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Biology and targeting of the Jumonji-domain histone demethylase family in childhood neoplasia: a preclinical overview.

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Abstract

Introduction: Epigenetic mechanisms of gene regulatory control play fundamental roles in developmental morphogenesis, and, as more recently appreciated, are heavily implicated in the onset and progression of neoplastic disease, including cancer. Many epigenetic mechanisms are therapeutically targetable, providing additional incentive for understanding of their contribution to cancer and other types of neoplasia.

Areas covered: The Jumonji-domain histone demethylase (JHDM) family exemplifies many of the above traits. This review summarizes the current state of knowledge of the functions and pharmacologic targeting of JHDMs in cancer and other neoplastic processes, with an emphasis on diseases affecting the pediatric population.

Expert opinion: To date, the JHDM family has largely been studied in the context of normal development and adult cancers. In contrast, comparatively few studies have addressed JHDM biology in cancer and other neoplastic diseases of childhood, especially solid (non-hematopoietic) neoplasms. Encouragingly, the few available examples support important roles for JHDMs in pediatric neoplasia, as well as potential roles for JHDM pharmacologic inhibition in disease management. Further investigations of JHDMs in cancer and other types of neoplasia of childhood

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Declaration of interest

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can be expected to both enlighten disease biology and inform new approaches to improve disease outcomes.

Keywords

Jumonji; demethylase; epigenetics; cancer; neoplasia; pediatric

1. Introduction

Epigenetic mechanisms, long known to play key roles in development, have more recently emerged as playing diverse and important roles in the initiation and progression of cancer. In classical genetic terms, an epigenetic mechanism refers to a change in cellular phenotype that is not due to an alteration in DNA sequence, or genetic material. On a mechanistic level, epigenetic changes entail stable alterations in genomic output, or gene expression, due to changes in the chemical composition or/and structural conformation of chromatin. Chromatin, the structural and functional unit of the cellular genome, consists of repeating units of DNA wound around an octameric complex of histones, which together comprise the nucleosome. The DNA and protein components of chromatin each undergo dynamic chemical modifications. These include methylation and demethylation of DNA, and a variety of post-translational modifications involving specific residues in unstructured “tails” of the core histones. Such modifications collectively constitute the “histone code”, which helps control the expression states of associated genes.

DNA and histone modifications are deposited by enzymes collectively termed “writers”, and removed by enzymes termed “erasers” or “editors”. The resulting information is in turn interpreted by protein factors termed “readers”, in the form of differential interactions with variously modified forms of chromatin. An additional class of protein factors, the “remodelers”, through both post-translational histone modifications and ATP-dependent mechanisms, affects the packing and positioning of nucleosomes on chromatin. Many epigenetic modifying factors are endowed with multi-functionality by virtue of possessing multiple functional domains, such as a writer/eraser domain and reader domain(s). Together, this dynamic machinery of epigenetic modifiers plays a critical role in the gene expression output and phenotypic identity of the cell, with wide-ranging impacts on normal development and homeostasis.

This regulatory machinery is itself commonly dysregulated in cancer^{1–3}. Alterations in epigenetic control in cancer are diverse, ranging from mutation and altered expression of the various epigenetic modifiers and their cofactors, to mutations in constituent histones themselves. Changes in gene expression effected by these alterations impact all steps and processes of cancer initiation and progression. Epigenetic mechanisms of cancer initiation and progression are gradually being unraveled. Since many epigenetic factors are therapeutically targetable, such efforts have the potential to unlock new treatments for cancer.

Epigenetic mechanisms in cancer have been the subject of many recent reviews. The purpose of this review is to summarize and update the state of knowledge of the biology and targeting of a large, and potentially druggable, family of histone mark “erasers” – the

Jumonji-domain histone demethylase (JHDM) family – in cancer and other types of neoplasia, with emphasis on neoplasms of childhood. Epigenetic mechanisms have emerged as playing particularly prominent roles in pediatric cancers and other neoplasms, which typically carry low mutational burdens^{4, 5}. Consequently, understanding of such mechanisms is likely to have very important prognostic and therapeutic implications in this age group.

The JHDM family contains roughly 20 genes/proteins in humans, which share a Jumonji-C (JmjC) demethylase domain (and thus druggable enzymatic activity)^{6–10}. The JmjC domain carries out demethylation of histones, and in some cases other proteins, using Fe²⁺ and α -ketoglutarate as cofactors. This mechanism is distinct from that utilized by the proteins LSD1 and LSD2, which constitute the second demethylase family in humans. JHDMS can be further divided into subfamilies with unique, as well as some overlapping, specificities for different histone methyl marks (summarized in Table 1). Reflecting a feature of many epigenetic modifiers noted above, JHDMS contain additional conserved functional domains with nucleic acid-binding, protein-protein interaction, chromatin reader or/and other motifs (also summarized in Table 1).

As true of most, and likely all, epigenetic regulators, the roles of JHDMS in cancer initiation and progression show context-specificity. That said, many JHDMS have been demonstrated to exert disease-promoting roles in cancer. Based on such findings, the development of pharmacologic inhibitors of the JHDM family, both broadly acting and specific, has been an area of substantial activity^{11–13}. Where relevant, information on inhibitors showing preclinical promise will be discussed.

2. KDM subfamilies in cancer and other neoplastic disease

2.1 KDM2

The KDM2 subfamily consists of two genes, KDM2A (JHDM1A/FBXL11) and KDM2B (JHDM1B/FBXL10). The JmjC domain of KDM2A and KDM2B catalyzes the removal of mono- and di-methyl marks at H3K36^{6, 8, 9}. H3K36me2 is associated with coding regions of transcribed genes¹⁴, and also plays a role in the recruitment of DNA repair factors to sites of DNA damage¹⁵. H3K36 methylation has been proposed to play roles both in activation and repression of gene expression¹⁵. The JmjC domain of KDM2B is also able to remove the tri-methyl mark at H3K4^{6, 8, 9}, a post-translational modification strongly associated with active promoters¹⁴. A recent study has shown that KDM2B can additionally remove di- and tri-methyl marks from H3K79, a modification associated with active transcription and involved in DNA repair¹⁶. Utilizing their demethylase activity, members of the KDM2 family may thus activate or repress gene expression depending on context. In addition to the JmjC demethylase domain, KDM2A and KDM2B each also possess a CXXC-type zinc finger domain, capable of DNA and RNA interactions, two different types of protein-protein interaction domains (F-box and multiple leucine-rich repeat (LRR) domains), and a Plant Homeodomain (PHD) finger chromatin reader domain^{6, 8, 9}.

