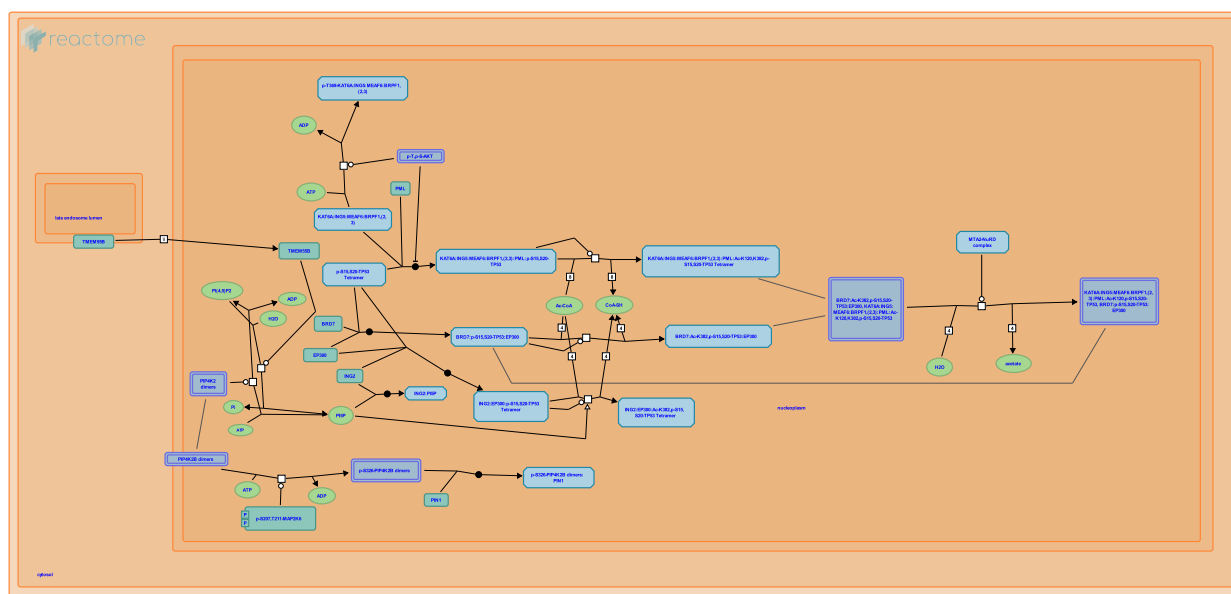


Regulation of TP53 Activity through Acetylation



Divecha, N., Inga, A., Orlic-Milacic, M., Zaccara, S.

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/page/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/page/faq).

16/05/2024

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

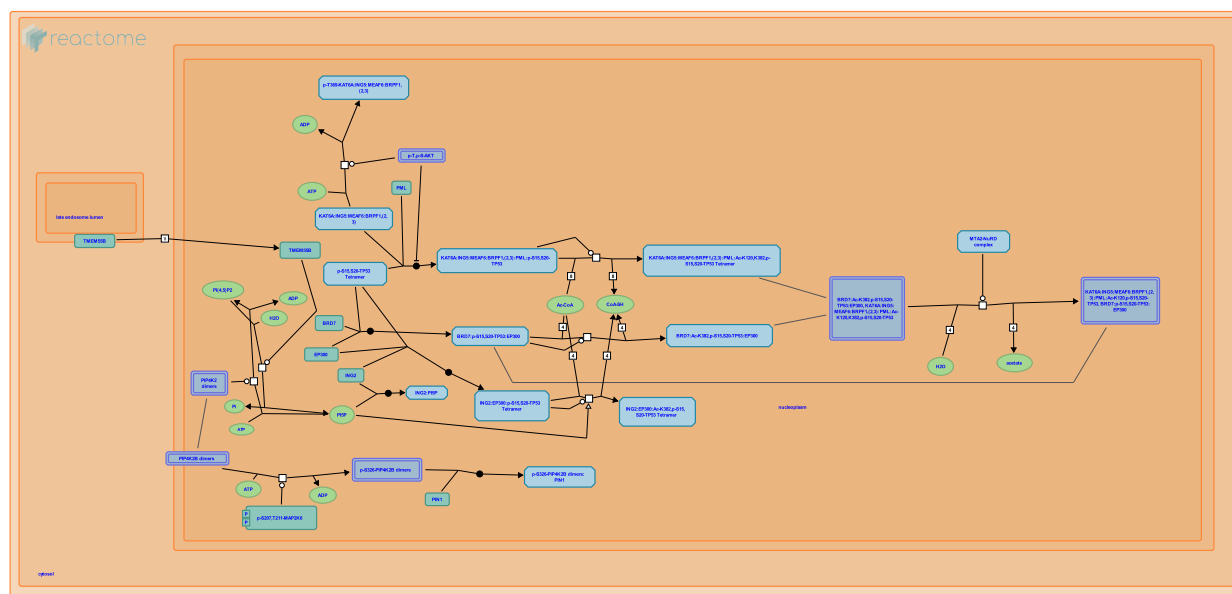
- Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics*, 18, 142. [↗](#)
- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). 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 2 pathways and 6 reactions ([see Table of Contents](#))

