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Review Article

The critical role of histone lysine demethylase KDM2B in cancer

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Abstract: The discovery of histone demethylases has revealed the dynamic nature of the regulation of histone methylation. KDM2B is an important histone lysine demethylase that removes methyl from H3K36me2 and H3K4me3. It participates in many aspects of normal cellular processes such as cell senescence, cell differentiation and stem cell self-renewal. Recent studies also showed that KDM2B was overexpressed in various types of cancers. This review focuses primarily on the current knowledge of KDM2B and its function in cancer development.

Keywords: KDM2B, histone demethylase, epigenetic regulation, cancer

Introduction

Epigenetics is defined as mitotically heritable changes in gene expression without altering primary DNA sequence [1, 2]. In general, DNA methylation, histone post-translational modifications, nucleosome positioning, and post-transcriptional gene regulation by non-coding RNAs are the main components of epigenetic regulation [3, 4]. Among these epigenetic modifications, histone post-translational modifications largely control chromatin structure, recruit effector proteins, and play essential roles in cancer [5-9]. NH2-terminal histone tails from the nucleosome are the major dynamic and reversible sites for histone modifications, which mainly include methylation, acetylation phosphorylation, ADP-ribosylation, ubiquitination, and biotinylation [10, 11].

Histone methylation, the most common histone modification, is highly dynamic in regulating gene transcription [12, 13]. Moreover, histone methylation can either activate gene expression or silence gene expression that depends on its methylation site [14, 15]. It has been demonstrated that methylation at H3K4, H3K36, and H3K79 was usually associated with gene activation, whereas methylation at H3K9, H3K27, and H4K20 was associated with gene silencing [16]. In general, histone methylation is performed by methyltransferases, thus resulting in mono-, di-, or trimethyl. However, it was thought to be irreversible for a long time until the first histone demethylase, LSD1 (Lysine-specific demethylase-1) was identified and characterized in 2004 [17-19]. Up to now, more than 20 demethylases have been found, and they are categorized into two families: LSD family and JmjC family [20]. Furthermore, the two families oxidatively remove methyl groups from histones with distinct mechanisms. The LSD family is flaying adenine dinucleotide (FAD) dependent monoamine oxidases [20], whereas, the JmjC family is Fe(II) and α-ketoglutarate (α-KG) dependent dioxygenases [21]. The lysine (K)-specific demethylase 2B (KDM2B) is one of the members of JmjC family. In this review, we summarize the structure and biological function of KDM2B, and highlight its key findings in cancer.

Structure of KDM2B

KDM2B, also known as JHDM1B/FBXL10/NDY1, is a conserved and ubiquitously expressed nuclear protein. It targets H3K36me2 and H3K4me3 for demethylation [22, 23]. KDM2B contains multiple functional domains: an N-terminal JmjC domain, a CxxC domain, a PHD domain, an F-box domain, and seven leucine-rich repeats. The JmjC domain is necessary for

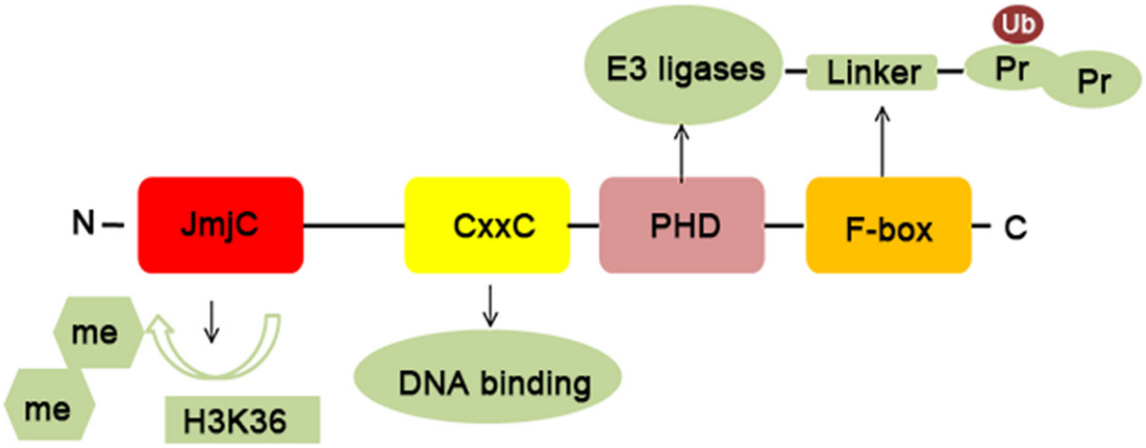

Figure 1. Basic protein structure and biochemical characteristics of KDM2B. KDM2B consists of four distinct domains: a JmjC domain, a CxxC domain, a PHD domain, and an F-box domain. The JmjC domain exerts a function in binding H3K36me2; The CxxC domain is a DNA binding domain and specifically recognizes CpG islands; The PHD domain has E3 ubiquitin ligase activity and acts as a histone modification reader domain; The F-box domain acts as a linker protein between a target protein and an E3 ubiquitin ligase.

