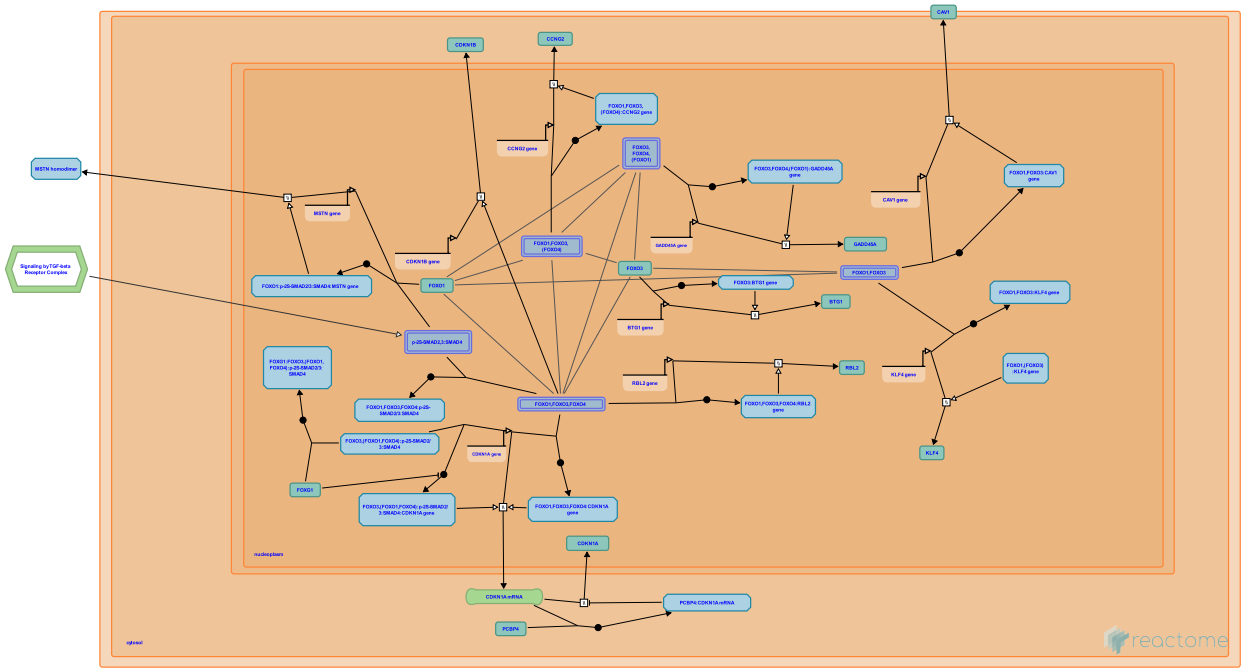
FOXO-mediated transcription of cell cycle genes



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04/05/2024

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. ↗

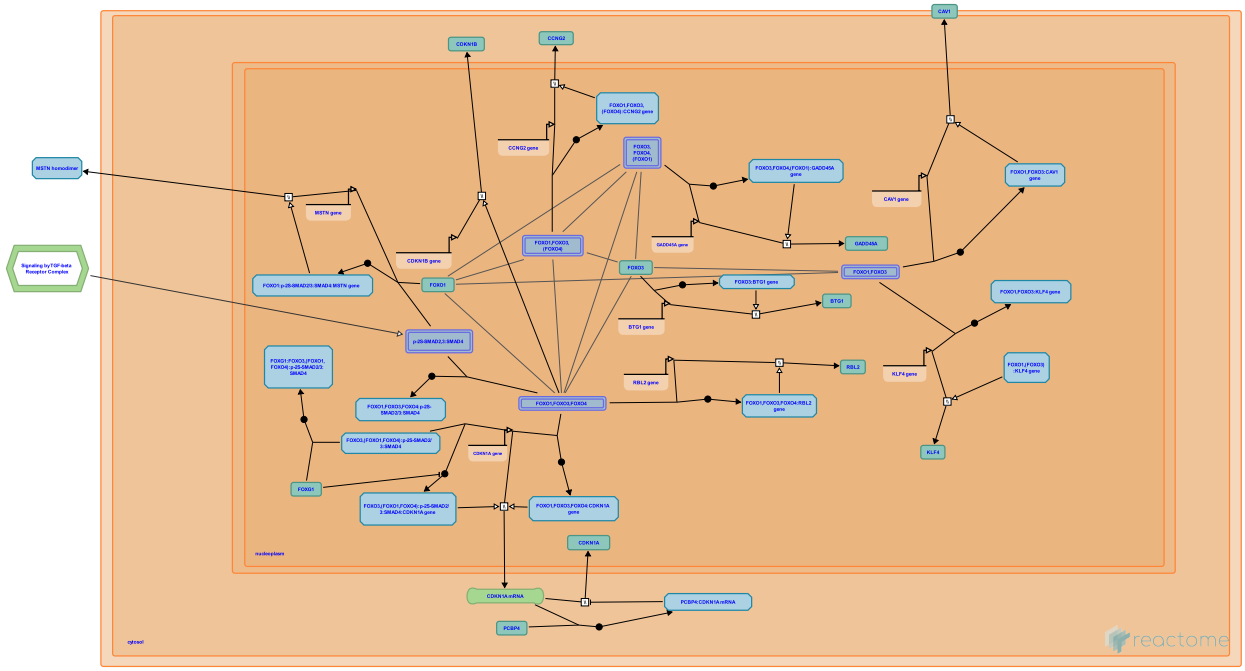
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

FOXO-mediated transcription of cell cycle genes ↗

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., Coffer, 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.
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2018-10-26	Reviewed	Bertaggia, E.
2018-10-31	Edited	Orlic-Milacic, M.

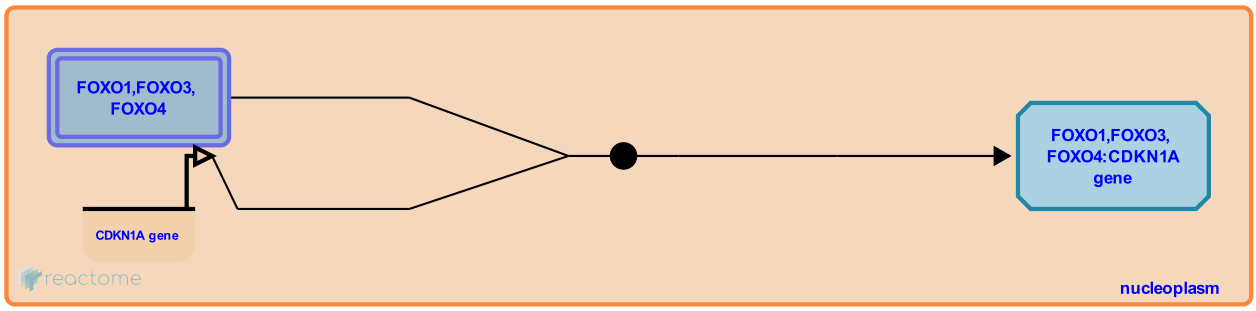
FOXO1,FOXO3,FOXO4 bind CDKN1A gene promoter ↗

Location: FOXO-mediated transcription of cell cycle genes

Stable identifier: R-HSA-9617840

Type: binding

Compartments: nucleoplasm



FOXO1, FOXO3 and FOXO4 can all bind to forkhead box elements in the promoter region of the CDKN1A gene, encoding CDK inhibitor p21Cip1 (Seoane et al. 2004, Tinkum et al. 2013).

Followed by: CDKN1A gene transcription is stimulated by FOXO1,FOXO3,FOXO4

Literature references

Massague, J., Shen, L., Le, HV., Anderson, SA., Seoane, J. (2004). Integration of Smad and forkhead pathways in the control of neuroepithelial and glioblastoma cell proliferation. *Cell, 117*, 211-23. ↗

Piwnica-Worms, H., Herzog, E., White, LS., Marpegan, L., Piwnica-Worms, D., Tinkum, KL. (2013). Forkhead box O1 (FOXO1) protein, but not p53, contributes to robust induction of p21 expression in fasted mice. *J. Biol. Chem., 288* , 27999-8008. ↗

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2018-10-11	Authored	Orlic-Milacic, M.
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2018-10-31	Edited	Orlic-Milacic, M.

