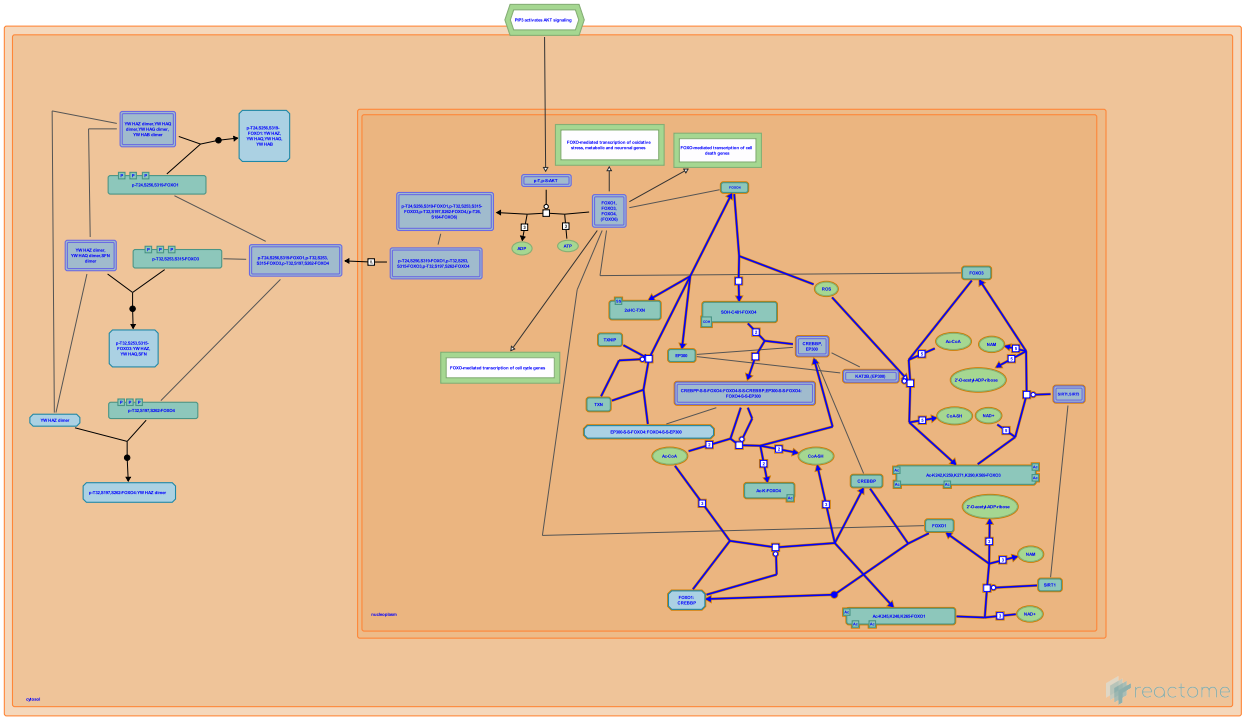
Regulation of FOXO transcriptional activity by acetylation



