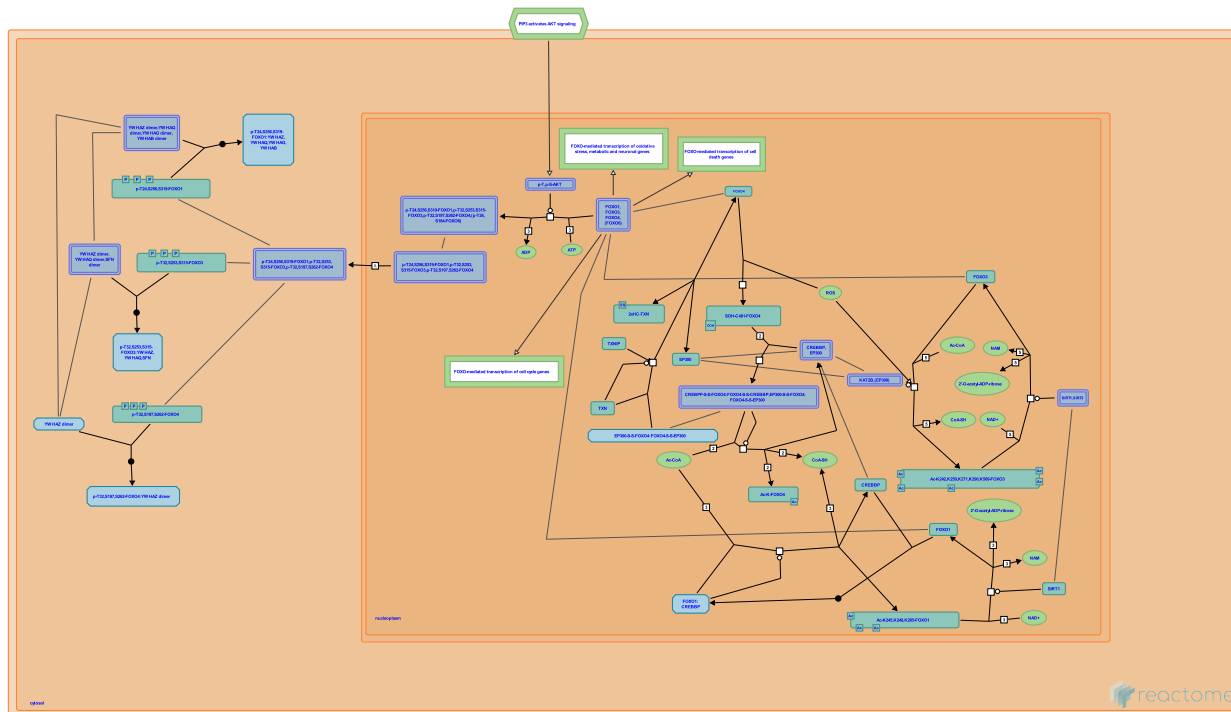


# FOXO-mediated transcription



Bertaggia, E., Donlon, T., Orlic-Milacic, M.

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

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of [Creative Commons Attribution 4.0 International \(CC BY 4.0\) License](https://creativecommons.org/licenses/by/4.0/). For more information see our [license](https://reactome.org/faq).

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](https://reactome.org/Textbook).

