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Tipping the Lysine Methylation Balance in Disease

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Abstract

Genomic instability is a major contributing factor to the development and onset of diseases such as cancer. Emerging evidence has demonstrated that maintaining the proper balance of histone lysine methylation is critical to preserve genomic integrity. Genome-wide association studies, gene sequencing, and genome-wide mapping approaches have helped identify mutations, copy number changes, and aberrant gene regulation of lysine methyltransferases (KMTs) and demethylases (KDMs) associated with cancer and cognitive disorders. Structural analysis of KMTs and KDMs has demonstrated the drugability of these enzymes and has led to the discovery of small molecule inhibitors. Use of these inhibitors has allowed better understanding of the biochemical properties of KMTs and KDMs and demonstrated potential for therapeutic use. This review will highlight the methyl modifications, KMTs and KDMs associated with cancer and neurological disorders and how KMT and KDM and the potential for treatment of these conditions with small molecule inhibitors.

Introduction

Methylation of histones was originally identified in the 1960s and was known to be catalyzed by enzymes that required S-adenosyl-methionine (SAM).^{1–4} However, it wasn't until 2000 when the first histone lysine methyltransferase family [Su(var)3–9] was discovered that the importance of histone lysine methylation was recognized.⁵ Maintaining a proper balance of histone methylation is critical for genomic stability, cell cycle progression, gene regulation, DNA replication, and cancer prevention.⁶ The methylation balance is maintained by the opposing activities of the lysine methyltransferases (KMTs) and the lysine demethylases (KDMs). In the last 12 years, numerous KMTs and KDMs have been identified (Table 1) and crystallized, which has revealed tremendous information about the biochemical properties and regulation of these enzymes.

Two classes of KMTs have been identified, the SET domain containing enzymes, and the Dot1L/KMT4 family (Table 1).⁷ Both classes of KMTs use SAM as the methyl donor and have exquisite specificity for the lysine modified and the degree of modification. For instance, the G9a/KMT1C methyltransferase can methylate histone 3 lysine 9 from an unmodified state (H3K9) to a dimethylated state (H3K9me2). However, reaching trimethylation (H3K9me3) requires Suv39H1/2/KMT1A/B. Two classes of histone demethylases have also been identified, the FAD-dependent amine oxidases (LSD1/KDM1A and LSD2/KDM1B) and the Jumonji C (JmjC) domain containing demethylases (Table 1).⁸ KDMs also have exquisite substrate and degree of lysine specificity. For instance JMJD2A/KDM4A preferentially demethylates H3K9me3, H3K36me3 and H1.4K26me3 to

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the dimethylated state, while JMJD2D/KDM4D prefers H3K9me3 and can demethylate to H3K9me1.^{8,9}

Crystal structures for many KMTs and KDMs have been solved, including co-crystals with substrate peptides, co-factors and important protein domains. Structural analysis of these enzymes has provided biochemical evidence for the mechanism of specificity for both the lysine residue as well as the degree of methylation.^{7,8} These small molecules will ultimately allow better biological characterization of KMTs and KDMs as well as possible treatment of diseases arising from the misregulation of these enzyme classes. The following sections will highlight the relationships between KMTs, KDMs, histone methylation and the diseases they are associated with. We will also profile potential inhibitors of KMTs and KDMs that have started to emerge and disease states that may be improved by targeting these enzymes.

Methyltransferases and Demethylases in Disease

The mis-regulation of methyltransferases and demethylases has been associated with many diseases including aging, cancer and neurological pathologies. These diseases correlate with amplifications, deletions, mutations and mis-expression of KMTs and KDMs. Evidence is accumulating that changes in histone lysine methylation are crucial determinants in neuronal development and differentiation, cognitive function, addiction, behavioral changes, mental retardation, and neuropsychiatric disorders. The importance of maintaining methylation balance in cancer is highlighted by the increased incidence of liver cancer that is observed in animals fed methyl deficient diets.¹⁰ Consistent with this idea, numerous laboratories have demonstrated the importance of lysine methylation balance in maintaining genome integrity, gene regulation, and cancer evasion.^{11,12}