The KDM2 subfamily plays context-dependent roles in solid as well as hematopoietic neoplastic diseases. KDM2A is overexpressed in breast cancer, and promotes stem-like

properties, chemoresistance, and angiogenesis by upregulating JAG1 expression¹⁷. KDM2A also acts as a disease-promoting factor in non-small cell lung cancer (NSCLC) by repressing HDAC3 expression, and thereby increasing the expression of cell cycle-associated and invasion-related genes¹⁸. In contrast, KDM2A exerts disease-suppressive effects in colon cancer by demethylating p65 (RelA) leading to inhibition of NF- κ B activity¹⁹. Consistent with a disease-promoting role, KDM2B inhibits both replicative and Ras oncogene-induced senescence in fibroblasts via repression of the *Ink4a/Arf* tumor suppressor locus²⁰. Further, KDM2B is a poor prognostic factor in gastric cancer, and its knockdown induces autophagy via PI3K/Akt/mTOR inhibition in gastric cancer cells²¹. In contrast, however, KDM2B inhibits cell proliferation in HeLa cells, and its expression is decreased in Glioblastoma Multiforme (GBM), a highly aggressive brain neoplasm affecting both adult and pediatric patients, relative to normal brain and less aggressive CNS neoplasms²².

KDM2B has also been examined, and found to have context-dependent roles, in acute leukemias, which include the most common malignant neoplasias of childhood. KDM2B plays a pro-leukemic role in Acute Lymphoblastic Leukemia (ALL), a disease predominantly affecting the pediatric population, where it cooperates with polycomb and trithorax complexes to control lineage commitment²³. In Acute Myeloblastic Leukemia (AML), a malignant hematopoietic neoplasm affecting both adults and children, KDM2B is required for disease initiation and maintenance, via mechanisms that include p15^{Ink4b} silencing²⁴, and action of the non-canonical Polycomb PRC1.1 complex, of which it is part²⁵. In the context of Ras-driven myeloid transformation, however, KDM2B plays a restrictive rather than promotional role²³.

KDM2A and KDM2B both enhance somatic cell reprogramming, via a vitamin C-dependent mechanism that suppresses senescence and increases cell proliferation²⁶. KDM2A and KDM2B are also both positively regulated by hypoxia inducible factor (HIF) at the mRNA level²⁷. It is unknown at this point how such functions might impact cancer initiation or/and progression, though one may speculate that they could be disease-promoting.

2.2 KDM3

KDM3A (JMJD1A/JHDM2A), and its two homologs KDM3B (JMJD1B/JHDM2B) and JMJD1C (JMJD1C/JHDM2C), comprise the KDM3 subfamily. The JmjC domain of KDM3A and KDM3B has specificity for removal of mono- and di-methyl marks from H3K9^{6, 8, 9}. The H3K9me2 mark at gene regulatory elements is associated with inactive gene expression^{14, 28}; biology of the H3K9me1 mark is less well understood. JMJD1C has a JmjC domain, but whether it possesses intact demethylase activity is unclear^{29, 30}. KDM3A has been shown to homodimerize and to use a substrate channeling mechanism to remove H3K9 methyl groups³¹. Interestingly, a recent study found that KDM3B also has arginine demethylase activity, directed toward H4R3me2s (symmetric H4R3me2) and its intermediate H4R3me1³². Like H3K9me2, H4R3me2s correlates with less active gene expression³². Thus, by virtue of removing repressive H3K9me2, and in the case of KDM3B also H4R3me2, repressive marks, KDM3A and KDM3B utilize their demethylase activity to increase gene expression. All members of the KDM3 subfamily additionally have a zinc finger domain, with potential for DNA or/and RNA interactions³³.

KDM3A is overexpressed in a variety of adult cancers, and has been shown to promote disease progression via multiple mechanisms, including cell proliferation and survival, cell motility and invasion, stem-like properties, angiogenesis and chemotherapy resistance^{34–40}. KDM3A also functions as an estrogen receptor (ER) cofactor in breast cancer and androgen receptor (AR) cofactor in prostate cancer^{41–43}. As both target and cofactor of hypoxia-inducible factor (HIF1 α), KDM3A additionally contributes to the cancer-modulating effects of hypoxia^{36, 38, 44}. In hematopoietic neoplasms, KDM3A has been shown to promote cell survival in multiple myeloma via a KLF4-IRF2 axis⁴⁵. Interestingly, in contrast to the above disease-promoting roles in most cancers, KDM3A behaves as a tumor suppressor in germ cell neoplasms of the testis⁴⁶, diseases affecting both the adult and pediatric population. Interestingly, the testis is the tissue in which KDM3A is normally the most strongly expressed⁴⁷. KDM3B is overexpressed and disease-promoting in ALL, via repression of cell differentiation and activation of the LMO2 oncogene⁴⁸. Interestingly and in contrast, however, KDM3B is deleted and disease-suppressive in AML^{49, 50}. JMJD1C has been the most extensively studied member of the KDM3 subfamily in hematopoietic neoplasms, with multiple reports demonstrating its role as a disease-promoting factor in AML, including roles in survival and stem cell renewal^{51, 52}, and leukemia maintenance⁵³. JMJD1C has also been found to be overexpressed, and to functionally behave as a disease-promoting factor, in esophageal and colorectal cancer^{54, 55}. However, JMJD1C also plays a role in the DNA damage response, where its function may be disease-suppressive⁵⁶. Similar to KDM3A, a splicing variant of JMJD1C, s-JMJD1C, has been shown to act as a coactivator of the androgen receptor⁵⁷.

