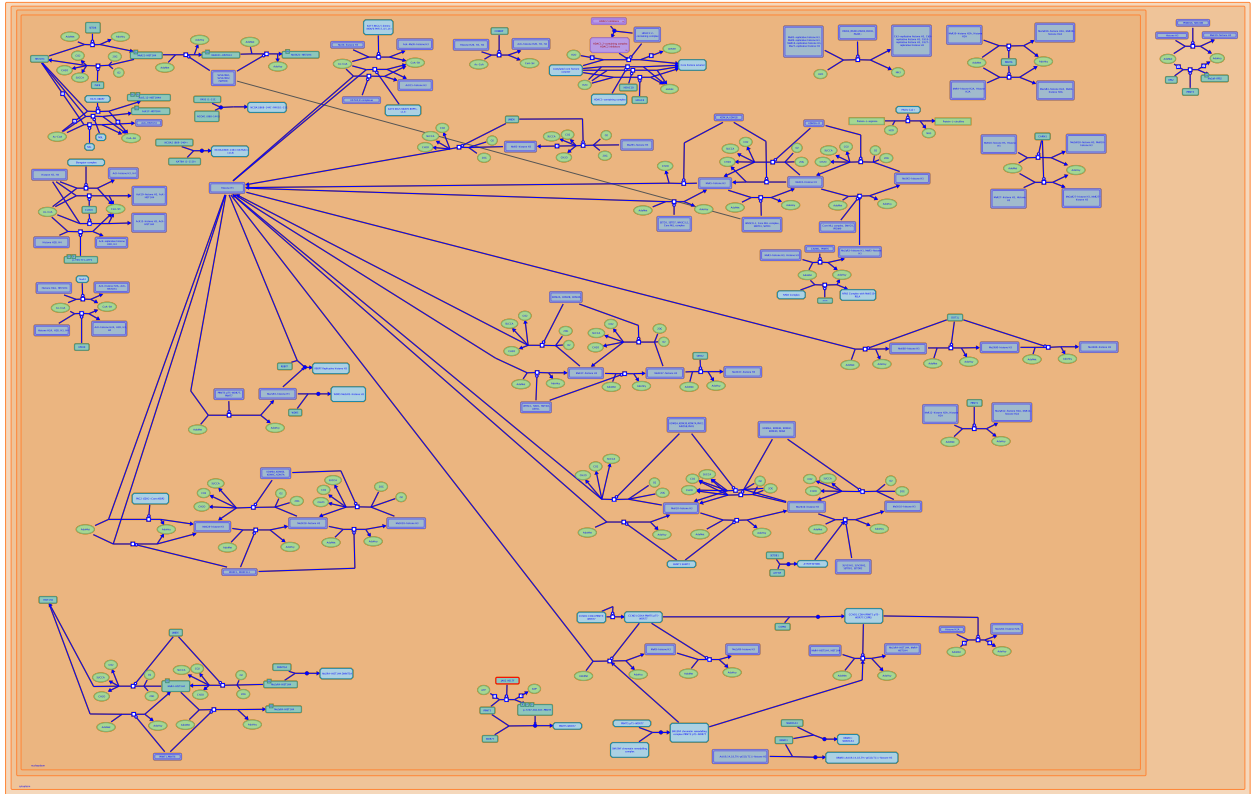


# Chromatin modifying enzymes



D'Eustachio, P., Duenas, C., Fischle, W., Guccione, E., Hopkinson, J., Jassal, B., Jupe, S., Karagiannis, T., Mandal, M., Meldal, BH., Motamedi, M., Orlic-Milacic, M., Schofield, CJ., Walport, LJ., Yang, XJ.

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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.

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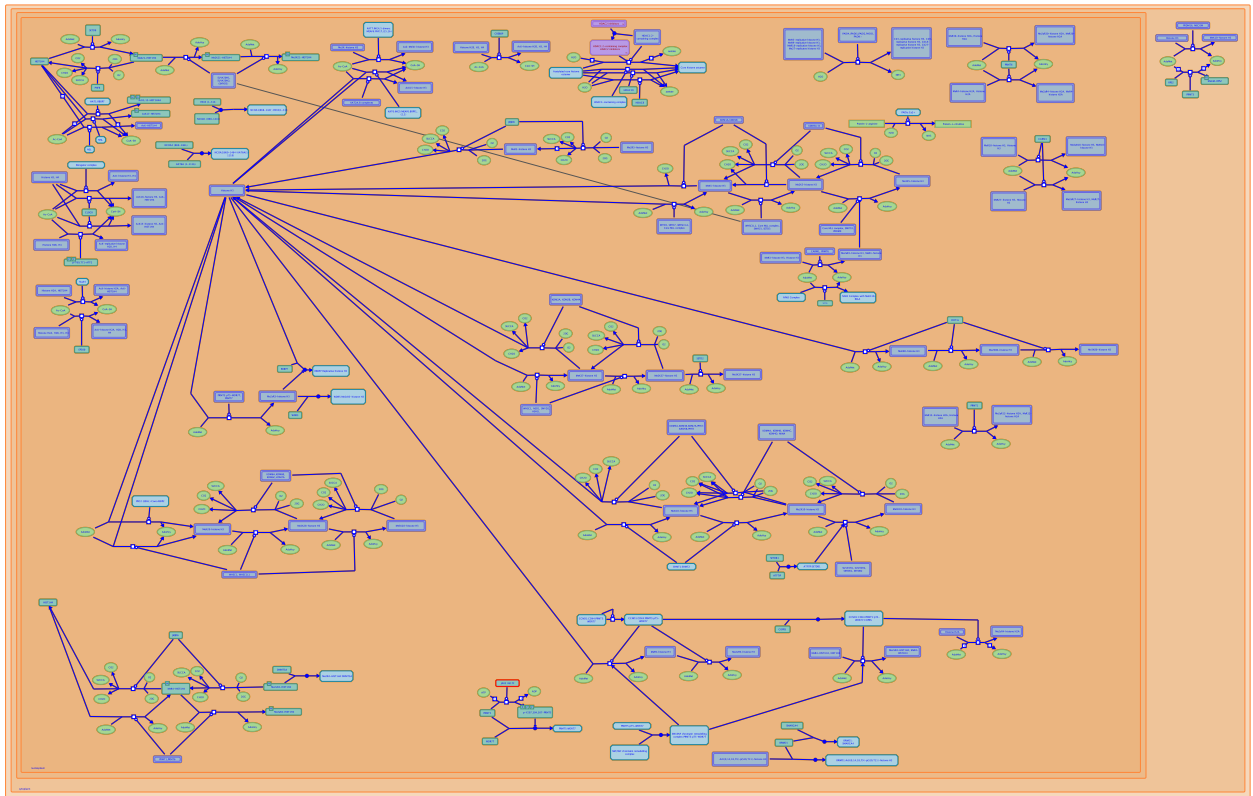
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Reactome database release: 77