H3K4 Methylation

MLL1/KMT2A was originally identified as a common translocation partner in myeloid and lymphoid leukemias (reviewed in ¹³). MLL1/KMT2A catalyzes H3K4me3 and is important for gene activation. In AML, a frequent MLL1/KMT2A rearrangement involves a duplication of the 3' end of the gene that retains the methyltransferase activity. Knock-in experiments in mice with this protein, MLL-PTD (partial tandem duplication), have demonstrated that the methyltransferase activity is required for leukemia related phenotypes of this partial gene fusion/duplication.¹⁴ Overexpression of MLL-PTD induces H3K4me3 at the HoxA locus, which leads to HoxA overexpression. Overexpression of HoxA is a common feature of leukemias. MLL1/KMT2A can also undergo numerous chromosomal translocations resulting in fusions to AF10, ENL, AF4, AF9, ELL1-3, and many other translocation partners.¹³ Most of these translocations are to the N-terminus of MLL and lack the H3K4 methyltransferase activity. Interestingly, many of these translocation partners are subunits of the Super Elongation Complex (SEC). This complex is required for efficient elongation by RNA polymerase II and may be inappropriately recruited to MLL1/KMT2A target genes by MLL1 fusion proteins, which would then promote leukemogenesis.¹⁵ In support of this model, depletion of the structural core of the SEC (AFF4) reduced HoxA gene expression in leukemia cells.¹⁵ These data suggest there may be an unappreciated role for transcriptional elongation in cancer.

MLL fusion proteins also require the ability to interact with the tumor suppressor menin in order to promote leukemogenesis. This interaction has recently been exploited to design new therapeutics to target MLL1/KMT2A-dependent malignancies.¹⁶ For example, mouse bone marrow cells (BMCs) transformed with MLL fusion proteins treated with the small molecule MLL-menin inhibitors resulted in growth arrest, differentiation, suppression of HoxA9 gene expression, and decreased colony formation. While these small molecule

inhibitors appear promising for treatment of leukemia, determining the potential side effects of targeting the wild type MLL-menin interaction still remains an important issue to resolve.

Work in mouse models has demonstrated a role for H3K4 methylation in behavior, learning, and memory. After fear conditioning, mice had increased H3K4me3 in the hippocampus, which returns to baseline levels within 24 hours after stimulation. In addition to the general increase in H3K4me3, this modification was enriched at both the *zif268* and *bdnf* genes following fear conditioning, which paralleled the increase in gene expression. Mice lacking the H3K4me3 methyltransferase MLL1/KMT2A had decreased response to fear stimulation following conditioning, which indicates that MLL1/KMT2A is required for proper memory formation.¹⁷ Interestingly, fear conditioning is a model for schizophrenia and schizophrenic patients also exhibit loss of H3K4me3 in the prefrontal cortex and altered expression of GABAergic promoters.¹⁸ Of particular interest are changes in expression of *GAD1*, which is required for GABA synthesis. MLL1/KMT2A deficient mice exhibited reduced H3K4me3 at the *GAD1* promoter and decreased *GAD1* expression.¹⁸ These findings implicate misregulation of MLL1/KMT2A and H3K4me3 as factors in schizophrenia. These results also suggest that while MLL1/KMT2A inhibitors could be important in cancer therapy, MLL inhibition could potentiate anxiety and schizophrenia.

Aberrant demethylation of H3K4 has also been implicated in cancer, epithelial to mesenchymal transition (EMT) and neurological disorders. For example, H3K4me1/2 demethylase LSD1/KDM1A promotes proliferation in bladder cancer, small cell lung cancer, and colorectal cancer.¹⁹ In the case of breast cancer, LSD1/KDM1A functions to suppress invasion and metastasis and is commonly down regulated in breast carcinomas.²⁰ LSD1/KDM1A is an FAD-dependent amine oxidase and has been found susceptible to inhibitors of monoamine oxidases such as trans-2-phenylcyclopropylamine (PCPA, tranlycypromine).²¹ PCPA covalently modifies FAD, creating an adduct that irreversibly inhibits LSD1/KDM1A. PCPA is used to treat clinical depression and schizophrenia, and thus suggests that LSD1/KDM1A will have important neuronal functions as well.²² While the amine oxidase inhibitors, including PCPA, are not specific to LSD1/KDM1A they represent excellent starting scaffolds for the design of specific inhibitors.²³

The JmjC-containing H3K4 demethylating enzymes are also linked to cancer and neurological disorders. For example, increased expression of the H3K4me3 demethylase PLU-1/KDM5B causes increased proliferation in breast cancer.²⁴ SMCX/KDM5C, another H3K4me3 demethylase, is mutated in patients with cognitive impairments.²⁵ In zebrafish, these mutations have been shown to impact demethylation and results in aberrant neural branching.²⁶ These data highlight the importance H3K4me3 balance in cancer and neurological disorders. These results also emphasize that loss of function and increased expression are associated with different disease states, which emphasizes the importance of examining side effects of treatment with small molecules that inhibit certain KMTs and KDMs (Figure 1).