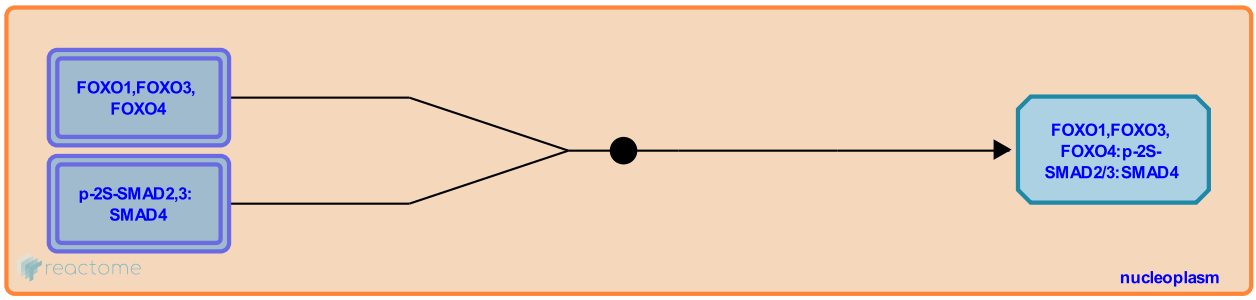
FOXO1,FOXO3,FOXO4 bind p-2S-SMAD2/3:SMAD4 ↗

Location: FOXO-mediated transcription of cell cycle genes

Stable identifier: R-HSA-9617996

Type: binding

Compartments: nucleoplasm



In response to TGF-beta signaling, forkhead box transcription factors FOXO1, FOXO3 and FOXO4 bind to phosphorylated SMAD2/3:SMAD4 trimers by direct interaction between FOXO proteins and SMAD3 or SMAD4. FOXO proteins do not interact with all splicing isoforms of SMAD2 (Seoane et al. 2004).

Followed by: FOXG1 binds FOXO:SMAD complexes, FOXO:SMAD complex binds CDKN1A gene promoter

Literature references

Massague, J., Shen, L., Le, HV., Anderson, SA., Seoane, J. (2004). Integration of Smad and forkhead pathways in the control of neuroepithelial and glioblastoma cell proliferation. *Cell, 117*, 211-23. ↗

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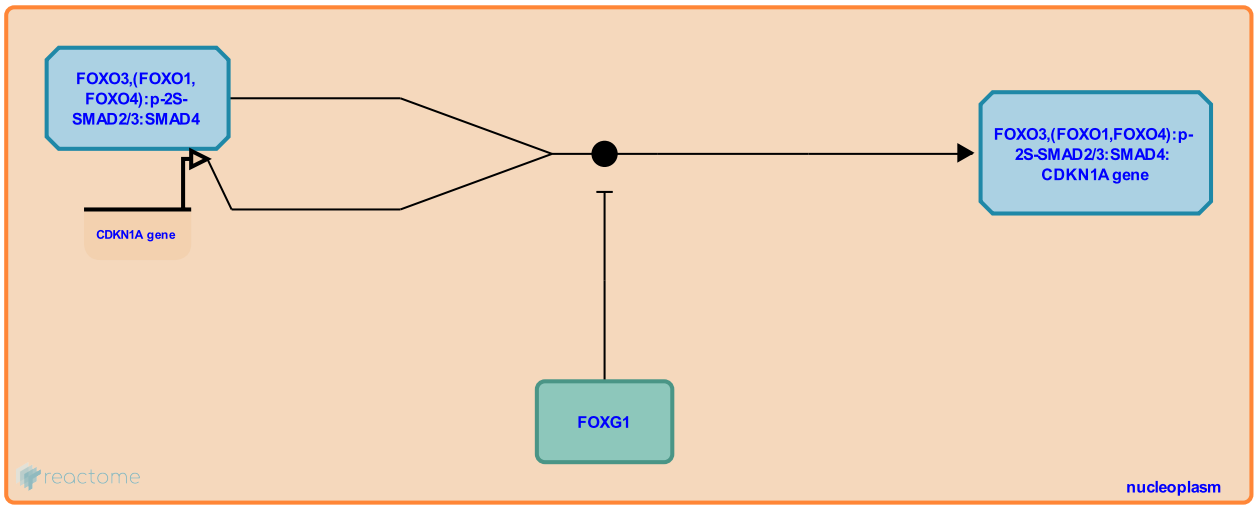
FOXO:SMAD complex binds CDKN1A gene promoter ↗

Location: FOXO-mediated transcription of cell cycle genes

Stable identifier: R-HSA-9618004

Type: binding

Compartments: nucleoplasm



The complex of phosphorylated SMAD2/3 and SMAD4, bound to FOXO3, binds to the promoter of the CDKN1A gene. The p-2S-SMAD2/3:SMAD4 complex bound to FOXO1 or FOXO4 can probably also bind to the CDKN1A gene promoter. FOXG1 binding to the FOXO:SMAD complex inhibits FOXO:SMAD-mediated upregulation of CDKN1A transcription. FOXG1 plays an important role in sustained proliferation of telencephalic neuroepithelial progenitor cells (Seoane et al. 2004).

Preceded by: FOXO1,FOXO3,FOXO4 bind p-2S-SMAD2/3:SMAD4

Followed by: CDKN1A gene transcription is stimulated by FOXO1,FOXO3,FOXO4

Literature references

Massague, J., Shen, L., Le, HV., Anderson, SA., Seoane, J. (2004). Integration of Smad and forkhead pathways in the control of neuroepithelial and glioblastoma cell proliferation. *Cell, 117*, 211-23. ↗

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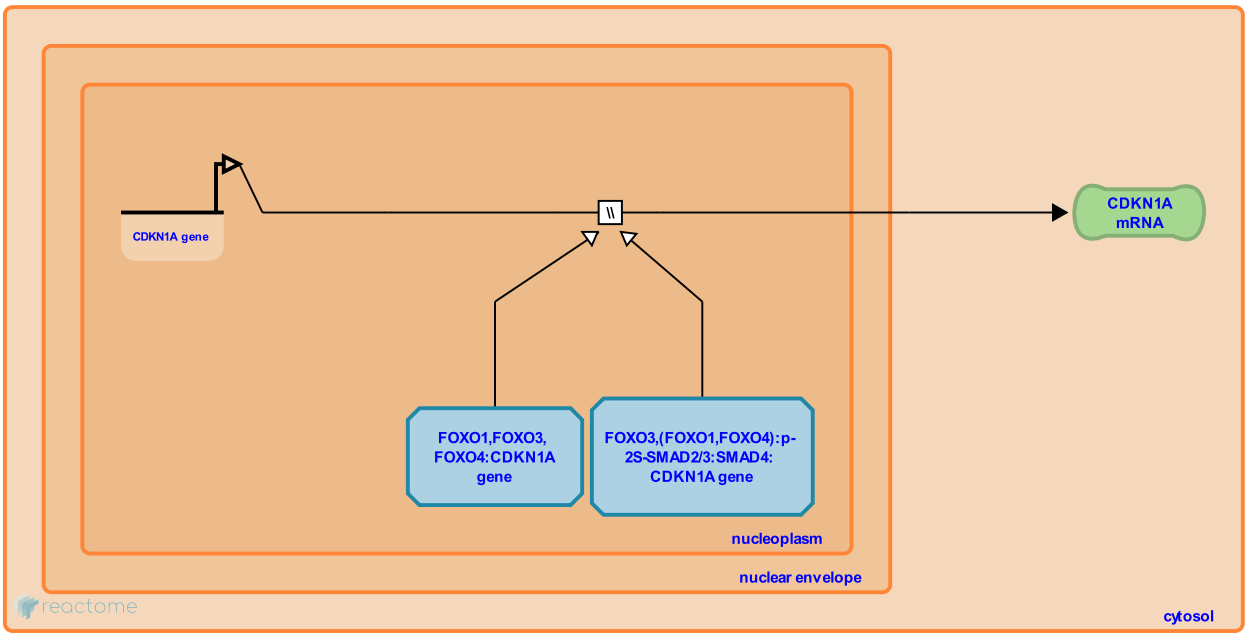
CDKN1A gene transcription is stimulated by FOXO1,FOXO3,FOXO4 ↗

Location: FOXO-mediated transcription of cell cycle genes

Stable identifier: R-HSA-9617838

Type: omitted

Compartments: nucleoplasm, cytosol



FOXO1, FOXO3 and FOXO4 stimulate transcription from the CDKN1A gene promoter. In response to TGF-beta signaling, FOXO transcription factors may cooperate with the active SMAD2/3:SMAD4 complexes to upregulate CDKN1A transcription (Seoane et al. 2004). FOXO1-mediated induction of CDKN1A gene transcription is implicated in CDKN1A upregulation in liver cells during fasting (Tinkum et al. 2013). Acetylation of FOXO4 by EP300 (p300) or CREBBP (CBP) in response to oxidative stress does not affect FOXO4-mediated induction of CDKN1A gene transcription (Dansen et al. 2009).