This document contains 6 pathways and 4 reactions ([see Table of Contents](#))

## Chromatin modifying enzymes ↗

Stable identifier: R-HSA-3247509



 reactome

Eukaryotic DNA is associated with histone proteins and organized into a complex nucleoprotein structure called chromatin. This structure decreases the accessibility of DNA but also helps to protect it from damage. Access to DNA is achieved by highly regulated local chromatin decondensation.

The 'building block' of chromatin is the nucleosome. This contains ~150 bp of DNA wrapped around a histone octamer which consists of two each of the core histones H2A, H2B, H3 and H4 in a 1.65 left-handed superhelical turn (Luger et al. 1997, Andrews & Luger 2011).

Most organisms have multiple genes encoding the major histone proteins. The replication-dependent genes for the five histone proteins are clustered together in the genome in all metazoans. Human replication-dependent histones occur in a large cluster on chromosome 6 termed HIST1, a smaller cluster HIST2 on chromosome 1q21, and a third small cluster HIST3 on chromosome 1q42 (Marzluff et al. 2002). Histone genes are named systematically according to their cluster and location within the cluster.

The 'major' histone genes are expressed primarily during the S phase of the cell cycle and code for the bulk of cellular histones. Histone variants are usually present as single-copy genes that are not restricted in their expression to S phase, contain introns and are often polyadenylated (Old & Woodland 1984). Some variants have significant differences in primary sequence and distinct biophysical characteristics that are thought to alter the properties of nucleosomes. Others localize to specific regions of the genome. Some variants can exchange with pre-existing major histones during development and differentiation, referred to as replacement histones (Kamakaka & Biggins 2005). These variants can become the predominant species in differentiated cells (Pina & Suau 1987, Wunsch et al. 1991). Histone variants may have specialized functions in regulating chromatin dynamics.

The H2A histone family has the highest sequence divergence and largest number of variants. H2A.Z and H2A.XH2A are considered 'universal variants', found in almost all organisms (Talbert & Henikoff 2010).

Variants differ mostly in the C-terminus, including the docking domain, implicated in interactions with the (H3-H4)<sub>2</sub> tetramer within the nucleosome, and in the L1 loop, which is the interaction interface of H2A-H2B dimers (Bonisch & Hake 2012). Canonical H2A proteins are expressed almost exclusively during S-phase. There are several nearly identical variants (Marzluff et al. 2002). No functional specialization of these canonical H2A isoforms has been demonstrated (Bonisch & Hake 2012). Reversible histone modifications such as acetylation and methylation regulate transcription from genomic DNA, defining the 'readability' of genes in specific tissues (Kouzarides 2007, Marmorstein & Trievel 2009, Butler et al. 2012).

N.B. The coordinates of post-translational modifications represented here follow Reactome standardized naming, which includes the 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 histone residues described here are frequently +1 when compared with the literature. For more information on Reactome's standards for naming pathway events, the molecules that participate in them and representation of post-translational modifications, please refer to Naming Conventions on the Reactome Wiki or Jupe et al. 2014.

