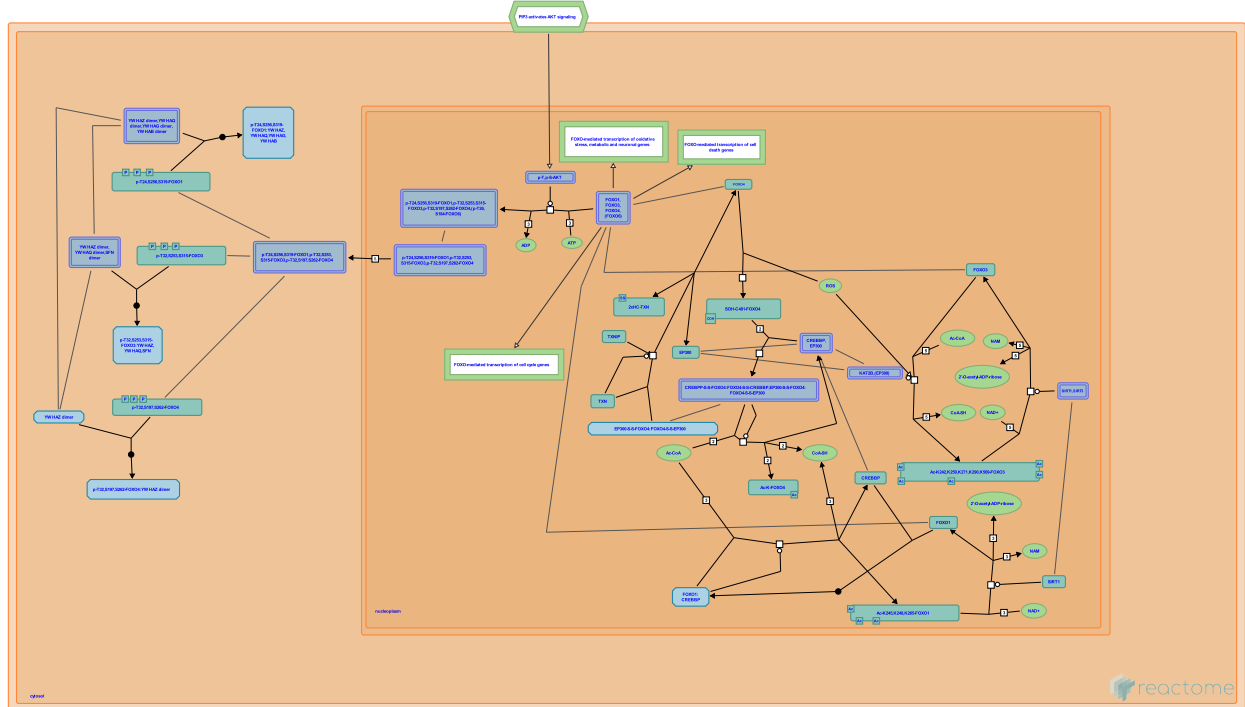


# FOXO-mediated transcription



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26/04/2024

## 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).

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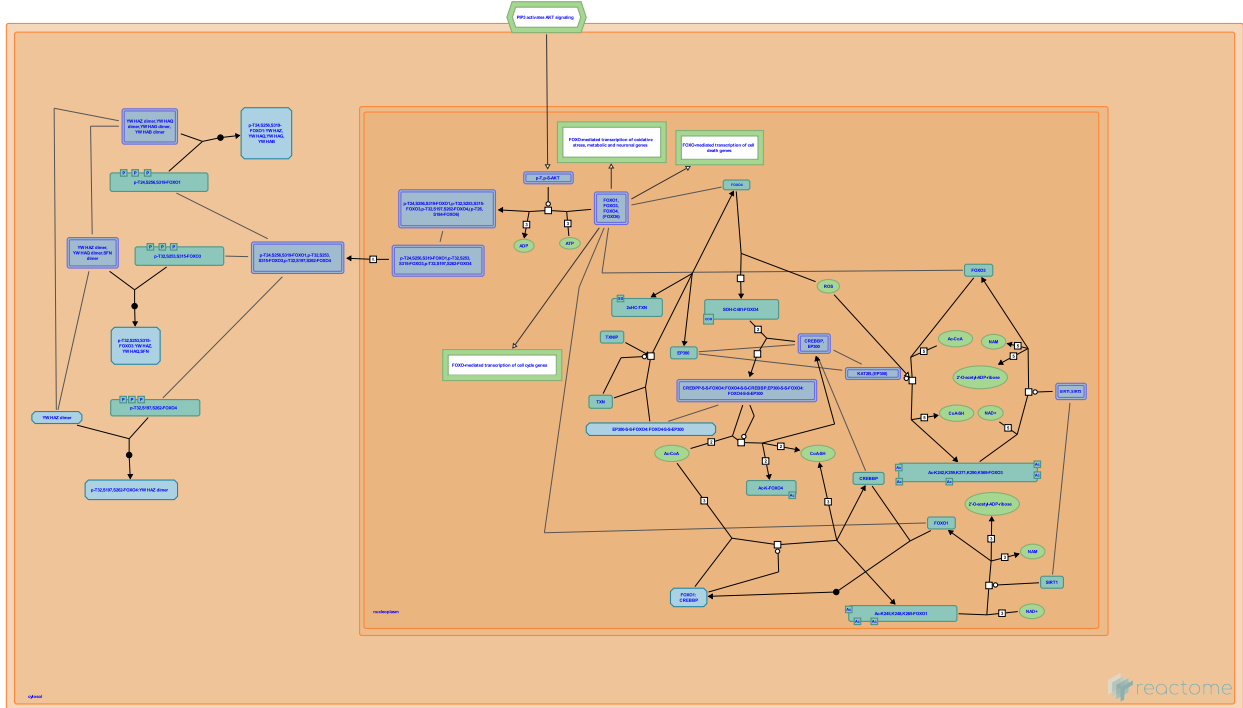