H3K79 Methylation

In addition to being linked to the SEC, MLL-AF10, MLL-AF9 and MLL-ENL fusions can also directly recruit the H3K79 methyltransferase DOT1L/KMT4.^{27,28} Recruitment of catalytically active DOT1L/KMT4 is required for leukemogenesis and is associated with increased H3K79 methylation at HoxA genes.²⁹ DOT1L/KMT4 is also involved in transcriptional elongation and it remains to be determined whether abnormal transcriptional elongation occurs at key leukemogenic genes (*i.e.*, HoxA9 and HoxA10) and directly causes the malignancies. Since the catalytic domain of Dot1L/KMT4 is distinct from the SET domain-containing methyltransferases, progress has been made on designing Dot1L/KMT4

specific inhibitors such as EPZ004777.^{30,31} This compound is of particular interest because the treatment of MLL cells with EPZ004777 resulted in decreased expression of aberrantly regulated MLL1/KMT2A-target genes (including HoxA9) and the inhibition of leukemogenesis in mouse models.³¹ These results suggest Dot1L/KMT4 specific inhibitors could be potent anti-leukemia compounds and an important area for future research.

H3K27 Methylation

The H3K27me3 methyltransferase EZH2/KMT6 is frequently overexpressed or mutated in solid tumors.³² Overexpression of EZH2/KMT6 is common in breast, prostate, lung, skin, and colon cancer. Additionally, overexpression of EZH2/KMT6 increases invasiveness of breast and prostate cancer cells in a manner dependent on the H3K27me3 catalytic activity.³² Furthermore, depletion of EZH2/KMT6 in breast cancer and prostate cancer xenografts ameliorated tumor growth.^{33–35} Overexpression of EZH2/KMT6 is thought to function through repression of numerous tumor suppressors including BRCA1, INK4A/ARF, and E-cadherin.³⁵ Restoration of normal EZH2/KMT6 levels can reduce proliferation, invasion and metastasis.

Tumors that overexpress EZH2/KMT6 may be potential targets for treatment with DZNep or other S-adenosylhomocysteine (SAH) hydrolase inhibitors. SAH is a catabolite of SAM and is produced during the methylation reaction and competes with SAM for binding KMTs. SAH is normally processed by SAH hydrolase into homocysteine and adenosine. DZNep inhibition of SAH hydrolase leads to increased concentrations of SAH, which is a competitive inhibitor of SAM-dependent methyltransferases. Interestingly, this leads to degradation of EZH2/KMT6 and its associated PRC2 components, Suz12, EED, and BMI1. This decrease results in global loss of H3K27me3.³⁶ DZNep treatment results in increased apoptosis, decreased proliferation, and decreased invasion and migration potential.³⁷ While DZNep is not a specific EZH2/KMT6 inhibitor, it does suggest that specific EZH2/KMT6 inhibitors could be strong chemotherapeutics for cancers with amplification or overexpression of EZH2/KMT6. These data also highlight the possibility of regulating these enzymes through parallel reactions affecting metabolites (Figure 1)

The H3K27me3 methyltransferase EZH2/KMT6 is also a critical regulator of neuronal differentiation and development. EZH2/KMT6 is required to maintain pluripotency but is displaced from genes activated during neuronal differentiation.³⁸ Consistent with a critical role in neural development, mice lacking EZH2/KMT6 have a severe decrease in neurons in the cerebral cortex. Interestingly, this decrease in neurons is accompanied by an increase in early neuroprogenitors that appear early during cortical development. There is also an inability to produce the normal number of neurons later in development.³⁹ These observations are consistent with an increase in expression of the EZH2/KMT6-repressed cell cycle inhibitors Cdkn2A and 2B in the neuroprogenitors cells.³⁹