KDM3A has been studied in two different solid malignant neoplasms of childhood. In neuroblastoma, a malignancy of peripheral nervous system origin, KDM3A is induced by the disease driver and poor prognostic factor MYCN, and itself upregulates the expression of the long noncoding RNA MALAT1⁵⁸. This pathway increases the migratory and invasive potency of neuroblastoma cells, and treatment with dimethyloxallylglycine (DMOG), an α -ketoglutarate analog with inhibitory activity against JHDMS and other dioxygenases, results both in reduced MALAT1 expression and diminished cell migration and invasion. In the aggressive bone and soft tissue cancer Ewing Sarcoma, KDM3A expression is upregulated downstream of the driver oncofusion EWS/Fli1, in part through a microRNA mechanism, resulting in promotion of colony and tumor growth⁵⁹. Furthermore, acting directly, and through induction of expression of the Ets1 transcription factor, KDM3A upregulates expression of the cell surface protein MCAM, resulting in increased cell motility and metastasis⁶⁰. Ewing Sarcoma cells are also highly sensitive to the pan-JHDM pharmacologic inhibitor JIB-04⁶¹.

Developmentally, KDM3A is essential for spermatogenesis⁶², and plays an important role in sex determination⁶³. Adult KDM3A-deficient mice additionally develop metabolic defects and obesity^{64, 65}. JMJD1C also plays a role in spermatogenesis, being required for long-term germ cell maintenance⁶⁶. In embryonic stem cells (ESCs), KDM3A is induced by Oct4 and activates the expression of pluripotency-associated genes and ESC self-renewal⁶⁷. In keeping with the promotion of stemness-related phenotypes, the KDM3 family has been shown to augment the tumorigenic potential of colorectal cancer stem-like cells⁶⁸.

Interestingly, stem-like colorectal cancer cells are also susceptible to targeting by the pan-JHDM pharmacologic inhibitor JIB-04⁶⁹.

2.3 KDM4

The KDM4 (JMJD2/JHDM3) subfamily consists of six genes (KDM4A-F). Five of these (KDM4A-E) encode functional proteins, while KDM4F appears to be a pseudogene^{6, 8, 9}. With regard to histone mark specificity, KDM4A-C demethylate H3K9me2/3, H3K36me2/3 and H1.4K26me3 marks, while KDM4D/E are able to demethylate H3K9me2/3 and H1.4K26me3, but not H3K36me2/3 marks^{6, 8, 9}. H3K9me2/3 marks at gene regulatory elements are associated with inactive gene expression, and the H3K9me3 is a canonical mark of transcriptionally silent heterochromatin^{14, 28}. As discussed above (KDM2 subfamily), H3K36 methylation can exert context-dependent effects on gene expression and also plays a role in DNA damage and repair¹⁵. PTMs of H1.4, a linker histone, are less well characterized, but methylation of the K26 residue appears to be repressive⁷⁰. The demethylase activities of KDM4 family members thus have the capacity to activate, as well as potentially repress, gene expression. KDM4A-C, but not KDM4D/E, additionally contain chromatin reader PHD and Tudor domains^{6, 8, 9}. Adding a further level of functional and regulatory complexity, KDM4A and KDM4C, but not KDM4B, form homodimers and heterodimers via the N-terminal JmjN domain, and this interaction appears to be required for their demethylase activities³³.

Investigations of the KDM4 subfamily in cancer point to disease-promoting roles in both solid and hematopoietic neoplasms. KDM4A, KDM4B or/and KDM4C are overexpressed, and play disease-promotional roles, in common adult cancers, including those of skin, breast, prostate, colon and lung^{11, 71}. Important mechanisms include facilitation of hormone receptor action in breast and prostate cancer, and control of cell cycle progression, DNA replication and DNA repair^{9, 71, 72}. KDM4A-C have each also been specifically implicated in cancer progression, namely promotion of epithelial cancer metastasis^{73–76}. Furthermore, KDM4B and KDM4C are hypoxia-induced genes⁷⁷, and thus likely contribute to the cancer-modulating properties of varying oxygen levels in tumor cells. In hematopoietic neoplasms, KDM4B and KDM4C are upregulated in AML⁷⁸, and KDM4C cooperates with the H3K4 histone methyltransferase (HMT) PRMT1 to promote AML leukemic transformation⁷⁹. Complementing findings from human cancer studies, data from genetically engineered mouse models (GEMMs), namely analyses of the loss of H3K9 methyltransferase function, suggest that decreased H3K9 methylation is generally supportive to oncogenesis (reviewed in¹¹). From a pharmacologic targeting perspective, studies have shown activity of KDM4-targeting inhibitors in both solid (breast cancer) and hematopoietic (AML) neoplasms^{78–80}. The pan-JHDM inhibitor JIB-04 also restores sensitivity to cytarabine in SETD2-mutant leukemia, presumably via inhibition of KDM4 H3K36 demethylase activity⁸¹.

To date, investigations of the KDM4 subfamily in pediatric solid neoplasms have focused on the nervous system. In neuroblastoma, expression of KDM4B was found to correlate with that of the high-risk disease gene MYCN, and high KDM4B expression to segregate with poor disease outcome⁸². KDM4B was further shown to physically associate with MYCN,

and to contribute to control of the MYCN expression signature, resulting in promotion of cell and tumor growth, and impairment of differentiation. Subsequent studies used a chemical genetic approach to identify compounds with an expression signature simulating KDM4B depletion and opposing a MYCN-high signature⁸³. These identified HDAC inhibitors and Ciclopirox as leading candidates, and the latter (an off-patent antifungal agent) was shown to have activity against neuroblastoma cells *in vitro* and in xenograft models *in vivo*. In medulloblastoma, a malignant neoplasm of central nervous system origin, analysis of copy number alterations implicated diminished H3K9 methylation as a mechanism of disease pathogenesis, including amplification or/and overexpression of KDM4B and KDM4C⁸⁴. KDM4B and KDM4C have also been shown to be overexpressed in osteosarcoma, especially in metastatic disease, and to promote invasive properties of this cancer⁸⁵.

