Targeting histone demethylases as a potential cancer therapy (Review)

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Abstract. Post-translational modifications of histones by histone demethylases have an important role in the regulation of gene transcription and are implicated in cancers. Recently, the family of lysine (K)-specific demethylase (KDM) proteins, referring to histone demethylases that dynamically regulate histone methylation, were indicated to be involved in various pathways related to cancer development. To date, numerous studies have been conducted to explore the effects of KDMs on cancer growth, metastasis and drug resistance, and a majority of KDMs have been indicated to be oncogenes in both leukemia and solid tumors. In addition, certain KDM inhibitors have been developed and have become the subject of clinical trials to explore their safety and efficacy in cancer therapy. However, most of them focus on hematopoietic malignancy. This review summarizes the effects of KDMs on tumor growth, drug resistance and the current status of KDM inhibitors in clinical trials.

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1. Introduction

There were an estimated 19.3 million new cases and 10 million cancer-related deaths in 2020, causing a great burden worldwide. The prevalence and mortality of cancer are also rapidly increasing (1). Therefore, there is an urgent need to develop effective cancer therapies. Although immunotherapy, particularly cytotoxic T lymphocyte-associated protein 4 inhibitors and programmed death 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors have been proven to be effective in cancer therapy, the presence of immune-mediated side effects (e.g., myocarditis, colitis, pruritus, hepatitis) limits their use in clinical practice (2,3). Furthermore, chemoresistance is becoming a key obstacle for effective cancer therapy. Therefore, more potential cancer targets should be identified to improve future cancer therapy in addition to investigating better combinatorial strategies for cancer therapy.

Histone methylation is a major type of post-translational modification that has an important role in epigenetic modification and contributes to numerous biological processes, particularly carcinogenesis (4). Methyl groups may be added to the side chains of arginine, lysine or histidine residues of histones during histone methylation, among which methylation on lysine residues is the most common (5). In addition, the methylated lysine residues of histones may exhibit mono-, di- or tri-methylated patterns (me1/me2/me3) (6-8).

The lysine (K)-specific demethylase (KDM) family of proteins are histone demethylases that have the ability to remove methyl groups from lysine residues, which are in turn involved in numerous biological processes and diseases, such as development, differentiation, neurological diseases and cancer (9). Histone lysine methylation and demethylation are post-translational modifications that are highly specific to the site and degree of methylation (6-8,10-14). The presence of histone lysine demethylases has been debated for numerous years, until lysine-specific demethylase 1 (LSD1/KDM1A)

was discovered. LSD1/KDM1A, which belongs to the flavin adenine dinucleotide (FAD)-dependent lysine-specific histone demethylases, was characterized as the first histone lysine demethylase with the ability to mediate histone 3 lysine 4 (H3K4) demethylation (15-17). Furthermore, the KDM2 to KDM8 families belong to the Jumonji (JmjC) domain-containing histone demethylases. Similar to FAD-dependent lysine-specific histone demethylases, JmjC domain-containing histone demethylases also contribute to various biological processes by catalyzing demethylation on histone lysine (18-24).

Different histone demethylases would target different sites of histone lysine and demethylation on different sites of histone lysine would have different effects on downstream gene expression (Fig. 1). Since methylated H3K4 and methylated H3K36 are activating factors for gene expression, demethylation on H3K4 or H3K36 would repress downstream gene expression (25-27). However, demethylation on H3K9, H3K27 or H4K20 would contribute to downstream gene activation (Fig. 1) (27).

Overall, histone lysine methylation is closely associated with histone lysine demethylases and participates in gene expression regulation. As a result, histone demethylation performed by histone demethylases has an important role in numerous biological processes, particularly cancer development. In the present review, the role of histone lysine demethylases in cancer is discussed and their potential as a target for cancer therapy is further illustrated.

2. Overview of the role of histone demethylases in cancer

KDM1 family and cancer. The KDM1 family consists of KDM1A (also named LSD1) and KDM1B (also named LSD2). Both KDM1A and KDM1B have a FAD-dependent amine oxidase domain and SWIRM domain. Furthermore, KDM1A also contains a Tower domain, which is responsible for protein interaction (28). The FAD-dependent amine oxidase domain is responsible for removing a methyl group from monomethylated (me1) or dimethylated (me2) lysine residues, while the SWIRM domain is responsible for assisting demethylation. Both KDM1A and KDM1B are able to catalyze the demethylation of H3K4 with mono-methylation or di-methylation (H3K4me1/me2) (29). However, apart from demethylating H3K4me1/me2, KDM1A is also able to catalyze H3K9me1/me2 demethylation (30,31).

In general, KDM1A was indicated to be overexpressed and associated with poor prognosis in a variety of cancers, indicating the oncogenic role of KDM1A (32-35). Therefore, numerous studies have been performed to elucidate how KDM1A contributes to cancer development and progression. First, KDM1A was reported to regulate the cell cycle, which in turn modulated tumor growth. In an early study, KDM1A was indicated to remove dimethylation at the K370 of p53 to inhibit its interaction with p53 binding protein 1, thus inhibiting apoptosis and promoting tumor cell growth (36). In addition, KDM1A-dependent demethylation of myosin phosphatase target subunit 1 (MYPT1) destabilized MYPT1 and reduced its expression level. Thus, downregulation of MYPT1 led to retinoblastoma protein 1 phosphorylation, finally enhancing the G1/S transition of cancer cells (37). In addition, KDM1A has the ability to reduce hypoxia-inducible factor 1α (HIF-1α) degradation and maintain HIF-1α protein levels, thus promoting tumor growth (38). Furthermore, it was recently reported that the immune landscape is regulated by KDM1A by modulating the expression of immune checkpoint regulators and related chemokines, such as PD-L1, C-C motif chemokine ligand 5, C-X-C motif chemokine ligand 9 (CXCL9) and CXCL10 (39). Apart from these three most studied mechanisms, a variety of downstream genes regulated by KDM1A (E2F1, STAT3 and AGO2) were identified to participate in cancer development (35).

Unlike KDM1A, only a small number of studies have identified the role of KDM1B in cancer. KDM1B is overexpressed in cancers, such as breast cancer (40), colorectal cancer (41) and lung cancer (42), functions in tumor growth and correlates with poor prognosis by catalyzing H3K4 demethylation (43). According to the limited literature, the ability of KDM1B to inhibit apoptosis in a demethylation-dependent manner is the key mechanism for tumor growth and progression (40,41,43,44).