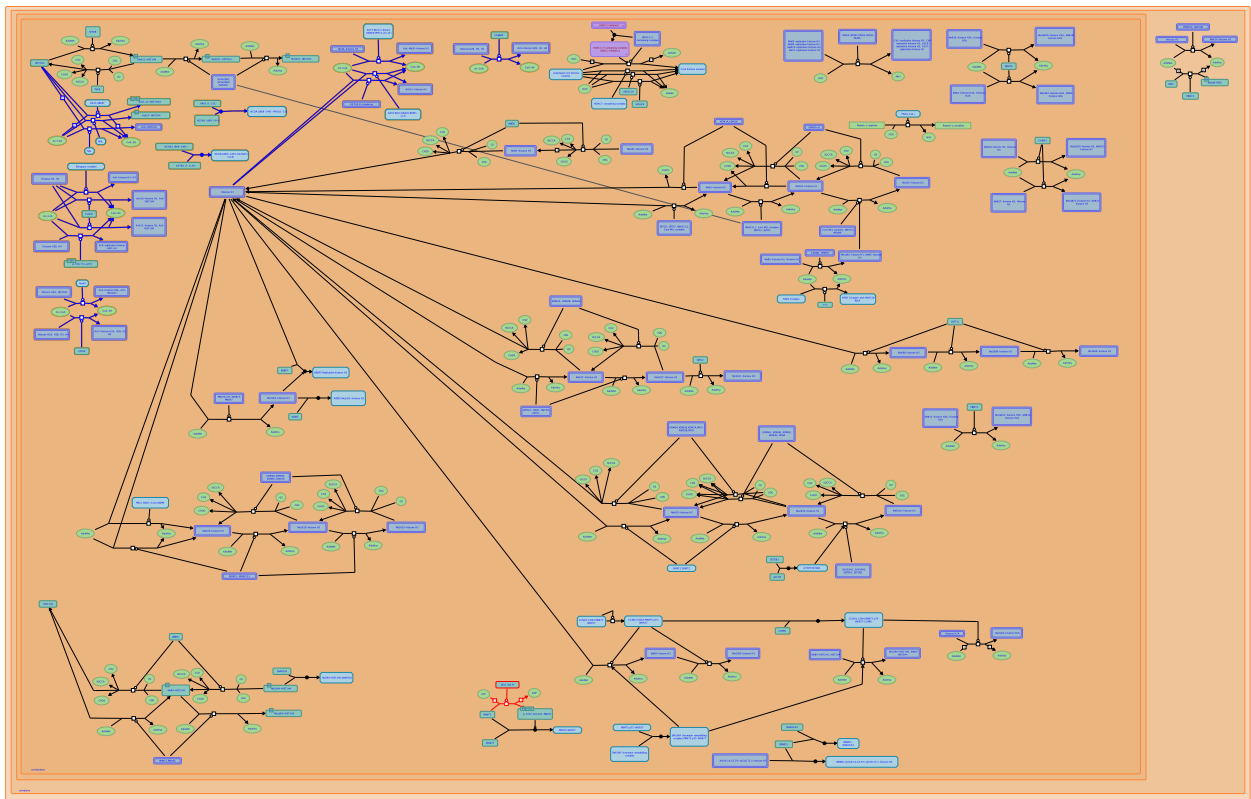
## **Editions**

2013-03-12	Authored	Jupe, S.
2013-11-18	Edited	Jupe, S.
2013-11-18	Reviewed	Karagiannis, T.

## HATs acetylate histones ↗

**Location:** Chromatin modifying enzymes

**Stable identifier:** R-HSA-3214847



 reactome

Histone acetyltransferases (HATs) involved in histone modifications are referred to as A-type or nuclear HATs. They can be grouped into at least four families based on sequence conservation within the HAT domain: Gcn5/PCAF, MYST, p300/CBP and Rtt109. The p300/CBP and Rtt109 families are specific to metazoans and fungi respectively (Marmorstein & Trievel 2009). Gcn5/PCAF and MYST family members have no significant sequence homology but share a globular alpha/beta fold with a common structure involved in acetyl-Coenzyme A (ACA) binding. Both use a conserved glutamate residue for the acetyl transfer reaction but may not share a common catalytic mechanism (Trievel et al. 1999, Tanner et al. 1999, Yan et al. 2002, Berndsen et al. 2007). The p300/CBP HAT domain has no homology with the other families but some structural conservation within the ACA-binding core (Liu et al. 2008). In addition to histone acetylation, members of all 3 human HAT families have been shown to acetylate non-histones (Glozak et al. 2005).

HATs and histone deacetylase (HDAC) enzymes generally act not alone but as part of multiprotein complexes. There are numerous examples in which subunits of HAT or HDAC complexes influence their substrate specificity and lysine preference, which in turn, affect the broader functions of these enzymes (Shahbazian & Grunstein 2007).

N.B. 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.

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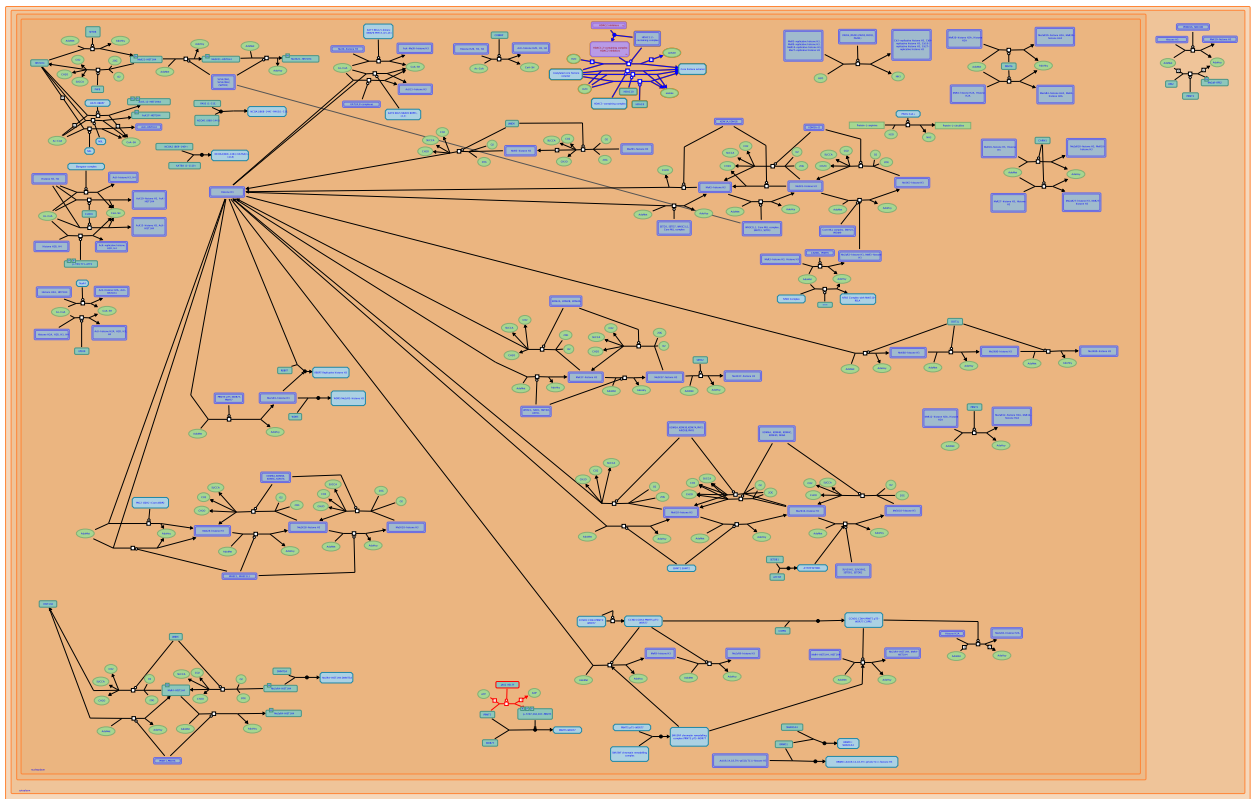
## Editions

2013-03-12	Authored	Jupe, S.
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2013-11-18	Reviewed	Karagiannis, T.

