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EPIGENETICS AND PHYTOCHEMICALS (RL ECKERT, SECTION EDITOR)

Histone Demethylases in Cancer

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Abstract Epigenetic regulation, which involves with covalent modifications of DNA and the protein that bundles DNA, namely histones, is an exciting and variable phenomenon that affects normal cellular genetic character and contributes to human diseases. One key histone modification is methylation, regulated by methyl transferases and demethylases. Recent studies have demonstrated that histone demethylases as new therapeutic targets in different diseases including cancers. In this manuscript, we summarize the current view of the histone demethylase families and their role as activators or repressors of various genes in cancer. It has been demonstrated that hypoxia is a driving force for the regulation of histone demethylases in different cancers. We have also discussed the latest development of the role of hypoxia in regulating histone demethylases and its effects on tumor progression.

Keywords Epigenetics · DNA methylation · Histone demethylases · Cancer · Hypoxia

Introduction

It is well known that DNA is packaged into nucleus in highly organized fashion and is wrapped around histone proteins and together with other proteins, known as chromatin [1••]. In the basic unit of chromatin—the nucleosomes- 145-147- base pairs of DNA wrapped around by the histones H2A, H2B, H3 and H4. This unit is repeated throughout the chromatin and is an important determinant of cellular function [1••]. Major component in the regulation of cellular processes by chromatin structure is the posttranslational modifications including acetylation, methylation, phosphorylation, ubiquitylation, and SUMOylation [1••]. Each of these influences the structure of chromatin and the degree and the type of modifications due to different functional outcomes [1••]. Posttranslational epigenetic modifications to chromatin including methylation of DNA and histones substantially contribute to the regulation of gene expression by affecting the accessibility of DNA transcription [1••, 2–4, 5•].

Gene expression and cellular identity are significantly associated with the developmental biology, neurological disorders, and in many cancer types [1••, 6, 7]. During the past decade, the focus has shifted towards histone methylation due to the discovery of new enzymes that can catalyze the addition and removal of methyl groups at lysine (Lys) and arginine (Arg) residues on histone tails. Before the discovery of the first histone demethylase LSD1 [8•], methylation of histone was thought to be a permanent and irreversible phenomena [1••]. Methylation control is now considered to strongly correlate with disease progression that has led to considering the possibility of regulating histone methylation [8•].

Cancer is one of the most complicated diseases characterized by abnormal and uncontrolled growth of cells resulting in the formation of cellular masses and production of localized tumors. Different types of cancers affect about 13 million people worldwide and cause the death of 8 million people annually [9••]. Recent studies have demonstrated that cell growth and proliferation are controlled by histone methylation patterns. Hence, understanding how histone methylation that is tightly regulated by the enzymes regulates transcriptional

Topical Collection on *Epigenetics and Phytochemicals*

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machinery in cancers could have significant bearing on developing therapeutic interventions targeting this process [6, 7].

Histone Lysine Demethylase Families

Histone methylation occurs in lysine residues of histones 3 and 4 (H3 and H4), and the linker histone H1, isotype 4 (H1.4). All histones have the capability to be methylated on one or more residues but some residues are targeted more frequently than others. Commonly methylated sites are Lys-4, −9, −27, −36, and −79 of histone H3 and Lys20 of Histone H4 [1••]. In mammalian cells, up to 40–80 % of all histones are demethylated at positions H3K9, H3K27, H3K36, or H4K20 [10, 11] correlating with enhanced transcription. These histones marks could be mono (me1), di (me2), and tri (me3) methylation, and depending on the gene, would affect gene expression [12•].