KDM2 family and cancer. KDM2A and KDM2B belong to the KDM2 family, the early discovered JmjC domain-containing proteins. Both KDM2A and KDM2B have a JmjC domain and one plant homeodomain (PHD) (29). However, KDM2A has H3K36me2 demethylation activity, while KDM2B demethylates H3K4me3 and H3K36me2 (18,45). KDM2A and KDM2B were indicated to be overexpressed in cancer tissues and contribute to tumor growth and progression in various malignancies, including colorectal cancer, gastric cancer, ovarian cancer and cervical cancer (46-55).

KDM2A mediates H3K36me2 demethylation at the histone deacetylase 3 (HDAC3) promoter, thereby suppressing HDAC3 expression and promoting carcinogenesis and invasiveness of lung cancer (56). Similarly, KDM2A was observed to repress dual-specificity phosphatase 3 (DUSP3) expression through KDM2A-dependent H3K36me2 demethylation at the DUSP3 promoter, which enhanced the ERK1/2 signaling pathway and facilitated lung tumorigenesis (25). In breast cancer, KDM2A promoted cancer stemness and angiogenesis through the upregulation of signaling molecules, such as Jagged1 and Notch receptor 1 (NOTCH1), in a demethylation-dependent manner, hence leading to poor prognosis (57). Likewise, recent research has also indicated that higher KDM2A expression in cancer-associated fibroblasts is associated with advanced tumor stage and poor survival in patients with breast cancer (58).

KDM2B was able to epigenetically suppress the expression of Mps1 binding protein, an important component of the Hippo pathway, contributing to the progression of pancreatic cancer and leading to poor prognosis (59). In addition, among lung and pancreatic cancer cell lines, KDM2B participates in TGF-β induced epithelial-mesenchymal transition, contributing to cancer invasion and metastasis (60). In malignant hematopoiesis, knocking down of KDM2B markedly reduced cell proliferation *in vitro*. Furthermore, knocking down KDM2B delayed or even abrogated leukemogenesis in humanized xenograft models (61). Several studies have indicated the oncogenic role of KDM2B. However, one study identified the tumor-suppressive effect of KDM2B, as silencing of KDM2B triggered invasion of breast cancer cell lines (62).

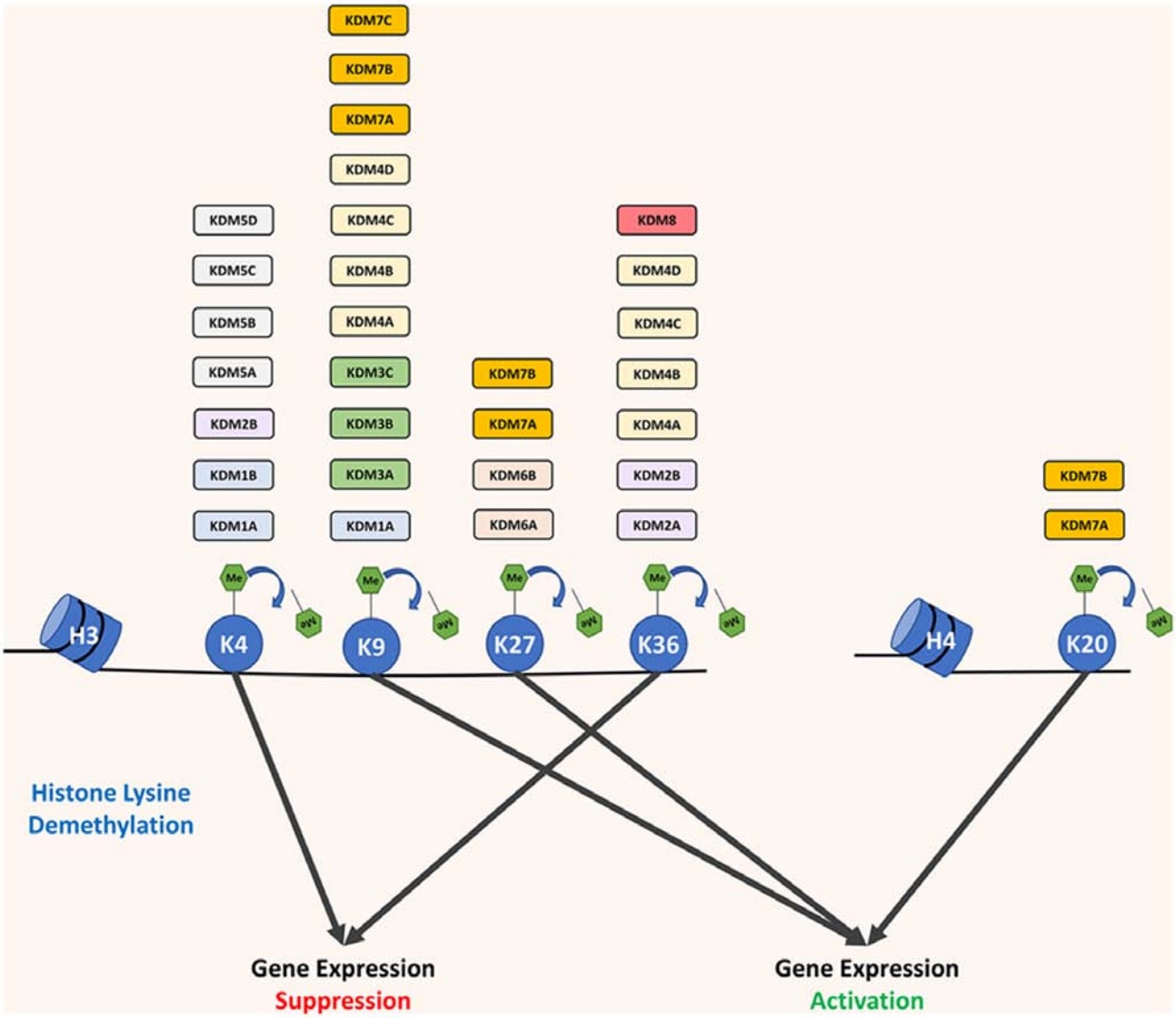

Figure 1. Overview of histone demethylases targeting the site of histone lysine and their effect on gene expression. KDM1A, KDM1B, KDM2B and the KDM5 family target H3K4. KDM1A and the KDM3, KDM4 and KDM7 families target H3K9. KDM6A, KDM6B, KDM7A and KDM7B target H3K27. The KDM2, KDM4 and KDM8 families target H3K36. KDM7A and KDM7B target H4K20. Demethylation of H3K4 and H3K36 would result in suppressing downstream gene expression, while demethylation of H3K9, H3K36 and H4K20 would result in the activation of downstream gene expression. KDM, lysine-specific demethylase; H3K4, histone 3 lysine 4; Me, methyl group.

