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The role of *KMT2* gene in human tumors

Zhi-Long Zhang[1,2], Peng-Fei Yu[3] and Zhi-Qiang Ling[1]

[1]Zhejiang Cancer Institute (Experimental Research Center), Zhejiang Cancer Hospital, Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences, [2]The Second Clinical Medical College of Zhejiang Chinese Medicine University and [3]Department of Gastric Surgery, Zhejiang Cancer Hospital, Institute Basic Medicine and Cancer (ICBM), Chinese Academy of Sciences, Hangzhou, PR China

Summary. Histone methylation plays a crucial role in the regulation of gene transcriptional expression, and aberration of methylation-modifying enzyme genes can lead to a variety of genetic diseases, including human cancers. The histone modified protein KMT2 (lysin methyltransferase) family are involved in cell proliferation, growth, development and differentiation through regulating gene expression, and are closely related with many blood cancers and solid tumors. In recent years, several studies have shown that mutations in the *KMT2* gene occur frequently in a variety of human cancers and the mutation status of the *KMT2* gene may be correlated with the occurrence, development and prognosis of some tumors. Research uncovering the clinical characteristics and molecular mechanisms of *KMT2* mutation in human tumors will be helpful for early diagnosis and prognosis of tumors as well as drug development for targeted therapies.

Key words: *KMT2A*, *KMT2C*, *KMT2D*, Gene mutation, Tumorigenesis

Introduction

In the past few years, the development and extensive use of next-generation sequencing technology has enabled us to gain insight into many cancer-related mutations, including the *KMT2* mutations. The relationship between cancer occurrence and mutations in the genes encoding epigenetic modifiers has been explored by several studies, allowing us to identify abnormal histone methylation in cancer caused by gene mutations, translocations, or dysregulation of histone methyltransferase. Since 11q23 / *KMT2A* translocation was first identified in acute lymphoblastic leukemia in 1991 (Ziemin-van der Poel et al., 1991), *KMT2A* has been reported to be frequently involved in translocation-associated gene fusion in childhood leukemia. Further studies have confirmed that the *KMT2* gene is often mutated in blood and solid tumors, and that heterozygote mutations of *KMT2C* and *KMT2D* genes are involved in the occurrence and development of a variety of malignancies (Fagan and Dingwall, 2019), which are the most frequently mutated genes of the *KMT2* family. This paper will elaborate the function of the *KMT2* gene in tumors and the possible molecular mechanisms of mutation-induced tumorigenesis. In so doing, we hope this paper can help us have a deeper understanding of the value of *KMT2* mutation in clinical diagnosis and treatment.

Corresponding Author: Zhi-Qiang Ling, MD., PhD, Zhejiang Cancer Institute (Experimental Research Center), Zhejiang Cancer Hospital, Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences. No.1 Banshan East Rd., Gongshu District, Hangzhou 310022, PR China. e-mail: lingzq@zjcc.org.cn or Peng-Fei Yu, MD., PhD, Department of Gastric Surgery, Zhejiang Cancer Hospital, Institute Basic Medicine and Cancer (ICBM), Chinese Academy of Sciences. No.1 Banshan East Rd., Gongshu District, Hangzhou 310022, PR China. e-mail: yupf@zjcc.org.cn

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Domains and members of the KMT2 family

All the members of the *KMT2* family are highly conserved in eukaryotes, possibly because all *KMT2s* contain an evolutionarily conserved SET domain. The SET domain acts as the kinase domain in regulating the activation of histone modifying enzymes of the *KMT2* family, which then leads to the methylation of H3K4. Mutations in the SET domain are found in human cancers, suggesting that they can extensively affect gene-regulated chromatin modification. *KMT2A-F* has a number of specific domains (Fig. 1) that interact with DNA, histones, and other proteins (Rao and Dou, 2015). *KMT2A-D* has plant homologous domain (PHD) finger clusters, but only the PHD3 of *KMT2A* can bind to H3K4Me3 to perform epigenetic reading, while other PHD fingers are involved in the recognition of other histone modifications or interact with other proteins (Poreba et al., 2020). *KMT2A* and *KMT2B* both have sites cleaved by Taspase 1 (black arrow). There are two cleavage sites in *KMT2A* and one cleavage site in *KMT2B*. A large amino-terminal fragment and a small carboxy-terminal fragment are generated by cleavage,

and the functional heterodimer complex is formed through the interaction of the Fy-rich N-terminal (FyRn) and Fy-rich C-terminal (FyRc) domains. Other protein domains that have important biological functions in *KMT2A/B* include AT-hook, CXXC, and Bromo involved in DNA binding or protein-protein interactions. The *KMT2C/D* protein contains an HMG domain that provides DNA binding similar to A T-hook, as well as the LXXLL motif (also known as the NR frame), which is characteristic of the interaction of transcription factors and cofactors with nuclear receptors. *KMT2F* and *KMT2G*, the smallest KMT2 subgroup, contain an N-terminal RNA recognition motif (RRM) and a C-terminal N-SET domain, which interact with WD repeat protein 82 (WDR82) and ubiquitin hiprotein H2B, respectively.

