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Research Progress of EZH2 in Tumors and Translational Perspectives

Yu Tian, Hu-Li Li, You-Fu Pan*

Department of Medical Genetics, Zunyi Medical University, Zunyi 563000, Guizhou, China

***Corresponding author:** You-Fu Pan, panyf9@sina.com

Abstract: Enhancer of zeste homolog 2 (EZH2) is a key epigenetic regulatory protein and enzyme catalytic subunit of the polycomb repressor complex 2 (PRC2), responsible for catalyzing the trimethylation of histone H3K27 and subsequent repression of gene transcription. Abnormal *EZH2* expression or mutation is associated with various cancers, particularly lymphoma, and breast and prostate cancer. EZH2 has been investigated as an important target in cancer therapy and potential EZH2-targeted drugs have been developed. This article reviews the research progress on the mechanism of transcriptional regulation of *EZH2* and the development and clinical use of some inhibitors targeting EZH2.

Keywords: EZH2; Polycomb repressor complex 2; Cell signaling; Inhibitor

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1. Introduction

The *EZH2* gene is located on human chromosome 7q36.1. It has 20 exons and 19 introns and encodes 746 amino acid residues. Each of the 10 EZH2 protein domains has a distinct structure and function. These domains include the SANT1L-binding domain (SBD), the EED-binding domain (EBD), the β-addition motif (BAM), the SET-activation loop (SAL), the stimulus-responsive motif (SRM), the motif that connects SANT1L and SANT2L (MCSS), two SANT structural domains, the CXC domains and SET domains (**Figure 1A**) [1]. The histone methyltransferase activity of EZH2 is mainly maintained by the SET structural domain, and the CXC structural domain is also required for binding to the SET structural domain. The structural domain at the N-terminal end of the SET structural domain is a protein interaction domain, that is required for the assembly of the corresponding subunits for polycomb repressor complex 2 (PRC2) function [2]. PRC2 is a member of the PCG proteins, an evolutionarily conserved class of protein complexes originally discovered in *Drosophila* [3]. PRCs consist primarily of two core complexes: polycomb repression complex 1 (PRC1) and polycomb repression complex 2 (PRC2) [4]. The PRC2 complex is an S-adenosyl-L-methionine (SAM)-dependent histone methyltransferase (HMTases), which contains four major core subunits: EZH2/1, ZESTE12 (SUZ12), embryonic ectodermal developmental

repressor 1-4 (EED1-4), and RBAP46/48 [5,6].

Our analysis of the TCGA data shows that mutations, amplifications, and deletions are common in many tumor types (**Figure 1B**). Mutations, including missense, truncating, frameshift, and others, can occur in all structural domains (**Figure 1C**). This suggests that it may play an important role in cancers.

