Update of research on the role of EZH2 in cancer progression

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Abstract: Accumulating evidence shows that enhancer of zeste homolog 2 (EZH2) is upregulated in a broad range of cancer types, such as breast cancer, prostate cancer, ovarian cancer, and colon cancer. Therefore, inhibiting EZH2 expression may be a promising strategy for anticancer therapy. This review focuses on the current understanding of the mechanisms underlying EZH2 regulation that are involved in cancer progression. Also, it introduces two EZH2 inhibitors that target EZH2 and could be potentially applied in the treatment of cancer in the future.

Keywords: EZH2, PRC2, cancer

Introduction
Enhancer of zeste homolog 2 (EZH2) encodes a histone methyltransferase, which is the catalytic core protein of the polycomb repressor complex 2 (PRC2).1,2 PRC2 is well known for initiating target gene silencing by promoting H3K27 trimethylation, which is catalyzed by EZH2. Several articles implicated that the EZH2 is involved in the cell proliferation, invasion, apoptosis, angiogenesis, and metastasis of cancer progression.

Underlying mechanism of EZH2 in cancer progression
Polycomb group proteins maintain the gene expression pattern of different cells that is set during early development by modifying chromatin structure.3 In mammals, there are two main polycomb group complexes, PRC1 and PRC2. The PRC2 complex mainly consists of four core components: EZH2, suppressor of zeste 12 homolog (SUZ12), embryonic ectoderm development protein (EED), and retinoblastoma-associated protein 46/48. EZH2 via the SET domain catalyzes H3K27 methylation, which is catalyzed by EZH2. Several articles implicated that the EZH2 is involved in the cell proliferation, invasion, apoptosis, angiogenesis, and metastasis of cancer progression.

Cancer stem cells are a subgroup of cancer cells with several features: unlimited self-renewal potential, tumorigenicity, and chemoresistance.5 Several papers showed that signal transducer and activator of transcription 3 (STAT3) and EZH2 are involved in the self-renewal, pluripotency, and proliferation of cancer stem cells.6 Akt-dependent Ser21 phosphorylation of EZH2 has been reported in breast cancer cells treated with insulin-like growth factor 1 or estrogen.7 Furthermore, Chen et al confirmed the c-Jun N-terminal kinase (JNK) regulation of STAT3 and link the JNK–STAT3–Akt signaling axis to the phosphorylation of EZH2.8 Suva et al provided evidence that direct downregulated transcriptional regulation of c-Myc by EZH2 may constitute a novel mechanism underlying glioblastoma cancer stem cell maintenance.9

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Xu et al discovered that in the castration-resistant prostate there is another mechanism for EZH2 in prostate cancer. The linkage of 7q to aggressive prostate cancer. Genetic variations of the EZH2 gene are not responsible for there are eleven genetic variations in EZH2 in prostate cancer, lopetidase inhibitor 3 in prostate cancer cells. Their research provided another promising approach for the treatment of BRCA1-deficient breast cancers. They discovered that DZNep promotes an increase of Cdc25C, an essential player for G2/M checkpoint control. Puppe et al observed increased EZH2 protein levels in human BRCA1-deficient tumor sections compared with other breast tumors. Furthermore, they used the EZH2 inhibitor 3-deazaneplanocin (DZNep) to treat the BRCA1-deficient cancer cell and BRCA1-positive cancer cells. They discovered that DZNep showed remarkable selectivity in inhibiting BRCA1-deficient tumor cells compared with BRCA1-proficient tumor cells. Their research provided another promising approach for the treatment of BRCA1-mutated breast cancers.

Besides the transcript repressor, EZH2 activation could switch to an activator via two different ways. In luminal-like estrogen receptor-positive cells, EZH2 overexpression can lead to an interaction with the Wnt signaling pathway, leading to the activation of c-Myc and cyclin D1. In basal-like,
estrogen receptor-negative cells, EZH2 activates nuclear factor-xB target genes by formation of a ternary complex with the nuclear factor-xB components RelA and RelB.\(^3\)

**EZH2 in ovarian cancer**

Several authors have indicated that EZH2 is involved with invasion and metastasis in ovarian carcinoma. Rao et al found that high expression of EZH2 was found in none of the normal ovaries, in 3% of the cystadenomas, in 23% of the borderline tumors, and in 50% of the ovarian carcinomas.\(^24\)

Drug resistance is a major clinical obstacle for ovarian cancer therapy. Rizzo et al found that EZH2 played a key role in the maintenance of a drug-resistant, tumor-sustaining subpopulation of cells in ovarian cancers undergoing chemotherapy.\(^25\) Furthermore, ALDH1A1 – a putative marker for epithelial ovarian cancer stem cells – is found as a novel EZH2 target gene in epithelial ovarian cancer cells.\(^26\)

Lu et al identified EZH2 as a key regulator of tumor angiogenesis in ovarian cancer.\(^27\) In endothelial cells, vascular endothelial growth factor stimulation could lead to increased expression of E2F transcription factors, which directly mediate EZH2 levels. Then, EZH2 causes the silence of VASH1 – an anti-angiogenic gene – and subsequently increases angiogenesis.

**EZH2 in non-small-cell lung cancers**

Kikuchi et al analyzed the immunohistochemical assessment of 157 surgically resected non-small-cell lung cancers.\(^28\) They found that high EZH2 expression significantly correlated with non-adenocarcinoma histology, moderate and poor differentiation, advanced pathologic tumor classification, and high Ki-67 and cyclin E. Furthermore, Huqen et al found that positive EZH2 expression was associated significantly with cell proliferation, invasion, adhesion, and metastasis in several cancer types. Inhibitors of EZH2, including DZNep and GSK126, seem very promising anticancer agents to help reach the ultimate goal of cancer prevention and remission.

**Potential cancer therapy function**

It is known that EZH2 plays an important role in cancer development. EZH2 expression can be reduced with S-adenosylhomocysteine hydrolase inhibitor DZNep, which inhibits methyltransferases and induces degradation of EZH2, SUZ12, and EED as well as the associated H3K27me3. DZNep treatment was shown to result in reactivation of EZH2 repressed target genes, inhibited cell growth, and reduced tumor formation in various cancers.\(^31\)

For example, Fiskus et al found that treatment with DZNep induced p16, p21, p27, and F-box protein 32 while depleting cyclin E and homeobox A9 levels in the cultured human acute myeloid leukemia cells and in primary acute myeloid leukemia cells.\(^32\) Furthermore, combined with gemcitabine, DZNep synergistically enhanced the antiproliferative activity of gemcitabine, reduced the percentage of cells in the G2/M phase, and significantly increased apoptosis.\(^33\)

Recently, McCabe et al discovered a potent, highly selective, S-adenosylmethionine-competitive, small molecule inhibitor called GSK126. GSK126 can effectively inhibit the proliferation of EZH2 mutant diffuse large B-cell lymphoma cell lines and significantly inhibit the growth of EZH2 mutant diffuse large B-cell lymphoma xenografts in mice.\(^34\)

**Conclusion**

This review highlights that overexpression of EZH2 is correlated with cell proliferation, invasion, adhesion, and metastasis in several cancer types. Inhibitors of EZH2, including DZNep and GSK126, seem very promising anticancer agents to help reach the ultimate goal of cancer prevention and remission.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**


