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KDM5B is a master regulator of the H3K4-methylome in stem cells, development and cancer

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Abstract

Epigenetic regulation of chromatin plays a critical role in controlling stem cell function and tumorigenesis. The histone lysine demethylase, KDM5B, which catalyzes the demethylation of histone 3 lysine 4 (H3K4), is important for embryonic stem (ES) cell differentiation, and is a critical regulator of the H3K4-methylome during early mouse embryonic pre-implantation stage development. KDM5B is also overexpressed, amplified, or mutated in many cancer types. In cancer cells, KDM5B regulates expression of oncogenes and tumor suppressors by modulating H3K4 methylation levels. In this review, we examine how KDM5B regulates gene expression and cellular fates of stem cells and cancer cells by temporally and spatially controlling H3K4 methylation levels.

Keywords

KDM5B; H3K4me3; embryonic stem cells; cancer; pluripotent; epigenetics; chromatin; gene expression; differentiation; histone demethylase

Introduction

Initiation and maintenance of mammalian cellular diversity is achieved in part by regulating expression of distinct sets of genes which define cellular states. Regulation of gene expression, which is an essential cellular process that is critical for establishing and maintaining cellular identity, is tightly controlled by DNA binding transcription factors and chromatin modifying enzymes. Packaging of DNA into nucleosomes and higher-order chromatin structures is critical to regulate gene expression, DNA replication, segregation and

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COMPETING INTERESTS

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DNA repair mechanisms [1]. Packaging of mammalian genomes in the nucleus is mediated by chromatin, which is a macromolecular complex composed of DNA and associated proteins. Nucleosomes, which are the basic unit of chromatin, are comprised of 146 bp of DNA wrapped around an octamer of histones. The histone octamer is composed of two subunits of histone H3, H4, H2A and H2B, and histone H1, which is associated with the linker DNA sequences between nucleosomes [2, 3].

Epigenetic regulation of chromatin, including posttranslational modification of histone tails, is a reversible process that plays an important role in genome stability, X-chromosome inactivation, imprinting and transcriptional activation [4]. Posttranslational modification of histone tails, such as methylation of lysine and arginine residues, acetylation, sumoylation, ubiquitination and phosphorylation, mediate the recruitment of protein complexes that modulate chromatin structure at target gene loci, and participate in the regulation of many biological processes such transcription, cell cycle control and DNA repair [1, 5]. Histone modifying enzymes such as histone methyltransferases (HMTs) and lysine demethylases (KDMs), histone acetyltransferases (HATs) and deacetylases (HDACs), ubiquitin ligases, and various kinases and phosphatases, catalyze these posttranslational events [3, 6]. The histone epigenetic transcriptional response largely depends on three factors; the residue on the histone tail that is being targeted for methylation, the level of methylation (e.g. mono-, di-, or tri-methylation) and the cross-talk with other proteins such as transcription factors and chromatin regulators [7, 8]. Chromatin modifying enzymes control transcriptional processes by fine-tuning gene transcription and regulating gene silencing [4]. Alterations in chromatin structure are correlated with transcriptional events such as transcription initiation, elongation, termination of gene transcription or repression [9, 10].

There are two major classes of histone lysine demethylases (KDMs): The first class is comprised of members of the KDM1 subfamily, which includes flavin-adenine-dinucleotide (FAD) dependent amino oxidases. The second class (KDM2-KDM7 demethylases) includes Fe(II) and 2-oxoglutarate (2-OG)-dependent oxygenases, which contain a JumonjiC (JmjC) domain and a conserved catalytic domain [7]. This review focuses on the role of histone 3 lysine 4 (H3K4) histone demethylase KDM5B in stem cell function, pre-implantation embryo development, and cancer.