## HDACs deacetylate histones ↗

**Location:** Chromatin modifying enzymes

**Stable identifier:** R-HSA-3214815



 reactome

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 (Gregoretto 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<sup>+</sup> cofactor to perform deacetylation (Milne & Denu 2008, Yang & Seto 2008), the others classes use a metal-dependent mechanism (Gregoretto 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 Zn<sup>2+</sup>-containing enzymes, though *in vivo* HDAC8 exhibits increased activity when substituted with Fe<sup>2+</sup> (Gantt et al. 2006). The structurally-related enzyme acetylpolyamine amidohydrolase (APAH) (Leipe & Landsman 1997) exhibits optimal activity with Mn<sup>2+</sup>, followed closely by Zn<sup>2+</sup> (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, in-

flammation, 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-tubulin (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.

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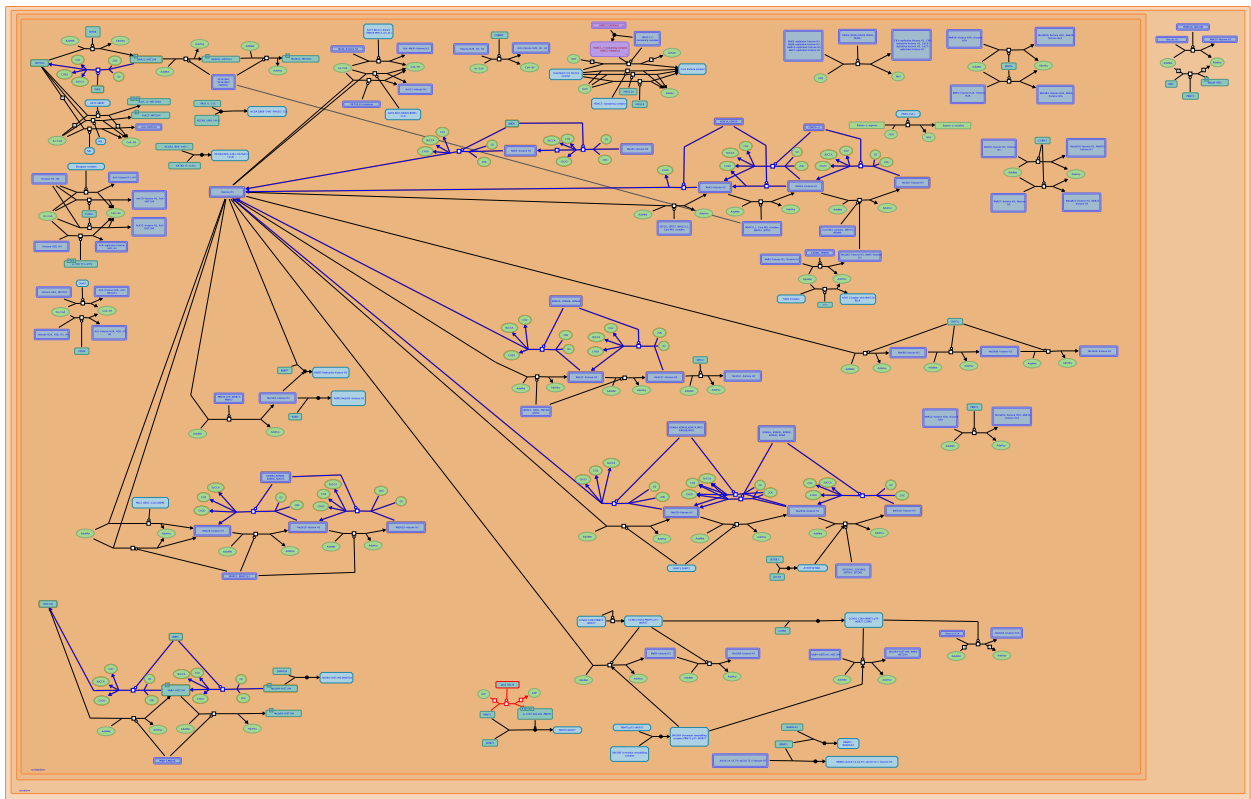
2013-03-12	Authored, Edited	Jupe, S.
2014-05-08	Reviewed	Yang, XJ.



## HDMs demethylate histones ↗

**Location:** Chromatin modifying enzymes

**Stable identifier:** R-HSA-3214842



 reactome

Histone lysine demethylases (KDMs) are able to reverse N-methylations of histones and probably other proteins. To date KDMs have been demonstrated to catalyse demethylation of N-epsilon methylated lysine residues. Biochemically there are two distinct groups of N-epsilon methylated lysine demethylases with different catalytic mechanisms, both of which result in methyl group oxidation to produce formaldehyde. KDM1A, formerly known as Lysine Specific Demethylase 1 (LSD1), belongs to the flavin adenine dinucleotide (FAD)-dependent amino oxidase family. The KDM1A reaction mechanism requires a protonatable lysine epsilon-amine group, not available in trimethylated lysines, which consequently are not KDM1 substrates. Other KDMs belong to the Jumonji C (JmjC) -domain containing family. These are members of the Cupin superfamily of mononuclear Fe (II)-dependent oxygenases, which are characterised by the presence of a double-stranded beta-helix core fold. They require 2-oxoglutarate (2OG) and molecular oxygen as co-substrates, producing, in addition to formaldehyde, succinate and carbon dioxide. This hydroxylation-based mechanism does not require a protonatable lysine epsilon-amine group and consequently JmjC-containing demethylases are able to demethylate tri-, di- and monomethylated lysines.

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In general, methylation at histone H3 lysine-5 (H3K4) and lysine-37 (H3K36), including di- and trimethylation at these sites, has been linked to actively transcribed genes (reviewed in Martin & Zhang 2005). In contrast, lysine-10 (H3K9) promoter methylation is considered a repressive mark for euchromatic genes

and is also one of the landmark modifications associated with heterochromatin (Peters et al. 2002).

The first reported JmjC-containing demethylases were KDM2A/B (JHDM1A/B, FBXL11/10). These catalyse demethylation of histone H3 lysine-37 when mono- or di-methylated (H3K36Me1/2) (Tsukada et al. 2006). They were found to contain a JmjC catalytic domain, previously implicated in chromatin-dependent functions (Clissold & Ponting 2001). Subsequently, many other JmjC enzymes have been identified and discovered to have lysine demethylase activities with distinct methylation site and state specificities.