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Reactome database release: 88

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).

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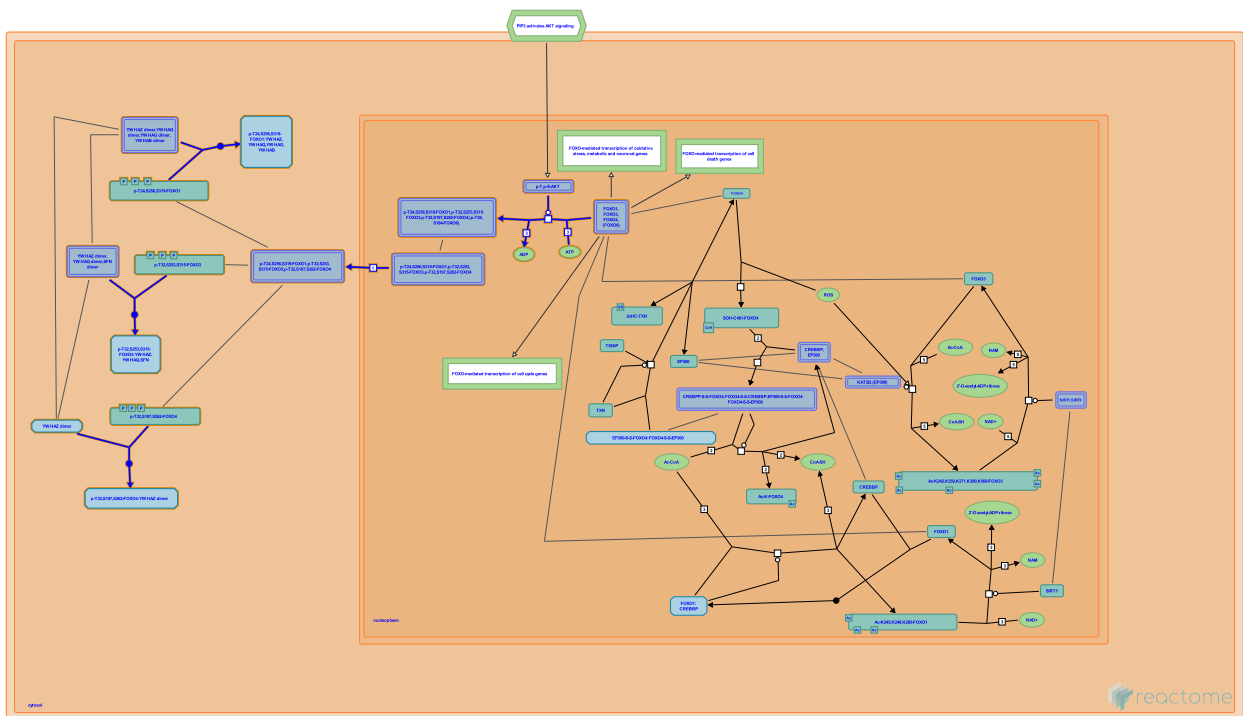
## Editions