Structural features of KDM5 enzymes

The KDM5 family of enzymes play a pivotal role in the steady-state regulation of stem cell function, development, pathological conditions and cancer [7, 8, 11]. KDM5B catalyzes the demethylation of mono-, di-, and tri-methylation states of H3K4, and KDM5 histone demethylases have traditionally been thought to be transcriptional repressors because they catalyze the removal of H3K4 methylation (H3K4me3, H3K4me2), which is predominantly found at promoters of actively transcribed genes [7, 9, 12–17]. KDM5B may also regulate enhancers by demethylating H3K4me3/me2 to H3K4me1. The presence of H3K4me1 distinguishes enhancers from proximal promoters [18], and H3K4me1 is found at active and primed enhancer regions, which can be distinguished by the presence or absence of H3K27ac, respectively[19, 20]. The KDM5 subfamily consists of KDM5A (also known as JARID1A or RBP2), KDM5B (also known as JARID1B or PLU1), and the sex chromosome

linked KDM5C (also known as JARID1C or SMCX) and KDM5D (also named JARID1D or SMCY) proteins [12, 21]. KDM5 Jumonji-domain containing demethylases are highly conserved from yeast to humans and play an important role in regulating the H3K4 methylation landscape [7]. KDM5 proteins contain a DNA-binding ARID (AT-Rich Interactive Domain) that binds to GC-rich DNA sequences[7], a JumonjiC (JmjC) domain that catalyzes demethylation of methylated histone lysine residues (mono-, di-, and tri-methylated H3K4)[22], a JumonjiN domain (JmjN), a C_5HC_2 zinc finger motif, an uncharacterized PLU-1 motif and two or three histone-binding PHD domains (denoted PHD1, PHD2, PHD3 from the N-terminus to the C-terminus) [7, 11]. JmjC-domain containing proteins are members of the dioxygenase superfamily which utilize a demethylation mechanism distinct from LSD1/KDM1[5, 23]. JmjC-mediated demethylation requires the co-factors Fe(II), O_2, and α-ketogluterate, which act together to hydroxylate the methyl group, and the unstable carbinolamine group is released as formaldehyde [5]. The chemical reaction for JmjC-mediated histone demethylation has been reviewed previously[24]. The ARID and PHD1 domains are located within the Jumonji catalytic domain split it into two fragments; the JmjN and the JmjC domains [7, 11, 25].

How are KDM5 family members targeted or recruited to chromatin? PHD domains of KDM5 enzymes are presumed to drive the specificity of target substrate recognition. PHD domains provide accuracy for KDM5 target occupancy at specific genomic regions by recognizing various lysine modifications in a sequence specific manner [7, 10]. For example, the PHD1 domain in KDM5B facilitates targeting of unmethylated H3K4 to prevent re-methylation, while the same domain in KDM5C targets H3K9me2/3 [7, 16]. In addition to their involvement in recognizing specific lysine modifications, PHD domains have been also shown to regulate the demethylase activity of KDM5 enzymes [16]. KDM5B contains additional domains such as three PHD domains (PHD1, PHD2, PHD3), an ARID domain, a JmjN domain, a JmjC domain, a C_5HC_2 zinc finger motif, and the PLU-1 motif.

Interactions between KDM5 family members and transcription factors may direct their localization to specific genes, thus contributing to distinct transcriptional repertoires that persist in diverse cell types. Findings from several studies lend support to this possibility. Biochemical analyses have revealed that KDM5B interacts with several proteins such as the transcription factor PAX9 [26], which is expressed in embryonic tissues [27]. KDM5B has also been shown to associate with the transcription factor, FOXG1[26], which strongly regulates telencephalic progenitor proliferation [28]. Moreover, KDM5B has been shown to associate with various nuclear receptors such as estrogen receptor α, androgen receptor, and progesterone receptor to activate or repress target genes [29–32]. Another member of the KDM5 family of demethylases, KDM5A, has been shown to interact with retinoblastoma protein (Rb), which is a crucial regulator of cell cycle control and differentiation [8, 33]. KDM5A exhibits similar structural features as KDM5B, and has been shown to regulate HOX gene activity and occupy promoter regions of HOXA1, HOXA5 and HOXA7 during development [12]. In bilateral organisms, HOX genes tightly regulate the anterior-posterior body axis and stem cell differentiation [34]. Unlike KDM5A and KDM5B, two additional members of the KDM5 family, KDM5C and KDM5D, which are located on the X and Y chromosomes, respectively [16], do not have a PHD3 domain [16]. While there is limited domain diversity between KDM5 family members, differences in domain spacing and 3D

orientation, and tissue-specific expression patterns, may facilitate differential targeting to chromatin. Further studies aimed at identifying genome-wide binding patterns of KDM5 family members, and interacting chromatin constituents and transcription factors, in a diverse set of cell types, would shed light on targeting mechanisms of KDM5 family members to specific chromatin regions.