Developmentally, the KDM4 subfamily plays important roles in stem/progenitor cell maintenance and differentiation. KDM4B and KDM4C have both unique and overlapping functions in embryonic stem cell self-renewal, contributing to the action of key stem cell regulatory modules, including Myc, the PRC complex and Nanog circuitry, in the maintenance of stem cell identity^{67, 86}. KDM4A and KDM4B also play roles in neural crest specification and osteogenic differentiation, respectively^{87, 88}. More recently, KDM4C has been found to function as a critical molecular scaffold in the assembly of lineage-specific enhancer complexes involved in the control of cell differentiation states⁸⁹. The above mechanisms could potentially contribute to deregulated cell differentiation inherent to developmentally related neoplasms of childhood.

2.4 KDM5

The KDM5 (JARID1) subfamily of histone demethylases consists of four members, KDM5A-D, all of which remove H3K4 di- and tri-methyl (H3K4me2/3) histone marks^{6, 8, 9}. As discussed above (KDM2 subfamily), H3K4me3 is strongly associated with promoters of active genes¹⁴. Through removal of this mark, the canonical role of members of the KDM5 family is therefore that of transcriptional repressors. Indeed, KDM5A (also known as JARID1A, and Retinoblastoma (Rb) Binding Protein 2 or RBP2, associates with multiple repressor complexes^{90–92}. However, the control of gene expression by members of the KDM5 family is complex and incompletely understood, with demonstration of both repressive and activating effects in normal cells⁹³, as well as cancer (see below). Particularly interesting is the observation that activation of gene expression is not necessarily demethylase activity-independent, as might be predicted^{93, 94}. KDM5C (JARID1C/SMCX), located on the X chromosome and originally identified as a gene that escapes X-chromosome inactivation⁹⁵, has also been identified as a modulator of enhancer activity^{96, 97}. In addition to the JmjC domain, KDM5A-D each also have: AT-rich interaction domain (ARID) and zinc finger protein modules capable of DNA or/and RNA interactions; a JmjN domain with potential for protein-protein interactions; chromatin reader PHD domains; and a “PLU” motif of unknown function, common to the KDM5 family^{6, 8, 9, 33}.

The KDM5 subfamily, especially KDM5A, has been quite extensively investigated in the context of normal cell physiology revealing complex effects on the growth and

differentiation of normal cells. Notably, KDM5A has been shown to be able to both activate⁹³ and repress^{98, 99} the expression of pro-proliferative cell cycle genes during cell differentiation. KDM5A and KDM5B (JARID1B/PLU-1) have also been demonstrated to contribute to Rb-mediated gene silencing during senescence¹⁰⁰. KDM5A has moreover been shown to promote reprogramming of induced pluripotent stem cells (iPSCs)¹⁰¹. KDM5A-D all play roles in normal development, and KDM5C has been specifically implicated in the pathogenesis of X-linked mental retardation (XLMR) syndrome⁶.

All members of the KDM5 subfamily have been investigated in cancer. KDM5A has been found to be overexpressed, and disease-promoting, in a number of different cancers, including lung^{102, 103}, breast¹⁰⁴, pancreas¹⁰⁵, kidney¹⁰⁶, and stomach¹⁰⁷. Cancer phenotypes augmented by KDM5A include both cell/tumor growth and motile/metastatic properties, as well as promotion of stem-like properties and the epithelial-mesenchymal transition. Mechanisms entail both increased (Cyclins D1 and E1, ITGB1, TNC) and decreased (p21, p27 and p57) gene expression. Interestingly, some studies have found the promotion of growth and motility by KDM5A to be dependent on its demethylase activity¹⁰², while other studies have found similar phenotypes to be demethylase-independent^{104, 105}. Whether this reflects different mechanisms/pathways in different cancers, or the complexity of KDM5A function in the same biological processes (as seen in the control of normal growth, discussed above), remains to be determined. In further support of a cancer-promoting role, KDM5A has been shown to be required for both the onset¹⁰⁸ and maintenance¹⁰⁹ of Rb-deficient tumors in genetically engineered mice. Perhaps not surprisingly, in some contexts KDM5A can play a disease-suppressive role, as shown in breast cancer cells treated with PI3K inhibitors¹¹⁰. Similar to KDM5A, KDM5B is amplified and overexpressed in breast cancer, and promotes disease progression¹¹¹. KDM5C promotes cell motility and invasion in breast and hepatocellular cancer^{112, 113}, and is overexpressed in prostate cancer¹¹⁴, but behaves as a tumor suppressor in renal cancer¹¹⁵. Studies of KDM5D (JARID1D/SMCY), a KDM5C paralog located on the Y chromosome, have thus far demonstrated loss, and functionally a metastasis-suppressive role, in prostate cancer^{116–118}.

KDM5A and KDM5B have also been implicated in chemoresistance. KDM5A is required for induction of a “drug-tolerant persister” state in non-small cell lung cancer treated with EGFR inhibitors¹¹⁹, and is a mediator of temozolomide resistance in GBM¹²⁰. KDM5B marks a slow-cycling cell population in melanoma that is required for long-term tumor growth and is selected by pharmacotherapy¹²¹. KDM5B overexpression also contributes to chemotherapy resistance in ovarian cancer¹²². KDM5A and KDM5B, along with a number of other JHDMs, are additionally upregulated in taxane/platin-resistant NSCLC cells¹²³. Identification of the KDM5-dependent drug-tolerant persister state motivated the development of the KDM5-specific pharmacologic inhibitor CPI-455¹²⁴. This inhibitor has been shown to have efficacy against drug-resistant NSCLC, melanoma, colon, and breast cancer cells¹²⁴, as well as KDM5B-high oral cancer¹²⁵. Other inhibitors targeting the demethylase activity of the KDM5 family have also been developed, as recently reviewed¹²⁶. Moreover, the pan-JHDM inhibitor JIB-04, which shows particular potency against the KDM5 family^{127, 128}, has been shown to have efficacy against taxane/platin-resistant NSCLC¹²³ and temozolomide-resistant GBM¹²⁹.