05/05/2024

## 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. [↗](#)

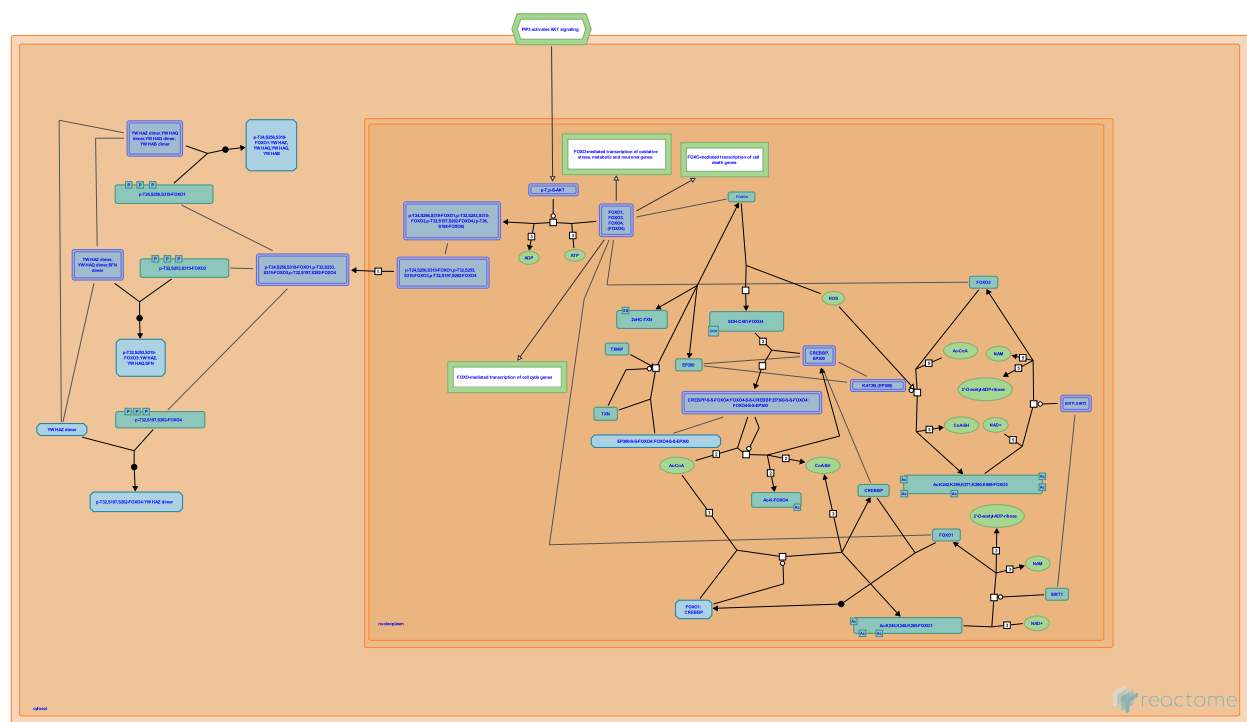
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology*, 14, e1005968. [↗](#)

Reactome database release: 88

This document contains 6 pathways ([see Table of Contents](#))

FOXO-mediated transcription ↗

Stable identifier: R-HSA-9614085



The family of FOXO transcription factors includes FOXO1, FOXO3, FOXO4 and FOXO6. FOXO transcription factors integrate pathways that regulate cell survival, growth, differentiation and metabolism in response to environmental changes, such as growth factor deprivation, starvation and oxidative stress (reviewed by Accili and Arden 2004, Calnan and Brunet 2008, Eijkelenboom and Burgering 2013).

Literature references

Accili, D., Arden, KC. (2004). FoxOs at the crossroads of cellular metabolism, differentiation, and transformation. *Cell*, 117, 421-6. ↗

Burgering, BM., Eijkelenboom, A. (2013). FOXOs: signalling integrators for homeostasis maintenance. *Nat. Rev. Mol. Cell Biol.*, 14, 83-97. ↗

