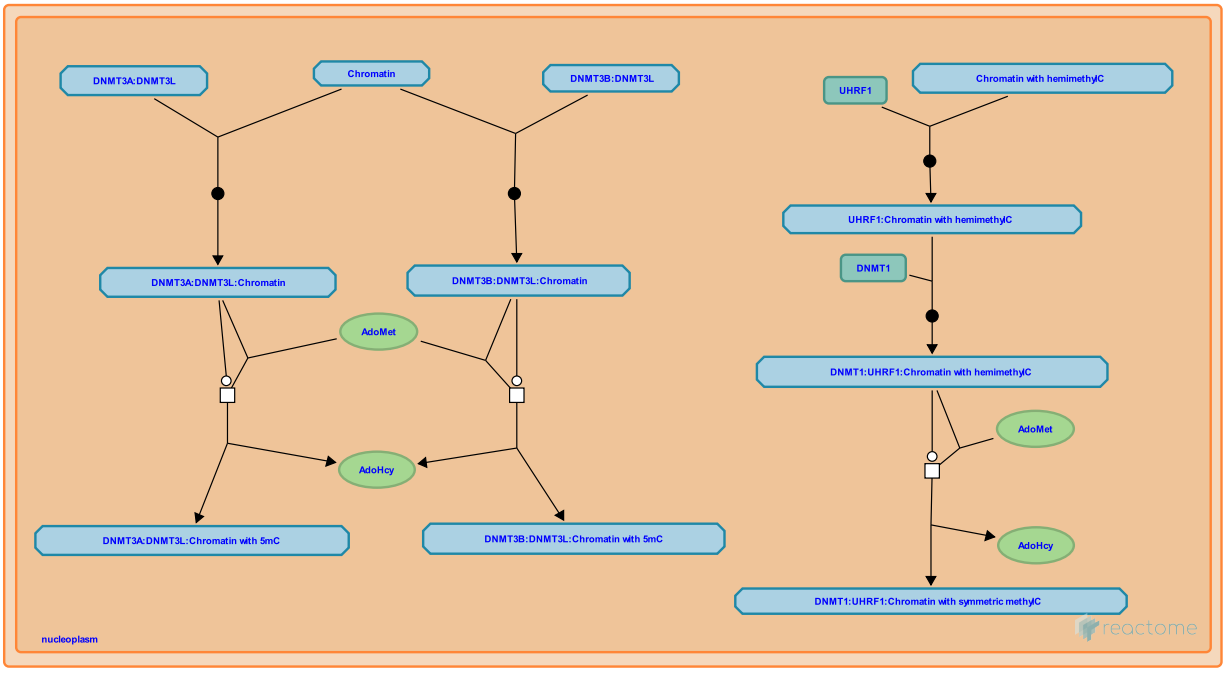
DNA methylation



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19/04/2024

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. ↗

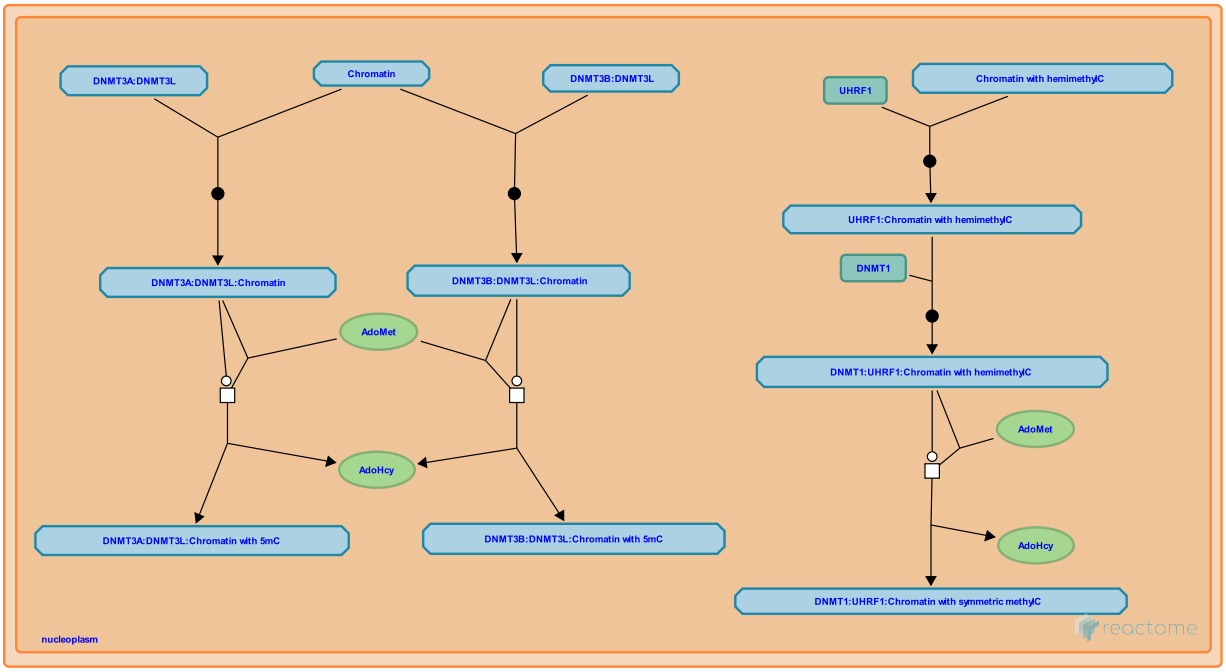
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