2018-10-11	Authored	Orlic-Milacic, M.
2018-10-17	Reviewed	Donlon, T.
2018-10-26	Reviewed	Bertaglia, 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).

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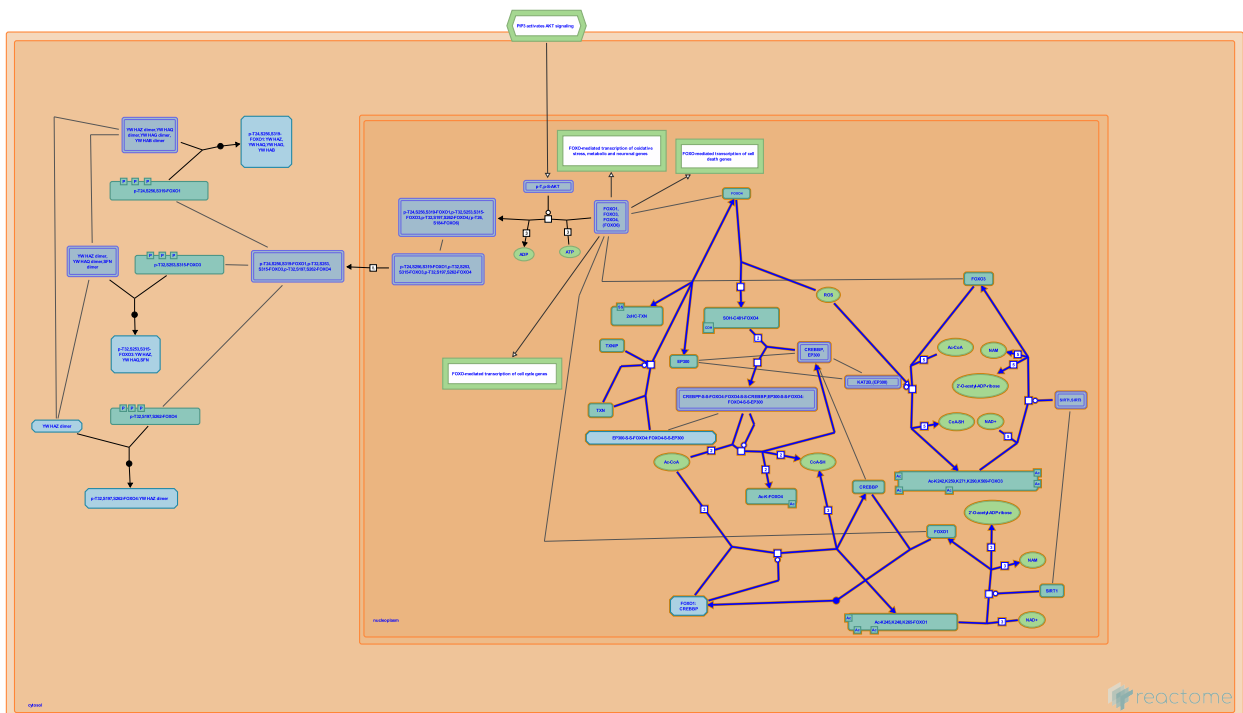
## Editions

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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, Bertaggia et al. 2012).