Studies of the KDM5 subfamily in childhood neoplasms have thus far been relatively limited. KDM5B has been investigated in neuroblastoma, where its high expression segregates with poor patient outcome¹³⁰. This same study showed that KDM5B is more highly expressed in MYCN-amplified cell lines, and its expression is further enriched in tumor spheres derived from both MYCN-amplified and non-amplified cell lines. Such KDM5B^{high} tumor spheres show enhanced stem-like properties, and are more resistant to the chemotherapeutic agents doxorubicin, etoposide and cisplatin. Functionally, studies in MYCN-amplified cells show that KDM5B promotes tumor sphere forming potency, invasiveness and cisplatin resistance. Mechanistically, KDM5B promotes the epithelial-mesenchymal transition, and expression of the Notch pathway components Jagged 1 and Notch 1 and 2. More recently, KDM5A has been shown to repress p53 expression via a translational mechanism, resulting in augmented growth of p53 wild-type cancers, including neuroblastoma¹³¹. In hematologic malignancies, mutations of KDM5C have been identified in a subset of both *de novo* and relapsed pediatric acute lymphoblastic leukemia (ALL) patients¹³², as well as in relapsed chemorefractory pediatric acute myeloid leukemia (AML) patients¹³³, but the functional consequences of these mutations have not been investigated.

2.5 KDM6

The KDM6 subfamily consists of three genes, KDM6A-C. Each member has a JmjC domain with specificity for removal of di- and tri-methyl marks on Lysine 27 of histone H3 (H3K27me_{2/3})^{6, 8, 9}. H3K27me₃ is associated with inactive promoters¹⁴, and poised enhancers¹³⁴. By removing these repressive marks, members of the KDM6 family thus utilize their JmjC domain to activate gene expression. KDM6A (UTX) is located on the X chromosome, and escapes X-inactivation to be broadly expressed^{135, 136}. KDM6C (UTY), a KDM6A homologue located on the Y chromosome, has been shown to have only weak demethylase activity *in vitro* and *in vivo*¹³⁷. In addition to a JmjC demethylase domain, KDM6A and KDM6C each also contain tetratricopeptide repeats involved in protein-protein interactions¹³⁸. KDM6B (JMJD3), an autosomal gene with more tissue and context-specific expression, has a JmjC demethylase domain, but no tetratricopeptide repeats or other known additional functional domains. Members of the KDM6 subfamily have both demethylase activity-dependent and independent roles in development^{6, 139}. KDM6A and KDM6B have also been studied in the context of iPSC reprogramming, with KDM6A shown to be promotional, and KDM6B inhibitory, of this process¹³⁹.

Investigations of the KDM6 subfamily in cancer have revealed both disease-promoting and disease-suppressive roles. In T-cell ALL, a disease predominantly affecting the pediatric population, KDM6A is mutated in male patients and functionally behaves as a tumor suppressor^{136, 140}. Interestingly, however, in a subtype of the same disease, TAL1-driven T-cell ALL, KDM6A has been demonstrated to act as an oncogenic cofactor essential for disease maintenance¹⁴¹. KDM6A mutations have also been identified in pediatric B-cell ALL, and adult cancers of colon and kidney¹³⁹. Moreover, KDM6A is mutated in group 3 and 4 subtypes of medulloblastoma, and such mutations correlate with worse prognosis¹⁴². In breast cancer, however, KDM6A acts as a disease-promoting factor, cooperating with the estrogen receptor and the H3K4 methyltransferase MLL4 to augment gene expression driving cell growth and metastasis^{143, 144}. More recently, also in breast cancer, KDM6A has

been further shown to play a critical role in the resolution of promoter bivalency at genes upregulated during EMT-MET transition, a process necessary for efficient metastasis ¹⁴⁵. KDM6A has additionally been shown to be increased in expression in AML ⁷⁸.

Similar to KDM6A, there is evidence in the published literature for disease-promoting as well as disease-suppressive roles of KDM6B in cancer. In T-cell ALL, KDM6B is required for leukemia initiation and maintenance ¹⁴⁰ and its expression is upregulated in AML ¹⁴⁶. In liver cancer, KDM6B promotes epithelial-mesenchymal transition, and stem-like and invasive phenotypes ¹⁴⁷, while in melanoma it enhances disease progression via effects on the tumor microenvironment ¹⁴⁸. In contrast, KDM6B has been reported to exert disease-suppressive effects in cancers of the colon, pancreas and lung ¹⁴⁹.

A cell-active, pharmacologic inhibitor with high selectivity for the KDM6 subfamily has been developed (GSK-J4) ¹⁵⁰. Encouragingly, this drug has shown activity against multiple pediatric malignancies. GSK-J4 inhibited T-cell ALL in both of the above-cited studies of the KDM6 family in this disease ^{136, 141}. More recently, GSK-J4 was shown to be effective against high-risk neuroblastoma ¹⁵¹. Mechanistically, GSK-J4 induced tumor cell differentiation and endoplasmic reticulum stress, resulting in cell death, and showed efficacy both in context of chemoresistance and retinoic acid resistance. Further, GSK-J4 sensitized MYCN-amplified neuroblastoma to the BCL2 inhibitor venetoclax. Whether GSK-J4 acts through inhibition of KDM6A, KDM6B or both in neuroblastoma was not clarified. GSK-J4 has also been shown to be effective against pediatric brain stem glioma ¹⁵², a highly aggressive and lethal neoplasm characterized by histone H3.3 K27 mutations (most commonly K27M). Such mutations, which are heterozygous, exert a dominant effect on wild-type H3K27, resulting in reduced levels of H3K27 methylation via sequestration of the polycomb repressive complex 2 (PRC2) ^{140, 153, 154}. Treatment of brain stem glioma cells with GSK-J4 was able to reverse this downregulation of H3K27 methylation, at least in part via inhibition of KDM6B, and inhibited cell and tumor growth ¹⁵². GSK-J4 has also been shown to be effective in diffuse large B-cell lymphoma, as a chemotherapy-sensitizing agent ¹⁵⁵, AML ¹⁴⁶, breast cancer ¹⁵⁶, taxane/platin-resistant lung cancer ¹²³, and prostate cancer ¹⁵⁷, including its castration-resistant subtype ¹⁵⁸.