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06/05/2024

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. ↗

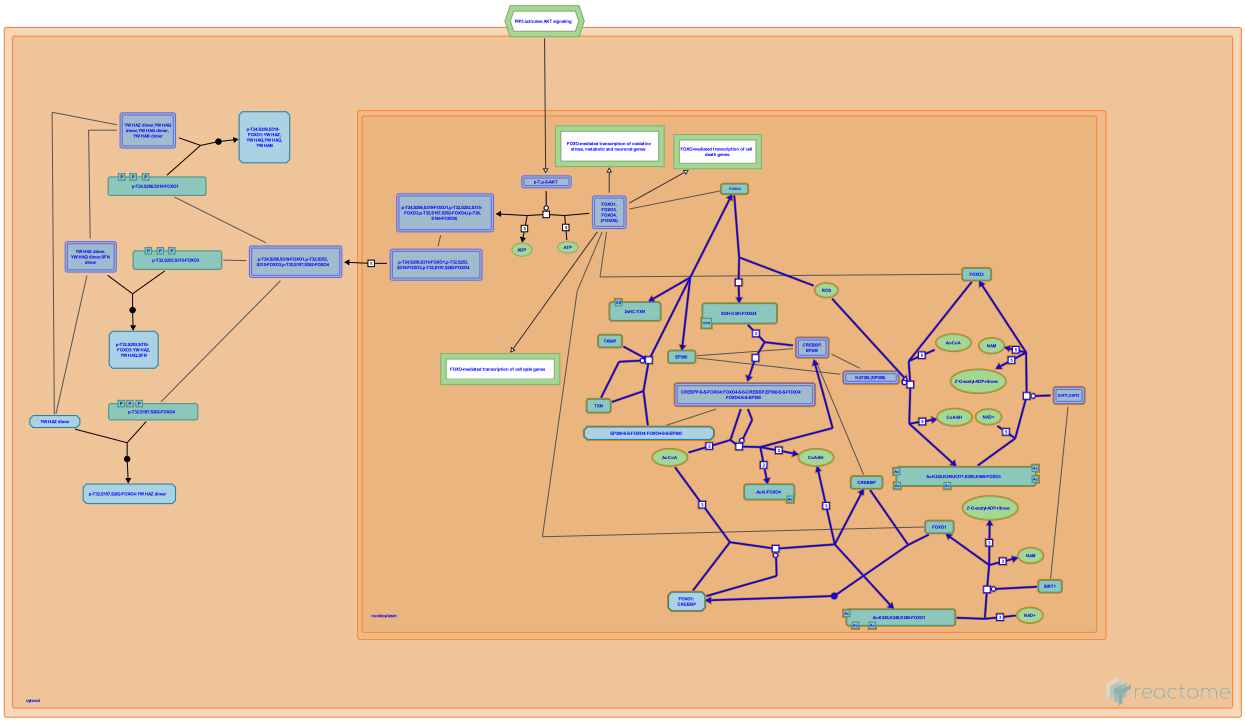
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 1 pathway and 9 reactions (see Table of Contents)

Regulation of FOXO transcriptional activity by acetylation ↗

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).

Literature references

Coletto, L., Sandri, M., Bertaggia, 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*, 2011-5. ↗

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

ROS oxidize FOXO4 cysteine residues ↗

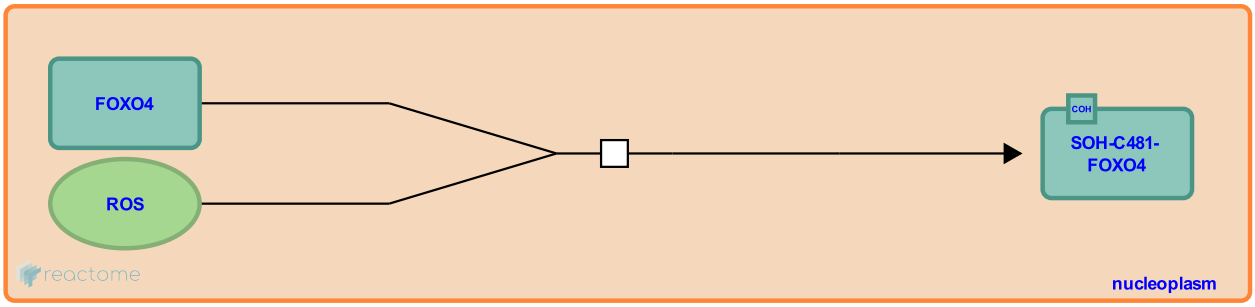
Location: Regulation of FOXO transcriptional activity by acetylation

Stable identifier: R-HSA-9617660

Type: transition

Compartments: nucleoplasm

Inferred from: ROS oxidize Foxo4 cysteine residues (Mus musculus)



Reactive oxygen species (ROS) oxidize cysteine residue(s) of FOXO4. There are five cysteine residues in FOXO4, of which two residues, C31 (corresponds to C27 in mouse Foxo4) and C481 (corresponds to C477 of mouse Foxo4) are conserved in other FOXO family members. Oxidation of C481 of FOXO4 has the most significant functional implications (Dansen et al. 2009).

Followed by: EP300,CREBBP bind SOH-C481-FOXO4

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.

