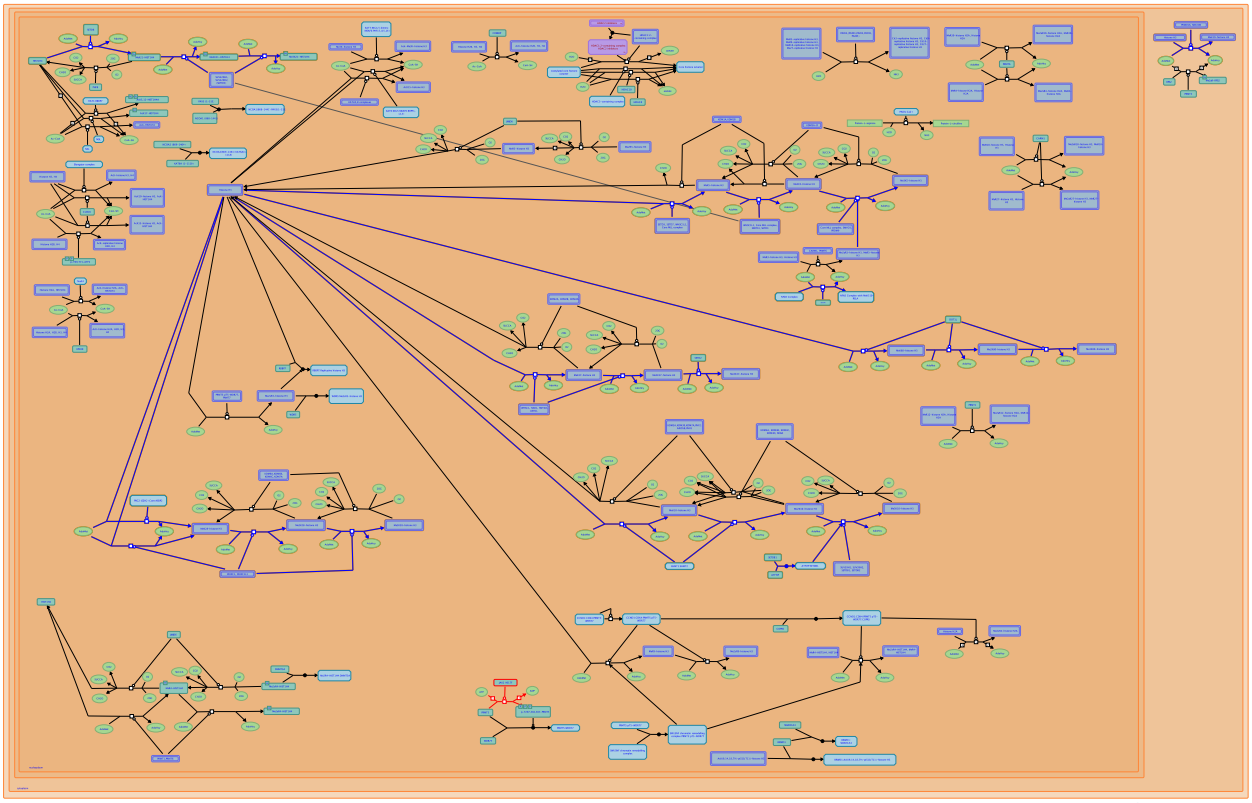
PKMTs methylate histone lysines



Cheng, X., Jupe, S., Motamedi, M.

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08/09/2021

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. ↗

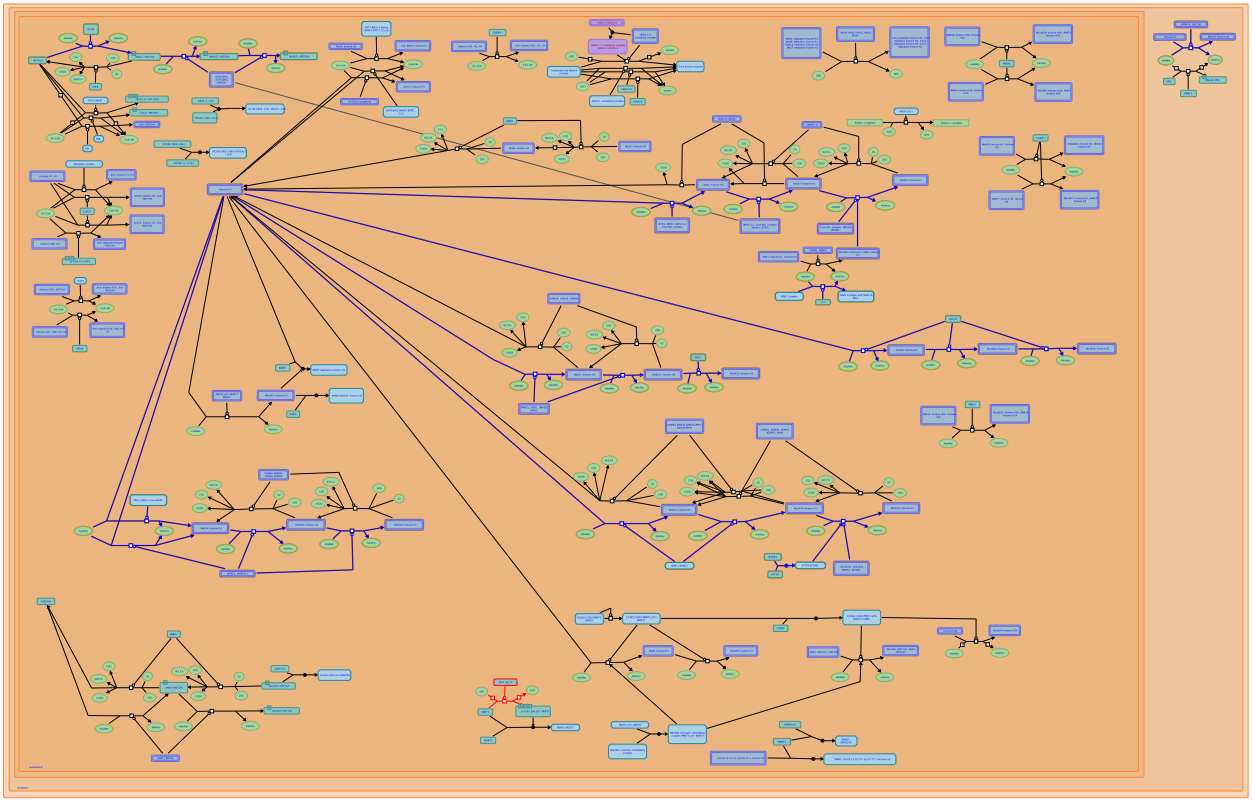
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

PKMTs methylate histone lysines ↗

Stable identifier: R-HSA-3214841



Lysine methyltransferases (KMTs) and arginine methyltransferases (RMTs) have a common mechanism of catalysis. Both families transfer a methyl group from a common donor, S-adenosyl-L-methionine (SAM), to the nitrogen atom on the epsilon-amino group of lysine or arginine (Smith & Denu 2009) using a bimolecular nucleophillic substitution (SN2) methyl transfer mechanism (Smith & Denu 2009, Zhang & Bruice 2008). All human KMTs except DOT1L (KMT4) (Feng et al. 2002, van Leeuwen et al. 2002, Lacoste et al. 2002) have a ~130 amino acid catalytic domain referred to as the SET domain (Del Rizzo & Trievel 2011, Dillon et al. 2005, Herz et al. 2013).

Some KMTs selectively methylate a particular lysine residue on a specific histone type. The extent of this methylation (mono-, di- or tri-methylation) also can be stringent (Herz et al. 2013, Copeland et al. 2009). Many KMTs also have non-histone substrates (Herz et al 2013), which are not discussed in this module.

The coordinates of post-translational modifications represented and described here follow UniProt standard practice whereby coordinates refer to the translated protein before any processing. Histone literature typically refers to specific residues by numbers which are determined 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 to the histone literature.

SET domain-containing proteins are classified in one of 7 families (Dillon et al. 2005). First to be discovered were the SUV39 family named after founding member SUV39H1 (KMT1A), which selectively methylates lysine-10 of histone H3 (H3K9) (Rea et al. 2000). Family member EHMT2 (KMT1C, G9A) is the predominant H3K9 methyltransferase in mammals (Tachibana et al. 2002). SETDB1 (KMT1E, ESET) also predominantly methylates H3K9, most effectively when complexed with ATF7IP (MCAF, hAM) (Wang et al. 2003).

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).

Literature references

Kouzarides, T. (2002). Histone methylation in transcriptional control. *Curr. Opin. Genet. Dev., 12*, 198-209. ↗

Copeland, RA., Solomon, ME., Richon, VM. (2009). Protein methyltransferases as a target class for drug discovery. *Nat Rev Drug Discov, 8*, 724-32. ↗

Editions

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

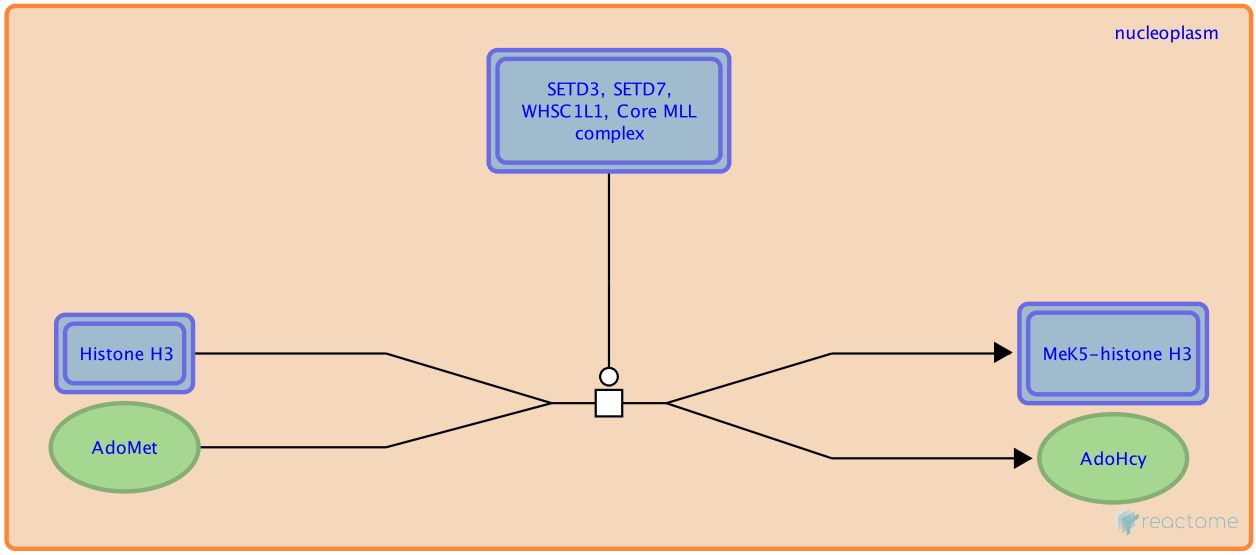
SETD3, SETD7 (KMT7), WHSC1L1 (KMT3F), Core MLL complex methylate lysine-5 of histone H3 (H3K4)