H3K27me3 is also linked to behavior and neuropsychiatric disorders. Mice exposed to social defeat stress have a global increase in H3K27me3.⁴⁰ Furthermore, levels of H3K27me3 at the *bdnf* gene anti-correlate with changes in its expression in mice exposed to chronic stress.^{40,41} H3K27me3 also regulates GABAergic transcriptional changes during differentiation at the important schizophrenia loci *Gad1*, *Npy* and *Sst*, suggesting H3K27me3 may be another potential modulator of schizophrenia.¹⁸ This is further supported by the observation that JARID2 is contained within the 6p22 schizophrenia susceptibility locus.^{42,43} Since JARID2 assists in PRC2 targeting, this potentially links EZH2/KMT6 and PRC2 to schizophrenia.⁴⁴ Once again, there is a need to balance methylation to prevent cancer and neurological disorders (Figure 1). Since there is a gain of expression in one context and loss in the other, future studies evaluating inhibitors should

pay particular attention to neurological function and behavior of the patients while targeting cancers with increased expression for inhibition.

Just as methylation of H3K27me3 is aberrant in many cancers, H3K27me3 demethylases are also mis-regulated and mutated. For instance, JMJD3/KDM6B is down regulated in lung and liver cancers.⁴⁵ Likewise, UTX/KDM6A contains frequent inactivating mutations in numerous tumors, which result in increased cell proliferation.⁴⁶ Conversely, down regulation and mutation within UTX/KDM6A correlate with poor outcome in multiple cancers.⁴⁷ Since mutation and loss of JMJD3/KDM6B and UTX/KDM6A correlate with cell proliferation and poor prognosis, they may be potential targets for agonist compounds. Increasing activity of JMJD3/KDM6B or UTX/KDM6A could provide useful therapy in cancers with heterozygous loss of function mutations, loss of heterozygosity or even potentially in tumors with overexpression or amplification EZH2/KMT6. Alternatively, UTX/KDM6A inhibitors could be important in cancers dependent on MLL2/3/KMT2B/C, which resides in a complex with UTX/KDM6A.⁴⁸

H3K9 Methylation

Imbalances in methylation of H3K9 are associated with numerous malignancies. Loss of the H3K9me3 methyltransferases Suv39H1/2/KMT1A/B results in B-cell lymphoma in mice.⁴⁹ Decreased expression of the H3K9me2 methyltransferase G9a/KMT1C is associated with genome instability and is down-regulated or deleted in medulloblastomas.^{50,51} Furthermore, elevated expression of G9a/KMT1C correlates with poor outcome in advanced lung cancer patients.⁵² The overexpression of G9a/KMT1C increases migration and metastasis, while G9a/KMT1C depletion inhibits lung cancer cell migration *in vitro* and invasion *in vivo*. Since G9a/KMT1C co-localizes with PCNA and depletion of G9a/KMT1C results in chromosome instability, G9a/KMT1C may play a fundamental role in DNA replication. Thus G9a/KMT1C could make an important contribution to cancer independent of changes in transcriptional targets. This is an area that needs further exploration.

Suv39H1/2/KMT1A/B, G9a/KMT1C and GLP/KMT1D are inhibited by the fungal toxin chaetocin, which acts as a competitive inhibitor of SAM. Chaetocin has anti-tumor activity through regulation of KMT1A/B, KMT1C, KMT1D as well as hypoxia signaling, and regulation of reactive oxygen species levels through thioredoxin reductase.^{53,54} KMT1C and KMT1D can also be inhibited by the small molecule BIX01294, which acts as a competitive inhibitor to the H3 histone tail.^{55,56} Inhibition by BIX01294 reduces global H3K9 dimethylation as well as levels of H3K9me2 at KMT1C target promoters. While chaetocin is a non-specific methylation inhibitor, BIX-2194 is a promising lead compound and provides a chemical base to modify for more potent inhibitors of KMT1C and KMT1D. These compounds would be potentially helpful in treatment of lung cancers with elevated expression of KMT1C.⁵²

Recent work is beginning to illuminate the roles of H3K9 histone demethylases in cancer as well. The H3K9me3 demethylases JMJD2B/KDM4B and JMJD2C/KDM4C have been demonstrated to be amplified in medulloblastomas.⁵¹ In addition, JMJD2C/KDM4C has also been found amplified in AML, breast and squamous carcinomas.⁵⁷⁻⁵⁹ When JMJD2C/KDM4C is overexpressed in breast cancer there is an increase in tumor potential. However, depletion from cells containing the amplification results in a decrease in cellular proliferation.⁶⁰ Another family member, JMJD2A/KDM4A, is overexpressed in prostate cancers and has been implicated in regulating proliferation, migration, and invasion in breast cancer.^{61,62} JMJD2A/KDM4A is also an important regulator of cell cycle and DNA replication timing.⁶³ JMJD2A/KDM4A protein levels are regulated during cell cycle through a ubiquitin-dependent proteosomal degradation.⁶⁴ Proper regulation of JMJD2A/