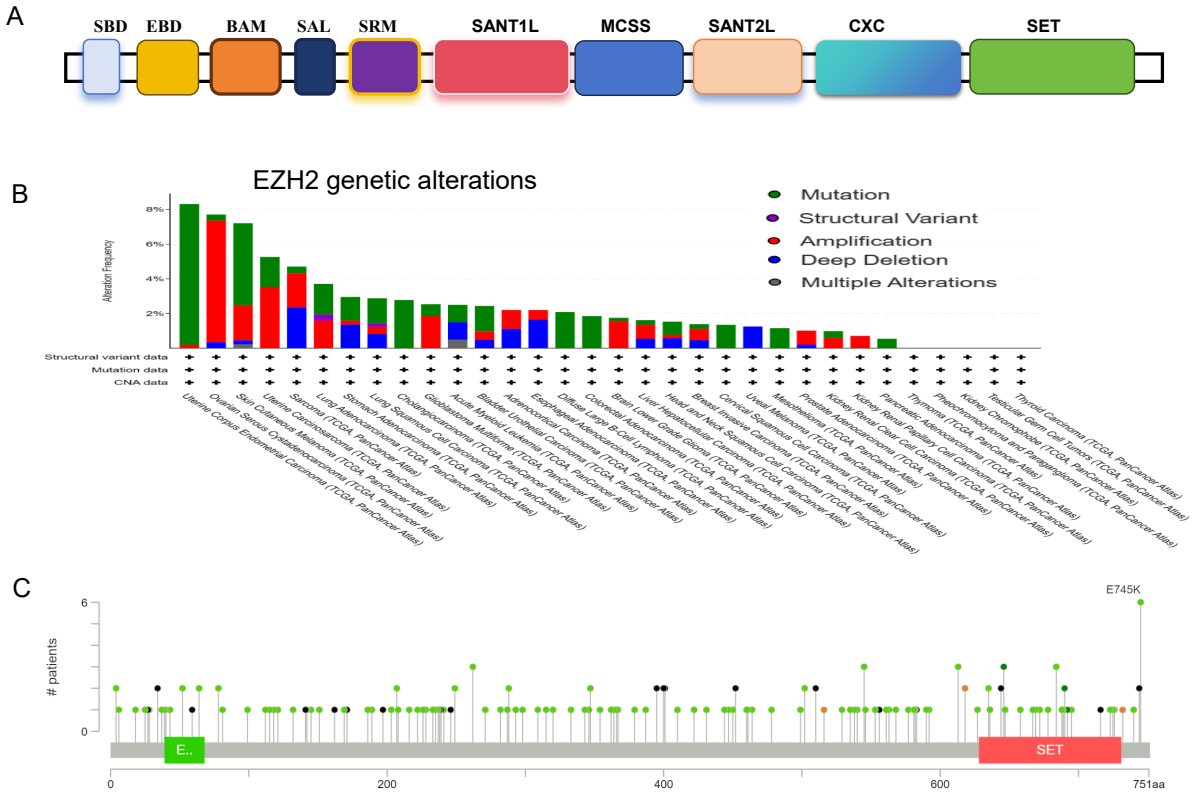


Figure 1. The structural domains of EZH2 and genetic alterations. (A) EZH2 consists of 10 structural domains, of which the SET domain predominantly catalyzes the methylation of H3K27. (B) The genetic alterations in TCGA pan-cancer samples. (C) Mutations occur across EZH2 domains.

2. Modes of action of EZH2

EZH2 is the PRC2 core subunit with catalytic activity, and PRC2 is a key member of the PCG family. PRC2 can regulate gene expression via trimethylation of H3K27 (H3K27me3), a major epigenetic marker involved in gene repression. The PCG protein family plays a crucial role in gene silencing, regulation of cell development and differentiation, maintenance of stem cell pluripotency, and tumor development through its epigenetic regulatory functions [7,8]. EZH2 may exert its function either dependent on PRC2 or independently.

2.1. PRC2-dependent H3K27 methylation

When PRC2 is bound to chromatin, this complex catalyzes the methylation of Lys 27 in histone H3 (H3K27me3) using its SET domain. Methylation of H3K27 leads to the compaction of chromatin, which prevents RNA polymerases and transcription factors from accessing DNA. Consequently, this process contributes to the modulation of transcriptional repression [9]. Furthermore, EZH2 exhibits DNA methyltransferase capabilities that enable methylation of specific target genes and their repression [10].

2.2. PRC2-dependent non-histone methylation

Beyond its traditional role in histone methylation, EZH2 has also been found to methylate non-histone proteins. One notable target is GATA4, a process that is dependent on PRC2. This methylation at lysine residues of GATA4 by EZH2 directly hinders its transcriptional function. Such type of repression plays a crucial epigenetic regulatory role in processes of development and cell differentiation through non-histone methylation [11].

2.3. PRC2-independent gene transactivation

In addition to its traditional gene silencing function, EZH2 also has a transcriptional activation function that helps tumor cells survive and escape the effects of DNA damage by activating specific genes [12]. EZH2 can function as a coactivator to directly activate androgen receptor (AR) transcriptional activity. Therefore, it can play a non-catalytic role as it is PRC2 and methylation-independent [13].

3. Dysregulation of EZH2 and related signaling pathways in tumors

As one of PRC2's main constituents, EZH2 is often dysregulated. As shown in **Figure 1**, its role in tumors is often accompanied by genetic changes. In most cases, mutations and amplification, as well as overexpression, provide the driving force in the process.

3.1. Dysregulation of EZH2

One of the most common alterations affecting epigenetic mechanisms is the gain-of-function mutations in *EZH2*. Studies have shown that seven different activating mutations affect the catalytic SET structural domain of the protein, with mutations located in exon 16 and exon 18 [14]. Activating mutations in *EZH2*, such as the common mutation at the Y646 site, improve its ability to catalyze H3K27 trimethylation. This leads to abnormal silencing of tumor suppressor genes, which in turn promotes abnormal cell proliferation and tumor formation [15]. This is more common in diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) [16]. In DLBCL and FL, gain-of-function mutations were also identified in residues Y641, A677, or A687 in the catalytic domain of *EZH2* [17,18].

