EZH2, An On-Off Valve in Signal Network of Tumor Cells

Shanshan Sun¹, Feng Yu², Lun Zhang¹, Xuan Zhou¹

1. The Maxillary Facial and Otorhinolaryngology Head & Neck Surgery, Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer, Tianjin Key Laboratory of Cancer Prevention and Therapy, Huanhuxi Road, Tiyanbei, Hexi District, TJ, China, 300060.

2. Department of tumor cell biology, Key Laboratory of Cancer Prevention & Therapy of Tianjin; Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer, Huanhu West Road, Hexi District, Tianjin, PR China, 300060

Correspondence to: Dr. Xuan Zhou (Email: byron2000zhou@163.com)

Dr. Lun Zhang (Email: lunzhangchina@163.com)

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Abstract

Enhancer Zeste 2 (EZH2) is a histone methyltransferase catalyzing histone H3K27me3 to mediate gene silence. It is implicated in governing various biological behaviors of human malignancies. In this review, we over-review EZH2 serves as an “ON-OFF VALVE”---not only as a critical epigenetic repressor, but as a brand-new activator for specific downstream targets as well. Time and space it “SWITCHING ON-OFF” depends on the context and its cellular type. Moreover, EZH2 could act as a Tumor-Defender under certain circumstances. Moreover, the “Mutual-Inhibition” relationship between EZH2 and microRNAs is elaborated. In addition, we focus on different functions of phosphorylated EZH2 in tumor cells. Finally, EZH2 inhibitors are summarized and newly-discovered strategies of targeting-EZH2 treatment are prospected.

1. Introduction

Nowadays, histone methylation focused on epigenetic modifications widely regulates genomic biological processes, including gene expression, activity and function. The methyltransferase EZH2 catalyzes histone H3 lysine 27methylation to form H3K27me3. The polycomb repressor complex2 (PRC2) comprises three core subunits EZH2, EED, and SUZ12¹. EZH2 interacts within PRC2/3 context with DNA methyltransferases (DNMTs) and serves as a recruitment platform for DNMTs². H3K27me3 acts as repressive marks in promoter-targeted transcriptional silence. EZH2 is essential for lncRNAs-conducted gene-silence, which is exerted by interaction with histone repressive proteins Polycomb group (PcG) family and recruitment them to gene loci³. There are two opposing groups of histone modifying complexes, the trithorax group (TrxG) of H3K4 histone methyltransferase (HMTase) and the PcG H3K27 HMTase, maintaining open and closed chromatin domains in HOX loci, respectively⁴. ncRNAs transcription *in cis* might enhance accessibility of TrxG proteins while PRC2 recruitment might be programmed by ncRNAs produced *in trans*, resulting in H3K4 or H3K27 methylation and transcriptional activation or silence³. Dysregulation of EZH2 PcG body formation thus depression its tumor-related genes promotes tumor progression⁵.

EZH2 is aberrantly and frequently overexpressed in various tumors⁶⁻¹³. Along with PRC2/EED-EZH2 epigenetic silencing complex, EZH2 is related to aggressive phenotype (high proliferation rate, triple-negative) of breast cancers⁹, lymph node metastasis¹⁴, glioblastoma(GBM) cancer stem cell (CSC) maintenance, self-renewal and tumor-initiating¹⁵. EZH2 exists in complex and atypical hyperplasia¹⁶, and early pathogenesis of squamous cell carcinoma (SCC). High EZH2 expression influences the cell sensitivity

to cisplatin¹⁷ or tamoxifen¹⁰.

2. Context-specific Dependent Transcriptional Activation or Repression

2.1 Epigenetically Switch Off---Mediating Tumor-related Gene Silence

Jack-of-All-Trades:

2.1.1 An Epigenetic Gatekeeper

Due to the canonical function of EZH2 as an epigenetic silencer, the biology responses depend on its interaction with some functional molecules and its downstream targets, which are summed up into the following aspects.

EZH2 Promotes Cancer Progression

EZH2 is implicated in Epithelial-Mesenchymal Transition (EMT) process. Mechanistically, it epigenetically suppresses the epithelial marker---E-cadherin via H3K27me3 modification of its promoter^{18, 19}, which is facilitated by MER/ERK activation²⁰. Otherwise, EZH2 interacted with HDAC1/HDAC2 and Snail to form a multi-molecular complex contributing to E-cadherin silence²¹. EZH2 is required for Snail-Ring1A/B recruitment to E-cadherin promoter locus. EZH2 and Ring1B form distinct complexes with Snail²². As a result, E-cadherin inhibition is associated with advanced stage and poor clinical outcome.

