

REVIEW

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# Tackling malignant melanoma epigenetically: histone lysine methylation

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## Abstract

Post-translational histone modifications such as acetylation and methylation can affect gene expression. Histone acetylation is commonly associated with activation of gene expression whereas histone methylation is linked to either activation or repression of gene expression. Depending on the site of histone modification, several histone marks can be present throughout the genome. A combination of these histone marks can shape global chromatin architecture, and changes in patterns of marks can affect the transcriptomic landscape. Alterations in several histone marks are associated with different types of cancers, and these alterations are distinct from marks found in original normal tissues. Therefore, it is hypothesized that patterns of histone marks can change during the process of tumorigenesis.

This review focuses on histone methylation changes (both removal and addition of methyl groups) in malignant melanoma, a deadly skin cancer, and the implications of specific inhibitors of these modifications as a combinatorial therapeutic approach.

**Keywords:** Histone methylation, Melanoma, Epigenetics, Histone demethylase, Histone methyltransferase, Small molecule inhibitor

## Background

### Histone modifications

The nucleosome, the fundamental structural unit of chromosomes, is composed of two copies each of four core histones (i.e., H2A, H2B, H3, and H4), around which 147 bp of DNA is coiled [1, 2]. N-terminal tails of histone polypeptides can be altered by a variety of post-translational modifications, including methylation, acetylation, phosphorylation, ubiquitylation, glycosylation, ADP-ribosylation, carbonylation, and SUMOylation (collectively known as histone modifications) [3–6]. The acetylation of histones is controlled by the balanced action of histone acetyltransferases (HATs) and histone deacetylases (HDACs). Acetylated histones have been associated with actively expressed genes. However, histone methylation may have both repressive (H3K9, H3K27) or enhancing (H3K4) effects on transcription, depending

on the residue that is modified [7]. Histone methylation can occur on lysine and/or arginine residues. Lysine residues at various positions along the histone N-terminal tail are common sites for methylation (Fig. 1). Lysine (K) methylation occurs by stepwise addition of one to three methyl groups, which can lead to unique functions of a genomic region. This stepwise conversion, from an unmethylated to a trimethylated lysine residue, is facilitated by histone methyltransferases (writers), and the backward demethylation process is catalyzed by histone demethylases (erasers). Further, a group of proteins (readers) recognize methyl-lysines throughout the genome [8]. Epigenetic changes along with genetic alterations can determine cell fate, either to maintain cell homeostasis or to promote tumorigenesis. Because epigenetic changes are reversible, understanding such changes is of crucial significance for drug development and exploring therapeutic strategies [9].

Several histone methylation alterations are known to play a role in the transition of melanocytes to melanoma cells. These alterations are the consequence of deregulation of their corresponding enzymes. In this review, we focus on major erasers and writers of histone lysine

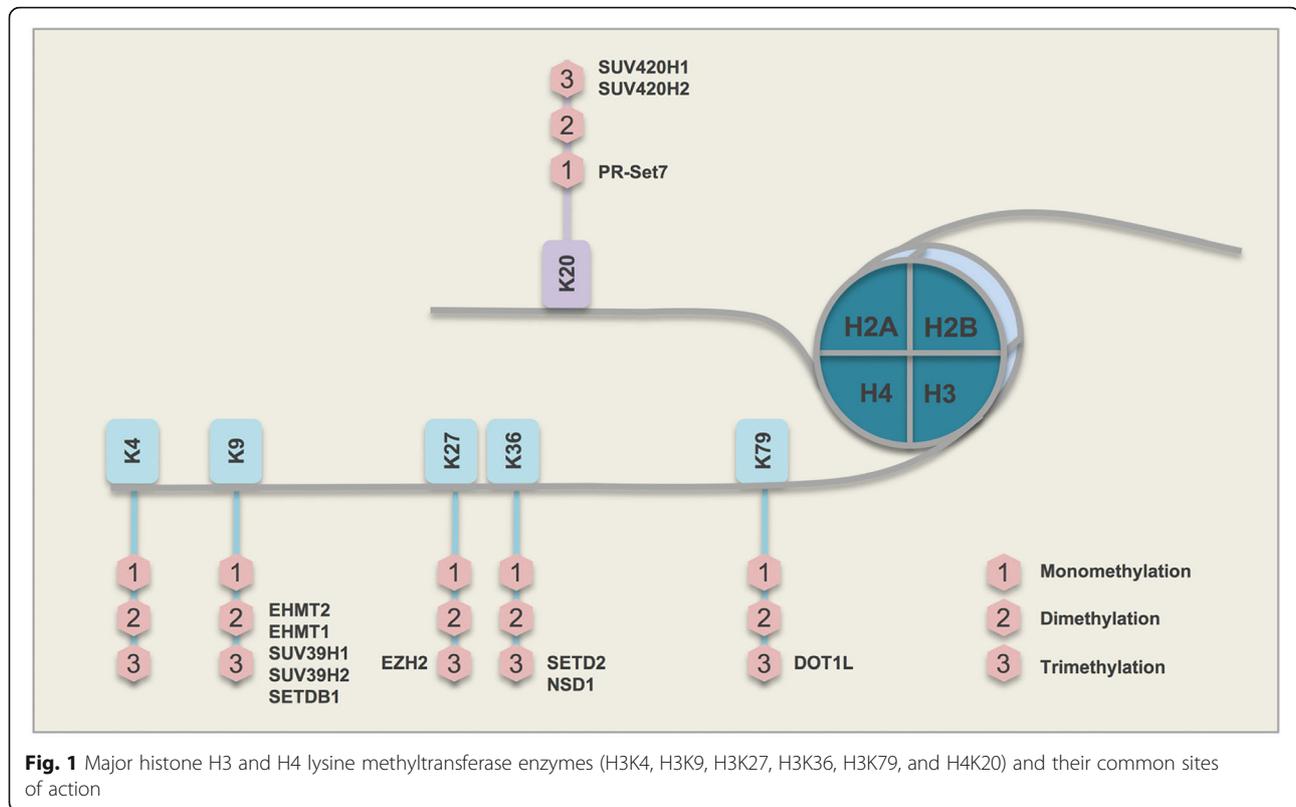
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methylation as regulated via two categories of demethylase and methyltransferase enzymes and discuss compounds available to target these enzymes and reverse their impact.

## Main body

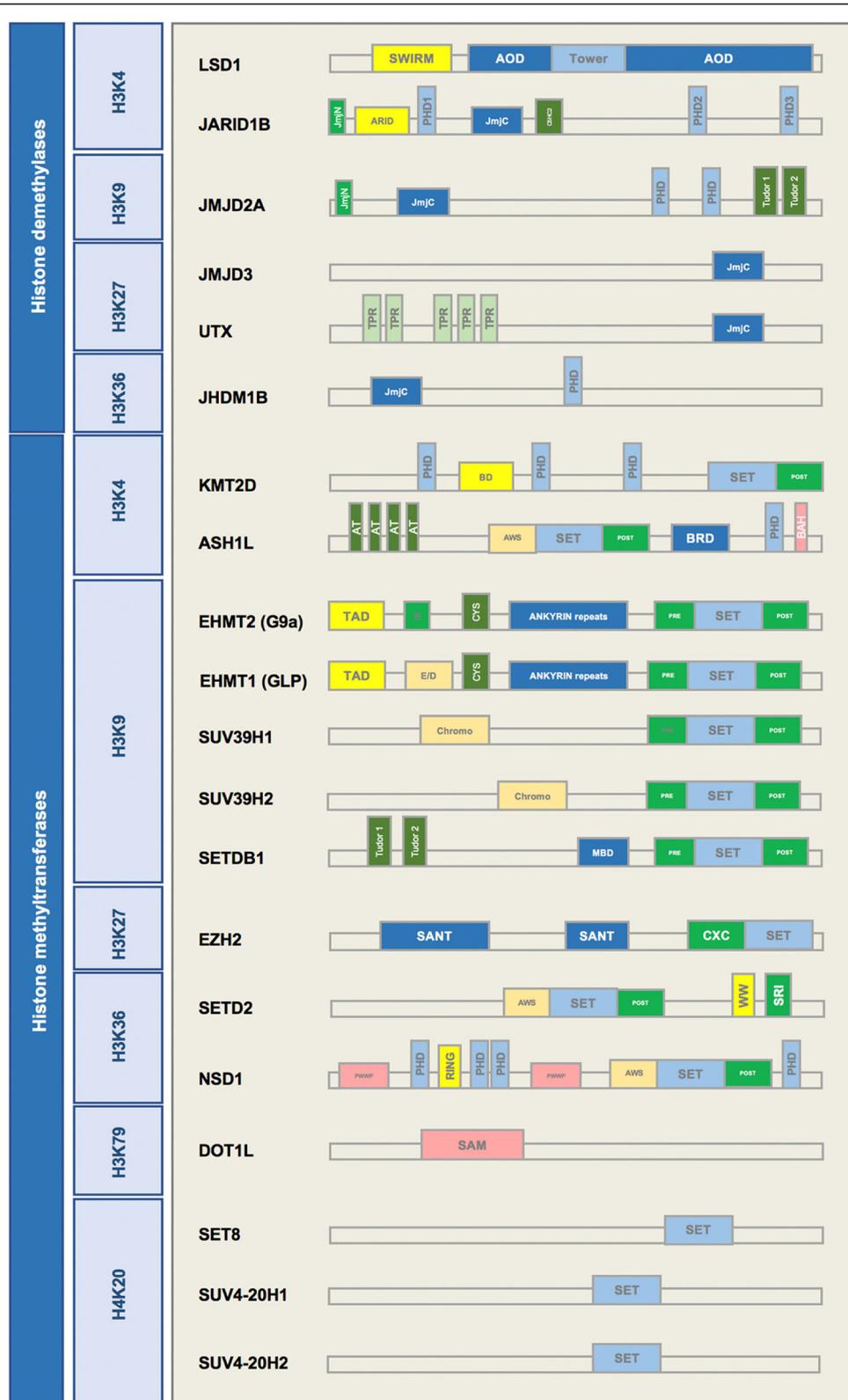
### Histone demethylases

#### *JARID1B* (H3K4-demethylase)

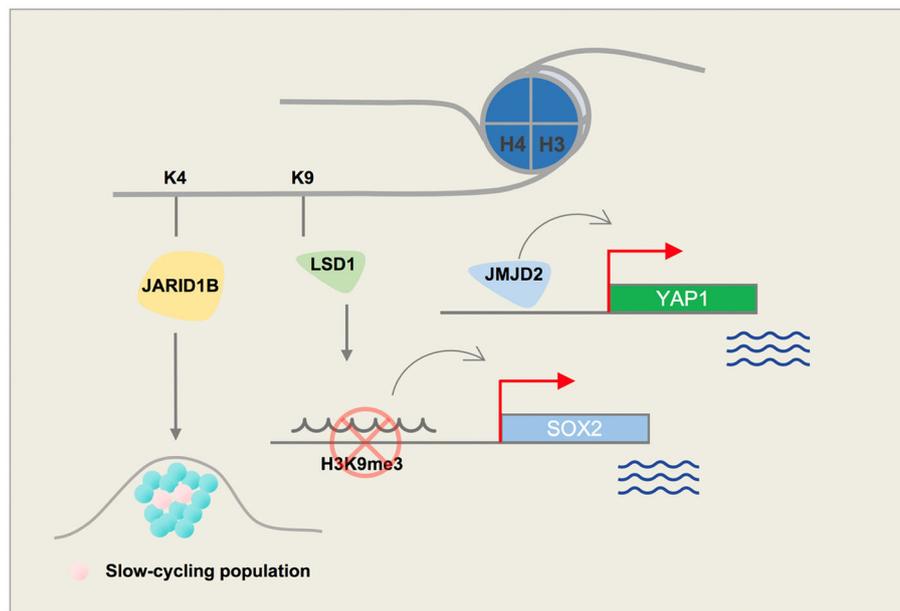
Several enzymes demethylate histone 3 at the position 4 lysine residue. One such enzyme, H3K4 demethylase JARID1B (PLU-1, KDM5B), plays a role in the development of melanoma, and regulates gene transcription and cell differentiation [10]. It has three plant homeodomain (PHD) finger domains in its structure (Fig. 2). PHD fingers are approximately 50–80 aa long and are usually involved in chromatin-mediated gene regulation. Two of these PHD fingers in JARID1B can bind to histones. JARID1B binds to its substrate through distinct PHD fingers. Finger PHD1 is highly specific for unmethylated H3K4 (H3K4me<sub>0</sub>). PHD3 is more specific to H3K4me<sub>3</sub> [11]. The H3K4 demethylase JARID1B is highly expressed in nevi but not in melanoma; however, it marks a small subpopulation of melanoma cells that can cycle very slowly throughout the tumor mass and is essential for continuous tumor growth [12, 13] (Fig. 3). Interestingly, different treatments, including BRAF inhibitors (e.g., vemurafenib) as well as cytotoxic agents (e.g., cisplatin), lead to enrichment of slow-cycling,

long-lasting melanoma tumor cells that express H3K4-demethylase JARID1B [14]. Eliminating this subpopulation of tumor cells might help overcome resistance to conventional treatments.

