Chapter 10
Enhancer of Zeste Homology 2 (Ezh2), an Epigenetic Regulator: A Possibility for Prostate Cancer Treatment

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Abbreviations

ATRA	All Trans retinoic form
CRPC	Castration-resistance prostate cancer
DAB2IP	Disabled homology 2-interaction protein
DNMT	DNA methyltransferase
DZNep	3Deanzeaneplanocin-A
EED	Embryonic ectoderm development
HDAC	Histone deacetylase
miRNA	microRNA
MMP	Matrix metalloproteinase
PCAT	Prostate cancer-associated noncoding RNA transcript
PcG	Polycomb group
PI3K	Phosphoinositide-3-kinase
PRC	Polycomb repressive complex
RKIP	Raf-1 kinase inhibitors protein
SAHA	Suberoylanilide hydroxamic acid
SUZ12	Suppressor of Zeta 12

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10.1 Introduction

Enhancer of zeste homology 2 (Ezh2) is a histone-lysine *N*-methyltransferase enzyme. It is regulated by *Ezh2* gene that is involved in DNA methylation, which ultimately leads to the suppression of transcription. Ezh2 catalyzes the addition of methyl (–CH3) groups to histone H3 at lysine 27 with the help of a cofactor *S*-adenosyl-L-methionine (SAM). The methylation in Ezh2 induces heterochromatization, which is responsible for the remodeling of chromatin thereby silencing gene function(s). Further, Ezh2 is the functional catalytic core protein of Polycomb Repressor Complex 2 (PRC2), which is essential for normal embryonic development through the epigenetic modifications. Ezh2 is also responsible for PRC2 methylation and catalyzes the trimethylation of histone3 lysine27 (H3K27). Ezh2 induces silencing of target genes, which are involved in suppressing tumor growth and cellular homeostasis [1–7]. These target genes are associated with cellular proliferation, invasiveness, senescence, angiogenesis and metastasis of cancer development [8]. Studies suggest that over expression/dysregulation of Ezh2 could be an important factor for tumor development and progression [2–7]. Therefore, the prevention of Ezh2 over expression is a promising strategy for effective therapeutic interventions in many aggressive cancers including prostate cancer [2–7].

Studies have established the location of the *Ezh2* gene on chromosome 21q22.2 in almost all mammals [9]. However, later findings presented by Cardoso and his colleagues found the location of *Ezh2* on chromosome number 7q35 and the sequence isolated from chromosome 21 corresponded to a pseudo gene [10]. Structurally, the human *Ezh2* gene contains 20 exons, which encode 746 amino acid residues respectively. Additionally, human *Ezh2* gene has evolutionarily conserved sequences such as domain-1, domain-2 and a cysteine-rich amino acid stretch that leads to the carboxy-terminal SET domain. The SET domain is directly associated with the activation of histone methyltransferases (HMTase). The removal of a single amino acid (Tyr641) in SET domain significantly reduces histone methyltransferase (HMTase) activity *in vitro* [11–13]. However, studies on human PRC2 demonstrated that optimal HMTase activity requires Ezh2, Embryonic Ectoderm Development (EED), and SUZ12 [11]. Biochemically, EED is essential to the enzymatic activity of Ezh2 which organizes the EED-Ezh2 complex. The formation of this important protein complex typically leads to increased activity and functionality of PRC2's HMTase [12, 13]. The WD40 (Trp-Asp) domain of EED is crucial to the proper funcition of the EED-Ezh2 complex; however, point mutations in WD40 domain showed interrupted interaction between EED and Ezh2 [11, 14]. Studies show that PRC2-induced activation of H3K27me3 plays an important role in cell proliferation, senescence and carcinogenesis [8, 15, 16]. Therefore, targeting over expression of EZh2 in cancer cells will certainly prove successful in paving the way to novel epigenetic drug discoveries and presenting as a viable therapeutic regimen in the treatment of cancer.