DNA methylation ↗

Stable identifier: R-HSA-5334118

Compartments: nucleoplasm



Methylation of cytosine is catalyzed by a family of DNA methyltransferases (DNMTs): DNMT1, DNMT3A, and DNMT3B transfer methyl groups from S-adenosylmethionine to cytosine, producing 5-methylcytosine and homocysteine (reviewed in Klose and Bird 2006, Ooi et al. 2009, Jurkowska et al. 2011, Moore et al. 2013). (DNMT2 appears to methylate RNA rather than DNA.) DNMT1, the first enzyme discovered, preferentially methylates hemimethylated CG motifs that are produced by replication (template strand methylated, synthesized strand unmethylated). Thus it maintains existing methylation through cell division. DNMT3A and DNMT3B catalyze de novo methylation at unmethylated sites that include both CG dinucleotides and non-CG motifs.
DNA from adult humans contains about 0.76 to 1.00 mole percent 5-methylcytosine (Ehrlich et al. 1982, reviewed in Klose and Bird 2006, Ooi et al. 2009, Moore et al. 2013). Methylation of DNA occurs at cytosines that are mainly located in CG dinucleotides. CG dinucleotides are unevenly distributed in the genome. Promoter regions tend to have a high CG-content, forming so-called CG-islands (CGIs), while the CG-content in the remaining part of the genome is much lower. CGIs tend to be unmethylated, while the majority of CGs outside CGIs are methylated. Methylation in promoters and first exons tends to repress transcription while methylation in gene bodies (regions of genes downstream of the promoter and first exon) correlates with transcription (reviewed in Ehrlich and Lacey 2013, Kulis et al. 2013). Proteins such as MeCP2 and MBDs specifically bind 5-methylcytosine and may recruit other factors.
Mammalian development has two major episodes of genome-wide demethylation and remethylation (reviewed in Zhou 2012, Guibert and Weber 2013, Hackett and Surani 2013, Dean 2014). In mice about 1 day after fertilization the paternal genome is actively demethylated by TET proteins together with thymine DNA glycosylase and the maternal genome is demethylated by passive dilution during replication, however methylation at imprinted sites is maintained. The genome has its lowest methylation level about 3.5 days post-fertilization. Remethylation occurs by 6.5 days post-fertilization. The second demethylation-remethylation event occurs in primordial germ cells of the developing embryo about 12.5 days post-fertilization. DNMT3A and DNMT3B, together with the non-catalytic DNMT3L, play major roles in the remethylation events (reviewed in Chen and Chan 2014). How the methyltransferases are directed to particular regions of the genome remains an area of active research. The mechanisms at each locus may differ in detail but a connection between histone modifications and DNA methylation has been observed (reviewed in Rose and Klose 2014).