KDM5B in stem cells and early embryonic development

Fundamental cellular processes such as gene expression, DNA repair and DNA replication are tightly regulated by chromatin states [35]. Chromatin accessibility controls promoter and enhancer activity, insulators and locus control regions [36] which in turn dictates cell fate and developmental decisions. During embryonic development, chromatin undergoes dynamic remodeling in order to facilitate expression of transcriptional programs necessary for cellular differentiation and proliferation in various cell types. KDM5B has been shown to play a fundamental role during mouse ES cell differentiation [37, 38], where depletion of KDM5B lead to extended ES cell self-renewal in the absence of the self-renewal factor, leukemia inhibitor factor (LIF) [37]. Moreover, KDM5B was shown to be a barrier to the reprogramming process, where depletion of KDM5B lead to accelerated induced pluripotent stem (iPS) cell reprogramming[37]. A follow-up study also showed that KDM5B decommissions the H3K4 methylation landscape of self-renewal genes during trophoblast stem cell differentiation. The role for KDM5B during embryonic development is controversial[39]. It was first reported that knockout of KDM5B in mice is lethal around E4.5 to E7.5[29]. Another study reported that KDM5B null embryos exhibit major neonatal lethality largely due to respiratory failure, and skeletal and neuronal developmental defects [40]. Accumulation of H3K4me3 and expression of neural transcription factors, *Pax6* and *Otx2*, was associated with these defects. However, mice expressing KDM5B with an ARID deletion (ΔARID) were largely normal except for delayed mammary gland development[29]. Another study, which utilized an alternative strategy to generate KDM5B knockout mice, reported mostly viable mice with decreased size, reduced female fertility, decreased uterine weight, and delayed mammary development[39]. The authors also observed decreased serum estrogen levels and expression of mammary morphogenesis and gene expression. These results demonstrate that KDM5B regulates the female reproductive system and mammary epithelium during development. Overall, these findings suggest that KDM5B regulation of H3K4 methylation during development is a central mechanism for facilitating cell fate changes.

Genome-wide analyses have demonstrated that H3K4me3, which is predominantly found nearby transcriptional start sites (TSS) of active genes, is tightly associated with gene activation in mouse pre-implantation stage embryos [41]. While many studies have explored the H3K4 methylation epigenomic landscape of ES cells, due to the paucity of cells in early embryos, few studies have evaluated the epigenomic state of H3K4 methylation in preimplantation-stage embryos, and the role of KDM5 demethylases, during early preimplantation stage development [42]. Studies in mouse ES cells revealed that KDM5B co-localizes with H3K4me3 at enhancers and promoters of active genes, where it plays a crucial role in focusing H3K4me3 near promoter regions to prevent it from spreading to gene bodies [43]. Likewise, complimentary studies have revealed that KDM5B is a master

regulator of the epigenome during early mouse embryonic preimplantation stage development, by focusing H3K4me3 marks during development to prevent an increase in the breadth of H3K4me3 domains [44]. Recent studies have explored the location and the level of enrichment of H3K4me3 in gametes and in early embryos [42, 44–46]. Results from these studies showed that in contrast to ES cells, where H3K4me3 is predominantly found near the transcription start sites (TSS) of highly expressed genes, in metaphase II (MII) oocytes, the majority of H3K4me3 domains (75%) are localized far from TSS regions with low levels of enrichment across broad (10 kb) genomic regions [46]. In this case, global ChIP-Seq using low cell numbers demonstrated that oocytes exhibit a unique epigenetic architecture, where broad H3K4me3 domains (>10 kb) covered a significant region of the genome (22%) [45]. Because KDM5A and KDM5B demethylases are expressed at an elevated level in 2-cell stage embryos relative to oocytes or 8-cell embryos [45], it was hypothesized that these enzymes may play instrumental roles in regulating zygotic genome activation (ZGA). Demethylation of broad H3K4me3 domains by KDM5A and KDM5B has been shown to be essential for ZGA and early embryo development[45]. In this case, depletion of both enzymes, KDM5A and KDM5B, resulted in high levels of H3K4me3 at the late 2-cell stage[45]. Moreover, depletion of KDM5A and KDM5B resulted in downregulation of ZGA genes, thus demonstrating a critical role for KDM5A and KDM5B in regulating oocyte-specific H3K4me3 and ZGA. It was also demonstrated that overexpression of KDM5B leads to demethylation of broad H3K4me3 domains and ZGA in oocytes [46]. These findings implicate a dynamic role for KDM5B in regulating gene expression by modulating the breadth of H3K4me3 domains in ES cells and preimplantation embryos.