Ezh2 resides in both the nucleus and the cytoplasm of the cell. It produces nuclear localization signals (NLS) that activate downstream signaling of F-actin polymerization, which may eliminate the possibility of Ezh2-mediated prostate cancer progression and invasion [17]. A past study showed that increased expression of Ezh2 was observed in malignant prostate cancer tissues as compared to normal prostate tissues, which suggest that over expression of Ezh2 is associated with prostate cancer development and progression [18]. Therefore, inhibition of Ezh2 can be achieved using pharmacological inhibitors such as 16-hydroxycleroda-3, 13-dien-15, 16-olide (PL3) and small moles DZNep. Besides these pharmacological strategies, silencing of gene function using microRNA has gained great attention for further research in this direction. The use of microRNAs, specifically microRNA-101 is crucial to this avenue of research [16]. Several studies suggest that the expression of microRNA-101 decreases during cancer progression; however, in some cases there exists an inverse relationship between microRNA-101 and Ezh2 expression [19]. Anti-parallel expression profiles have been observed between microRNA-101 and Ezh2 further cementing such studies [16]. Furthermore, knockdown of microRNA-101 in cancer may lead to over expression of Ezh2 and deregulation of epigenetic pathways, thus resulting in cancer progression [3, 20–22]. Interestingly, it was found that AKT phosphorylates Ezh2, which also increases the likelihood of carcinogenesis [23, 24]. In addition, Akt-dependent ser-21 phosphorylation was found in breast cancer cells after treatment with IGF-1 or estrogen. Therefore, it is believed that phosphorylation results in the weak interaction between Ezh2 and other PRC2 subunits, which has shown decrease methylation of H3K27. Furthermore, phosphorylation results in activation of JNK-STAT3-AKT signaling that leads to trimethylation of histone H3 lysine 27 (H3K27me3) [25, 26].

10.2 Role of Ezh2 in Prostate Cancer

Previous studies suggest that Ezh2 is highly expressed in a wide range of malignancies, including: cancers of prostate, colon, bladder, lung, breast, pancreatic cancer as well as lymphomas and sarcomas as compared to normal tissue/cells [1, 8, 19, 20, 27–51]. Increased expression of Ezh2 is often correlated with an advanced state of cancer progression and poor survivability [8]. Cells that express more Ezh2 demonstrate a high rate of cellular proliferation and oncogenic properties [4, 12, 18, 28, 52–56]. Li et al. showed over expression of Ezh2 in mammary epithelial cells of the tumorigenic mouse model results in the development of an epithelial hyperplasia phenotype [57]. Furthermore, mutations in Ezh2 result in B cell lymphoma, follicular lymphoma, myelodysplasic and myelo-proliferative disorders [1, 2, 21, 49–51, 58–62].

It has been shown that prostate cancer patients showed enhanced expression of Ezh2 with increased cellular proliferation, invasiveness, and metastasis of cancer cells [63]. In cases of human prostate cancer, increased expression of Ezh2 results in extra prostatic extension, positive surgical margins and a recurrence of prostatic

specific antigens [63]. Opposite to this, knockdown of endogenous Ezh2 using siRNA showed reduce cellular proliferation, differentiation and invasion in prostate cancer patients [18]. Additionally, Ezh2 induced prostate cancer cell invasion and metastasis by repressing RKIP (Raf-1 kinase inhibitor protein), which is a metastasis suppressor gene [15]. Therefore, it may be plausible to assume that metastasis is the outcome of Ezh2 over expression. In addition, studies indicate that Ezh2 plays a vital role in the regulation and suppression of the expression of metalloproteinase and the inhibitors of metalopeptidases-2 and -3 in prostate cancer cells [64]. However, Ezh2 showed 11 genetic variations in prostate cancer, which are not accountable for the linkage of 7q to prostate cancer [65]. The individual variation did not show significant differences in the allele frequencies between the experimental and controls. Although, one haplotype may be higher in frequency than those of another haplotype which showed significantly higher levels in low grade tumors and vice versa in high grade tumors [65]. Therefore, the mechanism of Ezh2 over expression in prostate cancer is not well understood and requires further investigation. In castration-resistance prostate cancer cells, Ezh2 may be a transcriptional co-activator of androgen receptor instead of a transcriptional repressor of PCR2 [66]. Moreover, the phosphatidylinositol 3-kinase-Akt pathway mediated by Ezh2 phosphorylation at ser-21 could act as transcriptional activator [36].

PCR2 maintains cellular homeostasis during chromatin remodeling [67]. In mammals, there are two types of polycomb group complexes, PCR1 and PCR2. The PCR2 complex consists of four core components: Ezh2, Suppressor of Zeta 12 (SUZ12), EED, and retinoblastoma associated protein 46/48 [13]. Ezh2 with SET domain forms a complex, which catalyzes H3K27me3 and is involved in the silencing of tumor suppressor genes such as Disabled homology2-interaction protein (DAB2IP) (Fig. 10.1) [75].