KDM3 family and cancer. The KDM3 family is composed of three components: KDM3A (also named JMJD1A), KDM3B (also named JMJD1B) and KDM3C (also named JMJD1C). All of the three demethylases contain a JmjC domain at the C terminal, a zinc-finger domain and an LXXLL motif. The JmjC domain is responsible for histone demethylation, while the zinc-finger domain and LXXLL motif are separately responsible for DNA binding and nuclear receptor interaction (63). Among these demethylases, KDM3A and KDM3B were observed to specifically demethylate H3K9me1/me2 *in vitro* and *in vivo*, whereas KDM3C mainly demethylated H3K9me2 (64-67). Most studies performed to date indicate the oncogenic role of the KDM3 family in various cancer types.

In colorectal cancer, upregulation of KDM3A was indicated to be associated with tumorigenesis, advanced stage and poor prognosis (68,69). To achieve this effect, KDM3A specifically demethylates H3K9me2, promoting Wnt/β-catenin pathway activation *in vitro* (70). In addition, H3K9me2 demethylation of the Hippo pathway was facilitated by KDM3A and contributed to colorectal cancer tumorigenesis (71). Among breast cancers, KDM3A is essential for the tumorigenic growth of cancer stem cells and promotes invasion by demethylating p53-K372me1 and inhibiting p53 transcription (72). In another study focusing on breast cancer, KDM3A was indicated to increase estrogen receptor (ER) activity via demethylation of H3K9me2/1 and activation of ER target genes, therefore facilitating tumor growth (73). Apart from colorectal cancer and breast cancer, the oncogenic role of KDM3A was observed in prostate cancer (74-76), lung cancer (77,78), pancreatic cancer (79), liver cancer (80,81) and Ewing sarcoma (82,83) through a variety of *in vivo* and *in vitro* experiments.

To date, research on the relationship between KDM3B and cancer is limited. In HepG2 cells, the expression of cyclin D1 decreased significantly, the cell cycle was mostly halted in the G2/M phase and cell proliferation was reduced when KDM3B was knocked down (84). In addition, loss of KDM3B was

associated with slower growth of castration-resistant prostate cancer cells, although it did not alter the androgen receptor signaling pathway (85). Recently, KDM3B was observed to activate the Wnt/β-catenin signaling pathway, further enhancing the invasion and metastasis of breast cancer (86). In hematopoietic malignancies, KDM3B is recruited to the LIM domain-only protein 2 (lmo2) promoter and transcriptionally activates lmo2, a hematopoietic oncogene that promotes leukemogenesis (87). By contrast, a recent study indicated that KDM3B is highly expressed in patients with acute myeloid leukemia (AML) with favorable prognoses, although KDM3B is highly expressed in hematopoietic malignancies compared to solid tumors. Further examination suggested that KDM3B has an important role in maintaining the fusion protein promyelocytic leukemia/retinoic acid receptor-α levels and the chromatin state during cell differentiation in a demethylation-dependent manner, thus inhibiting acute promyelocytic leukemia progression (88).

Of note, the oncogenic effects of KDM3C on solid tumors and hematopoietic malignancies were identified, although only a small number of studies on KDM3C exist. In AML, KDM3C was able to be recruited by the fusion gene runt related transcription factor 1 (RUNX1)/RUNX1 partner transcriptional co-repressor 1 and demethylated H3K9me2, thus maintaining expression of the fusion gene and its targeting genes, such as p21, fms related receptor tyrosine kinase 1 and serine/threonine/tyrosine kinase 1, and increasing AML cell proliferation (65). Similarly, the use of small molecular modulators of KDM3C, which significantly decreased KDM3C expression, was able to effectively inhibit AML cell growth (89). Among esophageal and colorectal cancers, KDM3C epigenetically sustained the expression of yes-associated protein 1 (YAP1) and activating transcription factor 2 separately and promoted tumor growth and metastasis (90,91).

KDM4 family and cancer. KDM4A (also named JMJD2A), KDM4B (also named JMJD2B), KDM4C (also named JMJD2C), KDM4D (also named JMJD2D), KDM4E (also named JMJD2E) and KDM4F belong to the KDM4 family. Of these, KDM4A, KDM4B and KDM4C have catalytic JmjN and JmjC domains, and non-catalytic PHD and Tudor domains, whereas KDM4D only has catalytic domains (92). The KDM4 family has the ability to catalyze the demethylation of H3K9me2/me3 and H3K36me2/me3 (13,92). In a previous study, the KDM4 family, except for KDM4E and KDM4F with unclear functions in cancer, is mainly overexpressed and acts as oncogenes in different cancer cell lines and tissues (93-96).

KDM4A has a critical role in tumor growth and invasion. KDM4A-mediated H3K9 demethylation has been reported to contribute to androgen receptor activation and affect transcriptional activation through demethylating H3K9me2/me3 (13). In another study, researchers corroborated that KDM4A is responsible for the epigenetic upregulation of YAP1 through recruitment by ETS variant transcription factor 1, ultimately promoting tumor growth in prostate cancer (97). In lung cancers, KDM4A upregulated distal-less homeobox 5, thereby activating the expression of the Myc gene and the downstream Wnt/β-catenin signaling pathway to promote the growth, metastasis and the occurrence of lung cancer (98). In gastric cancer, KDM4A was also observed to promote tumor growth by suppressing apoptosis (99).

KDM4B is both functionally and structurally homogeneous to KDM4A. However, the mechanism by which KDM4B contributes to tumor growth, invasion and metastasis is not similar to that of KDM4A. KDM4B was able to be upregulated by HIF-α, further promoting G2/M phase transition by upregulating cyclin A1 (CCNA1) and downregulating WEE1 G2 checkpoint kinase. KDM4B was also able to promote G1 phase transition by epigenetically downregulating CCND1 through demethylating H3K9me2/me3, ultimately promoting the proliferation of breast cancer (100). This process of KDM4B regulation was also effective in promoting colorectal cancer growth (101). On the other hand, recent studies have emphasized the significance of KDM4B in inducing glucose uptake in tumor growth and progression (102,103). After the knockdown of KDM4B, H3K9me3 levels at the promoter of glucose transporter 1 (GLUT1) increased; thus, the expression of GLUT1 decreased, leading to a reduction in glucose uptake in colon cancer cells (104).