KDM5B in cancer

KDM5B is involved in pathogenic responses such as metastasis[29, 47–49], and sequencing of human cancer genomes revealed the presence of somatic mutations in the histone modifying enzyme, KDM5B[50]. KDM5B has been shown to be overexpressed in multiple human cancers including breast [49], ovarian cancer [51], prostate cancer [48, 52], bladder cancer [53], lung cancer[53], colorectal cancer [54], gastric cancer [55], gliomas [56], malignant melanoma [57] and hepatocellular carcinoma [58]. While KDM5B is overexpressed in multiple cancer types, the role for KDM5B in tumorigenesis is largely unknown. Overexpression of KDM5B could potentially influence the expression of cancer-related genes by regulating global levels and distributions of H3K4me3 near promoters of tumor suppressors or oncogenes. Overexpression of KDM5B may be oncogenic in certain cancers by creating aberrantly restrictive chromatin unable to activate tumor suppressor or apoptosis genes while downregulation may be tumorigenic in other cases by creating aberrantly permissive chromatin that leads to stochastic activation of oncogenes. Along this line, a previous study demonstrated a correlation between increased KDM5B activity and downregulated expression of *BRCA-1* [59], *CAV1*, *HOXA5* tumor suppressor genes. The authors also found that downregulation of KDM5B resulted in upregulated expression of tumor suppressor genes. Moreover, it was found that KDM5B directly binds to CAV1, HOXA5, and BRCA1[13], and depletion of KDM5B leads to increased H3K4me3 marks at target genes, suggesting that KDM5B acts as a transcriptional repressor in MCF-7 breast cancer cells [13]. Moreover, expression analysis of clinical tumor tissues revealed that

elevated levels of KDM5B is correlated with increased expression of the cell cycle regulators E2F1 and E2F2 transcription factors [53, 60], which are upregulated in multiple cancer types and serve as prognostic markers for carcinogenesis [53, 61].

KDM5B is highly expressed in malignant breast tumors relative to benign breast tumors [49], and KDM5B is also differentially expressed in breast cancer molecular subtypes. Breast tumors are categorized by expression of estrogen receptor (ER^+), progesterone receptor (PR^+), and human epidermal growth factor receptor 2 ($HER2^+$) into ER^+ (luminal), $HER2^+$, and $ER^-PR^-HER2^-$ (triple-negative breast cancer [TNBC]) disease [62]. KDM5B was first found to be overexpressed in $HER2^+$ breast cancer cells[49], and subsequently in invasive and *in situ* primary breast cancers [49]. KDM5B has also been shown to be amplified and overexpressed, or mutated, in breast cancer cells[29, 62] [63], where it occupies promoter and enhancer regions of genes highly expressed in luminal cells to modulate expression of differentiated luminal expression programs [62]. These results indicate that KDM5B is a luminal lineage-driving oncogene and as such may represent a therapeutic target for luminal-specific breast cancer [62]. While KDM5B binding is high at active genes in luminal and basal-like breast cancer cell types, luminal-specific genes were enriched with KDM5B binding while basal-specific genes were not enriched[62], suggesting that KDM5B preferentially regulates luminal-specific genes in breast cancer cells. Results from this study also show that KDM5B expression is lower in basal-like breast cancer cells relative to luminal and $HER2^+$ breast cancer cells. These findings suggest that the expression level of KDM5B may potentially be used as a biomarker to stratify hormone positive versus triple-negative breast cancer patients.

KDM5B may participate in regulating transcription of luminal genes by associating with the genomic insulator, CCCTC-binding factor (CTCF)[62]. Along this line, KDM5B and CTCF co-binding was observed in breast cancer cells, suggesting that CTCF may modulate KDM5B occupancy. KDM5B-CTCF associations may regulate gene expression, as CTCF binding in promoter regions pauses RNA polymerase II (RNAPII)[64, 65], which is a key transcriptional regulatory mechanism. In support of this model, KDM5B has been shown to regulate transcriptional events including RNAPII occupancy, transcriptional initiation and elongation, and alternative splicing in ES cells [66].