Role of *KMT2A*, *KMT2C*, and *KMT2D* in human tumors

KMT2A

The *KMT2A* gene (also known as MLL) is located on chr11q23 and encodes an H3K4 methyltransferase, which plays an important role in regulating gene expression during early development and hematopoiesis. Chromosomal translocations involving this gene are responsible for some kinds of acute lymphoblastic leukemia and acute myeloid leukemia. In both lymphoid and myeloid malignancies, *KMT2A* is the most common alteration, and chromosomal translocations result in rearrangement of the *KMT2A* gene at 11q23 and fusion with multiple partner genes to produce the *KMT2A* fusion protein. The fusion protein contains only the DNA-binding N-terminal domain of *KMT2A*, whereas the C-terminal SET domain regulating the H3K4 methyltransferase activity is lost. The *KMT2A* fusion protein interacts directly with the histone H3 lysin79 (H3K79) methyltransferase DOT1L, as well as with other epigenetic regulators. This inappropriate interaction leads to aberrant H3K79 methylation, which subsequently results in aberrant gene expression and leukemic transformation (Winters and Bernt., 2017). *KMT2A* fusion protein can effectively convert hematopoietic cells into leukemia stem cells and thus is important for the development and maintenance of leukemia (Krivtsov and Armstrong, 2007). In addition, the wild-type *KMT2A* allele (WT *KMT2A*) also plays an important role in the development of hematologic malignancies caused by *KMT2A* fusion proteins. WT *KMT2A* is necessary for the KMT2A-AF9 fusion protein-induced leukemia and the maintenance of KMT2A-AF9 transformed cells (Thiel et al., 2010). Heterozygous mutations in the *KMT2* gene are common in most malignancies, and all tumors with heterozygous mutations in the *KMT2* gene contain at least one WT allele. Homozygous mutations are rare in genomic malignancies. These data further support the notion that the WT allele is critical for maintaining the viability of cancer cells (Ford and Dingwall, 2015).

KMT2A rearrangement generally occurs in leukemia, but recently it has also been found in some solid tumors such as sarcomas (Massoth et al., 2020). *KMT2A* mutations are uncommon in hematologic malignancies, but are common in many solid tumors (e.g., colon, lung, bladder, endometrial, and breast cancers). *KMT2A* plays an important role in the development and maintenance of cancer. For example, knockdown of KMT2A by antisense oligonucleotide in cervical cancer cells leads to increased apoptosis. Tumor cells are more sensitive to

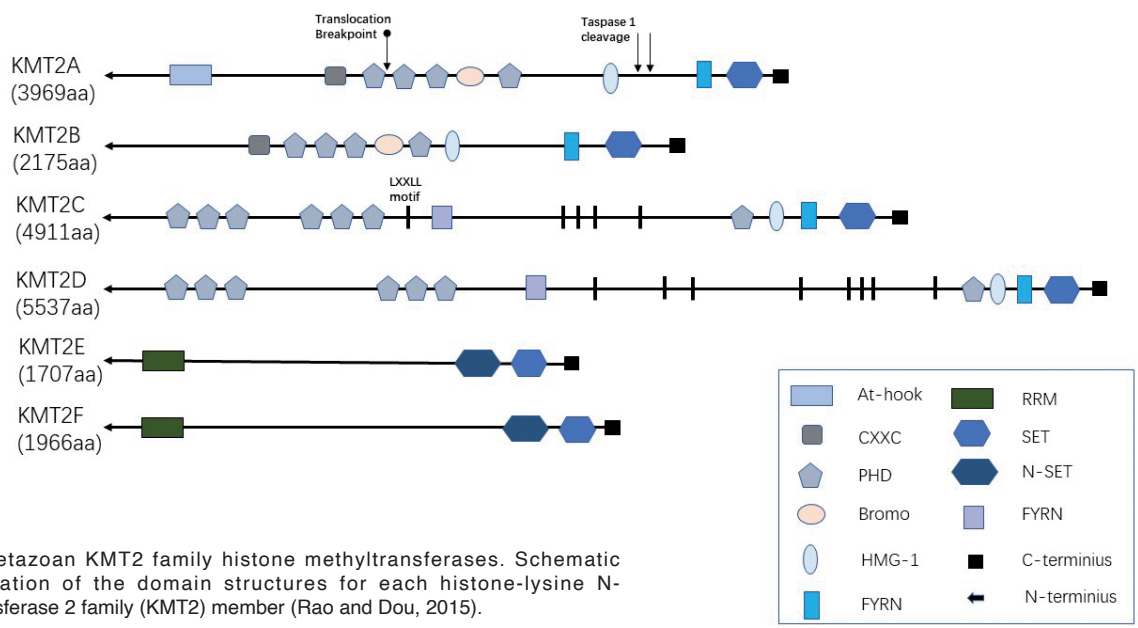

Fig. 1. Metazoan KMT2 family histone methyltransferases. Schematic representation of the domain structures for each histone-lysine N-methyltransferase 2 family (KMT2) member (Rao and Dou, 2015).

the loss of *KMT2A* activity than normal cells, and the cell apoptosis rate is faster in tumor cells compared with normal cells (Ansari et al., 2013). Ansari et al demonstrated for the first time that *KMT2A* knockdown can inhibit the expression of *HIF1A, VEGF* and *CD31* in tumor tissue, thereby affecting tumor growth and the level of angiogenesis in vivo. These data suggest that KMT2A is a key factor in cell proliferation and tumor growth, and knockdown of *KMT2A* can inhibit tumor growth and angiogenesis in vivo. Similarly, in another mouse tumor model, *KMT2A* is necessary for the initiation and maintenance of salivary gland tumors (Zhu et al., 2019a). Zhu et al also demonstrated that *KMT2A* ablation blocks Wnt/β-catenin-driven tumorigenesis and identify that *KMT2A* acts as a pivotal regulator in the downstream of Wnt/β-catenin to control self-renewal, proliferation, and apoptosis of salivary glands, and head and neck cancers. In addition, in tumors with gain of function (GOF) of *p53* mutants, expression of chromatin regulatory genes such as *KMT2A, KMT2D* and *MOZ* acetyltransferase (KAT6A) can be bound and upregulated by the *p53* GOF mutants, resulting in overall enhanced H3K4 methylation and histone acetylation. *KMT2A* knockdown or drug inhibition of *KMT2A* can significantly inhibit the proliferation of cancer cells, suggesting that *KMT2A* is a key player in driving the proliferation of tumor cells with *p53* GOF mutants (Zhu et al., 2015).