Structurally, histone lysine demethylases are two different classes of proteins. First is the lysine-specific demethylase (LSD1 also known as KDM1A), which along with structurally similar KDM1B (LSD2), consist of the flavin adenine nucleotide (FAD)-dependent enzyme amine oxidases that can remove mono and dimethyl in histone marks [12•] (Fig. 1a). These amine oxidases, however, are unable to demethylate trimethyl lysine residues because they require a single pair of electrons only present in mono- or dimethyl lysine histone residues (Fig. 1a). The second family of histone demethylases consists of the Jumonji C (JmjC)-domain containing proteins which employs oxygenase mechanism to demethylate specific mono-, di-, and tri- methyl-lysine residues. The enzymatic function of the JmjC domain relies on α-ketoglutarate (α-KG), Fe (II), and molecular oxygen as cofactors in demethylation reaction [12•, 13] (Fig. 1b). It has been revealed that humans encode 32 such JmjC domain containing genes, 24 of which showed demethylase activity.

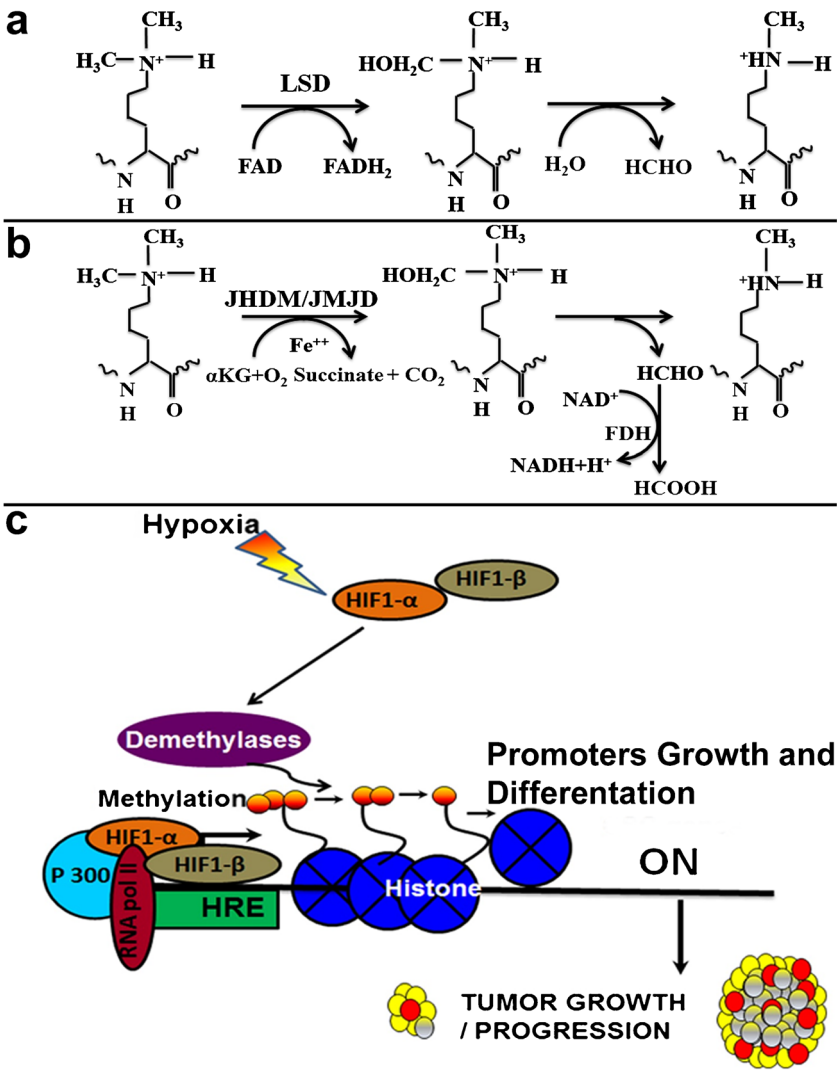

Fig. 1 **a** Lysine-specific demethylase (LSD) catalyzes demethylation of histone. These enzymes are responsible for a FAD-dependent activity that implicates at least one atom of hydrogen on the amine group of lysine suggesting the activity of these enzymes on the mono- and dimethylated of lysine. **b** Jumonji domain demethylase protein (*JHDM/JMJD*) catalyzes demethylation of dimethylated histone. These enzymes are dependent on oxygenase activities which are capable of adding a hydroxyl group to methyl group in lysine residue in α-ketoglutarate (α-kg) and Fe++-dependent manner during the conversion of α-kg into succinate and CO_2 followed by spontaneous release of formaldehyde. **c** Model of hypoxia induces activation of demethylase enzymes and hence enhances tumor formation. Hypoxia most prominently controls malignant properties of cancer cells by stimulating hypoxia inducible factor 1 (*HIF1*). The fact that HIF1 binds to its responsible elements (*HREs*) in the histone demethylase promoters and subsequently upregulates the histone demethylase enzymes Then, histone demethylase removes the methylation of histone from tri- to di- to mono-methylated state of enzyme that exacerbates tumor progression