KDM4C was able to remove the methyl group from H3K9me2/me3. When accompanied by KDM1A, KDM4C contributed to altering the expression of genes related to the androgen receptor and promoting prostate carcinogenesis (105). A recent study indicated that KDM4C served as an oncogene in glioblastoma with a dual function of inactivating p53 by demethylating p53K372me1 and activating c-Myc by directly binding to its promoter (106). In addition, similar to KDM4B, KDM4C was also able to remove methyl groups of H3K9 on HIF-α and promote tumor growth (107-109).

KDM4D is able to activate the HIF pathway (110,111) via demethylation of H3K9me3 and H3K36me3 (110) at the promoter region, activate downstream regulatory networks, and promote tumor initiation and progression. Through demethylation of H3K9me3 on the promoters of Hedgehog target genes or β-catenin target genes and activating Hedgehog or β-catenin signaling pathways, KDM4D was able to promote tumor proliferation, progression and invasion (112,113). Furthermore, KDM4D was able to directly antagonize p53 and inhibit p53 binding to its target gene in a demethylase-independent manner; as a result, it functions as an oncogene in liver cancer (114).

KDM5 family and cancer. The KDM5 family includes four members, KDM5A (also named JARID1A), KDM5B (also named JARID1B), KDM5C (also named JARID1C), and KDM5D (also named JARID1D), having highly similar structures. All members contain five domains: JmjC, JmjN, a zinc finger an ARID (DNA-binding domain), as well as a PHD (histone-binding domain) lining between JmjC and JmjN (115,116). Thus, all four members were able to demethylate H3K4me2/me3 and participate in the epigenetic regulation of biological processes related to cancer (117,118). However, Both KDM5A and KDM5B have 3 PHD domains, while KDM5C and KDM5D have only 2 PHD domains. Since the PHD domain is important for the binding of H3K4 with the JmjC domain, KDM5C and KDM5D may exhibit poor catalytic function and different effects in cancer compared to KDM5A and KDM5B (29).

Compared to normal tissues, KDM5A is overexpressed in cancer tissues and contributes to tumor growth and poor prognosis. KDM5A has the ability to repress p27, a cyclin-dependent kinase (CDK) inhibitor in cancer, trigger G1/S phase transition and promote tumor malignancy (119-122). Furthermore, by demethylating H3K4me2/me3 at the promoter, KDM5A was able to suppress the expression of insulin-like growth factor 2 mRNA binding protein 2 and NOTCH2, facilitating tumor proliferation, invasion and metastasis (123,124).

KDM5B mainly has oncogenic effects in cancers. In breast cancer, KDM5B was indicated to be overexpressed and associated with poor prognosis (125). Furthermore, it was indicated that KDM5B suppressed BRCA1, caveolin 1 and homeobox A5 expression by reducing H3K4me3 levels and facilitated G1 progression and tumor growth in breast cell lines (126). Through activating the c-Met signaling pathway or inhibiting p53 accumulation, KDM5B promoted lung cancer cell aggressiveness (127,128). In addition, other studies also indicated that knockdown of KDM5B led to cell cycle arrest at the G1/S phase; the ability of KDM5B to influence tumor proliferation by adjusting the cell cycle was identified in liver cancer, bladder cancer and acute lymphoblastic leukemia (129-131). Furthermore, the oncogenic effect of KDM5B in prostate cancer and colorectal cancer by demethylating H3K4 was identified (132,133).

Unlike that of KDM5A and KDM5B, the role of KDM5C in tumors has remained elusive. In clear-cell renal cell carcinoma xenograft models, tumor cells highly expressing KDM5C were able to significantly suppress tumor growth (134). Furthermore, patients with renal cancer and KDM5C-inactivating mutations had shorter overall survival, suggesting the tumor-suppressive role of KDM5C (135,136). Of note, the tumor-suppressive effect of KDM5C was also observed in intrahepatic cholangiocarcinoma (137). However, KDM5C exhibits a tumor-promoting effect in other cancer types. In lung cancer, KDM5C facilitates tumor proliferation and metastasis by promoting H3K4me2 demethylation modification of the promoter of miR-133a and downregulation of miR-133a (138). Furthermore, KDM5C highly expressed in liver cancer was indicated to be associated with distant metastasis and poor prognosis by demethylating at H3K4 (139). In colon cancer, KDM5C was also observed to promote cell proliferation by demethylating H3K4me2/me3 (140). In addition, KDM5C upregulated ER expression and inhibited type I IFN expression in a breast cancer cell line, and, as a result, promoting breast carcinogenesis and cancer cell growth in a demethylase-independent manner (141).

KDM5D was mainly observed to have a tumor-suppressive effect. Upon specific knockdown of KDM5D, tumor cell apoptosis was reduced and tumor proliferation was promoted in a prostate cancer cell line (142). In addition, KDM5D repressed the invasion-associated genes matrix metallopeptidase 1 (MMP1), MMP2, MMP3 and MMP7 by demethylating H3K4me3, thus suppressing prostate cancer invasion and metastasis (143). Apart from prostate cancer, the mechanism of KDM5D to inhibit cancer cell growth and contributing to a better prognosis through its demethylating activity was also observed in gastric cancer and lung cancer (144-146).

KDM6 family and cancer. KDM6A (also named UTX), KDM6B (also named JMJD3) and KDM6C (also named UTY) belong to the KDM6 family. KDM6A is located at the X chromosome, KDM6C is located at the Y chromosome and KDM6B is located at chromosome 17 (147,148). All three contain the JmjC domain and have the ability to catalyze the demethylation of H3K27me2/me3 (147,149), although KDM6C has relatively poor catalytic activity compared to KDM6A and KDM6B (148).