Literature references

Le, T., Moore, LD., Fan, G. (2013). DNA methylation and its basic function. *Neuropsychopharmacology, 38*, 23-38. ↗

McCune, RA., Gehrke, C., Midgett, RM., Kuo, KC., Gama-Sosa, MA., Huang, LH. et al. (1982). Amount and distribution of 5-methylcytosine in human DNA from different types of tissues of cells. *Nucleic Acids Res., 10*, 2709-21. ↗

Dean, W. (2014). DNA methylation and demethylation: A pathway to gametogenesis and development. *Mol. Reprod. Dev., 81*, 113-25. ↗

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Chen, BF., Chan, WY. (2014). The de novo DNA methyltransferase DNMT3A in development and cancer. *Epigenetics, 9*. ↗

Editions

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DNMT3A:DNMT3L binds chromatin ↗

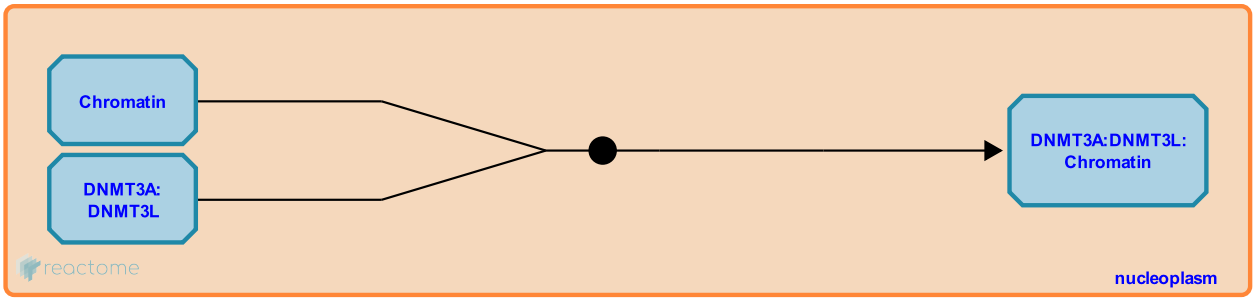
Location: DNA methylation

Stable identifier: R-HSA-5334179

Type: binding

Compartments: nucleoplasm

Inferred from: Dnmt3a:Dnmt3l binds chromatin (Mus musculus)



DNMT3L is a non-catalytic homologue of DNMT3A and DNMT3B which binds unmethylated lysine-4 of histone H3 (H3K4, Ooi et al. 2007) and recruits DNMT3A-isoform2 (germ cell specific) (Chen et al. 2005, Kareta et al. 2006, Ooi et al. 2007) and, to a lesser extent, other isoforms of DNMT3A via an interaction between the C-terminal regions of DNMT3L and DNMT3A (Chen et al. 2005). Furthermore, DNMT3A binds unmodified tails of histone H3 (Otani et al. 2009). DNMT3L and DNMT3A form tetramers (DNMT3L:DNMT3A:DNMT3A:DNMT3L) that bind DNA located in euchromatic regions (Holz-Schietinger et al. 2011, also inferred from mouse). DNMT3A without DNMT3L forms oligomers that are located in heterochromatin.

Followed by: DNMT3A:DNMT3L methylates cytosine in DNA

Literature references

Chédin, F., Mann, JR., Hsieh, CL., Chen, ZX., Riggs, AD. (2005). Physical and functional interactions between the human DNMT3L protein and members of the de novo methyltransferase family. *J. Cell. Biochem., 95*, 902-17. ↗

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Chédin, F., Botello, ZM., Ennis, JJ., Kareta, MS., Chou, C. (2006). Reconstitution and mechanism of the stimulation of de novo methylation by human DNMT3L. *J. Biol. Chem., 281*, 25893-902. ↗

Matje, DM., Reich, NO., Harrison, MF., Holz-Schietinger, C. (2011). Oligomerization of DNMT3A controls the mechanism of de novo DNA methylation. *J. Biol. Chem., 286*, 41479-88. ↗

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Editions

2014-02-21	Authored, Edited	May, B.
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DNMT3A:DNMT3L methylates cytosine in DNA ↗