Regulation of TP53 Activity through Acetylation ↗

Stable identifier: R-HSA-6804758



Transcriptional activity of TP53 is positively regulated by acetylation of several of its lysine residues. BRD7 binds TP53 and promotes acetylation of TP53 lysine residue K382 by acetyltransferase EP300 (p300). Acetylation of K382 enhances TP53 binding to target promoters, including CDKN1A (p21), MDM2, SERPINE1, TIGAR, TNFRSF10C and NDRG1 (Bensaad et al. 2010, Burrows et al. 2010, Drost et al. 2010). The histone acetyltransferase KAT6A, in the presence of PML, also acetylates TP53 at K382, and, in addition, acetylates K120 of TP53. KAT6A-mediated acetylation increases transcriptional activation of CDKN1A by TP53 (Rokudai et al. 2013). Acetylation of K382 can be reversed by the action of the NuRD complex, containing the TP53-binding MTA2 subunit, resulting in inhibition of TP53 transcriptional activity (Luo et al. 2000). Acetylation of lysine K120 in the DNA binding domain of TP53 by the MYST family acetyltransferases KAT8 (hMOF) and KAT5 (TIP60) can modulate the decision between cell cycle arrest and apoptosis (Sykes et al. 2006, Tang et al. 2006). Studies with acetylation-defective knock-in mutant mice indicate that lysine acetylation in the p53 DNA binding domain acts in part by uncoupling transactivation and transrepression of gene targets, while retaining ability to modulate energy metabolism and production of reactive oxygen species (ROS) and influencing ferroptosis (Li et al. 2012, Jiang et al. 2015).

Literature references

- Taya, Y., Rokudai, S., Prives, C., Arnal, SM., Laptenko, O., Kitabayashi, I. (2013). MOZ increases p53 acetylation and premature senescence through its complex formation with PML. *Proc. Natl. Acad. Sci. U.S.A.*, 110, 3895-900. ↗
- Vidal, MN., Bensaad, K., Selak, MA., Tsuruta, A., Nakano, K., Gottlieb, E. et al. (2006). TIGAR, a p53-inducible regulator of glycolysis and apoptosis. *Cell*, 126, 107-20. ↗
- Jiang, L., Gu, W., Baer, RJ., Zhao, Y., Ludwig, T., Tan, M. et al. (2012). Tumor suppression in the absence of p53-mediated cell-cycle arrest, apoptosis, and senescence. *Cell*, 149, 1269-83. ↗
- Tocco, F., Del Sal, G., Drost, J., Elkon, R., Holstege, H., Kerkhoven, R. et al. (2010). BRD7 is a candidate tumour suppressor gene required for p53 function. *Nat. Cell Biol.*, 12, 380-9. ↗
- Gu, W., Luo, J., Tang, Y., Zhang, W. (2006). Tip60-dependent acetylation of p53 modulates the decision between cell cycle arrest and apoptosis. *Mol. Cell*, 24, 827-39. ↗

