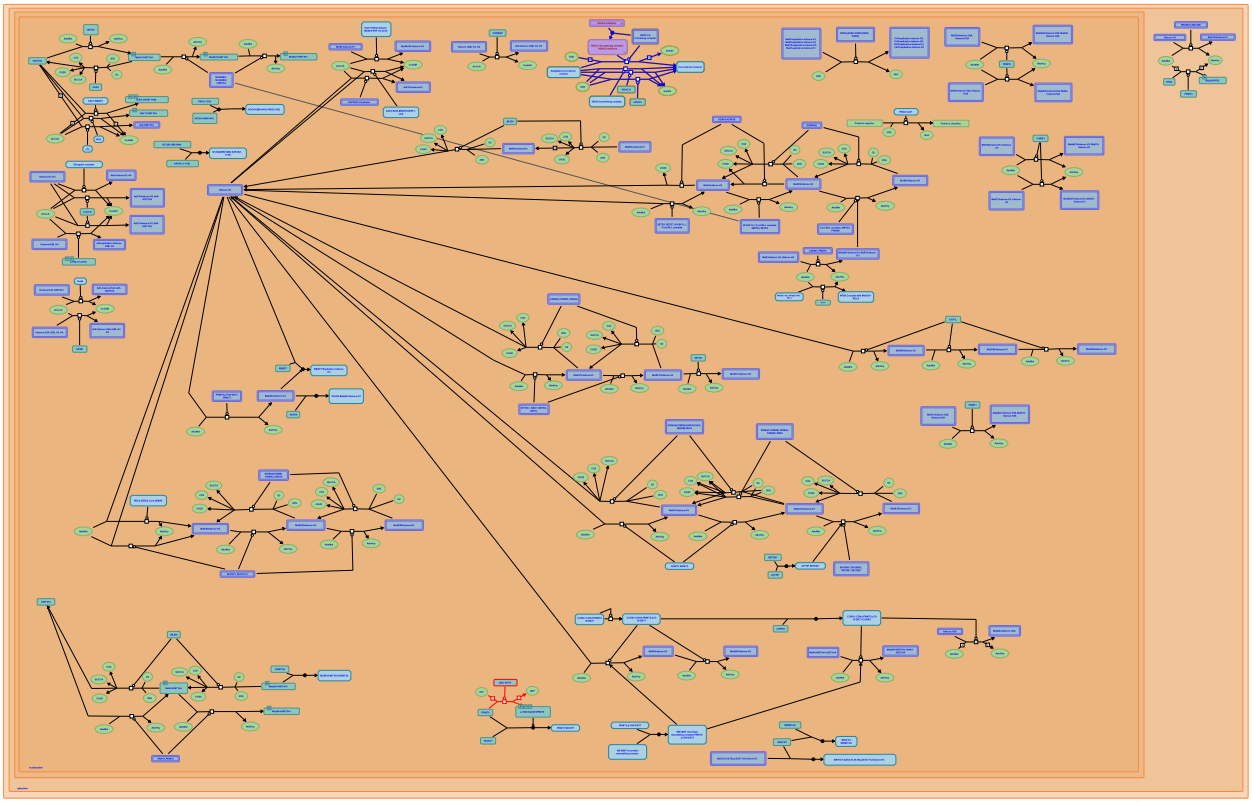
HDACs deacetylate histones



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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.

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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

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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. ↗