KDM3A/B (JHDM2A/B) are specific for mono or di-methylated lysine-10 on histone H3 (H3K9Me1/2) (Yamane et al. 2006, Kim et al. 2012). KDM4A-C (JMJD2A-C/JHDM3A-C) catalyse demethylation of di- or tri-methylated histone H3 at lysine-10 (H3K9Me2/3) (Cloos et al. 2006, Fodor et al. 2006), with a strong preference for Me3 (Whetstine et al. 2007). KDM4D (JMJD2D) also catalyses demethylation of H3K9Me2/3 (Whetstine et al. 2007). KDM4A-C (JHDM3A-C) can also catalyse demethylation of lysine-37 of histone H3 (H3K36Me2/3) (Klose et al. 2006). KDM5A-D (JARID1A-D) catalyses demethylation of di- or tri-methylated lysine-5 of histone H3 (H3K4Me2/3) (Christensen et al. 2007, Klose et al. 2007, Lee et al. 2007, Secombe et al. 2007, Seward et al. 2007, Iwase et al. 2007). KDM6A and KDM6B (UTX/JMJD3) catalyse demethylation of di- or tri-methylated lysine-28 of histone H3 (H3K27Me2/3) (Agger et al. 2007, Cho et al. 2007, De Santra et al. 2007, Lan et al. 2007, Lee et al. 2007).

KDM7A (KIAA1718/JHDM1D) catalyses demethylation of mono- or di-methylated lysine-10 of histone H3 (H3K9Me1/2) and mono- and di-methylated lysine-28 of histone H3 (H3K27Me1/2) (Horton et al. 2010, Huang et al. 2010). PHF8 (JHDM1E) catalyses demethylation of mono- or di-methylated lysine-10 of histone H3 (H3K9Me1/2) and mono-methylated lysine-21 of histone H4 (H4K20Me1) (Loenarz et al. 2010, Horton et al. 2010, Feng et al. 2010, Kleine-Kohlbrecher et al. 2010, Fortschegger et al. 2010, Qi et al. 2010, Liu et al. 2010). PHF2 (JHDM1E) catalyses demethylation of mono- or di-methylated lysine-10 of histone H3 (H3K9Me1/2) (Wen et al. 2010, Baba et al. 2011). JMJD6 was initially characterized as an arginine demethylase that catalyses demethylation of mono- or di-methylated arginine 3 of histone H3 (H3R2Me1/2) and arginine 4 of histone H4 (H4R3Me1/2) (Chang et al. 2007) although it was subsequently also characterized as a lysine hydroxylase (Webby et al. 2009).

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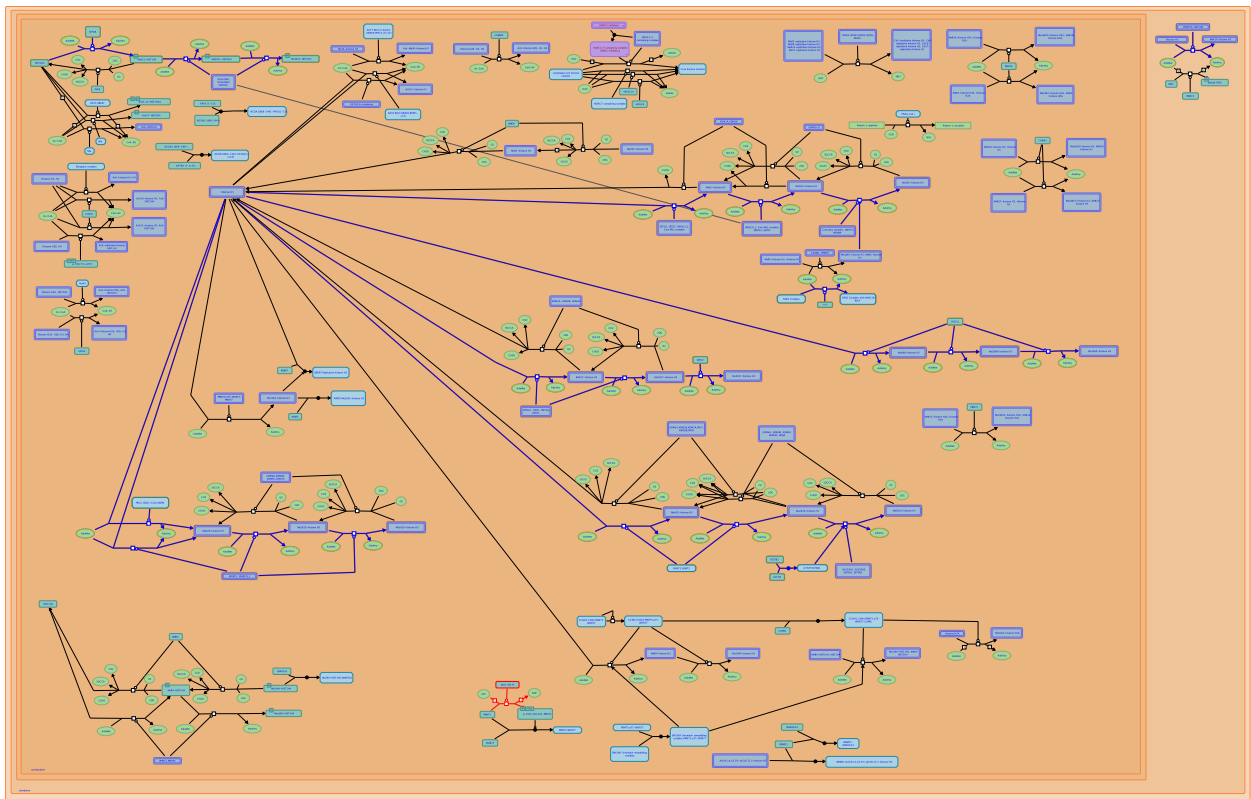
## Editions

2013-03-12	Authored	Jupe, S.
2014-02-05	Edited	Jupe, S.
2014-05-08	Reviewed	Schofield, CJ., Hopkinson, J., Walport, LJ.