2.6 KDM7

The KDM7 subfamily has three members, KDM7A-C. KDM7A (JHDM1D) is also known as KIAA1718, while KDM7B (JHDM1F) and KDM7C (JHDM1E) are more commonly referred to in the literature as PHF8 and PHF2, respectively. The JmjC domain of each factor has activity against repressive H3K9me2 marks, with KDM7A and PHF8 also able to demethylate H3K9me1 ^{6, 8, 9}. KDM7A is additionally able to remove repressive H3K27me1/2 marks ^{6, 8, 9}. PHF8 displays additional demethylase activity against repressive H3K27me2, as well as H4K20me1, a mark that can be associated with active as well as repressed genes ^{6, 8, 9}. All three factors can thus activate gene expression via their JmjC-associated demethylase activity against H3K9 and H3K27 methyl marks. PHF8 additionally has the potential to repress gene expression, via its demethylase activity against H4K20me1 in some contexts, as well as interactions with repressor complexes ^{159, 160}. All members of the KDM7 subfamily also possess an N-terminal PHD domain, which confers the ability to

differentially bind modified histones. Notably, both PHF2 and PHF8 have been shown to interact via their PHD domains with H3K4me2/3, marks typically associated with active gene regulatory elements ^{161, 162}, suggesting a role in the regulation of genes primed for transcription. Developmentally, PHF8 plays important roles in central nervous system and craniofacial morphogenesis, and, like KDM5C, has been implicated in the pathogenesis of X-linked mental retardation (XLMR) syndrome ⁶.

Members of the KDM7 subfamily have been shown to play somewhat divergent roles in cancer. PHF8, thus far the most extensively studied, has been shown to be upregulated in expression and to be disease-promoting in a number of different cancers, including breast ^{163, 164}, prostate ¹⁶⁵, lung ¹⁶⁶ and esophagus ¹⁶⁷. Demonstrated functional roles for PHF8 in these cancers include augmentation of cell and tumor growth, enhancement of motile properties and metastasis, and a role in DNA repair. Mechanistically, in prostate cancer, PHF8 is induced by c-Myc and hypoxia/HIF, and functions both in concert with and downstream of AR to promote disease progression ^{168, 169}. PHF8 also controls rRNA synthesis ¹⁶¹, promotes cell cycle progression by multiple mechanisms ^{170–172}, and controls cytoskeletal dynamics ¹⁷³. In adult-onset ALL, PHF8 plays an oncogenic role via a positive feedback loop with MEK/ERK signaling ¹⁷⁴. Studies of the other members of the KDM7 family in cancer have thus far been more limited, and have uncovered both disease-promoting and disease-suppressive roles. In prostate cancer, KDM7A is upregulated in expression and plays a role in AR-dependent gene expression and cell proliferation ¹⁷⁵. However, KDM7A expression is also induced under nutrient deprivation, and its ectopic overexpression in HeLa cells inhibits xenograft growth and angiogenesis ¹⁷⁶. In PANC-1 pancreatic cancer cells, KDM7A positively regulates E-cadherin expression, a cell junction protein typically expressed in normal epithelial cells ¹⁷⁷. PHF2 has been shown to be downregulated in expression in colon and gastric cancer, and to promote p53-driven gene expression under genotoxic stress and chemoresponse, thus acting as a tumor suppressor in these contexts ¹⁷⁸. In breast cancer, PHF2 had been shown to be phosphorylated by PKA and to promote cAMP-induced mesenchymal-epithelial transition (MET) ¹⁷⁹. In Clear Cell Renal Cell Carcinoma (CCRCC), high expression of PHF2 is associated with longer survival and smaller tumor size ¹⁸⁰.

Investigations of the KDM7 subfamily in neoplastic diseases of childhood have thus far focused on hematopoietic cancers. In Notch-driven Tc-ALL, PHF8 is part of the Notch nuclear complex and is required for Notch-mediated gene expression ¹⁸¹. In Acute Promyelocytic Leukemia, PHF8 functions as a cofactor of the disease-driving RAR α oncofusions, and is required for a therapeutic response of the disease to all-trans retinoic acid ¹⁸². PHF2, on the other hand, is downregulated in a subset of ALL patients with deletions of the PHF2 upstream regulator Ikaros, and low PHF2 expression correlates with cell proliferation and increased levels of markers of poor prognosis ¹⁸³.

Multiple approaches have been undertaken toward development of pharmacologic inhibitors of the KDM7 subfamily, all at relatively early stages. A structure-based approach identified a compound with activity against KDM7A/PHF8, and the closely related KDM2A, which inhibited proliferation of cancer cells ¹⁸⁴. A different KDM2/7 inhibitor was identified in a

screen of analogues of the JmjC domain cofactor α -ketoglutarate¹⁸⁵. A cyclic, cell-penetrating peptide inhibitor of PHF8 has also recently been developed¹⁸⁶.

3. Conclusion

Epigenetic mechanisms have long been known to play fundamental roles in normal development. As evident more recently, they are also frequently dysregulated in neoplastic disease including cancer, where they make important contributions to disease pathogenesis. Epigenetic mechanisms present potential therapeutic targets, as they frequently rely on enzymatic activities susceptible to small molecule inhibition. The Jumonji-domain histone demethylase (JHDM) family exemplifies all of the above traits. With respect to cancer and other neoplasias, at this time, the JHDM family has largely been studied in the context of adult diseases. Here, the various members have been demonstrated to exert diverse, and frequently profound, disease-modifying effects. Not surprisingly for epigenetic regulators, most JHDM demonstrate a degree of context dependence for their biological effects in cancer. However, encouragingly, from a pharmacologic targeting standpoint, a number of JHDMs (eg: KDM3A, KDM4A/B/C, KDM5A/B and PHF8) appear to behave predominantly to exclusively as disease-promoting factors. At this time, JHDMs have been far less studied in cancers and other neoplasias of childhood. However, available examples, mainly from diseases of the hematopoietic and nervous systems, support important roles, and in some cases therapeutic potential, of JHDMs in pediatric neoplasia. Further studies of JHDMs in childhood cancers and other neoplastic disorders can be expected to both inform disease biology and point to new options for disease management.