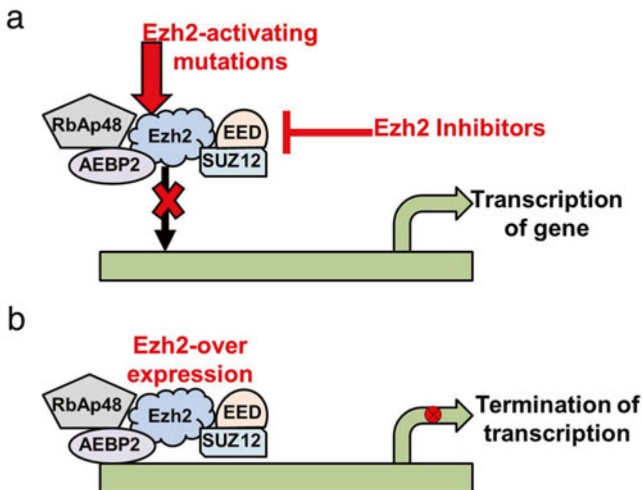

Fig. 10.1 Role of Ezh2 in tumor progression. (**a**) The mutation in Ezh2 activates gene transcription. (**b**) Over expression of Ezh2 results in trimethylation of H3K27 to terminate gene transcription, especially the inhibition of tumor suppressors [53, 58, 68–74]

It has been shown that Ezh2 and STAT3 (signal transducer and activator of transcription 3) affect self-renewal, tumorigenicity, chemo-resistance, pluropotency, and proliferation in cancer cells [22, 76, 77]. Akt-dependent Ezh2 phosphorylation at ser21 was also observed in breast cancer cells treated with insulin-like growth factors 1 or estrogen [23]. Furthermore, JNK-STAT3 and JNK-STAT3-Akt signaling induces phosphorylation of Ezh2 [24]. Transcriptional repression of c-Myc by Ezh2 may be a novel mechanism for the treatment of gliomablastoma and stem cells maintenance [78]. In addition, phosphorylation of Ezh2 induces H3K29 trimethylation and target gene silencing. Cyclin-dependent kinase (CDK) is a family of protein kinases, which are involved in cell cycle regulation. CDKs have also been found to be involved in gene transcription, mRNA processing, and differentiation. Mutations alter the functions of CDKs, which may result in uncontrolled cell division and progression of cancer. In addition, CDKs also induced Ezh2 over expression by phosphorylating Thr350 [79]. CDK1/2 harbors and phosphorylates Thr350 of Ezh2; however, Ezh2 has a mutation at a site of an amino acid located within Thr350 (Thr350A) that silences CDK1/2 thus decreasing the expression of Ezh2. Therefore, CDKs regulates the expression of Ezh2 and cancer cell proliferation. Further, chromatin immune-precipitation shows that inhibition of Ezh2 decreased H3K27me3 levels in the promoter of HOXA9 and DAB2IP, which are downstream targets of Ezh2 (Table 10.1) [79]. In the mammalian cell system, phosphorylation of Ezh2 results in altered biological functions by suppressing the transcription of other genes [1, 13, 51, 91]. Furthermore, a large number of genes that were transcriptionally repressed by CDK1/2 restored wild type Ezh2 expression [16]. It is suggested that the phosphorylation of Ezh2 is critical to ensuring the proper regulation of targeted genes [1, 13, 56, 91–93]. In addition, Ezh2 is frequently over expressed in several types of cancers, such as advanced human prostate [18, 65, 76, 94, 95]. It has been shown that thr350 phosphorylation is essential for the tumorigenic function of Ezh2 in prostate cancer cells. However, dephosphorylation of Ezh2 at the site of Thr350 increases its tumor suppressor gene DAB2IP expression in LNCaP cells, while abnormal activation of CDK1/2 contributes to the aggressive phenotypes

Table 10.1 List of Ezh2 targets in prostate cancer

Ezh2 targets in prostate cancer		
Gene	Roles in pathways inhibition	Role in carcinogenic
DAB2IP	NF-kB/Ras pathways	Invasion, proliferation and transformation [75, 80, 81]
PCAT-1	Transcription	Proliferation [82–84]
TIMP2/3	ECM deletion	Invasion [85]
RKIP	Raf and NF-kB pathways	Invasion [15]
PSP94	MPM secretion	Invasion [86]
CDH1	Cell adhesion	Invasion [87]
SLIT2	Chemorepellent protein	Proliferation and invasion [88, 89]
ADRB2	Anderenegic signaling	Invasion and transformation [90]

typically found in tumors. This is accomplished via phosphorylation and the subsequent tumorigenic/gene silencing mechanisms of Ezh2 (Table 10.1) [79, 96, 97]. Therefore, dephosphorylation of Ezh2 at Thr350 may serve as a viable therapeutic target to prevent the tumor inducing functions of Ezh2 in human prostate cancer [79, 98] (Table 10.1).