KMT2C

As an important regulatory factor of epigenetics, *KMT2C* is often mutated in a variety of human tumors and is believed to play an important role in tumorigenesis and development of cancer. *KMT2C* mutations, including frameshift, truncation or missense mutations, most of which could affect the expression of the SET domain at the carboxyl terminal. Whole exon sequencing of tumor specimens from 27 patients with diffuse gastric adenocarcinoma (DGA) reveals that KMT2C is the most common mutated gene in DGA. Knockdown of KMT2C in DGA promotes epithelial-mesenchymal transformation (EMT) and is associated with poor overall survival (Cho et al., 2018). Moreover, restoration of KMT2C expression in colorectal cancer cells inhibits cell proliferation and enhances genome-wide H3K4ME1 deposition at enhancers, suggesting that inactivated KMT2C may promote the development of colorectal cancer through transcriptional dysregulation (Larsson et al., 2020).

KMT2C mutations are also common in breast cancer. Chen et al have compared the mutation status of KMT2C between Chinese and western patients with breast cancer using next-generation sequencing, and have identified the relationship between *KMT2C* mutations and the clinicopathological characteristics of breast cancer patients (Chen et al., 2019). Compared with western breast cancer patients, *KMT2C* mutations in Chinese breast cancer patients are significantly associated with patients over 50 years of age, and the *KMT2C* mutation rate in HR+/HER2- breast cancer patients is higher than other subtypes. In addition, the mutation rate of *KMT2C* in invasive lobular breast cancer (ICL) is up to 30.8%, indicating that *KMT2C* may be the susceptibility gene of Chinese ILC patients. In a mouse organ model generated from breast stem cells, Zhang et al have found that inactivation of KMT2C can promote PI3K-driven breast tumorigenesis (Zhang et al., 2016). KMT2C inactivation leads to disruption of mammary differentiation and enhances stem cell activity by activating the hypoxia-inducible factor (HF) pathway. These data suggest that KMT2C is an important carcinogenic factor in breast cancer. In estrogen receptor-alpha + (ER-α +) HER2-breast cancer cell lines, KMT2C is involved in promoting hormone-stimulated cell proliferation. KMT2C deficiency impairs the proliferation of estrogen-driven ER+ breast cancer cells, but promotes the proliferation of hormone-independent ER+ breast cancer cells. These data suggest that KMT2C is a key cofactor in promoting ERα function and can mediate estrogen dependence of breast cancer by regulating estrogen receptor α enhancer (Gala et al., 2018).

KMT2D

KMT2D is a histone methyltransferase and a key regulator of transcriptional enhancer. KMT2D methylates histone H3 lysine 4 (H3K4) through the SET domain, and its methylation acts as a gene activation marker, which plays an important role in regulating gene transcription. A recurring feature of tumorigenesis is genomic instability, and *KMT2D* mutations are prone to genomic instability, which thus may be a driver of many different types of cancer (Kantidakis et al., 2016). In recent years, *KMT2D* has become one of the most common mutated genes in several cancers and other human diseases, including lymphoma, medulloblastoma, cancers of the lung, stomach, and colon, as well as Kabuki syndrome. *KMT2D* can alter proteins due to missense mutations or truncated mutations. KMT2D can be considered as a tumor suppressor in various tissues. Once *KMT2D* mutations lead to loss of function, it may result in the occurrence of tumors. For example, KMT2D has been shown to act as a tumor suppressor in diffuse large B-cell lymphoma, and its gene ablation promotes tumor progression in mice (Ortega-Molina et al., 2015). In addition, KMT2D mutations can promote the development of tumors by affecting the expression of tumor suppressor genes that control the B cell activation pathway. *KMT2D* can also act as a tumor suppressor in lung cancer (Alam et al., 2020). Knockdown of *KMT2D* extensively weakens enhancer/super-enhancer epigenetic signaling and thus up-regulates tumor-promoting processes including glycolysis, which subsequently promote the development of lung cancer. Super-enhancers have a unique tumor inhibition mechanism, in which *KMT2D* is necessary to maintain extensive

H3K4Me3 and super-enhancers (Dhar et al., 2018). However, *KMT2D* does not play as a tumor suppressor in all tumors, and whether it plays a tumor suppressive role depends on the tumor type (Guo et al., 2013). Guo et al found that *KMT2D* defects can lead to reduced proliferation and defective cell migration of colorectal cancer and medulloblastoma cells using the gene editing method. Similarly, in the experiment of *KMT2D* knockdown using siRNAs or lentivirus transfection of gastric cancer (GC) cells, the downregulation of *KMT2D* inhibits cell proliferation and induces cell apoptosis (Xiong et al., 2018). These data suggest that *KMT2D* has an inhibition effect only in some special tumor cells, whereas inhibition of *KMT2D* may be an effective cancer treatment strategy in other cancers such as GC. KMT2D mutation may have more than tumorigenic and antitumor effects. In exome sequencing, M. Zhu et al have found that there were recurrent mutations of KMT2D in cirrhosis and the deletion of KMT2D promoted clonal expansion (Zhu et al., 2019b). This suggests that recurrent mutations in KMT2D confer adaptive changes that promote stem cell adaptation and regeneration in response to chronic injury, and that this ability may be independent of cancer formation.