Preceded by: FOXO:SMAD complex binds CDKN1A gene promoter, FOXO1,FOXO3,FOXO4 bind CDKN1A gene promoter

Followed by: PCBP4 binds the CDKN1A mRNA

Literature references

Massague, J., Shen, L., Le, HV., Anderson, SA., Seoane, J. (2004). Integration of Smad and forkhead pathways in the control of neuroepithelial and glioblastoma cell proliferation. *Cell, 117*, 211-23. ↗

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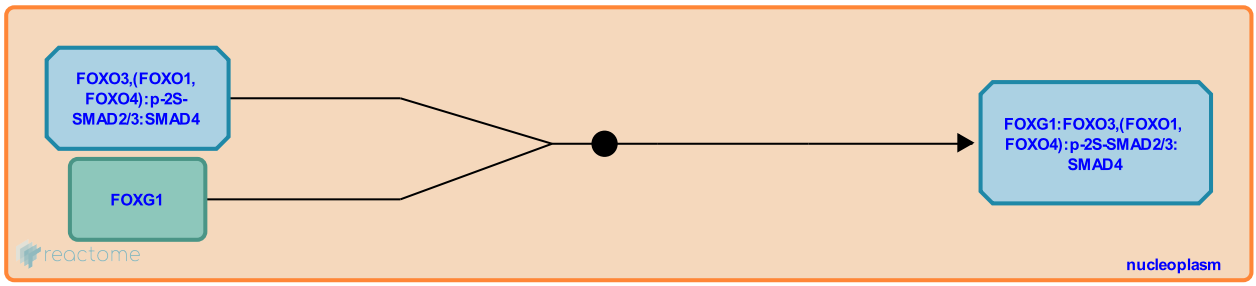
FOXG1 binds FOXO:SMAD complexes ↗

Location: FOXO-mediated transcription of cell cycle genes

Stable identifier: R-HSA-9618021

Type: binding

Compartments: nucleoplasm



FOXG1 can bind to complexes of FOXO transcription factors and activated SMAD2/3:SMAD4 via direct interaction with FOXO3, and probably also FOXO1 or FOXO4 (Seoane et al. 2004).

Preceded by: FOXO1,FOXO3,FOXO4 bind p-2S-SMAD2/3:SMAD4

Literature references

Massague, J., Shen, L., Le, HV., Anderson, SA., Seoane, J. (2004). Integration of Smad and forkhead pathways in the control of neuroepithelial and glioblastoma cell proliferation. *Cell, 117*, 211-23. ↗

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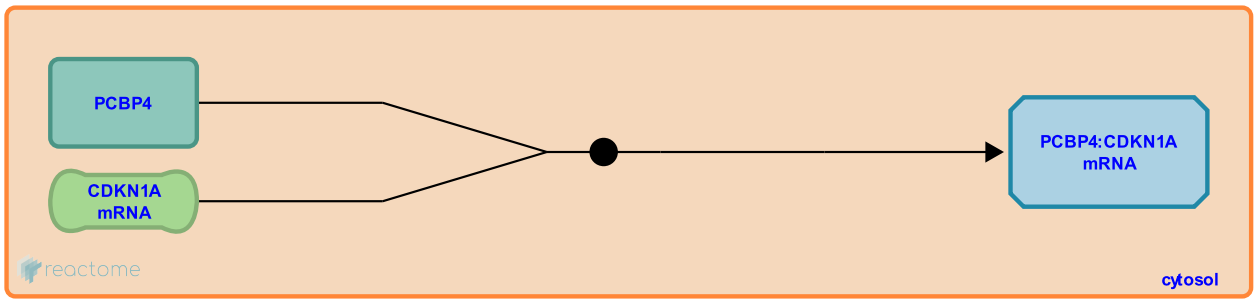
PCBP4 binds the CDKN1A mRNA ↗

Location: FOXO-mediated transcription of cell cycle genes

Stable identifier: R-HSA-6803403

Type: binding

Compartments: cytosol



PCBP4 binds the 3'-UTR of the CDKN1A (p21) mRNA and reduces its stability (Scoumanne et al. 2011).

Preceded by: CDKN1A gene transcription is stimulated by FOXO1,FOXO3,FOXO4

Followed by: PCBP4 modulates CDKN1A translation

Literature references

Chen, X., Cho, SJ., Scoumanne, A., Zhang, J. (2011). The cyclin-dependent kinase inhibitor p21 is regulated by RNA-binding protein PCBP4 via mRNA stability. *Nucleic Acids Res., 39*, 213-24. ↗

Editions

2015-10-14	Authored, Edited	Orlic-Milacic, M.
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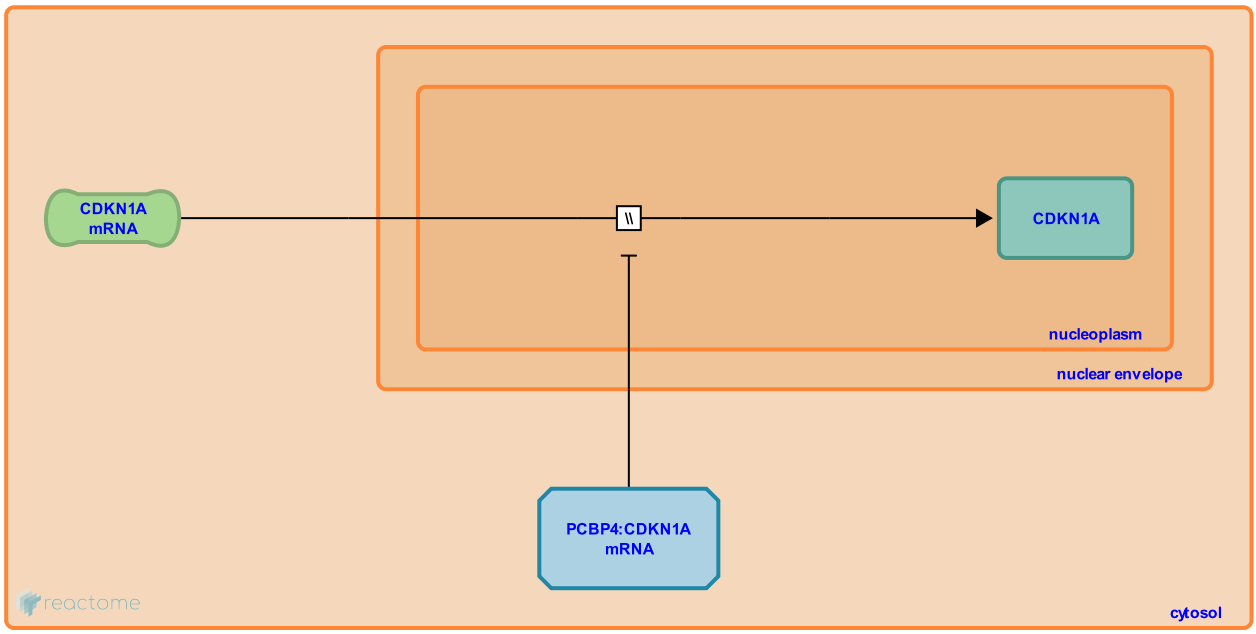
PCBP4 modulates CDKN1A translation ↗

Location: FOXO-mediated transcription of cell cycle genes

Stable identifier: R-HSA-6803411

Type: omitted

Compartments: nucleoplasm, cytosol



PCBP4 binding to the 3'-UTR of the CDKN1A (p21) mRNA reduces half-life of the CDKN1A mRNA and the amount of CDKN1A protein. Upon DNA damage, TP53-mediated induction of CDKN1A is rapid, while the induction of PCBP4 is more gradual. It is hypothesized that, under prolonged stress, PCBP4-mediated down-regulation of CDKN1A may switch from G1 cell cycle arrest to G2 arrest, which may precede apoptosis (Scoumanne et al. 2011).