Studies have shown that somatic mutations in the *EZH2* gene are also present in myelodysplastic syndromes (MDS) and that these mutations, which can impair or completely lose the methyltransferase activity of EZH2, are associated with a poor prognosis and can also accelerate the progression of MDS to acute myeloid leukemia (AML) [19]. Stasik *et al.* revealed a low frequency but significant adverse prognostic impact of *EZH2* mutations in AML by analyzing genomic data from 1,604 newly diagnosed AML patients, a finding that provides potential direction for personalized treatment of AML, particularly the development of targeted therapies against EZH2 [20].

The PBRM1-SWI/SNF complex and EZH2 exhibit an antagonistic relationship in epigenetic and cell cycle regulation. In renal cell carcinoma (RCC) with *PBRM1* mutations, EZH2 activity is frequently upregulated, potentially driving accelerated cancer cell proliferation. Consequently, EZH2 inhibitors are anticipated to represent a promising targeted therapeutic approach for *PBRM1*-mutant RCC [21]. Overexpression of EZH2 has been found in a variety of solid tumors, including lung cancer [22], breast cancer [23], melanoma [24], prostate cancer [25], and bladder cancer [26].

3.2. EZH2 activates the PI3K/AKT/mTOR signaling pathway

The PI3K/AKT signaling pathway has a well-established effect on the initiation and spread of cancer. In cancers, this signaling is essential for fostering cell division and viability [27]. Studies have shown that AKT hyperphosphorylates Rb and releases large amounts of E2F1, which activates cell cycle proteins and cell cycle protein-dependent kinases (CDKs). When E2F1 binds to the EZH2 promoter, transcription of *EZH2* is activated [28].

EZH2 can activate the PI3K/AKT/mTOR signaling pathway by epigenetically silencing the expression of PTEN via increasing the H3K27me3 level. PTEN is an important negative regulator that inhibits this signaling pathway [29,30]. PTEN and PTENP1 expression are suppressed when YY1 and EZH2 cooperate, which raises the phosphorylation level of S473-AKT and T308-AKT and activates AKT [31]. Thus, EZH2 forms a positive feedback loop with AKT. Moreover, EZH2 can also directly promote PI3K and AKT signaling pathways by interaction with the PI3K or AKT signaling components.

Studies have shown that interaction between KDM2B and EZH2 results in increased levels of AKT and PI3K in colorectal cancer [32]. EZH2 increases AKT phosphorylation by activating TNFSF13B [33].

3.3. EZH2 activates the Wnt/β-catenin signaling pathway

The Wnt/β-catenin signaling pathway plays a variety of roles, such as cell proliferation, differentiation, and migration. Down-regulation of Wnt significantly reduces the level of β-catenin and cyclin D1 [34]. There are two mechanisms of action: (1) EZH2 promotes sustained Wnt signaling activation by silencing Wnt signaling repressors such as DKK1 and SFRP1. Through histone H3K27me3 modification, EZH2 reduces the expression of these repressors, which in turn deregulates the negative feedback regulation of Wnt signaling, therefore β-catenin can accumulate and translocate to the nucleus, where it activates the expression of downstream oncogenes [35,36]. (2) Studies have shown that EZH2 can directly interact with β-catenin to stabilize it in the nucleus and increase its transcriptional activity. This interaction contributes to the binding of β-catenin to Tcf/Lef and promotes the expression of Wnt target genes, thereby promoting tumor cell proliferation and invasion [37].

3.4. EZH2 and other signaling pathways

In cervical cancer HeLa cells, it has been reported that EZH2 binds to the CARD structural domain of VISA and disrupts the interaction between RIG-I and VISA, thereby attenuating downstream signaling and the innate immune response [38]. GAS5 induces apoptosis of smooth muscle cells and subsequent abdominal aortic aneurysms via activation RIG-I signaling pathway mediated by EZH2 [39]. PVT1 is a long-stranded non-coding RNA that interacts with EZH2 in non-small cell lung cancer (NSCLC), mediates methylation of the miR-497 promoter, and prevents the upregulation of miR-497 and YAP1 [40].

