Review Article

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Multidimensional Roles of EZH2 and Its Therapeutic Potential in Cancer Therapy

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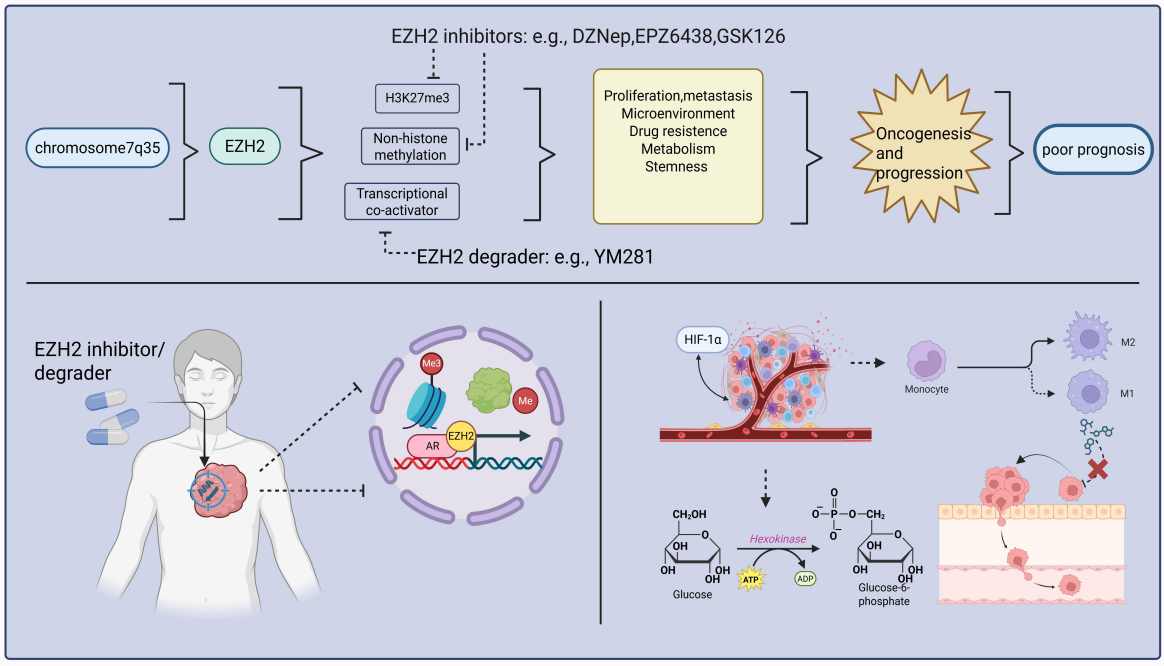
Graphical Abstract



https://doi.org/10.71321/q01vae55

 L. Conflux. Vol. 1, No. 4 (2025)

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Multidimensional Roles of EZH2 and Its Therapeutic Potential in Cancer Therapy

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Received: 2025-06-27 | Accepted: 2025-07-16 | Published online: 2025-08-25

Abstract

Enhancer of zeste homolog 2 (EZH2), a core member of the Polycomb Group (PcG) family, is a pivotal epigenetic regulator. As the catalytic subunit of Polycomb Repressive Complex 2 (PRC2), EZH2 mediates trimethylation of histone H3 lysine 27 (H3K27me3), leading to chromatin condensation and altered expression of downstream genes. This mechanism enables EZH2 to exert multidimensional roles in development, tumors, immunity, and the nervous system. Given its critical role in epigenetic regulation and multidimensional oncogenesis, EZH2 has emerged as a hot target for cancer therapy. This review summarizes EZH2's regulatory functions and specific pro-tumorigenic mechanisms, detailing its roles in epigenetic regulation, tumor proliferation and metastasis, tumor microenvironment, stemness maintenance, drug resistance, metabolic reprogramming, and dysregulated signaling pathways, aiming to inspire new perspectives in cancer treatment research.

Keywords: EZH2; epigenetic modification; methylation; H3K27me3; cancer.

Background

Cancer occurrence is highly correlated not only with genetics, diet, infection, microbiota, smoking, alcohol consumption, and other factors [1-4], but also with epigenetic dysregulation (such as DNA methylation, histone modifications, and non-coding RNA regulation), which silences tumor suppressor genes and activates oncogenes, thereby playing a key role in driving cancer formation [5-7].

Histone modification, as one of the core mechanisms in epigenetics for regulating gene expression, alters chromatin structure through chemical modifications, thereby affecting DNA accessibility and gene transcriptional activity [3, 8]. Among these, trimethylation of histone H3 lysine 27 (H3K27me3), catalyzed by Polycomb Repressive Complex 2 (PRC2), is a key type of histone modification and serves as a critical repressive mark in epigenetic regulation [9, 10].

Enhancer of zeste homolog 2 (EZH2), as the core subunit of PRC2, exerts its oncogenic effects mainly via two modes: the PRC2-dependent classical function and the PRC2-independent non-classical function (Figure 1). The classical function involves EZH2 participating in the formation of the PRC2 complex and binding to the promoter regions of target genes, where it catalyzes H3K27me3 to create a condensed chromatin structure, thereby hindering the binding of RNA polymerase II and transcription factors and affecting downstream gene expression [11, 12]. The non-classical function involves EZH2 directly methylating non-histone proteins, resulting in downstream gene activation or ubiquitin-mediated degradation without the need to form the PRC2 complex [13, 14]. However, recent studies have shown that EZH2 can even function independently of its methyltransferase activity by acting as a transcriptional co-activator that directly binds to target proteins to activate downstream targets, or by directly binding to the promoters of metabolic genes to regulate gene activation [15-17]; thus, these processes are not blocked by enzymatic EZH2 inhibitors.