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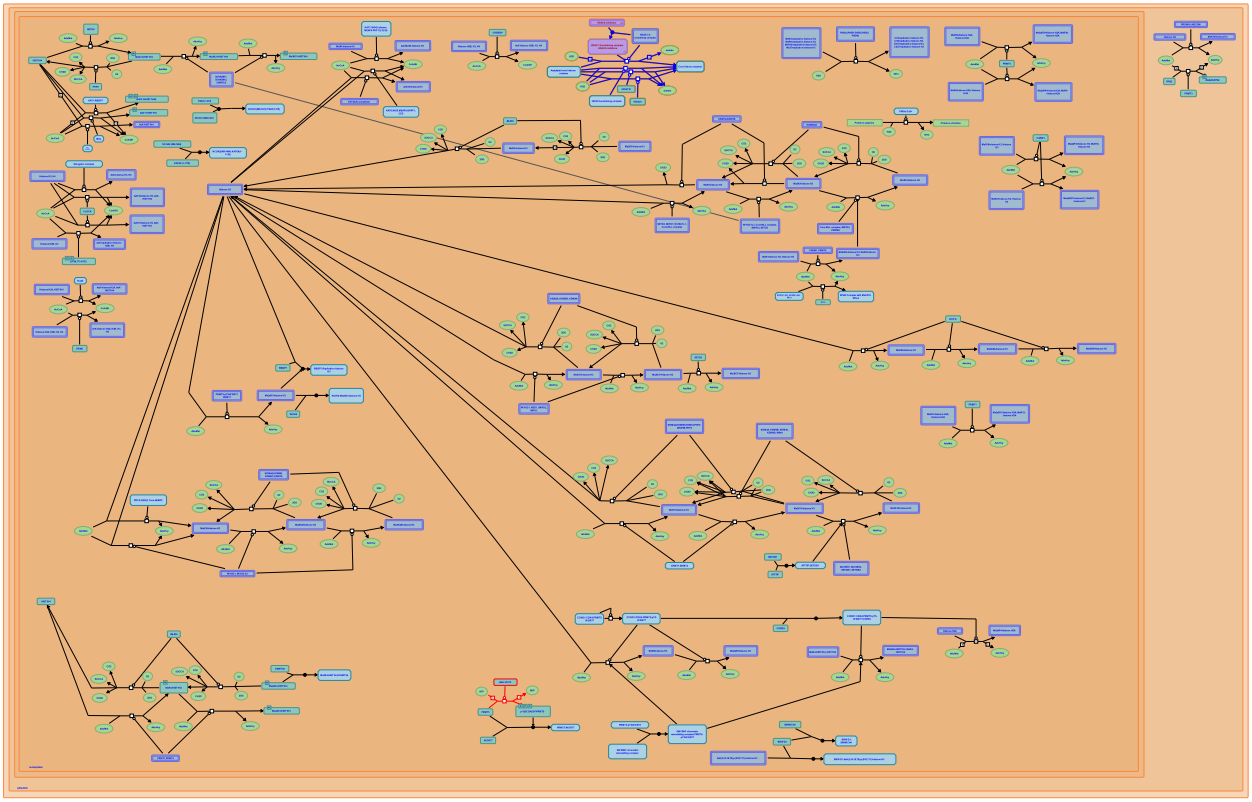
Reactome database release: 90

This document contains 1 pathway and 5 reactions (see Table of Contents)

HDACs deacetylate histones ↗

Stable identifier: R-HSA-3214815



Lysine deacetylases (KDACs), historically referred to as histone deacetylases (HDACs), are divided into the Rpd3/Hda1 metal-dependent 'classical HDAC family' (de Ruijter et al. 2003, Verdin et al. 2003) and the unrelated sirtuins (Milne & Denu 2008). Phylogenetic analysis divides human KDACs into four classes (Gregoretti et al. 2004): Class I includes HDAC1, 2, 3 and 8; Class IIa includes HDAC4, 5, 7 and 9; Class IIb includes HDAC6 and 10; Class III are the sirtuins (SIRT1-7); Class IV has one member, HDAC11 (Gao et al. 2002). Class III enzymes use an NAD+ cofactor to perform deacetylation (Milne & Denu 2008, Yang & Seto 2008), the others classes use a metal-dependent mechanism (Gregoretti et al. 2004) to catalyze the hydrolysis of acetyl-L-lysine side chains in histone and non-histone proteins yielding L-lysine and acetate. X-ray crystal structures are available for four human HDACs; these structures have conserved active site residues, suggesting a common catalytic mechanism (Lombardi et al. 2011). They require a single transition metal ion and are typically studied in vitro as Zn2+-containing enzymes, though in vivo HDAC8 exhibits increased activity when substituted with Fe2+ (Gantt et al. 2006). The structurally-related enzyme acetylpolyamine amidohydrolase (APAH) (Leipe & Landsman 1997) exhibits optimal activity with Mn2+, followed closely by Zn2+ (Sakurada et al. 1996).