Editions

2015-10-14	Authored, Edited	Orlic-Milacic, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

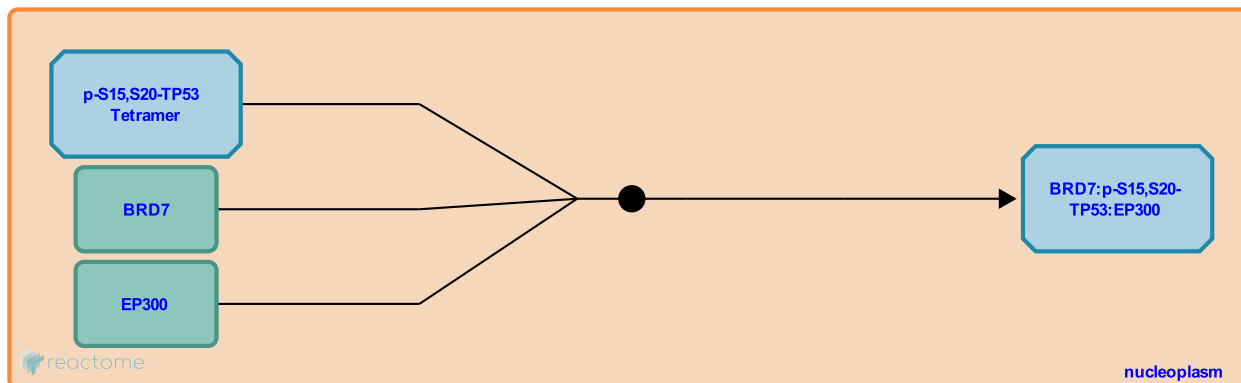
BRD7 binds TP53 and EP300 ↗

Location: [Regulation of TP53 Activity through Acetylation](#)

Stable identifier: R-HSA-3222093

Type: binding

Compartments: nucleoplasm



The N-terminal region of BRD7, upstream of its bromodomain that is responsible for interaction with chromatin, binds the C-terminus of TP53 (p53) (Drost et al. 2010, Burrows et al. 2010). BRD7 also binds and can recruit EP300 (p300) to TP53 target promoters CDKN1A and MDM2 (Drost et al. 2010). BRD7 positively regulates transcription of other TP53 targets: SERPINE1, TIGAR (Bensaad et al. 2006), TNFRSF10C and NDGR1, presumably via a similar mechanism as in the case of CDKN1A and MDM2 (Drost et al. 2010, Burrows et al. 2010).

Followed by: [BRD7 promotes EP300-mediated acetylation of TP53](#)

Literature references

Vidal, MN., Bensaad, K., Selak, MA., Tsuruta, A., Nakano, K., Gottlieb, E. et al. (2006). TIGAR, a p53-inducible regulator of glycolysis and apoptosis. *Cell*, 126, 107-20. ↗

Tocco, F., Del Sal, G., Drost, J., Elkon, R., Holstege, H., Kerkhoven, R. et al. (2010). BRD7 is a candidate tumour suppressor gene required for p53 function. *Nat. Cell Biol.*, 12, 380-9. ↗

Burrows, AE., Elledge, SJ., Smogorzewska, A. (2010). Polybromo-associated BRG1-associated factor components BRD7 and BAF180 are critical regulators of p53 required for induction of replicative senescence. *Proc. Natl. Acad. Sci. U.S.A.*, 107, 14280-5. ↗

Editions

2015-10-14	Authored, Edited	Orlic-Milacic, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