KDM4A protein levels is important for regulating gene expression and cell cycle progression.^{64,65} For these reasons, inhibitors of the JMJD2/KDM4 family have the potential to be potent chemotherapeutic agents. Progress has been made at designing inhibitors *in vitro*, however it remains to be determined whether family and member specific inhibitors can be developed.⁶⁶ One mechanism to achieve specificity may be to design agonists or inhibitors for the interaction between JMJD2A/KDM4A and its associated f-box proteins, which provide specificity for ubiquitin ligases. This strategy would allow family and enzyme specificity and perhaps even tissue specific control of expression. Similar to many of the inhibitors described in this review, it will be important to consider JMJD2/KDM4 inhibitors in the context of neurological problems. This particularly true with respect to autism as single nucleotide polymorphisms in JMJD2C/KDM4C and genomic deletions containing JMJD2B/KDM4B, have been reported in patients.^{67,68}

H3K9 methylation is also an important regulator of behavior and memory. Heterozygous mice for *GLP/KMT1D* share several behavioral characteristics with human 9q34.3 (where Human *GLP/KMT1D* is located) subtelomeric deletion syndrome patients.⁶⁹ These mice exhibit reduced activity and exploration, increased anxiety, and prolonged response to social encounters. Reduced exploration is a characteristic of autistic patients, often accompanied by elevated anxiety and disturbed social interactions.⁷⁰ Deletion of *GLP/KMT1D* (located in 9q34) or substitution within the protein have been linked to mental retardation, epileptic seizures, and autism.⁷¹ Mice deficient for *GLP/KMT1D* or *G9a/KMT1C* in post-natal forebrain neurons exhibit a de-repression of non-neuronal genes, leading to some complex behavioral abnormalities, including defects in learning and memory.⁶⁹ Demethylation of H3K9 has also been linked to mental retardation. The H3K9me1/2 and H4K20me1 demethylase PHF8/KMT7B is mutated in patients with X-Linked Mental Retardation (XLMR) with several common mutations altering the enzymatic activity of the enzyme⁷². PHF8/KMT7B is important in development, as loss of PHF8/KMT7B in zebrafish results in cleft palate and development defects in the brain and jaw. The zebrafish model provides an excellent system for testing PHF8/KMT7B agonists, which might have therapeutic value in XLMR patients with mutations that affect the catalytic activity of PHF8/KMT7B.

G9a/KMT1C has also been shown to be essential in cocaine-induced plasticity.⁷³ Repeated cocaine administration resulted in reduction of G9a/KMT1C and decreased H3K9me2 in the nucleus accumbens of rodents, a key component of the brain's reward circuitry. The down-regulation of G9a/KMT1C mediates cocaine's ability to regulate the dendritic spine density of neurons of this region. This suggests G9a/KMT1C or GLP/KMT1D agonists could help reduce addiction to cocaine and potentially treat other addictive behaviors. These agonists could also potentially benefit autistic patients or help treat epilepsy. Again, these results raise the importance of evaluating compounds that target G9a/KMT1C and GLP/KMT1D in the context of possible neurological deficits.

Another H3K9 tri-methyltransferase, SETDB1/KMT1E (SET domain, bifurcated 1), has also been shown to cause anti-depressant-like phenotypes when overexpressed in mice. SETDB1/KMT1E represses the expression of the NMDA receptor subunit *Grin2b* in neurons, leading to antidepressant-like behavior changes.⁷⁴ Intriguingly the authors found that SETDB1/KMT1E regulated a very small fraction of known coding genes (0.75%) with a high proportion being NMDA like receptors. This suggests that SETDB1/KMT1E agonists could potentially be a good target for future anti-depressant medications with more limited side effects. It also raises the question as to what other non-coding targets are important in the observed phenotypes.