Current evidence suggests both tumor-promoting and tumor-suppressive effects of KDM6A and KDM6B in cancers. KDM6A mutations frequently occur in various cancers. In hepatocellular carcinoma, overexpression of KDM6A significantly suppressed tumorigenesis (150). In addition, by inhibiting enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2)-mediated transcriptional repression through catalyzing demethylation of H3K27me3, KDM6A acts as a tumor suppressor in bladder cancer (151). However, a recent study identified the oncogenic role of KDM6A and KDM6B by epigenetically targeting stemness-controlling genes through demethylating H3K27me3, which makes KDM6A and KDM6B important in maintaining cancer cell stemness. At the same time, upregulation of KDM6B was indicated to be strongly associated with a higher recurrence rate and shorter survival in colorectal cancer (152). Furthermore, significantly increasing the levels of H3K27me3 using GSK-J4, a KDM6 family inhibitor, suppressed tumor growth in lung cancer mouse models, indicating an oncogenic effect of KDM6A and KDM6B (153).

KDM7 family and cancer. The KDM7 family is composed of KDM7A (also named JHDM1D), KDM7B (also named PHF8) and KDM7C (also named PHF2). All demethylases of the KDM7 family share the same composition, containing a JmjC domain at the C-terminus and a PHD domain at the N-terminus. The PHD domain binds to H3K4me3, while the JmjC domain is responsible for binding to H3K9me2 (154). However, the structure of each demethylase is slightly different, which may be the reason for the different functions. Among the KDM7 family, KDM7C only catalyzes H3K9me2 demethylation. However, KDM7A and KDM7B are able to catalyze demethylation of H3K9me1/me2, H3K27 me1/me2 and H4K20me1 (155).

An early study demonstrated that KDM7A acts as a tumor suppressor by inhibiting the *in vivo* growth of B16 and HeLa cells upon overexpression of KDM7A, even though this suppressive effect was not prominent *in vitro (*156). However, recent studies have discovered the oncogenic role of KDM7A, since KDM7A was indicated to be upregulated in prostate cancer tissue (157) and to promote the migration and invasion of breast cancer cells *in vitro* and *in vivo* (158). Therefore, the definitive role of KDM7A remains to be determined.

By contrast, KDM7B was indicated to have an oncogenic effect. KDM7B was determined to be associated with a higher Gleason score and poor prognosis by comparing prostate cancer tissue samples from 97 patients (159). In addition, KDM7B was indicated to act as an oncogene by activating genes related to tumor progression [PRKCA, ICAM-1, Snail (SNAI1), VIM and FIP200] in a demethylase-dependent or demethylase-independent manner and promote tumor

progression in gastric cancer and hepatocellular carcinoma (160-162). However, its demethylase-catalyzing ability is also responsible for other effects. By catalyzing demethylation of H3K4me3 and H3K9me2/1, KDM7B activates the expression of SNAI1, which contributed to breast cancer epithelial-to-mesenchymal transition, tumorigenesis and metastasis (163). In addition to SNAI1, forkhead box protein A2 was also epigenetically upregulated by KDM7B through demethylating H3K9me1/me2, H3K27me2 and H4K20me1, further illustrating the oncogenic effect of KDM7B (164).

By contrast, KDM7C acts as a tumor suppressor. KDM7C expression was indicated to be downregulated in hepatocellular, colon and stomach cancer tissues as compared with that in normal tissues. Upregulation of KDM7C was associated with a favorable prognosis in hepatocellular carcinoma and decreased tumor cell migration (165). Another study demonstrated that KDM7C demethylates H3K9me2 at p53 promoters, resulting in activation of p53 transcription and suppression of tumor growth (166).

KDM8 family and cancer. KDM8 (also named JMJD5) has a JmjC domain and β-barrel fold structure and has H3K36me2 demethylating activity (167). However, the effect of KDM8 in tumorigenesis has remained to be determined. In an early study, KDM8 was indicated to be overexpressed in breast cancer tissues, catalyzing H3K36me2 demethylation and leading to cyclin A1 overexpression. This results in the initiation of G2/M phase transition and the promotion of tumor cell proliferation (168). In addition, downregulation of KDM8 was indicated to inhibit tumor proliferation and metastasis in oral cancer by upregulating the expression of p53 and E-cadherin and downregulating the expression of N-cadherin and vimentin (169). However, in a large-scale, multi-cohort study of gene expression profiles in several cancer types, KDM8 was indicated to be downregulated in pancreatic cancer and liver cancer, and was reduced as the tumor grade increased. Furthermore, the expression of KDM8 was negatively correlated with the hypoxia score and the expression of cell cycle genes (such as CCNA2, CCNB1, CDK1 and CDK2), indicating the tumor-suppressive role of KDM8 (170). Therefore, further studies on KDM8 are warranted.

3. Role of histone demethylases in cancer therapy resistance

Current cancer therapies include surgery, chemotherapy, radiotherapy, targeted therapy and immunotherapy. For each treatment modality, significant progress has been achieved in the management of cancer. However, resistance to cancer therapy is a major problem in cancer treatment. Targeting histone demethylases not only has a critical role in tumor growth, invasion and metastasis, but also in chemoresistance, radioresistance and resistance to targeted therapy and immunotherapy (Table I). To date, most studies on the effect of histone demethylases in cancer therapy resistance were focused on the KDM1, KDM5 and KDM6 families.

Upregulation of KDM1A and KDM1B is associated with chemoresistance and poor survival. In liver cancer, both KDM1A knockdown and combination of KDM1A inhibitors with regorafenib improved resistance to regorafenib (171). In breast cancer, KDM1A overexpression was responsible for doxorubicin resistance (172) and regulation of the tumor microenvironment, and contributed to the resistance against PD-1 inhibitors *in vivo* (39). Similar to the role of KDM1A in chemoresistance, the downregulation of KDM1B improved cisplatin resistance in ovarian cancer (173). In enzalutamide-resistant prostate cancer, inhibition of KDM1B by tranylcypromine improved enzalutamide resistance by decreasing androgen receptor-depending anterior gradient 2 transcription epigenetically (174). Similarly, inhibition of KDM4B epigenetically suppressed c-Myc transcription and enhanced the efficacy of enzalutamide treatment *in vitro* and *in vivo* (175).