Epigenetic marks such as DNA methylation may also modulate KDM5B binding and function in cancer. Along this line, because CTCF co-localizes with KDM5B in promoter regions of breast cancer cells, and CTCF binding is inhibited by DNA methylation[62], alterations in DNA methylation may lead to dysregulated recruitment or binding of KDM5B to promoter regions. Moreover, because KDM5B binds CG-rich DNA sequences[62], and KDM5B-occupies promoters with decreased DNA methylation relative to unoccupied promoters in breast cancer cells, aberrant DNA methylation may result in altered binding of KDM5B in a CTCF-dependent or independent manner. While these findings implicate a role for KDM5B in cancer progression and proliferation, further work is necessary to understand potential relationships between DNA methylation, CTCF occupancy, and KDM5B in regulating gene expression and tumorigenesis. Moreover, because KDM5B chromatin binding and histone demethylase activity may be affected by proteins such as CTCF[62],

successful therapeutic targeting of KDM5B may require more than inhibiting its enzymatic activity.

Does modulation of DNA methylation and KDM5B activity reduce viability of breast cancer cells? To address this question, Leadem et al. utilized a small molecule inhibitor of KDM5-family proteins (KDM5i; CPI-455) in combination with the DNA-demethylating drug 5-aza-2-'deoxycytidien (DAC)[67] to treat breast cancer cells *in vitro*. Treatment with KDM5i alone resulted in altered expression of several genes, while combined treatment with KDM5i and DAC resulted in increased expression of hundreds of DAC-responsive genes[67]. Specifically, the authors found that combined treatment with KDM5i and DAC lead to reactivation of hypermethylated genes. Moreover, inhibition of KDM5 enhanced the effect of DAC, where combination treatment resulted in decreased viability of luminal breast cancer cells *in vitro*. While these results implicate a potential synergistic relationship between DNA methylation and KDM function in regulating gene expression in breast cancer cells, additional studies are needed to address the *in vivo* efficacy of this combination therapy regimen. Moreover, development of specific inhibitors of KDM5 family members (e.g. KDM5A, KDM5B, KDM5C, KDM5D) will provide greater insight into their respective function in regulating gene expression in cancer cells. The authors also note that KDM5 proteins function to fine-tune gene expression, a conclusion that supports results from a previous study, which describe a role for KDM5B in regulating H3K4 methylation in ES cells[43]. While KDM5B may fine-tune gene expression in a steady-state model where cell fates are unaltered, KDM5B imparts significant changes on the H3K4 methylation landscape and transcriptional profile of ES cells during differentiation, by demethylating self-renewal genes[43], and by facilitating acquisition of transcriptional programs that promote lineage-specific differentiation. KDM5B may also function to fine-tune expression of genes in tumor initiating cells or differentiated tumor cells, and more broadly regulate H3K4 methylation and gene expression of self-renewal genes during differentiation of tumor initiating cells. While these studies and hypotheses implicate a role for KDM5B in facilitating differentiation by regulating H3K4 methylation of self-renewal genes, it is unclear how KDM5B preferentially decommissions H3K4 methylation at self-renewal genes during differentiation. Further studies are needed to understand how KDM5B is recruited to specific genes in a cell-type specific manner. KDM5B may exhibit differential gene targeting during self-renewal and differentiation by associating with distinct sets of genes containing H3K4 methylation in undifferentiated versus differentiated cells. In this case, exit from self-renewal and subsequent decreased expression and promoter binding of stem cell-specific transcription factors (TF) may lead to decreased binding of RNAPII and H3K4 methyltransferases. In the absence of transcriptional machinery and maintenance of H3K4 methylation, persistent KDM5B activity may lead to depletion of H3K4 methylation marks.