Treatment of melanoma tumors with MAPK inhibitors increases the H3K4 demethylase JARID1B-positive subpopulation of melanoma cells [15]. These cells are slow-cycling and treatment-resistant. Thus, in addition to curbing tumor growth with MAPK inhibitor, a supplementary agent is needed to effectively treat this subpopulation of cells. Several compounds inhibit JARID1B activity. KDM5-C49 is a potent inhibitor of the JARID1 enzyme family; however, its cellular permeability is limited. Therefore, KDM5-C70 was developed to be used in cellular assays and in vivo [16]. KDM5-C70 inhibits myeloma cells, increasing levels of H3K4me<sub>3</sub> at the whole genome level [16]. 2,4-PDCA (2,4-pyridinedicarboxylic acid) acts in vitro to inhibit JARID1B and KDM4 demethylases. A high throughput screen of >15,000 compounds conducted to identify inhibitors of JARID1B confirmed the activity of 2,4-PDCA and also revealed a novel compound, 2-(4-(4-methylphenyl)-1,2-benzisothiazol-3(2H)-one) (PBIT) that can effectively inhibit JARID1B in vitro with no activity toward H3K27 demethylases, UTX or JMJD3 [17]. KDOAM-25 was recently introduced as a potent and selective JARID1 inhibitor with the ability to impact multiple myeloma cells [18].



**Fig. 2** Schematic structures of histone lysine demethylases (H3K4, H3K9, H3K27, H3K36), histone lysine methyltransferases (H3K4, H3K9, H3K27, H3K36, H4K20) with SET domain, and histone methyltransferases without the SET domain (H3K79)



**Fig. 3** Schematic figure demonstrating key roles of histone lysine demethylases (H3K4 and H3K9) in melanoma

#### **LSD1 (H3K4-demethylase | H3K9-demethylase)**

H3K4 methyl groups can also be removed by members of the LSD (lysine-specific histone demethylase) family [19, 20]. LSD1, also known as KDM1A, demethylates histone 3 on lysine residues at positions 4 and 9 (H3K4 and H3K9). LSD1 specifically removes 1 or 2 methyl groups from H3K4me<sub>2</sub>, converting it to H3K4me<sub>1/0</sub>. Monomethylation of H3K4 is a histone modification that marks enhancers throughout the genome. The histone demethylase role of LSD1 could change the gene transcription status by generating a H3K4me<sub>1</sub> mark and activating enhancers, or by removing another methyl group and generating unmethylated H3K4. LSD1 has a SWIRM domain and 2 amino oxidase domains (AODs) in its structure (Fig. 2). A SWIRM domain is usually present in proteins with a role in chromatin remodeling and in expression of genes such as SMARC2 and SWI3.

LSD1 can bind to both gene promoters and distal elements. This feature of LSD1 is in line with its demethylation role on H3K4 (promoter) as well as H3K9 (distal) [21]. Trimethylated H3K9 is a well-known heterochromatin mark, which often highlights closed chromatin regions and is present on distal regions of genes. H3K9me<sub>3</sub>-active demethylase LSD1 is reported to disable senescence in melanocytes. Senescence halts the proliferation of melanocytes and further progression to melanoma cells; this role of LSD1 may cause Ras/Braf-induced transformation. Yu Y. et al. showed that enforced LSD1 expression *in vivo* can promote BRAF<sup>V600E</sup>-driven melanomagenesis [22]. Differentiated melanoma cells have an elevated level of H3K9 methylation. The presence of this repressive histone mark

at the promoter region of pluripotency marks (e.g., SOX2) can inhibit expression that is essential to maintaining self-renewal and tumorigenicity. The H3K9 demethylase activity of LSD1 can epigenetically control SOX2 transcription and thus maintain cancer stem cell pluripotency [23, 24] (Fig. 3).

Depletion of histone demethylase LSD1 in cancer cells increases repetitive element expression that can stimulate anti-tumor T cell immunity and inhibit tumor growth [25]. LSD1 inhibition also suppresses colony formation and the growth of melanoma xenografts; LSD1 has not yet been pharmacologically targeted for treatment of melanoma [26].

Several known inhibitors of LSD1 have been identified, one of which is GSK2879552. This small molecule is an irreversible, selective, orally bioavailable inhibitor of LSD1. Anti-proliferative effects of this inhibitor have been reported in small cell lung carcinoma (SCLC) [27]. LSD1 interacts with pluripotency factors in human embryonic stem cells (hESCs) and is also critical for hematopoietic differentiation. Several studies have reported on effects of LSD1 inhibitors on hematological malignancies. In acute myeloblastic leukemia (AML) cell lines, GSK2879552 treatment inhibited proliferation [28, 29]. Treatment of neuroblastoma or breast cancer cell lines with tranlycypromine (TCP), another LSD1 inhibitor, or its analogs also resulted in the inhibition of cell proliferation [30]. Although LSD1 inhibition does not affect global levels of H3K4me<sub>1/2</sub>, its impact is observed near the TSS of LSD1 target genes. In GBM cell lines, the combination of TCP and an HDAC inhibitor led to a synergistic increase of apoptosis

[30]. Recently, compound S2101, a new LSD1 inhibitor, is shown to have a greater effect than TCPs. Several other LSD1 inhibitors including T-3775440, NCD38, and RN1 are in pre-clinical stages of investigation [31–34].

#### ***JMJD2A (H3K9-demethylase | H3K36-demethylase)***

H3K9/36me3 lysine demethylase JMJD2A (KDM4A) overexpression leads to copy gain of certain loci in chromosomes without global chromosome instability. JMJD2A-amplified tumors demonstrate copy gains for these regions [35]. Histone demethylase JMJD2A is involved in regulation of cell proliferation, interacts with RNA polymerase I, and is associated with active ribosomal RNA genes. Cellular localization of JMJD2A is controlled through the PI3K signaling pathway [36]. JMJD2A upregulation is observed in various cancers including the breast, colon, lung, and prostate [37–40]. Its overexpression in prostate cancer is positively correlated with tumor metastasis. ETV1 recruits JMJD2A to the YAP1 (a Hippo pathway component) promoter, leading to changes in histone lysine methylation in prostate cancer cells [40]. Yap1 also promotes melanoma metastasis through its TEAD-interaction domain [41]. A potential mechanism for this activity could be recruitment of JMJD2A to the Yap1 promoter, thus modulating its methylation (Fig. 3). Interestingly, another member of the JMJD2 family, histone demethylase JMJD2C, is increased in a subset of melanoma patients and promotes growth of aggressive tumors with metastasis [22].

#### ***JMJD3 (H3K27-demethylase)***

H3K27 demethylase JMJD3 (KDM6B) plays a key role in transcriptional elongation and cell differentiation. Complexes of JMJD3 and proteins involved in transcriptional elongation, demethylate H3K27me3 on their target genes. This demethylation can abolish transcriptional repression of genes initially maintained by a H3K27me3 mark. JMJD3 modulates melanoma tumor microenvironment and promotes tumor progression and metastasis. JMJD3 does not alter proliferation in melanoma cells but does enhance other tumorigenic features of melanoma cells such as clonogenicity, self-renewal, and trans-endothelial migration. JMJD3 also promotes angiogenesis and macrophage recruitment [42]. Finally, JMJD3 can neutralize polycomb-mediated silencing at the INK4b-ARF-INK4a locus in melanoma. JMJD3 expression is upregulated in melanocytic nevi in response to oncogenic RAS signaling that leads to oncogenic-induced senescence [43, 44].

#### ***UTX (H3K27-demethylase)***

Another mechanism of tumorigenesis is the activity of polycomb repressive complex 2 (PRC2). Any disruption in this complex can inhibit this process. Mutations in histone methyltransferase MLL3 (a subunit of the COMPASS

complex with H3K4me1 methyltransferase activity) or BAP1 (a tumor suppressor) in cancer cells can inhibit H3K27 demethylase UTX and MLL3 recruitment to gene enhancers. Thus, inhibition of H3K27 methyltransferase PRC2 in these cells can restore normal transcription patterns [45]. A recent study proposed a mechanism for the role of UTX in suppressing myeloid leukemogenesis through deregulation of ETS and GATA programs [46]. H3K27-demethylase UTX activates gene transcription in melanoma at sites with poised promoters that are marked with trimethylated H3K27. Recruitment of UTX and another activating histone modifier, P300, is promoted through MEK1-mediated phosphorylation of RNF2 [47], indicating that UTX-mediated histone demethylation is a histone modification that may activate melanomagenesis.

GSK-J1 is a selective inhibitor of H3K27 demethylases JMJD3 and UTX and is inactive against a panel of other demethylases in JMJD family [48]. GSK-J4 is an ethyl ester pro-drug produced by masking the polarity of acidic groups of GSK-J1. GSK-J4 administration increases total nuclear H3K27me3 levels in cells [48]. High throughput screening of epigenetic compounds revealed sensitivity of neuroblastoma tumor cells to GSK-J4, a dual inhibitor of H3K27 demethylases UTX and JMJD3 [49].

#### ***JHDM1B (H3K36-demethylase | H3K79-demethylase)***

JHDM1B (KDM2B), which is a known H3K36 demethylase member of the Jumonji C family of proteins, also plays a role as an H3K79 demethylase and a transcriptional repressor via SIRT1-mediated chromatin silencing [50]. JHDM1B specifically recognizes non-methylated DNA in CpG islands and recruits the polycomb repressive complex 1 (PRC1) that is required for sustaining synovial sarcoma cell transformation [51, 52]. JHDM1B is found to be highly expressed in glioblastoma compared to normal brain tissue and regulates the apoptotic response of GBM cells to TNF-related apoptosis-inducing ligand [53]. JHDM1B also plays a major role early in the reprogramming process for generation of induced pluripotent stem cells [54]. JHDM1B contributes to embryonic neural development by regulating cell proliferation and cell death [55] and plays a key role in cellular senescence and tumorigenesis [56].

A concise schematic picture of the role of major histone lysine demethylases that are involved in melanoma is provided in Fig. 3, and a list of these enzymes along with their known inhibitors are shown in Table 1.

### **Histone methyltransferases**

#### ***H3K4 methyltransferases***

*KMT2D (MLL2)*. Monomethylation of H3K4 is a widely known feature of enhancers and gene promoters [57]. In mammals, KMT2D is part of a huge complex that induces monomethylation of promoter/enhancer regions [58, 59]. KMT2D is a member of the histone lysine

**Table 1** Histone lysine demethylases (KDMs) and their selective inhibitors

	Enzyme	Alias		Structure	Inhibitor	Reference
H3K4	LSD1	KDM1A	AOF2	SWIRM/AOD	GSK2879552 Tranylcypromine (TCP) Compound S2101 T-3775440 NCD38 OG-L002 RN1	[24–27]
	JARID1A	KDM5A	RBP2	PHD/ARID/ZF		
	JARID1B	KDM5B	PLU-1	PHD/ARID/ZF	KDM5-C49 KDM5-C70 2,4-PDCA PBIT KDOAM-25	[13–15]
	JARID1C	KDM5C	SMCX	PHD/ARID/ZF		
H3K9	JARID1D	KDM5D	SMCY	PHD/ARID/ZF		
	LSD1	KDM1A	AOF2	SWIRM/AOD		
	JMJD1A	KDM3A	JHDM2A	JmjC		
	JMJD1B	KDM3B	JHDM2B	JmjC		
	JMJD2A	KDM4A	JHDM3A	PHD/Tudor	2,4-PDCA	[14]
H3K27	JMJD2B	KDM4B	JHDM3B	PHD/Tudor		
	JMJD2C	KDM4C	JHDM3C	PHD/Tudor		
	UTX	KDM6A		TPR/JmjC	GSK-J1 GSK-J4	[41, 42]
H3K36	JMJD3	KDM6B		JmjC		
	FBXL11	KDM2A	JHDM1A	PHD/ZF/LRR		
	FBXL10	KDM2B	JHDM1B	PHD/ZF/LRR		
	JMJD2A	KDM4A	JHDM3A	PHD/Tudor		
	JMJD2B	KDM4B	JHDM3B	PHD/Tudor		
H4K20	JMJD2C	KDM4C	JHDM3C	PHD/Tudor		
	LSD1n		neuroLSD1			