Location: PKMTs methylate histone lysines

Stable identifier: R-HSA-5159245

Type: transition

Compartments: nucleoplasm



Tri-methylation of lysine-5 of histone H3 (H3K4) has been linked to transcriptional activation in a variety of eukaryotic species (Ruthenberg et al. 2007). Several H3K4 methyltransferases have been identified in mammals, predominantly members of the Mixed Lineage Leukemia (MLL) protein family. Five of these, KMT2A (MML1), KMT2D (MLL2), KMT2C (MLL3), KMT2B (MLL4) and SETD1A (KMT2F) have been shown to display H3K4 mono-, di- and tri-methyltransferase activity (Milne et al. 2002, Hughes et al. 2004, Cho et al. 2007, Wysocka et al. 2003). KMT2G (SETD1B) is believed to have similar activity on the basis of sequence homology (Ruthenberg et al. 2007). MLLs are a component of large multiprotein complexes that also include WDR5, RBBP5, ASH2 and DPY30, assembled to form the core MLL complex (Nakamura et al. 2002, Hughes et al. 2004, Dou et al. 2006, Tremblay et al. 2014). The WD40 domain of WDR5 recognizes and binds the histone H3 N-terminus, presenting the lysine-4 side chain for methylation by one of the catalytically active MLL family (Couture et al. 2006, Ruthenburg et al. 2006). Histone H3 recognition by WDR5 is regulated by the methylation state of adjacent arginine (H3R2) residue. H3R2 methylation abolishes WDR5 interaction with the H3 histone tail (Couture et al. 2006); H3K4 di-/trimethylation and H3R2 methylation have an inverse relationship (Guccione et al. 2006).

SETD7 (KMT7, SET9, SET7/9) is an H3K4 mono-methytransferase (Wang et al. 2001, Xiao et al. 2003, Hu & Zhang 2006) that can also methylate a wide range of non-histone proteins (Dhayalan et al. 2011). SETD3 can mono- and di-methylate H3K4 and H3K36 (Eom et al. 2011).

Literature references

Xiao, B., Jing, C., Wilson, JR., Walker, PA., Vasisht, N., Kelly, G. et al. (2003). Structure and catalytic mechanism of the human histone methyltransferase SET7/9. *Nature, 421*, 652-6.

Kim, SM., Kee, HJ., Eom, GH., Choe, NW., Kim, JY., Kim, YS. et al. (2006). Characterization of a novel WHSC1-associated SET domain protein with H3K4 and H3K27 methyltransferase activity. *Biochem. Biophys. Res. Commun., 345*, 318-23.

Demers, C., Chaturvedi, CP., Ranish, JA., Juban, G., Lai, P., Morle, F. et al. (2007). Activator-mediated recruitment of the MLL2 methyltransferase complex to the beta-globin locus. *Mol. Cell, 27*, 573-84. ↗

Lee, S., Lee, DK., Dou, Y., Lee, J., Lee, B., Kwak, E. et al. (2006). Coactivator as a target gene specificity determinant for histone H3 lysine 4 methyltransferases. *Proc. Natl. Acad. Sci. U.S.A., 103*, 15392-7. ↗

Cho, YW., Hong, T., Hong, S., Guo, H., Yu, H., Kim, D. et al. (2007). PTIP associates with MLL3- and MLL4-containing histone H3 lysine 4 methyltransferase complex. *J. Biol. Chem., 282*, 20395-406. ↗

Editions

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

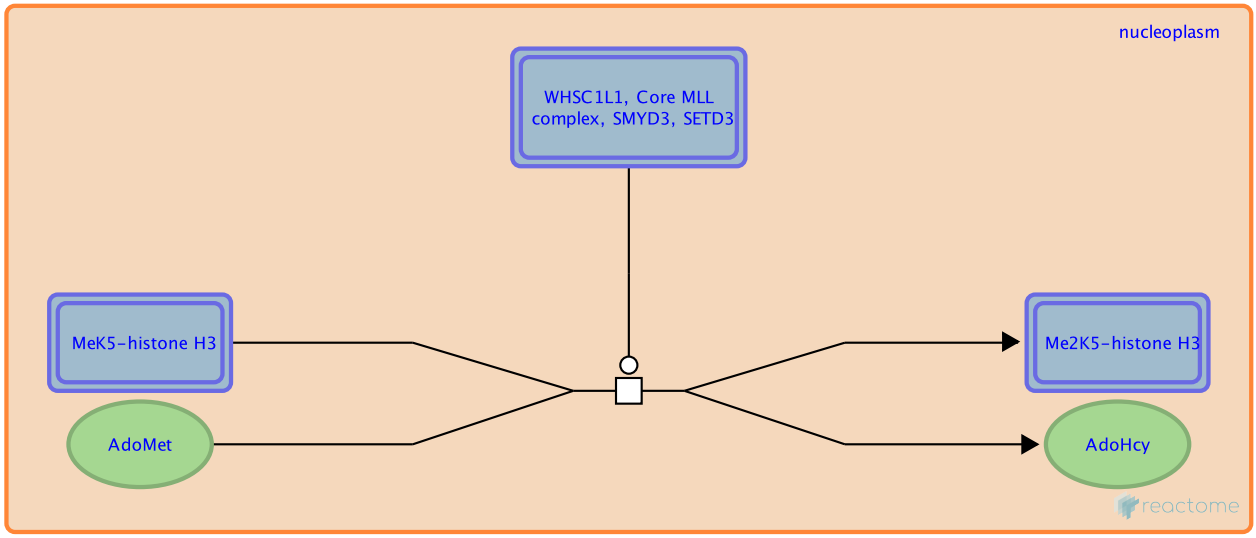
WHSC1L1 (KMT3F), Core MLL complex, SMYD3 (KMT3E) methylate methyl-lysine-5 of histone H3 (H3K4)

Location: PKMTs methylate histone lysines

Stable identifier: R-HSA-5637686

Type: transition

Compartments: nucleoplasm



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WHSC1L1 (KMT3F, WHISTLE), SMYD3 (KMT3E) and SETD3 are able to di-methylate H3K4 (Kim et al. 2006, Hamamoto et al. 2004, Eom et al. 2011).

Literature references

Kim, SM., Kee, HJ., Eom, GH., Choe, NW., Kim, JY., Kim, YS. et al. (2006). Characterization of a novel WHSC1-associated SET domain protein with H3K4 and H3K27 methyltransferase activity. *Biochem. Biophys. Res. Commun., 345*, 318-23.

Milne, TA., Dou, Y., Martin, ME., Brock, HW., Roeder, RG., Hess, JL. (2005). MLL associates specifically with a subset of transcriptionally active target genes. *Proc. Natl. Acad. Sci. U.S.A., 102*, 14765-70.

Hughes, CM., Rozenblatt-Rosen, O., Milne, TA., Copeland, TD., Levine, SS., Lee, JC. et al. (2004). Menin associates with a trithorax family histone methyltransferase complex and with the hoxc8 locus. *Mol. Cell, 13*, 587-97.

Demers, C., Chaturvedi, CP., Ranish, JA., Juban, G., Lai, P., Morle, F. et al. (2007). Activator-mediated recruitment of the MLL2 methyltransferase complex to the beta-globin locus. *Mol. Cell, 27*, 573-84.

Lee, S., Lee, DK., Dou, Y., Lee, J., Lee, B., Kwak, E. et al. (2006). Coactivator as a target gene specificity determinant for histone H3 lysine 4 methyltransferases. *Proc. Natl. Acad. Sci. U.S.A., 103*, 15392-7.

Editions

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

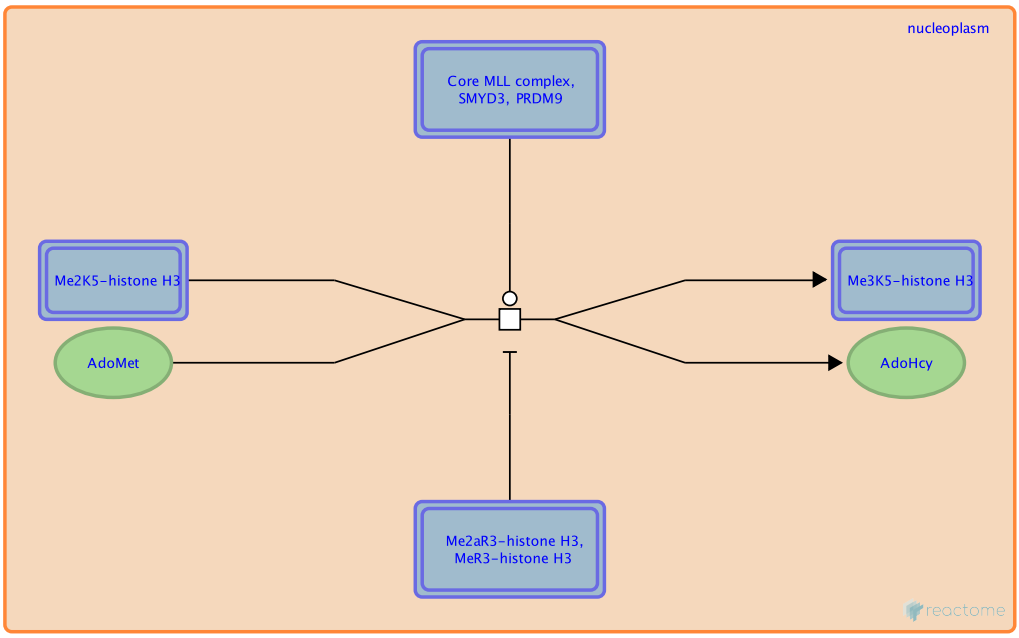
Core MLL complex, SMYD3, PRDM9 methylate dimethyl-lysine-5 of histone H3 (H3K4) ↗

Location: PKMTs methylate histone lysines

Stable identifier: R-HSA-5244692

Type: transition

Compartments: nucleoplasm



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SMYD3 (KMT3E) and PRDM9 (KMT8B) are able to tri-methylate H3K4 (Hamamoto et al. 2004, Hayashi et al. 2005, Koh-Stenta et al. 2014).