EP300,CREBBP bind SOH-C481-FOXO4 ↗

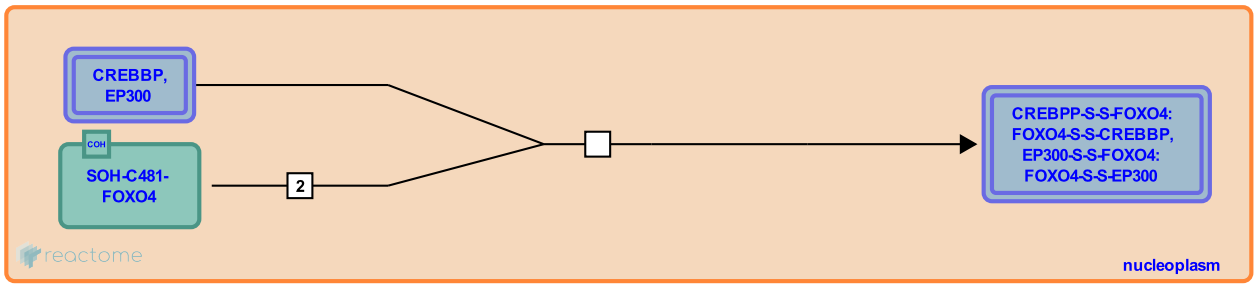
Location: Regulation of FOXO transcriptional activity by acetylation

Stable identifier: R-HSA-9617683

Type: transition

Compartments: nucleoplasm

Inferred from: Crebbp binds SOH-C477-Foxo4 (Mus musculus), EP300 binds SOH-C477-Foxo4 (Mus musculus)



After oxidation of FOXO4 cysteine residues by reactive oxygen species (ROS), FOXO4 forms a complex with a protein acetyltransferase EP300 (p300) or CREBBP (CBP). A covalent disulfide bond between FOXO4 and EP300 or CREBBP facilitates complex formation (Dansen et al. 2009).

Preceded by: ROS oxidize FOXO4 cysteine residues

Followed by: TXN disrupts FOXO4 complex with EP300

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

TXN disrupts FOXO4 complex with EP300 ↗

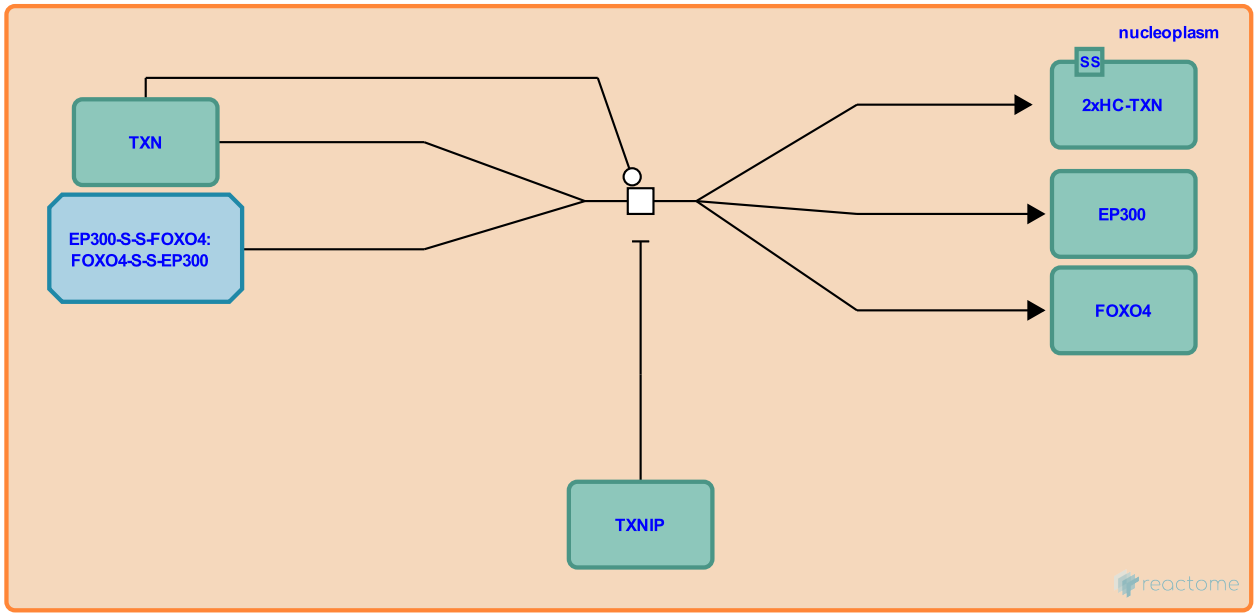
Location: Regulation of FOXO transcriptional activity by acetylation