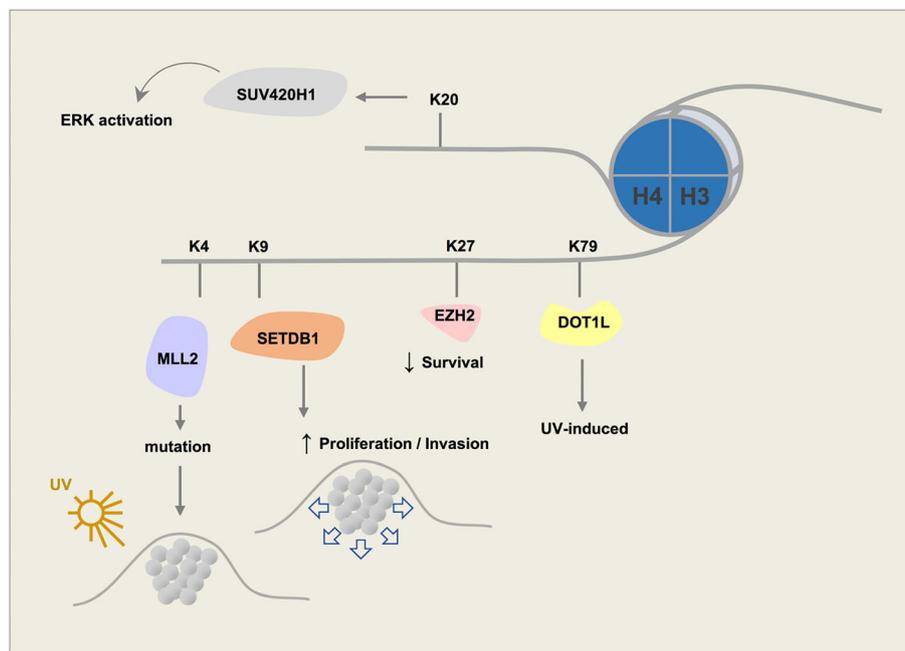
methyltransferase (HKMTase) family that can induce genome accessibility and transcription and promotes an open chromatin state. The Cancer Genome Atlas (TCGA) data reveal that KMT2D is mutated in 15% of melanoma patients. Despite no clear association in TCGA cases between KMT2D and conventional subtypes of melanoma such as NRAS or BRAF, a subsequent study showed that KMT2D deregulates specific enhancers and genes in NRAS-mutant melanoma [60]. KMT2D is encoded by genes with the highest number of UVB signature mutations [61] (Fig. 4).

H3K4me2 is also an active histone mark enriched in sites toward the 5'-end of transcribing genes and present in several melanoma cell lines. An increase in the level of H3K4me2 has been observed in melanoma samples compared to normal skin of the same patients [62]. Interestingly, H3K4me2 levels were found to be lower in metastatic melanoma compared to primary tumors [63].

H3K4me3 is generally associated with promoters of actively transcribing genes [64, 65] or with genes that are poised for activation. H3K4me3 is linked to promoter

activity. Global changes in H3K4me3 were observed in zebrafish when comparing melanoma and normal skin [66]. Comparison of metastatic to primary melanoma revealed that decreased levels of H3K4me3 in metastases are significantly associated with repressed expression of genes in embryonic stem cells (ESCs), including targets of PRC. Further, increased levels of H3K4me3 are associated with interferon and inflammatory response genes [59]. Finally, HDAC inhibitors that promote an open chromatin state also increase H3K4 trimethylation in vitro [67].

*ASH1L (ASH1, KMT2H)*. ASH1L is an H3K4/H3K36 methyltransferase. Nucleotide excision repair (NER) is a known mechanism to prevent formation of UV-induced melanoma tumors. The NER mechanism is in place upon recruitment of H3K4 histone methyltransferase ASH1L [68]. Loss of Ash1l leads to increased proliferation of keratinocytes [69]. ASH1L can act as an H3K36 dimethyltransferase to recruit MLL to chromatin and maintain hematopoiesis. This action supports a role of ASH1L in MLL-mediated leukemia oncogenesis and indicates that it could be a target for leukemia therapy [70].



**Fig. 4** Schematic figure demonstrating key roles of histone lysine methyltransferases involved in the tumorigenesis and survival of melanoma

WDR5 is an essential part of the KMT2 (MLL) complex that trimethylates H3K4. An interaction exists between this protein and the catalytic domains of KMT2. Despite the lack of chemical compounds that directly target the SET domain in KMT2 complexes, several compounds can specifically disrupt the interaction between WDR5 and MLL [71]. MM-102 specifically targets MLL-WDR5 interaction, inhibits cell growth, and induces apoptosis in leukemia cells [72]. MM-401 also specifically inhibits MLL activity by blocking MLL-WDR5 interaction [73]. A third compound, WDR5-0103, antagonizes the interaction of WDR5 with MLL by competing with MLL for their mutual binding site on WDR5 [74].

### H3K9 methyltransferases

Monomethylated H3K9 is shown to be enriched in the TSS of active genes [75]. Unlike H3K9me1, both di- and trimethylated H3K9 are often found in silenced genes; however, monomethylated H3K9 may also mark distinct regions of silent chromatin in the presence of a monomethylated H4K20 mark [76].

**EHMT.** Dimethylated H3K9 has a higher global level in melanoma samples compared to the normal skin tissue [62]. EHMT2 (G9A) mono- and dimethylates H3K9. Methylated H3K9 recruits HP1 proteins that cause transcriptional repression [77]. HP1 proteins harbor a methyl lysine binding chromodomain that binds to methylated H3K9 [78]. HP1 proteins in human cells include HP1 $\alpha$ ,  $\beta$ , and  $\gamma$  that play key roles in the formation of transcriptionally inactive heterochromatin. Interestingly, in several

cancer types (not including melanoma), inhibition of EHMT2 resulted in the arrest of cancer cell proliferation and a decrease in cell survival [79]. Another study proposed that G9A contributes to ovarian cancer metastasis [80]. EHMT1 (GLP) is also a histone methyltransferase that specifically mono- and dimethylates H3K9 in euchromatin.

**SUV39.** Three known members in this family have been identified. SUV39H1 is a histone methyltransferase that specifically trimethylates H3K9me1 and plays a crucial role in establishment of constitutive heterochromatin at pericentromeric and telomeric regions. Formation of various cancer types including rhabdomyosarcoma and melanoma are sensitive to the loss of SUV39H1 [81]. In differentiated melanoma cells, silencing SUV39H1 or the other H3K9 methyltransferase, G9A, can elevate their self-renewal capabilities [24]. SUV39H2, a second member of the family, has a similar structure to SUV39H1 (Fig. 2). SUV39H2 may play a role in higher order chromatin structure during spermatogenesis [82, 83]. SUV39H2 trimethylates histone lysine demethylase LSD1 and prevents degradation of this protein due to polyubiquitination, thus stabilizing its structure in the cell [84]. SETDB1 (ESET) is the third member of the SUV39 family of proteins. It is overexpressed in several cancers including human melanomas [85]. SUV39 proteins, unlike the HP1 chromodomain of the EHMT complex that shows high affinity for dimethyl, prefer the trimethyl state [86]. Hence, histone lysine methyltransferase SETDB1 also primarily trimethylates H3K9. SETDB1 is known to accelerate melanoma

progression [85] (Fig. 4). Previously, SETDB1 was reported to be highly amplified in melanoma and to be associated with a more aggressive phenotype through regulation of thrombospondin 1 [87].

Chaetocin is a competitive inhibitor of S-adenosyl-L-methionine (SAM) and was the first histone lysine methyltransferase inhibitor to be identified. It specifically inhibits lysine histone methyltransferases of the SUV39 family, making the compound useful in the study of heterochromatin-mediated gene repression [88]. BIX01294 is an inhibitor of GLP and G9A methyltransferase [89]. This compound does not compete with cofactor SAM but acts as a competitive inhibitor of N-terminal peptides of H3 [90]. It selectively impairs the generation of H3K9me2 in vitro. UNC0321 is a newer modification of BIX12094 with a greater potency against G9A and GLP [91].

### **H3K27 methyltransferases**

**EZH2.** Unlike monomethylated H3K27, which is associated with gene activation, di-/trimethylated H3K27 act as repressive marks [75, 92]. Histone lysine methyltransferase EZH2 is mostly responsible for trimethylation of lysine 27 on histone 3 (H3K27me3). EZH2 is the catalytic subunit of the polycomb repressive complex 2 (PRC2). PRC2 has 3 other subunits EED, SUZ12, and RBBP4. PRC2 mediates gene repression through chromatin reorganization by methylating H3K27. Therefore, H3K27me3 is associated with repressed chromatin. Mutations in EZH2 could result from the replacement of a tyrosine in its SET domain (Tyr641). This change can reduce enzymatic activity of EZH2 resulting in a higher affinity to mono- or dimethylated H3K27 [93]. In addition, in various melanoma cell lines, Tyr641 mutations of EZH2 have shown to alter the substrate specificity of EZH2 to H3K27me2, causing an increase in H3K27me3 and depletion of H3K27me2 [94]. H3K27me1/me2 produced by wild-type EZH2 could be methylated by Tyr641-mutant EZH2 to generate elevated levels of H3K27me3 that can promote tumorigenesis [95]. High levels of EZH2 activation are observed in neuroblastoma, hepatocellular carcinoma, small cell lung cancer, and melanoma [96]. Increased expression of EZH2 is associated with melanoma progression and decreased overall patient survival [97]. Protein levels of EZH2 increase incrementally from benign nevi to cutaneous malignant melanoma, which also suggests that EZH2 may play a role in the pathogenesis and tumorigenesis of melanoma [98–100] (Fig. 4). EZH2 suppresses senescence in melanoma by repressing CDKN1A expression independent of p16<sup>INK4a</sup> expression or p53 function [98]. In addition, aggressive melanoma cells have excessive levels of H3K27me3 accompanied by EZH2 overexpression [101], in which EZH2 controls melanoma progression and metastasis by silencing tumor suppressors [102].

Several available EZH2 inhibitors have been used in numerous studies. EPZ-6438 (Tazemetostat) is an EZH2 inhibitor in phase 1 and 2 clinical trials. This drug has been investigated for multiple cancer types, including B cell non-Hodgkin lymphoma and advanced solid tumors [103]. EPZ011989 is a potent and orally bioavailable EZH2 inhibitor [104]. GSK126 is a potent and also highly selective inhibitor of EZH2 that decreases global H3K27me3 levels and reactivates silenced PRC2 target genes. GSK126 inhibits proliferation of EZH2-mutant diffuse large B cell lymphoma (DLBCL) cell lines and mouse xenografts [105]. EZH2 inhibition using this small molecule is proposed to increase NK cell death suggesting an immunosuppressive effect of EZH2 [106]. Treatment with another EZH2 inhibitor, GSK503, in a melanoma mouse model, blocked tumor growth and metastasis formation. In human melanoma cells, GSK503 impaired cell proliferation and invasiveness, along with re-expression of tumor suppressors associated with increased patients' survival [102]. In osteosarcoma, GSK343, another inhibitor of EZH2, restricts cell viability and promotes apoptosis. GSK343 inhibits EZH2 expression and its substrate, H3K27me3. It also inhibits fuse binding protein 1 (FBP1) expression, a c-Myc regulator [107]. In cancers with genetic alteration in EZH2, such as various forms of lymphoma, EPZ005687 reduces H3K27 methylation. Mutations in EZH2 result in a dependency on its enzymatic activity for proliferation that could make EPZ005687 a treatment for cancers in which EZH2 is genetically altered [108].

Another approach to inhibit the PRC2 complex and subsequently H3K27 methylation is to block another component of this complex, such as EED. In a recent study, a compound, EED226, was developed to block PRC2. EED226 is a potent and selective PRC2 inhibitor that directly binds to the H3K27me3 binding pocket of EED. It induces regression of human lymphoma xenograft tumors [109, 110].

### **H3K36 methyltransferases**

Di-/trimethylation of H3K36 is usually associated with transcriptional activation and double-strand break repair. H3K36me2 can be deposited near the breaks and can recruit early repair factors [111]. H3K36me3 is considered as a hallmark of active gene transcription. It is commonly enriched at the body of active genes and particularly at their 3'-terminal regions. Its activity produces a methylation pattern distinct from that of other histone methylations [112]. H3K36me3 is involved in defining exons which are enriched in nucleosomes. Nucleosomes are more frequent in areas with this particular histone mark [113]. H3K36 trimethylation is also shown to play a role in homologous recombination (HR) repair in human cells [114]. Another study proposes a less known role of H3K36me3 in combination with other histone marks in

contributing to the composition of heterochromatin [115]. Also, H3K36 methylation antagonizes PRC2-mediated H3K27 methylation [116].