Preceded by: PCBP4 binds the CDKN1A mRNA

Literature references

Chen, X., Cho, SJ., Scoumanne, A., Zhang, J. (2011). The cyclin-dependent kinase inhibitor p21 is regulated by RNA-binding protein PCBP4 via mRNA stability. *Nucleic Acids Res., 39*, 213-24. ↗

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CDKN1B gene expression is stimulated by FOXO1,FOXO3,FOXO4 ↗

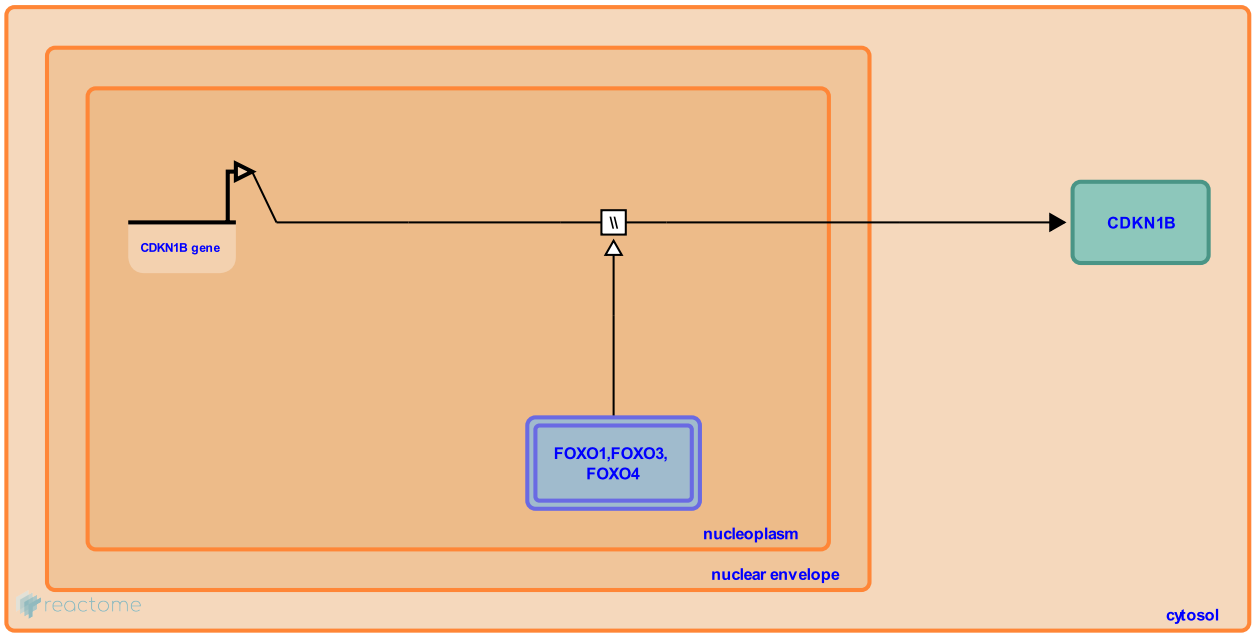
Location: FOXO-mediated transcription of cell cycle genes

Stable identifier: R-HSA-9617848

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Cdkn1b gene expression is stimulated by FOXO4 (Homo sapiens), Cdkn1b gene expression is stimulated by FOXO1,FOXO3 (Rattus norvegicus)



Promoter of the CDKN1B gene, encoding CDK inhibitor p27Kip1, contains forkhead box elements that are required for induction of CDKN1B gene transcription by FOXO transcription factors FOXO1, FOXO3 (Dijkers et al. 2000, Lees et al. 2008) and FOXO4 (Medema et al. 2000). Direct binding of FOXO transcription factors to the CDKN1B gene promoter has not been demonstrated. Acetylation of FOXO4 by EP300 (p300) or CREBBP (CBP) in response to oxidative stress interferes with FOXO4-mediated induction of CDKN1B gene transcription (Dansen et al. 2009).

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FOXO3,FOXO4,(FOXO1) bind GADD45A gene promoter ↗

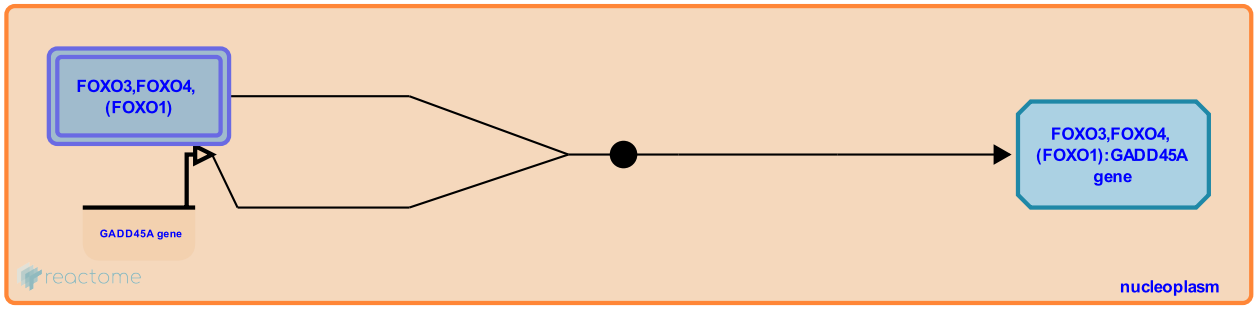
Location: FOXO-mediated transcription of cell cycle genes

Stable identifier: R-HSA-9617852

Type: binding

Compartments: nucleoplasm

Inferred from: Foxo4 binds GADD45A gene promoter (Homo sapiens)



GADD45A gene is the direct transcriptional target of FOXO transcription factors. Direct binding to the GADD45A gene promoter was demonstrated for FOXO3 (Tran et al. 2002, Furkawa-Hibi et al. 2002) and FOXO4 (Furukawa-Hibi et al. 2002). FOXO1 positively regulates GADD45A gene transcription (Hughes et al. 2011, Sengupta et al. 2011, Ju et al. 2014) and probably can also bind to the GADD45A promoter, but this has not been experimentally demonstrated. FOXO transcription factors may bind to the GADD45A gene promoter cooperatively with the SMAD2/3:SMAD4 complex (Gomis et al. 2006).

Followed by: GADD45A gene expression is stimulated by FOXO3,FOXO4,(FOXO1)

Literature references

Greenberg, ME., Brunet, A., Datta, SR., Tran, H., Fornace, AJ., Grenier, JM. et al. (2002). DNA repair pathway stimulated by the forkhead transcription factor FOXO3a through the Gadd45 protein. *Science, 296*, 530-4. ↗

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GADD45A gene expression is stimulated by FOXO3,FOXO4,(FOXO1) ↗

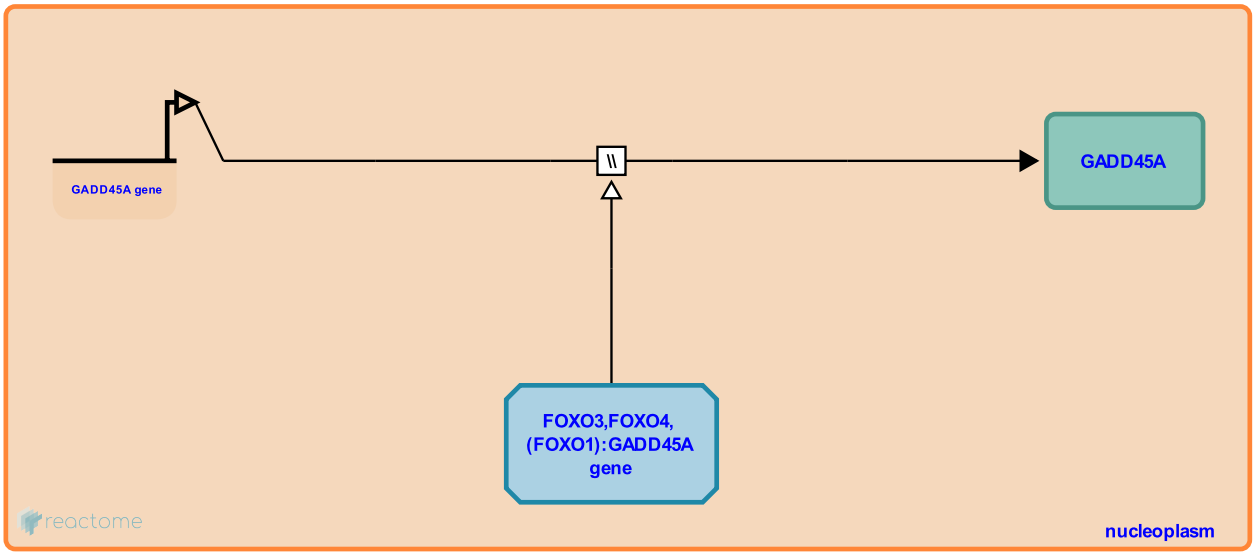
Location: FOXO-mediated transcription of cell cycle genes

Stable identifier: R-HSA-9617853

Type: omitted

Compartments: nucleoplasm

Inferred from: GADD45A gene expression is stimulated by Foxo4 (Homo sapiens)



GADD45A gene transcription is stimulated by FOXO1, FOXO3 and FOXO4 (Tran et al. 2002, Furukawa-Hibi et al. 2002, Hughes et al. 2011, Sengupta et al. 2011, Ju et al. 2014). Direct transcriptional regulation was demonstrated for FOXO3 (Tran et al. 2002, Furukawa-Hibi et al. 2002) and FOXO4 (Furukawa-Hibi et al. 2002). Acetylation of FOXO4 by EP300 (p300) or CREBBP (CBP) in response to oxidative stress interferes with FOXO4-mediated induction of GADD45A gene transcription (Dansen et al. 2009). Under oxidative stress, deacetylation of FOXO3 by SIRT1 deacetylase promotes FOXO3-mediated induction of GADD45A gene transcription (Brunet et al. 2004).