Brunet, A., Calnan, DR. (2008). The FoxO code. *Oncogene*, 27, 2276-88. ↗

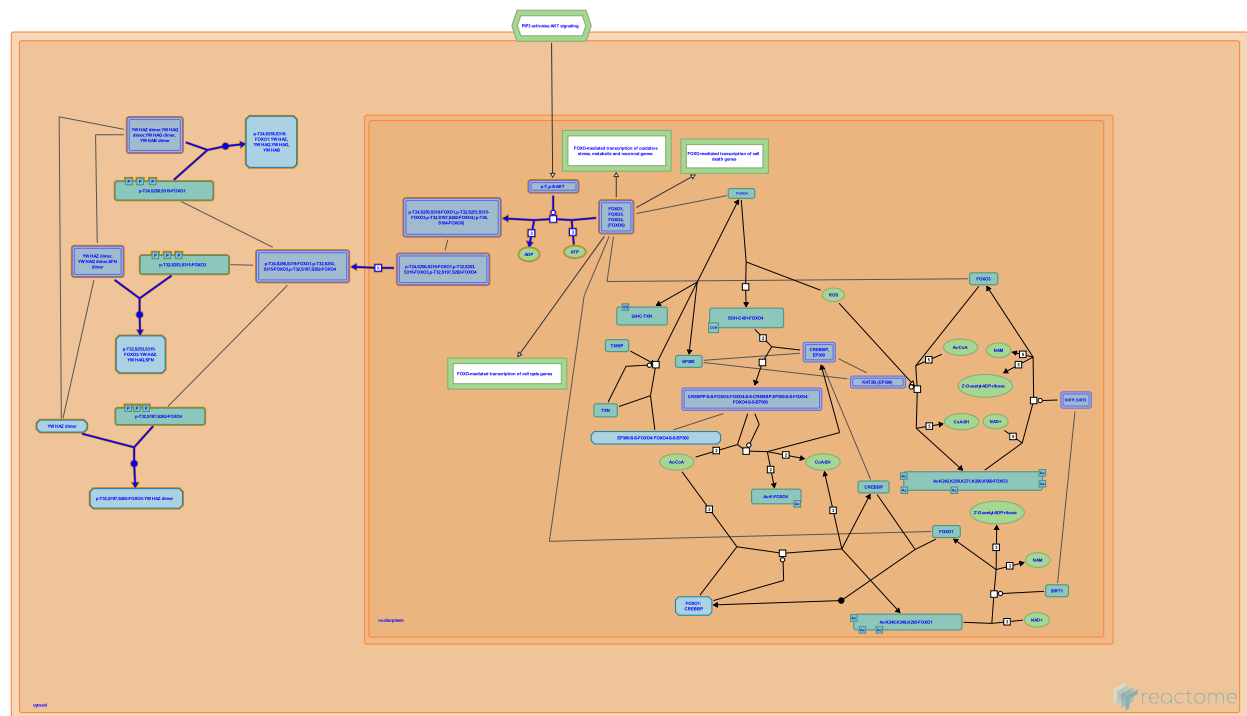
Editions

2018-10-11	Authored	Orlic-Milacic, M.
2018-10-17	Reviewed	Donlon, T.
2018-10-26	Reviewed	Bertaggia, E.
2018-10-31	Edited	Orlic-Milacic, M.

# Regulation of localization of FOXO transcription factors ↗

**Location:** FOXO-mediated transcription

**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. ↗

Powell, DR., Burgering, BM., De Vries-Smits, AM., de Ruiter, ND., Bos, JL., Kops, GJ. (1999). Direct control of the Forkhead transcription factor AFX by protein kinase B. *Nature*, 398, 630-4. ↗