Epigenetic Regulation of EZH2 in Tumors

EZH2 Catalyzes Methylation of Histone

Histone methylation, as the most central catalytic function of EZH2, drives gene silencing by mediating H3K27 trimethylation, thereby suppressing the expression of tumor suppressor genes and promoting cycle progression. In a controlled RT-

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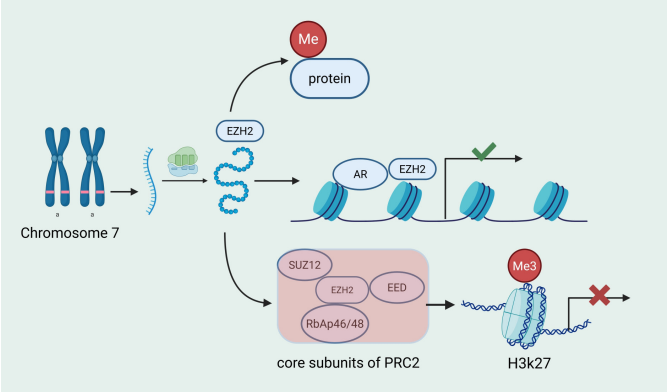
Figure 1. The main mechanisms through which EZH2 exerts its effects are: histone methylation, non-histone methylation, and transcriptional co-activation.



PCR study comparing cholangiocarcinoma tissues with or without EZH2 depletion, it was found that EZH2 knockdown led to significant upregulation of 12 key tumor suppressor genes (such as PAX3, SFRP1, CDKN1A, and GAS1), suggesting that EZH2 may promote cholangiocarcinoma cell growth through epigenetic silencing of tumor suppressor genes [11]. Overexpression of miR-139-5p can induce cellular senescence and inhibit hepatocellular carcinoma cell proliferation. EZH2 promotes TOP2A expression by epigenetically silencing miR-139-5p via H3K27me3, thereby driving hepatocellular carcinoma cell proliferation and malignant progression [12]. Regarding dysregulated cell cycle control in cancer cells, a study found that inhibition of EZH2 expression in multiple myeloma cells increased the levels of cyclin-dependent kinase inhibitors p15 and p21, and this upregulation was associated with the CDKN2B and IFIT3/MYC/CDKN1A pathways [18]. Pan-cancer analyses have shown that PRC2 is enriched at the promoter regions of EMT-related genes, directly suppressing the expression of epithelial markers such as E-cadherin [19-21].

Non-Coding RNA Regulates EZH2 Stability

Studies have revealed that in hepatocellular carcinoma cells, non-coding RNA such as miR-26a, miR-138-5p, and miR-144/451a form a negative feedback loop with EZH2 to regulate cancer cell growth: EZH2-mediated H3K27me3 modification at the promoter regions suppresses the transcription of these miRNAs, while luciferase reporter assays demonstrate that these miRNAs directly target the 3'UTR of EZH2 mRNA, directing post-transcriptional repression and thus modulating gene expression [22-24]. FUS protein is a multifunctional nucleic acid-binding protein that can recognize and bind specific sequence elements within the 3'UTR of target mRNA in cells, thereby preventing the binding of other factors that promote mRNA degradation or structurally enhancing mRNA stability; it thus exerts important biological functions [25, 26]. Non-coding RNA such as hsa_circ_0006232, LINC00313, and LINC SNHG14 have been found to promote the interaction between FUS protein and EZH2, prolong the half-life of EZH2 mRNA, increase its stability, and consequently enhance EZH2-mediated epigenetic silencing of downstream factors (e.g., PTEN and EPHA7), thereby facilitating tumor progression [27-29].

Dynamic Assembly of PRC2 Complex

EZH2 Y641 mutation promotes multiround H3K27 methylation by altering H-bonding patterns and/or steric crowding within the enzyme–bisubstrate ternary complex active site; in other words, the Y641-mutant EZH2 changes substrate preference, preferentially catalyzing the conversion of H3K27me2 to H3K27me3, leading to the formation of lymphoma-specific H3K27me3 hyperdomains [30, 31]. Mutations in SUZ12 and EED are highly conserved; among them, the Suz12 D605V and Eed G255D mutations markedly reduce the histone methyltransferase activity of the PRC2 complex and impair the catalytic formation of H3K27me3 [32].

The Role of EZH2 in Tumor Proliferation,Invasion and Metastasis

EZH2-Related Signaling Axes and Non-Coding RNA Regulatory Networks Influence EMT Process

Epithelial-mesenchymal transition (EMT) in tumor cells is crucial for promoting metastasis and invasion, and this process can be regulated by multiple signaling axes, such as EZH2-MIR-293A-SNAI [33], Snail/Slug-MIR-101-EZH2 [34], MIR-217-MALAT1-EZH2-H3K27me3 [35], and TGF-β-MTA1-SMAD7-SMAD3-SOX4-EZH2 [36]. Long non-coding RNA can recruit EZH2 to exert targeted repression of epithelial markers, thereby facilitating EMT; for example, LINC01133 brings EZH2 and LSD1 to the promoters of KLF2, P21 and E-cadherin to silence their transcription and enhance tumor invasion and metastasis [37]; LINC00978 recruits EZH2 to the promoters of P21 and E-cadherin to promote EMT [19]. In addition to recruitment, LINC00152 can release EZH2 after binding to the PRC2 complex, thereby reducing H3K27me3 enrichment at the ZEB1 promoter and blocking its transcriptional repression, which promotes EMT and oxaliplatin resistance in esophageal cancer cells [38].