HDACs are often part of multi-protein transcriptional complexes that are recruited to gene promoters, regulating transcription without direct DNA binding. With the exception of HDAC8, all class I members can be catalytic subunits of multiprotein complexes (Yang & Seto 2008). HDAC1 and HDAC2 interact to form the catalytic core of several multisubunit complexes including Sin3, nucleosome remodeling deacetylase (NuRD) and corepressor of REST (CoREST) complexes (Grozinger & Schreiber 2002). HDAC3 is part of the silencing mediator of retinoic acid and thyroid hormone receptor (SMRT) complex or the homologous nuclear receptor corepressor (NCoR) (Li et al. 2000, Wen et al. 2000, Zhang et al. 2002, Yoon et al. 2003, Oberoi et al. 2011) which are involved in a wide range of processes including metabolism, inflammation, and circadian rhythms (Mottis et al. 2013).

Class IIa HDACs (HDAC4, -5, -7, and -9) shuttle between the nucleus and cytoplasm (Yang & Seto 2008, Haberland et al. 2009). The nuclear export of class IIa HDACs requires phosphorylation stimulated by calcium or other stimuli. They appear to have been evolutionarily inactivated as enzymes, having acquired a histidine substitution of the tyrosine residue in the active site of the mammalian deacetylase domain (H976 in humans) (Lahm et al. 2007, Schuetz et al. 2008). Instead they function as transcriptional corepressors for the MEF2 family of transcription factors (Yang & Gregoire 2005) .

Histones are the primary substrate for most HDACs except HDAC6 which is predominantly cytoplasmic and acts on alpha-tublin (Hubbert et al. 2002, Zhang et al. 2003, Boyault et al. 2007). HDACs also deacetylate proteins such as p53, E2F1, RelA, YY1, TFIIE, BCL6 and TFIIF (Glozak et al. 2005).

Histone deacetylases are targeted by structurally diverse compounds known as HDAC inhibitors (HDIs) (Marks et al. 2000). These can induce cytodifferentiation, cell cycle arrest and apoptosis of transformed cells (Marks et al. 2000, Bolden et al. 2006). Some HDIs have significant antitumor activity (Marks and Breslow 2007, Ma et al. 2009) and at least two are approved anti-cancer drugs.

The coordinates of post-translational modifications represented and described here follow UniProt standard practice whereby coordinates refer to the translated protein before any further processing. Histone literature typically refers to coordinates of the protein after the initiating methionine has been removed. Therefore the coordinates of post-translated residues in the Reactome database and described here are frequently +1 when compared with the literature.

Literature references

van Gennip, AH., Kemp, S., Caron, HN., van Kuilenburg, AB., de Ruijter, AJ. (2003). Histone deacetylases (HDACs): characterization of the classical HDAC family. *Biochem. J., 370*, 737-49. ↗

Cole, KE., Dowling, DP., Christianson, DW., Lombardi, PM. (2011). Structure, mechanism, and inhibition of histone deacetylases and related metalloenzymes. *Curr. Opin. Struct. Biol., 21*, 735-43. ↗

Editions

2013-03-12	Authored, Edited	Jupe, S.
2014-05-08	Reviewed	Yang, XJ.