## PKMTs methylate histone lysines ↗

**Location:** Chromatin modifying enzymes

**Stable identifier:** R-HSA-3214841



SETD2 (KMT3A, HYPB), a member of the SET2 family, specifically methylates histone H3 lysine-37 (H3K36) (Sun et al. 2005). WHSC1 (KMT3G, NSD2, MMSET) a member of the same family, targets H3K36 when provided with nucleosome substrates but also can methylate histone H4 lysine-45 when octameric native or recombinant nucleosome substrates are provided (Li et al. 2009); dimethylation of histone H3 at lysine-37 (H3K36me2) is thought to be the principal chromatin-regulatory activity of WHSC1 (Kuo et al. 2011). Relatives NSD1 (KMT3B) and WHSC1L1 (KMT3F, NSD3) also methylate nucleosomal H3K36. NSD1 is active on unmethylated or a mimetic monomethylated H3K36, but not di- or trimethylated H3K36 mimetics (Li et al. 2009). Human SETD7 (KMT7, SET7/9), not classified within the 7 SET-domain containing families, mono-methylates lysine-5 of histone H3 (H3K4) (Xiao et al. 2003).

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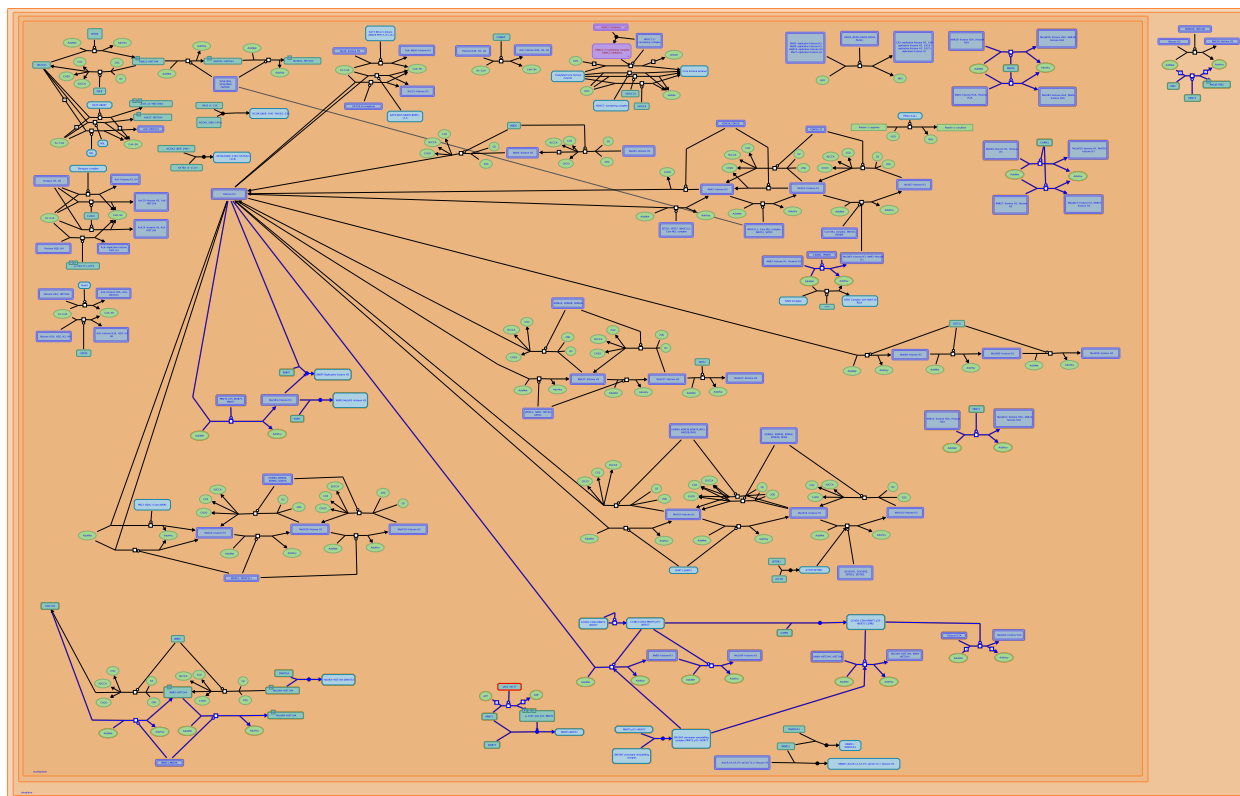
## Editions

2013-03-12	Authored	Jupe, S.
2014-09-10	Edited	Jupe, S.
2014-11-17	Reviewed	Motamedi, M.

## RMTs methylate histone arginines ↗

**Location:** Chromatin modifying enzymes

**Stable identifier:** R-HSA-3214858



 reactome

Arginine methylation is a common post-translational modification; around 2% of arginine residues are methylated in rat liver nuclei (Boffa et al. 1977). Arginine can be methylated in 3 different ways: monomethylarginine (MMA); NG,NG-asymmetric dimethylarginine (ADMA) and NG,N'G-symmetric dimethylarginine (SDMA). The formation of MMA, ADMA and SDMA in mammalian cells is carried out by members of a family of nine protein arginine methyltransferases (PRMTs) (Bedford & Clarke 2009).

Type I, II and III PRMTs generate MMA on one of the two terminal guanidino nitrogen atoms. Subsequent generation of asymmetric dimethylarginine (ADMA) is catalysed by the type I enzymes PRMT1, PRMT2, PRMT3, co-activator-associated arginine methyltransferase 1 (CARM1), PRMT6 and PRMT8. Production of symmetric dimethylarginine (SDMA) is catalysed by the type II enzymes PRMT5 and PRMT7. On certain substrates, PRMT7 also functions as a type III enzyme, generating MMA only. PRMT9 activity has not been characterized. No known enzyme is capable of both ADMA and SDMA modifications. Arginine methylation is regarded as highly stable; no arginine demethylases are known (Yang & Bedford 2013).

Most PRMTs methylate glycine- and arginine-rich (GAR) motifs in their substrates (Boffa et al. 1977). CARM1 methylates a proline-, glycine- and methionine-rich (PGM) motif (Cheng et al. 2007). PRMT5 can dimethylate arginine residues in GAR and PGM motifs (Cheng et al. 2007, Branscombe et al. 2001).