Histone Demethylases and Cancer

Much effort has been made to identify and characterize the various demethylases after discovery of LSD1. Among the most important histone demethylases associated with cancer are LSD1/KDM1A, and members of the Jumonji family JARID1A/KDM5A, JHDM1B/KDM2B, JHDM2A/KDM3A/JMJD1A, JMJD2C/KDM4C, JMJD2A/KDM4A, JMJD3/KDM6B, and UTX/KDM6A (Table 1).

LSD-1 and LSD-2

LSD-1/KDM1A was the first demethylase protein to be identified [8•, 13]. LSD-1 is considered to be an important regulator of the formation of organs and tissues of the heart, brain, and skeletal muscle [9••, 13–16]. It is also involved in regulating cellular energy expenditure, inflammatory responses, and hematopoiesis [17–19]. LSD-1 can change its substrate to the mono-methylated form of Lys-9 residue due to interactions with another histone demethylase, JMJD2C. Both proteins together have been associated with the development of prostate and bladder cancer through putative interactions with androgen receptors [20–24]. Increased activity and expression of LSD-1 have shown to be related to the development of different types of cancer, such as neuroblastoma [25], leukemia [21, 26] sarcoma [27], lung [28], and ER-negative breast cancer [29]. On the contrary, low levels of this protein have been demonstrated in hepatocellular, GI, hepatobiliary, and metastatic breast carcinomas [30, 31]. The understanding related to the molecular mechanism on LSD-1 activity is dependent on the determination of 3D structure [32] and that information is leading towards the discovery of the development of novel inhibitors for therapeutic potential [33–37]. LSD-1 is also thought to be potential marker for early diagnosis and treatment of the malignant tumors [38].

Another member of this amine oxidase protein family is LSD-2/AOF1/KDM1B. Although structurally, LSD-2 has similarity with LSD-1, it does not contribute in the chromatin-modeling complexes [39, 40]. The enzyme activity of LSD-2 is dependent on mono- and dimethylated Lys-4 of histone H3 and is important for its association with the regulation of the inflammatory process mediated via NF-kB [41]. This enzyme is also related to genomic imprints [42] and is also an important factor for generation of induced pluripotent stem cells [43]. The biological function of LSD2 and its exact role in human cancer is likely to be tissue or cell type specific [39, 44, 45].

JARID1

JARID1/KDM5A family of oxygenases acts on bi- and trimethylated Lys-4 of histone H3. This enzyme has been implicated in cell cycle regulation [46] because it interacts with retinoblastoma protein that affects pathways dependent on cyclins in gastric cancer [47] and in leukemia [48]. It has been identified as a relevant marker to assess the multiform survival of glioblastoma [49]. JARD1A has demonstrated as critical factor for the development of drug tolerance in lung cancer cells [50]. The current understanding related to the function of this protein at a molecular and cellular level is still under investigation although it has been suggested that JARID1A has a role as a regulator of cellular growth through the Notch signaling pathway [51]. Both JARID1A and JARID1B demethylases could be linked to the silencing of retinoblastoma genes in senescent cells [52].

The second member of this family, JARID1B/PLU1/KDM5B, has been implicated as an important regulator for cellular development and differentiation [53–56]. The high expression of this enzyme has also been found in leukemia, prostate, breast, testicular, and ovarian cancers due to the repressor of tumor suppressor gene, BRCA1. It also acts as a co-activator of transcription factors TIEG1/KLF10 and/or the androgen receptor in those cancer types [57–64].