MEK-ERK1/2-Elk-1 regulates EZH2 in association with breast cancer aggressiveness²³. Elk-1 is an important molecule downstream from ERK for EZH2, leading to chromatin remodeling at certain foci, such as E-cadherin and RUNX3^{24, 25}. Emerging evidences reveal RB-E2F3-EZH2 as a key oncogenic axis in cancer development and aggressiveness^{26, 27}. EZH2 affects bladder cancer progression in recurrence, which is primarily facilitated by E2F3a²⁸.

Conversely, EZH2 epigenetically silences the mesenchymal markers (TWIST and SLUG) in company with SUZ12 and HDAC2. The circadian clock gene Period2 (PER2), which serves as a transcriptional co-repressor, recruits them to binding sites of EMT genes (TWIST and SLUG) promoters to inhibit them. However, hypoxia induces PER2 degradation and suppression thus the co-repressors are dissociated, resulting in reactivation of the EMT genes²⁹. Another mesenchymal marker, Integrin alpha2 (ITGa2), is repressed by EZH2 after ERK/AKT activation in colon cancer³⁰.

EZH2 Determines Cell Fate

Several growth-suppressive genes (such as p21, p16, p27) and pro-death genes (such as FBXO32) are EZH2 downstream targets^{31, 32}. Therefore, EZH2 participates in **proliferation, cell cycle arrest, senescence and apoptosis** of tumor cells, *particularly TP53 related*. Targeting EZH2 leads to growth inhibition only in TP53 wild-type cells but not in TP53 mutant-type cells. Combination of EZH2 inhibitor with a Mutant p53 Re-activator can restore the sensitivity of TP53 mutant-type cells to DZNep³³. Gastric cancer proliferation is altered after EZH2 downregulated, p53 upregulated by TET1³⁴. Cell proliferative arrest caused by doxorubicin is promoted by EZH2 depletion in p53-mutant rather than in p53 wild-type cells³⁵. In both p53 wild-type and p53-deficient cancer cells, EZH2 depletion abrogates both cell cycle G1 and G2/M checkpoints thus promotes DNA-damage induced apoptosis in response to genotoxic stress. In p53 wild-type cells, EZH2 modulates DNA damage response mainly through transcriptional repressing its direct target FBXO32, which interacts with p21 to induce its degradation. Whereas, EZH2 regulates p53-deficient cells through Chk1 activation without any relationship with FBXO32³⁶. Additionally, Interferon γ Receptor 1 (IFNGR1) is a target directly silenced by EZH2 in MYC-driven prostate cancer cells. EZH2-mediated inactivation of IFN- γ -JAK-STAT1 signaling confers proliferation and survival advantages³⁷. EZH2 signals through CDK-pRb-E2F pathway to regulate cell cycle. In this regard, an EZH2-mediated signal loop,

EZH2-CDK4/6-pRb-E2F1 induces GBM proliferation and cell cycle³⁸. EZH2 is required for rapid growth in SCLC, in which the E2F/Rb deregulation prominently occurs. The E2F/Rb pathway is disrupted not only through loss or mutation of Rb but also through DNA copy number gains of E2F transcription factors, leading to EZH2 activation and aberrant methylation promotion³⁹.

EZH2 is specifically downregulated in **senescent** cells. Activated p53 repressed EZH2 through inhibiting its promoter via p21⁴⁰. Likewise, EZH2 restrain promotes cellular senescence in gastric cancer cells by p21 and p16⁴¹. Notably, EZH2 is modulated by NF-κB pathway, which is associated with cellular senescence (the canonical NF-κB pathway) and malignancies (the alternative one). As a direct NF-κB target gene, EZH2 is inhibited by loss of NF-κB2/RelB in an Rb/E2F manner⁴². In fibroblasts, EZH2 antagonizes a panel of p53 target related to senescence. Thus, it is presumed that the alternative NF-κB pathway promotes tumorigenesis probably through suppression of p53 dependent senescence⁴³.

Early in 2003, it has been illustrated that EZH2 is downstream of the pRb-E2F pathway, essential for proliferation of tumors⁴². As an E2F1 target, EZH2 serves as a critical regulator of E2F1-dependent **apoptosis** by antagonizing pro-apoptosis target Bim⁴⁴.