Non-Canonical Pathways Promote Tumor Invasion and Metastasis

In addition to epigenetic regulation of histones, splicing-dependent mechanisms also play important roles in cancer cell EMT. Studies have shown that LINC01348 competitively binds to splicing factor 3B subunit 3 (SF3B3), blocking efficient splicing of EZH2 pre-mRNA and leading to loss of functional EZH2 protein, thereby inhibiting hepatocellular carcinoma invasion [39]. Moreover, the EZH2-catalyzed product H3K27me3 has been found to act as an atypical repressor driving peritoneal metastasis in triple-negative breast cancer. Specifically, H3K27me3 is markedly enriched at the promoter of the KRT14 gene; it compresses the GC-box region within the KRT14 promoter to prevent binding of the repressor SP1 and permits RNA polymerase II to initiate transcription of KRT14, thereby promoting triple-negative breast cancer migration, invasion, and peritoneal metastasis. In this study, enrichment of H3K27me3 at the KRT14 promoter did not repress but instead enhanced its transcription [40]. In addition, post-translational modifications of non-histone proteins—such as phosphorylation, methylation, acetylation, and ubiquitination—closely influence protein stability, activity modulation, and protein–protein interactions [3, 41-45]. It has been reported that EZH2, acting as a methyltransferase, directly catalyzes trimethylation of lysines K53 and K333

on SMAD3 under stimulation by the tumor suppressor TGF-β; subsequently, methylated SMAD3 modulates SMAD3 S423/S425 phosphorylation through regulated membrane recruitment, thereby promoting tumor metastasis [46].

EZH2-Regulated Tumor Proliferation and Metastasis via Wnt/β-catenin Signaling Pathway

According to the FpClass database, EZH2 can interact with metal-response element-binding transcription factor 2 (MTF2), and the Wnt pathway antagonist secreted frizzled-related protein 1 (SFRP1) has been identified as a target gene of EZH2. Subsequent studies demonstrated that MTF2 promotes EMT progression in osteosarcoma via the EZH2/SFRP1/Wnt signaling axis [47, 48]. Beyond osteosarcoma, EZH2-mediated regulation of the Wnt/β-catenin pathway in tumor proliferation and metastasis has been validated in multiple cancer types, including colorectal cancer [49, 50], gastric cancer [51], melanoma [52, 53], glioma [54], laryngeal cancer [55], cervical cancer [56], and liver cancer [57], establishing a pan-cancer theoretical and practical basis for EZH2-targeted therapy to suppress the Wnt/β-catenin pathway driving malignant progression. Nevertheless, the precise mechanisms may vary according to tumor heterogeneity and tissue specificity.

Tumor Microenvironment Remodeling

Studies have found that EZH2 deletion or inhibition causes opposite CCL2 expression and thus influences different polarization states of tumor-associated macrophages (TAMs). Whether this depends on histone methyltransferase activity can explain the up-regulation: after treatment with the EZH2 inhibitor EPZ-6438, increased CCL2 levels lead to elevated M2-type TAMs and higher tumor vascular density, further promoting tumor metastasis. Meanwhile, EZH2 can recruit DNMT1 to the miR-124-3p promoter that targets CCL2, forming a hypermethylated structure; this explains why EZH2 loss results in CCL2 down-regulation [58]. Therefore, the above studies indicate that EZH2 exerts opposite regulatory effects on TAMs polarization in breast cancer through its enzymatic or non-enzymatic activities. In addition, contradictory findings show that EZH2 inhibitors can reprogram tumor cells into a more immunogenic state. Specifically, EZH2 inhibitors up-regulate genes related to adhesion, inflammatory response, and B-cell activation in the tumor microenvironment, thereby inhibiting tumor progression and metastasis [59, 60]. From these studies we can see that EZH2-mediated regulation of the tumor immune microenvironment involves highly complex mechanisms with dual roles, reminding us to be especially cautious when choosing EZH2 inhibitors in different tumor microenvironments; otherwise, not only may the expected therapeutic effect not be achieved, but tumor progression may even be exacerbated. Beyond differences in immune cell types and distribution, the hypoxic tumor microenvironment is also a major challenge in solid tumor therapy; in hepatocellular carcinoma cells, hypoxia-induced elevation of LINC00839 is closely associated with a series of malignant phenotypes [61]. Related studies have shown that under hypoxic conditions EZH2 expression and activity increase, thereby affecting tumor cell proliferation, invasion, and metastasis. Moreover, EZH2 can actively participate in remodeling the tumor microenvironment by regulating hypoxia-related factors such as HIF-1α, promoting tumor EMT and malignant progression [62–64].