Literature references

Milne, TA., Dou, Y., Martin, ME., Brock, HW., Roeder, RG., Hess, JL. (2005). MLL associates specifically with a subset of transcriptionally active target genes. *Proc. Natl. Acad. Sci. U.S.A., 102*, 14765-70. ↗

Hughes, CM., Rozenblatt-Rosen, O., Milne, TA., Copeland, TD., Levine, SS., Lee, JC. et al. (2004). Menin associates with a trithorax family histone methyltransferase complex and with the hoxc8 locus. *Mol. Cell, 13*, 587-97. ↗

Demers, C., Chaturvedi, CP., Ranish, JA., Juban, G., Lai, P., Morle, F. et al. (2007). Activator-mediated recruitment of the MLL2 methyltransferase complex to the beta-globin locus. *Mol. Cell, 27*, 573-84.

Lee, S., Lee, DK., Dou, Y., Lee, J., Lee, B., Kwak, E. et al. (2006). Coactivator as a target gene specificity determinant for histone H3 lysine 4 methyltransferases. *Proc. Natl. Acad. Sci. U.S.A., 103*, 15392-7.

Cho, YW., Hong, T., Hong, S., Guo, H., Yu, H., Kim, D. et al. (2007). PTIP associates with MLL3- and MLL4-containing histone H3 lysine 4 methyltransferase complex. *J. Biol. Chem., 282*, 20395-406.

Editions

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

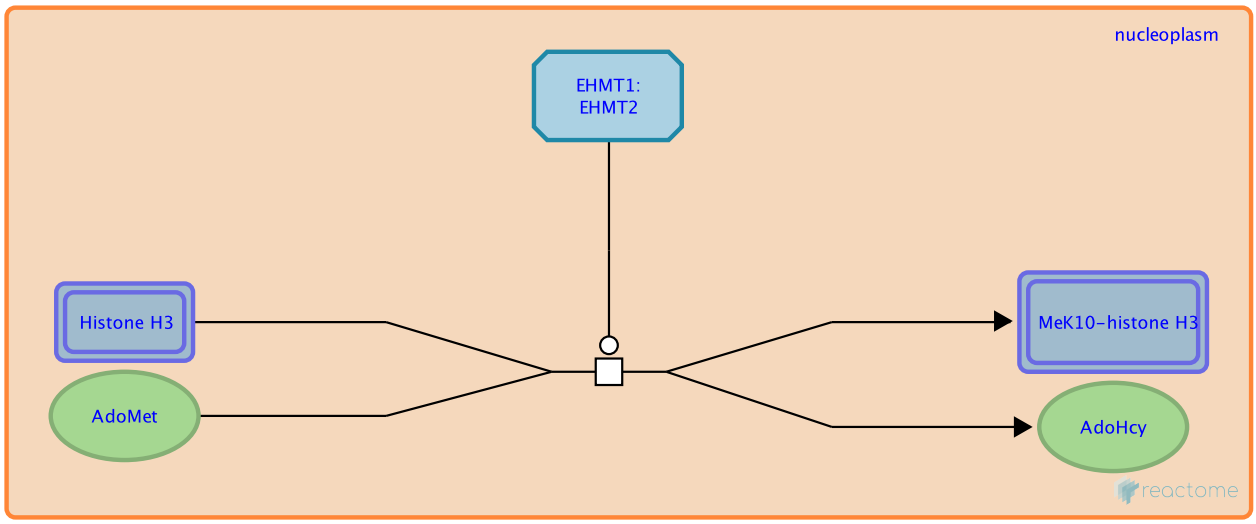
EHMT1:EHMT2 (KMT1D:KMT1C) methylates lysine-10 of histone H3 (H3K9) ↗

Location: PKMTs methylate histone lysines

Stable identifier: R-HSA-5634750

Type: transition

Compartments: nucleoplasm



EHMT2 (KMT1C, G9A) and EHMT1 (KMT1D, GLP) are the euchromatic histone H3 lysine-10 (H3K9) mono and di-methyltransferases in mammals (Tachibana et al. 2002, Rice et al. 2003, Tachibana et al. 2005). In vivo they exist predominantly as a heteromeric complex together with WIZ, a multi-zinc finger protein, (Ueda et al. 2006) and are responsible for global H3K9 mono- and di-methylation (Shinkai & Tchibana 2011).

Literature references

Tachibana, M., Sugimoto, K., Nozaki, M., Ueda, J., Ohta, T., Ohki, M. et al. (2002). G9a histone methyltransferase plays a dominant role in euchromatic histone H3 lysine 9 methylation and is essential for early embryogenesis. *Genes Dev., 16*, 1779-91. ↗

Rice, JC., Briggs, SD., Ueberheide, B., Barber, CM., Shabanowitz, J., Hunt, DF. et al. (2003). Histone methyltransferases direct different degrees of methylation to define distinct chromatin domains. *Mol Cell, 12*, 1591-8. ↗

Editions

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

EHMT1:EHMT2 (KMT1D:KMT1C) methylates methyl-lysine-10 of histone H3 (H3K9)

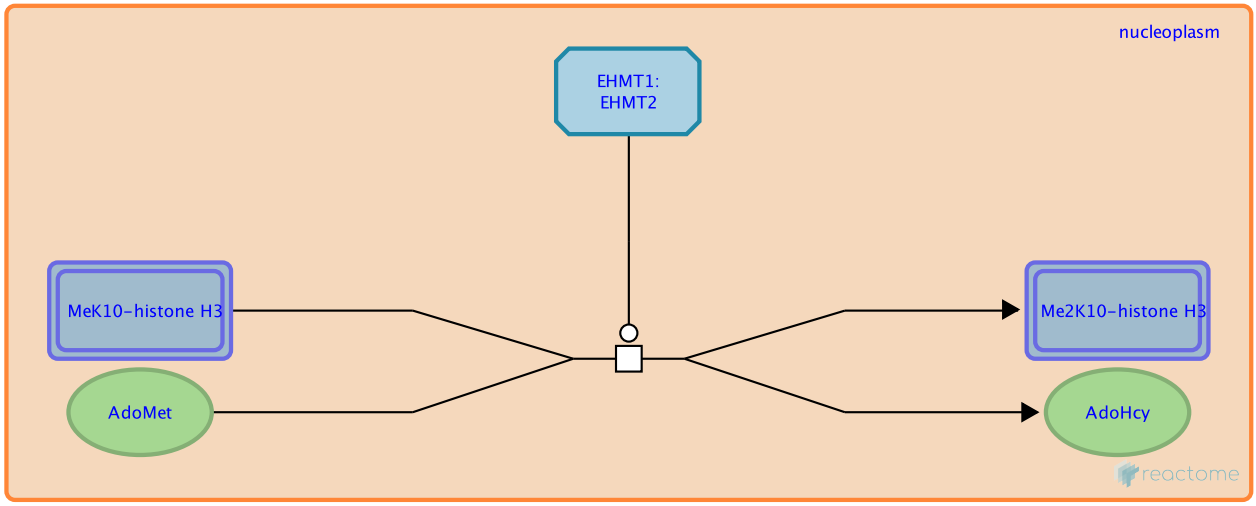
↗

Location: PKMTs methylate histone lysines

Stable identifier: R-HSA-5634729

Type: transition

Compartments: nucleoplasm



EHMT2 (KMT1C, G9A) and EHMT1 (KMT1D, GLP) are the euchromatic histone H3 lysine-10 (H3K9) mono and di-methyltransferases in mammals (Tachibana et al. 2002, Rice et al. 2003, Tachibana et al. 2005). In vivo they exist predominantly as a heteromeric complex together with WIZ, a multi-zinc finger protein, (Ueda et al. 2006) and are responsible for global H3K9 mono- and di-methylation (Shinkai & Tchibana 2011).

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Tachibana, M., Sugimoto, K., Nozaki, M., Ueda, J., Ohta, T., Ohki, M. et al. (2002). G9a histone methyltransferase plays a dominant role in euchromatic histone H3 lysine 9 methylation and is essential for early embryogenesis. *Genes Dev., 16*, 1779-91. ↗

Rice, JC., Briggs, SD., Ueberheide, B., Barber, CM., Shabanowitz, J., Hunt, DF. et al. (2003). Histone methyltransferases direct different degrees of methylation to define distinct chromatin domains. *Mol Cell, 12*, 1591-8. ↗

Editions

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

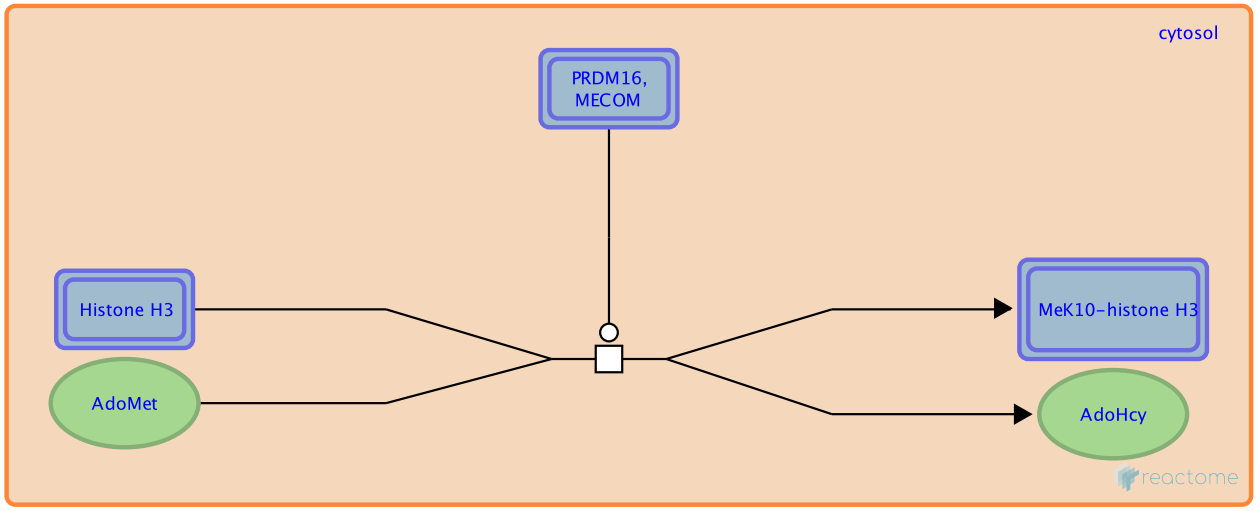
MECOM (KMT8E), PRDM16 (KMT8F) methylate lysine-10 of replicative histone H3 (H3K9)

Location: PKMTs methylate histone lysines

Stable identifier: R-HSA-5634802

Type: transition

Compartments: cytosol



MECOM (KMT8E, PRDM3) and PRDM16 (KMT8F) are histone 3 lysine-10 (H3K9) methyltransferases responsible for cytoplasmic H3K9 mono-methylation.