the demethylation of H3K36me2. The CxxC zinc-finger domain is a DNA binding domain, which specifically recognizes CpG islands and recruits polycomb repressive complex 1 (PRC1) to target genes [24]. The PHD domain can act as an E3 ligase or a histone modification reader domain [25]. The F-box domain functions as a linker protein between a target protein and an E3 ubiquitin ligase (**Figure 1**) [26].

Biological function of KDM2B

KDM2B inhibits cell senescence, promotes cell proliferation and migration

KDM2B was initially identified as a novel regulator of lifespan in mouse embryonic fibroblasts (MEFs) [27]. Knockdown of KDM2B in MEFs delayed cell proliferation and induced senescence. ChIP assays further confirmed that KDM2B directly inhibited $p15^{Ink4b}$ and this function was mediated by H3K36me2 demethylation. Subsequent studies demonstrated that KDM2B protected MEFs from senescence by repressing the expression of $p16^{Ink4a}$ and $p19^{Arf}$ [28]. In details, KDM2B overexpression upregulated EZH2 and histone H3K27me3, the latter complex facilitated the binding of Bmi1 and Ink4a/Arf locus, then silenced the expression of $p16^{Ink4a}$ and $p19^{Arf}$. Besides, KDM2B demethylated the locus-associated H3K36me2 and H3K4me3, which inhibited the binding of RNA Pol II to Ink4a locus. In addition to these findings, other studies demonstrated that KDM2B could repress the expression of EZH2-associated miRNAs, let-7b and miR-101, then further inhibited cell senescence and promoted cell proliferation [29]. Moreover, the deletion of JmjC domain of KDM2B in germline stem cells also led to a reduction of cell proliferation [30]. Correlations analysis of the gene expression from the TCGA database revealed that KDM2B has significant correlations with many cell cycle related genes [31].

Another study indicated that KDM2B promoted cell migration via directly targeting migration-associated genes, such as Areg, Mdk, Lmnb1, Thbs1, Mgp and Cxcl12 [32]. To sum up, these findings provide a novel epigenetic mechanism of KDM2B in cell senescence, proliferation, and migration (**Figure 2**). As is well-known, cancer cells can evade senescence and activate proliferation signaling. We think KDM2B overexpression might contribute to tumor's continuous proliferative signaling.

KDM2B prevents cell differentiation

It was confirmed that KDM2B could recruit polycomb repressive complex (PRC) to CpG islands (CGIs) [24, 33, 34]. CGIs were usually enriched in cell development and differentiation genes [35-37]. It was substantiated that KDM2B was highly expressed in mouse embryonic stem cells (mESCs) [38]. Conditional deletion of KDM2B in mESCs induced cell early differentiation. The mechanism was that KDM2B recruit-