Preceded by: FOXO3,FOXO4,(FOXO1) bind GADD45A gene promoter

Editions

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FOXO1,FOXO3,FOXO4 binds RBL2 gene ↗

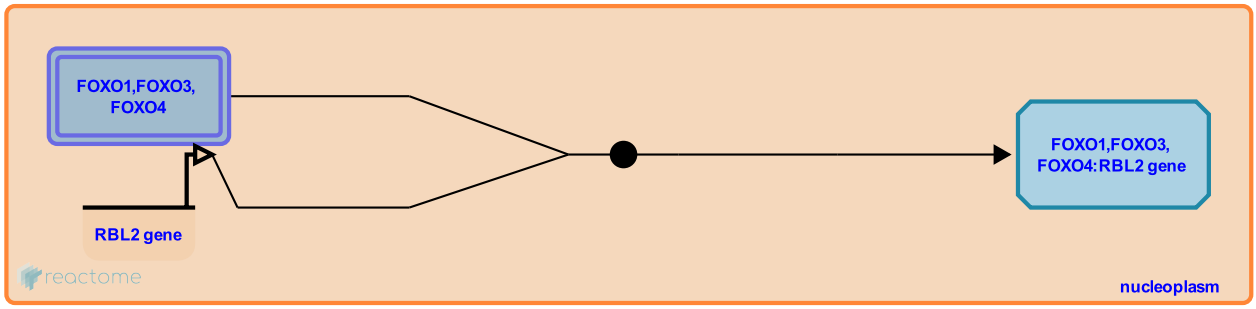
Location: FOXO-mediated transcription of cell cycle genes

Stable identifier: R-HSA-9620788

Type: binding

Compartments: nucleoplasm

Inferred from: FOXO1,FOXO3 binds Rbl2 gene (Homo sapiens)



FOXO family transcription factors, FOXO1, FOXO3 and FOXO4, bind FOXO elements in the first intron and/or the promoter region of the RBL2 (p130) gene. Direct binding was demonstrated between human FOXO4 and human p130 gene locus (Kops et al. 2002) and human FOXO1 and FOXO3 and mouse p130 gene locus (Chen et al. 2006).

Followed by: RBL2 gene expression is stimulated by FOXO1,FOXO3,FOXO4

Literature references

Medema, RH., Burgering, BM., Glassford, J., Kops, GJ., Lam, EW., Coffer, 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. ↗

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RBL2 gene expression is stimulated by FOXO1,FOXO3,FOXO4

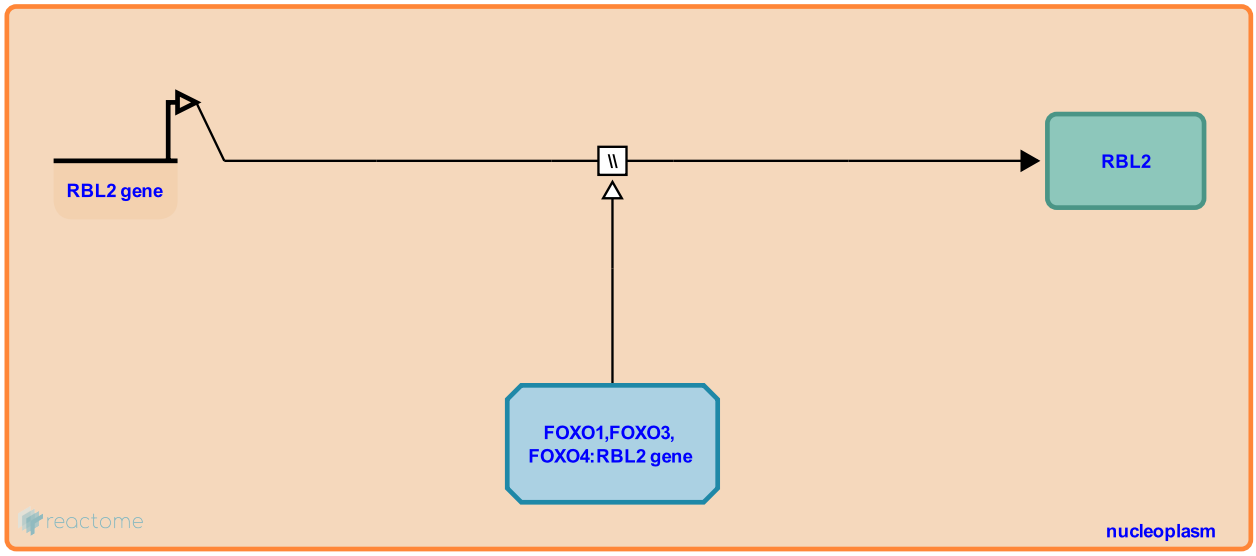
Location: FOXO-mediated transcription of cell cycle genes

Stable identifier: R-HSA-9620813

Type: omitted

Compartments: nucleoplasm

Inferred from: Rbl2 gene expression is stimulated by FOXO1,FOXO3 (Homo sapiens)



Transcription of the RBL2 gene is directly stimulated by FOXO family transcription factors FOXO1, FOXO3 and FOXO4 (Kops et al. 2002, Chen et al. 2006). Direct transcriptional stimulation by human FOXO4 was demonstrated for human RBL2 gene (Kops et al. 2002), and by human FOXO1 and FOXO3 for mouse Rbl2 gene (Chen et al. 2006). The retinoblastoma family member RBL2 is needed for the establishment and maintenance of quiescent, G0, state.

Preceded by: FOXO1,FOXO3,FOXO4 binds RBL2 gene

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FOXO1,FOXO3,(FOXO4) binds CCNG2 gene promoter ↗

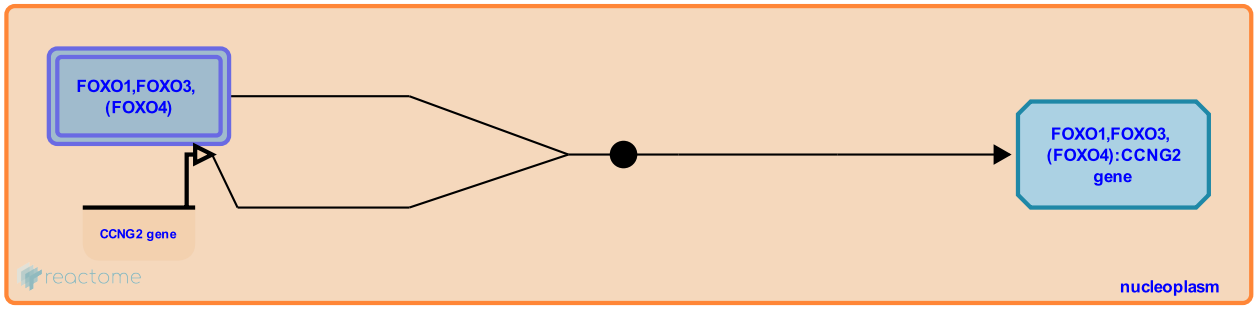
Location: FOXO-mediated transcription of cell cycle genes

Stable identifier: R-HSA-9620828

Type: binding

Compartments: nucleoplasm

Inferred from: FOXO1,FOXO3 binds Ccng2 gene (Homo sapiens)



Forkhead box family transcription factors, FOXO1, FOXO3, and probably FOXO4, bind forkhead box elements in the promoter region of the CCNG2 gene, encoding Cyclin-G2 (Martinez-Gac et al. 2004, Chen et al. 2006).