**SETD2.** SETD2 is the only known gene in human cells responsible for trimethylation of lysine 36 of Histone H3 (H3K36) [117]. This enzyme is mutated in 11.5% of renal clear cell carcinoma tumors [118]. The H3K36me3 mark is associated with DNA methylation in actively transcribed gene regions [119]. A TCGA study also suggests crosstalk between H3K36 methylation and DNA methylation. Renal clear cell carcinoma tumors with SETD2 mutations had DNA hypomethylation at non-promoter regions that are marked by H3K36me3 [118]. A similar pattern is found in sarcoma where H3K36 mutation prevents methylation as well as mesenchymal progenitor cell differentiation and induces sarcoma [120]. SETD2 counteracts Wnt signaling and signaling loss promotes intestinal tumorigenesis in vivo. Mechanistically, SETD2 downregulation affects alternative gene splicing leading to tumor inhibition [121].

**NSD1.** NSD1 binds near various promoter elements and interacts with H3K36 and RNA Pol II, to regulate transcription [122]. H3K36me2 methyltransferase NSD1 is a modulator of PRC2 function and demarcates H3K27me2 and H3K27me3 domains in ESCs [123]. NSD1 inactivating mutations define a hypomethylated subtype in different cancer types such as head and neck squamous cell carcinoma (HNSC) and lung squamous cell carcinoma (LUSC) [124–126]. This subtype is also characterized by low T cell infiltration into the tumor microenvironment, suggesting an identification of this subtype prior to immunotherapy [125]. NSD1 inactivation along with SETD2 mutation that causes a distorted H3K36 is a key feature of clear cell renal cell carcinoma [127]. NSD1 mutations may have a genome-wide impact on DNA methylation [128]. NSD1 expression in patient-derived metastatic cell lines is significantly higher compared to normal melanocytes; however, NSD1 upregulation does not apply to primary tumors developing to metastatic lesions [129].

N-propyl sinefungin (Pr-SNF) is shown to interact preferentially with SETD2 and act as an inhibitor of this protein [130]. However, no compounds that can target NSD proteins selectively have been identified. Due to the high similarity of the SET domain of NSDs to that of GLP and G9A, BIX01294 would be capable of inhibiting H3K36 methyltransferase NSD1/2/3 [131].

### H3K79 methyltransferases

**DOT1L.** H3K79 is a histone mark associated with active chromatin and transcriptional elongation [132]. DOT1L is the only enzyme identified that methylates H3K79. Interestingly, DOT1L has no SET domain in its protein structure (Fig. 2). It is linked to both active and repressed genes. However, H3K79 methylation is mainly a mark of active transcription. DOT1L methylates at 3 levels, mono-di-, and

trimethylation. H3K79 methylation has a crucial role in heterochromatin formation and chromosome integrity [133]. An oncogenic role of DOT1L histone H3 lysine 79 (H3K79) methyltransferase in MLL-rearranged leukemia has been established. Unlike leukemia, DOT1L plays a repressive role in UV-induced melanoma development. DOT1L is frequently mutated in human melanoma, leading to a reduced level of H3K79 methylation. DOT1L depletion will cause UV-induced DNA damage not to be efficiently repaired, thus encouraging progression of melanoma [134] (Fig. 4).

Pinometostat (EPZ5676) is a selective, small molecule inhibitor of DOT1L. MLL-rearranged cells and xenograft models treated with this inhibitor showed reduced levels of H3K79me2 [135, 136]. This drug is currently in phase 1 clinical trials and has modest clinical activity [137, 138]. EPZ004777 is a specific, SAM-competitive inhibitor of DOT1L. It selectively kills leukemia cells with MLL rearrangements. A chemical analog of this drug, SGC 0946, with improved solubility and potency has also been developed [139].

### H4K20 methyltransferases

**PR-Set7 (SET8).** H4K20me1 is linked to transcriptional activation, a modification that is present in highly transcribed genes. Histone H4 lysine methyltransferase PR-Set7 (SET8) mono-methylates H4K20 [140, 141]. This enzyme plays a role in several processes including DNA damage response, chromatin compaction, DNA replication, transcriptional regulation, and tumorigenesis [140, 142]. Loss of SET8 could cause cell cycle defects and promote DNA damage [143]. Depletion of SET8 in melanoma cells under treatment with the NEDD inhibitor, pevonedistat, indicated that preventing degradation of SET8 is essential for effective impact of this drug in melanoma suppression because of its role in DNA re-replication and senescence [144].

**SUV420H1/H2.** Dimethylation of H4K20 is the most abundant methylation state and is present in about 80% of H4 histones [145]. H4K20me2 plays a role in cell cycle control and DNA damage response whereas H4K20me3 takes part in transcriptional repression and is a hallmark of silenced heterochromatin regions. Loss of trimethylated H4K20 is considered a common mark of cancer. Both these methyltransferases have a Zn-binding post-SET domain [146]. SUV420H1 and SUV420H2 play roles in NHEJ-directed DNA repair by di- and trimethylation of H4K20 [146]. Further, overexpression of SUV420H1 may lead to activation of ERK through enhancement of ERK phosphorylation and transcription [147] (Fig. 4).

A-196 is a selective inhibitor of SUV420H1 and SUV420H2. This drug induces a genome-wide decrease in H4K20me2/me3 and increases H4K20me1 [148].

A concise schematic picture of the role of major histone lysine methyltransferase involved in melanoma is provided in Fig. 4, and a list of these enzymes along with their known inhibitors is shown in Table 2.

## Discussion

### Future direction

Despite the emergence of several new targeted therapies and immunotherapy drugs, tumor resistance to these novel therapies is a major hurdle that reflects a need for more efficient therapeutic strategies. Numerous studies have been

published in recent years to clarify the role of histone methylation and associated enzymes in tumorigenesis. Because of the reversible nature of histone methylation, demethylase and methyltransferase enzymes as well as chemical compounds that inhibit the activities of the enzymes and can therefore change the level of methylation at specific histone sites are under comprehensive investigation as targets for cancer therapy. Current understanding of the role of these enzymes suggests that they regulate transcription activation and repression based on the histone involved and the specific amino acid residue being modified.

**Table 2** Histone lysine methyltransferases (KMTs) and their selective inhibitors

	Enzyme	Alias		Structure	Inhibitor	Reference
H3K4	MLL1	KMT2A	TRX1	SET/PHD/FYRC/BD	MM102* MM-401* WDR5-0103*	[66–68]
	MLL2	KMT2B	MLL4	SET/PHD/FYRC/BD		
	MLL3	KMT2C	HALR	SET/PHD/FYRC		
	MLL4	KMT2D	MLL2	SET/PHD/FYRC		
	MLL5	KMT2E		SET/PHD		
	SET1A	KMT2F	SETD1A	SET/RRM		
	SET1B	KMT2G	SETD1B	SET/RRM		
	ASH1L	KMT2H	ASH1	SET/PHD		
	SET7/SET9	KMT7	SETD7	SET		
H3K9	G9A	KMT1C	EHMT2	SET/TAD/ANK	BIX01294 UNC0321	[83, 85]
	GLP	KMT1D	EHMT1	SET/TAD/ANK		
	SUV39H1	KMT1A	H3-K9-HMTase 1	SET/CD	Chaetocin	[82]
	SUV39H2	KMT1B	H3-K9-HMTase 2	SET/CD		
	SETDB1	KMT1E	H3-K9-HMTase 4	SET/Tudor/MBD		
	RIZ1	KMT8	PRDM2	PR/ZF		
H3K27	EZH2	KMT6		SET/SANT	EPZ-6438 (Tazemetostat) EPZ011989 GSK126 GSK503 GSK343 EPZ005687 CPI-1205 CPI-169 EI1 EED226**	[96–99, 101–104]
H3K36	SET2	KMT3A	SETD2	SET/SRI	N-propyl sinefungin (Pr-SNF)	[124]
	NSD1	KMT3B	STO	SET/PHD		
	SMYD2	KMT3C	ZMYND14	SET/MYND	BIX01294	[125]
	ASH1L	KMT2H	ASH1	SET/PHD/BD		
H3K79	DOT1L	KMT4		LRR	EPZ5676 (Pinometostat) EPZ004777 SGC 0946	[129–133]
H4K20	PR-Set7	KMT5A	SETD8	SET	A-196	[142]
	SUV420H1	KMT5B	CGI85	SET		
	SUV420H2	KMT5C		SET		
	NSD1	KMT3B	STO	SET/PHD		

\*These compounds target MLL-WDR5 interaction

\*\*This compound blocks EED, another component of PRC2 to inhibit H3K27 methylation

Various compounds that target the epigenome, such as HDAC inhibitors (e.g., the entinostat, NCT00185302) or DNMT inhibitors (e.g., the decitabine, NCT00030615), have been used in clinical trials to treat melanoma patients, but the use of histone methylating/demethylating agents requires substantial additional investigation. As discussed in this review, different histone demethylases play a role in cell transformation, although H3K4 and H3K9 demethylases are most consistently reported [12–14, 22–24]. This result could be due to an insufficient body of evidence for lesser known erasers, but investigation of JARID1 or LSD1 inhibitors in extensive *in vivo* experiments, and eventually, in clinical trials, could be of clinical significance.

A different approach to clinical application of histone demethylase function might be used in these enzymes in removing methylation in regions of the genome that are unmethylated in normal cells. An enzyme recently used in this manner is LSD1. This enzyme was used in fusion with dCas9 to modulate histone methylation. It has been applied on certain gene enhancers in the genome to suppress specific gene transcription without disrupting local genomic architecture [149]. Lack of impact to the genomic structure is key because disruption of the chromatin structure can change DNA-protein interactions at the global level with unpredictable consequences. The use of such enzymes in combination with gene editing technology could allow development of novel treatment modalities involving removal of active histone marks on promoter regions of oncogenes or repressive histone marks on distal elements of tumor suppressor genes, both of which are common features seen particularly in cutaneous melanoma.

As we have summarized here, past literature leads us to several epigenetic patterns that seem to be frequently repeated in distinct types of cancer, including the role of histone methylation modifiers on the promoters of major known drivers of a particular type of cancer. These drivers (i.e., MITE, *c-Myc* in melanoma) have been recently associated with clusters of non-coding regions on the genome called super enhancers that are usually marked with enhancer marks such as H3K4me1 as well as H3K27ac [150]. Inactivation of these frequently methylated histone tails could help to restore cell homeostasis.

Lastly, epigenome-wide studies have partly elucidated the function of combinations of histone methylation marks in melanoma, although understanding of the melanoma epigenome is still unclear. These studies reveal that in a given region of DNA, more than one histone methylation mark could be active in regulating gene expression. Further, the 3D structure of the genome can juxtapose certain regions of the DNA harboring specific histone marks and other regions, thereby activating or repressing genes that may be mega-bases down or upstream.

As per the available information, a comprehensive therapeutic approach, involving minimal disruption of the genome architecture, seems to be essential. Such a therapeutic strategy could help reverse or halt the function of a combination of histone modifications that lead to cell transformation.

#### Abbreviations

AOD: Amino oxidase domain; DLBCL: Diffuse large B cell lymphoma; ESC: Embryonic stem cell; ESET: ERG-associated protein with SET domain; EZH2: Enhancer of zeste homolog 2; HAT: Histone acetyltransferase; HDAC: Histone deacetylase; HKMTase: Histone lysine methyltransferase; HNSC: Head and neck squamous cell carcinoma; LUSC: Lung squamous cell carcinoma; MAPK: Mitogen-activated protein kinase; NER: Nucleotide excision repair; NHEJ: Non-homologous end joining; PHD: Plant homeodomain; PRC: Polycomb repressive complex; SAM: S-adenosyl-L-methionine; SCLC: Small cell lung carcinoma; TCGA: The Cancer Genome Atlas; TCP: Tranylcyproline; TSS: Transcription start site

#### Acknowledgements

Not applicable.

#### Funding

This work has been supported by the RTG2099 Hallmarks of Skin Cancer.

#### Availability of data and materials

Not applicable.

#### Authors' contributions

EO and JU wrote the manuscript, prepared the figures, and revised the manuscript to its final form. Both authors read and approved the final manuscript.

#### Ethics approval and consent to participate

Not applicable.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

#### Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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Received: 24 September 2018 Accepted: 9 November 2018

Published online: 22 November 2018

#### References

- Portela A, Esteller M. Epigenetic modifications and human disease. *Nat Biotechnol.* 2010;28(10):1057–68 PubMed PMID: 20944598. Epub 2010/10/15. eng.
- Baylin SB, Jones PA. A decade of exploring the cancer epigenome - biological and translational implications. *Nat Rev Cancer.* 2011;11(10):726–34 PubMed PMID: 21941284. Pubmed Central PMCID: PMC3307543. Epub 2011/09/24. eng.
- Feinberg AP, Tycko B. The history of cancer epigenetics. *Nat Rev Cancer.* 2004;4(2):143–53 PubMed PMID: 14732866. Epub 2004/01/21. eng.
- Gronbaek K, Hother C, Jones PA. Epigenetic changes in cancer. *APMIS.* 2007; 115(10):1039–59 PubMed PMID: 18042143. Epub 2007/11/29. eng.