Stable identifier: R-HSA-9617735

Type: transition

Compartments: nucleoplasm

Inferred from: TXN disrupts Foxo4 comples with EP300 (Homo sapiens)



Thioredoxin (TXN) reduces oxidized FOXO4 and disrupts interaction between FOXO4 and EP300 (p300). TXN-mediated disruption of FOXO4:EP300 complexes is negatively regulated by TXNIP (TBP-2), a TXN binding protein (Dansen et al. 2009).

Preceded by: EP300,CREBBP bind SOH-C481-FOXO4

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.

EP300,CREBBP acetylate FOXO4 ↗

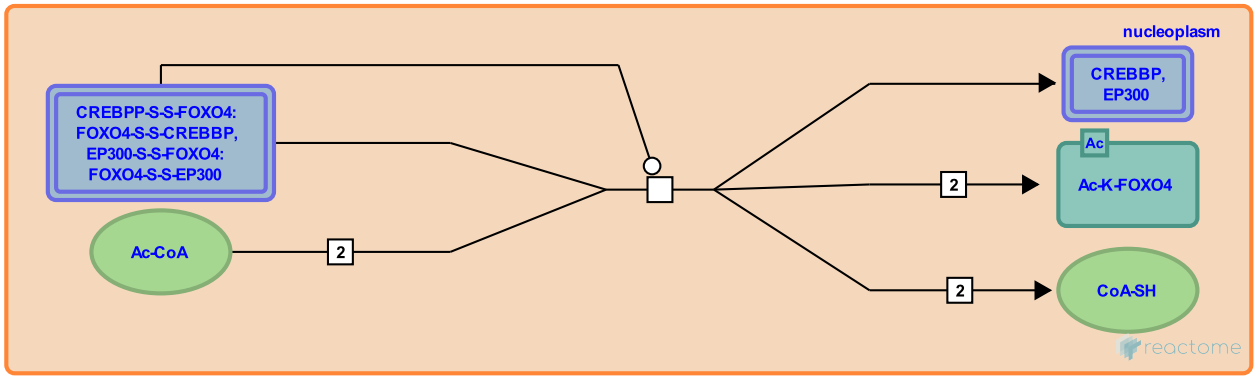
Location: Regulation of FOXO transcriptional activity by acetylation

Stable identifier: R-HSA-9617758

Type: transition

Compartments: nucleoplasm

Inferred from: EP300 acetylates Foxo4 (Homo sapiens), Crebbp acetylates Foxo4 (Mus musculus)



EP300 and CREBBP histone acetyltransferases acetylate FOXO4 (Dansen et al. 2009).

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.

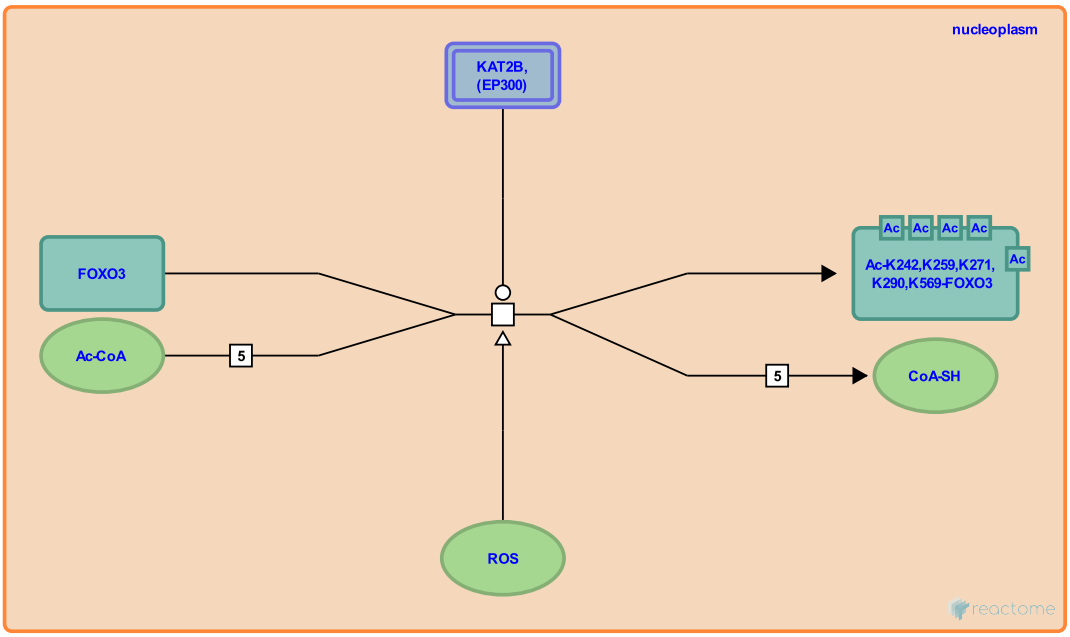
KAT2B,EP300 acetylate FOXO3 under oxidative stress ↗