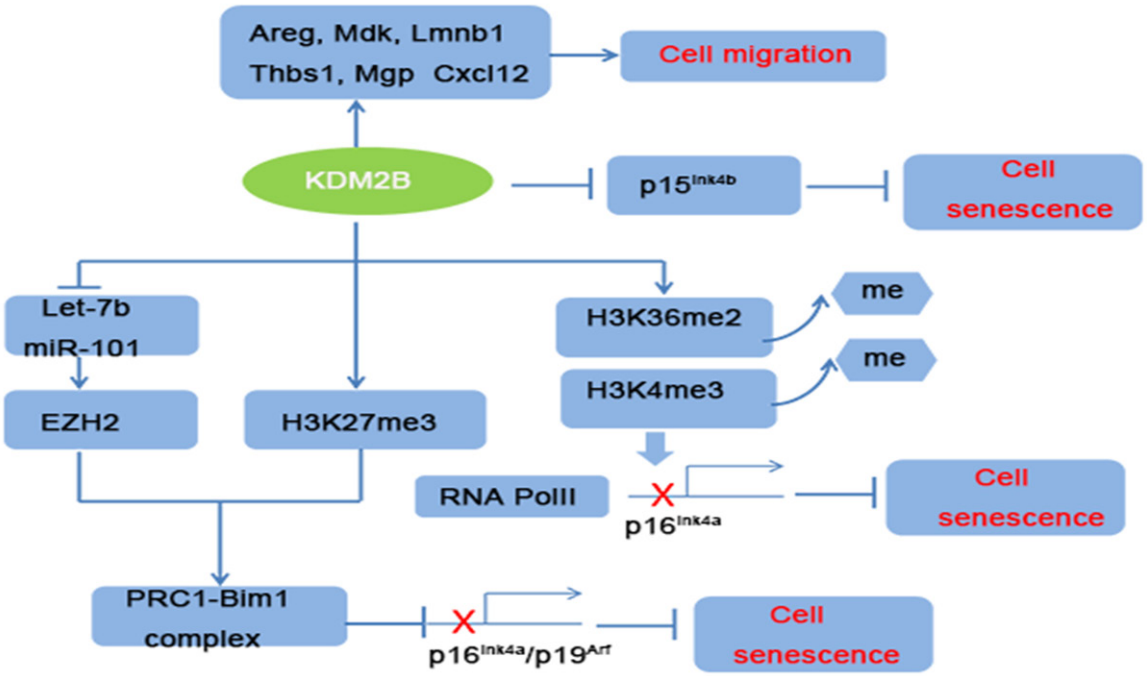

Figure 2. Mechanisms of KDM2B in regulating cell migration and senescence. KDM2B can bind directly to migration-associated genes to promote cell migration. Moreover, KDM2B promotes cell proliferation and inhibited cell senescence by repressing senescence-associated Ink4a/Arf/Ink4b locus and this function was via upregulation EZH2/H3K27me3 and H3K36me2/H3K4me3 demethylation.

ed PRC1 to the CGIs of early lineage-specific genes [38]. Interestingly, the role of KDM2B in maintaining the undifferentiated state of mESCs depended on its CxxC domain. Furthermore, KDM2B also inhibited differentiation signaling pathways to maintain the self-renewal of hematopoietic stem cells (HSCs) [39]. In addition, it has been reported that KDM2B overexpression inhibited the expression of the chondrogenic differentiation markers, COL1, COL2 and SOX9 [40]. Consistent with these findings, it was explored and found that KDM2B attracted a noncanonical PRC1 containing RING1B, SKP1 to the key adipogenic genes, such as Cdk1, Uhrf1, Pparg1, Pparg2, and prevented 3T3-L1 cells differentiate into adipose cells [41]. The role of KDM2B in adipogenesis was mediated by the F-box domain. Taken together, these results highlight the importance of KDM2B in cell differentiation and epigenetic regulation field (**Figure 3**). As is known to all, cancer stem cells are the root causes of tumorigrnicity, metastasis and chemoresistance [42, 43]. Other studies have found that KDM2B could form a different PRC1 containing BCoR (Bcl-6-interacting co-repressor), SKP1, PCGF1 (polycomb group RING finger1) and RING1B in cancer cells [44-47]. Thus, KDM2B might be an important molecular mechanism in maintaining cancer stem cell self-renewal.

KDM2B is a critical regulator for the somatic cell reprogramming

As well as regulating stem cell self-renewal, KDM2B also promoted somatic cell reprogramming into pluripotent stem cells (iPSCs). Somatic cell fate can be reprogrammed into a pluripotent embryonic stem cell (ESC)-like state by the use of key transcription factors including Oct4, Sox2, Klf4 and c-Myc [48, 49]. But the underlying mechanisms of somatic cell reprogramming remain poorly understood. Tao and his colleagues [50] reported that KDM2B can enable efficient generation of iPSCs, and enhanced Oct4 reprogramming by overcoming Ink4/Arf-triggered cell senescence. Moreover, during the process of reprogramming, KDM2B could cooperate with Oct4 to increase the expression of cell cycle-related miRNA cluster 302/367. Subsequent studies indicated that KDM2B enhanced Oct4-induced somatic reprogramming primarily through recruitment of a variant PRC1 to the CGIs of development genes