10.3 Ezh2: Prostate Cancer Therapy

The main difference between genetic and epigenetic mechanisms is the degree of reversibility of each respective process [7, 91, 93, 94, 99, 100]. Genetic changes that alter nucleotide sequences are difficult to restore and affect gene product(s). Conversely, epigenetic modifications have shown the ability to be reversed without disrupting the DNA sequence. Therefore, it is possible that Ezh2 can be targeted using several inhibitors against the enzymes, which are directly involved in the epigenetic modification of Ezh2 [91, 93, 100–103]. This may prove to be a novel therapeutic strategy for prostate cancer treatment and tumor elimination. A number of lead treatment studies are in the process to develop an effective pharmacological agent.

Keeping these facts in view, we analyzed effective molecular targets currently being used in prostate cancer treatment therapies such as 16-hydroxycleroda-3, 13-dien-15, 16-olide (PL3) and DZNep. It was demonstrated that small molecules like 3-deazaneplanocin-A (DZNep) can be used in inhibiting *S-adenosyl-l* -homocysteine (SAH) hydrolase, a cofactor, essential for Ezh2-dependent methylation and synergistically enhanced the anti-proliferative activity [104]. Furthermore, DZNep deplete PRC2 complex proteins (Ezh2) and inhibits H3K27me3; therefore, DZNep may be the first targeting compound in this area [105]. Furthermore, *in vivo* studies suggest that DZNep induces apoptosis in cancer cells without affecting normal cells [95, 105]. Therefore, treatment with DZNep not only showed anti-proliferative and anti-cancer activities but also blocked migration and invasion of prostate cancer cells [95, 106, 107]. As a result, DZNep has gained attention from cancer researchers and is being used as a chemotherapeutic agent against several types of human cancers. DZNep has a short half-life (1.10 h); therefore, the liposome method was used to improve the pharmacokinetics of DZNep [40, 108–110]. DZNep acts on enzymes H3K27me3 and H3K4me3, which stimulate gene transcription and inhibits histone methylation resulting in poor histone demarcation [106, 107]. DZNep can be implemented as a potential therapeutic agent due to its ability to suppress many cancers; however, it also has some limitations that need to be investigated in further detail.

The emerging approach to target Ezh2 over expression is to block HDAC and DNMTs activity. Inhibition of HDAC and DNMTs, which results in Ezh2-mediated epigenetic gene silencing, is depicted in Fig. 10.2. Inhibition of the enzymes can be achieved by suberoylamilide hydroxamic acid (SAHA) and desi-peptide (Romidespin) which are FDA approved inhibitors of enzymes HDAC and DNMTs