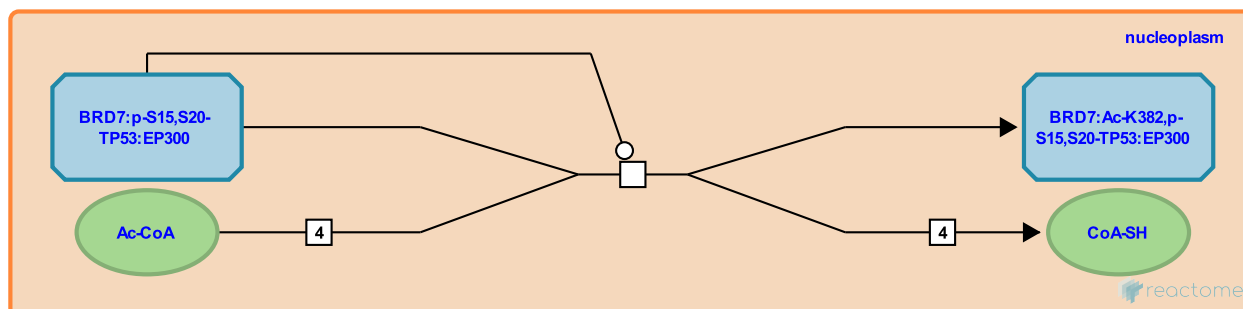
BRD7 promotes EP300-mediated acetylation of TP53 ↗

Location: [Regulation of TP53 Activity through Acetylation](#)

Stable identifier: R-HSA-5628871

Type: transition

Compartments: nucleoplasm



BRD7 promotes EP300 (p300)-mediated acetylation of TP53 on lysine residue K382, which enhances binding of TP53 to its target promoters. Also, BRD7 induces EP300-mediated acetylation of histone 3 on lysine residue K10 (also labeled in literature as K9), creating the H3K9 active chromatin mark at CDKN1A and MDM2 promoters (Drost et al. 2010), and possibly other TP53 promoters co-regulated by BRD7, such as SERPINE1, TIGAR, TNFRSF10C and NDRG1.

Preceded by: [BRD7 binds TP53 and EP300](#)

Followed by: [MTA2-NuRD complex deacetylates TP53](#)

Literature references

Tocco, F., Del Sal, G., Drost, J., Elkon, R., Holstege, H., Kerkhoven, R. et al. (2010). BRD7 is a candidate tumour suppressor gene required for p53 function. *Nat. Cell Biol.*, 12, 380-9. ↗

Editions

2015-10-14	Authored, Edited	Orlic-Milacic, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