Followed by: CCNG2 gene expression is stimulated by FOXO1,FOXO3,(FOXO4)

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CCNG2 gene expression is stimulated by FOXO1,FOXO3,(FOXO4) ↗

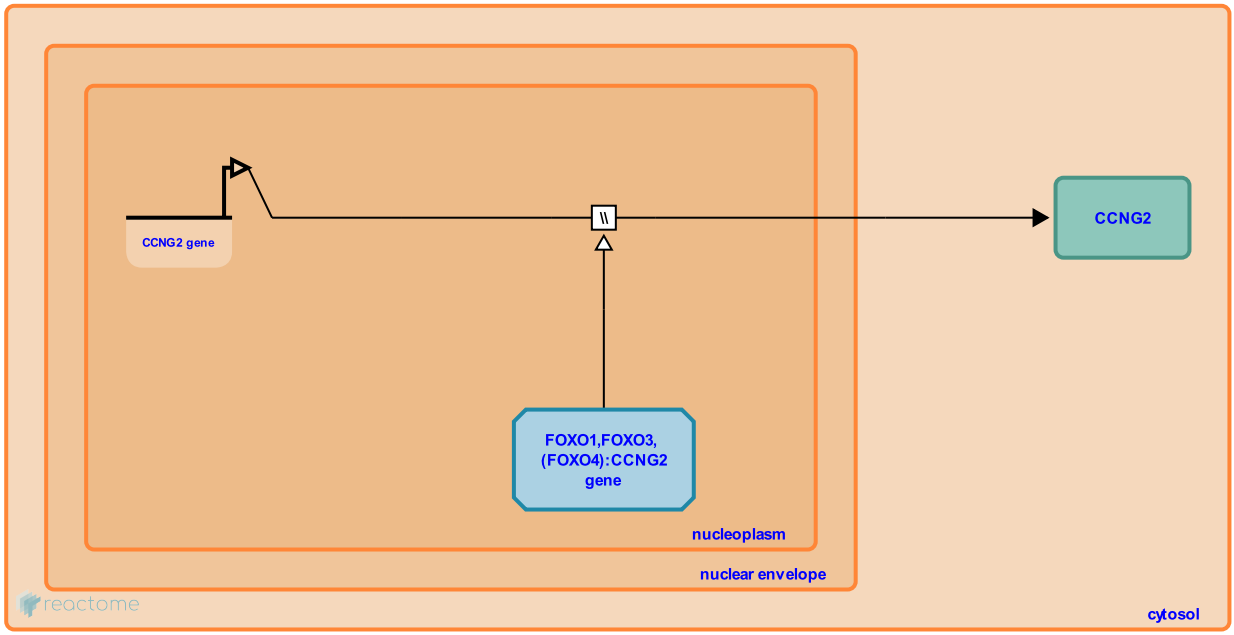
Location: FOXO-mediated transcription of cell cycle genes

Stable identifier: R-HSA-9620837

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Ccng2 gene expression is stimulated by FOXO1,FOXO3 (Homo sapiens)



FOXO1, FOXO3 and probably FOXO4 directly stimulate transcription of the CCNG2 gene, encoding a cell cycle inhibitor Cyclin-G2 (Martinez-Gac et al. 2004, Chen et al. 2006). FOXO4 stimulates CCNG2 transcription, but direct binding of FOXO4 to the CCNG2 gene promoter has not been demonstrated (Martinez-Gac et al. 2004).

Preceded by: FOXO1,FOXO3,(FOXO4) binds CCNG2 gene promoter

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.

FOXO3 binds BTG1 gene promoter ↗

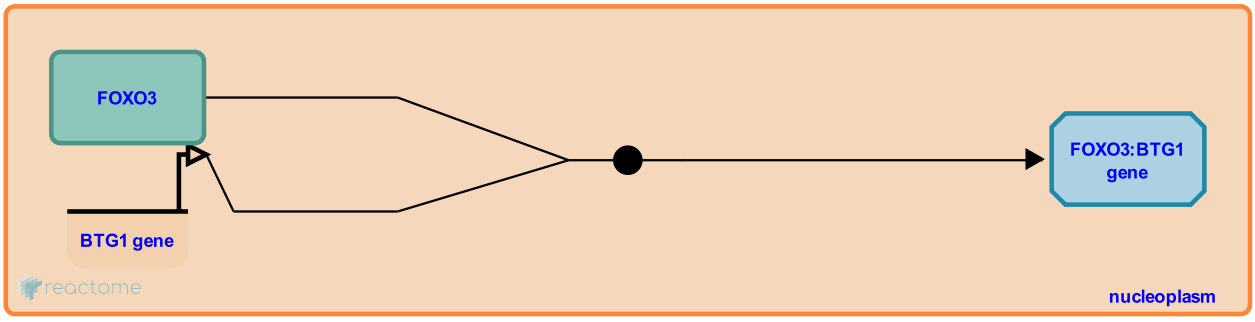
Location: FOXO-mediated transcription of cell cycle genes

Stable identifier: R-HSA-9620891

Type: binding

Compartments: nucleoplasm

Inferred from: FOXO3 binds Btg1 gene promoter (Homo sapiens)



FOXO3 binds to evolutionarily conserved forkhead box elements in the promoter region of the BTG1 gene, encoding antiproliferative Protein BTG1 (Bakker et al. 2007).

Followed by: BTG1 gene expression is stimulated by FOXO3

Editions

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

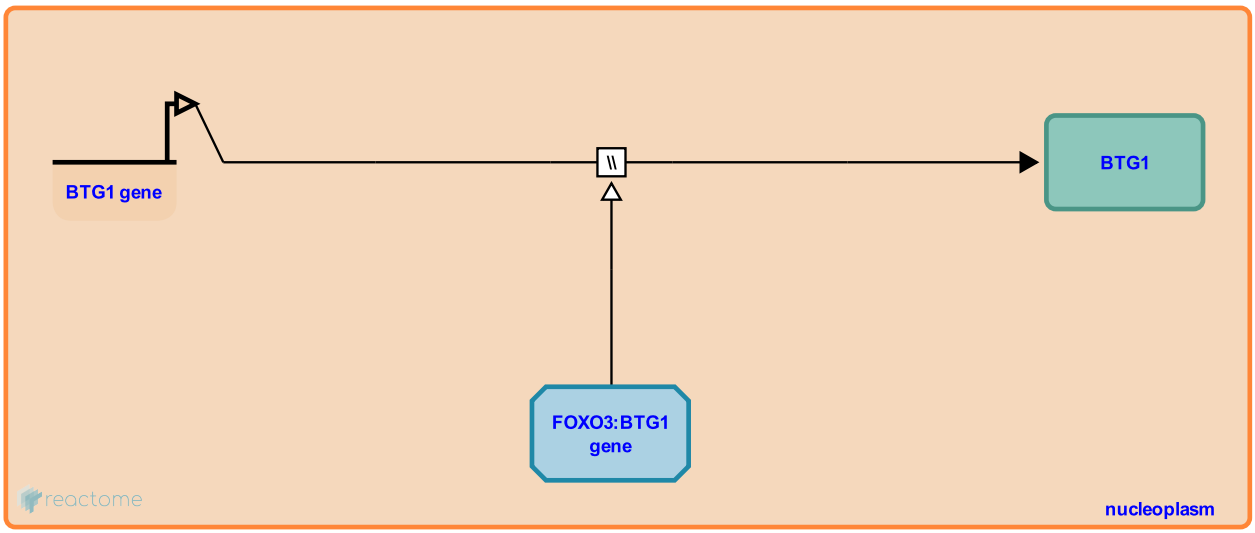
BTG1 gene expression is stimulated by FOXO3

Location: FOXO-mediated transcription of cell cycle genes

Stable identifier: R-HSA-9620915

Type: omitted

Compartments: nucleoplasm



Transcription of the BTG1 gene, encoding antiproliferative Protein BTG1 is directly stimulated by FOXO3 (Bakker et al. 2004, Bakker et al. 2007, Wang et al. 2015). BTG1 inhibits the outgrowth of erythroid colonies and promotes maturation of mouse (Bakker et al. 2004) and human (Wang et al. 2015) erythroid cells.

Preceded by: FOXO3 binds BTG1 gene promoter

Literature references

Qi, H., Liu, F., Yang, Y., Zheng, J., Zhang, Q., Wang, S. et al. (2015). Knockdown of transcription factor forkhead box O3 (FOXO3) suppresses erythroid differentiation in human cells and zebrafish. *Biochem. Biophys. Res. Commun., 460*, 923-30.

Editions

2018-10-11	Authored	Orlic-Milacic, M.
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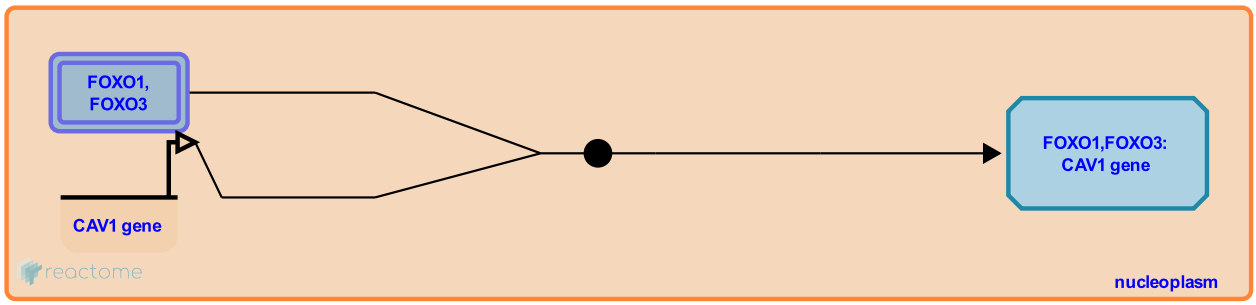
FOXO1,FOXO3 binds CAV1 gene promoter ↗

Location: FOXO-mediated transcription of cell cycle genes

Stable identifier: R-HSA-9624976

Type: binding

Compartments: nucleoplasm



FOXO3 binds the promoter of the CAV1 gene, encoding Caveolin-1 (van den Heuvel et al. 2005, Nho et al. 2013, Sisci et al. 2013). FOXO1 also binds the CAV1 gene promoter (Roy et al. 2008).