The third member of the family, JARID1C/KDM5C, has been involved in the development of renal carcinoma through the regulation of von Hippel-Lindau tumor suppressor protein [65, 66]. JARID1C has also been involved in cervical cancer as an oncogenic target of human papillomavirus [67].

JHDM1B

JHDM1B/KDM2B belongs to the Jumonji domain protein family and revealed oxygenase activity in mono- and bi-methylated lysine 36 of histone H3 [8•]. It has been suggested that this protein plays an important role in regulation of cell proliferation and senescence [68, 69]. It also acts as an enhancer in reprogramming of stem cells [70]. JHDM1B has been considered as a candidate for tumor suppressor gene because the expression levels of this protein is reduced in myeloid leukemia, lymphoma, and glioblastoma multiform [71, 72].

JHDM2A

JHDM2A/JMJD1A/KDM3A is lysine (k)-specific demethylase 3A that specifically demethylates Lys-9 of histone H3, thereby playing an important role in histone code. It demethylates preferably mono- and dimethylated residues while it has weak or no activity on trimethylated H3 on Lys-9. Demethylation of Lys residue generates formaldehyde and succinate. The enzyme is a member of non-heme Fe (II)-dependent dioxygenases that require molecular oxygen and 2OG for catalysis [73]. JHDM2A is involved in hormone-

Table 1 Histone demethylase gene of *Homo sapiens*: identification number and their regulation in different types of cancer

Gene Acc# symbol	Gene name	Histone demethylase regulation in different types of cancer		Gene affected
		Upregulation	Downregulation	
NM_015013 KDM1A/LSDI	Lysine-specific demethylase 1A	Prostate (15, 65, and 77), kidney (50), ER-negative breast (62), leukemia (19, 12, and 26), sarcoma (7) lung (70) neuroblastoma	GI, Hepatocellular and haptobiliary (72) metastatic breast carcinoma (122)	ANDR, DNMTI, PML, RARα
NM_001042811.1 (KDMIB)	Lysine-specific demethylase 1B	Cervical cancer (26, 19) breast (4,8)	Unknown	CCNLI, DNAJB1I
NM_001042603 JARIDIA/KDMSA	Lysine-specific demethylase 5A	Gastric (65, 130), leukemia (115), glioblastoma (99) lung (28), testis (60)	Unknown	CDKN1B, ITGB1, PcG, CDKI, CIO1, KIP1, INK4a
NM_006618 JARID1B/KDM5B	Lysine-specific demethylase 5B	Breast (10, 69, and 127), lung (28), testis (60)	Unknown	BRACA, OCT4, SOX2, NANOG, CX26
NM_004187.3 NM_001146702.1 JARIDIC/KDM5C	Lysine-specific demethylase 5C	Renal (61, 65, 85, 66, 116) and cervical (102)	Unknown	IGFBP3, DNAJC12, COL6A1, GDF15, DEP1
NM_032590 JHDM1B/FBX1L 10/KDM2B	Lysine-specific demethylase 5B	Myeloid leukemia (66, 68, 121)	Lymphoma (71, 72), glioblastoma (9,29)	OCT4, SOX2, PcG, MYC
NM_018433 JHDM2A/JMJD1A /KDM3A	Lysine-specific demethylase 5A	Renal (33 and 55), hepatocellular (86) melanoma (84), sarcoma (87), colon (85)	Unknown	PRM1, TMP1, PPARA, UCP1, ADM, GDF15
NM_15061 NM_001146694 NM_ 001146695 NM_001146696 JMJD2C/KDM4C	Lysine-specific demethylase 4C	Lung sacromatoid (45 and 65), esophageal carcinoma (65, 88), myeloid leukemia (39 and 82) lymphoma (79, 91, 92). breast (64, 126), medulloblastoma (25), glioblastoma multiforme (24)	unknown	NANOG, GLUTI, LDHA, PDKI, LOX, LOXL2, L1CAM, CITED2, MYOG
NM_014663 JMJD2A	Lysine-specific demethylase 4A	Kaposi sacroma (12), breast (58), prostate (14, 101), colon (52), bladder (35, 65), squamous (24)	Unknown	AP1, JUN, FOSL1, ARH1, ADAM12
NM_001080424 JMJD3/KDM6B	Lysine-specific demethylase 6B	Renal (22), colon (89) and melanoma (3, 75)	Lymphoma (65, 75)	NPM-ALK, BTG3, SNAI1
NM-021140 UTX/KDM6A	Lysine-specific demethylase 6B	Multiple myeloma (65, 114), leukemia (74, 81) and renal (32, 114)	Unknown	Mll1