EZH2 Regulates Angiogenesis in Inverse Manners

The role of EZH2 in angiogenesis could be divided into two conditions.

Most publications reported that EZH2 could exhibit an angiogenic effect, for instance in clear cell renal cell carcinoma⁶, inflammatory breast cancer⁴⁵, NPC and GBM⁴⁶. EZH2 and VEGF are highly expressed and correlated with adverse clinicopathologic characteristics and poor outcome in renal cancer⁶. In NPC, EZH2 promotes angiogenesis by inhibition of MiR-1/Endothelin-1, an autocrine regulator of endothelial cells as neovascularization in a VEGF-dependent manner¹².

Nonetheless, EZH2 represses angiogenesis under hypoxia and ischemia for the reason that EZH2 contains hypoxia response element (HRE)⁴⁷. In endothelial cells, hypoxia increases EZH2 to regulatory regions of two pro-angiogenic genes (eNOS and BDNF) promoters and augments the abundance of H3K27me3 at these locations⁴⁸.

2.2.2 A Novel Defender---EZH2 Antagonizes the Carcinogenesis Effect

Intriguingly, EZH2 exhibits tumor-suppressive ability in a couple of tumors. Camille proposed that high frequency of spontaneous γδ T-cell leukemia (T-ALL) occurs in EZH2 biallelic deletion mice. The tumor cells show little residual H3K27me3 marks compared with controls⁴⁹. Meanwhile, EZH2 links pancreatic regenerative proliferation to oncogenic transformation. Loss of EZH2 impairs pancreatic regeneration and accelerates KRas^{G12D}-driven neoplasia. Therefore, EZH2 might play an opposite role, namely, restraining the oncogenic process in the exocrine pancreas⁵⁰.

2.2 Epigenetically-independent Switch On---Triggering Signal Cascading

Apart from mediating transcriptional silence, the novel function of signaling activation of EZH2 has been uncovered recently. This non-canonic function is independent of histone methyltransferase activity to some extent in respective manners.

In Glioblastoma multiforme (GBMs), EZH2 facilitates STAT3 methylation and enhances its activity⁵¹. EZH2 promotes tumor growth independent of gain or loss of H3K27me3 via the upstream inducer Akt. EZH2 **enhances STAT3 activation** by trimethylating lysine 180 in STAT3 preferentially in glioma stem-like cells (GSCs). EZH2 along with PRC2, interacts with STAT3 specifically human neural progenitor cells and GSCs but not in differentiate isogenic progeny, nor in established glioma cell lines. Conversely, in bulk tumor cells the EZH2 with the unphosphorylated S21 trimethylates H3K27⁵².

In castration-resistant prostate cancer (CRPC) cells, phosphorylation of EZH2 at S21 induced by PI3K/AKT switches its function from a Polycomb repressor to **a transcriptional co-activator of androgen receptor (AR)** or other molecules, potentially⁵³. Strikingly, pS21 EZH2 level elevates more significantly in CRPC while H3K27me3 level decreases with prostate cancer progression. That strongly supports EZH2 oncogenic activity in CRPC is **independent of its Polycomb repressive function**⁵³. In natural killer/T-cell lymphoma (NKTL) cells, EZH2 **directly promotes cyclinD1 transcription** by binding to its promoter. Therefore, EZH2 overexpression confers a growth advantage **independently of histone methyltransferase activity**⁵⁴.

Concomitantly, Maria uncovered a unique role of EZH2 in **activating, rather than repressing**, NOTCH1 signaling in TNBC cells. Instead of dependence on histone methyltransferase activity and its PRC2-binding partners, EZH2 **positively regulates NOTCH1 transcriptional activity** to expend the breast stem cell pool, resulting in acceleration of breast cancer initiation and growth⁵⁵.

Additionally, the DNA repair gene---PCNA-associated factor (PAF) and EZH2 could induce Wnt/ β -catenin signaling hyper-activation. Upon activation, PAF facilitates interaction between β -catenin and EZH2 to form PAF-EZH2- β -catenin transcriptional complex, which enhance target gene transactivation, independently of EZH2's methyltransferase activity, to promote intestinal tumorigenesis⁵⁶.