To date, accumulating evidence has identified the role of the KDM5 family in chemotherapy resistance of cancers (117). An early study demonstrated that breast cancer cells with KDM5A amplification exhibited resistance to EGFR inhibitors (176). Furthermore, KDM5A also contributed to temozolomide resistance in glioblastoma through enhancing drug efflux, and knocking down KDM5A or using HDAC inhibitors to suppress histone demethylases was able to resolve temozolomide resistance (177). Furthermore, KDM5B also contributes to chemoresistance. Demethylation of H3K4, as a consequence of upregulation of KDM5B, was observed in cisplatin-resistant gastric cancer cells (178). Knockdown of KDM5B resolved multidrug resistance of melanoma *in vivo* by blocking the mitochondrial respiratory chain (179) and enhancing the transition from $CD34^-$ to $CD34^+$ melanoma-propagating cell subpopulations that are more sensitive to BRAF inhibitors through the demethylase-dependent pathway (180). In addition to chemoresistance, the KDM5 family also suppressed the sensitivity to endocrine therapy in breast cancer (181). Furthermore, inhibiting the expression of KDM5 family members in breast cancer cells increased DNA damage accumulation through ionizing radiation. This phenomenon suggested that breast cancer cell radiosensitivity may be improved by knocking down KDM5 demethylase expression (182). Certain studies have demonstrated that KDM5C aggravates drug resistance in colon cancer cells by catalyzing H3K4me3 demethylation (183). In prostate cancer cells, knocking down KDM5D led to reduced sensitivity to docetaxel. At the same time, overexpression of KDM5D in prostate cancer cells improved docetaxel sensitivity (184), demonstrating the effect of KDM5D to improve chemoresistance, consistent with its tumor-suppressive effect.

Both *in vitro* and *in vivo*, increasing H3K27me3 improved the sensitivity of osteosarcoma and colorectal carcinoma to platinum drugs due to the resulting downregulation of KDM6A and KDM6B (185,186). In addition, when GSK-J4, a KDM6 inhibitor, was added along with the standard treatment for diffuse large B-cell lymphoma, the cell apoptotic effect was significantly enhanced and a better therapeutic effect was achieved (187). Furthermore, KDM6A was also indicated to contribute to imatinib resistance in chronic myelogenous leukemia, independent of its demethylase activity (188). Under hypoxic conditions, overexpression of KDM3A and KDM6B was responsible for resistance to radiotherapy by reducing DNA damage and apoptosis in esophageal squamous cell carcinoma (189). Furthermore, overexpression of KDM3A was strongly associated with castration therapy resistance in prostate cancer (190).

Table I. Overview of histone demethylases in cancer and cancer therapy resistance.

Histone demethylase	Target	Effect on tumorigenesis	Effect on cancer therapy resistance
KDM1A	H3K4me1/me2 H3K9me1/me2	Oncogenic effect: - Liver cancer - Pancreatic cancer - Breast cancer - Glioblastoma	Promoting resistance: - Liver cancer: Regorafenib - Breast cancer: Doxorubicin - Breast cancer: Immune checkpoint inhibitor
KDM1B	H3K4me1/me2	Oncogenic effect: - Breast cancer - Colorectal cancer - Lung cancer	Promoting Resistance: - Ovarian cancer: Cisplatin - Prostate cancer: Enzalutamide
KDM2A	H3K36me2	Oncogenic effect: - Breast cancer - Colorectal cancer - Lung cancer - Gastric cancer	/
KDM2B	H3K4me3 H3K36me2	Oncogenic effect: - Pancreatic cancer - Lung cancer - Leukemia Tumor-suppressive effect: - Breast cancer	/
KDM3A	H3K9me1/me2	Oncogenic effect: - Colorectal cancer - Breast cancer - Prostate cancer - Lung cancer - Pancreatic cancer - Liver cancer - Ewing sarcoma	Promoting resistance: - Esophageal squamous cell carcinoma: Radiotherapy - Prostate cancer: Castration therapy
KDM3B	H3K9me1/me2	Oncogenic effect: - Liver cancer - Breast cancer - Prostate cancer Tumor-suppressive effect: - Leukemia	/
KDM3C	H3K9me2	Oncogenic effect: - AML - Esophageal cancer - Colorectal cancer	/
KDM4A	H3K9me2/me3 H3K36me2/me3	Oncogenic effect: - Prostate cancer - Lung cancer - Gastric cancer	/
KDM4B	H3K9me2/me3 H3K36me2/me3	Oncogenic effect: - Breast cancer - Colorectal cancer	Promoting resistance: - Prostate cancer: Enzalutamide
KDM4C	H3K9me2/me3 H3K36me2/me3	Oncogenic effect: - Prostate cancer - Glioblastoma - Breast cancer - Osteosarcoma - Lung cancer	/

Table I. Continued.

Histone demethylase	Target	Effect on tumorigenesis	Effect on cancer therapy resistance
KDM4D	H3K9me3 H3K36me3	Oncogenic effect: - Gastrointestinal stromal tumor - Colorectal cancer - Liver cancer	/
KDM5A	H3K4me2/me3	Oncogenic effect: - Lung cancer - Liver cancer - Breast cancer - Pancreatic cancer	Promoting resistance: - Breast cancer: EGFR inhibitors - Breast cancer: Endocrine therapy - Glioblastoma: Temozolomide
KDM5B	H3K4me2/me3	Oncogenic effect: - Breast cancer - Lung cancer - Liver cancer - Bladder cancer - Colorectal cancer - Acute lymphatic leukemia	Promoting resistance: - Gastric cancer: Cisplatin - Breast cancer: Endocrine therapy - Breast cancer: Radiotherapy - Melanoma: Multidrug therapy
KDM5C	H3K4me2/me3	Oncogenic effect: - Lung cancer - Liver cancer - Colon cancer - Breast cancer Tumor-suppressive effect: - Renal cancer - Intrahepatic cholangiocarcinoma	Promoting resistance: - Colon cancer: Multidrug therapy
KDM5D	H3K4me2/me3	Tumor-suppressive effect: - Prostate cancer - Gastric cancer - Lung cancer	Combatting resistance: - Prostate cancer: Docetaxel
KDM6A	H3K27me2/me3	Oncogenic effect: - Colorectal cancer - Lung cancer Tumor-suppressive effect: - Hepatocellular carcinoma - Bladder cancer	Promoting resistance: - Osteosarcoma: Cisplatin - Colorectal cancer: Oxaliplatin -Chronic myelogenous leukemia: Imatinib
KDM6B	H3K27me2/me3	Oncogenic effect: - Colorectal cancer - Lung cancer	Promoting Resistance: - Osteosarcoma: Cisplatin - Colorectal cancer: Oxaliplatin - Diffuse large B- cell lymphoma: Chemotherapy - Esophageal squamous cell carcinoma: Radiotherapy
KDM6C	H3K27me2/me3	/	/
KDM7A	H3K9me1/me2 H3K27me1/me2 H4K20me1	Oncogenic effect: - Prostate cancer - Breast cancer Tumor-suppressive effect: - Melanoma - Cervical cancer	/

Table I. Continued.