dependent transcriptional activation, by participating in recruitment of androgen receptor target genes such PRM1 and TMP1 which are required for packaging and condensation of sperm chromatin [74]. This enzyme is also involved in obesity resistance through regulation of metabolic genes namely PPARA and UCP1 [75]. Krieg et al. [76] demonstrated that the regulation of this enzyme by hypoxia-inducible transcription factors (HIF1α and HIF1β) enhances hypoxic gene expression particularly adrenomedullin (ADM) and the growth and differentiation factor 15 gene (GDF15), ultimately enhancing tumor growth in renal cancer. In another study, nickel ion-induced upregulation of JHDM2A expression in kidney cancer is antagonized by ascorbate, suggesting cancer preventive role of ascorbate via targeting JHDM2A [77]. JHDM2A regulates ADM-mediated cell proliferation in hepatocellular carcinoma, suggesting a role of this enzyme as a proliferation regulator in some cancer types [78]. Inhibition of this enzyme hinders angiogenesis and reduces tumor-associated macrophages, revealing an important role in tumor progression under hypoxia and nutrient starvation in different cancers including cervical, hepatic, epidermal, glioblastoma, and melanoma [79]. It has been shown that microRNA-22 regulates this enzyme, in turn, acts as a tumor promoter in Ewing sarcoma [80]. MicroRNA-627-mediated JHDM2A is downregulated by Vitamin D, in turn, suppresses the growth of colon cancer [81]. JHDM2A has been shown to be a novel prostatic marker in metastatic colorectal cancer cells that could be a promising therapeutic target for colon cancer [82].

JMJD2C

JMJD2C/KDM4C is another histone demethylase that exhibits oxygenase activity at the bi- and trimethylated Lys-9 in histone H3 [83], and this protein is involved in the development and self-renew of undifferentiated and embryonic stem cells for regulation of adipogenesis through hypoxia [74, 84–86]. It is considered as an amplified oncogene in different cancers such as sarcomatoid and esophageal carcinoma [87, 88], myeloid leukemia [88, 89], lymphoma [90–92], breast carcinoma [93, 94], desmoplastic medulloblastoma [95], and glioblastoma multiforme [96, 97]. JMJD2C could be a potential target for the development of specific treatments against those forms of cancer [36].

JMJD2A

JMJD2A/KDM4A is another Jumonji protein family associated with the transcription of cell proliferation genes due to its binding to chromatin, in turn, influences cell regulator proteins [98, 99]. The JMJD2A enzyme activity is demonstrated on bi- and trimethylated Lys-9 and 36 of histone H3 [85] and has played an important role on cell differentiation, the maintenance of maternal stem cells, and DNA repair [13, 100, 101]. JMJD2A is also involved in the development of different forms of cancer including Kaposi's sarcoma associated with herpes virus [101], prostate cancer via regulation through the activity of androgen receptor [102, 103], breast cancer [104], colon cancer [105], and bladder cancer [106]. JMJD2A interacts with the activating protein 1 (AP1) transcription factors that control cell proliferation, apoptosis, and differentiation [12•]. The demethylation of histone H3 by this enzyme can induce the expression of AP1 genes including JUN and FOSL1 which promote cell growth and metastasis [107]. All these information have raised significant interest towards the understanding for the function of JMJD2A in cancer, which is still unclear.

