Methyltransferase SETDB1

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SET domain bifurcated 1 (SETDB1) is a histone H3 lysine 9 (H3K9) methyltransferase that exerts important effects on epigenetic gene regulation. SETDB1 complexes (SETDB1-KRAB-KAP1, SETDB1-DNMT3A, SETDB1-PML, SETDB1-ATF7IP-MBD1) play crucial roles in the processes of histone methylation, transcriptional suppression and chromatin remodelling.

epigenetics methyltransferase SETDB1 H3K9 function

1. Overview

SET domain bifurcated 1 (SETDB1) is a histone H3 lysine 9 (H3K9) methyltransferase that exerts important effects on epigenetic gene regulation. SETDB1 complexes (SETDB1-KRAB-KAP1, SETDB1-DNMT3A, SETDB1-PML, SETDB1-ATF7IP-MBD1) play crucial roles in the processes of histone methylation, transcriptional suppression and chromatin remodelling. Therefore, aberrant trimethylation at H3K9 due to amplification, mutation or deletion of SETDB1 may lead to transcriptional repression of various tumour-suppressing genes and other related genes in cancer cells.

2. Epigenetic Gene Regulation

Epigenetic gene regulation eventually leads to changes in gene function and phenotype without changes in DNA sequence [1]. Among epigenetic gene regulation mechanisms, histone methylation is extremely important and participates in gene expression and chromatin organization [2]. The process of histone methylation involves two enzyme systems, histone methyltransferases (HMTs) and histone demethylases (HDMs), the imbalance of which is closely related to tumourigenesis [3].

Histone methylation occurs at the arginine and lysine residues of histone 3 (H3) and histone 4 (H4). Arginine and lysine residues can be monomethylated or dimethylated, and lysine residues can also be trimethylated [4][5]. Histone lysine methyltransferases (HKMTs) are important epigenetic modificatory enzymes containing SET domains. Being responsible for the enzymatic activity, the SET domain is included in most HKMTs. The HKMTs involved in human tumourigenesis consist mainly of the multicomb complex SMYD, NSD, SETD, SUV39, EHMT, MLL, DOT1L, and PRC2 [6][7]. SET domain bifurcated 1 (SETDB1), belonging to the SUV family of H3K9 methyltransferases, exploits its H3K9me1/2/3 functions by the conserved SET domain [8]. H3K9 trimethylation possesses the ability to form heterochromatin, which silences gene transcription and remodels the chromatin

structure [1][9][10]. Overexpression and downregulation of SETDB1 have been widely found in various cancers, but the detailed mechanisms are still unclear [2][11][12][13][14][15][16][17][18][19][20][21][22].

3. Biological Functions of SETDB1

SETDB1 is primarily involved in the processes of histone methylation, transcriptional suppression and chromatin gene silencing as well as chromatin remodelling in cells [9], either to maintain the structure of chromatin or to control the expression of specific genes. Simultaneously, SETDB1 exerts many other physiological functions, including cell apoptosis [23][24], antiviral response [25][26]; the establishment, growth and proliferation of pluripotent embryonic stem cells [27]; proviral silencing during embryogenesis and postnatal development [28]; and X-chromosome inactivation [29]. Most of these functions are dependent on its methyltransferase activity. More importantly, the expression of SETDB1 is upregulated in a variety of tumours, indicating that SETDB1 is closely related to the occurrence and development of cancers [21].

3.1 The Methylation of Histone H3 Lysine 9 by SETDB1

Histone methylation is a major regulator of epigenetic modification and plays a key regulatory role in gene expression. Histone lysine methylation is an important participant among these regulators and is associated with malignant conversion of tumours and the regulation of various physiological activities [30]. As a H3K9 methylase, SETDB1 was found to specifically methylate the lysine residue of histone 3 at site 9 [9], through which it maintains the structure of DNA and controls gene expression by regulating the extent of DNA compaction [31]. During the process of methylation, the SET domain of SETDB1 utilizes S-adenosylmethionine (SAM) to methylate the ε-amino group of the lysine residue [6][32].

SETDB1 individually dimethylates H3K9. The interaction with the human homologue of murine ATFa-associated modulator (hAM) (the cofactor of SETDB1) enhances its enzyme activity, which facilitates the SETDB1-dependent conversion at H3 in euchromatic regions from dimethyl H3K9 to a trimethyl state [10]. The trimethylation of H3K9 is associated with gene suppression, while monomethylation is associated with gene excitation [33]. Thus, association with hAM increases SETDB1-dependent transcriptional repression on a chromatin template [10].