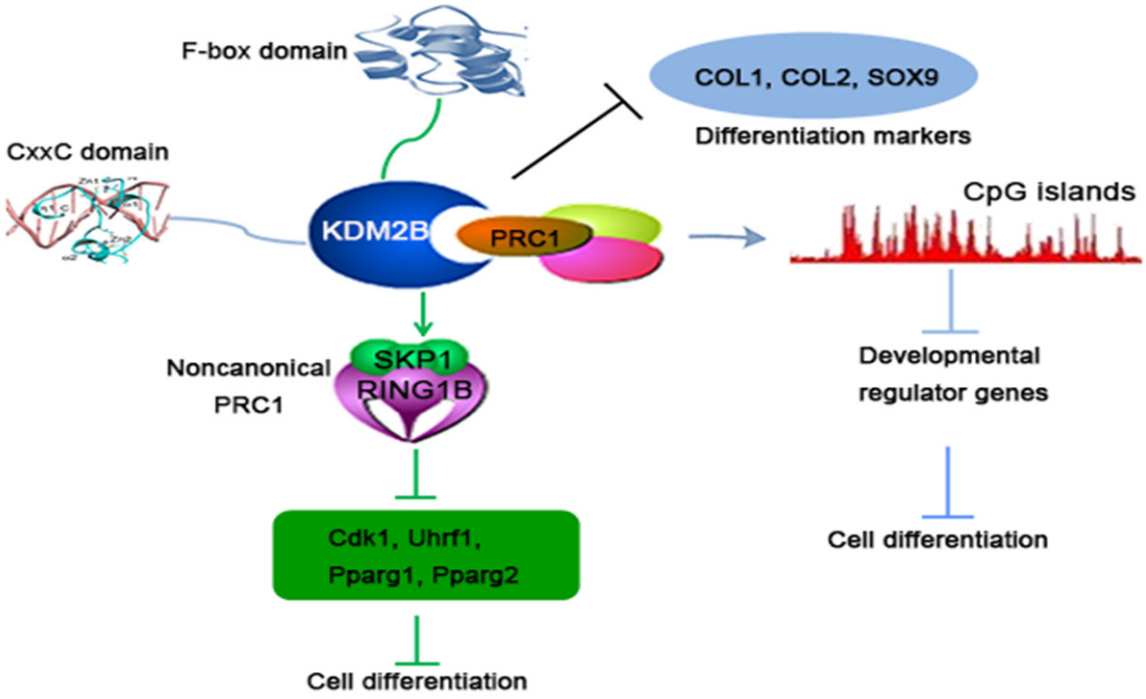

Figure 3. Different mechanisms of KDM2B-induced cell differentiation suppression. KDM2B could recruit PRC1 to CpG islands of developmental genes via its CxxC-ZF domain. In addition, KDM2B also attracts a noncanonical PRC1 to the key cell differentiation-associated genes through the F-box domain. Becides, KDM2B can also directly inhibit the expression of differentiation markers.

[51]. KDM2B overexpression also enhanced the expression of Oct4 and Sox2. It has been reported that Oct4/Sox2 was frequently overexpressed in lung cancer, breast cancer, esophageal carcinoma, and lymphoma [52-55]. Thus, KDM2B might take part in Oct4/Sox2- associated cancers.

The multifaceted role of KDM2B in human tumors

Dysregulation of KDM2B has been found in ALL, AML, breast cancer, pancreatic cancer, gastric cancer, lung cancer, and bladder cancer [31, 56-59]. It is worth mentioning that the regulatory mechanisms of KDM2B in these tumors are very complex and various.

KDM2B in malignant hematopoiesis

Previous study have revealed that KDM2B overexpression promoted the progression of MoMuLV-induced T cell lymphomas, acute lymphoblastic leukemia (ALL), and acute myelocytic leukemia (AML) [60-62]. Knockdown of KDM2B in ALL, CML, and AML cell lines not only decreased cell growth but also reduced lung metastasis in mice. In addition, KDM2B presented high levels in patients of AML, T-cell acute lymphoid leukemia, and B-cell acute lymphoid leukemia according to the Oncomine database. Other study revealed that KDM2B was upregulated in Hoxa9/Meis1-induced leukemic stem cells (LSCs) and was required for leukemic transformation and tumor progression [22]. The oncogenic function of KDM2B in leukemia was via silencing of $p15^{Ink4b}$. Besides, KDM2B also combined with other members to form a non-canonical Polycomb complex (PRC1.1), and PRC1.1 was critically important for LSCs [63]. Consist with these findings, other research demonstrated that KDM2B transgenic mice could develop myeloid and B-lymphocytic leukemias [64]. Molecular mechanism revealed that KDM2B induced the expression of Nsg2, which led to failure cell differentiation. Meanwhile, KDM2B increased oxidative phosphorylation related genes to promote cell cycle progression. Considering that KDM2B is often overexpressed in human malignant hematopoiesis, it might be a strong driver of epigenetic regulator that guides the way to leukemogenesis.