Location: Regulation of FOXO transcriptional activity by acetylation

Stable identifier: R-HSA-9620515

Type: transition

Compartments: nucleoplasm



KAT2B (PCAF) and possibly EP300 (p300) acetylate FOXO3 under conditions of oxidative stress (Brunet et al. 2004).

Followed by: SIRT1,SIRT3 deacetylate FOXO3

Literature references

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*, 2011-5. ↗

Editions

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

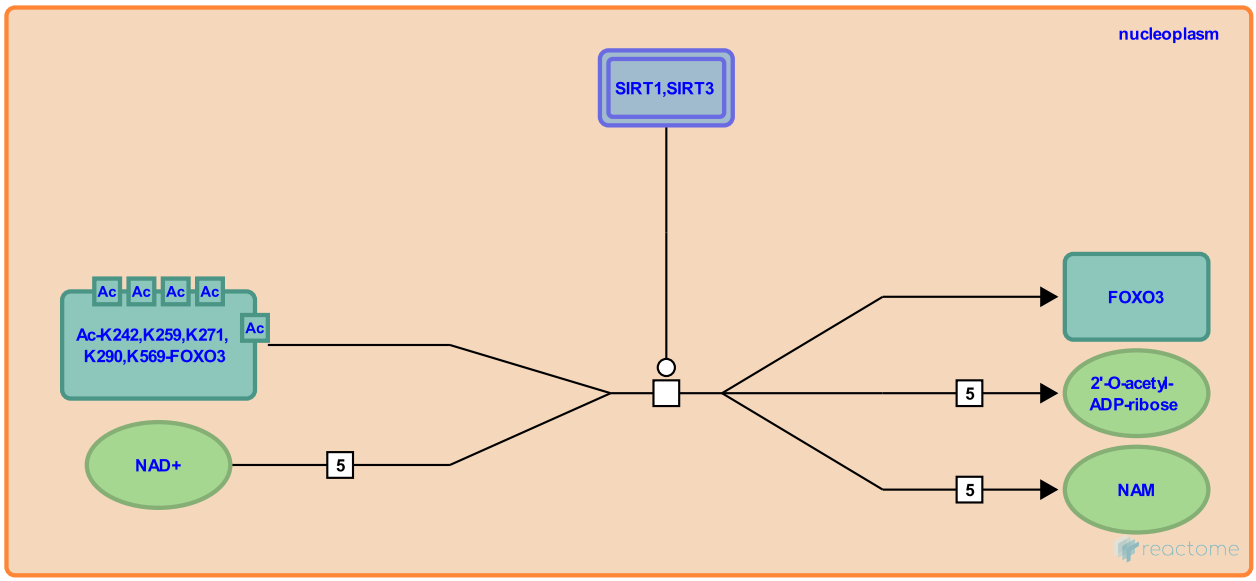
SIRT1,SIRT3 deacetylate FOXO3 ↗

Location: Regulation of FOXO transcriptional activity by acetylation

Stable identifier: R-HSA-9620532

Type: transition

Compartments: nucleoplasm



SIRT1, an NAD-dependent histone deacetylase, deacetylates FOXO3. SIRT1-mediated deacetylation of FOXO3 inhibits FOXO3-mediated cell death induced by oxidative stress while promoting FOXO3-mediated cell cycle arrest, which increases resistance to oxidative stress (Brunet et al. 2004).
FOXO3 can similarly be deacetylated by SIRT3, also an NAD-dependent histone deacetylase. Deacetylation of FOXO3 by SIRT3 in response to oxidative stress increases FOXO3 nuclear localization by interfering with AKT-mediated phosphorylation of FOXO3. SIRT3-mediated deacetylation of FOXO3 positively regulates FOXO3-mediated transcription of SOD2 and CAT genes which encode enzymes that process reactive oxygen species and reduce oxidative stress to the cell (Kim et al. 2010, Tseng et al. 2013).