3.2. Gene transcription silencing by the SETDB1-KRAB-KAP1 complex

The methyltransferase activity of SETDB1 at the H3K9 position in the nuclear euchromatic locus facilitates the combination of the *chromo-domain of heterochromatin protein 1α (HP1α)* and methylated Lys, which promotes HP1 deposition [9]. HP1 might dimerize with methylated H3K9 in close vicinity and form compacted heterochromatin [46], which contributes to gene silencing. *KRAB-associated protein-1 (KAP1)*, a transcriptional intermediary factor acting as a molecular scaffold among many transcriptional regulatory complexes, was reported to be able to associate with both SETDB1 and HP1α [9]. The connection between SETDB1 and HP1 has been previously confirmed[47]. Specifically, the repression domain of KAP1 binds to the chromo shadow domain of HP1α [48,49]. In addition, KAP1, a common corepressor for the *KRAB zinc finger protein (KRAB-ZFP)* family (the largest family of

sequence-specific DNA binding repressors [50]) of transcriptional repressors [51], connects to KRAB-ZFP through its 75-amino acid KRAB box to form a KRAB-KAP1 repression complex that establishes local microenvironments of heterochromatin at the N-terminal tail of histone H3. As a consequence, the heterochromatin status suppresses gene transcription at specific sites [9,51,52]. Thus, the SETDB1-KRAB-KAP1 repression complex leads to enriched SETDB1, H3K9me3, KRAB, KAP-1, and HP1 at the promoter sequences of specific euchromatic genes, which induces conversion of the target genes from euchromatin to facultative heterochromatin and subsequently represses gene expression [9,53-55].

In mammalian genomes, endogenous retroviruses (ERVs) comprise approximately 8% of the human genome [55]. Although retrotransposition contributes to genome diversification evolution and adaption, it can also lead to genome instability, insertional mutagenesis, or transcriptional perturbation, which is often harmful to host cells [56-59]. ERVs are responsible for 10-12% of the total spontaneous mutations in mice [60]. Aberrant expression of ERVs could alter the expression of neighbouring genes, some of which act as proto-oncogenes to transform host cells [61]. Therefore, multiple defence mechanisms have evolved to maintain the integrity of the genome and transcriptome against retroelement transposition, among which H3K9 methylation modification is important [55] and especially mediated by SETDB1 [34,35,62,63].

ERV silencing is initiated by the recruitment of KAP1 to the target by members of the KRAB-ZFP family. Then, the KAP1/KRAB-ZFP complex is thought to be a pivotal factor for SETDB1 recruitment to retroelements [58]. Simultaneously, HP1 and the NuRD complex are recruited by KAP1 [52]. In detail, KAP1 was discovered to autosumoylate its bromodomain to recruit both the NuRD complex and SETDB1 to the promoter regions of genes modulated by KRAB-ZFPs, which could establish a silent chromatin state by H3K9me3 at genes targeted by KAP1 [9,37]. Recent studies have reported that mouse embryonic stem cells (mESCs) enhance recruitment of SETDB1 to ERV retrotransposition and formation of a KAP1 suppression complex to repress proviral molecules [64]. Furthermore, Peter J. Thompson identified that RNA-binding protein and transcription cofactor *heterogeneous nuclear ribonucleoprotein K (hnRNP K)* are necessary for the SETDB1-dependent proviral silencing process, which acts as a binding partner of the SETDB1-KAP1 complex by direct interaction in mESCs [65]. Recently, studies of SETDB1 knockout adult mice and differentiated cells demonstrated that SETDB1 also represses retroelements in somatic cells, such as B lymphocytes [66], T lymphocytes [67], neural progenitor cells (NPCs) [68], and immortalized mouse embryonic fibroblasts (iMEFs) [69]. Mechanistically, SETDB1 is recruited to its target regions by KRAB-ZNF/KAP1 to take effect [70,71], confirming a more general role of SETDB1 in suppressing retroelements.

Recently, SETDB1-dependent ERV repression in cancer cells was also confirmed to be associated with evading recognition by the immune system [72-74]. As a negative regulator of innate immunity, SETDB1 was reported to repress the expression of ERVs through its H3K9-methylating function to preclude the immune response of B cells induced by ERVs, which enables acute myeloid leukaemia (AML) cells to escape innate immunity [72,73]. Above all, the model of SETDB1-KRAB-KAP1 initiated by the recruitment of KAP1 plays a pivotal role in maintaining genome stability and immune regulation, especially through ERVs silencing [74,75].