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. ↗

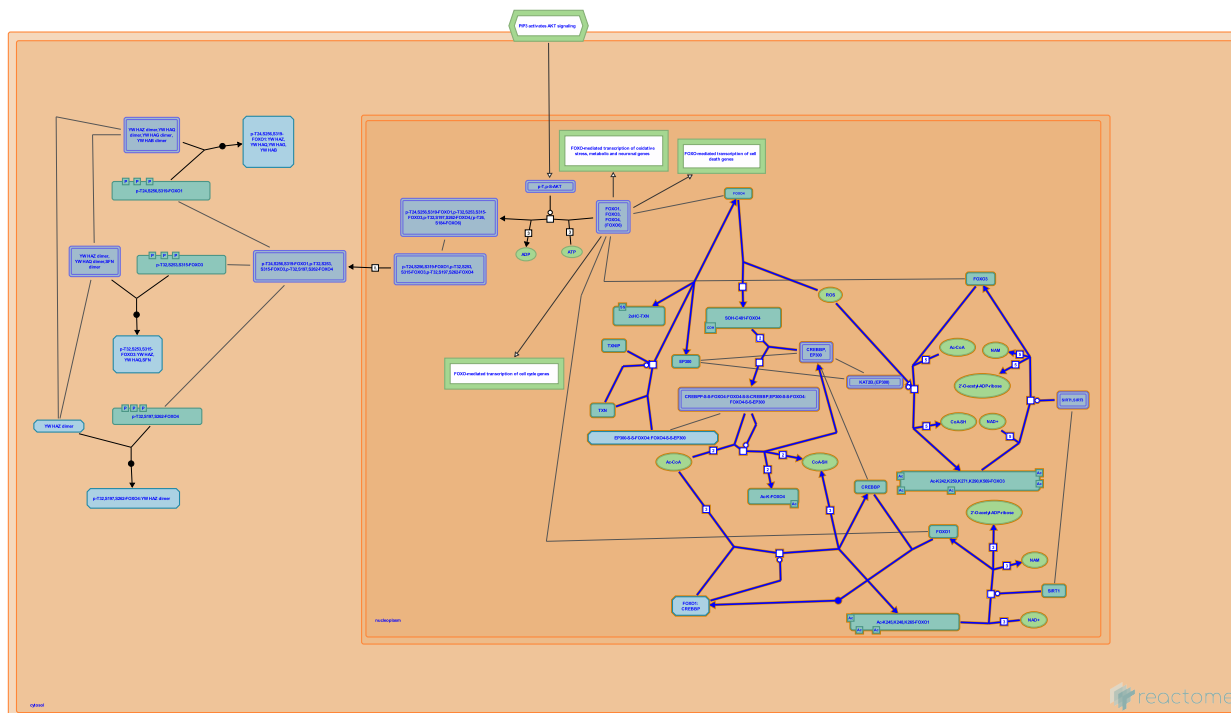
## Editions

2018-10-11	Authored	Orlic-Milacic, M.
2018-10-17	Reviewed	Donlon, T.
2018-10-26	Reviewed	Bertaggia, E.
2018-10-31	Edited	Orlic-Milacic, M.

# Regulation of FOXO transcriptional activity by acetylation ↗

**Location:** FOXO-mediated transcription

**Stable identifier:** R-HSA-9617629



Oxidative stress induces acetylation of FOXO transcription factors, which changes the preference of FOXO transcription factors for target DNA sequences. Histone deacetylases SIRT1 and SIRT3 deacetylate FOXO transcription factors (Brunet et al. 2004, Daitoku et al. 2004, Motta et al. 2004, Dansen et al. 2009, Kim et al. 2010, Tseng et al. 2013, reviewed by Hisahara et al. 2005). Acetylation can also regulate FOXO localization, overriding phosphorylation (Frescas et al. 2005, Bertagaglia et al. 2012).

## Literature references

- Coletto, L., Sandri, M., Bertagaglia, E. (2012). Posttranslational modifications control FoxO3 activity during denervation. *Am. J. Physiol., Cell Physiol.*, 302, C587-96. ↗
- Sinclair, DA., Jedrychowski, MP., Greenberg, ME., Brunet, A., Alt, FW., Gygi, SP. et al. (2004). Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase. *Science*, 303, 2071-5. ↗
- Tseng, AH., Shieh, SS., Wang, DL. (2013). SIRT3 deacetylates FOXO3 to protect mitochondria against oxidative damage. *Free Radic. Biol. Med.*, 63, 222-34. ↗
- van Leenen, D., Burgering, BM., Yodoi, J., van Triest, MH., Holstege, FC., Meppelink, A. et al. (2009). Redox-sensitive cysteines bridge p300/CBP-mediated acetylation and FoxO4 activity. *Nat. Chem. Biol.*, 5, 664-72. ↗
- Chiba, S., Horio, Y., Hisahara, S., Matsumoto, H. (2005). Transcriptional regulation of neuronal genes and its effect on neural functions: NAD-dependent histone deacetylase SIRT1 (Sir2alpha). *J. Pharmacol. Sci.*, 98, 200-4. ↗