Preceded by: KAT2B,EP300 acetylate FOXO3 under oxidative stress

Literature references

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*, 2011-5. ↗

Tseng, AH., Shieh, SS., Wang, DL. (2013). SIRT3 deacetylates FOXO3 to protect mitochondria against oxidative damage. *Free Radic. Biol. Med., 63*, 222-34. ↗

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

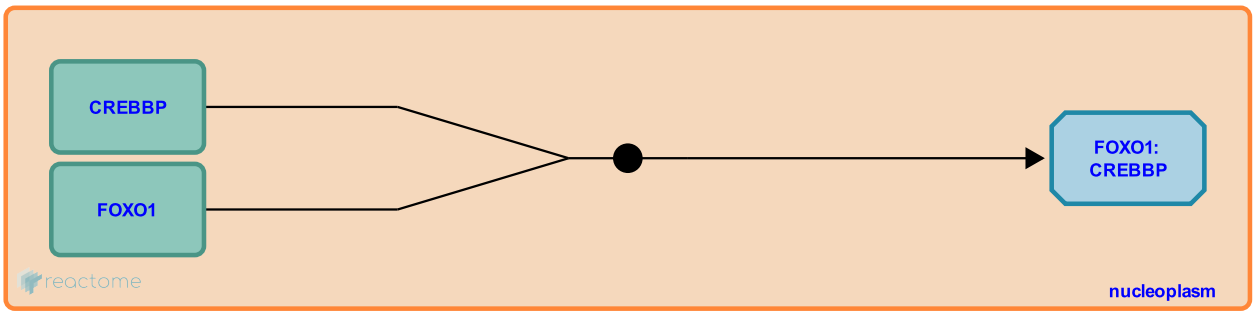
CREBBP binds FOXO1 ↗

Location: Regulation of FOXO transcriptional activity by acetylation

Stable identifier: R-HSA-9626928

Type: binding

Compartments: nucleoplasm



Endogenous human histone acetyltransferase CREBBP (CBP) binds to endogenous human FOXO1. The C-terminus of FOXO1 is needed for this interaction (Daitoku et al. 2004).

Literature references

Matsuzaki, H., Ohshima, T., Daitoku, H., Aratani, S., Miyagishi, M., Fukamizu, A. et al. (2004). Silent information regulator 2 potentiates Foxo1-mediated transcription through its deacetylase activity. *Proc. Natl. Acad. Sci. U.S.A., 101*, 10042-7. ↗

Editions

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

CREBBP acetylates FOXO1 ↗

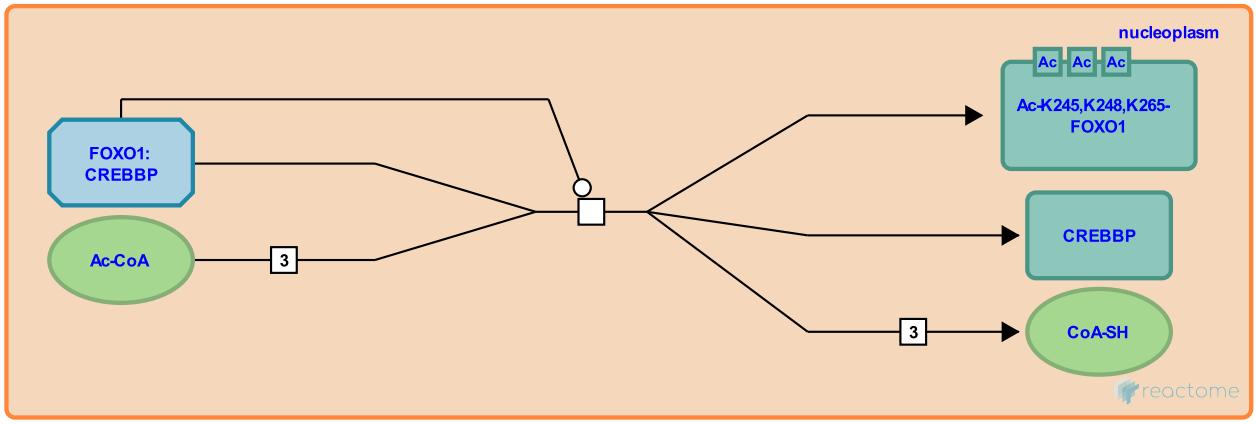
Location: Regulation of FOXO transcriptional activity by acetylation