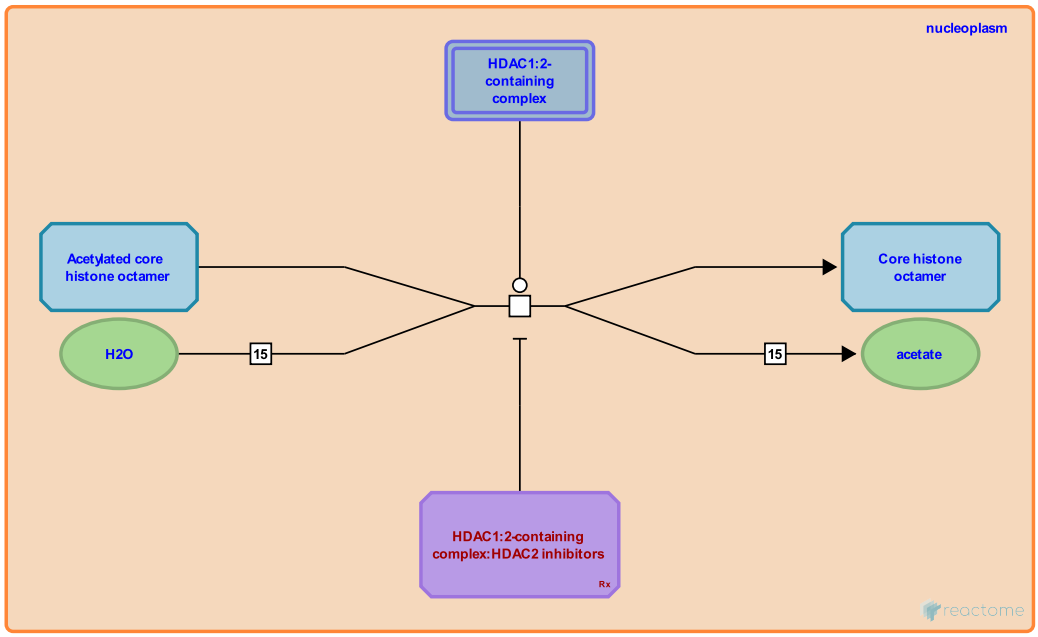
HDAC1:2-containing complex deacetylate histones ↗

Location: HDACs deacetylate histones

Stable identifier: R-HSA-3769447

Type: transition

Compartments: nucleoplasm



HDAC1 and HDAC2 interact to form the catalytic core of several multisubunit complexes including the Sin3, nucleosome remodeling deacetylase (NuRD) and corepressor of REST (CoREST) complexes (Grozinger & Schreiber 2002). A 'core complex' of HDAC1/2 and the histone binding proteins RBBP7 (RbAp46) and RBBP4 (RbAp48), has been described in vivo and in vitro (Zhang et al. 1999). The Sin3 complex consists of this core complex plus SAP18 and SAP30, which appear to aid in stabilizing the protein associations and Sin3A, which serves as a scaffold for assembly of the complex and its interaction with various DNA binding proteins (Ayer 1999). Mammals express two Sin3 proteins, Sin3A and Sin3B. The recognized Sin3A core complex contains the HDAC1-2 catalytic core, SAP18 (Zhang et al. 1997), SAP30 (Zhang et al. 1998), RBBP7/4 (Ahringer 2000), SUDS3 (SAP45, SDS3) (Alland et al. 2002), ARID4B (SAP180) and SAP130 (Fleischer et al. 2003). Additional members are BRMS1 (breast cancer metastasis suppressor 1), ARID4A (Rb-binding protein 1) (Meehan et al. 2004) and SAP30L (Viiri et al. 2006). The Sin3A complex preferentially binds to hypoacetylated histones through the RBBP7/4 subunits (Vermeulen et al. 2004, Yoon et al. 2005). It can also be recruited to chromatin through the H3K4-di/trimethyl mark by ING1/2 (Shi et al. 2006, Pena et al. 2008).

The Sin3B complex shares some subunits in common with the Sin3A complex but may also contain distinct subunits (Le Guezennec et al. 2006a).