The Role of EZH2 in Tumor Drug Resistance

EZH2 Affects Drug Resistance through Classical Pathways

In ovarian cancer, c-Myc enhances EZH2 expression by directly repressing miR-137, which targets EZH2 mRNA; conversely, EZH2 can silence miR-137, further strengthening the negative-feedback loop that modulates tumor resistance to cisplatin [65]. Similarly, in esophageal squamous carcinoma cells, CTCF recruits EZH2 and PXN proteins to the miR-137 promoter to inhibit its expression, while EZH2 and PXN mRNAs are downstream targets of miR-137, thereby regulating cellular radiosensitivity through this negative-feedback mechanism [66]. In non-small-cell lung cancer, EZH2 catalyzes H3K27me3 at the puma promoter to silence the apoptosis regulator puma and influence sensitivity to platinum-based agents [67]. In glioblastoma, a circular EZH2-encoded EZH2-92aa protein suppresses NKG2D-ligand expression, allowing tumor cells to evade NK-cell cytotoxicity; although no immunotherapeutics were directly tested, this finding suggests that cellular immunotherapy, immune-checkpoint inhibitors, and cytokine-based drugs (e.g., IL-2, IL-15) may be less effective in glioblastoma [68]. In chronic myeloid leukemia, the lncRNA HOTTIP recruits EZH2 to the PTEN promoter, causing hypermethylation and PTEN down-regulation, which induces resistance to imatinib mesylate [69]. Collectively, these studies demonstrate that EZH2-mediated epigenetic resistance mechanisms critically influence resistance to traditional platinum cytotoxics, immunotherapeutics, radiotherapy, and small-molecule targeted agents across both solid and hematologic malignancies, underscoring EZH2's broad significance in tumor drug resistance. While the precise mechanisms and hierarchical roles of EZH2 in resistance remain incompletely understood, combining EZH2 inhibitors with anticancer drugs holds promise for enhancing drug sensitivity and reducing resistance. To date, such combination studies are largely confined to preclinical models and have shown improved therapeutic outcomes; however, corresponding clinical data are scarce, highlighting the need for expanded translational and clinical investigations.

EZH2 Affects Drug Resistance through Non-Classical Pathways

BRAF mutation activation is the most frequent alteration in cutaneous malignant melanoma [70–72], and BRAF-targeted agents have been highly anticipated for melanoma therapy. Nevertheless, clinical data show that approximately 50% of patients develop varying degrees of resistance after 6–8 months of BRAF-inhibitor treatment [73]. One study found that adding the EZH2 inhibitor EPZ-6438 to vemurafenib markedly improves the response in BRAF-resistant melanoma cells (A375R), as evidenced by decreased viability, cell-cycle arrest, and increased apoptosis. The authors hypothesized that EZH2 may act as a transcriptional co-activator that stimulates transcription of the proto-oncogene PLK1 by associating with E2F1, thereby enhancing PLK1 expression. An alternative mechanism proposes that EZH2 directly methylates STAT3, increasing its phosphorylation; STAT3 then functions as a PLK1 transcriptional activator [74], ultimately leading to PLK1

overexpression [75]. However, several questions surround these mechanistic assumptions. First, if EZH2 indeed serves as a transcriptional co-activator that partners with E2F1 to drive PLK1 transcription, its effect should not be sensitive to methyltransferase inhibitors. Second, the study observed that EZH2 inhibition alone had no impact on PLK1 expression in melanoma cells, indicating that EZH2 inhibitors merely act synergistically with vemurafenib and do not directly suppress PLK1—an outcome that contradicts the proposed mechanism. Therefore, more complex regulatory networks likely remain to be uncovered.

EZH2-Regulated Tumor Drug Resistance via PI3K/AKT Pathway

The PI3K/AKT pathway is the most frequently reported signaling axis through which EZH2 influences tumor drug resistance. In most studies EZH2 acts as an activator of this pathway; however, owing to tissue- and tumor-specific contexts, the exact activation modes differ across cancer types. In acute myeloid leukemia, combined use of the EZH2 inhibitor DZNep and the selective BCL-2 inhibitor venetoclax achieved synergistic efficacy and markedly increased venetoclax sensitivity. Whole-transcriptome analysis revealed that PIK3IP1 (a negative regulator of PI3K/AKT/mTOR signaling) is inversely correlated with EZH2 expression, indicating that EZH2 epigenetically up-regulates the PI3K/AKT pathway to mediate cellular resistance [76]. In chronic myeloid leukemia, LINC-HOTTIP recruits EZH2 to the PTEN promoter, inducing hypermethylation and down-regulating PTEN, thereby driving imatinib resistance [69]. Although the study did not explicitly address PI3K/AKT activation, PTEN is a well-established lipid phosphatase that dephosphorylates PIP3 to PIP2 and suppresses AKT activity across numerous cancers [69, 77, 78]. While EZH2 generally functions as a PI3K/AKT activator, it can also inhibit this pathway in specific settings. In colorectal cancer, LINC-PiHL binds EZH2 and reduces its occupancy at the HMGA2 promoter, lowering H3K27me3 levels at this locus. Up-regulated HMGA2 then enhances PI3K/AKT phosphorylation, leading to oxaliplatin resistance [79]; here, EZH2 behaves as a PI3K/AKT inhibitor. Collectively, these findings illustrate EZH2's multi-target, cell-type, and microenvironment-dependent functions.

Stemness Maintenance

A large body of research has confirmed that EZH2 can act as a cancer stem cell marker and is highly expressed in neuroblastoma, epidermal carcinoma, high-risk cytomegalovirus-infected breast cancer, medulloblastoma, neural stem cells, pancreatic cancer, and other tumor types, thereby promoting tumor self-renewal and metastatic capacity [80-86]. Correspondingly, depletion of EZH2 suppresses the self-renewal ability of tumor cells and reduces their proliferation and invasive potential [87-89].