Histone demethylase	Target	Effect on tumorigenesis	Effect on cancer therapy resistance
KDM7B	H3K9me1/me2 H3K27me1/me2 H4K20me1	Oncogenic effect: - Prostate cancer - Gastric cancer - Hepatocellular carcinoma	/
KDM7C	H3K9me2	Tumor-suppressive effect: - Hepatocellular cancer - Colon cancer - Gastric cancer	/
KDM8	H3K36me2	Oncogenic effect: - Breast cancer - Oral squamous cell carcinoma Tumor-suppressive effect: - Pancreatic cancer - Hepatocellular carcinoma	/

KDM, lysine-specific demethylase; H3K4, histone 3 lysine 4; me1/2/3, mono-/di-/tri-methylation.

4. KDM inhibitors in cancer therapy

As the effects of KDMs on tumor growth, invasion and metastasis are being discovered (Fig. 2 and Table I), several inhibitors of KDMs have been identified or developed as novel cancer treatment strategies. Numerous potent KDM1A inhibitors have been developed and have demonstrated an excellent capacity to inhibit cancer cell growth and metastasis (Table II) (191-193).

Inhibitors of the JmjC family, including ML324 (inhibitor of KDM4) and GSK-J4 (inhibitor of KDM6), achieved excellent anti-tumor activity either alone or in combination therapy in both cell lines and animal models (194,195). However, to date, no clinical trial has been conducted to investigate the role of JmjC KDM family inhibitors in cancer therapy (196,197). The major obstacle to the therapeutic use of JmjC demethylase family inhibitors is the lack of selective and potent inhibitors, which is possibly due to the high similarity among catalytic domains (196-198). Under these circumstances, an increasing number of effective and selective inhibitors of the JmjC demethylases family, such as CBN209350 and purpurogallin analogs, are being developed for cancer therapy (199,200).

KDM1A inhibitors in clinical trials of cancer

Tranylcypromine (TCP) in clinical trials of cancer. TCP, a monoamine oxidase inhibitor used for depression, irreversibly inhibits KDM1A. A recently completed phase I clinical trial (NCT02273102) demonstrated that combined TCP and all-trans retinoic acid (ATRA) therapy exhibited satisfactory effects and acceptable safety by inhibiting KDM1A and sensitizing AML cells to ATRA (201). In addition, two further clinical trials (NCT02261779 and NCT02717884) investigated the feasibility of using TCP in relapsed or refractory AML, and a trial to assess the effect of TCP to sensitize ATRA in patients with non-M3 AML is still recruiting.

Iadademstat in clinical trials of cancer. Iadademstat (also called ORY-1001) is a selective covalent KDM1A inhibitor, which is at the forefront of clinical trials among all KDM1A inhibitors. In addition to the anti-cancer effect of iadademstat in cancer cell lines (202,203), it also has good bioavailability and significantly inhibits tumor growth *in vivo* (204). The first-in-human phase I study of iadademstat (EudraCT 2013-002447-29) demonstrated a favorable effect on relapsed or refractory AML with good safety, and one case achieved complete remission (205). Subsequently, a phase II trial to identify the effect of combined iadademstat and azacitidine was launched (EudraCT 2018-000482-36). In addition, a phase I trial of iadademstat in relapsed small cell lung cancer (SCLC) (NCT02913443) was completed with 18 participants, although the results have not been published.

GSK2879552 in clinical trials of cancer. GSK2879552 is a potent and selective small-molecule KDM1A inhibitor that exhibits anti-cancer activity in numerous cancer cell lines (206,207). All three clinical trials investigating the safety and clinical viability of GSK2879552 in AML (NCT02177812), SCLC (NCT02034123) and myelodysplastic syndrome (NCT02929498) have been terminated due to frequent adverse events and inadequate efficacy of cancer treatment. In the trial NCT02034123, 83% of participants developed adverse events, while 100% of participants in NCT02177812 and NCT02929498 developed adverse events. The most common adverse events were hematological toxicity (such as thrombocytopenia or neutropenia) and fatigue. However, the disease control rate in NCT02034123 was only 14% (208).

CC-90011 in clinical trials of cancer. CC-90011 is a potent, selective and reversible KDM1A inhibitor developed by adding a fluorine substitution at the 3-position of benzonitrile (209). In a phase I study of non-Hodgkin lymphoma,

Table II. Inhibitors of KDMs in clinical trials.

KDM inhibitor/trial identifier no.	Disease	Status
Tranylcypromine		
NCT02273102	AML and MDS	Completed
NCT02261779	Relapsed or refractory AML	Recruiting
NCT02717884	Non-M3 AML	Recruiting
Iadademstat		
EudraCT 2013-002447-29	Relapsed or refractory AML	Completed
EudraCT 2018-000482-36	AML	Recruiting
NCT02913443	Relapsed SCLC	Completed
GSK2879552		
NCT02177812	AML	Terminated
NCT02034123	SCLC	Terminated
NCT02929498	MDS	Terminated
CC-90011		
NCT02875223	Non-Hodgkin lymphoma	Recruiting
NCT04628988	Castration-resistant prostate cancer	Recruiting
NCT03850067	SCLC	Recruiting
NCT04350463	SCLC and squamous cell carcinoma	Recruiting

AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; SCLC, small-cell lung cancer; KDM, lysine-specific demethylase.