The NuRD complex contains a core histone deacetylase complex that consists of the HDAC1-2 catalytic core plus RBBP7 (RbAp46) and RBBP4 (RbAp48) (Ahringer 2000). The largest and key component is the Mi-2 remodelling subunit (dermatomyositis-specific autoantigen), which contains the ATPase/chromatin remodelling activity and physically associates with the other components. Mammals have two Mi-2 proteins: CHD3 (Mi-2alpha), and CHD4 (Mi-2 beta) (Seelig et al. 1996). CHD4 (Mi-2 beta) is the form predominantly associated with the NuRD complex (Zhang et al. 1998, Feng & Zhang 2001), although CHD3 is a member of the NuRD complex in a variety of human cell lines (Le Guezennec et al. 2006b). It is not clear whether functional differences exist between CHD3 and CHD4-containing complexes (McDonel et al. 2009). Further components are MBD3 (methyl CpG-binding domain 3), and a metastasis-associated (MTA) protein subunit. MTA subunits (e.g. Mta1, Mta2 or Mta3) appear to be mutually exclusive, possibly contributing to functional diversity of NuRD complexes (Bowen et al. 2004, Fujita et al. 2004). GATAD2A and GATAD2B proteins (formerly known as p66alpha and p66beta) are often reported as members of NuRD. MBD3 can be replaced by related protein MBD2, forming the MeCP1 complex (Feng & Zhang 2001, Le Guezennec et al. 2006b). The MeCP1 complex represents only a small proportion of the total NuRD complex in mammalian cells (Refs. in McDonel et al. 2009); MBD2 has been shown to be dispensable for normal mammalian development (Hendrich et al. 2001).

NuRD is recruited via MDB3 for DNA methylation-dependent gene silencing. It associates with MeCP1 (methyl CpG-binding protein 1) and MeCP2 to provide an intimate connection with DNA methylation (Denslow & Wade 2007, Klose & Bird 2006).

The CoREST complex minimally contains the HDAC1-2 catalytic core, REST (RE1-silencing transcription factor), RCOR1 (CoREST, KIAA0071) and KDM1A (BHC110, LSD1) (Andres et al. 1999, Humphrey et al. 2001). The BRAF–HDAC (BHC) complex consists of HDAC1-2, RCOR1, KDM1A, HMG20B (BRAF35) and PHF21A (BHC80) (Hakimi et al. 2002, Yang & Seto 2008).

This reaction represents a theoretical complete deacetylation of histone.

Literature references

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Ahringer, J. (2000). NuRD and SIN3 histone deacetylase complexes in development. *Trends Genet., 16*, 351-6. ↗

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Editions

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2014-05-08	Reviewed	Yang, XJ.

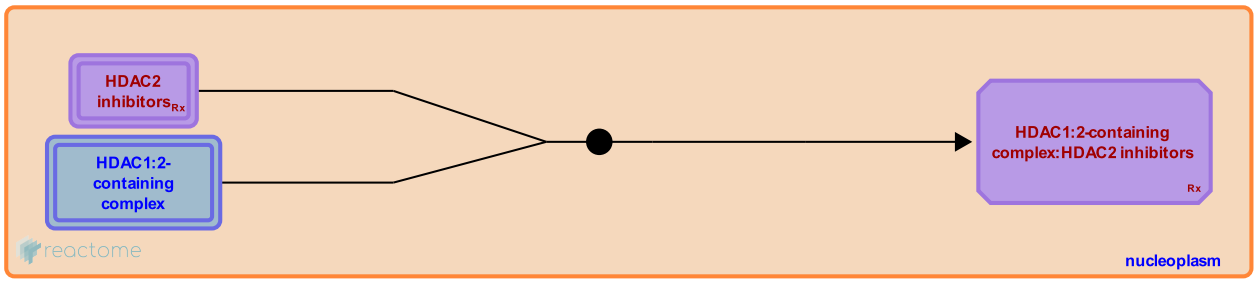
HDAC1:2-containing complex binds HDAC2 Inhibitors ↗

Location: HDACs deacetylate histones

Stable identifier: R-HSA-9679787

Type: binding

Compartments: nucleoplasm



To carry out gene expression, a cell must control the winding and unwinding of DNA around histones. This is mediated by histone acetyl transferases (HATs) and histone deacetylases (HDACs). HDAC inhibitors inhibit the proliferation of tumour cells by inducing cell cycle arrest, differentiation and/or apoptosis (Zhang et al. 2019). Belinostat (Marks et al. 2000, O'Connor et al. 2015), vorinostat (Marks & Breslow 2007) and romidepsin (Ueda et al. 1994, VanderMolen et al. 2011) are HDAC inhibitors approved for the treatment of Peripheral T-cell lymphomas (PTCLs) (Hood & Shah 2016). These drugs are believed to bind to many, if not all HDAC proteins.

