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Review

EZH2 as a new therapeutic target in brain tumors: Molecular landscape, therapeutic targeting and future prospects

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ABSTRACT

Brain tumors are responsible for high mortality and morbidity worldwide. The brain tumor treatment depends on identification of molecular pathways involved in progression and malignancy. Enhancer of zeste homolog 2 (EZH2) has obtained much attention in recent years in field of cancer therapy due to its aberrant expression and capacity in modulating expression of genes by binding to their promoter and affecting methylation status. The present review focuses on EZH2 signaling in brain tumors including glioma, glioblastoma, astrocytoma, ependymomas, medulloblastoma and brain rhabdoid tumors. EZH2 signaling mainly participates in increasing proliferation and invasion of cancer cells. However, in medulloblastoma, EZH2 demonstrates tumor-suppressor activity. Furthermore, EZH2 can regulate response of brain tumors to chemotherapy and radiotherapy. Various molecular pathways can function as upstream mediators of EZH2 in brain tumors including lncRNAs and miRNAs. Owing to its enzymatic activity, EZH2 can bind to promoter of target genes to induce methylation and affects their expression. EZH2 can be considered as an independent prognostic factor in brain tumors that its upregulation provides undesirable prognosis. Both anti-tumor agents and gene therapies such as siRNA have been developed for targeting EZH2 in cancer therapy.

Abbreviations: BBB, blood-brain barrier; TMZ, temozolomide; EMT, epithelial-to-mesenchymal transition; MMPs, matrix metalloproteinases; Pc, polycomb; PcG, polycomb group; EZH, enhancer of zeste homolog; PCRs, polycomb repressive complexes; AR, androgen receptor; siRNA, small interfering RNA; shRNA, short hairpin RNA; PROTACs, proteolysis targeting chimeras; EED, embryonic ectoderm development; GBM, glioblastoma; PTEN, phosphtase and tensin homolog; STAT3, signal transducer and activator of transcription 3; lncRNAs, long non-coding RNAs; EGFR, epidermal growth factor receptor; NF-κB, nuclear factor-kappaB; BP, n-butylidenephthalide; TGF-β, transforming growth factor-beta; mTOR, mammalian target of rapamycin; mTORC1, mTOR complex 1; TERT, telomerase reverse transcriptase; ATM, ataxia-telangiectasi-mutated; ATRX, alpha thalassemia/mental retardation syndrome X-linked; PAR5, Prader Willi/Angelman region RNA 5; RISC, RNA-induced silencing complex; NUSAP1, nucleolar and spindle associated protein 1; MMP-9, matrix metalloproteinase-9; MELK, maternal embryonic leucine-zipper kinase; EVs, extracellular vesicles; SIK1, serine/threonine-protein kinase 1; EPNs, ependymomas.

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1. Introduction

The brain tumors are responsible for high mortality and morbidity around the world and due to their anatomic position and intrinsic factors, treatment of these cancers is challenging [1,2]. The treatment of brain tumors with pharmacological agents seems to be difficult, as blood-brain barrier (BBB) prevents entrance of drugs and therapeutic compounds to brain [3–5]. A number of conventional therapies are utilized in brain tumor treatment that surgery and radiotherapy are the most common treatment modalities. Surgery is not recommended due to injuries to normal tissue brain. Furthermore, surgery is not effective in advanced stages of brain tumors, when cancer cells have diffused to neighboring and distant tissues. Radiotherapy also has its own disadvantageous including side effects, normal cell necrosis and vasculopathy [1,2]. In addition, due to their aggressive behavior, brain tumors are able to develop resistance to radiotherapy [6–8]. Chemotherapy is another option in brain tumor therapy, and drug resistance, side effects and presence of BBB reduce potential of chemotherapy in brain tumor suppression [9–11]. For instance, temozolomide (TMZ) is the most well-known chemotherapeutic agent in treatment of glioblastoma (GBM), but its bioavailability is low in brain and about 20% of its concentration is observed in central nervous system [12]. Immunotherapy can be considered as a new and emerging therapy for brain tumors. However, delivery of immuno-regulatory agents to brain is a challenge and brain tumors have an intrinsic ability in achieving immuno-suppressor activities [13–17].