Non-coding RNA Regulatory Networks

Similarly, EZH2 sustains tumor cell stemness through multiple mechanisms. Most commonly, lncRNA recruits EZH2 to the promoters of tumor-suppressor genes to catalyze H3K27me3 formation, thereby promoting CRC cell proliferation or stemness maintenance. For example, LINC01419 recruits EZH2 to the FBP1 promoter to enhance lung adenocarcinoma cell proliferation and stemness [90]; LINC-HOXB-AS3 recruits EZH2 to the Dicer promoter, epigenetically repressing its transcription to foster sorafenib resistance and stemness maintenance in hepatocellular carcinoma cells [91]. Beyond recruitment, lncRNA can also serve as molecular "sponges" to influence EZH2 expression. LINC-PDZD7, for instance, acts as a miR-101 sponge, preventing the latter from binding to EZH2 mRNA, thereby increasing EZH2 levels and suppressing the stemness regulator ATOH8 [92]. Intuitively, stronger tumor stemness should correlate with stronger immune evasion, and studies have already shown that certain lncRNA are closely linked to tumor immune features [93]. Therefore, it is reasonable to hypothesize that lncRNA may modulate tumor stemness via EZH2, in turn affecting immune responsiveness—a mechanism that clearly warrants further investigation.

Synergistic DNA Methylation Effect

Co-immunoprecipitation revealed that TRIM37 interacts with EZH2 to maintain glioma cell growth and stemness; the underlying mechanism involves down-regulation of the Sonic Hedgehog pathway inhibitor PTCH1, thereby activating the Sonic Hedgehog stem cell signaling pathway [94].

Metabolic Reprogramming

Glycolysis

Tumor cells reprogram metabolism to increase glucose uptake and accelerate glycolysis, producing energy mainly via glycolysis even under abundant oxygen—a phenomenon termed the "Warburg Effect" [95, 96]. Although this mode is energetically inefficient, it supplies proliferating cells with metabolic intermediates. Numerous studies have confirmed the close relationship between EZH2 and tumor metabolic abnormalities [97]. In glioblastoma, an EZH2-EAF2-pVHL-HIF-1α axis drives glycolysis and malignant progression: EAF2 binds and stabilizes pVHL (a tumor suppressor that mediates degradation of the glycolysis master regulator HIF-1α [98, 99]), whereas EZH2 epigenetically silences EAF2, elevating HIF-1α and reprogramming metabolism [100]. Additionally, the EZH2-miR-328-β-catenin axis has been shown to promote glioma glycolysis, indicating that EZH2 can modulate glycolysis via signaling pathways [101]. Intriguingly, in hypoxia-induced HIF-1α-upregulated non-small-cell lung cancer models, EZH2 expression is also increased; EZH2 then epigenetically represses FBXL7, reducing ubiquitin-mediated degradation of its substrate PFKFB4 and ultimately enhancing glucose metabolism and malignant phenotypes [102]. Given the cooperative, complementary oncogenic roles of HIF-1α and EZH2 in diverse tumors, the dual-target compound DYB-03 was screened and found to induce stronger apoptosis and angiogenesis inhibition in lung cancer cells than single-target inhibitors [103]. In bladder cancer, aldehyde oxidase 1 (AOX1) suppresses the tryptophan-kynurenine pathway, lowering NADP levels and decreasing pentose-phosphate-pathway flux and nucleotide synthesis, thereby weakening tumor invasion; EZH2-mediated epigenetic silencing of AOX1 reverses this, increasing pentose-phosphate-pathway flux and nucleotide synthesis [104]. In colorectal cancer, the homeobox transcription factor PROX1 recruits EZH2 to the SIRT3 promoter, repressing SIRT3 and promoting tumor cell

proliferation and glycolysis [105]. Non-canonical actions have also been described: in ovarian malignancies, cell-proliferation assays and immunoblotting after treatment with EZH2 inhibitor (DZNep), EZH2 degrader (YM281), or EZH2 catalytic inhibitors (GSK126, EPZ-6438) revealed that EZH2's oncogenic role is independent of its catalytic activity. Integrated ChIP-seq and RNA-seq data showed EZH2 directly binds and transcriptionally activates metabolic genes related to the TCA cycle and OXPHOS, such as IDH2 and OGDHL, thereby fostering metabolic adaptation and malignant progression [17]. In summary, EZH2 markedly promotes tumor-cell glycolysis to drive cancer cell proliferation.