3.3. Gene transcription silencing by interaction between SETDB1 and DNMT3A

A direct interaction between the N-terminal domain of SETDB1 and the plant homeodomain (PHD) of DNA methyltransferase 3A (DNMT3A) *in vivo* and *in vitro* has been shown to facilitate gene transcriptional repression [1]. The repression of the tumour-suppressing gene *RASSF1A* by a high frequency of methylation at its promoter is widely found in lung, breast, pancreas, kidney, liver, and other cancers [76]. The SETDB1-DNMT3A complex was essential for repressing the promoter of the *p53BP2* gene in HeLacells and the *RASSF1A* gene in MDA-MB-231 breast cancer cells [1,76]. The study also confirmed that SETDB1 is recruited by *methyl-CpG DNA Binding Domain Protein 1 (MBD1)* to the promoter region of *p53BP2* (it seems that MBD1 does not mediate the recruitment of SETDB1 to *RASSF1A*), and the co-occupation of DNMT3A and SETDB1 leads to a hypermethylated gene promoter [1]. Further study found that SETDB1, DNMT3A, and histone deacetylase 1 (HDAC1) formed a repressive functional complex. During the process, the SETDB1-HDAC1 complex is recruited to the promoter at first to establish trimethylated H3K9 status and represses gene transcription. DNMT3A is later recruited to form theSETDB1-HDAC1-DNMT3A complex and enhance DNA methylation to permanently inactivate the gene. It's a self-propagating epigenetic cycle, in which SETDB1 methylates H3K9 and recruits DNMT3A to reinforce and maintain DNA methylation [1]. Therefore, MBD1-dependent SETDB1-HDAC1 recruitment and SETDB1-mediated H3-K9 methylation initiate the establishment of trimethylated H3K9 status at *p53BP2* promoter. SETDB1 recruits DNMT3A which reinforces DNA methylation to connect histone methylation and DNA methylation.

3.4. Gene transcription silencing by interaction between SETDB1 and PML

Promyelocytic leukaemia nuclear bodies (PML-NBs) are large proteinaceous structures that participate in diverse cellular processes such as apoptosis, transcription, cellular senescence, neoangiogenesis, DNA damage response, antiviral response and maintenance of genomic stability, by interacting with multiple proteins [32,33]. Sunwha Cho et al. demonstrated a combination of endogenous SETDB1 and PML proteins from the cleavage stages of development in mice, and their colocalization at PML-NBs was also confirmed. SETDB1 was found to harbor dual functions in this complex. On the one hand, as a necessary part to maintain the structural integrity of PML-NB, SETDB1 physically interacts with the PML protein with its SIM motif [77,78]. On the other hand, SETDB1 acts as a transcriptional regulator of PML-NB-associated genes. The researchers discovered that SETDB1 occupies the promoter of *inhibitor of DNA binding 2 (ID2)* and methylates H3K9 to prevent *ID2* binding to RNA polymerase II, through which it suppresses ID2 expression. This inhibitory progress also depends on the integrity of the PML-NB structure [77,78]. SETDB1-mediated local heterochromatin formation involves a self-reinforcing mechanism: SETDB1-produced H3K9me3 marks recruit HP1 to localize at PML-NB foci [79]. With the aid of HP1, SETDB1 forms a solid platform of heterochromatin to which PML-NB can be riveted [78]. Above all, SETDB1 not only maintains the structure of PML-NB, but also represses the expression of PML-NB-associated genes such as *ID2* by trimethylating specific gene locus.

3.5. X chromosome inactivation by SETDB1-ATF7IP-MBD1 complex

X-Chromosome inactivation (XCI), an epigenetic silence caused by heterochromatin formation during the early phase of female mammalian embryonic development, is maintained throughout the lifetime of somatic cells [38].

According to many studies, the accumulation of lncRNA Xist on the X chromatin is the master factor leading to the initiation and maintenance of XCI [80-82]. Interestingly, SETDB1 was also discovered to be related to XCI [38,83]. SETDB1 is the most required methyltransferase to silence approximately 150 genes, which facilitates gene silencing and maintains XCI by alternating the conformation of the whole inactive X chromosome [84]. Minkovsky et al. suggested that during XCI, *activating transcription factor 7 interacting protein (ATF7IP or MCAF1)*, as a bridging factor, interacts with both SETDB1 and the transcriptional repressor domain of MBD1 to form the transcriptional repressor complex SETDB1-ATF7IP-MBD1, which leads to histone H3K9 trimethylation on the inactive X chromosome (Xi) [38,85]. Additional studies confirmed that the formation of the MBD1-*chromatin assembly factor-1 (CAF-1)* chaperone complex initiates the formation of the transcriptional repressive complex by mediating SETDB1 recruitment to the large subunit of CAF-1 [78,87,88] and maintaining XCI in somatic cells [38,89]. H3K9me3, considered a marker of heterochromatin [77], was enriched at the intergenic, poor gene and repetitive regions of Xi. The heterochromatin structure is inherited during DNA replication through association with MBD1 and ATF7IP [88].