Stable identifier: R-HSA-9626945

Type: transition

Compartments: nucleoplasm

Inferred from: CREBBP acetylates Foxo1 (Homo sapiens)



Based on experiments using recombinant human CREBBP and recombinant mouse Foxo1, CREBBP phosphorylates FOXO1 on conserved lysine residues K245, K248 and K265 (these residues correspond to K242, K245 and K262, respectively, in mouse Foxo1) (Daitoku et al. 2004).

Editions

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

SIRT1 deacetylates FOXO1 ↗

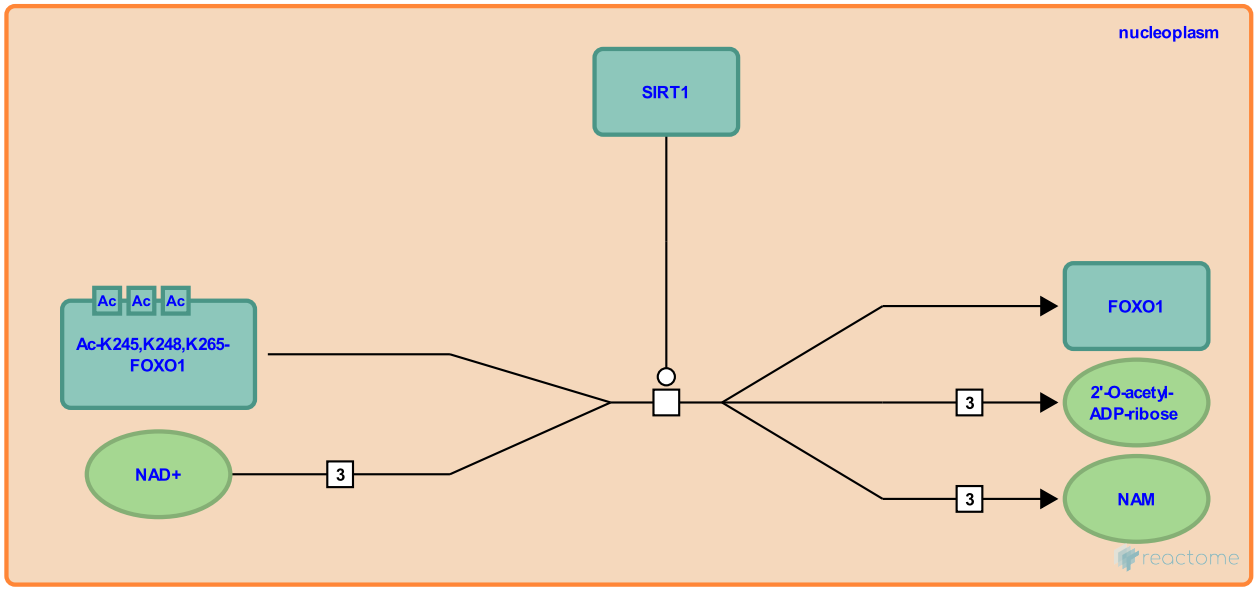
Location: Regulation of FOXO transcriptional activity by acetylation

Stable identifier: R-HSA-9626962

Type: transition

Compartments: nucleoplasm

Inferred from: Sirt1 deacetylates Foxo1 (Mus musculus)



A histone deacetylase SIRT1 deacetylates FOXO1. Deacetylation increases FOXO1-mediated upregulation of SOD2 and CDKN1B (Diatoku et al. 2004). SIRT-dependent deacetylation leads to retention of FOXO1 in the nucleus (Frescas et al. 2005).

Editions

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

Table of Contents