Therefore, novel strategies should be considered in treatment of brain tumors. Epigenetic alterations commonly occur in brain tumors to ensure their malignancy and progression [18]. The expression levels of genes undergo changes in brain tumors. For instance, STAT3 phosphorylation at tyrosine705 occurs to enhance brain tumor malignancy [19]. The activation of epithelial-to-mesenchymal transition (EMT) by EEF1A2 also occurs in brain tumors and mediates their metastasis [20]. The expression level of matrix metalloproteinases (MMPs) such as MMP-2 increases in brain tumors to promote their progression and invasion [21]. Hence, it is vital to identify and understand molecular landscapes responsible for brain tumor progression and then, gene therapy can be used for targeting them. Similar to other therapies, gene therapy has also problems in brain tumor therapy due to presence of BBB that can be addressed using nanostructures [22].

The present review focuses on EZH2 signaling and its role in progression of brain tumors. First, EZH2 signaling and its function in oncology are described and then, we specifically focus on EZH2 expression and mutation in various brain tumors based on pre-clinical and clinical studies. Future experiments can focus on developing gene therapy for targeting EZH2 signaling to effectively treat brain tumors.

2. EZH2 in oncology

It was found four decades ago that drosophila with mutation for Polycomb (Pc), has defects in body segmentation [23]. Further investigations revealed that Pc is responsible for encoding a negative regulator of homeotic genes involved in segmentation [24]. Then, a set of genes known as Polycomb group (PcG) were discovered that their mutation leads to generation of a phenotype similar to Pc, but it functions in mammalian cells [25]. PcG proteins are found in multiprotein complexes including Polycomb repressive complexes (PCRs) that have two distinct members, known as PCR1 and PCR2. PCRs are able to provide post-translational modification of proteins via affecting chromatin structure to induce gene silencing. The process of gene silencing by PCR2 is of interest. PCR2 has two main components including enhancer of zeste homolog 1 (EZH1) and EZH2 as enzymatic subunits that mediate trimethylation of Lys 27 of histone H3 (H3K57me3). The EZH2 should form complex with other noncatalytic proteins including EED, SUZ12 and RbAp48/46 to obtain its enzymatic activity. Besides, EZH2 has a domain at its COOH-terminus, known as SET that mediates its methyltransferase activity [26]. EZH2 has a unique structure and each of its domains are responsible for a certain role in cells. Overall, EZH2 has four distinct domains. The histone methyltransferase activity and its recognition are mediated by SET and CXC domains; the capacity of EZH2 in binding to DNA is provided by two SANT domains, leading to chromatin remodeling and transcriptional modulation [27,28]; ncRBD is responsible for providing the interaction of EZH2 with non-coding RNAs (ncRNAs) [29]. Fig. 1 demonstrates EZH2 signaling and related molecular pathways.

Increasing evidence demonstrates the role of EZH2 in cancer and its ability in regulating molecular landscapes that are responsible for tumor growth and aggressive behavior [30–35]. The EZH2 overexpression prevents apoptosis and autophagy in liver tumor to enhance progression. As a tumor-suppressor, microRNA (miRNA)– 638 down-regulates EZH2 expression to induce both apoptosis and autophagy in liver tumor cells [36]. Furthermore, LINC00152 upregulation enhances EZH2 expression to induce ZEB1 expression, resulting in EMT and oxaliplatin resistance of esophageal tumor cells [37]. In respect to tumor-promoting role of EZH2, its down-regulation can restrict tumor progression. In this way, HOTAIR/STAT3 axis stimulates EZH2 expression to diminish proapoptotic proteins and to enhance cell cycle progression [38]. It has been reported that colorectal tumor cells that are in III and IV stages, demonstrate high expression level of EZH2. Therefore, upregulation of EZH2 is vital for advanced stages of tumors [39]. EZH2 activation by upstream mediators can affect pathways that reduce tumor progression.