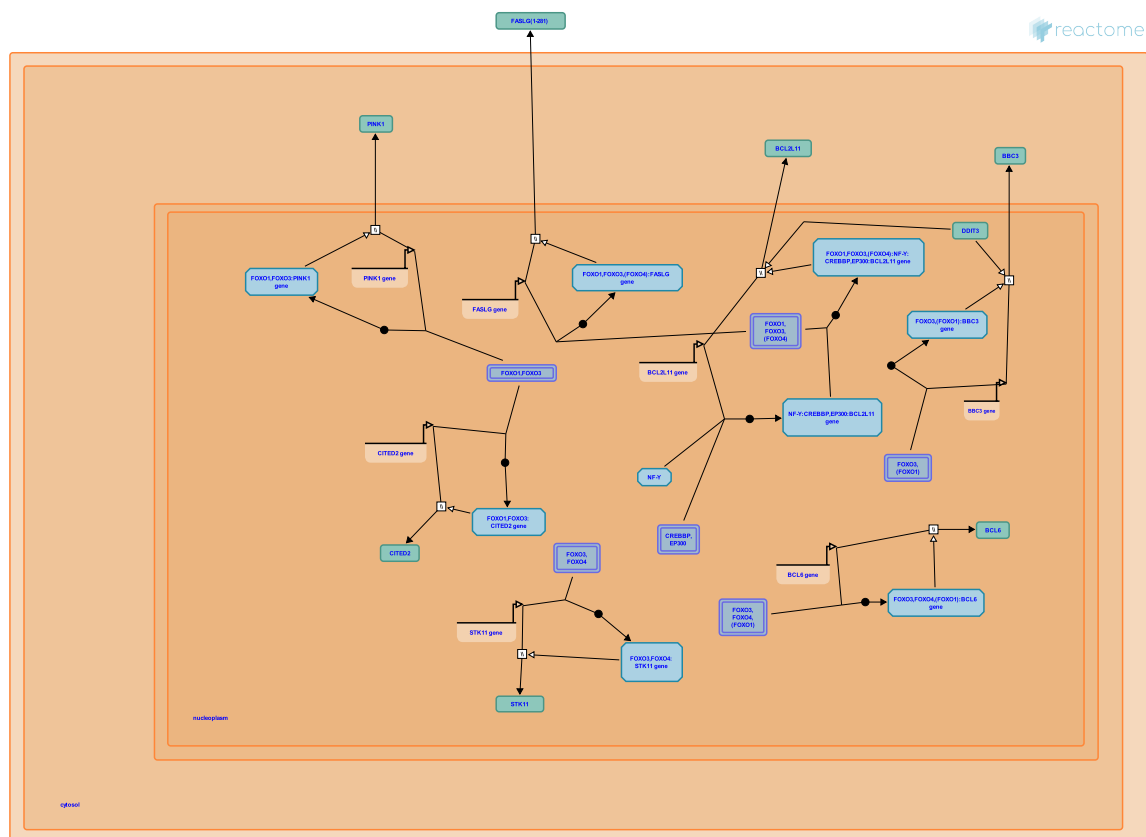
## Editions

2018-10-11	Authored	Orlic-Milacic, M.
2018-10-17	Reviewed	Donlon, T.
2018-10-26	Reviewed	Bertagaglia, E.
2018-10-31	Edited	Orlic-Milacic, M.

## FOXO-mediated transcription of cell death genes ↗

**Location:** FOXO-mediated transcription

**Stable identifier:** R-HSA-9614657



FOXO transcription factors promote expression of several pro-apoptotic genes, such as FASLG (Brunet et al. 1999, Ciechomska et al. 2003, Chen et al. 2013, Li et al. 2015), PINK1 (Mei et al. 2009, Sengupta et al. 2011), BCL2L1 (BIM) (Gilley et al. 2003, Urbich et al. 2005, Chuang et al. 2007, Hughes et al. 2011, Chen et al. 2013, Wang et al. 2016), BCL6 (Tang et al. 2002, Fernandez de Mattos et al. 2004, Shore et al. 2006) and BBC3 (PUMA) (Dudgeon et al. 2010, Hughes et al. 2011, Liu et al. 2015, Wu et al. 2016, Liu et al. 2017, Fitzwalter et al. 2018). FOXO-mediated induction of cell death genes is important during development, for example during nervous system development, where FOXO promotes neuronal death upon NGF withdrawal (Gilley et al. 2003), and also contributes to the tumor-suppressive role of FOXO factors (Arimoto Ishida et al. 2004). FOXO1 transcriptional activity is implicated in the cell death of enteric nervous system (ENS) precursors. RET signaling, which activates PI3K/AKT signaling, leading to inhibition of FOXO mediated transcription, ensures survival of ENS precursors (Srinivasan et al. 2005).