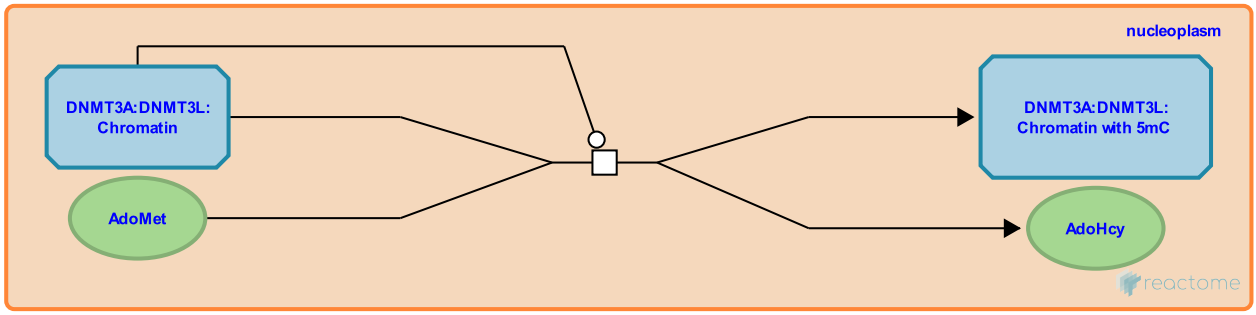
Location: DNA methylation

Stable identifier: R-HSA-5334152

Type: transition

Compartments: nucleoplasm

Inferred from: Dnmt3a:Dnmt3l methylates cytosine in DNA (Mus musculus)



DNMT3A methylates the 5 position of cytosine in DNA. As inferred from the mouse homolog, DNMT3A generates asymmetric methylation (methylation of only one strand) of CG dinucleotides and non-CG cytosine residues. DNMT3L interacts with and stimulates the catalytic activity of DNMT3A2 and DNMT3A (Chen et al. 2005, Kareta et al. 2006, Ooi et al. 2007, Holz-Schietinger and Reich 2010). DNMT3A preferentially methylates DNA in regions of transcriptionally active chromatin: DNMT3A-isoform1 transfected into human cells (293T cells) tended to methylate active regions of the genome that were associated with trimethylated lysine-4 of histone H3 (H4K4me3) (Choi et al. 2011). Likewise, in mouse oocytes and embryos CG islands methylated by DNMT3A tend to be located in active transcription units, but with low levels of methylated H3K4 (Smallwood et al. 2011). DNMT3A and its homologue DNMT3B have different preferences for flanking sequences of CG dinucleotides, with DNMT3A tending to methylate sites that have T at the -2 position and C at the +2 position (Wienholz et al. 2010). DNMT3L increases methylation by DNMT3A at sites that are weakly methylated by DNMT3A alone (Wienholz et al. 2010).

Preceded by: DNMT3A:DNMT3L binds chromatin

Literature references

Reich, NO., Holz-Schietinger, C. (2010). The inherent processivity of the human de novo methyltransferase 3A (DNMT3A) is enhanced by DNMT3L. *J. Biol. Chem., 285*, 29091-100. ↗

Chédin, F., Mann, JR., Hsieh, CL., Chen, ZX., Riggs, AD. (2005). Physical and functional interactions between the human DNMT3L protein and members of the de novo methyltransferase family. *J. Cell. Biochem., 95*, 902-17. ↗

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Editions

2014-02-21	Authored, Edited	May, B.
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DNMT3B:DNMT3L binds chromatin ↗

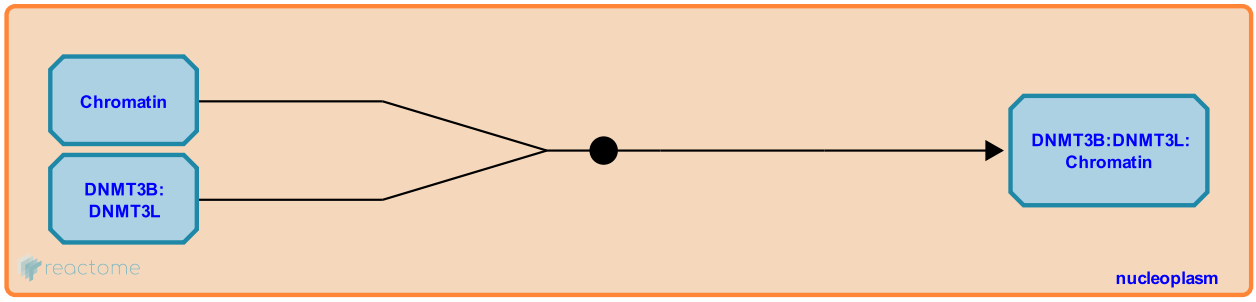
Location: DNA methylation

Stable identifier: R-HSA-5334164

Type: binding

Compartments: nucleoplasm

Inferred from: Dnmt3b:Dnmt3l binds chromatin (Mus musculus)