KMT2D also shows nonsense/frameshift/splicing site mutations in small cell lung cancer (SCLC). Augert et al have found that *KMT2D* mutations result in reduced levels of KMT2D protein and monomethylation of histone H3 lysine 4, which is a marker associated with transcription enhancer (Augert et al., 2017). Mutations in other genes related to transcription enhancer control are also found. These data suggest that the involvement of *KMT2D* mutation and related gene mutation on transcriptional enhancer control may be the potential cause of SCLC. Moreover, the epigenetic regulator *KMT2D* is one of the most common mutated genes in epithelial cancer. Epithelial tissue relies on a highly coordinated balance between self-renewal, proliferation, and differentiation, and *KMT2D* mutations can break this balance, and drive epithelial transformation to epithelial neoplasms. This is because *KMT2D* mutations can lead to reduced expression of p63 target genes and key genes involved in epithelial development and adhesion, as well as widespread loss of histone enhancers modified H3K4 monomethylation (H3K4ME1) and H3K27 acetylation (H3K27AC). These data suggest that *KMT2D* can maintain gene expression in epithelial progenitor cells and regulate appropriate terminal differentiation, thus playing a key role in controlling the expression of epithelial enhancer and *p63* target genes (Lin-Shiao et al., 2018). R. Li et al have found that early clonal development and final formation of urothelial carcinoma in urothelial tissue have potentially different molecular mechanisms. The driver gene mutations in normal urothelial tissue mainly focus on the genes related to chromatin remodeling (KMT2D gene and KDM6A gene), but less on the key driver genes with high-frequency mutations in tumors (PIK3CA gene and FGFR3 gene) (Li et al., 2020a). This indicates that KMT2D mutation occurs in the early stage of tumorigenesis and may lead to the proliferation of cancer initiating cells. Veeramachaneni et al have also demonstrated for the first time that the target gene KMT2D of head and neck squamous cell carcinoma (HNSCC) mutation changes in the early stage of cancer development (Veeramachaneni et al., 2019). By studying the gene mutation in the early stage of cancer progression, we may be able to more comprehensively understand the evolution of cancer, so as to develop cancer biomarkers and effective therapeutic interventions. Adult ovarian granulocytoma (AGCT) is a rare gynecological malignancy with a high frequency of somatic mutations. Single-allele *KMT2D* truncated mutations occur more frequently in recurrent AGCT than in primary AGCT. Immunohistochemical detection of KMT2D indicates that there may be non-genetic *KMT2D* inactivation in AGCT. These findings confirm that KMT2D inactivation is a novel factor driving the occurrence of AGCT, and that mutations in this gene may increase the risk of disease recurrence (Hillman et al., 2018).

KMT2E

KMT2E is a member of the KMT2 family, but its set domain does not have methyltransferase activity common to other family members. KMT2E plays an important role in controlling cell cycle progression, maintaining genomic stability, hematopoiesis and spermatogenesis (Zhang et al., 2017b). Therefore, KMT2E mutation may lead to gene expression disorder, cell cycle arrest, genomic instability and hematopoietic dysfunction, thus promoting the occurrence of tumors. MLL5 β It is a new MLL (KMT2E) subtype and a specific key regulator of E6/E7 gene transcriptional activation in HPV16/18 induced cervical cancer. The study of Yew et al emphasized MLL5 β Great potential as biomarkers and new therapeutic targets for primary HPV induced cervical cancer (Yew et al., 2011; Nin et al., 2015). Histone 3 variant H3.3 is a dynamic determinant of the functional characteristics of adult glioblastoma (GBM), which can antagonize self-renewal and promote differentiation. As an epigenetic inhibitor, KMT2E can antagonize H3.3 and induce chromatin recombination, which is conducive to the self-renewal of GBM cells. Gallo et al demonstrated that KMT2E is essential for the self-renewal and differentiation balance of GBM cells. Therefore, KMT2E inhibitors may be a potential therapeutic strategy for adult glioblastoma (Gallo et al., 2015). Androgen receptor (AR) transcription factor is the main regulator of cell proliferation and metastasis in prostate cancer. Lee et al have demonstrated that MLL5 can affect androgen receptor activity of prostate cancer cells by recruiting cofactors HCF1 and SET1 and regulating the methylation degree of histone H3K4 on the promoter of AR target gene, suggesting that KMT2E can play an important role as a new epigenetic regulator of AR in

prostate cancer (Lee et al., 2020).

KMT2 gene mutations in other human diseases

Kabuki syndrome is a rare autosomal dominant inherited disorder. The main features are typical facial gestalt, various organ malformations, postpartum undergrowth and intellectual disability. Kabuki syndrome is mainly caused by germline mutations in the histone methyltransferase *KMT2D* and demethylase *KDM6A*. Among the *KMT2D* mutant alleles, Cocciadiferro et al. have found impaired H3K4 methyltransferase activity in 9 alleles, suggesting that disruption of protein complex formation reduces H3K4 methyltransferase activity, which is of great significance for diagnosis and counseling of disease (Cocciadiferro et al., 2018). Schwenty-Lara et al demonstrated that *KMT2D* function loss inhibits crucial steps of neural crest development, demonstrating that Kabuki syndrome is a neural crest disease, and that *KMT2D* mutation is necessary for neural crest cell formation and migration in Kabuki syndrome patients (Schwenty-Lara et al., 2020).

Wiedemann-Steine syndrome (WSS) is a rare developmental retardation syndrome characterized by growth retardation, short height, mental retardation, increased body hair, and distinctive facial features (including thick eyebrows, long eyelashes, narrow and drooping eyelids, and widened nose bridge and tip). KMT2A mutations are a growing cause of intellectual disability (ID), and most KMT2A mutations in Wiedemann-Steiner syndrome are nonsense and frameshift mutations. Lebrun et al confirmed the harmful effects of nonsense and frameshift mutations of KMT2A located in two different functional regions regulating KMT2A expression, suggesting that loss of KMT2A function caused by KMT2A mutation is the main mechanism of disease (Lebrun et al., 2018). Recent loss of novel function (LOF) variants of KMT2A have been found to be associated with WSS. Chan et al have demonstrated that individuals with de nove LoF or missense variants in KMT2A may have a clinically unrecognized diagnosis of WSS, suggesting that detection of KMT2A variants in the clinical genetics and neurodevelopmental assessment of WSS is important (Chan et al., 2019).