Conclusion

Misregulation, mutation, amplification and deletion of KMTs and KDMs are prominent in cancer and neurological diseases and the ability to inhibit or activate them with drugs are excellent potential therapies. Substantial consideration has been given to the design of small molecules and peptides that can block active sites, interfere with co-factor binding, modify co-factors, or potentially disrupt protein-protein interactions. However, little effort has been expended at identifying agonists that would be applicable in cancers with reduced expression or neurological disorders that frequently lose KMT or KDM activity. Additional effort may be well spent in designing allosteric activators or inhibitors that may allow better specificity than active site compounds that may have difficulty in distinguishing between highly homologous family members. Furthermore, disrupting protein-protein interactions, a strategy similar to the menin-Mll inhibitor, may also provide increased specificity. For example, an inhibitor that targets LSD1/KDM1A interaction with CoREST may potentially block LSD1/KDM1A function *in vivo*. Another strategy might be to exploit endogenous regulatory machinery of the enzymes to promote or inhibit protein turnover.

It may also prove fruitful to target crosstalk of KMTs and KDMs as well as crosstalk between different modifications. For instance inhibiting EZH2/KMT6 in response to UTX/KDM6A or JMJD3/KDM6B amplification might minimize off-target effects. In the case of modification crosstalk, promoting H3K36me3 might also block effects of increased H3K27me3 levels from overexpression of EZH2/KMT6. Finally, identifying molecules that block recruitment of KMTs and KDMs through inhibition of their PHD, TUDOR, and other chromatin binding domains may provide specificity and potentially better function. This strategy has been highly successful for the recently discovered BRD4 inhibitors.⁷⁵

It is clearly emerging that KMTs and KDMs play roles in multiple tissue, often in opposing mechanisms (Figure 1). It will be important to evaluate inhibitors and agonists in the context of both cancer and neurological disease to minimize potential side effects. Therefore, it may be necessary to design not only enzyme specific inhibitors, but perhaps tissue specific targeting mechanisms as well.

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Figure 1.

A schematic emphasizing how too much or too little lysine methylation through aberrant expression, genomic alteration or regulation of KMTs and/or KDMs can impact cancer or neurological disease states.

Lysine Methyltransferases, Lysine Demethylases, and Their Histone Substrates. The table lists the known KMTs (green) and KDMs (red).

Table 1

	Nomenclature	Gene ID (H)	H3K4me			H3K9me			H3K27me			H3K36me			H3K79me			H4K20me			H1K26me		
			1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
KMTs	KMT1A	6839																					
	KMT1B	64707																					
	KMT1C	10919																					
	KMT1D	79813																					
	KMT1E	84505																					
	KMT1F	83852																					
	KMT2A	4297																					
	KMT2B	8085																					
	KMT2C	58508																					
	KMT2D	9757																					
	KMT2E	55904																					
	KMT2F	9739																					
	KMT2G	23067																					
	KMT2H	55870																					
	KMT3A	29072																					
	KMT3B	64324																					
	KMT3C	56950																					
	KMT3D	150572																					
	KMT3E	64754																					
	KMT3F	54904																					
	KMT3G	7468																					
	KMT4	84444																					
	KMT5A	387893																					
	KMT5B	610881																					
	KMT5C	613198																					
	KMT6	2146																					

		Gene ID (H)	H3K4me			H3K9me			H3K27me			H3K36me			H3K79me			H4K20me			H1K26me		
	Nomenclature		1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
	KMT7	80854																					
	KMT8A	7799																					
	KMT8B	56979																					
	KMT8C	93166																					
	KMT8D	56978																					
KDMs	KDM1A	23028																					
	KDM1B	221656																					
	KDM2A	22992																					
	KDM2B	84678																					
	KDM3A	55818																					
	KDM3B	51780																					
	KDM3C	221037																					
	KDM4A	9682																					
	KDM4B	23030																					
	KDM4C	23081																					
	KDM4D	55693																					
	KDM5A	5927																					
	KDM5B	10765																					
	KDM5C	8242																					
	KDM5D	8284																					
	KDM6A	7403																					
	KDM6B	23135																					
	KDM7A	80853																					
	KDM7B	23133																					
	KDM7C	5253																					
	KDM8	79831																					

Shaded boxes indicate the residues and degrees of methylation of histone tails on which the enzymes operate. For KMTs, a green shaded box indicates it can create that modification. For KDMs, a red shaded box indicates it can remove that modification. A ? indicates that an enzymatic activity has been demonstrated in vitro and detected using methods unable to determine the degree of methylation.