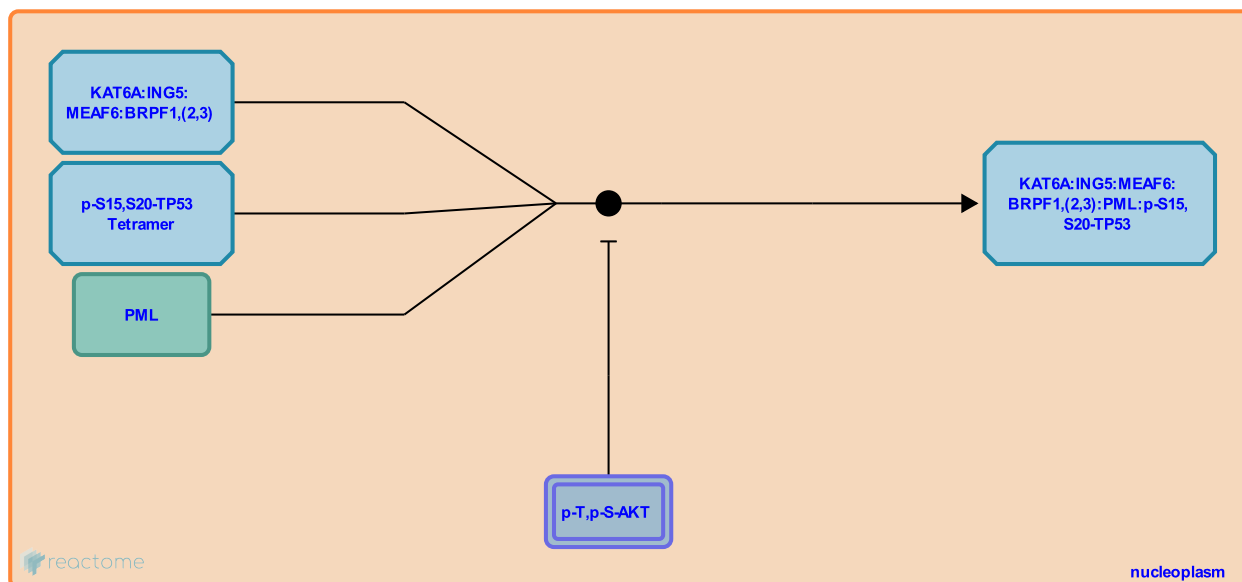
KAT6A and PML bind TP53 ↗

Location: [Regulation of TP53 Activity through Acetylation](#)

Stable identifier: R-HSA-6805620

Type: binding

Compartments: nucleoplasm



The histone acetyltransferase KAT6A, which functions as part of the MOZ/MORF complex (Ullah et al. 2008), associates with TP53 (p53) and PML (Rokudai et al. 2013). KAT6A can independently associate with TP53 and PML, but the presence of PML enhances KAT6A-mediated acetylation of TP53. Phosphorylation of KAT6A by activated AKT inhibits PML binding (Rokudai et al. 2013).

Followed by: [KAT6A acetylates TP53](#)

Literature references

Taya, Y., Rokudai, S., Prives, C., Arnal, SM., Laptenko, O., Kitabayashi, I. (2013). MOZ increases p53 acetylation and premature senescence through its complex formation with PML. *Proc. Natl. Acad. Sci. U.S.A.*, 110, 3895-900. ↗

Yang, XJ., Côté, J., Wang, K., Goh, SL., Pelletier, N., Degerny, C. et al. (2008). Molecular architecture of quartet MOZ/MORF histone acetyltransferase complexes. *Mol. Cell. Biol.*, 28, 6828-43. ↗

Editions

2015-10-14	Authored, Edited	Orlic-Milacic, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

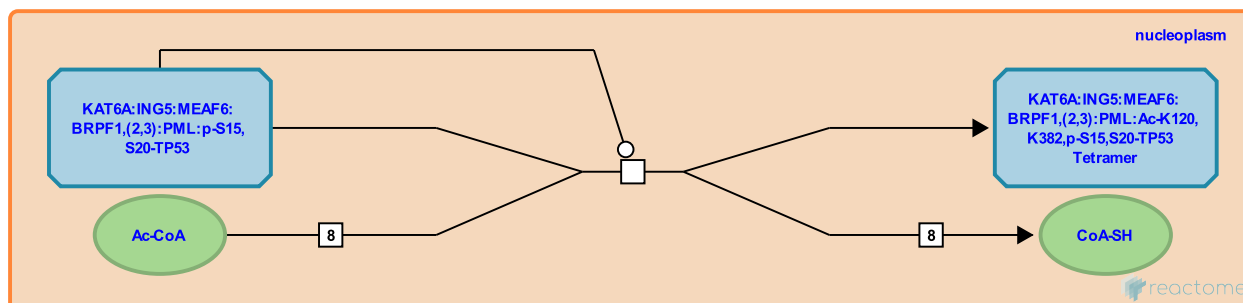
KAT6A acetylates TP53 ↗

Location: [Regulation of TP53 Activity through Acetylation](#)

Stable identifier: R-HSA-6805638

Type: transition

Compartments: nucleoplasm



KAT6A histone acetyltransferase, part of the MOZ/MORF complex, acetylates TP53 (p53) on lysine residues K120 and K382. The acetylation of TP53 by KAT6A is enhanced in the presence of PML and results in increased transcriptional activation of the CDKN1A (p21) gene by TP53 (Rokudai et al. 2013).

