FOXO-mediated transcription

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26/03/2022
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.

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Literature references


Reactome database release: 79

This document contains 6 pathways (see *Table of Contents*).
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**


**Editions**

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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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Regulation of FOXO transcriptional activity by acetylation

Location: FOXO-mediated transcription

Stable identifier: R-HSA-9617629


Acetylation can also regulate FOXO localization, overriding phosphorylation ( Frescas et al. 2005, Bertaggia et al. 2012).

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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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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).


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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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. 2011, 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:

FOXO1, FOXO3 and FOXO4 directly stimulate transcription of the IGFBP1 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).


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