Recently, the location of SETDB1 inside the nucleus was discovered to be mediated by ATF7IP, which increases the ubiquitination of SETDB1 to promote its enzymatic activity [90-92]. The fibronectin type-III (FNIII) domain of ATF7IP plays a certain role in the transcriptional repression function mediated by the SETDB1-ATF7IP complex. However, the FNIII domain seems to be unrelated to the nuclear localization of SETDB1 and to the ATF7IP-dependent integrated retroviral transgenes silencing [92]. Above all, by alternating the conformation of X chromosome through SETDB1-ATF7IP-MBD1 complex, SETDB1 also plays an important role in XCI.

3.6. Remodelling of chromatin associated with SETDB1 expression

In protein posttranscriptional modification, histone methyltransferases regulate the folding and remodelling of chromatin by modifying the N-tail of histones [42]. SETDB1 is a histone H3K9-specific methyltransferase that associates with various transcription factors to regulate gene expression via chromatin remodelling, reflecting that SETDB1 is closely related to chromatin modification and heterochromatin formation [20,93,94]. Recently, some studies reported that the master silencing factor KAP1 recruits other factors to establish interstitial heterochromatin in mESCs, especially SETDB1 [55,94]. During the formation of the SETDB1-KRAB-KAP1 repressive complex mentioned above, the interaction between HP1α and KAP1 triggers the conversion of target foci from euchromatin to heterochromatin, thereby inhibiting gene expression [9,51]. H3K9 methyltransferases have also been confirmed to be the "gatekeepers" of chromatin condensation. Methylated H3K9 can recruit H1 linker histones and HP1, while the localization of histone H1 is associated with the gliding of nucleosomes [95]. In addition, SETDB1 can also combine with DNMTs or HDACs to remodel the chromatin structure [96]. Many studies have confirmed that SETDB1 plays an essential role in chromatin remodelling, especially heterochromatin formation, through interacting with other factors and its H3K9 methylation function.

3.7. Early embryo development associated with SETDB1

In mouse embryos, SETDB1 holds a prominent position in early development. SETDB1 dysfunction has been found to induce the earliest lethality around peri-implantation compared with other H3K9-specific HKMTs such as

SUV39h1 (nonessential) [97], G9a (die around day 9.5) [98], and GLP (die around day 9.5) [99]. Cho et al. found that SETDB1 discontinuously appears in the pronucleus after fertilization, and its expression in males is higher than its expression in females [100,101], indicating that SETDB1 may participate in the restructuring of sperm-derived chromatin [22,102]. The expression of SETDB1 turns to a diffuse pattern until the 2-cell stage [102] but temporarily fades in the 8-cell stage before reappearing in a spotted form again in the blastocyst [77,103]. During the blastocyst phase, restored SETDB1 localizes to PML-NB foci [103] and is expressed equally in the inner cell mass (ICM) and trophectoderm (TE) cells.SETDB1 is then expressed only in the ICM during the blastocyst outgrowth phase [102]. The varying expression patterns of SETDB1 during the preimplantation stage suggest crucial functions of SETDB1 in mouse early embryonic development. The catalytic activity of SETDB1 is necessary in meiosis and early oogenesis, without it, a decrease in the number of mature eggs as a result [104,105].

3.8. Embryonic stem cell development associated with SETDB1

Blastocysts comprise ICM and TE cells. The punctate pattern of SETDB1, as mentioned in *2.7.*, was only expressed in ICM-derived Oct4-positive cells during the blastocyst outgrowth phase. Furthermore, ESCs can be established *in vitro* by extended culture of ICM cells [78], which is consistent with the result that SETDB1-null blastocysts fail to give rise to ESCs *in vitro* [106], suggesting the pivotal role of SETDB1 in the establishment and/or maintenance of ESCs.