The C-terminal region of DNMT3L associates with C-terminal regions of DNMT3B-isoform1 and DNMT3B-isoform2 (Chen et al. 2005, Van Emburgh and Robertson 2011, human DNMT3L with mouse Dnmt3b in Suetake et al. 2004). DNMT3L binds the unmethylated N-terminus of histone H3 (Ooi et al. 2007), leading DNMT3L to target DNMT3B to chromatin (Wienholz et al. 2010). As inferred from mouse homologs, DNMT3B also binds the unmodified N-terminus of histone H3.

Followed by: DNMT3B:DNMT3L methylates cytosine in DNA

Literature references

Chédin, F., Mann, JR., Hsieh, CL., Chen, ZX., Riggs, AD. (2005). Physical and functional interactions between the human DNMT3L protein and members of the de novo methyltransferase family. *J. Cell. Biochem., 95*, 902-17. ↗

Chédin, F., Moarefi, AH., Wienholz, BL., Ginno, PA., Gordon, CA., Kareta, MS. (2010). DNMT3L modulates significant and distinct flanking sequence preference for DNA methylation by DNMT3A and DNMT3B in vivo. *PLoS Genet., 6*, e1001106. ↗

Tajima, S., Miyagawa, J., Takeshima, H., Shinozaki, F., Suetake, I. (2004). DNMT3L stimulates the DNA methylation activity of Dnmt3a and Dnmt3b through a direct interaction. *J. Biol. Chem., 279*, 27816-23. ↗

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Lin, SP., Yang, Z., Li, K., Bernstein, E., Ooi, SK., Bestor, TH. et al. (2007). DNMT3L connects unmethylated lysine 4 of histone H3 to de novo methylation of DNA. *Nature, 448*, 714-7. ↗

Editions

2014-02-21	Authored, Edited	May, B.
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DNMT3B:DNMT3L methylates cytosine in DNA ↗

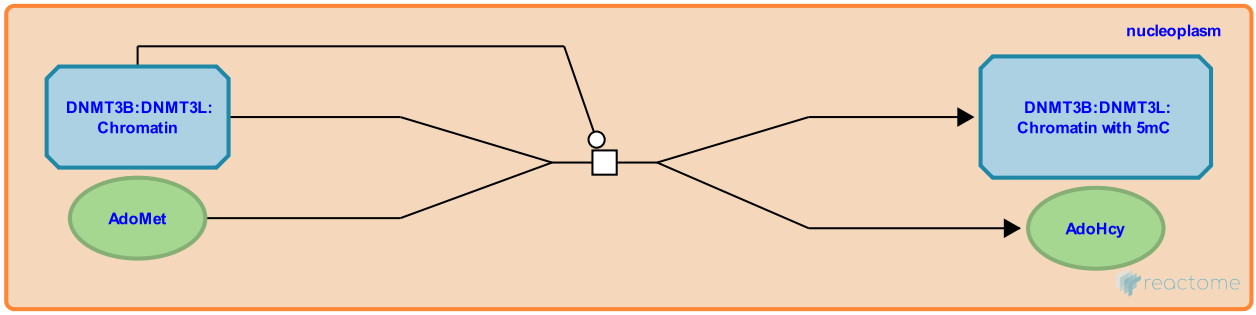
Location: DNA methylation

Stable identifier: R-HSA-5334097

Type: transition

Compartments: nucleoplasm

Inferred from: Dnmt3b:Dnmt3l methylates cytosine in DNA (Mus musculus)