KMT2B

KMT2B is located on chromosome 19Q13.12 and is widely expressed in the human body, with the highest expression in the cerebellum. KMT2B can mediate epigenetic disorders through frameshift, nonsense, splicing sites, missense and deletion mutations. Haploid defects or dysfunction of KMT2B affect downstream expression of key genes for neural development and motor control. The haploid defect of KMT2 often occurs in individuals with developmental disorders. KMT2 can be a candidate gene for dominant developmental disorders with higher transcription level, longer transcripts and more posttranslational modifications. The histone lysine methyltransferase encoded by KMT2 is the basis of gene regulation, and its histone lysine methylation is necessary for normal human development (Faundes et al., 2018). Dystonia is a dyskinesia syndrome characterized by dyskinesia in movement and posture caused by uncoordinated or excessive contraction of active and antagonistic muscles. Dystonia is characterized by dissonance and persistence, and early onset systemic dystonia is the most serious form of dystonia. Zech et al. confirmed that KMT2B haploid defects lead to the development of early systemic dystonia, and emphasized that transcriptional regulation of histone modification plays a key role in dystonia motor development (Zech et al., 2016). In the clinical observation of patients with KMT2D heterozygous mutant dystonia, it was found that dystonia of neck, skull and throat could be clearly identified, and the clinical effect was remarkable after deep brain stimulation (DBS) treatment. This new, clinically identifiable, and potentially treatable form of hereditary dystonia demonstrates the important role of KMT2B in the control of normal autonomous movement (Meyer et al., 2017).

KMT2B-related disorders are emerging as one of the most common causes of early hereditary dystonia. KMT2B-associated dystonia (DYT-KMT2B) is a complex childhood onset hereditary dystonia syndrome. The disease is characterized by progressive progression, usually from focal lower extremity dystonia to systemic dystonia, with obvious manifestations of cervical, cranial and laryngeal invasion. Swallowing disorders and mental retardation (ID)/developmental delay (DD) are also frequently observed. KMT2B mutation is considered to be an important cause of childhood onset dystonia. KMT2B mutations in childhood dystonia also cause complex neurodevelopmental syndroms, often with growth retardation and intellectual disability as additional phenotypic features (Carecchio et al., 2019). Childhood onset dystonia can be identified as a KMT2B mutation by next-generation sequencing and genome array technology to achieve DBS treatment. KMT2B mutation status can also be used as a predictor of DBS outcome by conducting prospective multicenter studies (Zech et al., 2019). Dystonia type 28 is a childhood-onset, progressive and complex form of dystonia caused by mutations in the KMT2B gene or microdeletions in the CHR19Q13.12 fragment. Defects in the function of KMT2B in DYT28 lead to specific DNA hypermethylation in promoters and other regulatory regions that are positive controls of gene expression, enabling DYT28 to have distinct DNA methylation features that enable accurate diagnosis and vague genetic findings of reclassification (Ciolfi et al., 2021). DYT28 can be treated by demethylation with DNA methyltransferase inhibitors or molecules targeting KDM5 demethylase. In recent years, the genotypes and phenotypes of Patients with KMT2B-related dystonia in

China have been further expanded. A hallmark of KMT2B-associated dystonia is a significant and long-lasting response to DBS, so DBS surgery may be the first choice for patients with severe KMT2B-associated dystonia (Li et al., 2020b).

O'Donnell Luria Rodan syndrome (odluro) is an autosomal dominant neurodevelopmental disorder caused by heterozygous mutation of the KMT2E gene. O'Donnel-Luria et al. first described this KMT2E related neurodevelopmental disorder in 38 patients (O'Donnell-Luria et al., 2019). Specific features of the syndrome include general retardation, language retardation, intellectual disability and subtle facial gestalt. Other common symptoms include autism, epilepsy, hypotonia and gastrointestinal dysfunction. O'Donnell-Luria et al have found in 31 different heterozygous variants and 4 chromosome 7q22.2-22.23 microdeletions of KMT2E that most individuals with protein truncated variants showed general mild developmental delay and intellectual impairment, autism was also common, and other common features were also visible. Epilepsy is not common in individuals with protein truncation variants. In contrast, all missense variants show epilepsy, including infantile epileptic encephalopathy and more severe developmental retardation. The individual performance of chromosome microdeletion is similar to that of protein truncation variation, but the degree of developmental delay is greater. In addition, by retrospectively analyzing cases of odluro syndrome and three new heterozygous mutations added to the *KMT2E* gene family, they found cerebellar hypoplasia in odluro syndrome for the first time (Comforti et al., 2021). Velmans et al reported another 18 odluro cases to further confirm and complete KMT2E related neurodevelopmental disorder phenotypes (Velmans et al., 2021).