Transcription of the STK11 (LKB1) gene, encoding Serine/threonine-protein kinase STK11 (also known as Liver kinase B1), which regulates diverse cellular processes, including apoptosis, is directly stimulated by FOXO3 and FOXO4 (Lutzner et al. 2012).

## Literature references

- Hu, W., Zhou, PH., Wang, W. (2016). Overexpression of FOXO4 induces apoptosis of clear-cell renal carcinoma cells through downregulation of Bim. *Mol Med Rep*, 13, 2229-34. ↗
- Desagher, S., Lassot, I., Mantovani, R., Ham, J., Hughes, R., Kristiansen, M. (2011). NF-Y is essential for expression of the proapoptotic bim gene in sympathetic neurons. *Cell Death Differ.*, 18, 937-47. ↗
- He, JC., Yu, Q., Fang, W., Chuang, PY., Uribarri, J. (2007). Advanced glycation endproducts induce podocyte apoptosis by activation of the FOXO4 transcription factor. *Kidney Int.*, 72, 965-76. ↗
- Li, J., Wu, J., Lu, F., Tian, C., Hu, L., Liu, L. (2015). microRNA-150 promotes cervical cancer cell growth and survival by targeting FOXO4. *BMC Mol. Biol.*, 16, 24. ↗
- Dowbenko, D., Lewin, DA., Dent, AL., Tang, TT., Lasky, LA., Toney, L. et al. (2002). The forkhead transcription factor AFX activates apoptosis by induction of the BCL-6 transcriptional repressor. *J. Biol. Chem.*, 277, 14255-65. ↗

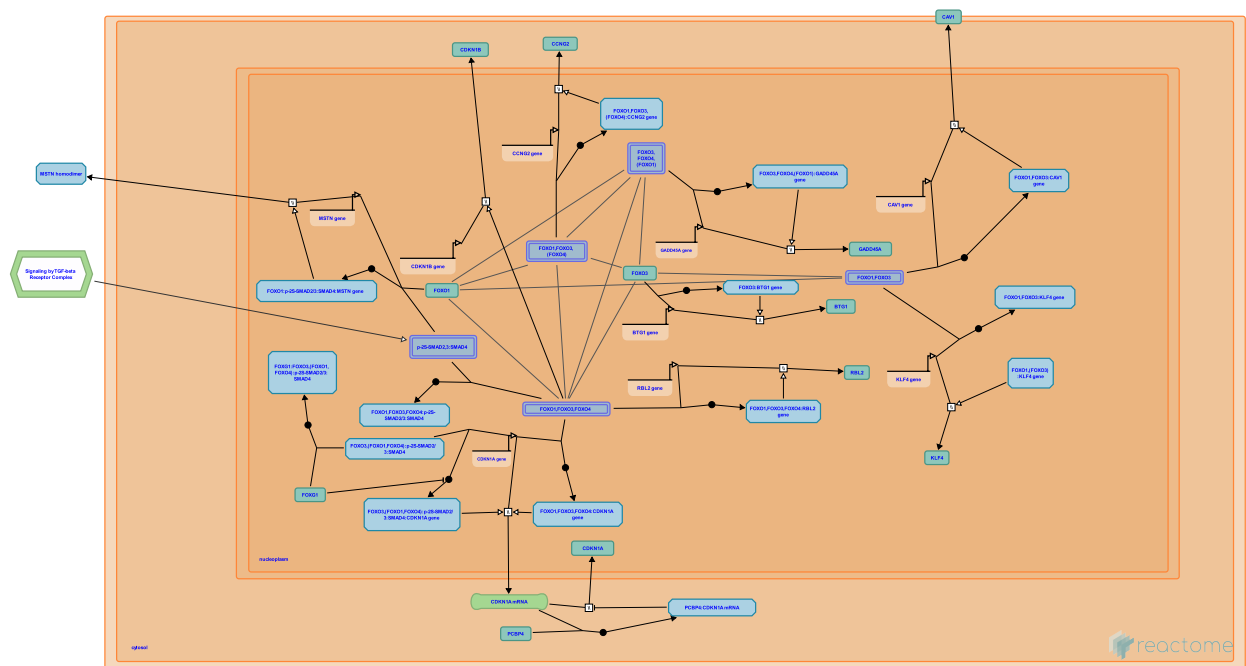
## Editions

2018-10-11	Authored	Orlic-Milacic, M.
2018-10-17	Reviewed	Donlon, T.
2018-10-26	Reviewed	Bertaggia, E.
2018-10-31	Edited	Orlic-Milacic, M.