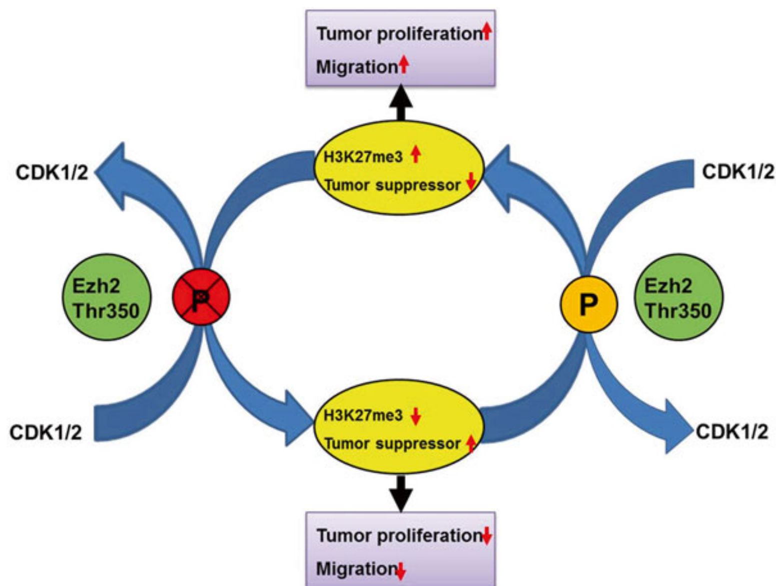

Fig. 10.2 Role of CDK1/2 in Ezh2 over expression and carcinogenesis. CDK1/2 induces Ezh2 phosphorylation at Thr350, which results in decreased expression of tumor suppressor genes by enhancing H3K27me3 at the promoters of Ezh2 targeted genes. However, inhibition of Ezh2 phosphorylation by of CDK1/2 or Thr350 of Ezh2 inhibitors suppressed cancer cell proliferation and migration [53, 58, 68–74]

[111]. SAHA directly targets the catalytic site of the enzymes HDAC and inhibits its activation while Romidespin, a pro-drug binds to zinc (Zn) present in HDAC's active site resulting in diminished catalytic activity [99, 112]. Therefore, SAHA and Romidepsin have been considered as potential inhibitors of prostate cancer growth and proliferation [98, 113, 114]. These enzymes are considered to be among the most effective emerging therapy strategies against prostate cancer [19, 20, 51, 106, 115, 116]. 5aza-2′-deoxycytodine (5aza), a nucleotide analogue to be a potent inducer of apoptosis in prostate cancer cells. Although, the specific mechanism remains to be elucidated [117, 118]. DZNep, HDAC, and DNMT inhibitors have number of limitations and serious concerns in their clinical applications (side effects).

Small molecules can inhibit the enzymatic activity of Ezh2 by blocking its phosphorylation [55, 72, 110]. Previous studies shows that the formulated drug 3,3′-diindolylmethan is able to inhibit Ezh2 over expression [21, 52, 55, 119–121]. In fact, prostate cancer patients treated with BR-DIM in phase-II clinical trials showed increase expression of let-7; however, Ezh2 expression was diminished significantly [21, 52, 55, 119–121]. Other molecules such as, 16-hydroxycleroda-3, 13dien-15, 16-olide (PL3), which is a naturally isolated compound from the bark of polyathialongifolia has shown great promise in therapeutic applications against prostate cancer [18, 22, 54, 63, 65, 84, 98, 122]. PL3 inhibited histone modifying enzymes

including two PRC2 components, Ezh2, and SUZ12 [54, 79, 113, 114, 121–124]. PL3 induced the reactivation of genes, which were repressed by PRC2 and induced apoptosis in K562 cells. Further studies show that PL3 also induced apoptosis in human leukemia cells by suppressing the expression of Ezh2 and SUZ12 which further leads to the reactivation of the PRC2 tumor suppressor gene [56, 92, 115, 116, 123–126]. These findings reveal the link between the anti-inflammatory and cytotoxic effects of PL3 against breast and hepatocellular carcinomas, and provide new insight into the modulation of Ezh2 over expression in prostate cancer [127]. Studies indicate that all trans-retinoic acid (ATRA), a potent anticancer agent, induces apoptosis in leukemia, gastric cancer, and prostate cancer by inhibiting Ezh2 and DNMT3B-induced hypermethylation of HOXB13 [54, 128–131]. However, Ezh2 recruits DNMT3B to the promoter regions of specific gene loci and induces DNA methylation [132]. In addition, ATRA treatment showed androgen-independent cell growth arrest in prostate cancer DU145 cells by blocking Ezh2 and DNMT3B methylation resulting in the subsequent reactivation of HOXB13 [54].

In order to analyze more therapeutic targets against Ezh2 over expression, we moved towards the agents that can act as competitive inhibitors against methyl transferase enzymes. For example, GSK-A acts as a competitive inhibitor against both Ezh2 and methyltransferase. GSK-A displaces the endogenous substrate for the enzymes, which results in the marked reduction of H3K27 trimethylation [5, 7, 58, 59, 133, 134]. Furthermore, *in vivo* studies suggest that a slightly different compound, GSK126, inhibits Ezh2 in a highly specific manner as compared to GSK-A [21, 59, 135, 136]. However, in lymphoma models, mutations in Ezh2 lead to enhance activity of GSK126, which reduces the activity of H3K27me3 and PRC2 target genes resulting in impeded growth and proliferation of cancer cells [137, 138]. Keeping these facts in view, it may be possible to assume that GSK compounds hold great therapeutic potential by targeting Ezh2 in prostate cancer but further investigations are needed to explore the underlying mechanisms.

