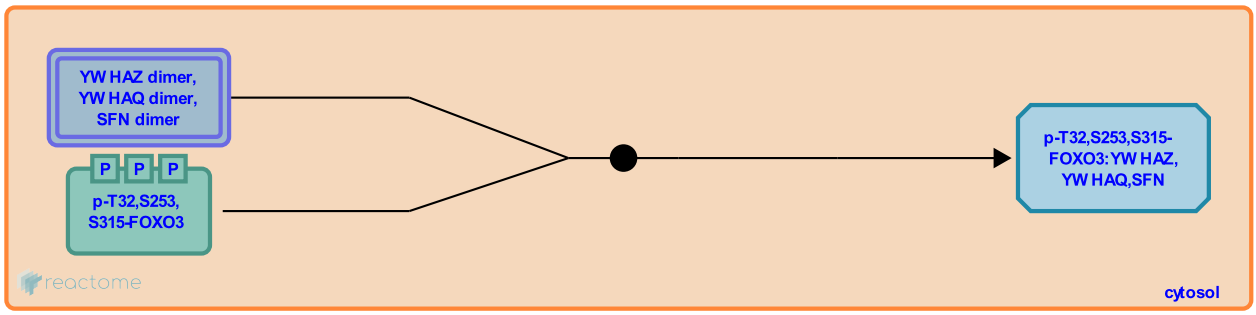
14-3-3 proteins bind AKT-phosphorylated FOXO3 ↗

Location: Regulation of localization of FOXO transcription factors

Stable identifier: R-HSA-9614562

Type: binding

Compartments: cytosol



Nuclear exclusion and cytoplasmic retention of AKT-phosphorylated FOXO3 is promoted by binding of FOXO3 to 14-3-3 proteins: YWHAZ (14-3-3 zeta), YWHAQ (14-3-3 theta), and SFN (14-3-3 sigma) (Brunet et al. 1999, Arimoto-Ishida et al. 2004).

Preceded by: AKT-phosphorylated FOXO1,FOXO3,FOXO4 translocate to the cytosol

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. ↗

Takahashi, T., Ohshima, C., Arimoto-Ishida, E., Nishio, Y., Sakata, M., Ohmichi, M. et al. (2004). Inhibition of phosphorylation of a forkhead transcription factor sensitizes human ovarian cancer cells to cisplatin. *Endocrinology, 145*, 2014-22. ↗

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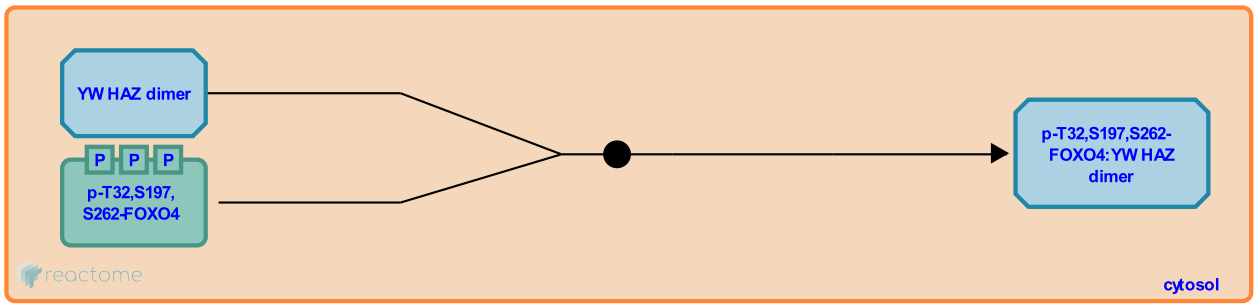
14-3-3 proteins bind AKT-phosphorylated FOXO4 ↗

Location: Regulation of localization of FOXO transcription factors

Stable identifier: R-HSA-9614564

Type: binding

Compartments: cytosol



Nuclear exclusion and cytoplasmic retention of AKT-phosphorylated FOXO4 is promoted by binding of FOXO4 to 14-3-3 zeta (YWHAZ) (Obsilova et al. 2005, Boura et al. 2007, Silhan et al. 2009).

Preceded by: AKT-phosphorylated FOXO1,FOXO3,FOXO4 translocate to the cytosol

Literature references

Sulc, M., Silhan, J., Obsil, T., Obsilova, V., Vecer, J., Strnadova, P. et al. (2009). 14-3-3 protein masks the DNA binding interface of forkhead transcription factor FOXO4. *J. Biol. Chem., 284*, 19349-60. ↗

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