While KDM5B is overexpressed in multiple cancers, it was reported that KDM5B expression in melanoma subpopulations is heterogeneous [47], suggesting a more dynamic role for KDM5B in regulating cellular heterogeneity of melanoma cells. In melanoma, KDM5B positive cells cycled more slowly than KDM5B negative cells, and exhibited increased tumorigenicity and greater heterogeneity in progeny cells. The authors also note that KDM5B expression is dynamically regulated in melanoma cells, and that fluctuations in KDM5B expression levels in melanoma tumors reflects temporarily distinct subpopulations

of cancer cells[47]. However, it is unclear whether the observed dynamic KDM5B expression levels is due to fluctuations in endogenous KDM5B expression levels or heterogeneous expression resulting from lentiviral genomic integration of the KDM5B-EGFP reporter construct. Further work utilizing a reporter gene knock-in approach may provide additional insight to support these conclusions. In a follow-up report, Roesch et al. showed that multi-drug treatment with cisplatin and vemurafenib enriches for slow-cycling tumor-maintaining melanoma cells expressing elevated levels of KDM5B [47], which are resistant to antiproliferative therapies[68]. These findings implicate a potential role for KDM5B in regulating primitive versus differentiated cellular states of cancer cells. KDM5B has also been implicated in regulating cell fate decisions of oral cancer cells. In this case, KDM5B has been shown to facilitate transdifferentiation or transitions between cellular states of cancer stem cells in oral cancer[69]. These findings suggest that KDM5B may regulate plasticity of tumor initiating cells in a context-dependent manner.

KDM5B has also been implicated in regulating tumorigenicity and stem cell function in leukemia. In acute myeloid leukemias (AML) induced by MLL oncogenes, which facilitate H3K4 methylation, H3K4me3 levels globally increase, and leukemia stem cells (LSCs) exhibit H3K4 hypermethylation[70]. In these AML cancers, KDM5B negatively regulates the oncogenic potential of LSCs by decommissioning the leukemia stem cell transcriptional repertoire. Moreover, overexpression of KDM5B in leukemia cells has been shown to suppress leukemogenesis by forcing differentiation of AML cells[70]. These findings, which propose a potentially dispensable role for KDM5B in LSC self-renewal, is in alignment with previous studies which demonstrate that depletion of KDM5B leads to extended ES cell self-renewal, and a requirement for KDM5B in normal ES cell differentiation [37, 43].

Clinically, these results suggest that in cancers where KDM5B acts to suppress tumor growth, activation of KDM5B may be more suitable as a therapeutic strategy rather than inhibition. These findings also highlight the complexity of targeting cancers comprised of a heterogeneous population of cells with varying proliferative and self-renewal characteristics, each with distinct and dynamic epigenomes and transcriptional programs.

KDM5 inhibitors

Chemical inhibitor tools that complement conventional gene targeting strategies such as RNAi knockdown or gene editing serve important roles in elucidating functions of specific domains and proteins. Because KDM5B is overexpressed or amplified in many cancers, identification of novel and efficient chemotherapeutic drugs to inhibit JmjC demethylase activity may be suitable to target KDM5B for cancer therapy. To this end, numerous preclinical studies are being investigated which utilize inhibitors of KDM5B to suppress tumorigenesis [11, 71]. KDM5 small molecule inhibitor development has undergone significant advancements recently. However, while several JmjC inhibitors for KDM proteins have been identified, their usage is limited due to toxicity or lack of selectivity [72–81]. Several studies have identified inhibitor scaffolds for the largest family of histone demethylases, the JmjC domain containing demethylases, which exhibit a wide range of substrate specificity [82]. Two inhibitors, N-oxalylglycine (NOG) and 2,4-pyridinedicarboxylic acid (2,4-PDCA), mediate the coordination of the catalytic metal in a

bidentate manner, a conserved feature in other 2-OG-oxygenases [83]. However, because 2,4-PDCA exhibits low selectivity as it targets KDM5, KDM4 and KDM6 family members [84], further studies in drug development commenced to identify specific inhibitors of KDM5B [85]. A high throughput screening of over 15,000 small molecules identified 2–4(4-methylphenyl)-1,2-benzisothiazol-3(2H)-one (PBIT) as a novel inhibitor of KDM5B [71]. However, PBIT displayed low selectivity as it inhibited the activity of other KDM5 family members KDM5C and KDM5A [71]. In another study, two inhibitors of the KDM5 family were identified, KDM5-C49 and KDM5-C70 [7]. KDM5-C49, which is an analog of 2,4-PDCA, exhibited low selectivity, where it inhibited activity of KDM5B, KDM4, and KDM6 [7]. In addition, GDK467 inhibited activity of KDM5C and KDM4 subfamily members [7]. While additional studies identified pan-KDM5 inhibitors, including an orally bioavailable pyrazolopyrimidinone[86] and KDOAM-25[81], the lack of highly specific inhibitors for KDM5B is likely attributed to the highly conserved protein structures and JmjC domains in KDM5 family histone demethylases [7, 77]. Although these inhibitors are not suitable to selectively inhibit individual members of the KDM5 family of histone demethylases, they provide a promising platform to improve inhibitor design to potently and selectively inhibit KDM5B.