Literature references

Pinheiro, I., Margueron, R., Shukeir, N., Eisold, M., Fritzsch, C., Richter, FM. et al. (2012). Prdm3 and Prdm16 are H3K9me1 methyltransferases required for mammalian heterochromatin integrity. *Cell, 150*, 948-60.

Editions

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

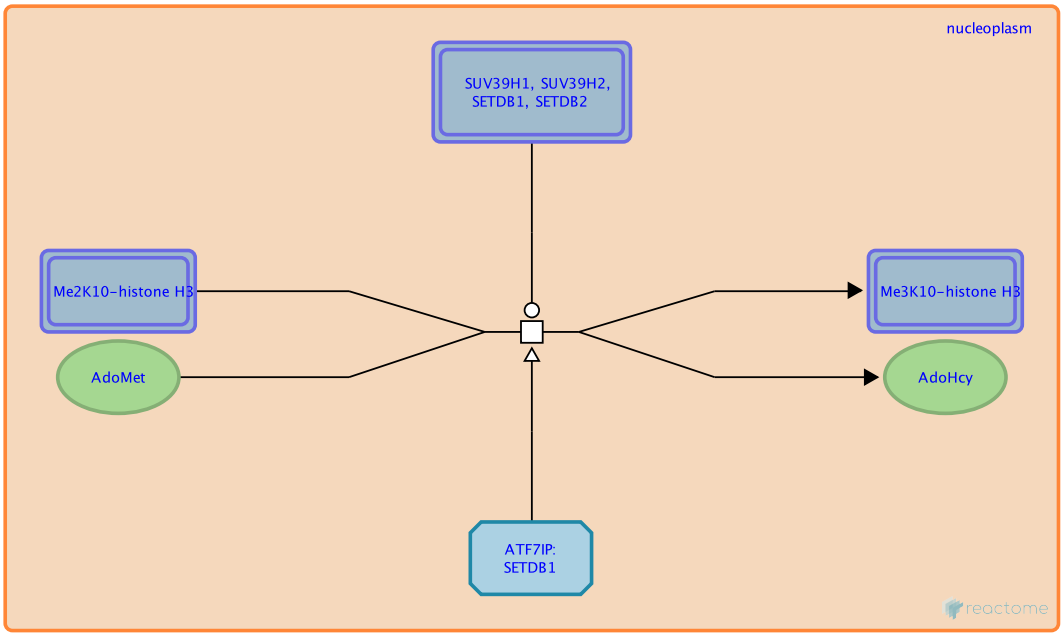
SUV39H1 (KMT1A), SUV39H2 (KTM1B), SETDB1 (KMT1E), SETDB2 (KMT1F) methylate dimethyl-lysine-10 of histone H3 (H3K9)

Location: PKMTs methylate histone lysines

Stable identifier: R-HSA-4827382

Type: transition

Compartments: nucleoplasm



SUV39H1 (KMT1A) and SUV39H2 (KMT1B) and SETDB2 (KMT1F) selectively methylate lysine-10 of histone H3 (H3K9) (Rea et al. 2000, Rice et al. 2003, Falandry et al. 2010). Their predominant activity is conversion of dimethylated H3K9 to trimethylated H3K9 (Peters et al. 2003, Rice et al. 2003, Chin et al. 2006). SETDB1 (ESET, KMT1E) also predominantly methylates dimethylated H3K9 (Schultz et al. 2002), most effectively when complexed with ATF7IP (MCAF, hAM) (Wang et al. 2003).

Literature references

Rea, S., Eisenhaber, F., O'Carroll, D., Strahl, BD., Sun, ZW., Schmid, M. et al. (2000). Regulation of chromatin structure by site-specific histone H3 methyltransferases. *Nature, 406*, 593-9.

Chin, HG., Patnaik, D., Estève, PO., Jacobsen, SE., Pradhan, S. (2006). Catalytic properties and kinetic mechanism of human recombinant Lys-9 histone H3 methyltransferase SUV39H1: participation of the chromodomain in enzymatic catalysis. *Biochemistry, 45*, 3272-84.

Rice, JC., Briggs, SD., Ueberheide, B., Barber, CM., Shabanowitz, J., Hunt, DF. et al. (2003). Histone methyltransferases direct different degrees of methylation to define distinct chromatin domains. *Mol Cell, 12*, 1591-8.

Schultz, DC., Ayyanathan, K., Negorev, D., Maul, GG., Rauscher, FJ. (2002). SETDB1: a novel KAP-1-associated histone H3, lysine 9-specific methyltransferase that contributes to HP1-mediated silencing of euchromatic genes by KRAB zinc-finger proteins. *Genes Dev., 16*, 919-32.

Editions

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

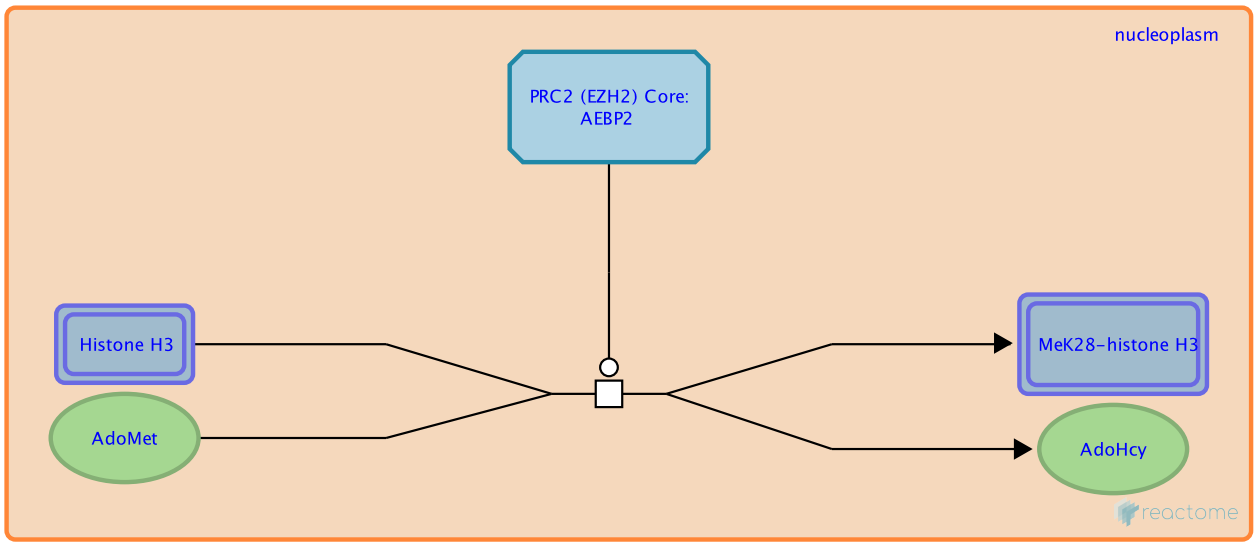
PRC2 (EZH2) Core:AEBP2 methylates lysine-28 of histone H3 (H3K27) ↗

Location: PKMTs methylate histone lysines

Stable identifier: R-HSA-5638332

Type: transition

Compartments: nucleoplasm



EZH2 (KMT6, PRC2) is the catalytic subunit of the PRC2 (EZH2) Core complex, which additionally contains EED, SUZ12, AEBP2 and one of RBBP4 or RBBP7. It methylates lysine-28 (H3K27) of histone H3 (Cao et al. 2002, Czermin et al. 2002, Kuzmichev et al. 2002, Muller et al. 2002) leading to transcriptional repression of the affected target gene. It is able to mono-, di- and trimethylate lysine-28 (Cao & Zhang 2004).

Editions

2014-11-13	Authored	Jupe, S.
2014-11-17	Reviewed	Motamedi, M.
2015-02-13	Edited	Jupe, S.

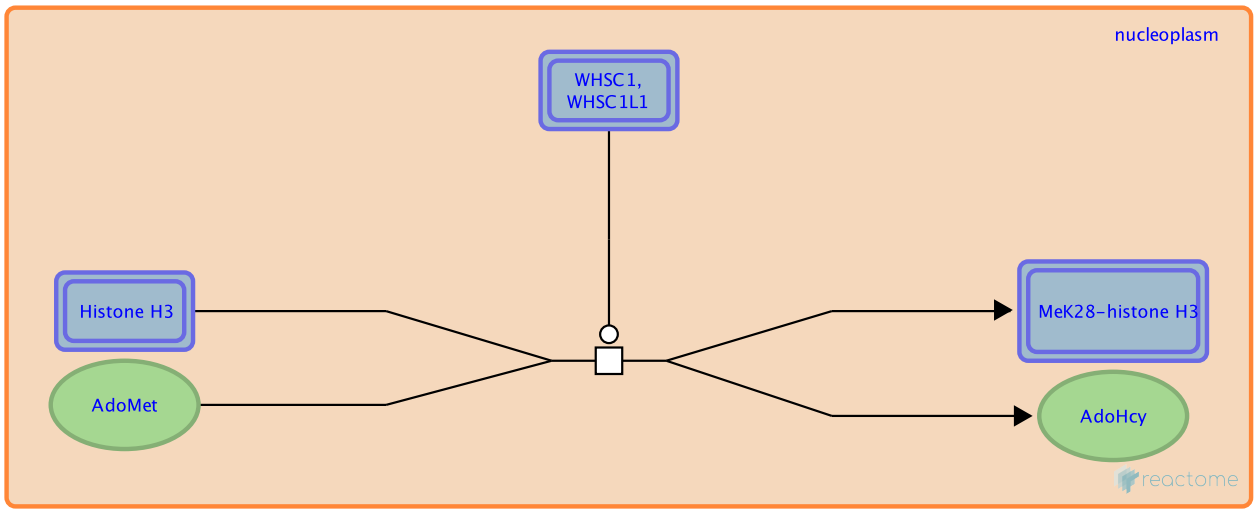
WHSC1 (KMT3G) methylates lysine-28 of histone H3 (H3K27)

Location: PKMTs methylate histone lysines

Stable identifier: R-HSA-5638333

Type: transition

Compartments: nucleoplasm



WHSC1 (KMT3G, MMSET) is able to mono-, di- and trimethylate lysine-28 (Kim et al. 2008).

Literature references

Kim, JY., Kee, HJ., Choe, NW., Kim, SM., Eom, GH., Baek, HJ. et al. (2008). Multiple-myeloma-related WHSC1/MMSET isoform RE-IIBP is a histone methyltransferase with transcriptional repression activity. *Mol. Cell. Biol., 28*, 2023-34.

Editions

2014-11-13	Authored	Jupe, S.
2014-11-17	Reviewed	Motamedi, M.
2015-02-13	Edited	Jupe, S.