EZH2-mediated upregulation of microRNA-375 promotes breast cancer progression by inhibiting FOXO1 and p53 signaling pathways [41]. Downregulation of EZH2 activates the JNK signaling pathway and increases the expression levels of inflammatory cytokines such as TNF-α, IL-17, IL-5, CCL20, and CCL2 [42]. EZH2 can promote bladder cancer proliferation and migration via the JAK2/STAT2 pathway [43].

3.5. EZH2 is involved in the metabolic reprogramming

Metabolic reprogramming is a process whereby tumor cells change their metabolic pathways to accommodate the demands of rapid growth and spread. Epigenetic control plays an important role in cancer development [44]. A crucial metabolic characteristic of the Warburg phenotype, aerobic glycolysis, is caused by active metabolic

reprogramming, which is necessary for the long-term growth and malignant development of cancer cells [45].

3.5.1. EZH2 and lipid metabolism

Disturbance of lipid metabolism is a striking metabolic change in cancer. Lipid metabolism is used for energy production, as components of biofilms, and as signaling molecules for proliferation, survival, invasion, metastasis, and tumor microenvironmental response in cancer cells [46]. EZH2 is a major regulator of lipid metabolism. Cumulative evidence suggests that EZH2 methyltransferase activity, which is required for adipogenesis during preadipocytes and adipogenesis, promotes differentiation of the adipocyte by epigenetic repression of the genes of the Wnt signaling pathway [47].

In cancer cells, dysregulation of lipid metabolism reduces the sensitivity to the EZH2-specific inhibitor GSK126, and treatment with GSK126 results in increased synthesis of lipids, as evidenced by increased unsaturated fatty acids [48]. GSK126 also induced lipid accumulation in human adipocytes without altering the expression of marker genes for adipocyte differentiation, one mechanism may be that inhibition or knockdown of EZH2 promoted lipoprotein-dependent lipid uptake and increased apolipoprotein E (ApoE) expression. Studies have shown that the absence of ApoE prevented GSK126 from promoting lipid-independent lipid accumulation in mouse adipocytes [49].

In an animal model, EZH2-deficient mice were leaner than normal mice and had less white adipose tissue in their bodies. Compared to controls, EZH2-deficient mice had smaller lipid droplets in brown adipocytes and more beige adipocytes (a type of cell that is intermediate between white and brown fat). Meanwhile, mice in the *EZH2* knockout group had reduced differentiation markers in white adipocytes and increased UCP1 and other browning markers in brown and beige adipocytes, better tolerance to cold stimuli, and resistance to obesity and insulin resistance induced by a high-fat diet [50]. Histone deacetylase 1 (HDAC1) negatively regulates the thermogenic program of brown adipocytes through the synergistic effect of EZH2-mediated H3K27 deacetylation and methylation. These findings provide new insights into the role of epigenetic regulation in metabolic regulation and could provide a basis for the development of new therapies to treat metabolic diseases such as obesity [51].

3.5.2. EZH2 and glucose metabolism

Even with sufficient oxygen supply, cancer cells obtain energy primarily through glycolysis, the so-called Warburg effect. In prostate cancer, EZH2 regulates aerobic glycolysis and cell growth by acting on the miR-181b/hexokinase 2 (HK2) axis [52]. However, the opposite effect is observed in that EZH2 inhibits tumor cell proliferation by inhibiting GLS expression and reducing glutamine metabolism, which is distinct from its classical role as the central histone methyltransferase of the PRC2 complex [53].

SIRT3 plays an important role in glycolysis and proliferation in colorectal cancer cells [54]. EZH2 inhibits the expression of SIRT3 by directly binding to its promoter region and decreases SIRT3 levels, resulting in increased sensitivity of radioresistant cells to glucose starvation. EZH2 inhibitors can increase the tolerance of cancer cells to glucose starvation by eliminating this inhibitory effect. Therefore, modulating SIRT3 expression by targeting EZH2 may help overcome radioresistance and improve therapeutic response to nutrient deficiency [55].

It has also been shown that activation of the EZH2/FBXL7/PFKFB4 axis resulted in the hypoxic environment allowing tumor cells to better adapt to glucose-deficient conditions and increase energy supply, which in turn accelerated NSCLC progression [56].