Table 1. Summary of the role of KDM2B in cancers so far

Cancer type	Function of KDM2B	Related gene	References
Leukemia (ALL, AML)	Tumor cell growth and proliferation	$p15^{Ink4b}$, Nsg2, PRC	[22, 60-64]
Breast cancer	Oncogenic (Proliferation, Cancer stem cell, anti-estrogen resistance)/Tumor suppressive (Down regulation of ribosome biogenesis)	Oncogenic (miR-101, PRC1, PRC2, CD44, ALDH)/Tumor suppressive (45S pre-rRNA)	[57, 66, 67]
Cervical cancer	Oncogenic (Cell glycolysis)/Tumor suppressive (Cell proliferation)	Oncogenic (RIP3 and Crabp2)/ Tumor suppressive (Ribosomal RNA, c-Fos)	[68-70]
Ovarian cancer	Oncogenic (Tumor growth, proliferation and metastasis)	EZH2	[65]
Pancreatic cancer	Oncogenic (Tumor growth, proliferation and metastasis, differentiation)	PRC, EZH2, MYC	[58]
Gastric cancer	Oncogenic (Poor prognostic factor)/Tumor suppressive (Decreased cell growth and proliferation)	Oncogenic (mTOR and p70S6K)/ Tumor suppressive (miR-448, MYC)	[59, 71]
Lung, Bladder cancer	Oncogenic (Tumor growth, proliferation and metastasis)	miR-101, EZH2	[79]
Nasopharyngeal carcinoma	Oncogenic	Oncogenic (mTOR and P70s6k)	[80]
Prostate cancer, Glioblastoma multiforme	Oncogenic (TRAIL-resistant)	Oncogenic (c-Fos/c-FLIP)	[77, 78]

KDM2B in gynecological cancers

Previous research showed that KDM2B was overexpressed in gynecological tumors [57, 65]. Knockdown of KDM2B in adenocarcinoma cell lines led to the upregulation of miR-101, miR-200a/b/c, miR-181a/b/b and miR-203, and these miRNAs downregulated PRC1 and PRC2 subunits, then further induced G1 arrest, decreased cell size and cancer stem cell markers in breast cancer [57]. KDM2B was also highly expressed in basal-like triple-negative (ER^-, PR^- and $Her2^-$) breast cancers, and was a poor prognostic factor [57]. Besides, functional genetic screens revealed that KDM2B was also a breast cancer anti-estrogen resistance (BCAR) gene [66]. However, in contrast, another research demonstrated that KDM2B acted as a tumor suppressor by controlling the ribosome biogenesis in breast cancer [67]. KDM2B knockdown in MDA-MB-231 cell triggered a more invasive and proliferative phenotype, suggesting the dual role of KDM2B in breast cancer.

In cervical cancer cell line Hela cells, KDM2B overexpression repressed ribosomal RNA genes, decreased cell size and cell proliferation [68]. And this function was mediated by H3K4me3 demethylation and c-Fos ubiquitylation [69]. However, it has been reported that KDM2B promoted proliferation and glycolysis by activating RIP3 and Crabp2 metabolic enzymes in HeLa cells [70]. These paradoxically phenomenon suggests the function of KDM2B in regulating cell proliferation might have different molecular mechanisms.

High levels of KDM2B was also found in ovarian cancer, and positively correlated with pathological grades [65]. Knockdown of KDM2B in ovarian cancer cells inhibited cell growth and migration.

KDM2B in pancreatic cancer and gastric cancer

Alexandros et al. [58] reported that KDM2B was markedly increased in pancreatic cancer (PDAC), and positively correlated with tumor grade. It is worth mentioning that, KDM2B was typically enriched in the poorly differentiated and invasive cancer cells. KDM2B knockdown suppressed cell proliferation and blocked xenograft tumor formation. Mechanistically, KDM2B interacted with Polycomb group proteins to silence cellular differentiation programs through H3K36 demethylation and H3K27 methylation; on the other hand, KDM2B activated the expression of MYC and KDM5A genes to promote PDAC progression.