Intriguingly, as for target gene NF- κ B, EZH2 functions as a double-facet molecule in ER-positive/negative breast cancer, either as a transcriptional activator or repressor. In aggressive breast cancer cells, EZH2 positively regulates NF- κ B target gene expression independently of histone methyltransferase activity. Mechanistically, EZH2 forms a ternary complex with RelA and RelB to modulate a subset of NF- κ B target genes by interdependent promoter occupancy. On the other hand, in ER-positive luminal-like breast cancer cells, EZH2 negatively regulates NF- κ B target genes. ER recruits PRC2 complex to the promoter of NF- κ B target genes, leading to epigenetic silence⁵⁷.

3. Silencing Confrontation: EZH2 versus MicroRNAs

The relationship between EZH2 and miRNAs could be divided into two sides:

On one side, EZH2 is negatively regulated by several miRNAs, such as miR-101⁵⁸, miR-26b^{59, 60}, miR-98⁶¹, miR-144⁶², let-7b⁶³, resulting in various responses in tumor cells. Mechanistically, miRNAs directly inhibit EZH2 by targeting its 3'UTR. Of most, the tumor suppressive microRNA---**miR-101** are frequently reported. MiR-101 weakens EZH2 and proliferation/migration capability and re-sensitizes drug-resistant cancer cells to cisplatin⁶⁴. **MiR-98, MiR-144, let-7b, MiR-32 and MiR-1297** are respectively evidenced to impair EZH2, responsible for malignant behaviors or cell fate in OCSC^{61, 65}, bladder cancer⁶², astrocytoma⁶⁶, and hepatocellular carcinoma (HCC)⁶⁷.

On the other side, some tumor-suppressive miRNAs are silenced by a repressive chromatin structure involving H3K27me3 and EZH2. After co-treatment with HDAC and EZH2 inhibitor, **miR-1246, miR-302a and miR-4448** are upregulated while their onco-targets DYRK1A, CDK2/BMI-1 and Girdin are downregulated, resulting in apoptosis, cell cycle arrest and reduced migration, respectively⁶⁸. **MiR-340** suppresses several oncogenes including EZH2 in GBM⁶⁹. Besides, EZH2 is recruited by MYC to **miR-26a** promoter and cooperatively represses miR-26a to alter aggressive B-cell lymphoma survival and clonogenicity abilities⁷⁰. Of interest, EZH2 negatively modulates **miR-200c** transcription to form an auto-regulatory loop named "**EZH2-miR200c-E2F3**" as a driving force for PCa development⁷¹. Noteworthy, the repressive effect on miRNAs is achieved by several components including EZH2. In

coordination with SOX4 and HDAC3, EZH2 forms a co-repressor complex binding to **miR-31** promoter, repressing miR-31 through an epigenetic mark by H3K27me3 and histone acetylation⁷².

4. Phosphorylation of EZH2---Separate Sites, Separate Effects

Early in 2005, Tai-Lung reported that Akt physically interacted with EZH2 and phosphorylated it at **Serine-21**, leading to *oncogenesis*⁷³. In human bronchial epithelial cells, As³⁺ induces pEZH2-S21 via JNK/STAT3 and Akt. Activated pEZH2 leads to PRC2 dissociation from chromatin, thereby weaken H3K27me3 in nuclei⁷⁴. Strikingly, H₂O₂, the most important form of reactive oxygen species of cells in response to extracellular stress signals, induces EZH2 phosphorylation and activation of JNK, STAT3 and Akt⁷⁵. As a result, several downstream genes are influenced by STAT3-induced EZH2 overexpression, such as the vitamin D receptor, resulting in cancer metastasis⁷⁶. Notably, in HCC, Akt-mediated pEZH2-Ser21 is indispensable for an epigenetic auto-regulatory loop, in which cell cycle-related kinase (CCRK) induces EZH2 phosphorylation, thereby promoting pEZH2-S21-AR physical interaction for CCRK promoter co-occupancy and transcriptional activation⁷⁷.

However, other researchers argued that Ser-21 was not a major phosphorylation site⁷⁸. They believed that EZH2 phosphorylation was *cell cycle-regulated*⁷⁹. The cyclin-dependent kinase, CDK1, phosphorylates EZH2 at **threonine-345** and **-487**, which are essential for *cell proliferation, embryonic stem cell self-renewal* and *lineage specification*^{78,80}. CDK1-EZH2 pathway is significant not only in cell cycle, but also in cancer *cell migration* and *invasion*. pEZH2-T487 disrupts EZH2 binding with other PRC2 components SUZ12 and EED, and thereby inhibits EZH2 methyltransferase activity, impairing *cancer cell invasion ability*⁸¹.

pEZH2-T345 is important for binding to ncRNA HOTAIR and the 5' end of Xist⁷⁹. CDK1 and CDK2 phosphorylate EZH2 at **Thr-350**, which is vital for EZH2 recruitment and H3K27me3 levels maintenance at EZH2-target loci, thus mediates cell proliferation and migration⁸². Meanwhile, CDK2 also phosphorylates EZH2 at **Thr-416** to contribute to TNBC malignancies⁸³.