4. Advances in studying EZH2 as a therapeutic target

EZH2 plays a critical role in the pathophysiology of cancer and is therefore a potential target for cancer therapy. Melanoma is a malignant skin tumor, and EZH2 is considered a potential therapeutic target for melanoma as it plays a role in the development and progression of melanoma [57]. Silencing of EZH2 with siRNA or treatment with DZNep (or MS1943) inhibited the growth of hypochromic melanoma cells and induced hyperchromic melanoma cells [58]. Epigenetic silencing of interferon gene-stimulating factor (STING) mediated by EZH2 resulted in low STING expression in melanoma cells. Targeted therapies consisting of EZH2 inhibitors (EZH2i) and STING agonists have improved preclinical antitumor immunity in melanoma [59]. EZH2i can not only directly inhibit CRC cell proliferation, but also regulate macrophages by tilting M2 macrophages toward effector M1 macrophages, thus exerting an anti-tumor effect [60].

High EZH2 expression in ovarian cancer is closely associated with a high tumor proliferation index, advanced tumor stage, and poor prognosis. Human cytomegalovirus infection has been associated with ovarian cancer and plasmacytoid ovarian cancer biopsy tissues are characterized by increased expression of EZH2, but also results in polyploidization, which can be observed as polyploid giant cells of tumors with cancer stem cell-like characteristics [61].

4.1. EZH2 inhibitors

EZH2 is a valuable target for cancer treatment and many EZH2 inhibitors have been extensively studied, including tazemetostat, GSK126, DZNPEP, and others.

Tazemetostat reduced β-catenin and CD13 protein expression in HepG-2 cells and their HBV-transfected cells through inhibition of EZH2, thereby reducing the survival of hepatocellular carcinoma cells. One study provides theoretical support for the potential use of tazemetostat in the treatment of hepatitis B-associated hepatocellular carcinoma and highlights the key role of EZH2 as a therapeutic target [62]. It had also been shown that tazemetostat has an anti-cancer activity against tumor cells in esophageal cancer [63]. The inhibitor is also a potential therapeutic option for overcoming multidrug resistance (MDR) in tumors and can synergize with a variety of conventional chemotherapeutic agents *in vitro*, especially in cancers resistant to conventional treatments, and has broad clinical applications [64]. In a recent clinical trial, tazemetostat demonstrated some clinical efficacy and was well tolerated in pediatric tumors with *SMARCB1*/*SMARCA4* or *EZH2* genetic alterations [65].

By using the EZH2 inhibitor DZNep, cell proliferation in germinal center B-cell-like diffuse large B-cell lymphoma (GCB-DLBCL) can be reduced. This may be mediated by upregulating p16. This suggests that DZNep could be a potential therapeutic option for GCB-DLBCL [66]. GSK-126, another effective inhibitor of EZH2, can affect apoptosis and protect brain cells after cerebral ischemia [67]. In a subcutaneous A375 xenograft mouse model, oral administration of ZLD1039 (100 mg per kg) selectively reduced H3K27 methylation in melanoma cells by inhibition of EZH2 methyltransferase activity [68].

IHMT-337 is a novel irreversible EZH2 inhibitor that prevents malignant tumor cell proliferation by simultaneously inhibiting EZH2 activity and downregulating *CDK4* transcription. This discovery provides a new idea for the development of targeted anticancer drugs against EZH2 and demonstrates a significant antitumor effect of IHMT-337 in preclinical models [69]. Another novel dual-target PARP1/EZH2 inhibitor, KWLX-12e, was used in wild BRCA-type triple-negative breast cancer and was nontoxic to normal breast cells. By inhibiting EZH2, KWLX-12e increases sensitivity to PARP1 lethality and induces cell death, representing a potential candidate for the treatment of triple-negative breast cancer [70].

DYB-03 is also a dual-target drug of HIF-1α and EZH2. Molecular predictions indicate that DYB-03 may form multiple hydrogen bonds with both proteins, effectively inhibiting their functions. The study also showed that DYB-03 has strong antitumor activity *in vitro* and *in vivo* (including in a mouse tumor model of transplantation) and was able to significantly inhibit lung cancer cell migration, invasion, and angiogenesis and promote apoptosis. In addition, DYB-03 may reverse the resistance of lung cancer to existing drugs such as 2-ME2 and GSK126 [71,72].