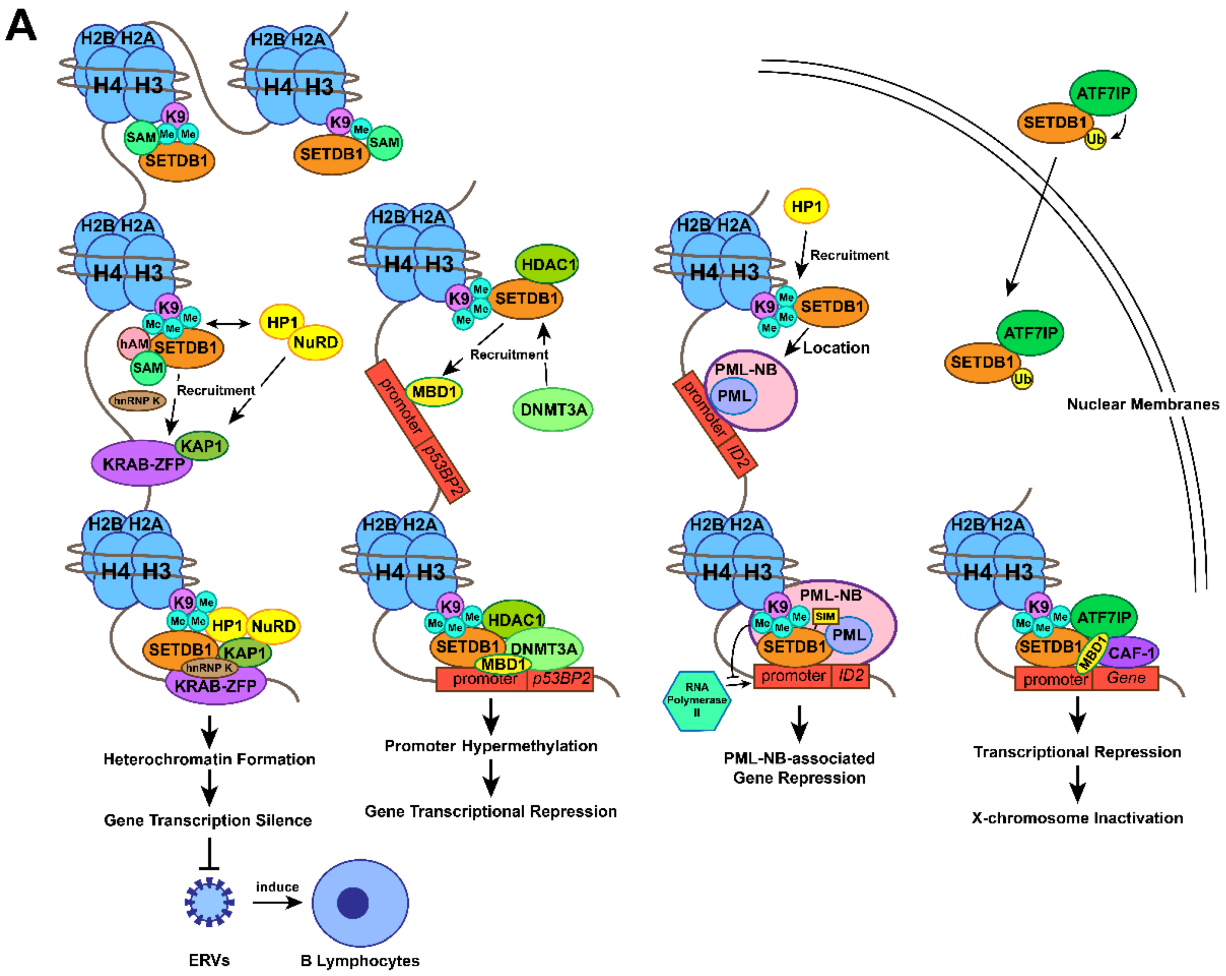
SETDB1 was found to maintain the pluripotency of mESCs by repressing differentiation-associated genes [78] and trophoblastic genes [107]. Conditional knockout of SETDB1 in mESCs induced the expression of trophectoderm differentiation markers such as *caudal type homeobox 2 (Cdx2)*, *transcription factor AP-2 alpha (Tcfap2a)*, and *heart and neural crest derivatives expressed 1 (Hand1)* [108]. Additional data found that SETDB1 interacts with Oct4, which in turn recruits SETDB1 to silence trophoblast-associated genes. These findings demonstrate that SETDB1 restricts the extraembryonic trophoblast lineage potential of pluripotent cells [108]. Recently, a study demonstrated that SETDB1 restricts the transition from pluripotency to totipotency in ESCs by silencing ERV and relevant genes [109]. SETDB1 is also essential to mESC self-renewal [107,110,111]. Lack of SETDB1 resulted in downregulation of *Nanog*, *SRY-box 2 (Sox2)* and *POU class 5 homeobox 1 (Pou5f1) genes* associated with *induced pluripotent stem cell (iPSC)* reprogramming and positive regulation of pluripotency and self-renewal of mESCs [108].

A recent study demonstrated that the H3K9 methylation reader M-phase phosphoprotein 8 (MPP8) cooperates with SETDB1 physically and functionally to coregulate a great number of common genomic targets, especially the DNA satellite, which silences satellite DNA repeats in mESCs [85].

4. Brief summary of the functions of SETDB1

Herein, we summarize the SETDB1 function as shown in Figure 1A. As mentioned above, SETDB1 primarily represses gene expression with chromatin remodelling based on its methyltransferase activity at H3K9, through which it exerts various functions, including ERVs silencing [72,73], XCI [38,83] and tumour-suppressive genes