PRMTs are widely expressed and are constitutively active as purified recombinant proteins. However, PRMT activity can be regulated through PTMs, association with regulatory proteins, subcellular compartmentalization and factors that affect enzyme-substrate interactions. The target sites of PRMTs are influenced by the presence of other PTMs on their substrates. The best characterized examples of this are for histones. Histone H3 lysine-19 acetylation (H3K18ac) primes the histone tail for asymmetric dimethylation at arginine-18 (H3R17me2a) by CARM1 (An et al. 2003, Daujat et al. 2002, Yue et al. 2007). H3 lysine-

10 acetylation (H3K9ac) blocks arginine-9 symmetric dimethylation (H3R8me2s) by PRMT5 (Pal et al. 2004). H4R3me2a catalyzed by PRMT1 favours subsequent acetylation of the histone H4 tail (Huang et al. 2005). At the same time histone H4 lysine-5 acetylation (H4K5ac) makes the H4R3 motif a better substrate for PRMT5 compared with PRMT1, thereby moving the balance from an activating ADMA mark to a suppressive SDMA mark at the H4R3 motif (Feng et al. 2011). Finally methylation of Histone H3 on arginine-3 (H3R2me2a) by PRMT6 blocks methylation of H3 lysine-5 by the MLL complex (H3K4me3), and vice versa, methylation of H3K4me3 prevents H3R2me2a methylation (Guccione et al. 2007, Kirmizis et al. 2007, Hyllus et al. 2007).

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## Literature references

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## Editions

2013-03-12	Authored	Jupe, S.
2013-03-15	Edited	Jupe, S.
2014-05-09	Reviewed	Guccione, E.
2014-07-23	Reviewed	Fischle, W.

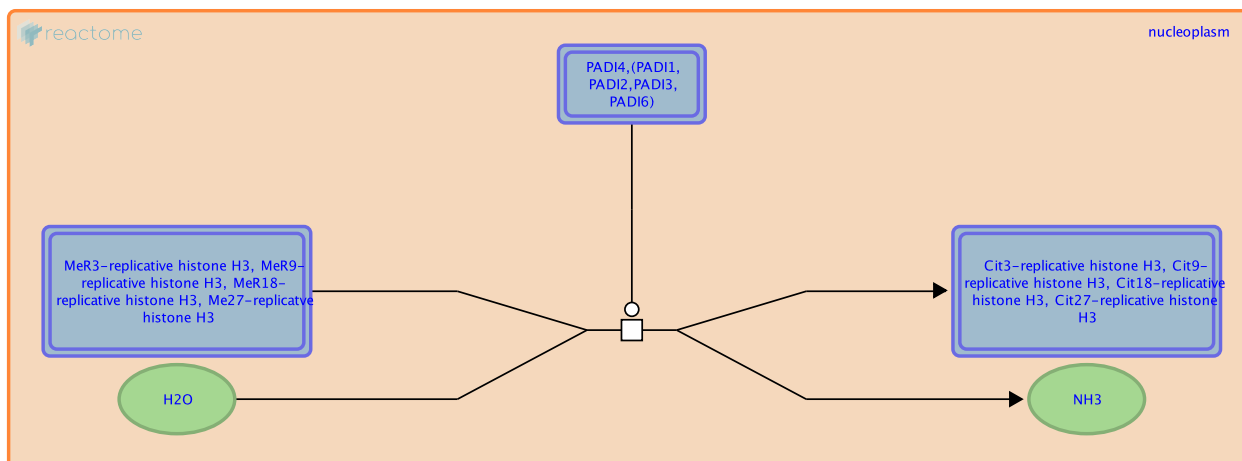
## PADI4 deiminates Histones ↗

**Location:** [Chromatin modifying enzymes](#)

**Stable identifier:** R-HSA-3247569

**Type:** transition

**Compartments:** nucleoplasm



Peptidyl arginine deiminase (PADI) 4, PADI2 and PADI3 are able to convert peptidyl arginine to peptidyl citrulline. The guanidino group of arginine is hydrolyzed, yielding a ureido group and ammonia. This deimination (citrullination) mechanism is proposed as an alternative pathway for the reversal of arginine methylation (Cuthbert et al. 2004, Wang et al. 2004), whereby the methyl group was removed from a monomethylarginine residue by conversion of the residue to citrulline, releasing methylamine instead of ammonia. PADI4 was reported to specifically deiminate methylated arginine residues 3, 9, 18, and 27 in Histone H3, preventing arginine methylation by CARM1 (Cuthbert et al. 2004). Deimination may stabilize interactions between Histone H2A and H2B (Shimoyama et al. 2010).

Dysregulation of PADI activity is associated with a range of diseases, including rheumatoid arthritis (RA), multiple sclerosis, ulcerative colitis, neural degeneration, COPD, and cancer (Lange et al. 2011, McElwee et al. 2012).