Preceded by: [KAT6A and PML bind TP53](#)

Followed by: [MTA2-NuRD complex deacetylates TP53](#)

Literature references

Taya, Y., Rokudai, S., Prives, C., Arnal, SM., Laptenko, O., Kitabayashi, I. (2013). MOZ increases p53 acetylation and premature senescence through its complex formation with PML. *Proc. Natl. Acad. Sci. U.S.A.*, 110, 3895-900. ↗

Editions

2015-10-14	Authored, Edited	Orlic-Milacic, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

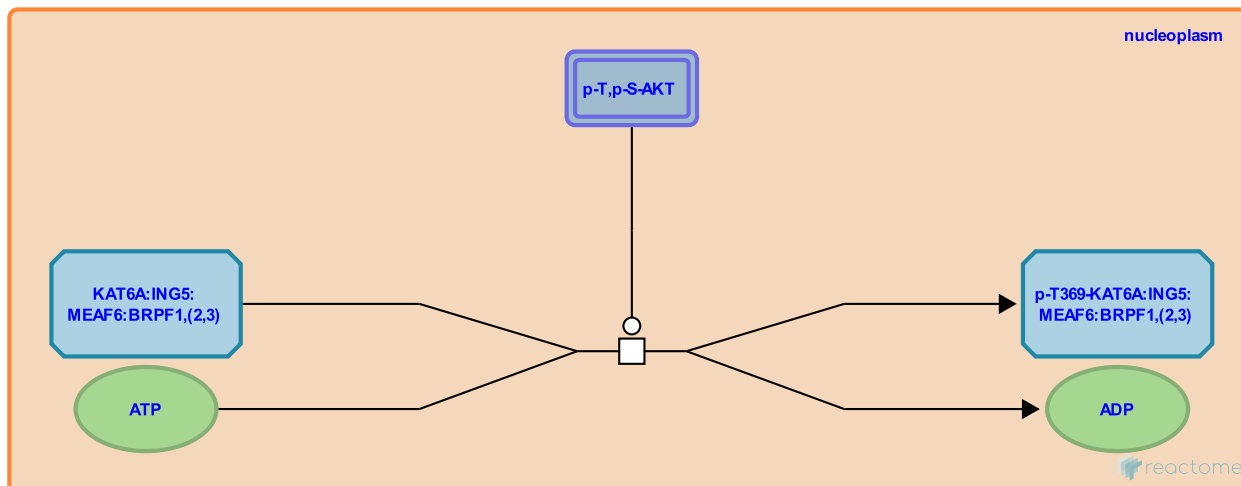
AKT phosphorylates KAT6A ↗

Location: [Regulation of TP53 Activity through Acetylation](#)

Stable identifier: R-HSA-6805640

Type: transition

Compartments: nucleoplasm



Activated AKT phosphorylates the histone acetyltransferase KAT6A on threonine residue T369, preventing association of PML with the KAT6A complex and repressing KAT6A-mediated acetylation of TP53 (p53) (Rokudai et al. 2013).

Literature references

Taya, Y., Rokudai, S., Prives, C., Arnal, SM., Laptenko, O., Kitabayashi, I. (2013). MOZ increases p53 acetylation and premature senescence through its complex formation with PML. *Proc. Natl. Acad. Sci. U.S.A.*, 110, 3895-900. ↗

Editions

2015-10-14	Authored, Edited	Orlic-Milacic, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