JMJD3

JMJD3/KDM6B, another member of the Jumonji family, specifically demethylates bi- and trimethylated Lys 27 residues of histone H3 [62]. It is also a part of the multi-protein complexes known as MLL3 and MLL4 that regulate the activity of polycomb family proteins [108–113]. This enzyme has been implicated in colon cancer [114] and melanoma [115]. JMJD3 has been shown to be associated with the different oncogenes such as NPM-ALK and BCL2 or tumor suppression genes such as BTG3 [116–119], although the role of this enzyme has not been yet clearly understood.

UTX

UTX acts on mono- and dimethylated forms of Lys 27 in histone H3 [45] and is a part of the MLL3/MLL4 complexes as shown similarity to JMJD3. UTX is the first histone demethylase known to be linked with cancer due to specific mutations [120]. This enzyme has characteristics as tumor suppressor like JHDM1B and has shown to be associated with the differentiation of tumor cells in multiple myeloma [121], acute lymphoblastic and chronic myelomonocytic leukemia [122–124], and renal carcinoma [121]. UTX has been linked to the retinoblastoma protein similar to JARID1A for its potential role as a tumor suppressor [9••].

Hypoxia regulates Histone Demethylases in Cancer Hypoxia is a characteristic feature of many solid tumors and affects major component of cancer for regulation of cellular processes such as proliferation, apoptosis, angiogenesis, cell differentiation, and metastasis [125]. Clinical data has clearly indicated that the occurrence of hypoxic tissue areas [i.e., areas with O2 tensions (pO2 values) ≤2.5 mmHg] is a characteristic feature of solid tumors

and could be a significant factor of the tumor [126]. Such areas have been found in a wide range of malignancies: cancers of the breast, uterine cervix, vulva, head and neck, prostate, rectum, pancreas, lung, brain tumors, soft tissue sarcomas, non-Hodgkin's Lymphomas, malignant melanomas, metastatic liver tumors, and renal cell cancer [76, 83, 125, 127].

Hypoxia induces the expression of histone modifying factors, resulting in changes of histone mark [76, 85]. The hypoxia-inducible transcription factors (HIFs such as HIF1α, HF1β) employ several transcriptional co-activators, that binds to hypoxia response element (HRE) of target genes causing demethylation on histone marks which promotes growth and differentiation in cancer (Fig. 1c). Although several transcription factors are activated in response to hypoxia, HIFs regulate a critical selection of genes that regulate the cellular response to hypoxia. HIFs are transcription factors consisting of oxygen-induced alpha unit (HIF-1α, HIF-2 α, or HIF-3 α) and constitutively expressed HIF-1β subunit arylhydrocarbon nuclear translocator (ARNT) [76, 85]. HIF is stimulated by hypoxic conditions in cancer [76, 125]. Oxygen plays an important role in stabilization and function of HIF-α. HIF-α is hydroxylated by the oxygen-dependent HIF prolyl hydroxylases (PHD1-3), targeting it for binding with the VHL ubiquitin ligase and proteosomal degradation. As oxygen level drops, PHDs become inactive, resulting into lower HIF-a prolyl-hydroxylation [76, 85]. As HIF-α escapes degradation, it dimerizes with HIF-α [76, 85]. Therefore, during hypoxia, HIF-α/β accumulates, recruits several transcriptional co-activators, and binds to hypoxia response element (HRE) of target genes causing overexpression of VEGF and other angiogenic factors [76, 85].

Recent studies have indicated that the Jumonji C (Jmj) domain containing iron (II), 2-oxoglutarate (2OG)-dependent histone lysine demethylases (KDMs) play an important role in hypoxia response [9••]. Hypoxia stimulates expression of four KDMs enzymes (Jarid1b, Jmjd1a, Jmjd2b, and Jmjd2c) through direct binding of HIF to the HREs present in their promoters. The members of Jmjd2 family KDMs are also overexpressed in a number of cancers and their inhibition suppresses cancer growth [76, 83, 125, 127].

The potential roles of histone demethylases in cancer are not all oncogenic but some of them also demonstrate tumor suppressor function [8, 71, 72]. There is the potential for cancer cells to regulate KDMs through changes in the metabolic programs as well as through mutations in metabolic genes [75, 79]. Given their key regulatory role in access to the genome for transcription and replication, there is an important need to consider KDMs in the overall molecular picture in cancer. We predict that this will be an exciting area for future exploration.