As in PDAC, KDM2B was also commonly expressed in human gastric cancer. It was a poor prognostic factor both in intestinal and disuse Lauren types gastric cancer [71]. However, ChIP analysis demonstrated that KDM2B directly acted on the MYC promoter, further then inhibited glycolysis in gastric cancer [59]. To be concluded, these above reports imply the significance of KDM2B in tumors (**Table 1**).

Regulation of signaling pathways by KDM2B

As discussed above, KDM2B regulated the cell proliferation, invasion, and cancer stem cells of

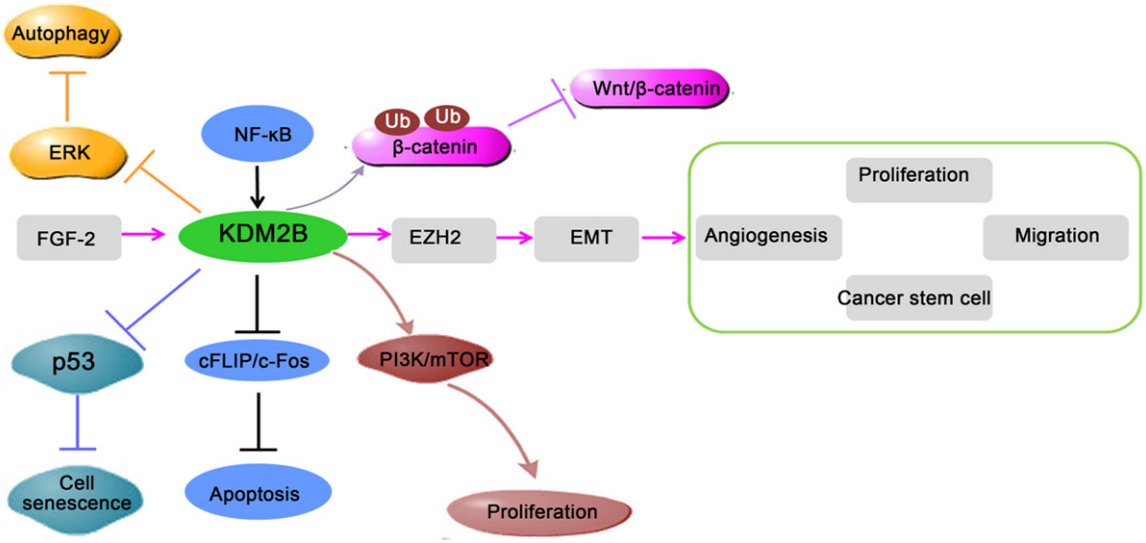

Figure 4. Regulation of cell signaling pathways involved in cancers by KDM2B. First, the activation of FGF-2-KDM2B-EZH2 pathway contributes to cell proliferation, migration, angiogenesis and self-renewal of cancer stem cells. Second, KDM2B inhibits cell apoptosis by repressing c-Fos/c-FLIP pathway. Finally, KDM2B also activates PI3K/Akt/mTOR pathway and inhibits P53 pathway in cancers. In contrast, KDM2B also inhibits Wnt/β-catenin signaling pathway by inducing degradation of β-catenin.

different cancers. Moreover, KDM2B has been actively involved in tumor-associated cell signaling pathways. AP-1 pathway was considered as an important regulator in tumor growth and metastasis [72-75]. AP-1 pathway consists of two proteins: c-Jun and c-Fos. C-Fos was an important regulator of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis [76]. KDM2B was reduced in TRAIL-sensitive cancer cell lines after treated with TRAIL, and KDM2B knockdown could change TRAIL-resistant cells into TRAIL -sensitive cells [77]. Further study confirmed that KDM2B restrained TRAIL-mediated apoptosis by repressing c-Fos/c-FLIP pathway. Besides, this anti-apoptotic of KDM2B was NF-kB pathway dependent. Recent research has shown that KDM2B decreased TRAIL response in glioblastoma multiforme (GBM) cells [78]. KDM2B silencing significantly enhanced the sensitivity of GBM cells to TRAIL, and promoted the activation of caspase-8, -3, -7 and PARP cleavage.