Mechanism of tumorigenesis induced by KMT2A and KMT2D

In melanoma, *KMT2A* gene knockout not only inhibits promoter activity and hTERT gene expression, but also inhibits tumor ball formation and tumor stem cell marker expression. However, hTERT overexpression can restore promoter activity, tumor ball formation and tumor stem cell marker expression. In addition, the results from the xenotransplantation mouse model prove that *KMT2A* promotes melanoma growth through activation of the *hTERT* signaling pathway (Zhang et al., 2017a). The expression of *KMT2A* in colorectal cancer tissue is higher than that in adjacent normal tissue, and is positively correlated with the invasion and metastasis of colorectal cancer. Therefore, *KMT2A* plays an important role in promoting tumor progression in vivo. Cathepsin Z (CTSZ) is one of the important downstream genes of *KMT2A*, which can promote the transcriptional activation of CTSZ through the trimethylation of H3K4. In addition, p65 can help the downstream gene CTSZ to recruit *KMT2A* in the promoter region. Current studies have shown that *KMT2A* promotes cancer progression by targeting CTSZ, which has specific functions in cancer invasion and metastasis (Fang et al., 2019). Zhang et al have proved that *KMT2A* regulates the growth of cervical cancer by targeting *VDAC1* (Zhang et al., 2020). *KMT2A* knockdown inhibits *VDAC1* expression through activating the *PARP*/caspase pathway, and inhibits proliferation and migration, as well as inducing apoptosis of cervical cancer cells (Fig. 2) (Zhang et al., 2020). However, *VDAC1* overexpression reverses the *KMT2A*-mediated regulation of cell proliferation, migration and apoptosis, and promotes the growth of cervical cancer. Therefore, the *KMT2A/VDAC1* signaling axis may be a potential new mechanism for the occurrence and development of cervical cancer.

KMT2D is highly mutated in prostate cancer (PCA) and is associated with a poor prognosis. *KMT2D* knockdown inhibits PCA cell proliferation and induces apoptosis, suggesting that *KMT2D* acts as an oncogene in the progression of PCA. Two key genes, leukemia suppressor receptor (*LIFR*) and Krupel-like factor-4 (*KLF4*) that are respective regulators of *PI3K/Akt* and EMT, are down-regulated by *KMT2D* expression. Current studies have shown that KMT2D promotes tumor growth and metastasis by targeting the *PI3K/Akt* pathway and EMT by regulating the *LiFR* and *KLF4* epigenetics (Fig. 3), and thus can be used as an epigenetic target for the treatment of prostate cancer (Lv

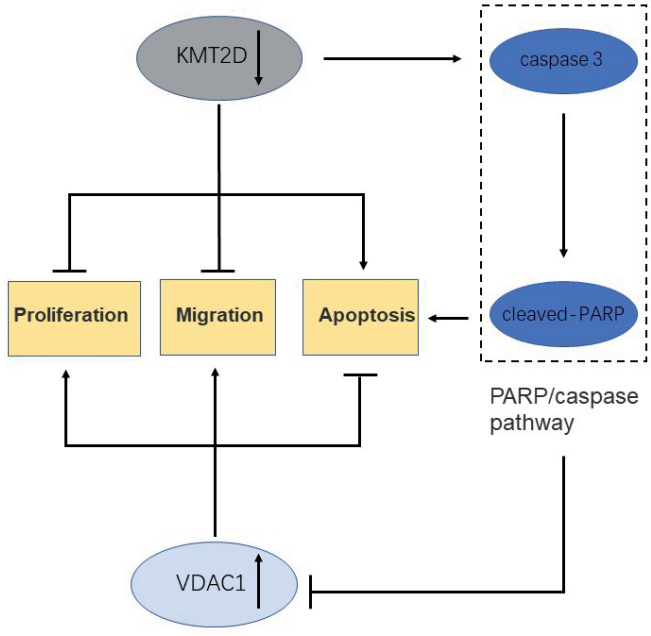

Fig. 2. Mechanism model of KMT2A/VDAC1 signal axis in cervical cancer. Down-regulation of KMT2A in cervical cancer can significantly inhibit proliferation and migration of cervical cancer cells, induce apoptosis, activate the PARP/caspase pathway and inhibit VADC1. Overexpression of VDAC1 reversed KMT2A down-regulated regulation of cell proliferation, migration and apoptosis (Zhang et al., 2020).

et al., 2018). Functional somatic point mutations in *KMT2D* have been found in a variety of tumor types, including melanoma. *KMT2D* is an effective tumor suppressor in melanoma. Tumors lacking *KMT2D* expression exhibit extensive reprogramming of key metabolic pathways, including glycolysis (Fig. 4) (Maitituoheti et al., 2020). This is because the loss of *KMT2D* leads to a decrease in the chromatin status of the genome-wide H3K4ME1 labeled activity enhancer. IgFBP5 enhancer loss and subsequent repression activate *IGF1R-Akt*, thereby increasing glycolysis in *KMT2D*-deficient cells. In general, *KMT2D* deficiency activates the glycolytic pathway through enhancer reprogramming, thereby promoting tumorigenesis and thus providing an opportunity for therapeutic intervention with glycolytic or IGF pathway inhibitors (Orouji et al., 2021). Similarly, the absence of *KMT2D* in lung cancer also induces abnormal metabolic reprogramming by injuring the superenhancer (Fig. 5), making lung cancer with *KMT2D* inactivation mutation sensitive to glycolytic inhibitors (Alam et al., 2020). Another possible mechanism is that KMT2D deletion damages the circadian rhythm inhibitor PER2 super-enhancer, resulting in the inhibition of the expression of downstream glycolytic genes regulated by PER2, so as to promote the development of tumor.