repression [1,76]. When SAM is available, SETDB1 could deliver its H3K9 trimethylation function with the help of hAM [6,10,44]. During the process of ERVs silencing, KRAB-ZFP initiates the formation of the transcriptional repressive complex by recruiting KAP1 to the target [58]. With the recruitment of other factors and construction of H3K9 trimethylation, it induces heterochromatin formation and ERVs silencing [9,37]. During the process of *p53BP2* repression, MBD1 mediates the recruitment of SETDB1 while SETDB1 facilitates H3K9 trimethylation and the recruitment of DNMT3A, which associates histone methylation and enhanced DNA methylation [1]. SETDB1 can also associate with PML-NB complex and repress the expression of PML-NB-associated genes with cooperation of HP1 [77,78]. In the context of XCI, MBD1 initiates the recruitment of SETDB1 to CAF-1 [78,87,88], and the formation of SETDB1-ATF7IP-MBD1 promotes XCI [38,85] (Figure 1A). Moreover, SETDB1 is essential to early embryo development, whose expression patterns vary during the preimplantation stage [77,102,103]. In blastocyst outgrowth phase, the interaction between SETDB1 and Oct4 in mESCs recruits SETDB1 to silence differentiation-associated and trophoblast-associated genes, through which SETDB1 maintains the pluripotency of mESCs [78,107,108]. Lack of SETDB1 in mESCs was found to induce the expression of trophectoderm differentiation markers [108] and downregulate the genes associated with iPSC reprogramming and self-renewal [107,110,111] (Figure 1B).



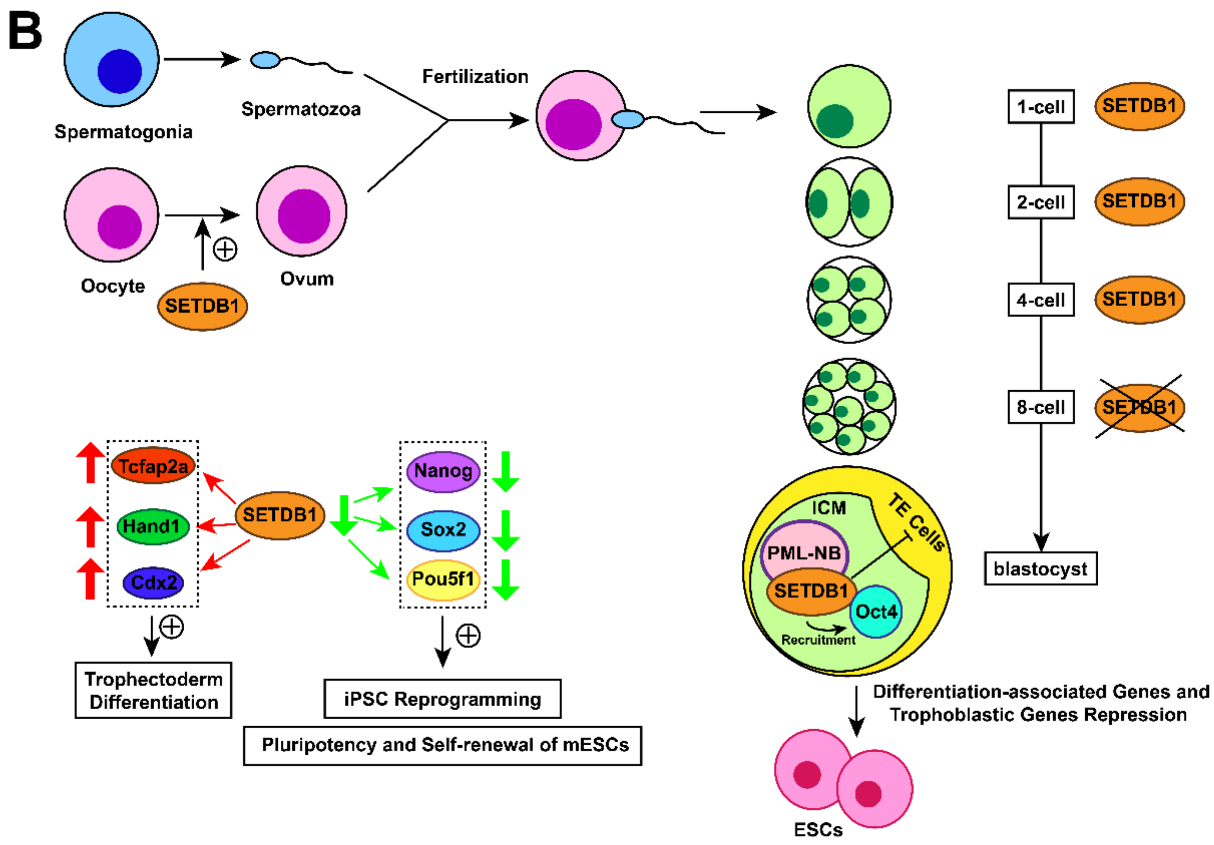


Figure 1. Action mechanisms and the subsequent functions of SETDB1 with its cofactors. (**A**) Together with H3K9 trimethylation on specific gene locus, the formation of SETDB1-KRAB-KAP1, SETDB1-DNMT3A, SETDB1-PML, SETDB1-ATF7IP-MBD1 complexes play crucial roles in the processes of histone methylation, chromatin remodelling and transcriptional suppression, which leads to corresponding physiological functions, including ERVs silencing, XCI and tumour-suppressive genes repression. (**B**) SETDB1 exerts different roles during the preimplantation stage due to its varying expression patterns. It maintains the pluripotency of mESCs by repressing differentiation-associated and trophoblastic genes while facilitating self-renewal by positively regulating the genes associated with iPSC reprogramming and self-renewal.