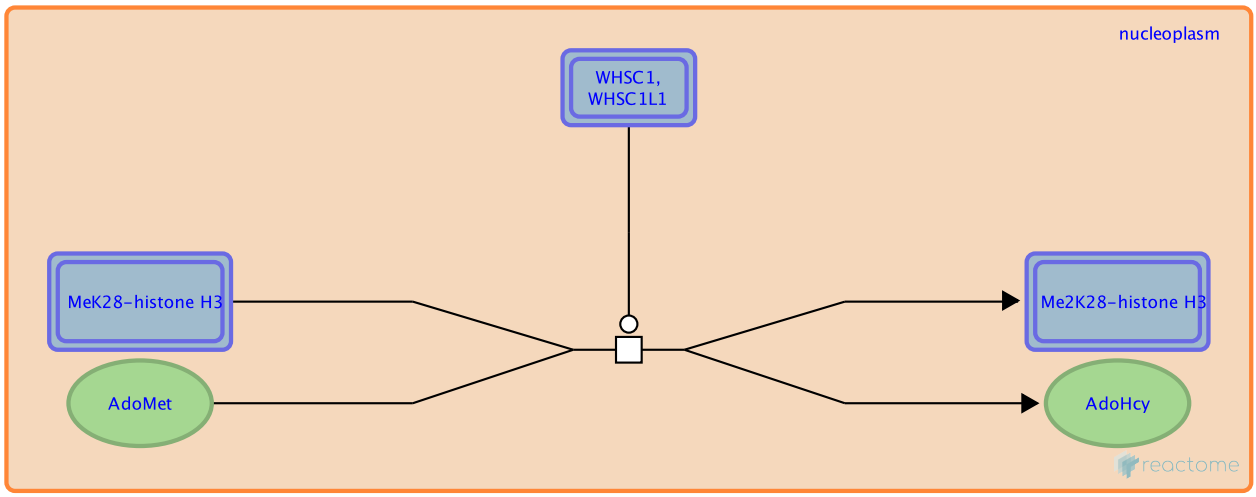
WHSC1L1 (KMT3F) methylates methyl-lysine-28 of histone H3 (H3K27) ↗

Location: PKMTs methylate histone lysines

Stable identifier: R-HSA-5649800

Type: transition

Compartments: nucleoplasm



WHSC1 (MMSET, KMT3G) is able to mono-, di- and trimethylate lysine-28 (Kim et al. 2008). WHSC1L1 (KMT3F, WHISTLE) can di-, and tri-methylate lysine-28 of histone H3 (H3K27) if it has been previously monomethylated at this residue (Kim et al. 2006).

Literature references

Kim, JY., Kee, HJ., Choe, NW., Kim, SM., Eom, GH., Baek, HJ. et al. (2008). Multiple-myeloma-related WHSC1/MMSET isoform RE-IIBP is a histone methyltransferase with transcriptional repression activity. *Mol. Cell. Biol., 28*, 2023-34. ↗

Kim, SM., Kee, HJ., Eom, GH., Choe, NW., Kim, JY., Kim, YS. et al. (2006). Characterization of a novel WHSC1-associated SET domain protein with H3K4 and H3K27 methyltransferase activity. *Biochem. Biophys. Res. Commun., 345*, 318-23. ↗

Editions

2014-11-13	Authored	Jupe, S.
2014-11-17	Reviewed	Motamedi, M.
2015-02-13	Edited	Jupe, S.

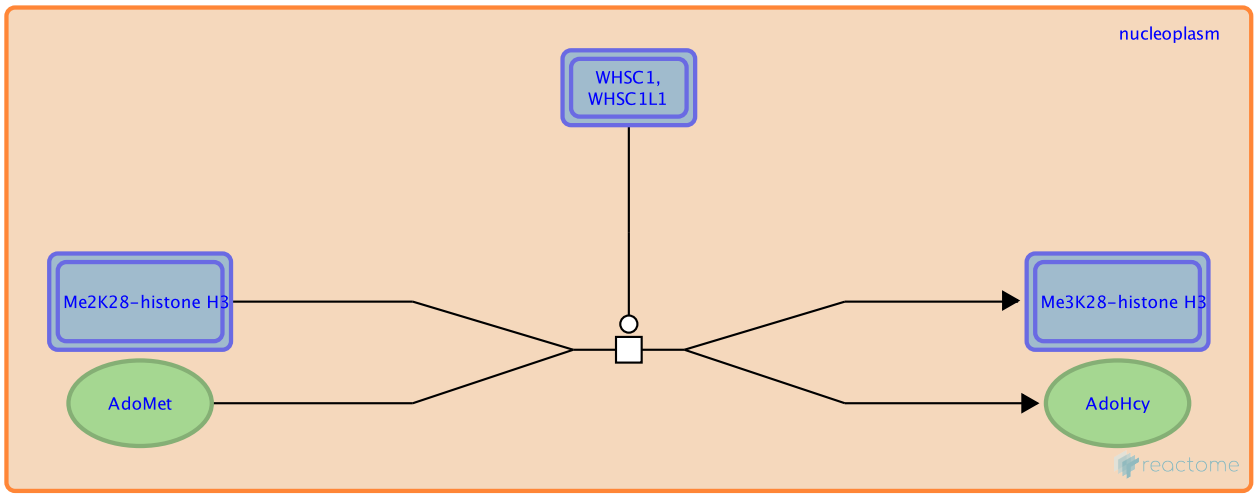
WHSC1L1 (KMT3F) methylates dimethyl-lysine-28 of histone H3 (H3K27)

Location: PKMTs methylate histone lysines

Stable identifier: R-HSA-5649802

Type: transition

Compartments: nucleoplasm



WHSC1 (MMSET, KMT3G) is able to mono-, di- and trimethylate lysine-28 (Kim et al. 2008). WHSC1L1 (KMT3F, WHISTLE) can di- and tri-methylate lysine-28 of histone H3 (H3K27) if it has been previously methylated at this residue (Kim et al. 2006).

Literature references

Kim, JY., Kee, HJ., Choe, NW., Kim, SM., Eom, GH., Baek, HJ. et al. (2008). Multiple-myeloma-related WHSC1/MMSET isoform RE-IIBP is a histone methyltransferase with transcriptional repression activity. *Mol. Cell. Biol., 28*, 2023-34.

Kim, SM., Kee, HJ., Eom, GH., Choe, NW., Kim, JY., Kim, YS. et al. (2006). Characterization of a novel WHSC1-associated SET domain protein with H3K4 and H3K27 methyltransferase activity. *Biochem. Biophys. Res. Commun., 345*, 318-23.

Editions

2014-11-13	Authored	Jupe, S.
2014-11-17	Reviewed	Motamedi, M.
2015-02-13	Edited	Jupe, S.

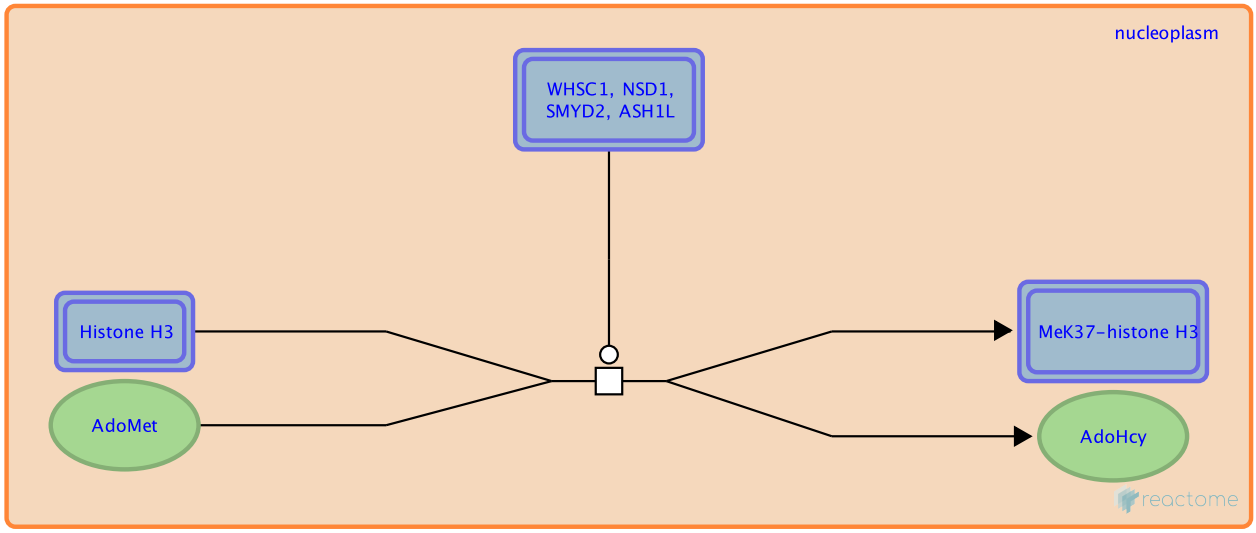
WHSC1 (KMT3G), NSD1 (KMT3B), SMYD2 (KMT3C) methylate lysine-37 of histone H3 (H3K36)

Location: PKMTs methylate histone lysines

Stable identifier: R-HSA-4827383

Type: transition

Compartments: nucleoplasm



Methylation of histone H3 lysine-37 (H3K36) is tightly associated with actively transcribed genes and appears to correspond primarily with coding regions (Wagner & Carpenter 2011).

WHSC1 (KMT3G, NSD2, MMSET), a member of the SET2 family, dimethylates H3K36 when provided with nucleosome substrates (Li et al 2009; Qiao et al. 2011). Dimethylation of histone H3 at lysine-37 (H3K36me2) is thought to be the principal chromatin-regulatory activity of WHSC1 (Kuo et al. 2011), SMYD2 (KMT3C) (Brown et al 2006) and NSD1 (KMT3B) (Li et al. 2009, Qiao et al. 2011).

Literature references

Li, Y., Trojer, P., Xu, CF., Cheung, P., Kuo, A., Drury, WJ. et al. (2009). The target of the NSD family of histone lysine methyltransferases depends on the nature of the substrate. *J. Biol. Chem., 284*, 34283-95.

Kuo, AJ., Cheung, P., Chen, K., Zee, BM., Kioi, M., Lauring, J. et al. (2011). NSD2 links dimethylation of histone H3 at lysine 36 to oncogenic programming. *Mol. Cell, 44*, 609-20.

Brown, MA., Sims, RJ., Gottlieb, PD., Tucker, PW. (2006). Identification and characterization of Smyd2: a split SET/MYND domain-containing histone H3 lysine 36-specific methyltransferase that interacts with the Sin3 histone deacetylase complex. *Mol. Cancer, 5*, 26.

Qiao, Q., Li, Y., Chen, Z., Wang, M., Reinberg, D., Xu, RM. (2011). The structure of NSD1 reveals an autoregulatory mechanism underlying histone H3K36 methylation. *J. Biol. Chem., 286*, 8361-8.