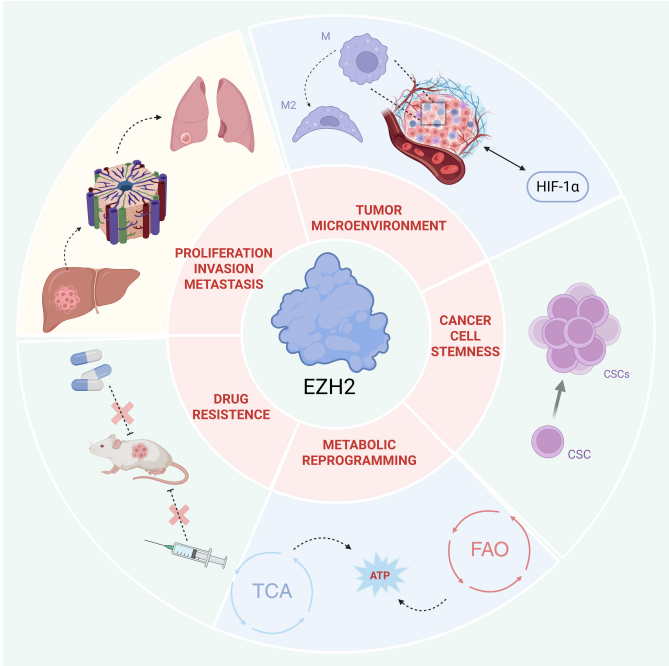
Lipid Metabolism

Rapidly proliferating tumor cells usually enhance fatty acid oxidation (FAO) and synthesis to satisfy the demand for membrane and signaling-molecule production [106]; yet EZH2's influence on tumor lipid levels exhibits contradictory, context-dependent effects across species and organs [107-110]. Thus, a comprehensive dissection of EZH2's specific lipid-metabolic targets and signaling axes—together with cell-type specificity—is urgently needed for precise clinical guidance. In triple-negative breast cancer, EZH2 interacts with the metabolic key enzyme PKM2 to form an epigenetic-regulatory complex that reprograms cellular metabolism from glycolysis toward FAO-β-oxidation, thereby supporting tumor growth [111]. In ARMH1-knockdown leukemia cells (MOLM-14 and HEL92.1.7), supplementation of exogenous lipid mixtures restored proliferation to levels comparable with wild-type controls, indicating ARMH1's involvement in leukocyte fatty acid (FA) synthesis. Subsequent CO-IP confirmed a physical interaction between ARMH1 and EZH2, suggesting functional interdependence linked to lipid metabolism [112]. Moreover, oHSV-infected glioblastoma cells exhibited elevated EZH2 expression and a pronounced increase in FAO, implying that EZH2 plays a key role in lipid-metabolic reprogramming in these tumors [113]. Notably, high intratumoral FA levels not only sustain energy supply and membrane synthesis but also broadly impact the anti-tumor efficacy of EZH2 inhibitors (GSK126, EPZ-6438): EZH2i reduces H3K27me3 at the promoters of lipid-synthesis genes SCD1 and ELOVL2, leading to elevated FA levels and attenuated suppression of melanoma growth. Combining EZH2i with lipid-lowering agents markedly enhanced tumor-growth inhibition, demonstrating that EZH2i profoundly influences tumor lipid metabolism and that lipid levels in turn modulate cellular sensitivity to EZH2i [114]. Accordingly, recent studies on targeted disruption of tumor oxidative defense further confirmed that various EZH2 inhibitors induce dysregulation of lipid-metabolic genes [115].

Amino-acid metabolism

EZH2 expression in colorectal cancer is inversely correlated with glutaminase levels; thus, EZH2 down-regulation accelerates glutamine hydrolysis to glutamate, increasing glutathione synthesis and enhancing cellular antioxidant capacity, thereby attenuating ROS-induced cell death under glucose deprivation—a mechanism potentially linked to tolerance to EZH2 inhibitors [116]. EZH2 influences amino-acid metabolism via two principal routes:(1) suppressing glutamine metabolism as described above, (2) promoting S-adenosyl-methionine (SAM) synthesis. Studies show EZH2 orchestrates a cascade that regulates methionine availability: EZH2 binds the retinoid X receptor α (RXRα) promoter to repress its transcription; diminished RXRα relieves inhibition of LAT1, whose up-regulation then increases methionine import. Elevated methionine satisfies tumor metabolic demand and serves as a methyl donor for DNA and histone methylation [117, 118]. In lung adenocarcinoma, EZH2 inhibition activates Gamma-Aminobutyric Acid (GABA) synthesis because the GAD1 and GAD2 genes are epigenetically silenced by H3K27me3; GABA, a key neurotransmitter, may modulate tumor–stromal cell communication within the tumor microenvironment [119]. Although amino acids act as carbon and nitrogen sources, fueling rapid proliferation and macromolecule synthesis, and their metabolites can act as signaling molecules to modulate oncogenic pathways, the underlying regulatory mechanisms remain poorly understood. Thus, elucidating how EZH2, already implicated in amino-acid metabolism, orchestrates metabolic reprogramming is of paramount importance (Figure 2).

Figure 2. The functions of EZH2 in influencing tumors include: proliferation, invasion and metastasis, drug resistance, metabolism, stemness, and tumor microenvironment.



Signaling Pathways Dysregulation

PI3K/AKT/mTOR Signaling Pathway

The PI3K/AKT/mTOR pathway is a key intracellular signaling axis that widely participates in proliferation, survival, differentiation, angiogenesis, drug resistance, and other biological processes [120–122]. In cancer, activation of this pathway is closely associated with tumor metastasis, invasion, and resistance [123–125]. Among all signaling cascades, the PI3K/AKT/mTOR pathway is the most tightly linked to EZH2: in multiple cancer types, EZH2 is recruited or bound by other biomarkers to epigenetically silence the PI3K/AKT inhibitor PTEN, thereby activating the pathway and influencing cancer-cell proliferation, stemness maintenance, metastasis, invasion, and drug resistance—examples include osteosarcoma [27],

leukemia [69], colorectal cancer [126], gastric cancer [127], and prostate cancer [128]. Interestingly, activation of PI3K/AKT can also directly or indirectly mediate phosphorylation of EZH2 at S21; for instance, in ablation cells, PI3K/AKT activity positively correlates with EZH2-S21 phosphorylation. Phosphorylation at S21 is precisely the switch that converts EZH2 from a Polycomb-dependent transcriptional repressor into a transcriptional co-activator that cooperates with factors such as the androgen receptor to activate downstream gene expression [129].