5. Gal-Yam EN, Saito Y, Egger G, Jones PA. Cancer epigenetics: modifications, screening, and therapy. *Annu Rev Med*. 2008;59:267–80 PubMed PMID: 17937590. Epub 2007/10/17. eng.
6. Rodriguez-Paredes M, Esteller M. Cancer epigenetics reaches mainstream oncology. *Nat Med*. 2011;17(3):330–9 PubMed PMID: 21386836. Epub 2011/03/10. eng.
7. Sigalotti L, Covre A, Fratta E, Parisi G, Colizzi F, Rizzo A, et al. Epigenetics of human cutaneous melanoma: setting the stage for new therapeutic strategies. *J Transl Med*. 2010;8:56 PubMed PMID: 20540720. Pubmed Central PMCID: PMC2901206. Epub 2010/06/15. eng.
8. Martin C, Zhang Y. The diverse functions of histone lysine methylation. *Nat Rev Mol Cell Biol*. 2005;6(11):838–49 PubMed PMID: 16261189. Epub 2005/11/02. eng.
9. Yoo CB, Jones PA. Epigenetic therapy of cancer: past, present and future. *Nat Rev Drug Discov*. 2006;5(1):37–50 PubMed PMID: 16485345. Epub 2006/02/18. eng.
10. Schmitz SU, Albert M, Malatesta M, Morey L, Johansen JV, Bak M, et al. Jarid1b targets genes regulating development and is involved in neural differentiation. *EMBO J*. 2011;30(22):4586–600 PubMed PMID: 22020125. Pubmed Central PMCID: PMC3243600. Epub 2011/10/25. eng.
11. Klein BJ, Piao L, Xi Y, Rincon-Arango H, Rothbart SB, Peng D, et al. The histone-H3K4-specific demethylase KDM5B binds to its substrate and product through distinct PHD fingers. *Cell Rep*. 2014;6(2):325–35 PubMed PMID: 24412361. Pubmed Central PMCID: PMC3918441. Epub 2014/01/15. eng.
12. Roesch A, Mueller AM, Stempfl T, Moehle C, Landthaler M, Vogt T. RBP2-H1/JARID1B is a transcriptional regulator with a tumor suppressive potential in melanoma cells. *Int J Cancer*. 2008;122(5):1047–57 PubMed PMID: 17973255. Epub 2007/11/02. eng.
13. Roesch A, Fukunaga-Kalabis M, Schmidt EC, Zabierowski SE, Brafford PA, Vultur A, et al. A temporarily distinct subpopulation of slow-cycling melanoma cells is required for continuous tumor growth. *Cell*. 2010;141(4):583–94 PubMed PMID: 20478252. Pubmed Central PMCID: PMC2882693. Epub 2010/05/19. eng.
14. Roesch A, Vultur A, Bogeski I, Wang H, Zimmermann KM, Speicher D, et al. Overcoming intrinsic multidrug resistance in melanoma by blocking the mitochondrial respiratory chain of slow-cycling JARID1B (high) cells. *Cancer Cell*. 2013;23(6):811–25 PubMed PMID: 23764003. Pubmed Central PMCID: PMC3810180. Epub 2013/06/15. eng.
15. Trousil S, Chen S, Mu C, Shaw FM, Yao Z, Ran Y, et al. Phenformin enhances the efficacy of ERK inhibition in NF1-mutant melanoma. *J Invest Dermatol*. 2017;137(5):1135–43 PubMed PMID: 28143781. Pubmed Central PMCID: PMC5392423. Epub 2017/02/02. eng.
16. Johansson C, Velupillai S, Tumber A, Szykowska A, Hookway ES, Nowak RP, et al. Structural analysis of human KDM5B guides histone demethylase inhibitor development. *Nat Chem Biol*. 2016;12(7):539–45 PubMed PMID: 27214403. Epub 2016/05/24. eng.
17. Sayegh J, Cao J, Zou MR, Morales A, Blair LP, Norcia M, et al. Identification of small molecule inhibitors of Jumonji AT-rich interactive domain 1B (JARID1B) histone demethylase by a sensitive high throughput screen. *J Biol Chem*. 2013;288(13):9408–17 PubMed PMID: 23408432. Pubmed Central PMCID: PMC3611010. Epub 2013/02/15. eng.
18. Tumber A, Nuzzi A, Hookway ES, Hatch SB, Velupillai S, Johansson C, et al. Potent and selective KDM5 inhibitor stops cellular demethylation of H3K4me3 at transcription start sites and proliferation of MM1S myeloma cells. *Cell Chem Biol*. 2017;24(3):371–80 PubMed PMID: 28262558. Pubmed Central PMCID: PMC5361737. Epub 2017/03/07. eng.
19. Cloos PA, Christensen J, Agger K, Helin K. Erasing the methyl mark: histone demethylases at the center of cellular differentiation and disease. *Genes Dev*. 2008;22(9):1115–40 PubMed PMID: 18451103. Pubmed Central PMCID: PMC2732404. Epub 2008/05/03. eng.
20. Secombe J, Eisenman RN. The function and regulation of the JARID1 family of histone H3 lysine 4 demethylases: the Myc connection. *Cell Cycle*. 2007;6(11):1324–8 PubMed PMID: 17568193. Epub 2007/06/15. eng.
21. Whyte WA, Bilodeau S, Orlando DA, Hoke HA, Frampton GM, Foster CT, et al. Enhancer decommissioning by LSD1 during embryonic stem cell differentiation. *Nature*. 2012;482(7384):221–5 PubMed PMID: 22297846. Pubmed Central PMCID: PMC4144424. Epub 2012/02/03. eng.
22. Yu Y, Schleich K, Yue B, Ji S, Lohneis P, Kemper K, et al. Targeting the senescence-overriding cooperative activity of structurally unrelated H3K9 demethylases in melanoma. *Cancer Cell*. 2018;33(2):322–36 e8. PubMed PMID: 29438700. Pubmed Central PMCID: PMC5977991. Epub 2018/02/14. eng.
23. Zhang X, Lu F, Wang J, Yin F, Xu Z, Qi D, et al. Pluripotent stem cell protein Sox2 confers sensitivity to LSD1 inhibition in cancer cells. *Cell Rep*. 2013;5(2):445–57 PubMed PMID: 24139802. Epub 2013/10/22. eng.
24. Tan Y, Tajik A, Chen J, Jia Q, Chowdhury F, Wang L, et al. Matrix softness regulates plasticity of tumour-repopulating cells via H3K9 demethylation and Sox2 expression. *Nat Commun*. 2014;5:4619 PubMed PMID: 25099074. Pubmed Central PMCID: PMC4133791. Epub 2014/08/08. eng.
25. Sheng W, LaFleur MW, Nguyen TH, Chen S, Chakravarthy A, Conway JR, et al. LSD1 ablation stimulates anti-tumor immunity and enables checkpoint blockade. *Cell*. 2018;18 PubMed PMID: 29937226. Epub 2018/06/26. eng.
26. Lian CG, Fang R, Zhan Q, Ma J, Lee C-W, Frank MH, et al. Inhibition of lysine-specific histone demethylase LSD1 suppresses melanoma growth. *FASEB J*. 2013;27(1\_supplement):1088 15–.15.
27. Mohammad HP, Smitheman KN, Kamat CD, Soong D, Federowicz KE, Van Aller GS, et al. A DNA Hypomethylation signature predicts antitumor activity of LSD1 inhibitors in SCLC. *Cancer Cell*. 2015;28(1):57–69 PubMed PMID: 26175415. Epub 2015/07/16. eng.
28. Cusan M, Cai SF, Mohammad HP, Krivtsov A, Chramiec A, Loizou E, et al. LSD1 inhibition exerts its antileukemic effect by recommissioning PU.1- and C/EBPalpha-dependent enhancers in AML. *Blood*. 2018;131(15):1730–42 PubMed PMID: 29453291. Pubmed Central PMCID: PMC5897868. Epub 2018/02/18. eng.
29. Mould DP, McGonagle AE, Wiseman DH, Williams EL, Jordan AM. Reversible inhibitors of LSD1 as therapeutic agents in acute myeloid leukemia: clinical significance and progress to date. *Med Res Rev*. 2015;35(3):586–618 PubMed PMID: 25418875. Epub 2014/11/25. eng.
30. Lynch JT, Harris WJ, Somerville TC. LSD1 inhibition: a therapeutic strategy in cancer? *Expert Opin Ther Targets*. 2012;16(12):1239–49 PubMed PMID: 22957941. Epub 2012/09/11. eng.
31. Cui S, Lim KC, Shi L, Lee M, Jearawiriyapaisarn N, Myers G, et al. The LSD1 inhibitor RN-1 induces fetal hemoglobin synthesis and reduces disease pathology in sickle cell mice. *Blood*. 2015;126(3):386–96 PubMed PMID: 26031919. Pubmed Central PMCID: PMC4504950. Epub 2015/06/03. eng.
32. Ishikawa Y, Gamo K, Yabuki M, Takagi S, Toyoshima K, Nakayama K, et al. A novel LSD1 inhibitor T-3775440 disrupts GF11B-containing complex leading to transdifferentiation and impaired growth of AML cells. *Mol Cancer Ther*. 2017;16(2):273–84 PubMed PMID: 27903753. Epub 2016/12/03. eng.
33. Sugino N, Kawahara M, Tatsumi G, Kanai A, Matsui H, Yamamoto R, et al. A novel LSD1 inhibitor NCD38 ameliorates MDS-related leukemia with complex karyotype by attenuating leukemia programs via activating super-enhancers. *Leukemia*. 2017;31(11):2303–14 PubMed PMID: 28210006. Epub 2017/02/18. eng.
34. Yamamoto R, Kawahara M, Ito S, Satoh J, Tatsumi G, Hishizawa M, et al. Selective dissociation between LSD1 and GF11B by a LSD1 inhibitor NCD38 induces the activation of ERG super-enhancer in erythroleukemia cells. *Oncotarget*. 2018;9(30):21007–21 PubMed PMID: 29765516. Pubmed Central PMCID: PMC5940392. Epub 2018/05/17. eng.
35. Black JC, Manning AL, Van Rechem C, Kim J, Ladd B, Cho J, et al. KDM4A lysine demethylase induces site-specific copy gain and rereplication of regions amplified in tumors. *Cell*. 2013;154(3):541–55 PubMed PMID: 23871696. Pubmed Central PMCID: PMC3832053. Epub 2013/07/23. eng.
36. Salifou K, Ray S, Verrier L, Aguirrebengoa M, Trouche D, Panov KI, et al. The histone demethylase JMJD2A/KDM4A links ribosomal RNA transcription to nutrients and growth factors availability. *Nat Commun*. 2016;7:10174 PubMed PMID: 26729372. Pubmed Central PMCID: PMC5157185. Epub 2016/01/06. eng.
37. Li LL, Xue AM, Li BX, Shen YW, Li YH, Luo CL, et al. JMJD2A contributes to breast cancer progression through transcriptional repression of the tumor suppressor ARHI. *Breast Cancer Res*. 2014;16(3):R56 PubMed PMID: 24886710. Pubmed Central PMCID: PMC4077733. Epub 2014/06/03. eng.
38. Kim TD, Fuchs JR, Schwartz E, Abdelhamid D, Etter J, Berry WL, et al. Pro-growth role of the JMJD2C histone demethylase in HCT-116 colon cancer cells and identification of curcuminoids as JMJD2 inhibitors. *Am J Transl Res*. 2014;6(3):236–47 PubMed PMID: 24936217. Pubmed Central PMCID: PMC4058306. Epub 2014/06/18. eng.
39. Xu W, Jiang K, Shen M, Qian Y, Peng Y. SIRT2 suppresses non-small cell lung cancer growth by targeting JMJD2A. *Biol Chem*. 2015;396(8):929–36 PubMed PMID: 25719312. Epub 2015/02/27. eng.
40. Kim TD, Jin F, Shin S, Oh S, Lightfoot SA, Grande JP, et al. Histone demethylase JMJD2A drives prostate tumorigenesis through transcription factor ETV1. *J Clin Invest*. 2016;126(2):706–20 PubMed PMID: 26731476. Pubmed Central PMCID: PMC4731184. Epub 2016/01/06. eng.