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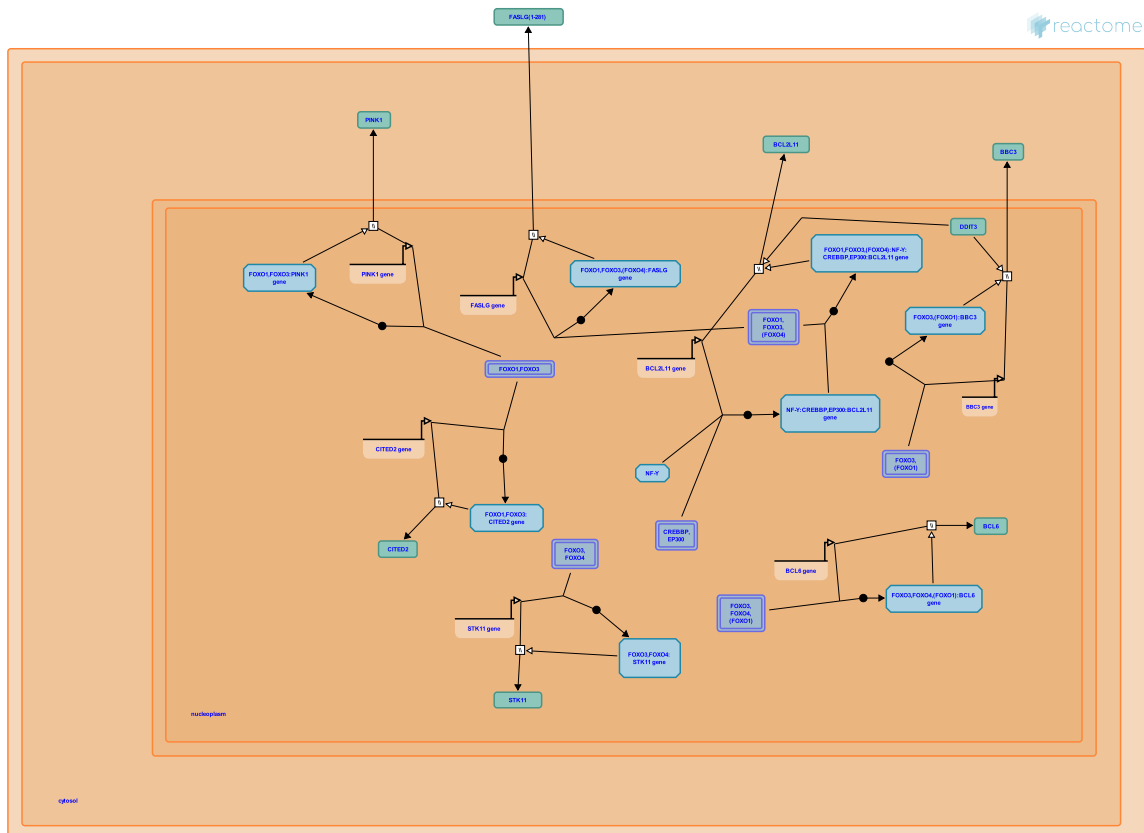
## Editions

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 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).

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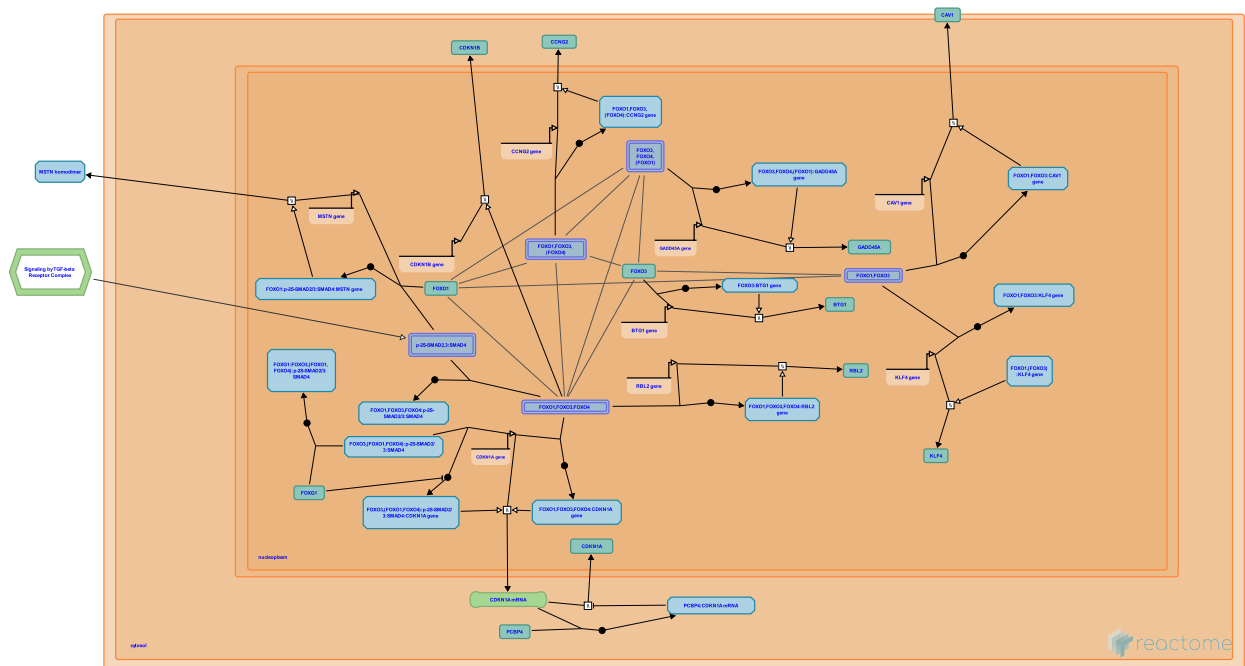
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2018-10-11	Authored	Orlic-Milacic, M.
2018-10-17	Reviewed	Donlon, T.
2018-10-26	Reviewed	Bertaggia, E.
2018-10-31	Edited	Orlic-Milacic, M.