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### Editions

2013-04-04	Authored	Jupe, S.
2015-07-08	Edited	Jupe, S.
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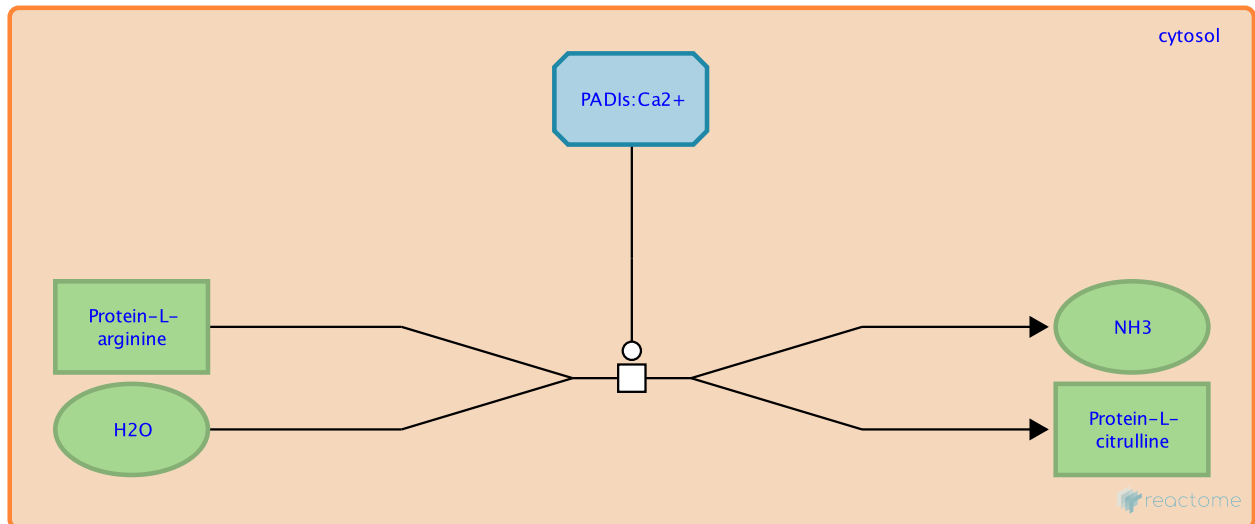
## PADIs:Ca2+ deiminate L-Arg to L-Cit in proteins ↗

**Location:** [Chromatin modifying enzymes](#)

**Stable identifier:** R-HSA-1183128

**Type:** transition

**Compartments:** cytosol



Methylation of histones by protein arginine methyltransferases (PRMTs), in general, is required for mammalian development and plays an important and dynamic role in gene regulation. Protein-arginine deiminases (PADIs) catalyse the deimination of L-arginine residues (L-Arg) in proteins to L-citrulline (L-Cit), thus playing a role in the regulation of development (Guerrin et al. 2003, Ishigami et al. 2002, Kanno et al. 2000, Wang et al. 2004, Nakayama-Hamada et al. 2005, Chavanas et al. 2004).

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2011-02-10	Authored, Edited	Jassal, B.
2016-01-11	Reviewed	D'Eustachio, P.



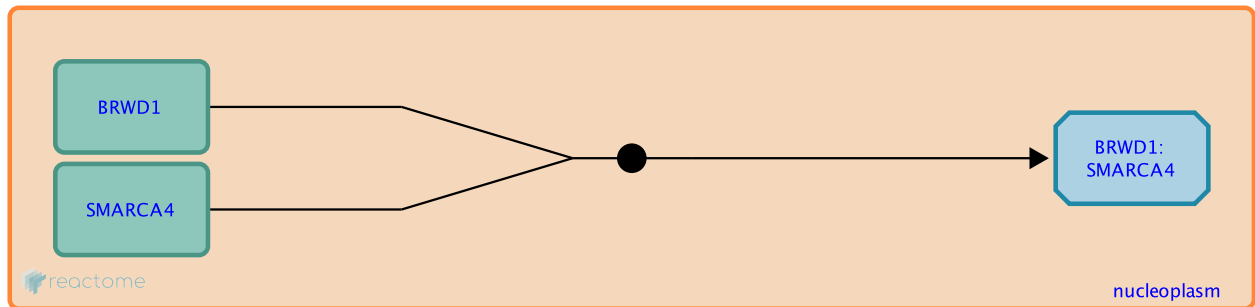
## BRWD1 binds SMARCA4 ↗

**Location:** [Chromatin modifying enzymes](#)

**Stable identifier:** R-HSA-8865605

**Type:** binding

**Compartments:** nucleoplasm



BRWD1 (WDR9) is a nuclear protein with eight WD repeats at the N-terminus and 2 centrally located bromodomains. BRWD1 is thought to be involved in chromatin remodelling and transcriptional regulation. BRWD1 binds to Transcription activator BRG1 (SMARCA4 or BRG1), a component of the SWI/SNF complex (Huang et al. 2003). Similar to BRWD1 (Mandal et al. 2015), SMARCA4 is also implicated in B-cell development (Choi et al. 2012, Bossen et al. 2015).

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2017-07-26	Edited	Duenas, C.

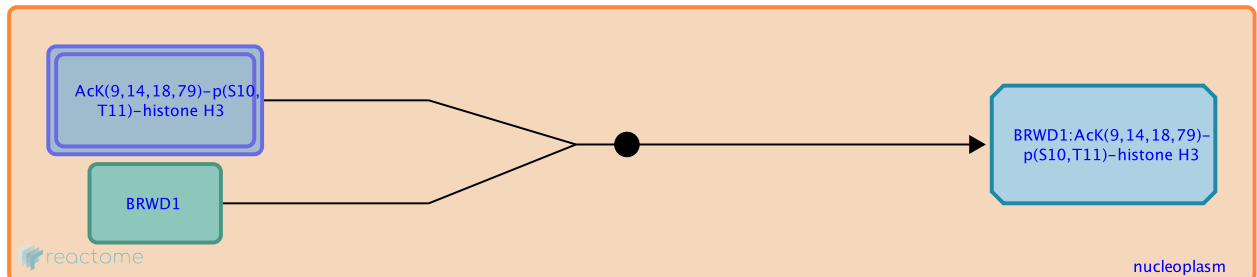
## BRWD1 binds AcK(9,14,18,79)-p(S10,T11)-histone H3 [↗](#)

**Location:** [Chromatin modifying enzymes](#)

**Stable identifier:** R-HSA-8865613

**Type:** binding

**Compartments:** nucleoplasm



Human Bromodomain and WD repeat-containing protein 1 (BRWD1) binds to histone H3 acetylated at lysine residues K9, K14, K18 and K79 and phosphorylated at serine residue S10 and threonine residue T11 in various combinations in vitro (Filippakopoulos et al. 2012). In mouse, it was confirmed that BRWD1 interacts with histone H3 acetylated at lysine residues K9 and K14, and phosphorylated at serine residue S10 (Mandal et al. 2015). Please note that the listed amino acid residues in mature histone H3 match nascent histone H3 residues K10, K15, K19, K80, S11 and T12, respectively. Amino acid positions in Reactome annotations of modified residues and Reactome systematic names correspond to positions in the nascent protein UniProt sequence.

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### Editions

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