DNMT3B methylates the 5 position of cytosine in DNA. DNMT3B preferentially methylates cytosine residues that have T at the -1 position and G at the +1 position (Wienholz et al. 2010). Sites methylated de novo by DNMT3B tend to be in transcriptionally inactive regions associated with histone H3 trimethylated at lysine-27 (Choi et al. 2011). Association with DNMT3L increases the processivity of DNMT3B (Van Emburgh and Robertson 2011) and increases methylation at sites that would have low methylation by the activity of DNMT3B alone (Wienholz et al. 2010). Interaction of DNMT3L with DNMT3B-isoform2 stimulates methylation activity significantly (Van Emburgh and Robertson 2011), but interaction of DNMT3L with DNMT3B-isoform1 has little effect on methylation activity (Chedin et al. 2002, Van Emburgh and Robertson 2011). Methylation in embryos but not in gametes (oocytes and spermatozoa) requires DNMT3B (Okano et al. 1999, Kaneda et al. 2004, Borgel et al. 2010, Kaneda et al. 2010).

Preceded by: DNMT3B:DNMT3L binds chromatin

Literature references

Chédin, F., Mann, JR., Hsieh, CL., Chen, ZX., Riggs, AD. (2005). Physical and functional interactions between the human DNMT3L protein and members of the de novo methyltransferase family. *J. Cell. Biochem., 95*, 902-17. ↗

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Chédin, F., Hsieh, CL., Lieber, MR. (2002). The DNA methyltransferase-like protein DNMT3L stimulates de novo methylation by Dnmt3a. *Proc. Natl. Acad. Sci. U.S.A., 99*, 16916-21. ↗

Robertson, KD., Van Emburgh, BO. (2011). Modulation of Dnmt3b function in vitro by interactions with Dnmt3L, Dnmt3a and Dnmt3b splice variants. *Nucleic Acids Res., 39*, 4984-5002. ↗

Editions

2014-02-21	Authored, Edited	May, B.
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UHRF1 binds chromatin with hemimethylated cytosine ↗

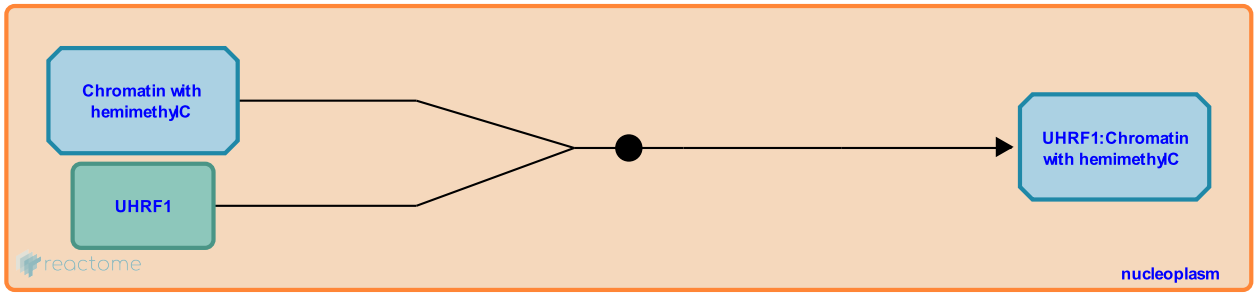
Location: DNA methylation

Stable identifier: R-HSA-5334099

Type: binding

Compartments: nucleoplasm

Inferred from: Uhrf1 binds chromatin with hemimethylC (Mus musculus)



UHRF1 (also known as Np95) preferentially binds hemimethylated CG dinucleotides in DNA via its SRA domain (Avvakumov et al. 2008, Qian et al. 2008, and inferred from the mouse homolog). The UHRF1-bound unmethylated cytosine base is flipped out of the DNA helix and into a pocket of UHRF1 (Avvakumov et al. 2008). UHRF1 also binds dimethylated and trimethylated lysine-9 of histone H3 through its tandem Tudor domain (Nady et al. 2011, Rothbart et al. 2012, Rothbart et al. 2013, Cheng et al. 2013) and unmethylated histone H3 through its PHD domain (Hu et al. 2011, Wang et al. 2011, Rajakumara et al. 2011, Cheng et al. 2013).