Wnt/β-catenin Signaling Pathway

It is well known that the Wnt/β-catenin pathway plays essential roles in embryonic development [130], cell proliferation, differentiation, and tissue homeostasis. In cancer, this pathway markedly promotes excessive extracellular-matrix degradation, tumor invasion and migration, drug resistance, and stemness maintenance [131]. In normal esophageal epithelial cells, EZH2 binds the WNT2 promoter and, via its histone methyltransferase activity, represses WNT2 expression, preventing aberrant Wnt activation. In contrast, esophageal squamous-cell carcinoma shows reduced EZH2 occupancy at the WNT2 promoter, relieving repression and increasing WNT2 transcription [132]. Similar mechanisms operate in glioblastoma, bladder cancer, and hepatocellular carcinoma, where LINC-H19 recruits EZH2 to the promoters of Wnt inhibitors AXIN2 and NKD1, depositing H3K27me3 and thereby up-regulating Wnt/β-catenin signaling [133, 134]. In glioblastoma, HP1 recruits histone deacetylases (HDACs) to H3K9me2-marked loci to silence gene transcription, but EZH2–HP1BP3 interaction impairs HP1-mediated HDACs recruitment, reducing H3K9me2 and derepressing WNT7B, which influences temozolomide resistance [135]. In colorectal cancer, PAF—an overexpressed translesion DNA-synthesis component—dissociates from PCNA upon Wnt activation, binds β-catenin directly, and recruits EZH2 to form a transcriptional activation complex that boosts β-catenin target gene expression, independent of EZH2 methyltransferase activity [136]. Collectively, EZH2 up- or down-regulates Wnt/β-catenin signaling in different tumors via both canonical and non-canonical mechanisms, thereby influencing proliferation, metastasis, drug resistance, and other malignant phenotypes. The precise mode of action depends on tumor type, cellular microenvironment, and pathway crosstalk.

STAT Signaling Pathway

Studies have shown that EZH2 can exert non-canonical functions by directly binding to and methylating STAT3. After methylation, STAT3 undergoes further phosphorylation at the Y705 site, leading to enhanced transcriptional activity—clearly a direct phosphorylation process mediated by EZH2 on STAT3. In addition to directly phosphorylating STAT3, EZH2 can also indirectly phosphorylate the STAT signaling pathway by regulating JAK2. The STAT3 pathway is widely upregulated in various cancers and is closely associated with malignant phenotypes such as tumor cell apoptosis, invasion, and drug resistance, including in glioblastoma [13, 137], melanoma [75], renal cancer [138], breast cancer [139], and colorectal cancer [140]. Moreover, it has been found that EZH2-mediated regulation of the STAT signaling pathway is involved in the glycolytic process of oral squamous cell carcinoma, providing energy and substrates for rapidly growing tumor cells and facilitating the EMT process [141–143], as well as in regulating the polarization of M1-type macrophages toward the M2 phenotype [144, 145]. Furthermore, after chemotherapy treatment, the EZH2/STAT3 pathway in breast cancer cells is activated, which in turn stimulates the secretion of exosomes carrying miR-378a-3p and miR-378d targeting DKK3 and NUMB, ultimately upregulating the Wnt/β-catenin and Notch pathways to promote tumor drug resistance and stemness maintenance [146]. In summary, the EZH2-regulated STAT signaling pathway plays multiple critical roles in tumor development, metabolic reprogramming, immune microenvironment modulation, invasion, metastasis, and resistance formation. This suggests great potential for the future development of combination therapies using EZH2 inhibitors/degraders and STAT3 inhibitors. However, the complex crosstalk mechanisms within these pathways also indicate that targeting crosstalk nodes may be more effective than inhibiting a single pathway alone.

ERK Signaling Pathway

Studies have shown that the MEK–ERK–Elk-1 signaling axis promotes EZH2 overexpression in triple-negative and ERBB2-overexpressing aggressive breast cancer subtypes by modulating Elk-1 binding sites within the EZH2 promoter. Using promoter assays, cellular experiments, and tissue analyses, the research team demonstrated that MEK inhibitors and Elk-1 siRNA markedly reduce EZH2 mRNA and protein levels. In this context, EZH2 functions as a downstream target gene of the MEK/ERK pathway, influencing breast cancer cell proliferation and invasion [147]. Meanwhile, EZH2 knockdown was found to down-regulate the AKT/ERK signaling cascade, thereby suppressing FSH secretion and inhibiting the development of ovarian cancer in sheep [148]. Additionally, EZH2-mediated silencing of the tumor-suppressor gene SMAD4 activates the ERK/c-Myc pathway, driving resistance in non-small-cell lung cancer [149].

YAP Signaling Pathway

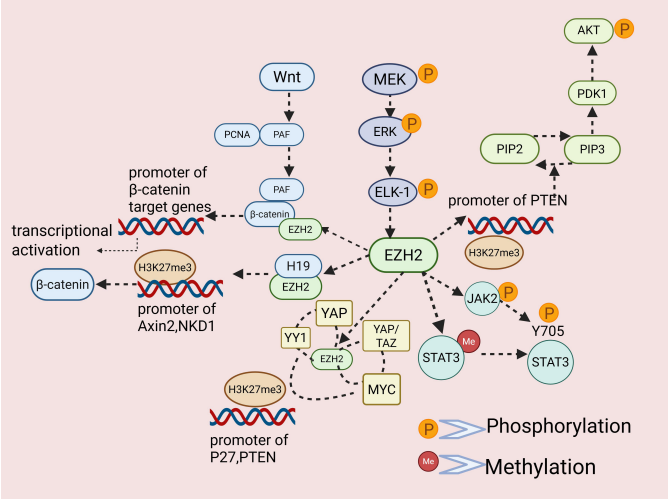
YAP functions as either an oncogene or a tumor suppressor in various cancers. Studies show that EZH2 can form a complex with YAP and the multifunctional transcription factor YY1, facilitating epigenetic modification of the cyclin-dependent kinase inhibitor P27 promoter region and thereby promoting cell proliferation [150]. Similarly, EZH2, together with MYC and YAP/TAZ proteins, can assemble a transcriptional repressor complex that down-regulates the tumor suppressor PTEN [151]. Beyond these transcriptional repressor complexes, the non-canonical Wnt pathway is also critical for maintaining YAP protein levels [152] (Figure 3).