Human papillomaviruses (HPVs) cause epithelial proliferative diseases. The HDAC inhibitors vorinostat, belinostat and panobinostat have been shown to inhibit HPV DNA amplification and cause apoptosis in preclinical experiments (Banerjee et al. 2018).

The antiepileptic drug valproic acid inhibits HDAC2 and therefore is a promising drug for cancer therapy (Göttlicher et al. 2001).

Literature references

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Sleeman, JP., Zhu, P., Göttlicher, M., Lo Coco, F., Minucci, S., Krämer, OH. et al. (2001). Valproic acid defines a novel class of HDAC inhibitors inducing differentiation of transformed cells. *EMBO J, 20*, 6969-78. ↗

Editions

2020-03-25	Authored, Edited	Jassal, B.
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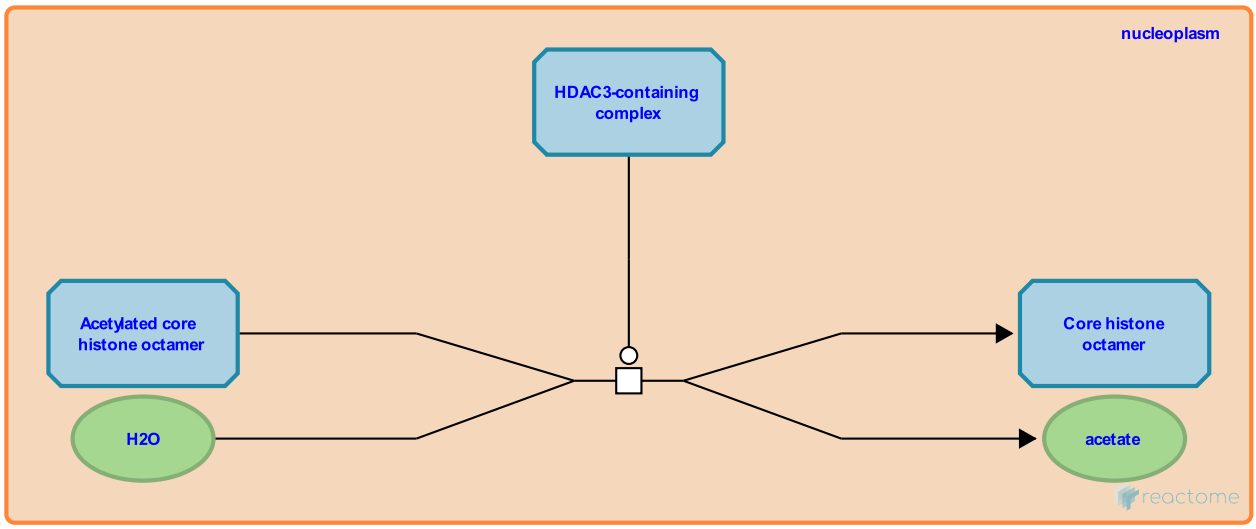
HDAC3 containing complexes deacetylate histone ↗