Therapeutic Approaches

Inhibition of histone demethylase has substantial potential for the regulation of gene expression by treatment with small molecules. Studies on the selective inhibition of catalytic domain of human KDM1/LSD and JmjC families KDM by small molecules are developing rapidly in recent days [128]. It is possible to make highly potent and selective inhibitors targeting catalytic domains of both families of KDMs [128]. Efforts have been made for inhibition of KDMs by known types of inhibitors for family of members of KDMs targeting either mechanism-based inhibition of KDMs or targeting active site of iron chelators for the JmjC KDMs. The specificity of those inhibitors is under serious thought because most KDMs share similar catalytic domains [9••]. Therefore, novel specific inhibitors targeting individual KDMs are needed. The challenges in the field are now to identify small molecule inhibitors that specifically can target KDM activity. Those inhibitors could be potential for therapeutic interest in cancer for future investigation.

Few inhibitors targeting LSD1 and other FAD-dependent polyamine oxidases are available [9••]. The designs of those inhibitors have been made on the basis on mechanism action of the enzymes. There are significant developments for identifying new potent inhibitors for LSD1 that inhibit LSD1 activity and also alter the growth of prostate cancer cells [129]. It has been demonstrated through in vitro and in vivo studies that nanomolar concentration phenocopied, a tranylcypromine analog, and an inhibitor of LSD1 showed a pro-apoptotic activity in primary acute myeloid leukemia (AML) without affecting hematopoietic stem cells and progenitor cells [130]. Inhibition of LSD1 can increase the sensitivity for treatment with all-trans-retinoic acid (ATRA) in promyelocytic leukemia [131]. All these information suggest that LSD1 is a key therapeutic target for leukemia.

In addition, iron and α-ketoglutarate-dependent JmjC family of histone demethylases are also important targets for identification of small inhibitors to understand the basis for the mechanism of the activity of these enzymes. One well-known inhibitor targeting α-ketoglutarate is N-oxalylglycine [131, 132]. These types of inhibitors usually compete with 2-oxoglutarate and Fe (II) binding to the catalytic domains of Jumanji-containing domain of histone demethylases.

All these discussions clearly indicate the potential of the histone demethylase family members as therapeutic target against cancer. In the future, crystallographic structural analysis of these enzymes will increase the understanding of the enzyme-inhibitor interactions that will promote the development of new generation of drugs targeting the histone demethylase family of enzymes.

Conclusions

Studies have been revealed that the involvement of histone lysine demethylases is vital for the epigenetic control of cellular differentiation and for the development and maintenance of cancer [9••]. The catalytic domain of these enzymes is well characterized with both full-length protein structure of the LSD family and some of the members of the JmjC domain-containing families. These domains have offered good understanding on mechanisms of enzyme activity and assisted in drug discovery. Hypoxia is a characteristic feature of many solid tumors and affects major components of cancer for regulation of cellular processes such as proliferation, apoptosis, angiogenesis, cell differentiation, and metastasis [125]. Hypoxia induces the expression of histone modifying factors, resulting in changes of histone mark. The hypoxia-inducible transcription factors (HIFs such as HIF1α, HF1β) recruit several transcriptional co-activators, binds to hypoxia response element (HRE) of target genes causing demethylation on histone marks that promotes growth and differentiation in cancer (Fig. 1c). For better understanding on the biological role of KDMs, there is a dire needed to develop genetic models to study the effects of KDMs on cellular function, transcription, and localization of histone marks. Deletion of multiple families of KDMs could be important requirement to characterize the dynamics of KDM target genes in cancer. The generation of knockdown cells and knock-out animals should also provide better understanding in functional roles of KDMs in cancer progression and metastasis.

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Compliance with Ethics Guidelines

Conflict of Interest Satheesh Sainathan, Santanu Paul, Satish Ramalingam, Joaquina Baranda, Shrikant Anant, and Animesh Dhar declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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