Followed by: CAV1 gene expression is stimulated by FOXO1,FOXO3

Literature references

Ferraro, A., Cesario, MG., Coroniti, R., Maris, P., Romeo, F., Sisci, D. et al. (2013). The estrogen receptor α is the key regulator of the bifunctional role of FoxO3a transcription factor in breast cancer motility and invasiveness. *Cell Cycle, 12*, 3405-20. ↗

Ignatenko, NA., Gerner, EW., Fultz, KE., Henkhaus, RS., Mora, J., Roy, UK. (2008). Wild-type APC regulates caveolin-1 expression in human colon adenocarcinoma cell lines via FOXO1a and C-myc. *Mol. Carcinog., 47*, 947-55. ↗

Peterson, M., Henke, CA., Nho, RS., Hergert, P. (2013). FoxO3a (Forkhead Box O3a) deficiency protects Idiopathic Pulmonary Fibrosis (IPF) fibroblasts from type I polymerized collagen matrix-induced apoptosis via caveolin-1 (cav-1) and Fas. *PLoS ONE, 8*, e61017. ↗

Burgering, BM., Schulze, A., van den Heuvel, AP. (2005). Direct control of caveolin-1 expression by FOXO transcription factors. *Biochem. J., 385*, 795-802. ↗

Editions

2018-10-23	Reviewed	Donlon, T.
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2018-10-31	Edited	Orlic-Milacic, M.

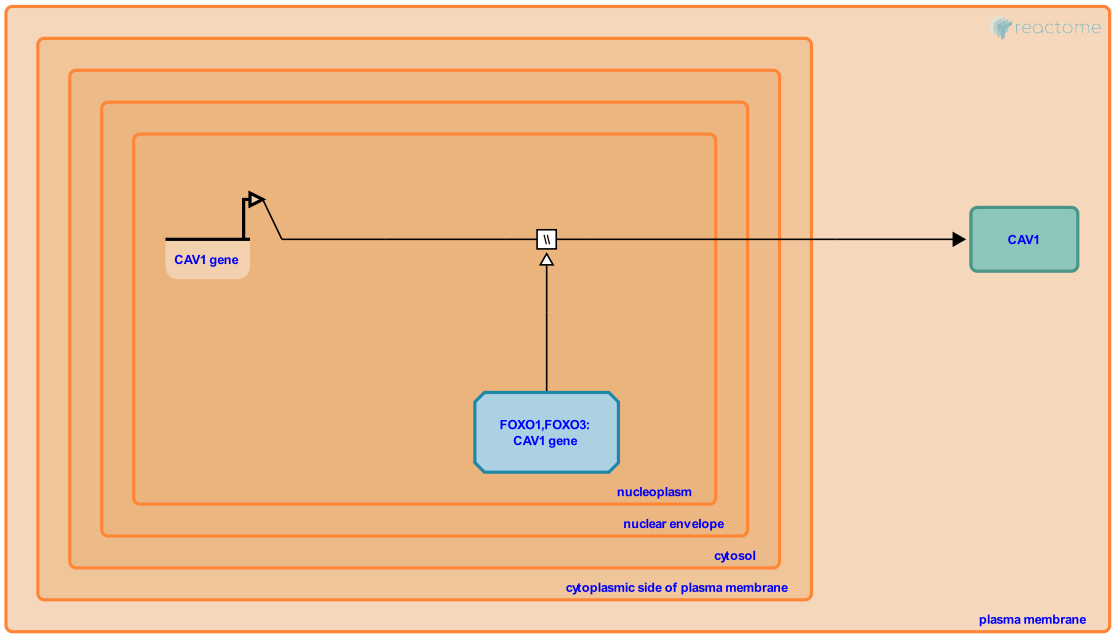
CAV1 gene expression is stimulated by FOXO1,FOXO3 ↗

Location: FOXO-mediated transcription of cell cycle genes

Stable identifier: R-HSA-9624985

Type: omitted

Compartments: nucleoplasm



Transcription of the CAV1 gene, encoding caveolin-1, is directly stimulated by FOXO3. Caveolin-1 is the main constituent of plasma membrane caveolae, involved in negative regulation of growth factor receptor signaling, which may contribute to the establishment of a senescent or quiescent cell phenotype. CAV1 expression decreases in the S phase, but FOXO-mediated regulation of CAV1 expression is cell cycle independent (van den Heuvel et al. 2005, Nho et al. 2013, Sisci et al. 2013). Transcription of the CAV1 gene is also directly stimulated by FOXO1 (Roy et al. 2008).

Preceded by: FOXO1,FOXO3 binds CAV1 gene promoter

Literature references

Ferraro, A., Cesario, MG., Coroniti, R., Maris, P., Romeo, F., Sisci, D. et al. (2013). The estrogen receptor α is the key regulator of the bifunctional role of FoxO3a transcription factor in breast cancer motility and invasiveness. *Cell Cycle, 12*, 3405-20. ↗

Ignatenko, NA., Gerner, EW., Fultz, KE., Henkhaus, RS., Mora, J., Roy, UK. (2008). Wild-type APC regulates caveolin-1 expression in human colon adenocarcinoma cell lines via FOXO1a and C-myc. *Mol. Carcinog., 47*, 947-55. ↗

Peterson, M., Henke, CA., Nho, RS., Hergert, P. (2013). FoxO3a (Forkhead Box O3a) deficiency protects Idiopathic Pulmonary Fibrosis (IPF) fibroblasts from type I polymerized collagen matrix-induced apoptosis via caveolin-1 (cav-1) and Fas. *PLoS ONE, 8*, e61017. ↗

Burgering, BM., Schulze, A., van den Heuvel, AP. (2005). Direct control of caveolin-1 expression by FOXO transcription factors. *Biochem. J., 385*, 795-802. ↗

Editions

2018-10-23	Reviewed	Donlon, T.
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FOXO1,FOXO3 bind KLF4 gene promoter ↗

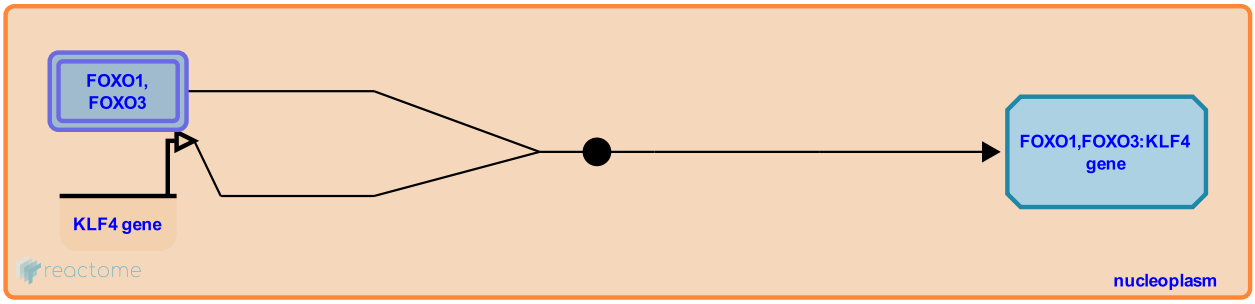
Location: FOXO-mediated transcription of cell cycle genes

Stable identifier: R-HSA-9625406

Type: binding

Compartments: nucleoplasm

Inferred from: Foxo1,Foxo3 bind Klf4 gene promoter (Mus musculus)



Based on studies in mice, FOXO1 and FOXO3 bind the KLF4 gene promoter (Yusuf et al. 2008).

Followed by: KLF4 gene expression is stimulated by FOXO1,FOXO3

Editions

2018-10-23	Reviewed	Donlon, T.
2018-10-23	Authored	Orlic-Milacic, M.
2018-10-31	Edited	Orlic-Milacic, M.