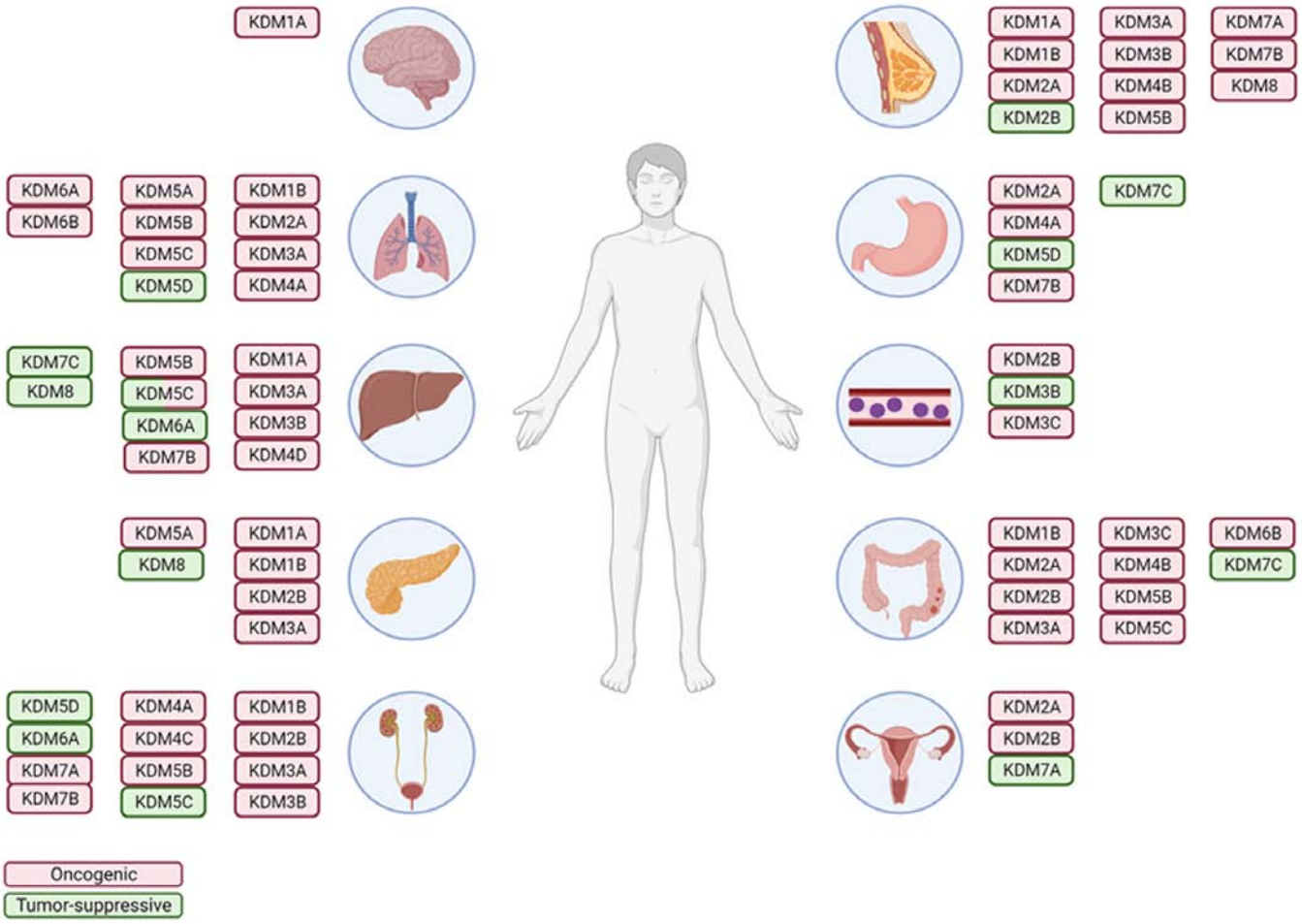

Figure 2. Overview of histone demethylases in cancer. Most histone demethylases exhibit oncogenic effects, while a minority (KDM5D and KDM7C) exhibit tumor-suppressive effects. In addition, the effect of KDM3B, KDM5C, KDM6A, KDM6B and KDM8 in cancer is not clear as they exhibit both oncogenic and tumor-suppressive effects. Red indicates oncogenic and green tumor-suppressive effects in cancer. KDM, lysine-specific demethylase.

CC-90011 was indicated to be well-tolerated and this clinical trial (NCT02875223) is still recruiting (210). In addition, a phase I functional imaging study to assess the effect of CC-90011 on metastatic castration-resistant prostate cancer (NCT04628988) is now recruiting. Furthermore, a phase Ib, multi-center clinical trial sponsored by Celgene was launched to demonstrate the safety and efficacy of combining CC-90011 with cisplatin and etoposide in SCLC (NCT03850067). Finally, a phase 2 clinical trial assessing the safety and efficacy of CC-90011 in combination with nivolumab in SCLC and squamous cell carcinoma (NCT04350463) by evaluating the treatment response has recently started recruiting.

5. Conclusions and perspectives

Previous reviews have provided insight into histone demethylases in cancer, metabolic disease, regeneration, inflammation and neurological diseases (29). At the same time, previous reviews have also concluded on the role of KDMs in cancer and the mechanisms by which KDMs participate in cancer development and progression (92,211). It is evident that most histone demethylases act as oncogenes in cancer development. However, the effects of KDM3B, KDM5C, KDM6A, KDM6B and KDM8 are still under debate, while KDM5D and KDM7C were proven to be tumor suppressive. Furthermore, histone demethylases have been indicated to contribute to chemoresistance and resistance to radiotherapy, targeted therapy and immunotherapy. However, only a small number of studies have illustrated how histone demethylases contribute to cancer therapy resistance. Therefore, it is important to perform further studies to answer this question. To date, several phase I clinical trials have been launched to identify the safety and efficacy of histone demethylase inhibitors in cancer therapy, whether combined with the current standard of treatment or not. Certain inhibitors demonstrated an ideal effect and most clinical trials for these drugs are still recruiting, although all clinical trials of GSK2879552 have already been terminated.

One important reason for the unclear effects of certain KDMs on cancer is that catalytic domains other than JmjC of these KDMs may also be involved in the biological processes; however, how these domains interact with the cancer development process remains largely elusive. Hence, further studies on the effect and interaction of the catalytic domains in biological processes should be performed to thoroughly illustrate the regulatory mechanism between KDMs and cancers.

It is evident that histone demethylases have the potential to be cancer therapeutics in the future; however, additional studies should be performed to facilitate their wide use in the clinic. On the basis of the success of KDM inhibitors resolving therapy resistance *in vitro* and *in vivo*, clinical trials examining the effect of KDM inhibitors on cancer therapy resistance are expected. Following the termination of JmjC KDM inhibitors, the development of more selective and potent inhibitors is essential for further clinical application. On the other hand, medication resolving the side effects of JmjC KDM inhibitors is desired to ensure the application of these inhibitors in the future. Recently, JIB-04, a histone lysine demethylase inhibitor, has been successfully delivered to prostate cancer cells and tumor spheroids by nanoparticles (212). Therefore, with the great success of nanoparticle drug delivery systems, it is foreseeable that delivering KDM inhibitors directly to tumors may reduce side effects and enable their wide use in solid tumors.

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Competing interests

The authors declare that they have no competing interests.

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