Editions

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

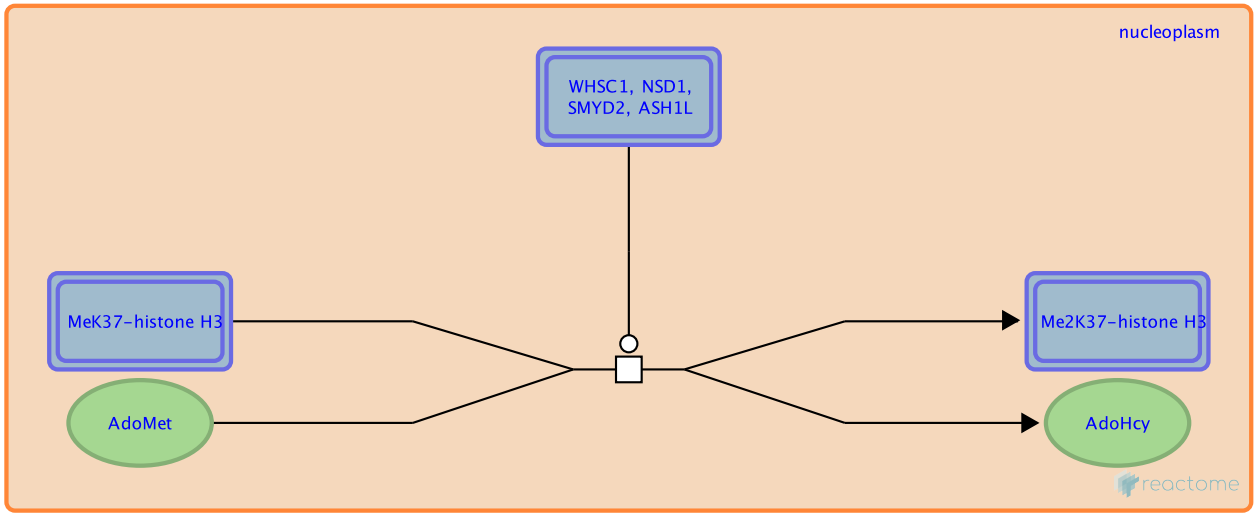
WHSC1 (KMT3G), NSD1 (KMT3B), SMYD2 (KMT3C), ASH1L methylate methyl-lysine-37 of histone H3 (H3K36)

Location: PKMTs methylate histone lysines

Stable identifier: R-HSA-5638157

Type: transition

Compartments: nucleoplasm



Methylation of histone H3 lysine-37 (H3K36) is tightly associated with actively transcribed genes and appears to correspond primarily with coding regions (Wagner & Carpenter 2011).

WHSC1 (KMT3G, NSD2, MMSET), a member of the SET2 family, dimethylates H3K36 when provided with nucleosome substrates (Li et al 2009; Qiao et al. 2011). Dimethylation of histone H3 at lysine-37 (H3K36me2) is thought to be the principal chromatin-regulatory activity of WHSC1 (Kuo et al. 2011), SMYD2 (KMT3C) (Brown et al 2006) and NSD1 (KMT3B) (Li et al. 2009, Qiao et al. 2011). ASH1L can perform histone H3 lysine-37 di-methylation (Tanaka et al. 2007, An et al. 2011, Miyazaki et al. 2013, Zhu et al. 2016).

Literature references

Li, Y., Trojer, P., Xu, CF., Cheung, P., Kuo, A., Drury, WJ. et al. (2009). The target of the NSD family of histone lysine methyltransferases depends on the nature of the substrate. *J. Biol. Chem., 284*, 34283-95.

Kuo, AJ., Cheung, P., Chen, K., Zee, BM., Kioi, M., Lauring, J. et al. (2011). NSD2 links dimethylation of histone H3 at lysine 36 to oncogenic programming. *Mol. Cell, 44*, 609-20.

Brown, MA., Sims, RJ., Gottlieb, PD., Tucker, PW. (2006). Identification and characterization of Smyd2: a split SET/MYND domain-containing histone H3 lysine 36-specific methyltransferase that interacts with the Sin3 histone deacetylase complex. *Mol. Cancer, 5*, 26.

Qiao, Q., Li, Y., Chen, Z., Wang, M., Reinberg, D., Xu, RM. (2011). The structure of NSD1 reveals an autoregulatory mechanism underlying histone H3K36 methylation. *J. Biol. Chem., 286*, 8361-8.

Tanaka, Y., Katagiri, Z., Kawahashi, K., Kioussis, D., Kitajima, S. (2007). Trithorax-group protein ASH1 methylates histone H3 lysine 36. *Gene, 397*, 161-8.

Editions

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

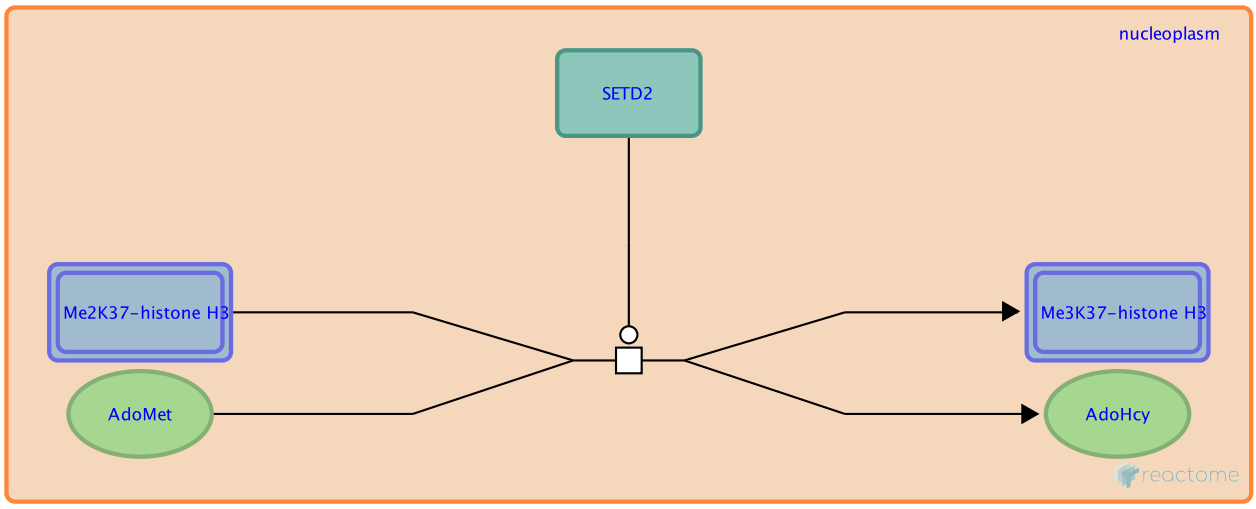
SETD2 (KMT3A) methylates dimethyl-lysine-37 of histone H3 (H3K36)

Location: PKMTs methylate histone lysines

Stable identifier: R-HSA-5638141

Type: transition

Compartments: nucleoplasm



SETD2 (KMT3A) trimethylates lysine-37 of histone H3 (H3K36) (Sun et al. 2005) and is thought to be the sole H3K36 methyltransferase in vivo (Edmunds et al. 2008, Yuan et al. 2009).

Literature references

Sun, XJ., Wei, J., Wu, XY., Hu, M., Wang, L., Wang, HH. et al. (2005). Identification and characterization of a novel human histone H3 lysine 36-specific methyltransferase. *J. Biol. Chem., 280*, 35261-71.

Editions

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

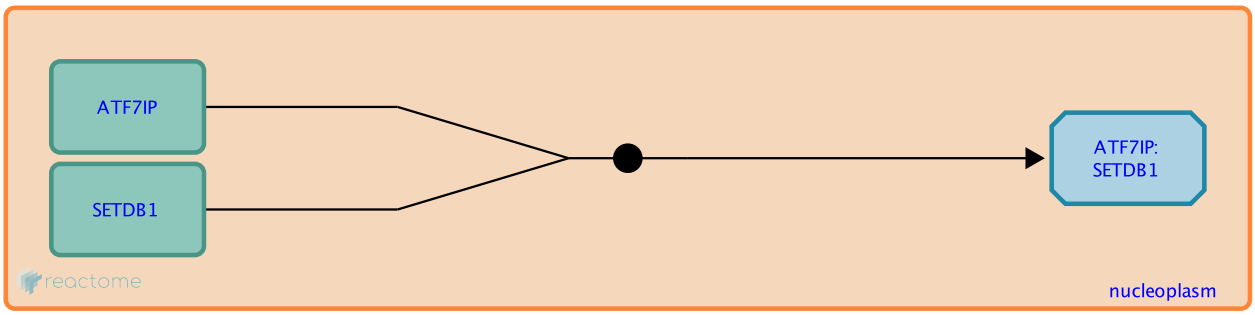
ATF7IP binds SETDB1 ↗

Location: PKMTs methylate histone lysines

Stable identifier: R-HSA-5159250

Type: binding

Compartments: nucleoplasm



SETDB1 (ESET, KMT1E) is one of several protein lysine methyltransferases which selectively methylate lysine-10 of the amino terminus of histone H3 (H3K9) (Rea et al. 2000). It is most effective when complexed with ATF7IP (MCAF, hAM) (Wang et al. 2003).