Location: HDACs deacetylate histones

Stable identifier: R-HSA-3777129

Type: transition

Compartments: nucleoplasm



HDAC3 mediates the gene silencing activity of Retinoic acid and thyroid hormone receptor (SMRT) complex or the homologous nuclear receptor corepressor (NCoR). These coregulators are involved in a wide range of developmental and homeostatic processes, including metabolism, inflammation, and circadian rhythms (Mottis et al. 2013). HDAC3 interacts with a conserved SANT-like domain known as the deacetylase activating domain (DAD) within NCOR2 (SMRT) or NCOR1 (Li et al. 2000, Wen et al. 2000, Zhang et al. 2002, Yoon et al. 2003, Oberoi et al. 2011). This interaction both recruits and activates HDAC3 (Wen et al. 2000, Guenther et al. 2001, Zhang et al. 2002). Recruitment of HDAC3 to the DAD is essential for repression by the nuclear thyroid hormone receptor and for the maintenance of normal circadian physiology (You et al. 2010, Yin et al. 2007). A second SANT-like domain has been reported to interact directly with histone tails and termed the histone interaction domain (HID) (Hartman et al. 2005, Yu et al. 2003). NCORs are largely unstructured platform proteins that act as a scaffold upon which the enzymatic machinery of the repression complex is built (Watson et al. 2012). They can recruit other deacetylases such as HDAC4 (Fischle et al. 2002), HDAC5, HDAC7 (Kao et al. 2000), Sirt1 (Picard et al. 2004), and via mSin3, HDAC1 (Heinzel et al. 1997, Nagy et al. 1997). The importance of these deacetylase enzymes is not yet established. It has been demonstrated HDAC3 was shown to be responsible for deacetylase activities associated with HDAC4 and HDAC7 (Fischle et al. 2002). Corepressor complexes are heterogeneous, context-specific and transient in nature, but in addition to HDAC3, some additional partners are regularly found in stoichiometric association with NCOR1/NCOR2 and are essential for repressive function. These partners include the G protein pathway suppressor (GPS2) and transducing beta-like 1 (TBL1) and its homologue, TBL-related 1 (TBLR1), which together form the core repression complex (Oberoi et al. 2011). Ins(1,4,5,6)P4 is a further component of the complex (Watson et al. 2012).

Literature references

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Editions

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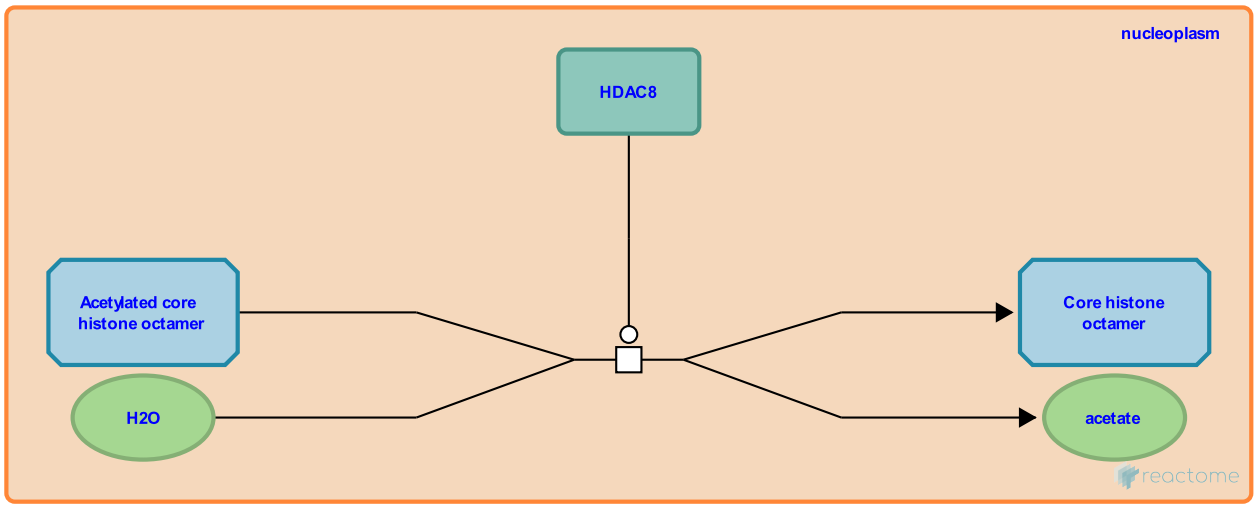
HDAC8 deacetylates histones ↗