5. Targeting-EZH2 Treatment

Currently, a diverse of EZH2 inhibitors have been identified. Among these, **3-deazaneplanocin A (DZNep)** is the most widely known to deplete EZH2 expression through an indirect pathway⁸⁴. The anti-tumor effect of DZNep is well elucidated in literatures. DZNep inhibits H3K27me3 activity to suppress proliferation⁶⁸, induce apoptosis and cell cycle arrest^{31, 85-88}. DZNep downregulates H3K9 HMTase-SETDB1 gene at transcription level and H3K27 HMTase-EZH2 at post-translational level in lung cancer⁸⁹. Aside from EZH2, DZNep also depletes SUZ12, EED, H3K27me3 and cyclinA, whereas increases p27^{kip188}. EZH2 inhibition in mixed lineage leukemia fusion leukemia is therapeutically effective by diminishing leukemia stem cells via p16 upregulation. DZNep not only suppresses proliferation but also reduces leukemia initiating cells frequency⁹⁰.

Moreover, DZNep-based EZH2 disruption remarkably attenuates GBM CSC self-renewal and tumor-initiating capacity¹⁵. Combination treatment of DZNep and IFN- γ completely causes tumor growth arrest³⁷. Co-treatment with DZNep and pan-histone deacetylase inhibitor (**panobinostat**) exerts superior anti-EZH2 effect, leading to p16, p21 and p27 induction more significantly³¹.

As the fact that EZH2 catalyzes H3K27 methylation via transfer of a methyl group from the cofactor S-(S'-adenosyl)-L-methionine (SAM)⁹¹, some highly potent, selective, SAM-competitive, and cell-active EZH2 inhibitors are recognized, as exemplified by **GSK926** and **GSK343**. Unlike DZNep, they directly and selectively inhibit PRC2 enzymatic activity⁹². GSK343 serves a more potent anticancer agent than DZNep

and enhances sorafenib sensitivity in HCC⁸⁴. SAM-competitive EZH2 inhibitors (including GSK343 and UNC1999) can induce autophagy in cancer cells⁸⁴.

In addition, another small molecule inhibitor **EI1** selectively inhibits proliferation and causes cell cycle arrest, and apoptosis in diffused large B-cell lymphomas (DLBCL) cells with EZH2 mutation (Y641F)---one of the hot-spot mutations of EZH2 identified in DLBCL and follicular lymphomas⁹³.

6. Concluding Remarks

Collectively, in view of EZH2 doublefacet properties in epigenetic repression and signaling activation, its interplay in signal network seems crucially significant in tumor cells. Apart from the traditional epigenetic field, the critical valve “SWITCH-ON” mechanism remains elusive. Therefore, each detail mechanism of context-specific activation should be further elucidated. From these above, it could be summarized that---Before we take measures to target EZH2, it is wise to identify the exact role of EZH2 in proper time and space, to polish eyes on the Polycomb-dependent/-independent downstream genes, to recognize whether it is a defender or a gatekeeper.

As some newly-developed inhibitors are emerging in recent years, we are looking forward to the effective, feasible and specific EZH2 inhibitors, which may provide a new avenue for development new strategies for treatment.

Conflict of Interests:

There is no conflict of interests declared in this review.

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Abbreviation:

Tumor-suppressive genes (TCG)

Glioblastoma multiforme (GBMs)

Cancer Stem Cell (CSC)

castration-resistant prostate cancer (CRPC)
androgen receptor (AR)
PCNA-associated factor (PAF)
triple-negative breast cancer (TNBC)
colon cancer (CC)
natural killer/T-cell lymphoma (NKTL)
vitamin D receptor (VDR)
ovarian cancer stem cells (OCSCs)
androgen receptor (AR)
squamous cell lung cancer (SCLC)
hepatocellular carcinoma (HCC)
T-cell factor(TCF)
p53 wild-type (p53-wt)
nasopharyngeal carcinoma (NPC)
rhabdomyosarcoma (RMS)
mixed lineage leukemia (MLL)
Prostate cancer (PCa)
F-box protein 32 (FBXO32)
cell cycle-related kinase (CCRK)