Followed by: UHRF1:Chromatin binds DNMT1

Literature references

Chédin, F., Wang, YX., Nady, N., Bronner, C., Lemak, A., Avvakumov, GV. et al. (2011). Recognition of multivalent histone states associated with heterochromatin by UHRF1 protein. *J. Biol. Chem., 286*, 24300-11. ↗

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Wang, P., Hu, L., Xu, Y., Li, Z., Lin, Y. (2011). Crystal structure of PHD domain of UHRF1 and insights into recognition of unmodified histone H3 arginine residue 2. *Cell Res., 21*, 1374-8. ↗

Fang, J., Wang, P., Cheng, J., Zhu, T., Yang, H., Chen, F. et al. (2013). Structural insight into coordinated recognition of trimethylated histone H3 lysine 9 (H3K9me3) by the plant homeodomain (PHD) and tandem tudor domain (TTD) of UHRF1 (ubiquitin-like, containing PHD and RING finger domains, 1) protein. *J. Biol. Chem., 288*, 1329-39 . ↗

Hu, W., Wu, H., Wang, C., Cao, C., Li, G., Chen, P. et al. (2011). Structural basis for site-specific reading of unmodified R2 of histone H3 tail by UHRF1 PHD finger. *Cell Res., 21*, 1379-82. ↗

Editions

2014-02-21	Authored, Edited	May, B.
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UHRF1:Chromatin binds DNMT1 ↗

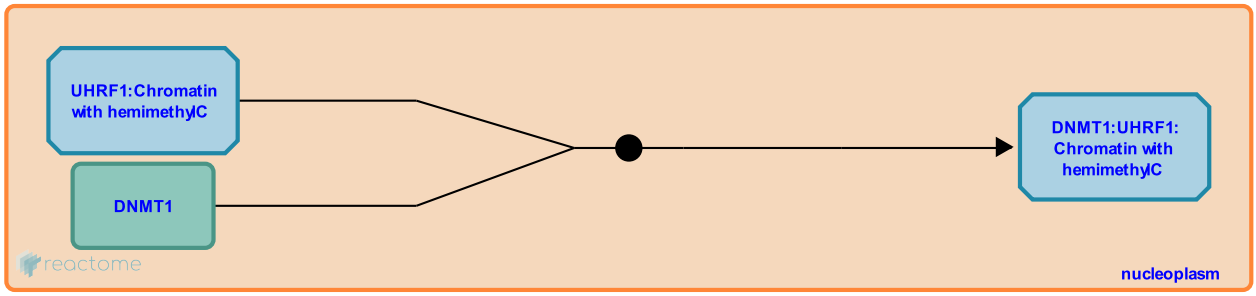
Location: DNA methylation

Stable identifier: R-HSA-5334160

Type: binding

Compartments: nucleoplasm

Inferred from: Uhrf1:Chromatin binds Dnmt1 (Mus musculus)



As inferred from the mouse homolog, UHRF1 associates with hemimethylated DNA and histone H3 tails methylated at lysine-9. UHRF1 recruits and tethers DNMT1 (Bostick et al. 2007). The association of UHRF1 with DNMT1 occurs preferentially during S-phase when DNA is hemimethylated as the newly replicated strand remains transiently unmethylated (Zhang et al. 2011, Hervouet et al. 2012). DNMT1 also forms complexes with transcription factors such as TP53 (p53) and YY1 at other times during the cell cycle (Hervouet et al. 2012).

Preceded by: UHRF1 binds chromatin with hemimethylated cytosine

Followed by: DNMT1 methylates cytosine in hemimethylated DNA

Literature references

Li, J., Koseki, H., Wu, W., Li, P., Zhang, J., Dong, S. et al. (2011). S phase-dependent interaction with DNMT1 dictates the role of UHRF1 but not UHRF2 in DNA methylation maintenance. *Cell Res., 21*, 1723-39. ↗

Vallette, FM., Hervouet, E., Cartron, PF., Nadaradjane, A., Gueguen, M. (2012). Kinetics of DNA methylation inheritance by the Dnmt1-including complexes during the cell cycle. *Cell Div, 7*, 5. ↗

Pradhan, S., Clark, A., Jacobsen, SE., Bostick, M., Kim, JK., Estève, PO. (2007). UHRF1 plays a role in maintaining DNA methylation in mammalian cells. *Science, 317*, 1760-4. ↗

Editions

2014-02-21	Authored, Edited	May, B.
2014-07-24	Reviewed	Beekman, R., Martín-Subero, JI.