The value of KMT2 gene in clinical diagnosis and treatment

KMT2 gene acts as a biomarker in tumors

KMT2C and *KMT2D* are new recurrent mutated genes in endometrioid carcinoma, which play a role in tumorigenesis and development, and can influence clinical outcomes to a certain extent. Therefore, the mutational status of *KMT2C* and *KMT2D* can be used as important prognostic markers to help predict the degree of myometrium infiltration (García-Sanz et al., 2017). In the first study to investigate the association between *KMT2* mutations and the clinical benefits of immune checkpoint inhibitor (ICI) therapy, patients with *KMT2A/C* mutations have better progression-free survival (PFS), objective response rate (ORR), sustained clinical benefit (DCB), and overall survival (OS) in the ICI-treated group. Patients with *KMT2A/C* mutation achieve better OS in most cancer subtypes than patients without *KMT2A/C* mutation. These data indicate that patients with *KMT2A/C* mutations are sensitive to ICI treatment and have better therapeutic effects. *KMT2A/C* mutation can be used as a new and potential predictive biomarker for ICI treatment in a variety of solid tumors (Zhang et al., 2020a,b). KMT2 family proteins can regulate chromatin structure and DNA accessibility through histone methylation, which is related to the occurrence, mutation and immune tolerance of a variety of cancers, indicating that it may be related to the output of immune checkpoint therapy (ICT). This shows that epigenetic factors play an important role in tumor immunity. P. Zhang et al have found a significant association between KMT2 family mutations and better immune checkpoint treatment response through comprehensive cancer genome analysis of tumor tissues of immunotherapy patients (Zhang and Huang, 2021). Further analysis of the clinical data of the correlation between KMT2 gene changes and the clinical benefits of ICT found that KMT2 mutation is the most important predictor of the clinical benefits of ICT, indicating that the genomic changes of KMT2 family may be a positive biomarker of the clinical benefits of cancer immunotherapy. Wang et al. Systematically studied the relationship between 56 gene mutations and immune checkpoint treatment response by using crispr-gemm screening model. They found that KMT2D mutation could lead to DNA damage, increased mutation burden, chromatin remodeling, intron retention and transposable factor activation, resulting in increased neoantigen levels. In addition, tumor cells showed increased protein turnover and IFN-γ Stimulated antigen presentation. These changes lead to higher levels of immune cell infiltration in the tumor microenvironment, making *kmt2d* mutant tumors sensitive to checkpoint blocking immunotherapy (Wang et al., 2020). Since *kmt2d* mutation is common in various cancers, this study helps to stratify patients. The patients with *kmt2d* mutation are divided into subgroups to improve the efficacy of ICB

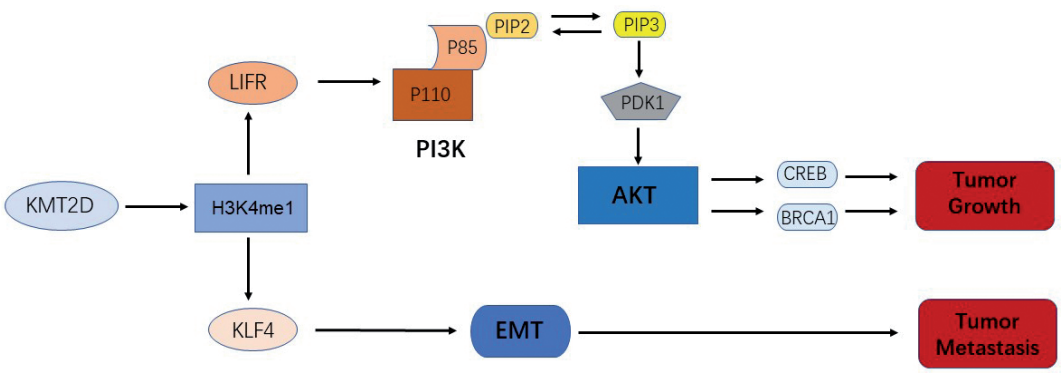

Fig. 3. The mechanistic model of KMT2D in prostate cancer. KMT2D maintains H3K4ME1 levels in prostate cancer cells and promotes the expression of genes LIFR and KLF4. After activating the PI3K pathway, LIFR also activates Akt to phosphorylate downstream targets such as CREB and BRCA1, promoting tumor growth. KLF4 promotes the transcription of the EMT pathway and leads to tumor metastasis (Lv et al., 2018).

treatment, which is of great significance to promote individualized treatment. Although the prognosis of mantle cell lymphoma has improved in recent years, a proportion of young patients with mantle cell lymphoma still experience early disease progression after receiving cytarabine-containing chemotherapy. A study by Ferrero et al has shown that *KMT2D* mutations and *TP53* destruction are poor prognostic biomarkers for mantle cell lymphoma treated with high doses of therapy (Ferrero et al., 2020). Therefore, it is necessary to identify high-risk mantle cell lymphoma patients with *KMT2D* mutation and *TP53* damage and adopt new therapeutic strategies.

Therapies targeting the KMT2 gene

As we mentioned above, *KMT2A* promotes the growth of melanoma through activation of the *hTERT* signaling pathway. Analysis of clinical samples from melanoma patients shows that high expression of *KMT2A* is usually associated with a poor prognosis. These data suggest that *KMT2A* may be a potential biomarker for the diagnosis of melanoma and a therapeutic target for treatment in the future (Zhang et al., 2017a). KMT2C/D is usually mutated in pancreatic ductal adenocarcinoma (PDAC), and these lesions can identify a group of patients with a good prognosis. In addition, low expression of KMT2C and KMT2D in biopsy also defines a better outcome group in PDAC, suggesting that low expression of KMT2C and KMT2D are both associated with improved prognosis in PDAC. Moreover, knockdown of KMT2D in the KC/KPC cell lines leads to an increased response to the nucleoside analogue 5 fluorouracil, suggesting that low levels of KMT2D may make PDAC more sensitive to some specific treatments. Therefore, targeted therapy for KMTC/D in patients with PDAC with high KTM2C/D expression may gain benefits from such therapy (Dawkins et al., 2016). In esophageal cancer, overexpression of MLL2/KMT2B often predicts a poor clinical prognosis and may promote the development of esophageal cancer by activating EMT. Therefore, MLL2/KMT2B can be used as a new prognostic factor and therapeutic target for patients with esophageal cancer (Abudureheman et al., 2018). Rampias et al have shown that downregulation of KMT2C in bladder cancer cells leads to extensive changes in epigenetic status,