Location: HDACs deacetylate histones

Stable identifier: R-HSA-3782637

Type: transition

Compartments: nucleoplasm



HDAC8 can catalyze the in vitro deacetylation of a number of acetylated histone variants including full-length H2A/H2B, H3, and H4 histones acetylated at nonspecific lysines (Hu et al. 2000, Buggy et al. 2000). Peptide sequences corresponding to the H4 histone tail with an acetylated lysine at position sixteen (AcK16) were also identified as in vitro substrates (Buggy et al. 2000, Van der Wyngaert et al. 2000). Subsequent studies have used the H4 histone tail sequence as a peptide template to investigate the amino acid sequence preference of HDAC8. HDAC8 can catalyze the in vitro deacetylation of AcK20 on the H4 histone tail though at a much slower rate than deacetylation of AcK16 peptides (Dose et al. 2011). HDAC8 can catalyze deacetylation in vivo in the absence of a protein complex (Dowling et al. 2010). The role of HDAC8 in catalyzing deacetylation of specific sites in histones in vivo remains unclear (Wolfson et al. 2013).

Literature references

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Editions

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2014-05-08	Reviewed	Yang, XJ.

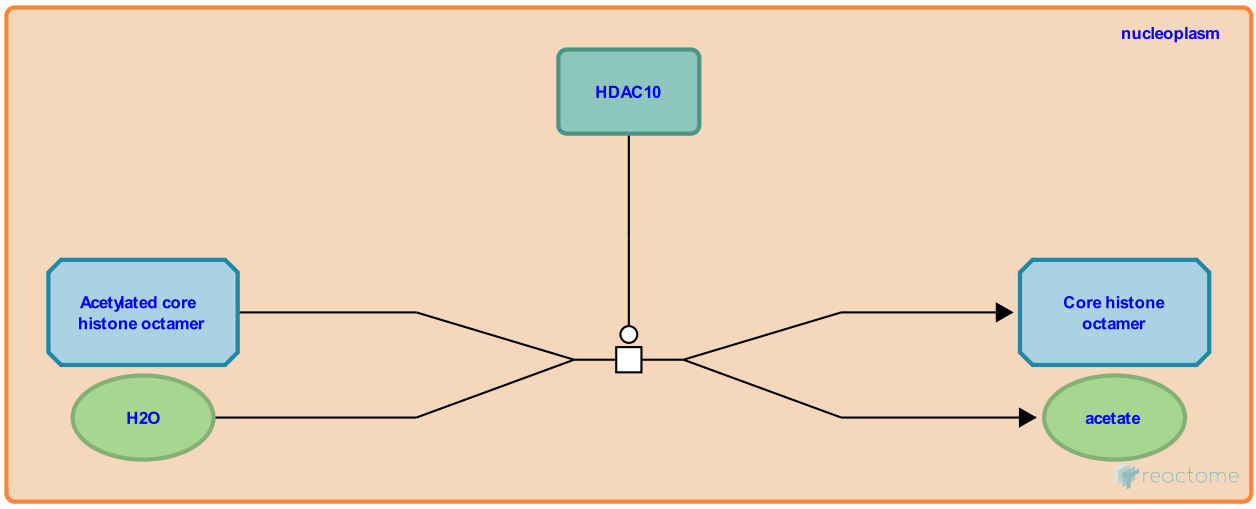
HDAC10 deacetylates histone ↗

Location: HDACs deacetylate histones

Stable identifier: R-HSA-3782655

Type: transition

Compartments: nucleoplasm



HDAC10 is a class IIb HDAC subfamily member with greatest sequence similarity to HDAC6. Unlike HDAC6, HDAC10 is found in the nucleus. It is able to deacetylate acetylated histone H4 N-terminal peptides (Fischer et al. 2002, Guardiola & Yao 2002, Kao et al. 2002, Tong et al. 2002).

Literature references

Trogani, N., Terry, R., Bhatia, U., Cai, R., Song, C., Cohen, D. et al. (2002). Isolation and characterization of a novel class II histone deacetylase, HDAC10. *J. Biol. Chem., 277*, 6656-66. ↗

Editions

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2014-05-08	Reviewed	Yang, XJ.

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