In addition, gene-expression profiling in T-ALL cell lines revealed that KDM2B knockdown decreased MYC and EZH2-dependent pathway, while tumor-suppressor pathways including p53, TGFB1, and SMARCA4 were upregulated [61]. Previous studies have also shown that KDM2B -miR-101-EZH2 pathway was active in at least 25 human cancer cell lines, including bladder cancer and lung carcinomas [79]. And this pathway contributed to cell proliferation, migration, angiogenesis and cancer stem cell self-renewal in bladder cancer by increasing the expression of EMT-promoting transcription factors [31]. Moreover, KDM2B could promoted nasopharyngeal carcinoma progression by activating PI3K/mTOR pathway [80]. In gastric cancer cells, KDM2B knockdown also induced autophagy via PI3K/Akt/mTOR inhibition and ERK1/2 activation [71]. In addition, a lot of evidence verified that Wnt/β-catenin pathway was essential in cancers [81, 82]. Another study confirmed that KDM2B could inhibit Wnt/β-catenin pathway by inducing degradation of non-phosphorylated β-catenin in the nucleus [83]. Whether KDM2B-Wnt/β-catenin pathway works in cancer still needs more research. Together, these findings indicated that KDM2B has both positive and negative effect in different oncogenic pathways (**Figure 4**).

KDM2B as a potential therapeutic target

Since histone methylation is reversible, a lot of histone demethylase inhibitors had been used for anti-cancer treatment [84-86]. For instance, N-oxalylglycine 2 (NOG) and its derivatives were identified to inhibit KDM4A, KDM2A, KDM2C and KDM2D [87]. 2,4-pyridinedicarboxylic acid

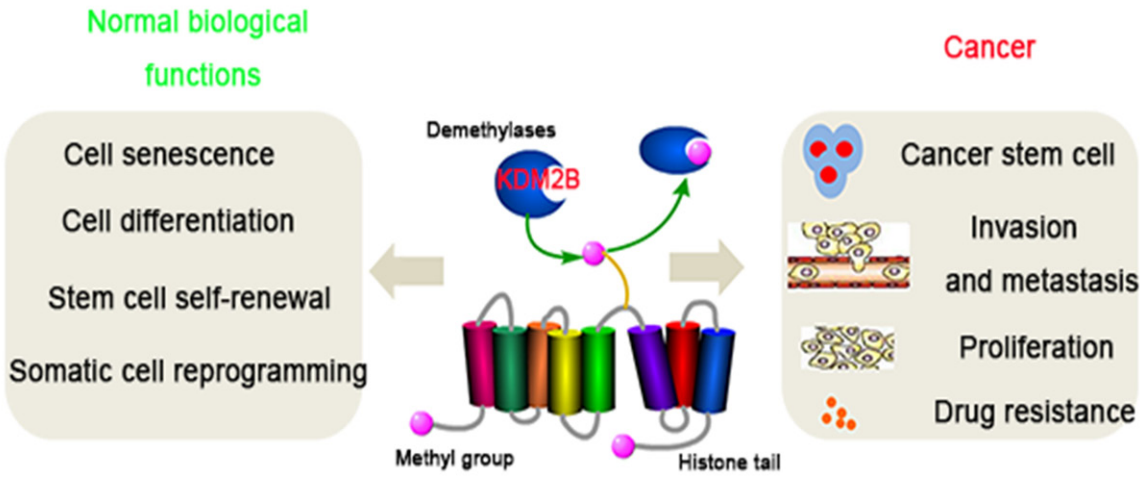

Figure 5. Pivotal role of KDM2B in normal biological functions and cancer. As an important histone lysine demethylase, KDM2B is very important in regulating cell senescence, cell differentiation, stem cell self-renewal and somatic cell reprogramming. The dysregulation of KDM2B might contribute to cancer progression including cell proliferation, metastasis and drug resistance.