41. Lamar JM, Stern P, Liu H, Schindler JW, Jiang ZG, Hynes RO. The hippo pathway target, YAP, promotes metastasis through its TEAD-interaction domain. *Proc Natl Acad Sci U S A*. 2012;109(37):E2441–50 PubMed PMID: 22891335. Pubmed Central PMCID: PMC3443162. Epub 2012/08/15. eng.
42. Park WY, Hong BJ, Lee J, Choi C, Kim MY. H3K27 demethylase JMJD3 employs the NF-kappaB and BMP signaling pathways to modulate the tumor microenvironment and promote melanoma progression and metastasis. *Cancer Res*. 2016;76(1):161–70 PubMed PMID: 26729791. Epub 2016/01/06. eng.
43. Barradas M, Anderton E, Acosta JC, Li S, Banito A, Rodriguez-Niedenfuhr M, et al. Histone demethylase JMJD3 contributes to epigenetic control of INK4a/ARF by oncogenic RAS. *Genes Dev*. 2009;23(10):1177–82 PubMed PMID: 19451218. Pubmed Central PMCID: PMC2685533. Epub 2009/05/20. eng.
44. Agger K, Cloos PA, Rudkjaer L, Williams K, Andersen G, Christensen J, et al. The H3K27me3 demethylase JMJD3 contributes to the activation of the INK4A-ARF locus in response to oncogene- and stress-induced senescence. *Genes Dev*. 2009;23(10):1171–6 PubMed PMID: 19451217. Pubmed Central PMCID: PMC2685535. Epub 2009/05/20. eng.
45. Wang L, Zhao Z, Ozark PA, Fantini D, Marshall SA, Rendleman EJ, et al. Resetting the epigenetic balance of Polycomb and COMPASS function at enhancers for cancer therapy. *Nat Med*. 2018;24(6):758–69 PubMed PMID: 29785026. Epub 2018/05/23. eng.
46. Gozdecka M, Meduri E, Mazan M, Tzelepis K, Dudek M, Knights AJ, et al. UTX-mediated enhancer and chromatin remodeling suppresses myeloid leukemogenesis through noncatalytic inverse regulation of ETS and GATA programs. *Nat Genet*. 2018;50(6):883–94 PubMed PMID: 29736013. Epub 2018/05/08. eng.
47. Rai K, Akdemir KC, Kwong LN, Fiziep P, Wu CJ, Keung EZ, et al. Dual roles of RNF2 in melanoma progression. *Cancer Discov*. 2015;5(12):1314–27 PubMed PMID: 26450788. Pubmed Central PMCID: PMC4670809. Epub 2015/10/10. eng.
48. Kruidenier L, Chung CW, Cheng Z, Liddle J, Che K, Joberty G, et al. A selective jumonji H3K27 demethylase inhibitor modulates the proinflammatory macrophage response. *Nature*. 2012;488(7411):404–8 PubMed PMID: 22842901. Pubmed Central PMCID: PMC4691848. Epub 2012/07/31. eng.
49. Lochmann TL, Powell KM, Ham J, Floros KV, Heisey DAR, Kurupi RJ, et al. Targeted inhibition of histone H3K27 demethylation is effective in high-risk neuroblastoma. *Sci Transl Med*. 2018;16:10(441) PubMed PMID: 29769286. Epub 2018/05/18. eng.
50. Kang JY, Kim JY, Kim KB, Park JW, Cho H, Hahm JY, et al. KDM2B is a histone H3K79 demethylase and induces transcriptional repression via sirtuin-1-mediated chromatin silencing. *FASEB J*. 2018; fj201800242R. PubMed PMID: 29763382. Epub 2018/05/16. eng.
51. Farcas AM, Blackledge NP, Sudbery I, Long HK, McGouran JF, Rose NR, et al. KDM2B links the polycomb repressive complex 1 (PRC1) to recognition of CpG islands. *elife*. 2012;1:e00205 PubMed PMID: 23256043. Pubmed Central PMCID: PMC3524939. Epub 2012/12/21. eng.
52. Banito A, Li X, Laporte AN, Roe JS, Sanchez-Vega F, Huang CH, et al. The SS18-SSX oncoprotein hijacks KDM2B-PRC1.1 to drive synovial sarcoma. *Cancer Cell*. 2018;33(3):527–41 e8. PubMed PMID: 29502955. Pubmed Central PMCID: PMC5881394. Epub 2018/03/06. eng.
53. Staberg M, Rasmussen RD, Michaelsen SR, Pedersen H, Jensen KE, Villingshøj M, et al. Targeting glioma stem-like cell survival and chemoresistance through inhibition of lysine-specific histone demethylase KDM2B. *Mol Oncol*. 2018;12(3):406–20 PubMed PMID: 29360266. Pubmed Central PMCID: PMC5830623. Epub 2018/01/24. eng.
54. Liang G, He J, Zhang Y. Kdm2b promotes induced pluripotent stem cell generation by facilitating gene activation early in reprogramming. *Nat Cell Biol*. 2012;14(5):457–66 PubMed PMID: 22522173. Pubmed Central PMCID: PMC3544197. Epub 2012/04/24. eng.
55. Fukuda T, Tokunaga A, Sakamoto R, Yoshida N. Fbx10/Kdm2b deficiency accelerates neural progenitor cell death and leads to exencephaly. *Mol Cell Neurosci*. 2011;46(3):614–24 PubMed PMID: 21220025. Epub 2011/01/12. eng.
56. He J, Kallin EM, Tsukada Y, Zhang Y. The H3K36 demethylase Jhdm1b/Kdm2b regulates cell proliferation and senescence through p15(Ink4b). *Nat Struct Mol Biol*. 2008;15(11):1169–75 PubMed PMID: 18836456. Pubmed Central PMCID: PMC2612995. Epub 2008/10/07. eng.
57. Heintzman ND, Stuart RK, Hon G, Fu Y, Ching CW, Hawkins RD, et al. Distinct and predictive chromatin signatures of transcriptional promoters and enhancers in the human genome. *Nat Genet*. 2007;39(3):311–8 PubMed PMID: 17277777. Epub 2007/02/06. eng.
58. Herz HM, Mohan M, Garruss AS, Liang K, Takahashi YH, Mickey K, et al. Enhancer-associated H3K4 monomethylation by Trithorax-related, the Drosophila homolog of mammalian Mll3/Mll4. *Genes Dev*. 2012;26(23):2604–20 PubMed PMID: 23166019. Pubmed Central PMCID: PMC3521626. Epub 2012/11/21. eng.
59. Cheng CS, Rai K, Garber M, Hollinger A, Robbins D, Anderson S, et al. Semiconductor-based DNA sequencing of histone modification states. *Nat Commun*. 2013;4:2672 PubMed PMID: 24157732. Pubmed Central PMCID: PMC3917140. Epub 2013/10/26. eng.
60. Bossi D, Cicalese A, Dellino GI, Luzi L, Riva L, D'Alesio C, et al. In vivo genetic screens of patient-derived tumors revealed unexpected frailty of the transformed phenotype. *Cancer Discov*. 2016;6(6):650–63 PubMed PMID: 27179036. Epub 2016/05/15. eng.
61. Lee JJ, Sholl LM, Lindeman NI, Granter SR, Laga AC, Shivdasani P, et al. Targeted next-generation sequencing reveals high frequency of mutations in epigenetic regulators across treatment-naive patient melanomas. *Clin Epigenetics*. 2015;7:59 PubMed PMID: 26221190. Pubmed Central PMCID: PMC4517542. Epub 2015/07/30. eng.
62. Uzdensky A, Demyanenko S, Bibov M, Sharifulina S, Kit O, Przhedetski Y, et al. Expression of proteins involved in epigenetic regulation in human cutaneous melanoma and peritumoral skin. *Tumour Biol*. 2014;35(8):8225–33 PubMed PMID: 24850177. Epub 2014/05/23. eng.
63. Kampilafkos P, Melachrinou M, Kefalopoulou Z, Lakoumentas J, Sotiropoulou-Bonikou G. Epigenetic modifications in cutaneous malignant melanoma: EZH2, H3K4me2, and H3K27me3 immunohistochemical expression is enhanced at the invasion front of the tumor. *Am J Dermatopathol*. 2015;37(2):138–44 PubMed PMID: 25614949. Epub 2015/01/24. eng.
64. Bernstein BE, Humphrey EL, Erlich RL, Schneider R, Bouman P, Liu JS, et al. Methylation of histone H3 Lys 4 in coding regions of active genes. *Proc Natl Acad Sci U S A*. 2002;99(13):8695–700 PubMed PMID: 12060701. Pubmed Central PMCID: PMC124361. Epub 2002/06/13. eng.
65. Santos-Rosa H, Schneider R, Bannister AJ, Sherriff J, Bernstein BE, Emre NC, et al. Active genes are tri-methylated at K4 of histone H3. *Nature*. 2002;419(6905):407–11 PubMed PMID: 12353038. Epub 2002/09/28. eng.
66. Anelli V, Santoriello C, Distel M, Koster RW, Ciccarelli FD, Mione M. Global repression of cancer gene expression in a zebrafish model of melanoma is linked to epigenetic regulation. *Zebrafish*. 2009;6(4):417–24 PubMed PMID: 20047469. Epub 2010/01/06. eng.
67. Bjornsson HT, Benjamin JS, Zhang L, Weissman J, Gerber EE, Chen YC, et al. Histone deacetylase inhibition rescues structural and functional brain deficits in a mouse model of Kabuki syndrome. *Sci Transl Med*. 2014;6(256):256ra135 PubMed PMID: 25273096. Pubmed Central PMCID: PMC4406328. Epub 2014/10/03. eng.
68. Balbo Pogliano C, Gatti M, Ruthemann P, Garajova Z, Penengo L, Naegeli H. ASH1L histone methyltransferase regulates the handoff between damage recognition factors in global-genome nucleotide excision repair. *Nat Commun*. 2017;8(1):1333 PubMed PMID: 29109511. Pubmed Central PMCID: PMC5673894. Epub 2017/11/08. eng.
69. Li G, Ye Z, Shi C, Sun L, Han M, Zhuang Y, et al. The histone methyltransferase Ash1l is required for epidermal homeostasis in mice. *Sci Rep*. 2017;7:45401 PubMed PMID: 28374742. Pubmed Central PMCID: PMC5379632. Epub 2017/04/05. eng.
70. Zhu L, Li Q, Wong SH, Huang M, Klein BJ, Shen J, et al. ASH1L links histone H3 lysine 36 dimethylation to MLL leukemia. *Cancer Discov*. 2016;6(7):770–83 PubMed PMID: 27154821. Pubmed Central PMCID: PMC4930721. Epub 2016/05/08. eng.
71. Hyun K, Jeon J, Park K, Kim J. Writing, erasing and reading histone lysine methylations. *Exp Mol Med*. 2017;49(4):e324 PubMed PMID: 28450737. Epub 2017/04/30. eng.
72. Karatas H, Townsend EC, Cao F, Chen Y, Bernard D, Liu L, et al. High-affinity, small-molecule peptidomimetic inhibitors of MLL1/WDR5 protein-protein interaction. *J Am Chem Soc*. 2013;135(2):669–82 PubMed PMID: 23210835. Pubmed Central PMCID: PMC5180416. Epub 2012/12/06. eng.
73. Cao F, Townsend EC, Karatas H, Xu J, Li L, Lee S, et al. Targeting MLL1 H3K4 methyltransferase activity in mixed-lineage leukemia. *Mol Cell*. 2014;53(2):247–61 PubMed PMID: 24389101. Pubmed Central PMCID: PMC3965208. Epub 2014/01/07. eng.
74. Senisterra G, Wu H, Allali-Hassani A, Wasney GA, Barsyte-Lovejoy D, Dombrowski L, et al. Small-molecule inhibition of MLL activity by disruption of its interaction with WDR5. *Biochem J*. 2013;449(1):151–9 PubMed PMID: 22989411. Pubmed Central PMCID: PMC3517986. Epub 2012/09/20. eng.