4. Expert opinion

Cancers and other neoplastic diseases of childhood commonly have a developmental basis, arising in immature developmental cell and tissue precursors, recapitulating molecular and histologic developmental programs, or manifesting both traits. Epigenetic mechanisms have long been known to play fundamental roles in development, and, more recently, their roles in the initiation and progression of neoplastic disease have come to be appreciated. It has also become apparent that epigenetic mechanisms play particularly important roles as disease drivers and promoters of disease progression in pediatric neoplasms with a developmental basis, which, in contrast to adult neoplastic processes, tend to be characterized by a relative paucity of mutations.

Genes belonging to the JHDM family first came to be known as developmental regulators^{6, 10}. More recently, JHDMs have emerged as important players in neoplasia and malignancy. As evident in this review, thus far, JHDMs have largely been studied in adult cancers. In this context, they have emerged as important modulators of disease progression, with predominantly disease-promoting roles. As summarized in Table 2, where studied in cancers of childhood, JHDMs have also been shown to function predominantly as disease-promoting factors. To date, in the pediatric age group, JHDMs have predominantly been investigated in hematopoietic malignancies and tumors of the nervous system. Given the important roles of JHDMs in development, it is likely that much interesting and important information remains to be uncovered regarding their roles in neoplastic processes with a

developmental basis arising in other organs and tissues, including common childhood cancers of the kidney (Wilms tumor), liver (hepatoblastoma), soft tissues (rhabdomyosarcoma) and bone (Ewing Sarcoma). Encouragingly, in the handful of available examples at this time, JHDM pharmacologic inhibition has shown activity in pediatric cancers (Table 3), underscoring the importance of this endeavor.

JHDMs are most readily targetable through their JmjC domain-dependent demethylase enzymatic activity. Whether this is the optimal approach in a given cancer depends on demonstration that such activity is critical to phenotypic effects and control of expression of key downstream genes. For many JHDMs, this information remains to be determined, both in adult and pediatric cancers. Further, all JHDMs are multi-domain proteins, as summarized in Table 1. However, at this time, the role of most of these additional domains in gene regulation, and normal and abnormal biology, including cancer, largely remains to be defined. A case in point illustrating both of the above-unanswered questions is KDM5A. Canonically a repressor of gene expression via its H3K4 demethylase activity, KDM5A has been shown to be able to activate gene expression both in normal and cancer cells, including pro-metastatic genes in the case of the latter. Mechanistic studies addressing gene activation have identified potential roles for both demethylase-dependent as well as independent mechanisms. With regard to the demethylase-independent mechanisms of gene activation, the structural/functional domains responsible have, in most cases, not been defined; moreover, some studies have suggested an unexpected role for the demethylase activity in gene activation. Lastly, on a broader level, the precise role of H3K4 methylation as a determinant of gene regulatory element activity is at present incompletely understood²⁸. Thus, at this point, optimal strategies for therapeutic targeting of JHDMs in cancer in many cases await further information on molecular mechanisms of action.

JHDMs are one of a number of druggable epigenetic modifier families to be studied and targeted in cancer. A short, but by no means exhaustive, list of other factors and families includes the writers EZH2, DOT1L and DNMT1, the erasers LSD1 and HDACs, and the BET chromatin reader family¹. Compounds targeting these have reached clinical testing, including some for aggressive cancers of childhood, namely EZH2 inhibitors for malignant rhabdoid tumors and BET inhibitors for NUT-rearranged midline carcinoma¹. Targetable epigenetic regulators have also emerged as potential alternative approaches to inhibition of “undruggable” transcription factor oncofusions in pediatric sarcomas, such as LSD1 in Ewing Sarcoma and BET inhibitors in fusion-positive rhabdomyosarcoma^{187, 188}. The biology of the JHDM family in cancer is undoubtedly intertwined with these and other chromatin factor families, but the nature and relevance of such interactions is largely undefined at this time. Understanding such intersections, both at the molecular mechanistic level and at the promising lead compound level, is likely to inform new and better therapeutic strategies.

In summary and closing, the Jumonji-domain histone demethylases (JHDMs) comprise a large family of epigenetic regulators with roles in developmental morphogenesis, increasingly demonstrated roles in adult cancer initiation and progression, and, at this time, largely uncharacterized roles in the pathogenesis of neoplasms of childhood, particularly those with developmental origins. JHDMs are all druggable via their enzymatic demethylase

activities, but are also multi-domain proteins, and at this time, much remains to be learned about the different domain requirements for their mechanisms of action. Similarly, much remains to be learned about JHDM mechanistic intersections with other classes of epigenetic, as well as transcriptional, regulators of gene expression. Such knowledge can be expected to inform our understanding of the mechanisms of neoplastic initiation and progression, and help guide strategies toward development of new and better therapies.

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Article highlights

- Epigenetic mechanisms of gene regulatory control play fundamental roles in developmental morphogenesis, and, as more recently appreciated, are heavily implicated in the onset and progression of neoplastic disease, including cancer. Many epigenetic mechanisms are therapeutically targetable. The Jumonji-domain histone demethylase (JHDM) family exemplifies these traits.
- The JHDM family consists of roughly 20 genes/proteins that remove methyl groups from modified histones, using the Jumonji-C (JmjC) domain, and Fe^{2+} and α -ketoglutarate as cofactors. Histone mark specificity varies among the different subfamily members and helps determine effects on gene expression. All JHDMs are multi-domain proteins, but, at this time, the biological functions of additional domains are much less well understood than those of the JmjC demethylase domain.
- The biology of most JHDMs has been investigated in adult cancers. Here, different JHDMs have been found to exert context-dependent effects ranging from predominantly disease-promoting to mainly disease-suppressive. Encouragingly, from a pharmacologic targeting perspective, several JHDMs appear to behave predominantly to exclusively as disease-promoting factors.
- At this time, comparatively few studies have addressed JHDM biology in cancer and other neoplastic diseases of childhood, especially solid (non-hematopoietic) neoplasms. However, the few available examples support important roles for JHDMs in pediatric neoplasia, as well as potential roles for JHDM pharmacologic inhibition in disease management.