Literature references

Wang, H., An, W., Cao, R., Xia, L., Erdjument-Bromage, H., Chatton, B. et al. (2003). mAM facilitates conversion by ESET of dimethyl to trimethyl lysine 9 of histone H3 to cause transcriptional repression. *Mol. Cell, 12*, 475-87. ↗

Editions

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

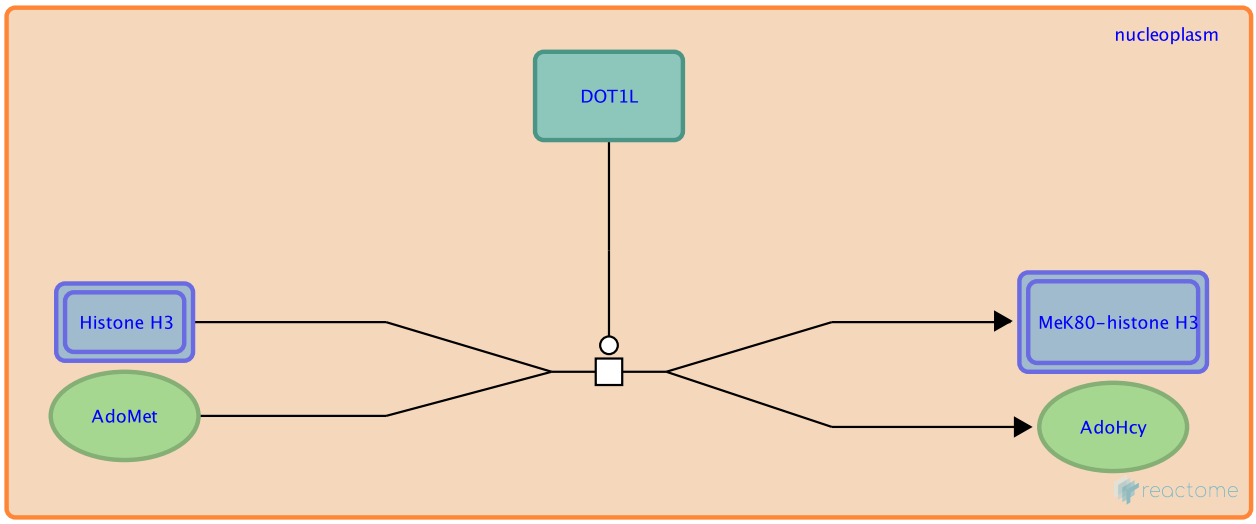
DOT1L (KMT4) methylates lysine-80 of histone H3 (H3K79)

Location: PKMTs methylate histone lysines

Stable identifier: R-HSA-5649801

Type: transition

Compartments: nucleoplasm



DOT1L is capable of catalyzing mono-, di-, and trimethylation in a nonprocessive manner (Min et al. 2003, Frederiks et al. 2008). It appear to be solely responsible for H3K79 methylation, since knockout of Dot1 in yeast, flies and mice results in complete loss of H3K79 methylation (van Leeuwen et al. 2002, Shanower et al. 2005, Jones et al. 2008).

Literature references

Feng, Q., Wang, H., Ng, HH., Erdjument-Bromage, H., Tempst, P., Struhl, K. et al. (2002). Methylation of H3-lysine 79 is mediated by a new family of HMTases without a SET domain. *Curr. Biol., 12,* 1052-8.

Editions

2014-11-13	Authored	Jupe, S.
2014-11-17	Reviewed	Motamedi, M.
2015-02-13	Edited	Jupe, S.

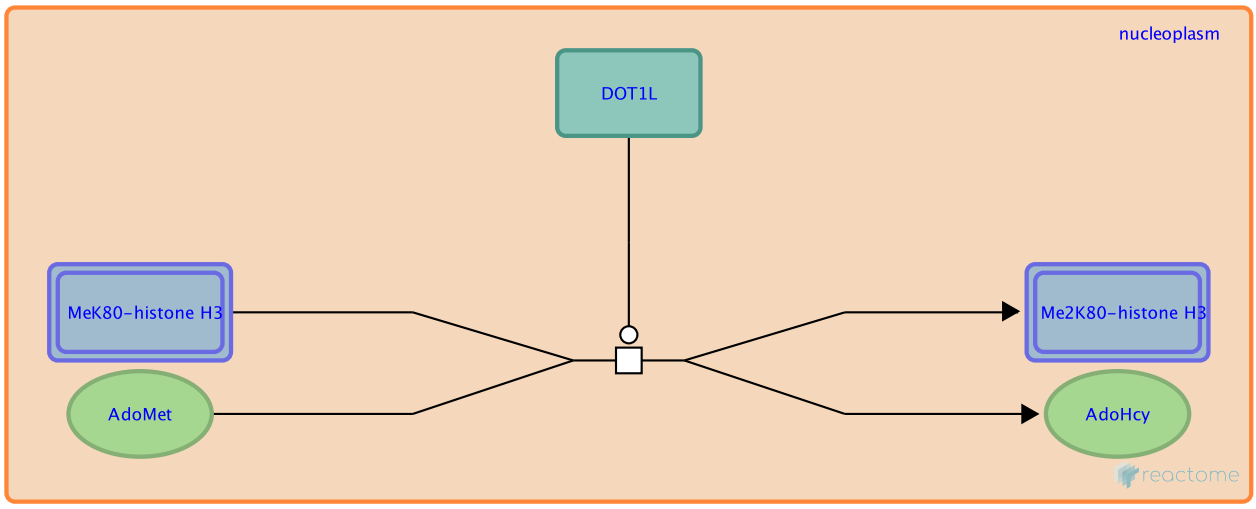
DOT1L (KMT4) methylates methyl-lysine-80 of histone H3 (H3K79)

Location: PKMTs methylate histone lysines

Stable identifier: R-HSA-5649764

Type: transition

Compartments: nucleoplasm



DOT1L is capable of catalyzing the mono-, di-, and trimethylation of histone H3 in a nonprocessive manner (Min et al. 2003, Frederiks et al. 2008). It appear to be solely responsible for H3K79 methylation, since knockout of Dot1 in yeast, flies and mice results in complete loss of H3K79 methylation (van Leeuwen et al. 2002, Shanower et al. 2005, Jones et al. 2008).

Literature references

Feng, Q., Wang, H., Ng, HH., Erdjument-Bromage, H., Tempst, P., Struhl, K. et al. (2002). Methylation of H3-lysine 79 is mediated by a new family of HMTases without a SET domain. *Curr. Biol., 12,* 1052-8.

Editions

2014-11-13	Authored	Jupe, S.
2014-11-17	Reviewed	Motamedi, M.
2015-02-13	Edited	Jupe, S.

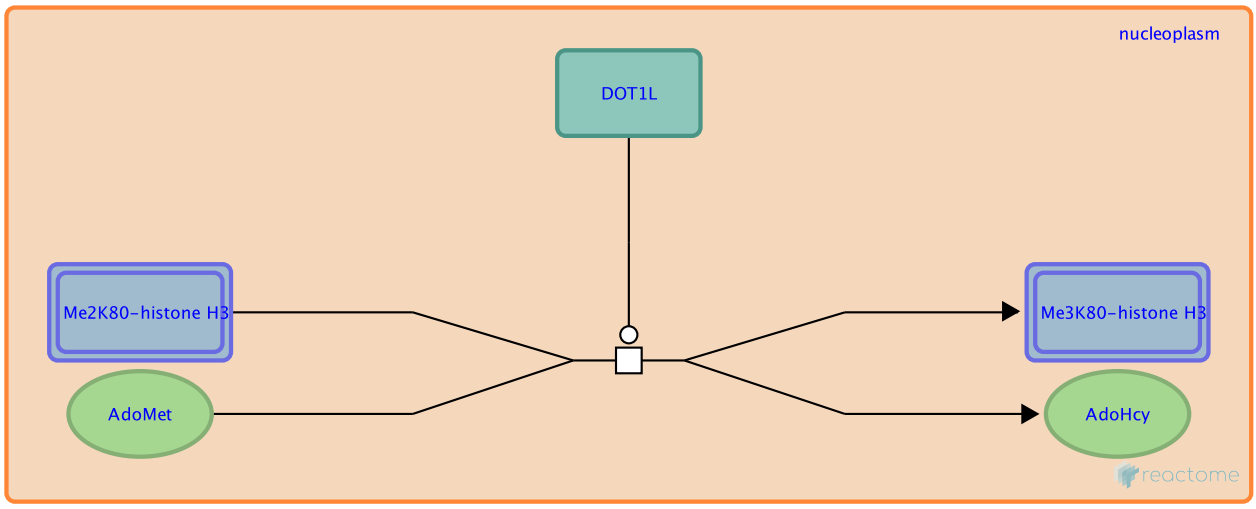
DOT1L (KMT4) methylates dimethyl-lysine-80 of histone H3 (H3K79)

Location: PKMTs methylate histone lysines

Stable identifier: R-HSA-5649799

Type: transition

Compartments: nucleoplasm



DOT1L is responsible for the mono-, di-, and trimethylation of histone H3 in a nonprocessive manner (Min et al. 2003, Frederiks et al. 2008). It appear to be solely responsible for H3K79 methylation, since knockout of Dot1 in yeast, flies and mice results in complete loss of H3K79 methylation (van Leeuwen et al. 2002, Shanower et al. 2005, Jones et al. 2008).

Literature references

Feng, Q., Wang, H., Ng, HH., Erdjument-Bromage, H., Tempst, P., Struhl, K. et al. (2002). Methylation of H3-lysine 79 is mediated by a new family of HMTases without a SET domain. *Curr. Biol., 12,* 1052-8.

Editions

2014-11-13	Authored	Jupe, S.
2014-11-17	Reviewed	Motamedi, M.
2015-02-13	Edited	Jupe, S.

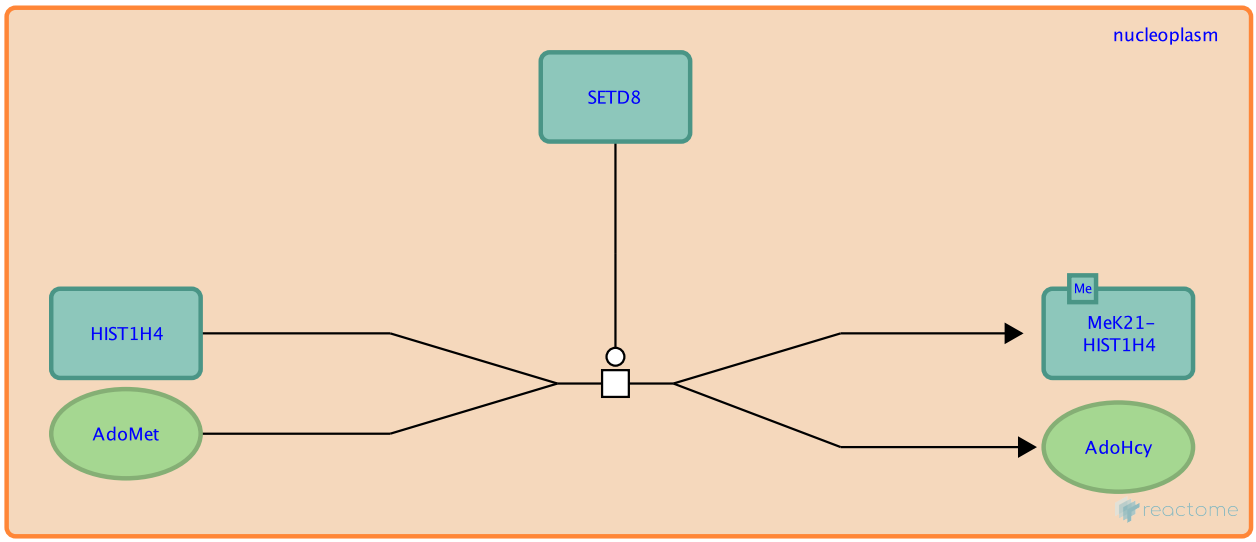
SETD8 (KMT5A) methylates lysine-21 of histone H4 (H4K20)

Location: PKMTs methylate histone lysines

Stable identifier: R-HSA-5423038

Type: transition

Compartments: nucleoplasm



Monomethylation of lysine-21 of histone H4 (H4K20) is performed by SETD8 (KMT5A) (Yin et al. 2005). Trimethylation, performed by SUV420H1 and SUV420H2 and possibly SMYD3 (Foreman et al. 2011), is associated with heterochromatin formation and gene repression (Schotta et al. 2004).