75. Barski A, Cuddapah S, Cui K, Roh TY, Schones DE, Wang Z, et al. High-resolution profiling of histone methylations in the human genome. *Cell*. 2007;129(4):823–37 PubMed PMID: 17512414. Epub 2007/05/22. eng.
76. Sims JK, Houston SJ, Magazinnik T, Rice JC. A trans-tail histone code defined by monomethylated H4 Lys-20 and H3 Lys-9 demarcates distinct regions of silent chromatin. *J Biol Chem*. 2006;281(18):12760–6 PubMed PMID: 16517599. Epub 2006/03/07. eng.
77. El Gazzar M, Yoza BK, Chen X, Hu J, Hawkins GA, McCall CE. G9a and HP1 couple histone and DNA methylation to TNFalpha transcription silencing during endotoxin tolerance. *J Biol Chem*. 2008;283(47):32198–208 PubMed PMID: 18809684. Pubmed Central PMCID: PMC2583293. Epub 2008/09/24. eng.
78. Jacobs SA, Taverna SD, Zhang Y, Briggs SD, Li J, Eissenberg JC, et al. Specificity of the HP1 chromo domain for the methylated N-terminus of histone H3. *EMBO J*. 2001;20(18):5232–41 PubMed PMID: 11566886. Pubmed Central PMCID: PMC125272. Epub 2001/09/22. eng.
79. Ding J, Li T, Wang X, Zhao E, Choi JH, Yang L, et al. The histone H3 methyltransferase G9a epigenetically activates the serine-glycine synthesis pathway to sustain cancer cell survival and proliferation. *Cell Metab*. 2013;18(6):896–907 PubMed PMID: 24315373. Pubmed Central PMCID: PMC3878056. Epub 2013/12/10. eng.
80. Hua KT, Wang MY, Chen MW, Wei LH, Chen CK, Ko CH, et al. The H3K9 methyltransferase G9a is a marker of aggressive ovarian cancer that promotes peritoneal metastasis. *Mol Cancer*. 2014;13:189 PubMed PMID: 25115793. Pubmed Central PMCID: PMC4260797. Epub 2014/08/15. eng.
81. Albacker CE, Storer NY, Langdon EM, Dibiasi A, Zhou Y, Langenau DM, et al. The histone methyltransferase SUV39H1 suppresses embryonal rhabdomyosarcoma formation in zebrafish. *PLoS One*. 2013;8(5):e64969 PubMed PMID: 23705022. Pubmed Central PMCID: PMC3660348. Epub 2013/05/25. eng.
82. Ait-Si-Ali S, Guasconi V, Fritsch L, Yahli H, Sekhri R, Naguibneva J, et al. A Suv39h-dependent mechanism for silencing S-phase genes in differentiating but not in cycling cells. *EMBO J*. 2004;23(3):605–15 PubMed PMID: 14765126. Pubmed Central PMCID: PMC1271807. Epub 2004/02/07. eng.
83. O'Carroll D, Scherthan H, Peters AH, Opravil S, Haynes AR, Laible G, et al. Isolation and characterization of Suv39h2, a second histone H3 methyltransferase gene that displays testis-specific expression. *Mol Cell Biol*. 2000;20(24):9423–33 PubMed PMID: 11094092. Pubmed Central PMCID: PMC102198. Epub 2000/11/30. eng.
84. Piao L, Suzuki T, Dohmae N, Nakamura Y, Hamamoto R. SUV39H2 methylates and stabilizes LSD1 by inhibiting polyubiquitination in human cancer cells. *Oncotarget*. 2015;6(19):16939–50 PubMed PMID: 26183527. Pubmed Central PMCID: PMC4627283. Epub 2015/07/18. eng.
85. Ceol CJ, Houvras Y, Jane-Valbuena J, Bilodeau S, Orlando DA, Battisti V, et al. The histone methyltransferase SETDB1 is recurrently amplified in melanoma and accelerates its onset. *Nature*. 2011;471(7339):513–7 PubMed PMID: 21430779. Pubmed Central PMCID: PMC3348545. Epub 2011/03/25. eng.
86. Al-Sady B, Madhani HD, Narlikar GJ. Division of labor between the chromodomains of HP1 and Suv39 methylase enables coordination of heterochromatin spread. *Mol Cell*. 2013;51(1):80–91 PubMed PMID: 23849629. Pubmed Central PMCID: PMC3752401. Epub 2013/07/16. eng.
87. Orouji E, Federico A, Larrubere L, Novak D, Utikal J. Abstract A180: the histone methyltransferase SETDB1 contributes to melanoma tumorigenesis. *Mol Cancer Ther*. 2018;17(1 Supplement):A180.
88. Greiner D, Bonaldi T, Eskeland R, Roemer E, Imhof A. Identification of a specific inhibitor of the histone methyltransferase SU(VAR)3-9. *Nat Chem Biol*. 2005;1(3):143–5 PubMed PMID: 16408017. Epub 2006/01/13. eng.
89. Kubicek S, O'Sullivan RJ, August EM, Hickey ER, Zhang Q, Teodoro ML, et al. Reversal of H3K9me2 by a small-molecule inhibitor for the G9a histone methyltransferase. *Molecular Cell*. 2007;25(3):473–81 PubMed PMID: 17289593. Epub 2007/02/10. eng.
90. Chang Y, Ganesh T, Horton JR, Spannhoff A, Liu J, Sun A, et al. Adding a lysine mimic in the design of potent inhibitors of histone lysine methyltransferases. *J Mol Biol*. 2010;400(1):1–7 PubMed PMID: 20434463. Pubmed Central PMCID: PMC2895764. Epub 2010/05/04. eng.
91. Liu F, Chen X, Allali-Hassani A, Quinn AM, Wigle TJ, Wasney GA, et al. Protein lysine methyltransferase G9a inhibitors: design, synthesis, and structure activity relationships of 2,4-diamino-7-aminoalkoxy-quinoxalines. *J Med Chem*. 2010;53(15):5844–57 PubMed PMID: 20614940. Pubmed Central PMCID: PMC2920043. Epub 2010/07/10. eng.
92. Tiffen J, Gallagher SJ, Hersey P. EZH2: an emerging role in melanoma biology and strategies for targeted therapy. *Pigment Cell Melanoma Res*. 2015;28(1):21–30 PubMed PMID: 24912396. Epub 2014/06/11. eng.
93. Morin RD, Johnson NA, Severson TM, Mungall AJ, An J, Goya R, et al. Somatic mutations altering EZH2 (Tyr641) in follicular and diffuse large B-cell lymphomas of germinal-center origin. *Nat Genet*. 2010;42(2):181–5 PubMed PMID: 20081860. Pubmed Central PMCID: PMC2850970. Epub 2010/01/19. eng.
94. Barsotti AM, Ryskin M, Zhong W, Zhang WG, Giannakou A, Loreth C, et al. Epigenetic reprogramming by tumor-derived EZH2 gain-of-function mutations promotes aggressive 3D cell morphologies and enhances melanoma tumor growth. *Oncotarget*. 2015;6(5):2928–38 PubMed PMID: 25671303. Pubmed Central PMCID: PMC4413628. Epub 2015/02/12. eng.
95. Sneeringer CJ, Scott MP, Kuntz KW, Knutson SK, Pollock RM, Richon VM, et al. Coordinated activities of wild-type plus mutant EZH2 drive tumor-associated hypertrimethylation of lysine 27 on histone H3 (H3K27) in human B-cell lymphomas. *Proc Natl Acad Sci U S A*. 2010;107(49):20980–5 PubMed PMID: 21078963. Pubmed Central PMCID: PMC3000297. Epub 2010/11/17. eng.
96. Cohen AL, Piccolo SR, Cheng L, Soldi R, Han B, Johnson WE, et al. Genomic pathway analysis reveals that EZH2 and HDAC4 represent mutually exclusive epigenetic pathways across human cancers. *BMC Med Genet*. 2013;6:35 PubMed PMID: 24079712. Pubmed Central PMCID: PMC3850967. Epub 2013/10/02. eng.
97. Asangani IA, Harms PW, Dodson L, Pandhi M, Kunju LP, Maher CA, et al. Genetic and epigenetic loss of microRNA-31 leads to feed-forward expression of EZH2 in melanoma. *Oncotarget*. 2012;3(9):1011–25 PubMed PMID: 22948084. Pubmed Central PMCID: PMC3663613. Epub 2012/09/06. eng.
98. Fan T, Jiang S, Chung N, Alikhan A, Ni C, Lee CC, et al. EZH2-dependent suppression of a cellular senescence phenotype in melanoma cells by inhibition of p21/CDKN1A expression. *Cell Cancer Res*. 2011;9(4):418–29 PubMed PMID: 21383005. Pubmed Central PMCID: PMC3078218. Epub 2011/03/09. eng.
99. McHugh JB, Fullen DR, Ma L, Kleer CG, Su LD. Expression of polycomb group protein EZH2 in nevi and melanoma. *J Cutan Pathol*. 2007;34(8):597–600 PubMed PMID: 17640228. Epub 2007/07/21. eng.
100. Bachmann IM, Halvorsen OJ, Collett K, Stefansson IM, Straume O, Haukaas SA, et al. EZH2 expression is associated with high proliferation rate and aggressive tumor subgroups in cutaneous melanoma and cancers of the endometrium, prostate, and breast. *J Clin Oncol*. 2006;24(2):268–73 PubMed PMID: 16330673. Epub 2005/12/07. eng.
101. Sengupta D, Byrum SD, Avaritt NL, Davis L, Shields B, Mahmood F, et al. Quantitative histone mass spectrometry identifies elevated histone H3 lysine 27 (Lys27) trimethylation in melanoma. *Mol Cell Proteomics*. 2016;15(3):765–75 PubMed PMID: 26621846. Pubmed Central PMCID: PMC4813699. Epub 2015/12/02. eng.
102. Zingg D, Debbache J, Schaefer SM, Tuncer E, Frommel SC, Cheng P, et al. The epigenetic modifier EZH2 controls melanoma growth and metastasis through silencing of distinct tumour suppressors. *Nat Commun*. 2015;6:6051 PubMed PMID: 25609585. Epub 2015/01/23. eng.
103. Italiano A, Soria JC, Toulmonde M, Michot JM, Lucchesi C, Varga A, et al. Tazemetostat, an EZH2 inhibitor, in relapsed or refractory B-cell non-Hodgkin lymphoma and advanced solid tumours: a first-in-human, open-label, phase 1 study. *Lancet Oncol*. 2018;19(5):649–59 PubMed PMID: 29650362. Epub 2018/04/14. eng.
104. Campbell JE, Kuntz KW, Knutson SK, Warholc NM, Keilhack H, Wigle TJ, et al. EPZ011989, a potent, orally-available EZH2 inhibitor with robust in vivo activity. *ACS Med Chem Lett*. 2015;6(5):491–5 PubMed PMID: 26005520. Pubmed Central PMCID: PMC4434464. Epub 2015/05/26. eng.
105. McCabe MT, Ott HM, Ganji G, Korenchuk S, Thompson C, Van Aller GS, et al. EZH2 inhibition as a therapeutic strategy for lymphoma with EZH2-activating mutations. *Nature*. 2012;492(7427):108–12 PubMed PMID: 23051747. Epub 2012/10/12. eng.
106. Hersey P, Gallagher S, Tiffen J, Shklovskaya E, Wilson S, Filipp F. Abstract 1676: EZH2 inhibitors in immunotherapy of melanoma. *Cancer Res*. 2017;77(13 Supplement):1676.
107. Xiong X, Zhang J, Liang W, Cao W, Qin S, Dai L, et al. Fuse-binding protein 1 is a target of the EZH2 inhibitor GSK343, in osteosarcoma cells. *Int J Oncol*. 2016;49(2):623–8 PubMed PMID: 27278257. Epub 2016/06/10. eng.
108. Knutson SK, Wigle TJ, Warholc NM, Sneeringer CJ, Allain CJ, Klaus CR, et al. A selective inhibitor of EZH2 blocks H3K27 methylation and kills mutant lymphoma cells. *Nat Chem Biol*. 2012;8(11):890–6 PubMed PMID: 23023262. Epub 2012/10/02. eng.