Table 1.

JHDM structural/functional domains and histone mark specificity.

PTM: post-translational modification; DM: demethylase; Prot: protein; Chrom: chromatin; JmjC: Jumonji-C; ARID: AT-rich interaction domain; GATAL: GATA-like; ZF: zinc finger; JmjN: Jumonji-N; LRR: leucine-rich repeat; TPR: tetratricopeptide repeat; PHD: plant homeodomain.

				Structural/functional domains										Histone PTM specificity									
				DNA and RNA interactions										Prot-Prot interactions				Chrom reader			Other		
				DM		JmjC	ARID	GATAD	ZF-C2HC4	ZF-C5HC2	ZF-CXXC	F-box	JmjN	LRR	TPR	PHD	Tudor	Other	PLU	H3K4	H3K9	H3K27	H3K36
KDM2	Alternative names			JHDM1A	×					×	×		×										
	KDM2A	FBXL11		×						×			×								me1/2		
	KDM2B	FBXL10		×						×			×								me1/2		
	KDM3A	JMJD1A		×														me3				H3K79me2/3	
KDM3				×															me1/2				
	KDM3B	JMJD1B		×															me1/2			H4R3me1/2	
	KDM3C	JMJD1C																					
KDM4	KDM4A	JMJD2A		×																			
	KDM4B	JMJD2B		×								×		×	×				me2/3		me2/3	H1.4K26me2/3	
	KDM4C	JMJD2C		×								×		×	×				me2/3		me2/3	H1.4K26me2/3	
	KDM4D	JMJD2D		×								×							me2/3			H1.4K26me2/3	
	KDM4E	JMJD2E		×															me2/3			H1.4K26me2/3	
	KDM5A	JARID1A		×					×			×		×			×	me2/3					
KDM5				×					×									me2/3					
	KDM5B	JARID1B		×					×														
	KDM5C	JARID1C		×					×									me2/3					
	KDM5D	JARID1D		×					×									me2/3					
	KDM6A	UTX		×															me2/3				
	KDM6B	JMJD3		×															me2/3				
	KDM6C	UTY		×																			
KDM7				×																			
	KDM7A	KIAA1718		×															me1/2				
	KDM7B	PHF8		×															me2			H4K20me1	
	KDM7C	PHF2		×															me2				

Table 2.
JHDMs implicated in cancers and other neoplasias affecting the pediatric population.

Summary of findings from published literature, as discussed in text (references in parentheses). ALL: Acute Lymphoblastic Leukemia; Bc-ALL: B-cell ALL; Tc-ALL: T-cell ALL; AML: Acute Myeloblastic Leukemia; APML: Acute Promyelocytic Leukemia; NB: Neuroblastoma; EwS: Ewing Sarcoma; OS: Osteosarcoma; MBL: Medulloblastoma; BSG: Brain Stem Glioma; GBM: Glioblastoma Multiforme; TR: Temozolomide-resistant.

		Expression/alteration			Function		
		up	down	mutated	promoting	suppressive	
KDM2	KDM2A						
	KDM2B		GBM (ref 22)		ALL (ref 23), AML (refs 24, 25)	AML (KRAS-driven) (ref 23)	
KDM3	KDM3A	NB (ref 58), EwS (ref 59)			NB (ref 58), EwS (refs 59, 60)		
	KDM3B	ALL (ref 48)		AML (refs 49, 50)	ALL (ref 48)	AML (refs 49, 50)	
	KDM3C	AML (refs 51, 53)			AML (refs 51–53)		
KDM4	KDM4A						
	KDM4B	AML (ref 78), NB (ref 82), MBL (ref 84), OS (ref 85)			NB (ref 82), OS (ref 85)		
	KDM4C	AML (ref 78), MBL (ref 84), OS (ref 85)			AML (ref 79), OS (ref 85)		
	KDM4D						
	KDM4E						
KDM5	KDM5A	GBM(TR) (ref 120), NB (ref 131)			GBM(TR) (ref 120), NB (ref 131)		
	KDM5B	NB (ref 130)			NB (ref 130)		
	KDM5C			ALL (ref 132), AML (ref 133)			
	KDM5D						
KDM6	KDM6A	AML (ref 78)		Bc-ALL (ref 139), Tc-ALL (refs 136, 140), MB (ref 142)	Tc-ALL (TAD-1+) (ref 141)	Tc-ALL (refs 136, 140)	
	KDM6B	AML (ref 146)			Tc-ALL (ref 140)		
	KDM6C						
KDM7	KDM7A						
	PHF8				Tc-ALL (ref 181), APML (ref 182)		
	PHF2		ALL (ref 183)			ALL (ref 183)	

Table 3.

Compounds with JHDM inhibitory activity that have been evaluated in cancers and other neoplasias affecting the pediatric population.

Summary of findings from published literature, as discussed in text (references in parentheses). ALL: Acute Lymphoblastic Leukemia; Tc-ALL: T-cell ALL; AML: Acute Myeloblastic Leukemia; NB: Neuroblastoma; EwS: Ewing Sarcoma; BSG: Brain Stem Glioma; GBM: Glioblastoma Multiforme; TR: Temozolomide-resistant; * with SETD2 mutation.

Drug	Selectivity	Disease
JIB-04	pan-JHDM	ALL/AML* (ref 81), EwS (ref 61), GBM(TR) (ref 129)
DMOG	?KDM3	NB (ref 58)
Ciclopox	?KDM4	NB (ref 83)
NSC636819	KDM4A/B	AML (ref 78)
SD70	KDM4C	AML (refs 78, 79)
GSK-J4	KDM6	Tc-ALL (refs 136, 141), AML (refs 78, 146), NB (ref 151), BSG (ref 152)