Huang and colleagues designed a dual EZH2-BRD4 inhibitor with excellent pharmacological activity by analyzing the nature of the heterodimeric compounds and the detailed structure-activity relationships. The compound demonstrated excellent inhibitory activity and cytotoxicity *in vitro* and was able to induce apoptosis and reduce tumor cell proliferation *in vivo*. These results suggest that the compound is a potential therapeutic agent for the treatment of solid tumors and provides a new idea for the development of novel EZH2-BRD4 dual inhibitors [73]. The above-mentioned inhibitors are listed in **Figure 2**.

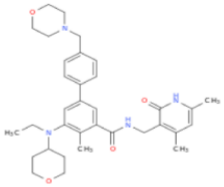
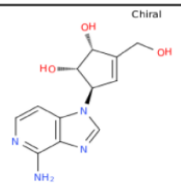
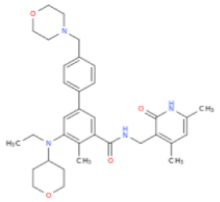
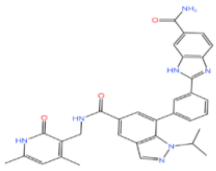
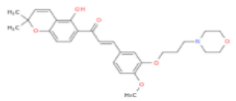
name	Compound structure	cancer type
Tazemetostat (EPZ6738)		liver cancer, pediatric tumor
DZNep (3-Deazaneplanocin A)		GCB-DLBCL
IHMT-337		lymphoma, prostate cancer, breast cancer
KWLX-12e		triple-negative breast cancer (TNBC)
DYB-03		lung cancer

Figure 2. Major inhibitors targeting EZH2

4.2. Combination therapy with EZH2 inhibitors

Advances in immunotherapy and targeted therapies have improved the treatment of tumors, but not all patients respond to these therapies and a large proportion of patients suffer from drug resistance. EZH2 is overexpressed in a variety of tumors and the mechanism of tumorigenesis has been extensively studied. In acquired or intrinsically

resistant ccRCC models, inhibition of EZH2 expression or activity restores the antitumor effect of sunitinib by inhibiting the phosphorylation of specific receptor tyrosine kinases. This suggests that EZH2 inhibitors have a better therapeutic effect when combined with other anticancer drugs [74].

By regulating the expression of immune-related genes, EZH2 helps tumor cells evade recognition by T cells and other immune cells, thereby promoting immune escape. The lncRNA EPIC1 is involved in many cellular processes that promote cell viability and invasion and cell cycle progression by interaction with MYC. Guo *et al.* showed that EZH2 is a key regulator in EPIC1-mediated tumor immune escape and immunotherapeutic resistance [75].

In breast cancer with BRCA1 deficiency, the combination of EZH2 inhibitors (e.g. tazemetostat) and ATM inhibitors significantly inhibits cell proliferation and induces DNA damage, resulting in cell death. This combination therapy has shown strong anti-tumor activity in *in vivo* and *in vitro* studies and provides a potential therapeutic strategy for treating BRCA1-defective cancers, particularly in patients resistant to existing therapies [76].

Androgen deprivation therapy (ADT) is a commonly used treatment for recurrent prostate cancer. After a period of response, almost all patients develop ADT resistance. BET and EZH2 inhibitors work better together than either one alone to effectively suppress cell viability, proliferation, and clonogenicity in metastatic prostate cancer cells [77].

When used in combination, BRAF inhibitors and EZH2 inhibitors significantly inhibit melanoma cell growth and increase apoptosis. This combination therapy is more effective than BRAF inhibitors or EZH2 inhibitors alone and has the potential to overcome drug resistance in particular [78].

5. Conclusion and prospects

EZH2 is a key histone methyltransferase and has been extensively investigated. The fact that EZH2 upregulation is closely related to the onset, progression, metastasis, and invasion of tumors is indicative of EZH2 being a prominent cancer target.

As a result, a number of specific inhibitors against EZH2 have been developed. Tazemetostat is the first EZH2 inhibitor available for clinical use. However, the genomic heterogeneity of tumors, complex epigenetic regulatory networks, and drug resistance may be reasons for the variable efficacy of EZH2 inhibitors. The development of dual-target drugs against EZH2 has led to new advances in optimizing tumor treatment. Moreover, a large body of evidence shows that chemotherapy drugs in combination with EZH2 inhibitors have a stronger antitumor effect. To improve the limitation of EZH2 inhibitors in clinical treatment, optimization of various combinations of metabolic modulators, immunotherapy, radiotherapy, and chemotherapy is a promising therapeutic strategy in the near future.

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Disclosure statement

The authors declare no conflict of interest.

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