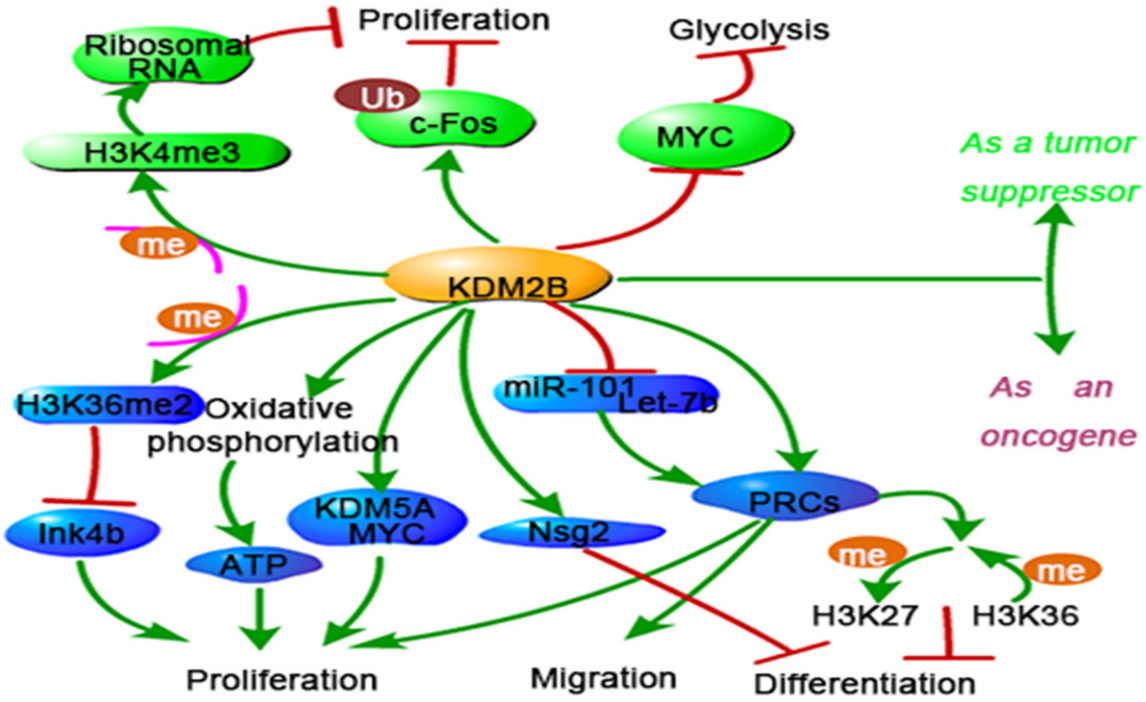

Figure 6. Overview of KDM2B mediated molecular mechanisms in cancer development. KDM2B acts as a double-edged sword in cancer development. On one hand, KDM2B inhibits $p15^{Ink4b}$ pathway, increases oxidative phosphorylation and enhances KDM5A/MYC protein expression, which promotes cancer cell proliferation. Becides, KDM2B recruits PRC and Nsg2 to enhance cell migration and controls self-renewal of cancer stem cells. On the other hand, KDM2B inhibits ribosomal RNA genes, MYC protein, and promots c-Fos ubiquitylation, which led to a decrease of cancer cell proliferation.

(2,4-PDCA) suppressed KDM5B [88]. Moreover, CPI-455 and GSK-J1/GSK-J4 were reported to be selective inhibitors of KDM5 and KDM6 subfamilies [89, 90]. However, the selective and specific inhibitors for KDM2B have not yet been found. It was due to the histone demethylases have high structural similarity. Therefore, more research is necessary to develop novel KDM2B

inhibitors. Nevertheless, Quanticel Pharmaceuticals have patented a series of pyridine derivatives as KDM2B inhibitors in 2016 [91]. 1,7-naphthyridones has exhibited high selectivity of KDM4C and KDM2B isoforms [92]. We think KDM2B inhibitors might be promising agents for anti-cancer therapy in the future.

Conclusions

A plethora of evidences have demonstrated the significant role of KDM2B in regulating cell cycle progression, cell differentiation, stem cell self-renewal, and cell apoptosis. It is also clear that elevated expression of KDM2B promotes cancer cell proliferation, metastasis, cancer stem cells self-renewal, and drug resistance (**Figure 5**). However, KDM2B could also decrease cancer cell proliferation by inhibiting the expression of oncogenes. KDM2B appears to function as a double-edged sword in the regulation of cancer development (**Figure 6**).

Up to now, the research of KDM2B in cancer is just on the way. The role of KDM2B in cancer may be more complex than originally believed. Now, most studies focus on the phenotype changes by KDM2B overexpression or knockdown. Future studies should seek to clarify the long-term effect of KDM2B in vivo studies. In addition, several questions still need to be addressed. For instance, what upstream signals trigger the expression of KDM2B, and why KDM2B has different function in cancers? It is under what conditions that KDM2B may act on H3K36me2 or H3K4me3. Besides, why the KDM2B displays multiaspect roles in the same cancer? This paradoxical phenomenon implies us whether the regulation of KDM2B changes during different stages of tumor. Moreover, it would be a challenge to identify potential inhibitors of KDM2B. Obviously, more research is required to further elucidate these questions. Here, we present evidence from multiple papers that may contribute to have a better understanding of KDM2B in tumor development. It may open new therapeutic approaches to suppress cancer progression.

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Disclosure of conflict of interest

None.

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