## FOXO-mediated transcription of cell cycle genes ↗

**Location:** FOXO-mediated transcription

**Stable identifier:** R-HSA-9617828



FOXO transcription factors induce expression of several genes that negatively regulate proliferation of different cell types, such as erythroid progenitors (Bakker et al. 2004, Wang et al. 2015) and neuroepithelial progenitor cells in the telencephalon (Seoane et al. 2004).

Transcription of cyclin-dependent kinase (CDK) inhibitors CDKN1A (p21Cip1) is directly stimulated by FOXO1, FOXO3 and FOXO4 (Seoane et al. 2004, Tinkum et al. 2013). FOXO transcription factors can cooperate with the SMAD2/3:SMAD4 complex to induce CDKN1A transcription in response to TGF-beta signaling (Seoane et al. 2004).

FOXO transcription factors FOXO1, FOXO3 and FOXO4 stimulate transcription of the CDKN1B (p27Kip1) gene, but direct binding of FOXOs to the CDKN1B gene locus has not been demonstrated (Dijkers et al. 2000, Medema et al. 2000, Lees et al. 2008).

FOXO3 and FOXO4, and possibly FOXO1, directly stimulate transcription of the GADD45A gene (Tran et al. 2002, Furukawa Hibi et al. 2002, Hughes et al. 2011, Sengupta et al. 2011, Ju et al. 2014).

Transcription of the retinoblastoma family protein RBL2 (p130), involved in the maintenance of quiescent (G0) state, is directly stimulated by FOXO1, FOXO3 and FOXO4 (Kops et al. 2002, Chen et al. 2006).

Transcription of the anti-proliferative protein CCNG2 is directly stimulated by FOXO1 and FOXO3, and possibly FOXO4 (Martinez Gac et al. 2004, Chen et al. 2006). Transcription of the anti-proliferative protein BTG1 is directly stimulated by FOXO3 (Bakker et al. 2004, Bakker et al. 2007, Wang et al. 2015).

Transcription of CAV1, encoding caveolin-1, involved in negative regulation of growth factor receptor signaling and establishment of quiescent cell phenotype, is directly stimulated by FOXO1 and FOXO3 (van den Heuvel et al. 2005, Roy et al. 2008, Nho et al. 2013, Sisci et al. 2013).

FOXO1 and FOXO3 promote transcription of the KLF4 gene, encoding a transcription factor Krueppel-like factor 4, which inhibits proliferation of mouse B cells (Yusuf et al. 2008).

FOXO1, together with the p-2S-SMAD2/3:SMAD4 complex, stimulates transcription of the MSTN gene, encoding myostatin, a TGF-beta family member that stimulates differentiation of myoblasts (Allen and Unterman 2007).

### Literature references

- Burgering, BM., Schulze, A., van den Heuvel, AP. (2005). Direct control of caveolin-1 expression by FOXO transcription factors. *Biochem. J.*, 385, 795-802. ↗
- Ikeda, K., Motoyama, N., Ohta, T., Yoshida-Araki, K., Furukawa-Hibi, Y. (2002). FOXO forkhead transcription factors induce G(2)-M checkpoint in response to oxidative stress. *J. Biol. Chem.*, 277, 26729-32. ↗
- Allen, DL., Unterman, TG. (2007). Regulation of myostatin expression and myoblast differentiation by FoxO and SMAD transcription factors. *Am. J. Physiol., Cell Physiol.*, 292, C188-99. ↗

Medema, RH., Burgering, BM., Glassford, J., Kops, GJ., Lam, EW., Coffey, PJ. et al. (2002). Control of cell cycle exit and entry by protein kinase B-regulated forkhead transcription factors. *Mol. Cell. Biol.*, 22, 2025-36. [↗](#)

Yu, A., Xu, T., Ju, Y., Zhang, H. (2014). FOXO1-dependent DNA damage repair is regulated by JNK in lung cancer cells. *Int. J. Oncol.*, 44, 1284-92. [↗](#)

## Editions

2018-10-11	Authored	Orlic-Milacic, M.
2018-10-17	Reviewed	Donlon, T.
2018-10-26	Reviewed	Bertaggia, E.
2018-10-31	Edited	Orlic-Milacic, M.