109. Qi W, Zhao K, Gu J, Huang Y, Wang Y, Zhang H, et al. An allosteric PRC2 inhibitor targeting the H3K27me3 binding pocket of EED. *Nat Chem Biol*. 2017;13(4):381–8 PubMed PMID: 28135235. Epub 2017/01/31. eng.
110. Huang Y, Zhang J, Yu Z, Zhang H, Wang Y, Lingel A, et al. Discovery of first-in-class, potent, and orally bioavailable embryonic ectoderm development (EED) inhibitor with robust anticancer efficacy. *J Med Chem*. 2017;60(6):2215–26 PubMed PMID: 28092155. Epub 2017/01/17. eng.
111. Fnu S, Williamson EA, De Haro LP, Brennen M, Wray J, Shaheen M, et al. Methylation of histone H3 lysine 36 enhances DNA repair by nonhomologous end-joining. *Proc Natl Acad Sci U S A*. 2011;108(2):540–5 PubMed PMID: 21187428. Pubmed Central PMCID: PMC3021059. Epub 2010/12/29. eng.
112. Mikkelsen TS, Ku M, Jaffe DB, Issac B, Lieberman E, Giannoukos G, et al. Genome-wide maps of chromatin state in pluripotent and lineage-committed cells. *Nature*. 2007;448(7153):553–60 PubMed PMID: 17603471. Pubmed Central PMCID: PMC2921165. Epub 2007/07/03. eng.
113. Schwartz S, Meshorer E, Ast G. Chromatin organization marks exon-intron structure. *Nat Struct Mol Biol*. 2009;16(9):990–5 PubMed PMID: 19684600. Epub 2009/08/18. eng.
114. Pfister SX, Ahrabi S, Zalmas LP, Sarkar S, Aymard F, Bachrati CZ, et al. SETD2-dependent histone H3K36 trimethylation is required for homologous recombination repair and genome stability. *Cell Rep*. 2014;7(6):2006–18 PubMed PMID: 24931610. Pubmed Central PMCID: PMC4074340. Epub 2014/06/17. eng.
115. Chantalat S, Depaux A, Hery P, Barral S, Thuret JY, Dimitrov S, et al. Histone H3 trimethylation at lysine 36 is associated with constitutive and facultative heterochromatin. *Genome Res*. 2011;21(9):1426–37 PubMed PMID: 21803857. Pubmed Central PMCID: PMC3166828. Epub 2011/08/02. eng.
116. Yuan W, Xu M, Huang C, Liu N, Chen S, Zhu B. H3K36 methylation antagonizes PRC2-mediated H3K27 methylation. *J Biol Chem*. 2011;286(10):7983–9 PubMed PMID: 21239496. Pubmed Central PMCID: PMC3048685. Epub 2011/01/18. eng.
117. Li J, Duns G, Westers H, Sijmons R, van den Berg A, Kok K. SETD2: an epigenetic modifier with tumor suppressor functionality. *Oncotarget*. 2016;7(31):50719–34 PubMed PMID: 27191891. Pubmed Central PMCID: PMC5226616. Epub 2016/05/19. eng.
118. TCGA. Comprehensive molecular characterization of clear cell renal cell carcinoma. *Nature*. 2013;499(7456):43–9 PubMed PMID: 23792563. Pubmed Central PMCID: PMC3771322. Epub 2013/06/25. eng.
119. Bannister AJ, Schneider R, Myers FA, Thorne AW, Crane-Robinson C, Kouzarides T. Spatial distribution of di- and tri-methyl lysine 36 of histone H3 at active genes. *J Biol Chem*. 2005;280(18):17732–6 PubMed PMID: 15760899. Epub 2005/03/12. eng.
120. Lu C, Jain SU, Hoelper D, Bechet D, Molden RC, Ran L, et al. Histone H3K36 mutations promote sarcomagenesis through altered histone methylation landscape. *Science*. 2016;352(6287):844–9 PubMed PMID: 27174990. Pubmed Central PMCID: PMC4928577. Epub 2016/05/14. eng.
121. Yuan H, Li N, Fu D, Ren J, Hui J, Peng J, et al. Histone methyltransferase SETD2 modulates alternative splicing to inhibit intestinal tumorigenesis. *J Clin Invest*. 2017;127(9):3375–91 PubMed PMID: 28825595. Pubmed Central PMCID: PMC5669571. Epub 2017/08/22. eng.
122. Lucio-Eterovic AK, Singh MM, Gardner JE, Veerappan CS, Rice JC, Carpenter PB. Role for the nuclear receptor-binding SET domain protein 1 (NSD1) methyltransferase in coordinating lysine 36 methylation at histone 3 with RNA polymerase II function. *Proc Natl Acad Sci U S A*. 2010;107(39):16952–7 PubMed PMID: 20837538. Pubmed Central PMCID: PMC2947892. Epub 2010/09/15. eng.
123. Streubel G, Watson A, Jammula SG, Scelfo A, Fitzpatrick DJ, Oliviero G, et al. The H3K36me2 methyltransferase Nsd1 demarcates PRC2-mediated H3K27me2 and H3K27me3 domains in embryonic stem cells. *Mol Cell*. 2018;70(2):371–9 e5. PubMed PMID: 29606589. Epub 2018/04/03. eng.
124. Papillon-Cavanagh S, Lu C, Gayden T, Mikael LG, Bechet D, Karamboulas C, et al. Impaired H3K36 methylation defines a subset of head and neck squamous cell carcinomas. *Nat Genet*. 2017;49(2):180–5 PubMed PMID: 28067913. Pubmed Central PMCID: PMC5549104. Epub 2017/01/10. eng.
125. Brennan K, Shin JH, Tay JK, Prunello M, Gentles AJ, Sunwoo JB, et al. NSD1 inactivation defines an immune cold, DNA hypomethylated subtype in squamous cell carcinoma. *Sci Rep*. 2017;7(1):17064 PubMed PMID: 29213088. Pubmed Central PMCID: PMC5719078. Epub 2017/12/08. eng.
126. Peri S, Izumchenko E, Schubert AD, Slifker MJ, Ruth K, Serebriiskii IG, et al. NSD1- and NSD2-damaging mutations define a subset of laryngeal tumors with favorable prognosis. *Nat Commun*. 2017;8(1):1772 PubMed PMID: 29176703. Pubmed Central PMCID: PMC5701248. Epub 2017/11/28. eng.
127. Su X, Zhang J, Mouawad R, Comperat E, Roupret M, Allanic F, et al. NSD1 inactivation and SETD2 mutation drive a convergence toward loss of function of H3K36 writers in clear cell renal cell carcinomas. *Cancer Res*. 2017;77(18):4835–45 PubMed PMID: 28754676. Epub 2017/07/30. eng.
128. Choufani S, Cytrynbaum C, Chung BH, Turinsky AL, Grafodatskaya D, Chen YA, et al. NSD1 mutations generate a genome-wide DNA methylation signature. *Nat Commun*. 2015;6:10207 PubMed PMID: 26690673. Pubmed Central PMCID: PMC4703864. Epub 2015/12/23. eng.
129. de Souza CF, Xander P, Monteiro AC, Silva AG, da Silva DC, Mai S, et al. Mining gene expression signature for the detection of pre-malignant melanocytes and early melanomas with risk for metastasis. *PLoS One*. 2012;7(9):e44800 PubMed PMID: 22984562. Pubmed Central PMCID: PMC3439384. Epub 2012/09/18. eng.
130. Zheng W, Ibanez G, Wu H, Blum G, Zeng H, Dong A, et al. Sinefungin derivatives as inhibitors and structure probes of protein lysine methyltransferase SETD2. *J Am Chem Soc*. 2012;134(43):18004–14 PubMed PMID: 23043551. Pubmed Central PMCID: PMC3504124. Epub 2012/10/10. eng.
131. Morishita M, Mevius DEHF, Shen Y, Zhao S, di Luccio E. BIX-01294 inhibits oncoproteins NSD1, NSD2 and NSD3. *Med Chem Res*. 2017;26(9):2038–47.
132. Steger DJ, Lefterova MI, Ying L, Stonestrom AJ, Schupp M, Zhuo D, et al. DOT1L/KMT4 recruitment and H3K79 methylation are ubiquitously coupled with gene transcription in mammalian cells. *Mol Cell Biol*. 2008;28(8):2825–39 PubMed PMID: 18285465. Pubmed Central PMCID: PMC2293113. Epub 2008/02/21. eng.
133. Nguyen AT, Zhang Y. The diverse functions of Dot1 and H3K79 methylation. *Genes Dev*. 2011;25(13):1345–58 PubMed PMID: 21724828. Pubmed Central PMCID: PMC3134078. Epub 2011/07/05. eng.
134. Zhu B, Chen S, Wang H, Yin C, Han C, Peng C, et al. The protective role of DOT1L in UV-induced melanomagenesis. *Nat Commun*. 2018;9(1):259 PubMed PMID: 29343685. Pubmed Central PMCID: PMC5772495. Epub 2018/01/19. eng.
135. Campbell CT, Haladyna JN, Drubin DA, Thomson TM, Maria MJ, Yamauchi T, et al. Mechanisms of pinometostat (EPZ-5676) treatment-emergent resistance in MLL-rearranged leukemia. *Mol Cancer Ther*. 2017;16(8):1669–79 PubMed PMID: 28428443. Epub 2017/04/22. eng.
136. Daigle SR, Olhava EJ, Therkelsen CA, Basavathruni A, Jin L, Boriack-Sjodin PA, et al. Potent inhibition of DOT1L as treatment of MLL-fusion leukemia. *Blood*. 2013;122(6):1017–25 PubMed PMID: 23801631. Pubmed Central PMCID: PMC3739029. Epub 2013/06/27. eng.
137. Stein EM, Garcia-Manero G, Rizzieri DA, Tibes R, Berdeja JG, Savona MR, et al. The DOT1L inhibitor pinometostat reduces H3K79 methylation and has modest clinical activity in adult acute leukemia. *Blood*. 2018;131(24):2661–9 PubMed PMID: 29724899. Epub 2018/05/05. eng.
138. Shukla N, Wetmore C, O'Brien MM, Silverman LB, Brown P, Cooper TM, et al. Final report of phase 1 study of the DOT1L inhibitor, pinometostat (EPZ-5676), in children with relapsed or refractory MLL-r acute leukemia. *Blood*. 2016;128(22):2780.
139. Yu W, Chory EJ, Wernimont AK, Tempel W, Scopton A, Federation A, et al. Catalytic site remodelling of the DOT1L methyltransferase by selective inhibitors. *Nat Commun*. 2012;3:1288 PubMed PMID: 23250418. Epub 2012/12/20. eng.
140. Beck DB, Oda H, Shen SS, Reinberg D. PR-Set7 and H4K20me1: at the crossroads of genome integrity, cell cycle, chromosome condensation, and transcription. *Genes Dev*. 2012;26(4):325–37 PubMed PMID: 22345514. Pubmed Central PMCID: PMC3289880. Epub 2012/02/22. eng.
141. Couture JF, Collazo E, Brunzelle JS, Trievel RC. Structural and functional analysis of SET8, a histone H4 Lys-20 methyltransferase. *Genes Dev*. 2005;19(12):1455–65 PubMed PMID: 15933070. Pubmed Central PMCID: PMC1151662. Epub 2005/06/04. eng.
142. Wang Z, Dai X, Zhong J, Inuzuka H, Wan L, Li X, et al. SCF(beta-TRCP) promotes cell growth by targeting PR-Set7/Set8 for degradation. *Nat Commun*. 2015;6:10185 PubMed PMID: 26666832. Pubmed Central PMCID: PMC4682171. Epub 2015/12/17. eng.
143. Oda H, Hubner MR, Beck DB, Vermeulen M, Hurwitz J, Spector DL, et al. Regulation of the histone H4 monomethylase PR-Set7 by CRL4(Cdt2)-mediated PCNA-dependent degradation during DNA damage. *Mol Cell*. 2010;40(3):364–76 PubMed PMID: 21035370. Pubmed Central PMCID: PMC2999913. Epub 2010/11/03. eng.

144. Benamar M, Guessous F, Du K, Corbett P, Obeid J, Gioeli D, et al. Inactivation of the CRL4-CDT2-SET8/p21 ubiquitylation and degradation axis underlies the therapeutic efficacy of pevonedistat in melanoma. *EBioMed*. 2016;10:85–100 PubMed PMID: 27333051. Pubmed Central PMCID: PMC5006603. Epub 2016/06/23. eng.
145. Schotta G, Sengupta R, Kubicek S, Malin S, Kauer M, Callen E, et al. A chromatin-wide transition to H4K20 monomethylation impairs genome integrity and programmed DNA rearrangements in the mouse. *Genes Dev*. 2008;22(15):2048–61 PubMed PMID: 18676810. Pubmed Central PMCID: PMC2492754. Epub 2008/08/05. eng.
146. Wu H, Siarheyeva A, Zeng H, Lam R, Dong A, Wu XH, et al. Crystal structures of the human histone H4K20 methyltransferases SUV420H1 and SUV420H2. *FEBS Lett*. 2013;587(23):3859–68 PubMed PMID: 24396869. Epub 2014/01/08. eng.
147. Vougiouklakis T, Sone K, Saloura V, Cho HS, Suzuki T, Dohmae N, et al. SUV420H1 enhances the phosphorylation and transcription of ERK1 in cancer cells. *Oncotarget*. 2015;6(41):43162–71 PubMed PMID: 26586479. Pubmed Central PMCID: PMC4791223. Epub 2015/11/21. eng.
148. Bromberg KD, Mitchell TR, Upadhyay AK, Jakob CG, Jhala MA, Comess KM, et al. The SUV4-20 inhibitor A-196 verifies a role for epigenetics in genomic integrity. *Nat Chem Biol*. 2017;13(3):317–24 PubMed PMID: 28114273. Epub 2017/01/24. eng.
149. Kearns NA, Pham H, Tabak B, Genga RM, Silverstein NJ, Garber M, et al. Functional annotation of native enhancers with a Cas9-histone demethylase fusion. *Nat Methods*. 2015;12(5):401–3 PubMed PMID: 25775043. Pubmed Central PMCID: PMC4414811. Epub 2015/03/17. eng.
150. Eliades P, Abraham BJ, Ji Z, Miller DM, Christensen CL, Kwiatkowski N, et al. High MITF expression is associated with super-enhancers and suppressed by CDK7 inhibition in melanoma. *J Invest Dermatol*. 2018;138(7):1582–90 PubMed PMID: 29408204. Pubmed Central PMCID: PMC6019629. Epub 2018/02/07. eng.

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