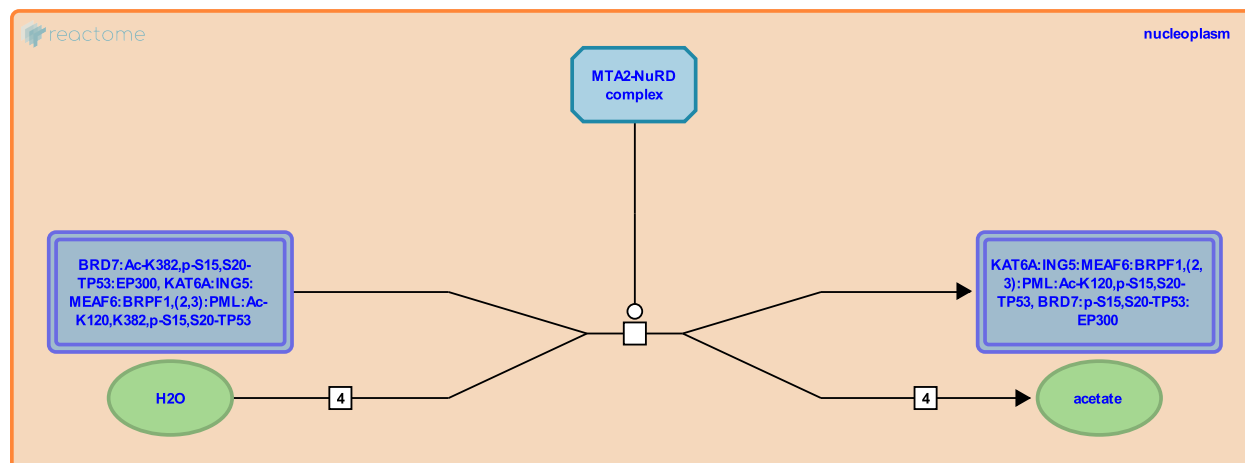
MTA2-NuRD complex deacetylates TP53 ↗

Location: [Regulation of TP53 Activity through Acetylation](#)

Stable identifier: R-HSA-6805650

Type: transition

Compartments: nucleoplasm



MTA2 (PID), a component of the NuRD complex, binds TP53 (p53) and thus targets histone deacetylases of the NuRD complex to TP53. The NuRD complex deacetylates the C-terminus of TP53, including acetylated lysine K382, thus inhibiting TP53 transcriptional activity (Luo et al. 2000).

Preceded by: [BRD7 promotes EP300-mediated acetylation of TP53](#), [KAT6A acetylates TP53](#)

Literature references

Su, F., Shiloh, A., Gu, W., Chen, D., Luo, J. (2000). Deacetylation of p53 modulates its effect on cell growth and apoptosis. *Nature*, 408, 377-81. ↗