Figure1

Silencing Confrontation: EZH2 versus MicroRNAs in Tumors

Table1

Table1. The Upstream Signal Modulators of EZH2 and PcG-mediating Silence in Tumors

Modulator	Organism/system	Mechanisms	Polycomb Target Loci	Effects	Ref.
BRCA1	Mouse ES cells;	BRCA1-binding region in EZH2 overlaps with HOTAIR-binding region	TCG	ES Cell Differentiation;	[101]
	Breast Cancer			Carcinogenesis	[100]
P53	Normal Fibroblast;	EZH2 modulates p53-wt cells by p21;	FBXO32, Chk1 p21 ^{WAF1}	Proliferation;	[106]
	Gastric Cancer;	EZH2 affects p53-deficient cell via Chk1		Antagonize Senescence;	[2]
	Thyroid Cancer			Regulate Cell Cycle	[15]
JAK/STAT	Bronchus	Activated pEZH2-Ser-21 causes PRC2 dissociation from chromatin to weaken H3K27me3 in nuclei.	VDR	Proliferation;	[51]
3	Epithelium; Colorectal Cancer			Metastasis	[53]
E2F/Rb	SCLC;	Hyperactivated EZH2 recurrently DNA level E2F/Rb disruption;	p21 ^{WAF1} , cyclinE, c-myc;	Proliferation;	[14]
	OCSC;	E2Fs transactivate and bind to PRC2 promoters;	CDK2; CDK4/6;		[56]
	Bladder Cancer;	Autoregulatory Feedback Loop (EZH2/miR-200c/E2F3);	Bim	Carcinogenesis ;	[88]
	PCa;	EZH2-CDK4/6-pRb-E2F1 Signal Loop		Repress Apoptosis;	[72]
	GBM;	Positive Epigenetic			
	HCC	Circuitry---CCRK/GSK-3β/β-catenin/TCF/E2F1/EZH2			[17]
MEK/ERK	Breast Cancer; PCa;	Enrichment of EZH2 and H3K27me3 on Target Promoters;	E-cadherin, Runx3; Elk;	Aggressiveness;	[23]
	Colon Cancer	EZH2 promoter occupancy by (JUN/FOS) AP-1components	ITGα2	Inhibit Anoikis	[18]
FOX					
Family	PCa;	FOXA1 inhibits EZH2 via its C-terminal histone binding motif;	p16 ^{INK4a}	Carcinogenesis;	[117]
FOXA1	Breast Cancer;	MELK-FOXM1-EZH2 axis;	-	Irradiation Resistance;	[46]
FOXM1	GSC;	Enrichment of EZH2 and H3K27me3 on FBXO32 Promoter;	FBXO32	Repress Apoptosis	[13]
FOXO1	RMS;	FOXP3 accelerates EZH2 Degradation by	Praja1	Mammosphere	[80]
FOXP3	Breast Cancer	polyubiquitination–proteasome pathway;		Formation,	
		Histone acetylation and H3K27me3 at FOXC1 promoter	FOXC1	Proliferation,	[16]
--				Migration;	
				Clonogenicity	

Table2

Table 2 Targets Activated by EZH2 in an Epigenetic-independent Manner

Targets	Organism/system	Mechanism	Effects	Ref.
STAT3	GBM	pS21-EZH2 by AKT signaling facilitates STAT3 methylation and enhances STAT3 activity.	GBM progression, GSC self-renewal	[19]
NF-κB	ER-negative Breast Cancer	EZH2 forms a ternary complex with RelA and RelB to positively regulate a subset of NF-κB target genes by interdependent promoter occupancy.	Basal-like breast cancer progression	[46]
AR	CRPC	pS21-EZH2 by AKT signaling transcriptionally activates AR via methyltransferase domain	Tumor progression	[104]
Wnt	CC	PAF-EZH2-βcatenin transcriptional complex to enhance Wnt target gene transactivation.	Initiate intestinal carcinogenesis	[36]
NOTCH	TNBC	EZH2 positively regulates NOTCH1 transcriptional activity and signaling	Accelerate breast cancer initiation and growth	[26]
	NKTL	EZH2 directly promotes cyclinD1 transcription by binding to its promoter	Promote proliferation	[106]