KLF4 gene expression is stimulated by FOXO1,FOXO3 ↗

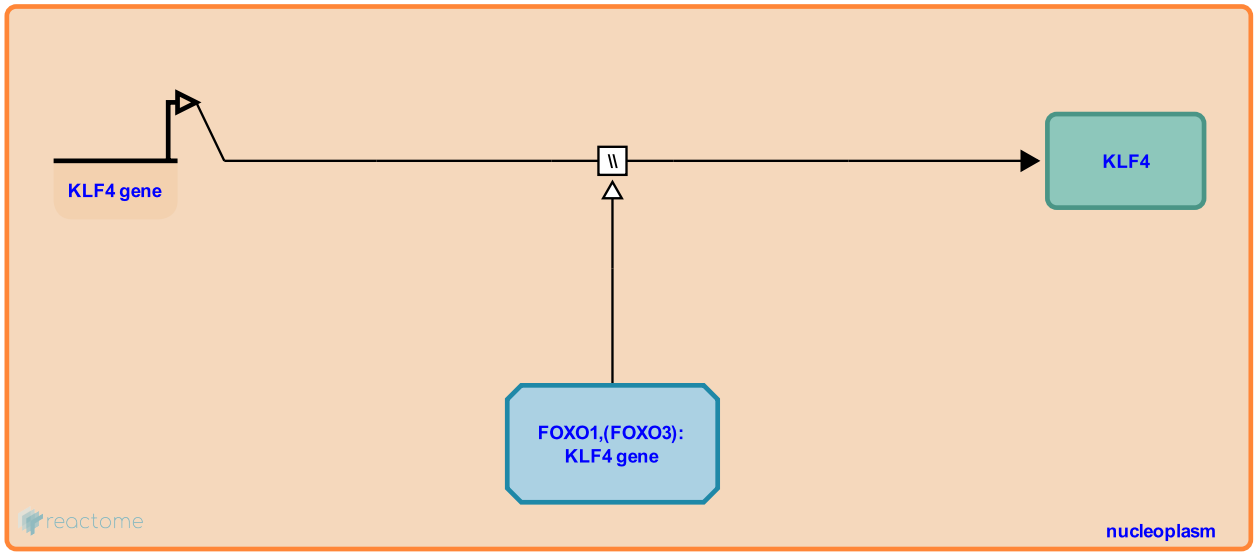
Location: FOXO-mediated transcription of cell cycle genes

Stable identifier: R-HSA-9625409

Type: omitted

Compartments: nucleoplasm

Inferred from: Klf4 gene expression is stimulated by FOXO1 (Mus musculus)



Based on studies in mice, FOXO1 and possibly FOXO3 directly stimulate transcription of the KLF4 gene, encoding a transcription factor Krueppel-like factor 4. KLF4 inhibits proliferation of mouse B cells (Yusuf et al. 2008). KLF4 has been reported to transcriptionally repress FOXO1 gene (Tang et al. 2016). In hypothalamic orexigenic neurons, KLF4 positively regulates expression of AGRP (agouti-related protein), an established FOXO target (Imbernon et al. 2014).

Preceded by: FOXO1,FOXO3 bind KLF4 gene promoter

Editions

2018-10-23	Reviewed	Donlon, T.
2018-10-23	Authored	Orlic-Milacic, M.
2018-10-31	Edited	Orlic-Milacic, M.

FOXO1 and p-2S-SMAD2/3:SMAD4 bind MSTN gene promoter ↗

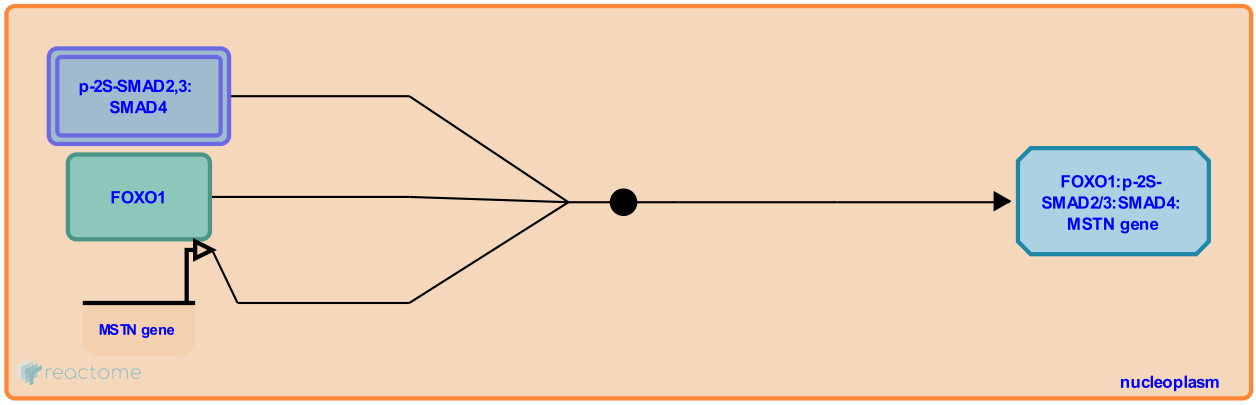
Location: FOXO-mediated transcription of cell cycle genes

Stable identifier: R-HSA-9625510

Type: binding

Compartments: nucleoplasm

Inferred from: FOXO1 and p-2S-Smad2/3:Smad4 bind Mstn gene promoter (Homo sapiens)



Based on studies in mice, FOXO1 and the p-2S-SMAD2/3:SMAD4 complex bind the promoter of the MSTN gene, encoding myostatin (Allen and Unterman 2007). FOXO3 and glucocorticoid receptor (NR3C1, also known as GR) were reported to bind MSTN promoter in porcine cells (Jia et al. 2016).

Editions

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MSTN gene expression is stimulated by FOXO1 and p-2S-SMAD2/3:SMAD4 ↗

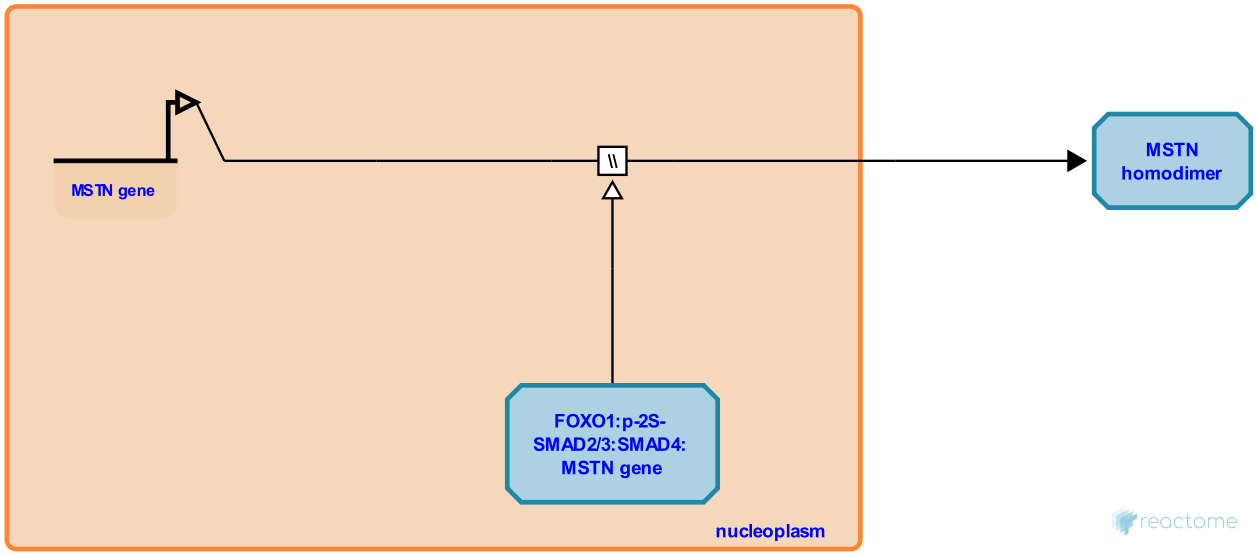
Location: FOXO-mediated transcription of cell cycle genes

Stable identifier: R-HSA-9625520

Type: omitted

Compartments: nucleoplasm, extracellular region

Inferred from: Mstn gene expression is stimulated by FOXO1 and p-2S-Smad2/3:Smad4 (Homo sapiens)



Based on studies in mice, FOXO1 and the p-2S-SMAD2/3:SMAD4 complex directly stimulate transcription of the MSTN gene, encoding myostatin. Myostatin is a TGF-beta family member that restricts muscle growth by stimulating differentiation of myoblasts (Allen and Unterman 2007).

Editions

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2018-10-23	Authored	Orlic-Milacic, M.
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