Literature references

Yin, Y., Liu, C., Tsai, SN., Zhou, B., Ngai, SM., Zhu, G. (2005). SET8 recognizes the sequence RHRK20VLRDN within the N terminus of histone H4 and mono-methylates lysine 20. *J. Biol. Chem., 280*, 30025-31.

Foreman, KW., Brown, M., Park, F., Emtage, S., Harriss, J., Das, C. et al. (2011). Structural and functional profiling of the human histone methyltransferase SMYD3. *PLoS ONE, 6*, e22290.

Editions

2014-11-13	Authored	Jupe, S.
2014-11-17	Reviewed	Motamedi, M.
2015-02-13	Edited	Jupe, S.

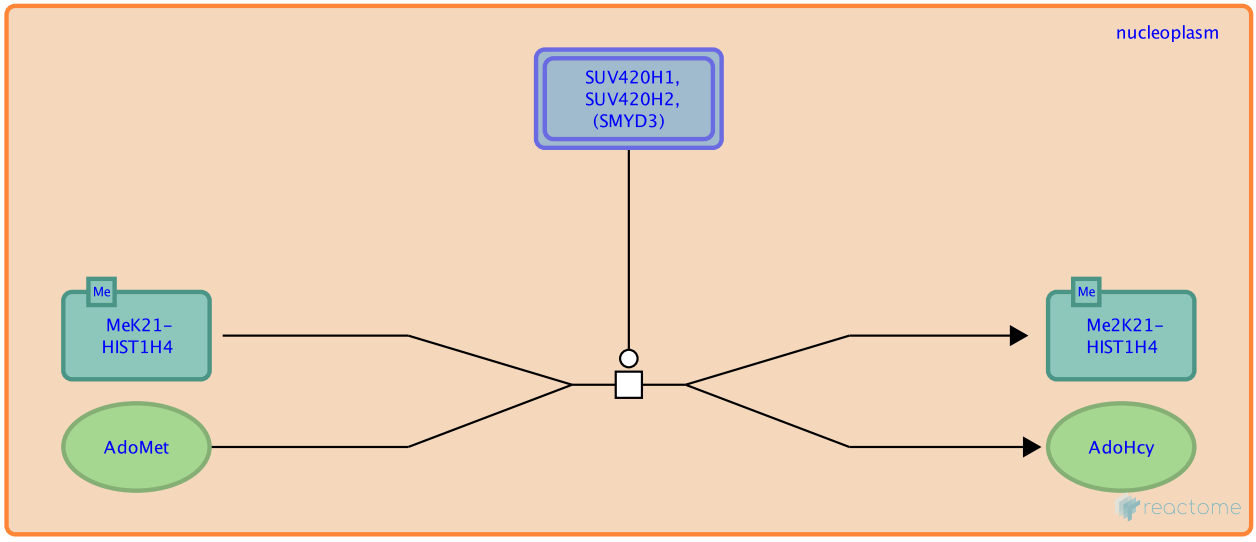
SUV420H1 (KMT5B), SUV420H2 (KMT5C), (possibly SMYD3 (KMT3E)) methylate methyl-lysine-21 of histone H4 (H4K20)

Location: PKMTs methylate histone lysines

Stable identifier: R-HSA-5651654

Type: transition

Compartments: nucleoplasm



The di- and tri-methylation of lysine-21 of histone H4 (H4K20) are performed by SUV420H1 (KMT5B), SUV420H2 (KMT5C) and possibly SMYD3 (KMT3E) (Foreman et al. 2011). Trimethylation is associated with heterochromatin formation and gene repression (Schotta et al. 2004). Monomethylation is performed by SETD8 (KMT5A) (Yin et al. 2005).

Literature references

Schotta, G., Lachner, M., Sarma, K., Ebert, A., Sengupta, R., Reuter, G. et al. (2004). A silencing pathway to induce H3-K9 and H4-K20 trimethylation at constitutive heterochromatin. *Genes Dev., 18*, 1251-62.

Editions

2014-11-13	Authored	Jupe, S.
2014-11-17	Reviewed	Motamedi, M.
2015-02-13	Edited	Jupe, S.

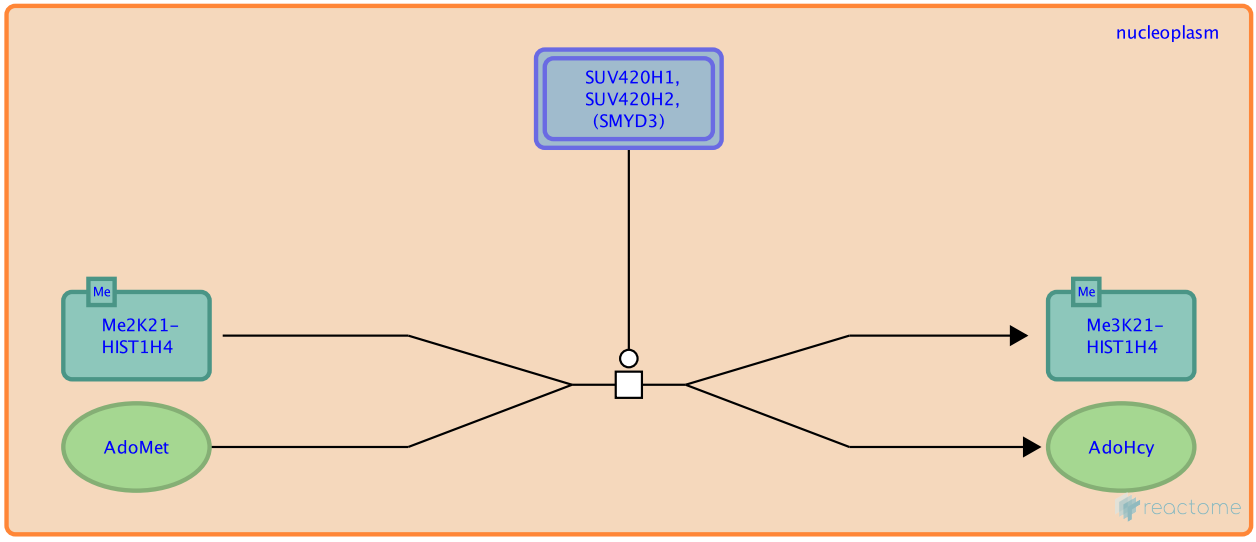
SUV420H1, SUV420H2, (possibly SMYD3 (KMT3E)) methylate dimethyl-lysine-21 of histone H4 (H4K20)

Location: PKMTs methylate histone lysines

Stable identifier: R-HSA-5651657

Type: transition

Compartments: nucleoplasm



The di- and tri-methylation of lysine-21 of histone H4 (H4K20) are performed by SUV420H1 (KMT5B), SUV420H2 (KMT5C) and possibly SMYD3 (KMT3E) (Foreman et al. 2011). Trimethylation is associated with heterochromatin formation and gene repression (Schotta et al. 2004). Monomethylation is performed by SETD8 (KMT5A) (Yin et al. 2005).

Literature references

Schotta, G., Lachner, M., Sarma, K., Ebert, A., Sengupta, R., Reuter, G. et al. (2004). A silencing pathway to induce H3-K9 and H4-K20 trimethylation at constitutive heterochromatin. *Genes Dev., 18*, 1251-62.

Editions

2014-11-13	Authored	Jupe, S.
2014-11-17	Reviewed	Motamedi, M.
2015-02-13	Edited	Jupe, S.

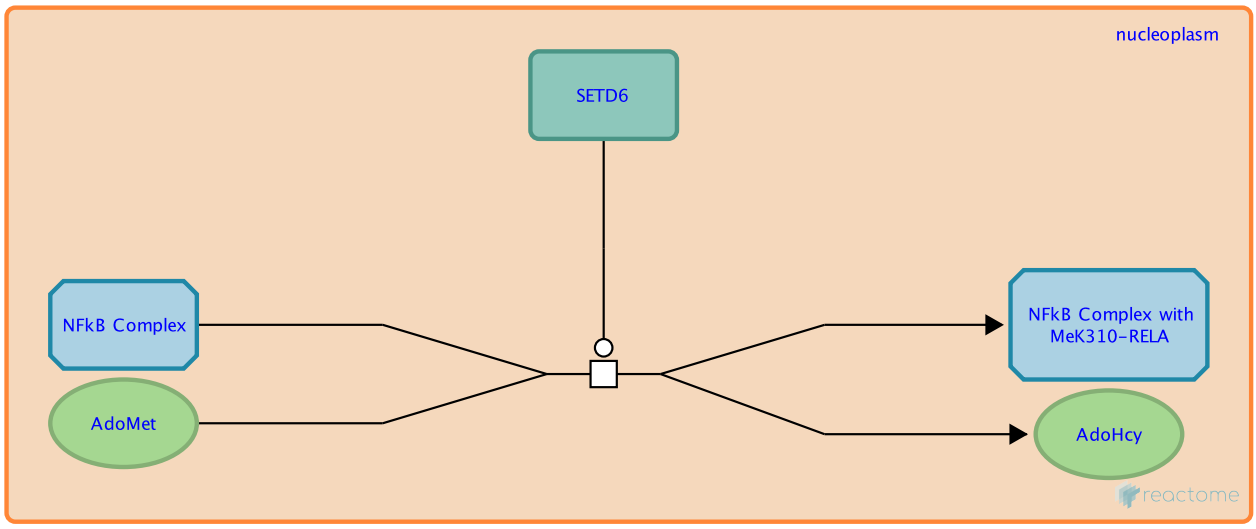
SETD6 methylates RELA in the NFkB complex ↗

Location: PKMTs methylate histone lysines

Stable identifier: R-HSA-8865237

Type: transition

Compartments: nucleoplasm



SET domain containing 6 (SETD6) is an N-lysine methyltransferase that monomethylates the RelA subunit of nuclear factor kappa B (NF-kB) at Lys-310 (Levy et al. 2011, Chang et al. 2011).

Literature references

Levy, D., Kuo, AJ., Chang, Y., Schaefer, U., Kitson, C., Cheung, P. et al. (2011). Lysine methylation of the NF-Î°B subunit RelA by SETD6 couples activity of the histone methyltransferase GLP at chromatin to tonic repression of NF-Î°B signaling. *Nat. Immunol., 12*, 29-36. ↗

Editions

2016-03-21	Authored	Jupe, S.
2016-07-06	Edited	Jupe, S.
2016-07-14	Reviewed	Cheng, X.

Table of Contents