References

1. Li, H.; Rauch, T.; Chen, Z.X.; Szabó, P.E.; Riggs, A.D.; Pfeifer, G.P. The histone methyltransferase SETDB1 and the DNA methyltransferase DNMT3A interact directly and localize to promoters silenced in cancer cells. J. Biol. Chem. 2006, 281, 19489–19500.
2. Cruz-Tapias, P.; Zakharova, V.; Perez-Fernandez, O.M.; Mantilla, W.; RamÍRez-Clavijo, S.; Ait-Si-Ali, S. Expression of the Major and Pro-Oncogenic H3K9 Lysine Methyltransferase SETDB1 in Non-Small Cell Lung Cancer. Cancers 2019, 11, 1134.

3. Jambhekar, A.; Dhall, A.; Shi, Y. Roles and regulation of histone methylation in animal development. Nat. Rev. Mol. Cell Biol. 2019, 20, 625–641.
4. Yu, C.; Zhuang, S. Histone Methyltransferases as Therapeutic Targets for Kidney Diseases. Front. Pharmacol. 2019, 10, 1393.
5. Bedford, M.T.; Richard, S. Arginine methylation an emerging regulator of protein function. Mol. Cell 2005, 18, 263–272.
6. Hamamoto, R.; Saloura, V.; Nakamura, Y. Critical roles of non-histone protein lysine methylation in human tumorigenesis. Nat. Rev. Cancer 2015, 15, 110–124.
7. McGrath, J.; Trojer, P. Targeting histone lysine methylation in cancer. Pharmacol. Ther. 2015, 150, 1–22.
8. Saha, N.; Muntean, A.G. Insight into the multi-faceted role of the SUV family of H3K9 methyltransferases in carcinogenesis and cancer progression. Biochim. Biophys. Acta Rev. Cancer 2021, 1875, 188498.
9. Schultz, D.C.; Ayyanathan, K.; Negorev, D.; Maul, G.G.; Rauscher, F.J., 3rd. 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. 2002, 16, 919–932.
10. Wang, H.; An, W.; Cao, R.; Xia, L.; Erdjument-Bromage, H.; Chatton, B.; Tempst, P.; Roeder, R.G.; Zhang, Y. mAM facilitates conversion by ESET of dimethyl to trimethyl lysine 9 of histone H3 to cause transcriptional repression. Mol. Cell 2003, 12, 475–487.
11. Sun, Q.Y.; Ding, L.W.; Xiao, J.F.; Chien, W.; Lim, S.L.; Hattori, N.; Goodglick, L.; Chia, D.; Mah, V.; Alavi, M.; et al. SETDB1 accelerates tumourigenesis by regulating the WNT signalling pathway. J. Pathol. 2015, 235, 559–570.
12. Rodriguez-Paredes, M.; Martinez de Paz, A.; Simó-Riudalbas, L.; Sayols, S.; Moutinho, C.; Moran, S.; Villanueva, A.; Vázquez-Cedeira, M.; Lazo, P.A.; Carneiro, F.; et al. Gene amplification of the histone methyltransferase SETDB1 contributes to human lung tumorigenesis. Oncogene 2014, 33, 2807–2813.
13. Wang, G.; Long, J.; Gao, Y.; Zhang, W.; Han, F.; Xu, C.; Sun, L.; Yang, S.C.; Lan, J.; Hou, Z.; et al. SETDB1-mediated methylation of Akt promotes its K63-linked ubiquitination and activation leading to tumorigenesis. Nat. Cell Biol. 2019, 21, 214–225.
14. Chen, B.; Wang, J.; Wang, J.; Wang, H.; Gu, X.; Tang, L.; Feng, X. A regulatory circuitry comprising TP53, miR-29 family, and SETDB1 in non-small cell lung cancer. Biosci. Rep. 2018, 38.