Recently, a pan-KDM5 selective inhibitor, CPI-455, was identified that displays 200-fold more selectively for KDM5 members than KDM4 demethylases, and 500-fold more selectively relative to other JmjC-domain containing enzymes [77, 87]. CPI-455 was developed from a parent molecule, which was identified from a screen utilizing a KDM4C construct that contained JmjC and JmjN domains, and was subsequently modified to increase specificity for KDM5-family members [77, 87]. Results from this study suggest that identification of KDM5B-specific molecules may be feasible. These findings also highlight that exploiting unique domain structural properties of KDM5B may aid in development of specific inhibitors. As KDM4 and KDM5 are the only two KDM sub-families that contain a JmjN domain, exploiting unique structural properties of KDM5B through scaffold development or side chain modifications may lead to the identification of bona fide KDM5B selective inhibitors.

Clinical relevance of KDM5B inhibitors for cancer therapy

Application of KDM5B inhibitors for the treatment of cancer follows that this enzyme is positively associated with cancer growth and/or drug resistance. However, it is unclear from the literature whether inhibition of KDM5B would lead to reduced cancer growth or increased drug sensitivity in patients. Because KDM5B is upregulated in various cancers including breast and prostate, and KDM5B has been shown to be important for melanoma cell growth[47], KDM5B has been on the radar of cancer biologists and clinicians as an attractive target for cancer therapy. However, there are several important considerations for the clinical application of KDM5B inhibitors for cancer therapy. First, KDM5B expression may inhibit cancer progression in some cases. To address this possibility, a systematic study is needed to investigate the function of KDM5B across multiple types of cancer to understand which cancers exhibit decreased proliferation following treatment with KDM5B inhibitors. Second, there is limited published data describing the role for KDM5B in regulating cancer stem cell function, a driving force in drug resistance and cancer relapse.

As KDM5B positively regulates stem cell differentiation, it is plausible that inhibition of KDM5B may lead to a persistent population of cancer stem cell-like cells which are resistant to anti-proliferative therapies. In support of this model, a previous report demonstrated that KDM5B negatively regulates leukemogenesis, as elevated levels of H3K4me3 promote leukemia stem cell self-renewal [70]. Moreover, depletion of KDM5B in ES cells leads to delayed differentiation and extended self-renewal in the absence of extrinsic or intrinsic self-renewal signals [37, 38, 88]. Further studies investigating the role for KDM5B in regulating cancer stem cell function will be important to aid our understanding of tumor progression and for development and preclinical evaluation of KDM5B inhibitors. Third, it is important to consider the effect of KDM5 inhibitors on neurological function, as mutations in KDM5 family members have been observed in children with neurological conditions[89], and KDM5 enzymes are involved in Huntington's disease[90].

Concluding remarks

In this review, we focused on the role of the histone H3K4 demethylase, KDM5B, in regulating embryonic development, stem cell function, and cancer biology. Evidence suggests that KDM5B plays a fundamental role in regulating ES cell differentiation and in fine-tuning gene transcription and gene silencing during mouse embryonic preimplantation-stage development. KDM5B is also thought to modulate the expression of tumor suppressing genes and oncogenes, thus affecting cancer cell proliferation and differentiation. Although preclinical studies are underway to design drugs to target KDM5B for cancer therapy, specific KDM5B inhibitors have not been discovered. Identification of specific inhibitors will aid in our understanding of the role for KDM5B in stem cell function and cancer biology. Moreover, future studies investigating the role for KDM5B in epigenomic regulation of H3K4 methylation will shed light on mechanisms of self-renewal and differentiation, and tumor initiation and progression.

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