DNMT1 methylates cytosine in hemimethylated DNA ↗

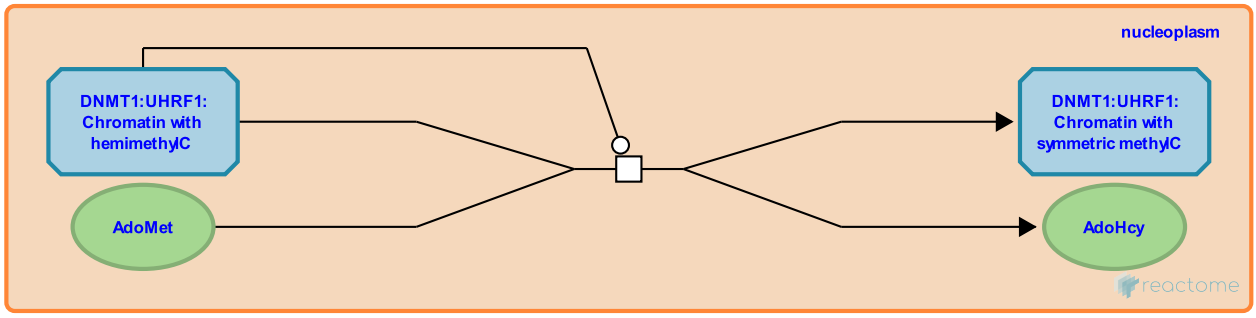
Location: DNA methylation

Stable identifier: R-HSA-5334151

Type: transition

Compartments: nucleoplasm

Inferred from: Dnmt1 methylates cytosine in hemimethylated DNA (Mus musculus)



DNMT1 transfers a methyl group from S-adenosylmethionine to the 5-position of the cytosine ring of cytosine residues in DNA. Purified human DNMT1 shows a 7 to 21-fold preference for hemimethylated CG motifs in DNA compared to unmethylated CG motifs (Pradhan et al. 1999) thus DNMT1 tends to maintain existing methylation through DNA replication. The binding of the CXXC motif of DNMT1 to cytosine in symmetrically unmethylated CG dinucleotides prevents access of cytosine to the active site and thereby prevents de novo methylation (Song et al. 2011). UHRF1 binds hemimethylated DNA and histone H3 tails methylated at lysine-9 and recruits DNMT1 to methylate hemimethylated DNA (Bostick et al. 2007, reviewed in Ooi and Bestor 2008). Interaction of UHRF1 with DNMT1 increases the methylation activity of DNMT1 about 5-fold (Bashtrykov et al. 2014).

Preceded by: UHRF1:Chromatin binds DNMT1

Literature references

Rechkoblit, O., Song, J., Bestor, TH., Patel, DJ. (2011). Structure of DNMT1-DNA complex reveals a role for autoinhibition in maintenance DNA methylation. *Science, 331*, 1036-40. ↗

Jurkowska, RZ., Bashtrykov, P., Ragozin, S., Jeltsch, A., Jankevicius, G. (2014). The UHRF1 Protein Stimulates the Activity and Specificity of the Maintenance DNA Methyltransferase DNMT1 by an Allosteric Mechanism. *J. Biol. Chem., 289*, 4106-15. ↗

Pradhan, S., Roberts, RJ., Bacolla, A., Wells, RD. (1999). Recombinant human DNA (cytosine-5) methyltransferase. I. Expression, purification, and comparison of de novo and maintenance methylation. *J Biol Chem, 274*, 33002-10. ↗

Pradhan, S., Clark, A., Jacobsen, SE., Bostick, M., Kim, JK., Estève, PO. (2007). UHRF1 plays a role in maintaining DNA methylation in mammalian cells. *Science, 317*, 1760-4. ↗

Ooi, SK., Bestor, TH. (2008). Cytosine methylation: remaining faithful. *Curr. Biol., 18*, R174-6. ↗

Editions

2014-02-21	Authored, Edited	May, B.
2014-07-24	Reviewed	Beekman, R., Martín-Subero, JI.

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