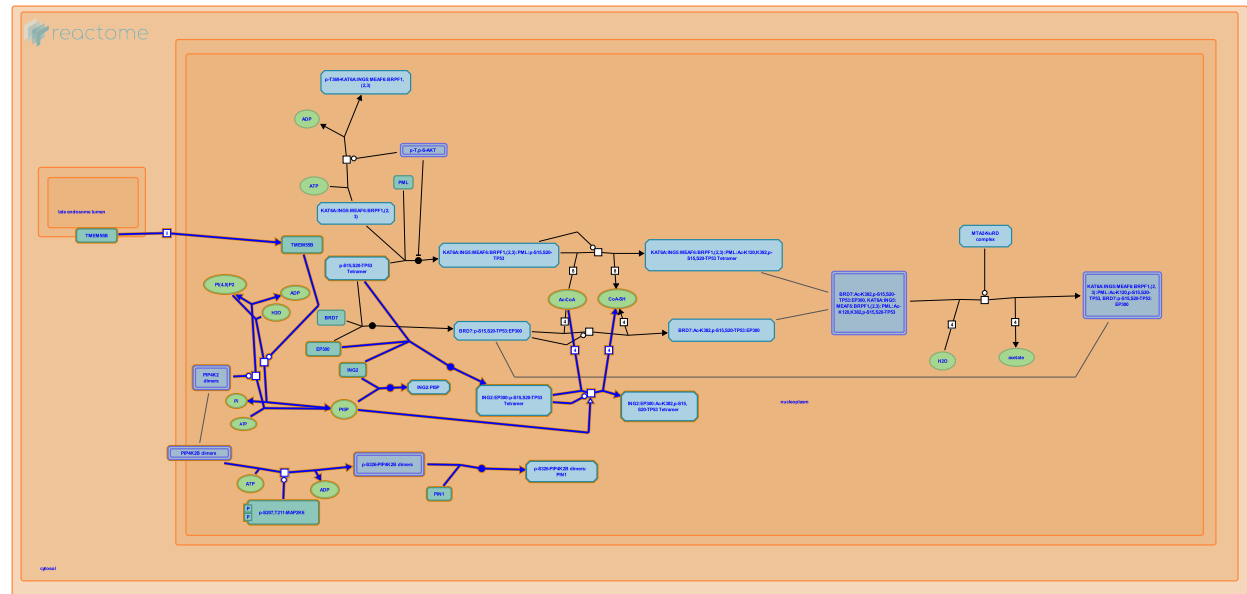
Editions

2015-10-14	Authored, Edited	Orlic-Milacic, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

PI5P Regulates TP53 Acetylation

Location: Regulation of TP53 Activity through Acetylation

Stable identifier: R-HSA-6811555



Under conditions of cellular stress, nuclear levels of phosphatidylinositol-5-phosphate (PI5P) increase and, through interaction with ING2, result in nuclear retention/accumulation of ING2. ING2 binds TP53 (p53) and recruits histone acetyltransferase EP300 (p300) to TP53, leading to TP53 acetylation. Increased nuclear PI5P levels positively regulate TP53 acetylation (Ciruela et al. 2000, Gozani et al. 2003, Jones et al. 2006, Zou et al. 2007, Bultsma et al. 2010).

Literature references

Jones, DR., D'Santos, CS., Bultsma, Y., Heck, AJ., Keune, WJ., Halstead, JR. et al. (2006). Nuclear PtdIns5P as a transducer of stress signaling: an in vivo role for PIP4Kbeta. *Mol. Cell*, 23, 685-95. [↗](#)

Marjanovic, J., Majerus, PW., Kisseleva, MV., Wilson, M., Zou, J. (2007). Type I phosphatidylinositol-4,5-bisphosphate 4-phosphatase regulates stress-induced apoptosis. *Proc. Natl. Acad. Sci. U.S.A.*, 104, 16834-9. [↗](#)

Ivanov, D., Jones, DR., Zhu, H., Baird, CL., Lessnick, SL., Gozani, O. et al. (2003). The PHD finger of the chromatin-associated protein ING2 functions as a nuclear phosphoinositide receptor. *Cell*, 114, 99-111. [↗](#)

Ciruela, A., Irvine, RF., Hinchliffe, KA., Divecha, N. (2000). Nuclear targeting of the beta isoform of type II phosphatidylinositol phosphate kinase (phosphatidylinositol 5-phosphate 4-kinase) by its alpha-helix 7. *Biochem. J.*, 346, 587-91. [↗](#)

Bultsma, Y., Keune, WJ., Divecha, N. (2010). PIP4Kbeta interacts with and modulates nuclear localization of the high-activity PtdIns5P-4-kinase isoform PIP4Kalpha. *Biochem. J.*, 430, 223-35. [↗](#)

Editions

2015-11-19	Authored	Orlic-Milacic, M.
2016-06-21	Reviewed	Divecha, N.
2016-06-28	Edited	Orlic-Milacic, M.

Table of Contents

Introduction	1
❏ Regulation of TP53 Activity through Acetylation	2
➤ BRD7 binds TP53 and EP300	3
➤ BRD7 promotes EP300-mediated acetylation of TP53	4
➤ KAT6A and PML bind TP53	5
➤ KAT6A acetylates TP53	6
➤ AKT phosphorylates KAT6A	7
➤ MTA2-NuRD complex deacetylates TP53	8
❏ PI5P Regulates TP53 Acetylation	9
Table of Contents	10