## 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).

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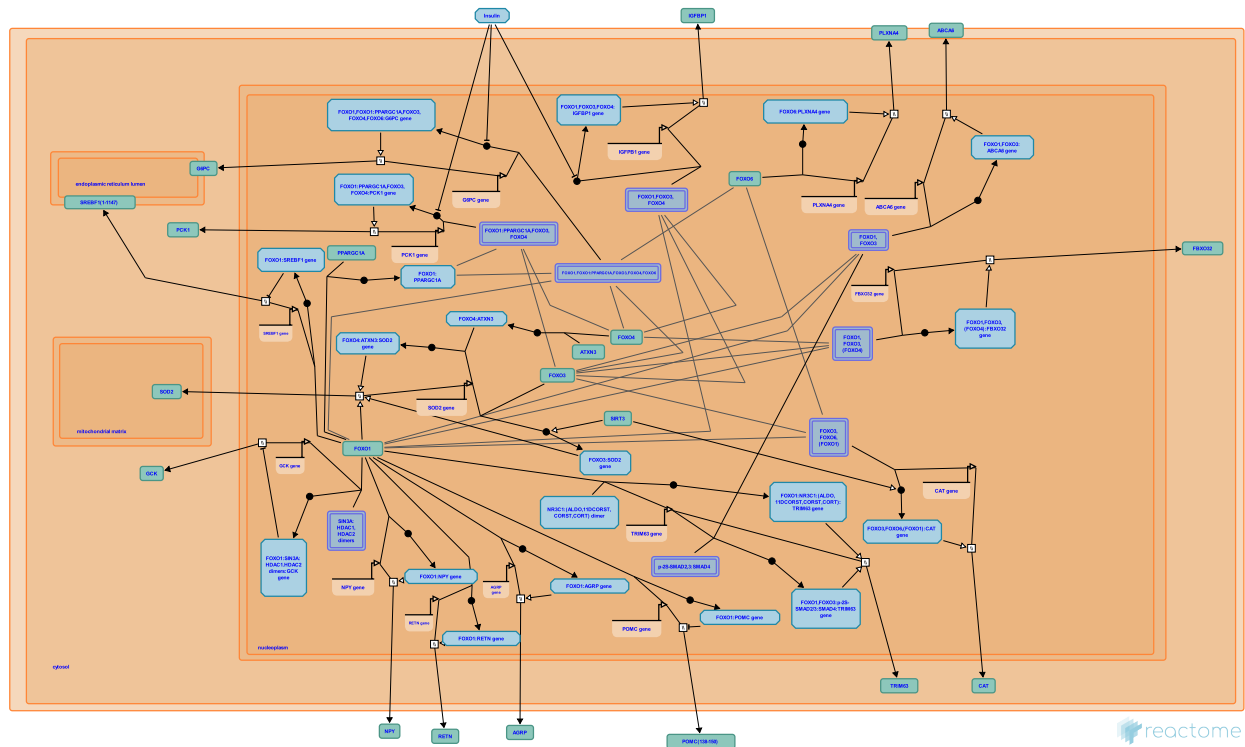
## Editions