Other pathways

In addition to the major signaling cascades described above, EZH2 participates in the regulation of several non-dominant yet important pathways. For example, in breast cancer the long isoform of NSD3 (NSD3-long) cooperates with EZH2 and RNA polymerase II to stimulate transcription of genes involved in NOTCH receptor cleavage, leading to nuclear accumulation of NICD1. Overexpressed NICD1 then mediates transcriptional repression of E-cadherin and promotes tumor EMT [153]. Other studies have demonstrated that EZH2 can elevate H3K27me3 levels at the GADD45A promoter to suppress its transcription; reduced GADD45A expression subsequently activates the p38/

MAPK pathway [154].

Figure 3. The main signaling pathways regulated or involved by EZH2 are: PI3K/AKT/mTOR, Wnt/β-catenin, STAT, ERK, and YAP Signaling Pathway.



Conclusion

EZH2, a pivotal epigenetic regulator, exerts complex and multidimensional roles in tumorigenesis, progression, metastasis, and drug resistance. Via the canonical PRC2 complex it catalyzes H3K27me3 to silence tumor-suppressor genes, thereby promoting proliferation and invasion, whereas non-canonical actions—direct methylation of non-histone proteins or functioning as a transcriptional co-activator—support stemness maintenance, metabolic reprogramming, and tumor-microenvironment remodeling. During invasion and metastasis, EZH2 drives migration through modulation of EMT-related axes, interference with splicing, and post-translational modification of non-histone proteins; its crosstalk with the Wnt/β-catenin pathway has been validated in multiple cancers, demonstrating both pan-cancer relevance and tissue specificity. In the tumor microenvironment, EZH2 depletion or inhibition can exert opposing effects on TAMs polarization, and its elevated expression and activity under hypoxia further fuel malignant progression. Regarding drug resistance, EZH2 participates in epigenetic silencing as well as non-canonical resistance mechanisms, influencing BRAF-inhibitor resistance and interacting with reprogrammed signaling pathways. As a stemness marker, EZH2 is highly expressed across tumors, fostering self-renewal and metastasis through non-coding RNA networks, cooperative DNA methylation, and signaling circuitries. Metabolically, EZH2 markedly enhances glycolysis, alters fatty-acid synthesis, and modulates amino-acid pathways to supply energy and biosynthetic precursors for rapid proliferation. Pathway-wise, EZH2 broadly regulates PI3K/AKT/mTOR, Wnt/β-catenin, STAT, ERK, YAP, and others, impacting proliferation, stemness, invasion, metastasis, and drug resistance. Despite its prevailing oncogenic image, accumulating evidence indicates context-dependent or even tumor-suppressive roles for EZH2, underscoring its functional complexity and prompting deeper investigation.

Given EZH2's multifaceted significance, it has become a prime therapeutic target. Multiple EZH2 inhibitors are in clinical trials and show favorable tolerability and antitumor activity. However, functional heterogeneity across tumor types and individuals necessitates further dissection of EZH2 mechanisms within distinct microenvironments, development of precision strategies, and mitigation of potential resistance. Combining EZH2-targeted agents with immunotherapy, chemotherapy, or other modalities holds great promise for breakthroughs that could improve patient outcomes and quality of life.

Abbreviations

Aldehyde Oxidase 1: AOX1; Androgen Receptors: AR; Epithelial-Mesenchymal Transition: EMT; Enhancer of Zeste Homolog 2: EZH2; Fatty Acid: FA; Fatty Acid Oxidation: FAO; Gamma-Aminobutyric Acid: GABA; Histone Deacetylases: HDACs; Metal-Response Element-Binding Transcription Factor 2: MTF2; Secreted Frizzled-Related Protein 1: SFRP1; Trimethylation of Histone H3 Lysine 27: H3K27me3; Polycomb Group: PcG; Polycomb Repressive Complex 2: PRC2; Retinoid X Receptor α: RXRα; S-Adenosyl-Methionine: SAM; Tumor-Associated Macrophages: TAMs.

Author Contributions

Mingfen Li and Hongsheng Lin were in charge of the proofreading and design of the manuscript. Hui Yin took responsibility for the writing of the manuscript. Jinna Tan and Jiaqian He were responsible for the collection and organization of literature. All authors read and approved the final manuscript.

Acknowledgements

Figures in the article were drawn using Biorender: https://www.biorender.com/.

Funding Information

This work was supported by Natural Science Foundation of Guangxi Zhuang Autonomous Region (2025GXNSFDA069035, 2025GXNSFAA069372).

Ethics Approval and Consent to Participate

Not Applicable

Competing Interests

The authors declare that they have no existing or potential commercial or financial relationships that could create a conflict of interest at the time of conducting this study.

Data Availability

All data needed to evaluate the conclusions in the paper are present in the paper or the Supplementary Materials. Additional data related to this paper may be requested from the authors.

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