GCK (glucokinase) gene is another gene involved in lipid homeostasis that is regulated by FOXOs. FOXO1, acting with the SIN3A:HDAC complex, directly represses the GCK gene transcription, thus repressing lipogenesis in the absence of insulin (Langlet et al. 2017). The SREBF1 (SREBP1) gene, which encodes a transcriptional activator required for lipid homeostasis, is directly transcriptionally repressed by FOXO1 (Deng et al. 2012). Transcription of the RETN gene, encoding resistin, an adipocyte specific hormone that suppresses insulin-mediated uptake of glucose by adipose cells, is directly stimulated by FOXO1 (Liu et al. 2014). Transcription of two genes encoding E3 ubiquitin ligases FBXO32 (Atrogin-1) and TRIM63 (MURF1), involved in degradation of muscle proteins and muscle wasting during starvation, is positively regulated by FOXO transcription factors (Sandri et al. 2004, Waddell et al. 2008, Raffaello et al. 2010, Senf et al. 2011, Bollinger et al. 2014, Wang et al. 2017).

## Literature references

- Jin, Y., Hu, C., Lv, Y., Yang, X., Deng, Z., Shuai, Y. et al. (2016). TNF- $\alpha$  Inhibits FoxO1 by Upregulating miR-705 to Aggravate Oxidative Damage in Bone Marrow-Derived Mesenchymal Stem Cells during Osteoporosis. *Stem Cells*, 34, 1054-67. [↗](#)
- Liu, H., Zhang, P., Zhang, C., Fan, M., Wang, J., He, J. et al. (2017). PGC-1 $\alpha$  over-expression suppresses the skeletal muscle atrophy and myofiber-type composition during hindlimb unloading. *Biosci. Biotechnol. Biochem.*, 81, 500-513. [↗](#)
- Elam, MB., Williams, JB., O-Sullivan, I., Raghow, R., Unterman, TG., Dong, Q. et al. (2012). FoxO1 inhibits sterol regulatory element-binding protein-1c (SREBP-1c) gene expression via transcription factors Sp1 and SREBP-1c. *J. Biol. Chem.*, 287, 20132-43. [↗](#)
- Liu, XH., Jiang, K., Deng, KY., Xiao, YF., Guan, XH., Wang, LF. et al. (2016). CD38 Deficiency Protects the Heart from Ischemia/Reperfusion Injury through Activating SIRT1/FOXOs-Mediated Antioxidative Stress Pathway. *Oxid Med Cell Longev*, 2016, 7410257. [↗](#)
- Tatar, M., Lee, KS., Jung, MS., Kim, AK., Hong, SH., Song, WJ. et al. (2012). Minibrain/Dyrk1a regulates food intake through the Sir2-FOXO-sNPF/NPY pathway in Drosophila and mammals. *PLoS Genet.*, 8, e1002857. [↗](#)

## Editions

2018-10-11	Authored	Orlic-Milacic, M.
2018-10-17	Reviewed	Donlon, T.
2018-10-26	Reviewed	Bertaggia, E.
2018-10-31	Edited	Orlic-Milacic, M.

# Table of Contents

Introduction	1
❖ FOXO-mediated transcription	2
❖ Regulation of localization of FOXO transcription factors	3
❖ Regulation of FOXO transcriptional activity by acetylation	4
❖ FOXO-mediated transcription of cell death genes	5
❖ FOXO-mediated transcription of cell cycle genes	7
❖ FOXO-mediated transcription of oxidative stress, metabolic and neuronal genes	9
Table of Contents	11