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 oxidative stress, metabolic and neuronal genes ↗

**Location:** FOXO-mediated transcription

**Stable identifier:** R-HSA-9615017



FOXO6, the least studied member of the FOXO family, directly stimulates transcription of PLXNA4 gene, encoding a co-factor for the semaphorin SEMA3A receptor. FOXO6-mediated regulation of PLXNA4 expression plays an important role in radial glia migration during cortical development (Paap et al. 2016).

FOXO-mediated up-regulation of genes involved in reduction of the oxidative stress burden is not specific to neurons, but plays an important role in neuronal survival and neurodegenerative diseases. FOXO3 and FOXO4, and possibly FOXO1, directly stimulate transcription of the SOD2 gene, encoding mitochondrial manganese-dependent superoxide dismutase, which converts superoxide to the less harmful hydrogen peroxide and oxygen (Kops et al. 2002, Hori et al. 2013, Araujo et al. 2011, Guan et al. 2016). FOXO4 stimulates SOD2 gene transcription in collaboration with ATXN3, a protein involved in spinocerebellar ataxia type 3 (SCA3) (Araujo et al. 2011). FOXO3 and FOXO6, and possibly FOXO1, directly stimulate transcription of the CAT gene, encoding catalase, an enzyme that converts hydrogen peroxide to water and oxygen, thus protecting cells from the oxidative stress (Awad et al. 2014, Kim et al. 2014, Rangarajan et al. 2015, Song et al. 2016, Liao et al. 2016, Guo et al. 2016).

FOXO transcription factors regulate transcription of several genes whose protein products are secreted from hypothalamic neurons to control appetite and food intake: NPY gene, AGRP gene and POMC gene. At low insulin levels, characteristic of starvation, FOXO transcription factors bind to insulin responsive elements (IRES) in the regulatory regions of NPY, AGRP and POMC gene. FOXO1 directly stimulates transcription of the NPY gene, encoding neuropeptide-Y (Kim et al. 2006, Hong et al. 2012), and the AGRP gene, encoding Agouti-related protein (Kitamura et al. 2006, Kim et al. 2006), which both stimulate food intake. At the same time, FOXO1 directly represses transcription of the POMC gene, encoding melanocyte stimulating hormone alpha, which suppresses food intake (Kitamura et al. 2006, Kim et al. 2006). When, upon food intake, blood insulin levels rise, insulin-mediated activation of PI3K/AKT signaling inhibits FOXO transcriptional activity.

In liver cells, FOXO transcription factors regulate transcription of genes involved in gluconeogenesis: G6PC gene, encoding glucose-6-phosphatase and PCK1 gene, encoding phosphoenolpyruvate carboxykinase. Actions of G6PC and PCK1 enable steady glucose blood levels during fasting. FOXO1, FOXO3 and FOXO4 directly stimulate PCK1 gene transcription (Hall et al. 2000, Yang et al. 2002, Puigserver et al. 2003), while all four FOXOs, FOXO1, FOXO3, FOXO4 and FOXO6 directly stimulate G6PC gene transcription (Yang et al. 2002, Puigserver et al. 2003, Onuma et al. 2006, Kim et al. 2011). FOXO-mediated induction of G6PC and PCK1 genes is negatively regulated by insulin-induced PI3K/AKT signaling.

FOXO1, FOXO3 and FOXO4 directly stimulate transcription of the IGF1 gene, encoding insulin growth factor binding protein 2 (Tang et al. 1999, Kops et al. 1999, Hall et al. 2000, Yang et al. 2002), which increases sensitivity of cells to insulin.

FOXO1 and FOXO3 directly stimulate transcription of the ABCA6 (ATP-binding cassette sub-family A member 6) gene, encoding a putative transporter protein that is thought to be involved in lipid homeostasis (Gai et al. 2013). The

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).

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## 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.

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