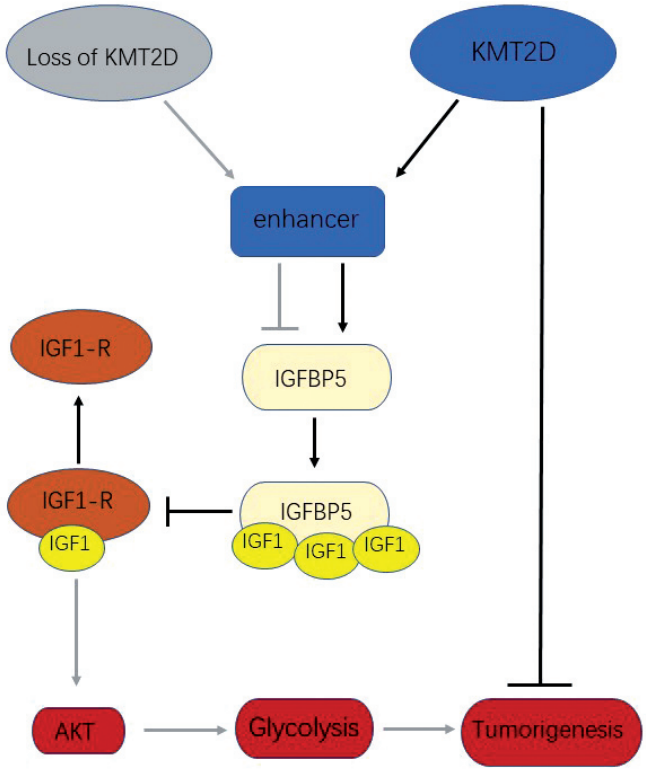

Fig. 4. The mechanism model of the presence and absence of KMT2D in melanomas. KMT2D acts as a tumor suppressor in melanoma, and its defective tumors exhibit substantial reprogramming of key metabolic pathways by reducing H3K4ME1 labeled activity enhancer, conferencing glycolysis and IGFR inhibitor sensitivity in melanomas with KMT2D inactivation mutations (Maitituoheti et al., 2020).

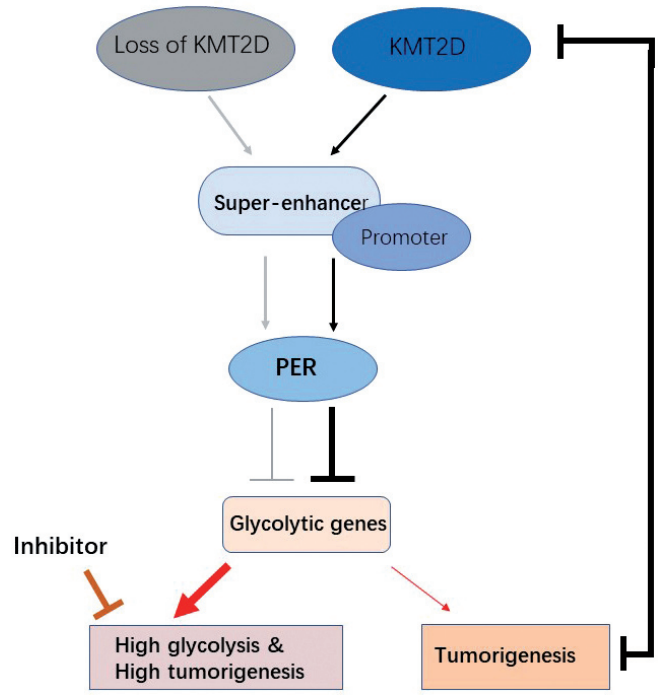

Fig. 5. The mechanism model of the presence and absence of KMT2D in lung cancer. Histone methyltransferase KMT2D is a lung tumor suppressor and is often mutated in lung tumors. KMT2D deficiency induces abnormal metabolic reprogramming by impairing superenhancers, such as tumor suppressor PER2, making lung cancers with KMT2D inactivation mutations sensitive to glycolytic inhibitors (Alam et al., 2020).

DNA damage response and DNA repair gene expression (Rampias et al., 2019). In addition, low expression of KMT2C in cancer cells cannot repair DNA and is prone to DNA damage, leading to genomic instability. These cancer cells thus may be killed by the PARP1/2 inhibitor olaparib due to synthetic lethality. This suggests that cancer cells with low KMT2C expression may be highly sensitive to PARP1/2 inhibitors. In the latest study, A. Chang et al revealed a new mechanism of KMT2C repairing damaged DNA. KMT2C can recruit ago2 and small non coding DNA damage response RNA at DNA damage sites to mediate H3K4 methylation, chromatin relaxation, secondary recruitment of DDR factors and amplification of DDR signals along chromatin to regulate DNA damage response. In addition, by destroying homologous recombination (HR) - mediated DNA repair, KMT2C and KMT2D mutations make non-small cell lung cancer more sensitive to PARP inhibitors. Therefore, high-frequency KMT2C/D mutations can be used as biomarkers for PARP in the treatment of NSCLC and other BRCA1/2 rare mutant cancers, which is of great significance for the new personalized treatment of lung cancer (Chang et al., 2021).

Perspective

The *KMT2* gene is frequently mutated in various solid tumors, and is closely related to tumor progression and prognosis. Therefore, *KMT2* mutation may be a biomarker for early diagnosis and prognosis of tumors. The emergence of next-generation sequencing technology has gradually revealed the regulation mechanism of epigenetic genes in the process of tumorigenesis, which is helpful to further identify the action sites of the *KMT2* gene. In recent years, although many targeted therapies for *KMT2* mutations have been applied in clinical practice, there are still some shortcomings to be improved. Therefore, the functions and molecular mechanisms of KMT2 mutations in tumors as well as their biological significance need to be further studied, which is conducive to the discovery of better targeted therapy and has positive significance for personalized cancer therapy.

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Author contributions. Zhang ZL drafted the manuscript. Yu PF and Ling ZQ were involved in the critical revision of the manuscript.

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