15. Bueno, R.; Stawiski, E.W.; Goldstein, L.D.; Durinck, S.; De Rienzo, A.; Modrusan, Z.; Gnad, F.; Nguyen, T.T.; Jaiswal, B.S.; Chirieac, L.R.; et al. Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. Nat. Genet. 2016, 48, 407–416.
16. Hmeljak, J.; Sanchez-Vega, F.; Hoadley, K.A.; Shih, J.; Stewart, C.; Heiman, D.; Tarpey, P.; Danilova, L.; Drill, E.; Gibb, E.A.; et al. Integrative Molecular Characterization of Malignant Pleural Mesothelioma. Cancer Discov. 2018, 8, 1548–1565.
17. Kang, H.C.; Kim, H.K.; Lee, S.; Mendez, P.; Kim, J.W.; Woodard, G.; Yoon, J.H.; Jen, K.Y.; Fang, L.T.; Jones, K.; et al. Whole exome and targeted deep sequencing identify genome-wide allelic loss and frequent SETDB1 mutations in malignant pleural mesotheliomas. Oncotarget 2016, 7, 8321–8331.
18. Yoshikawa, Y.; Emi, M.; Nakano, T.; Gaudino, G. Mesothelioma developing in carriers of inherited genetic mutations. Transl. Lung Cancer Res. 2020, 9, S67–S76.
19. Torricelli, F.; Lococo, F.; Di Stefano, T.S.; Lorenzini, E.; Piana, S.; Valli, R.; Rena, O.; Veronesi, G.; Billè, A.; Ciarrocchi, A. Deep Sequencing Analysis Identified a Specific Subset of Mutations Distinctive of Biphasic Malignant Pleural Mesothelioma. Cancers 2020, 12, 2454.
20. Karanth, A.V.; Maniswami, R.R.; Prashanth, S.; Govindaraj, H.; Padmavathy, R.; Jegatheesan, S.K.; Mullangi, R.; Rajagopal, S. Emerging role of SETDB1 as a therapeutic target. Expert Opin. Ther. Targets 2017, 21, 319–331.
21. Strepkos, D.; Markouli, M.; Klonou, A.; Papavassiliou, A.G.; Piperi, C. Histone Methyltransferase SETDB1: A Common Denominator of Tumorigenesis with Therapeutic Potential. Cancer Res. 2021, 81, 525–534.
22. Yu, L.; Ye, F.; Li, Y.Y.; Zhan, Y.Z.; Liu, Y.; Yan, H.M.; Fang, Y.; Xie, Y.W.; Zhang, F.J.; Chen, L.H.; et al. Histone methyltransferase SETDB1 promotes colorectal cancer proliferation through the STAT1-CCND1/CDK6 axis. Carcinogenesis 2020, 41, 678–688.
23. Bernardi, R.; Pandolfi, P.P. Structure, dynamics and functions of promyelocytic leukaemia nuclear bodies. Nat. Rev. Mol. Cell Biol. 2007, 8, 1006–1016.
24. de Thé, H.; Le Bras, M.; Lallemand-Breitenbach, V. The cell biology of disease: Acute promyelocytic leukemia, arsenic, and PML bodies. J. Cell Biol. 2012, 198, 11–21.
25. Groh, S.; Schotta, G. Silencing of endogenous retroviruses by heterochromatin. Cell. Mol. Life Sci. 2017, 74, 2055–2065.
26. Goodier, J.L. Restricting retrotransposons: A review. Mob. DNA 2016, 7, 16.
27. Murry, C.E.; Keller, G. Differentiation of embryonic stem cells to clinically relevant populations: Lessons from embryonic development. Cell 2008, 132, 661–680.

28. Matsui, T.; Leung, D.; Miyashita, H.; Maksakova, I.A.; Miyachi, H.; Kimura, H.; Tachibana, M.; Lorincz, M.C.; Shinkai, Y. Proviral silencing in embryonic stem cells requires the histone methyltransferase ESET. Nature 2010, 464, 927–931.
29. Minkovsky, A.; Sahakyan, A.; Rankin-Gee, E.; Bonora, G.; Patel, S.; Plath, K. The Mbd1-Atf7ip-Setdb1 pathway contributes to the maintenance of X chromosome inactivation. Epigenet. Chromatin 2014, 7, 12.
30. Li, F.; Ye, B.; Hong, L.; Xu, H.; Fishbein, M.C. Epigenetic modifications of histone h4 in lung neuroendocrine tumors. Appl. Immunohistochem. Mol. Morphol. AIMM 2011, 19, 389–394.
31. Fischle, W.; Wang, Y.; Allis, C.D. Histone and chromatin cross-talk. Curr. Opin. Cell Biol. 2003, 15, 172–183.
32. Herz, H.M.; Garruss, A.; Shilatifard, A. SET for life: Biochemical activities and biological functions of SET domain-containing proteins. Trends Biochem. Sci. 2013, 38, 621–639.
33. Barski, A.; Cuddapah, S.; Cui, K.; Roh, T.Y.; Schones, D.E.; Wang, Z.; Wei, G.; Chepelev, I.; Zhao, K. High-resolution profiling of histone methylations in the human genome. Cell 2007, 129, 823–837.