Taken together, Ezh2 inhibitors and agents that block HDAC and DNMT may work as potential anti-cancer agents and could be used in combination therapy to inhibit prostate cancer growth. Therefore, these therapeutic strategies may effectively reduce tumorigenesis/carcinogenesis without affecting the normal cells and reduce disease recurrence (Fig. 10.3).

10.4 Conclusion and Future Perspective

Previous studies have shown that expression of Ezh2 increase many times over during cancer progression and development [18, 68, 77]. In this chapter, we reviewed mechanism of Ezh2 regulation including over expression of Ezh2 can be regulated by various mechanisms such as the inhibition of , histone modification and chromosomal remodeling [40, 111, 134]. Therefore, it may be safe to assume that the modulation of Ezh2 regulatory mechanisms could highly impact Ezh2 activity and subsequently be therapeutically effective in many cancers. However, several inhibi-

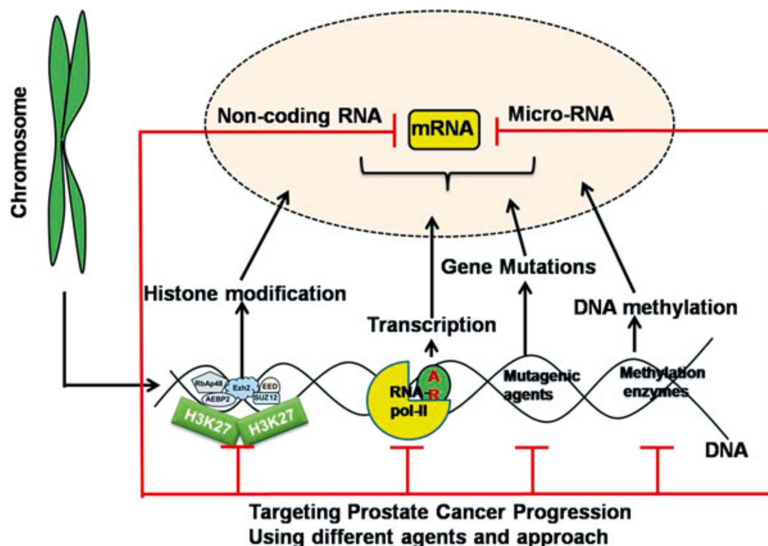

Fig. 10.3 A schematic representation of the regulation of prostate cancer progression using different regulatory mechanism(s) [15, 21, 40, 52, 55, 59, 64, 66, 77, 110, 115, 120, 121, 126, 135, 136, 139]

tors of enzymes like HDAC, DNMTs and Ezh2 are being used in clinical trials and have shown great potential in inhibiting cancer growth and metastasis [15, 41, 93, 140]. Evidence regarding these inhibitors suggests that the molecules could potentially act in suppressing Ezh2 over expression and prevents the recurrence of prostate cancer [57, 58, 68, 69, 73]. In addition, the use of DZNep, HDAC and DNMT inhibitors result in decreased expression of Ezh2, which further leads to inhibition of cancer cell proliferation [106, 107]. Therefore, use of these inhibitors may disable Ezh2-mediated tumorigenesis. More interestingly, inhibition of CDK1/2 also results in down regulation of the tumor suppressor gene DAB2IP, which plays an important role in inhibiting cancer growth by phosphorylating Ezh2 at Thr350 [79, 125, 141]. miRNA inhibits invasiveness and proliferation of cancer cells *in vitro* in a similar fashion like knocking down Ezh2 over expression [96, 116, 126]. Therefore, it will be interesting to test whether miR-101 treatment can be therapeutically effective *in vivo* as microRNA inhibition of overexpression has been exploited in preclinical and clinical trials as a potential cancer treatment regimen [7, 96, 116, 126]. Interestingly, other, studies show that the prevention of Ezh2 over expression in mouse adult stem cells could produce small imperfections in normal organ development or function [60–62, 134, 142–144]. In brief, the administration of Ezh2 inhibitors using specific delivery systems may be necessary to avoid adverse side effects in normal cells [92, 96, 111, 114, 118, 136]. Therefore, better characterization of blocking Ezh2-induced tumorigenesis targets/signaling pathways can be more practical and effective as compared to previously described techniques. Understanding the regulatory mechanisms and the function of *Ezh2* gene targets will help to expedite the development of novel cancer therapeutic regimens.

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