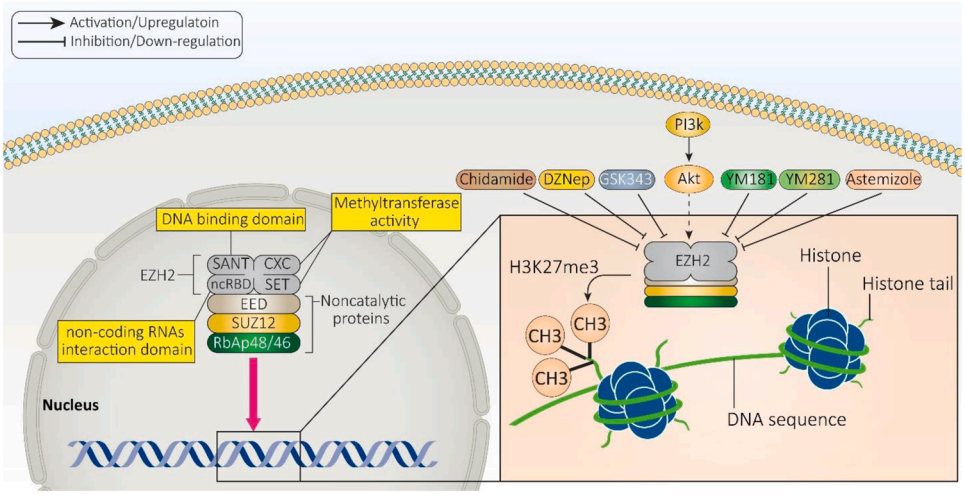

Fig. 1. A schematic representation of EZH2 signaling. The EZH2 has the capacity of binding to promoter of target genes to affect their expression levels. The H3K27me3 part of EZH2 contributes in regulating gene expression after binding to promoter. As it is shown, EZH2 has DNA-binding domain, a domain for interaction with non-coding RNAs, a part related to methyltransferase activity and non-catalytic proteins. In addition, EZH2 expression can be regulated by upstream mediators including PI3K/Akt and agents such as astemizole among others.

Table 1
The EZH2 expression profile in various tumors.

EZH2 expression	Cancer type	Remarks	Refs
Upregulation	Nasopharyngeal carcinoma	EZH2 induces EMT in increasing tumor metastasis miRNA-506 suppresses EMT-mediated metastasis via EZH2 down-regulation	[46]
Upregulation	Lung cancer	A combination of EZH2 inhibitors (GSK343 or DZNep) with EGFR-TKIs effectively prevent gefitinib resistance	[47]
Upregulation	Endometrial cancer	Down-regulation of TCF3 by EZH2 and DNMT3BEnhancing proliferation and survival rate of tumor cells	[48]
Upregulation	Breast cancer	Reducing expression level of EGR1 by EZH2 in a PRC2-dependent mannerEnhancing both proliferation and migration	[49]
Upregulation	Breast cancer	Overexpression of cytoplasmic EZH2Enhancing migratory ability of tumor cells	[50]
Not reported	Breast cancer	Reducing expression level of EZH2 by siRNA leads to an increase in FOXC1 expression, mediating drug resistance and unfavorable prognosis	[51]
Upregulation	Colorectal cancer	Cooperation of EZH2 and KDM2B in triggering PI3K/Akt signaling pathway, enhancing tumor stemness	[52]
Upregulation	Hepatocellular carcinoma	EZH2 enhances expression level of BMI by reducing miRNA-200c expression at post-transcriptional level	[53]
Upregulation	Papillary thyroid cancer	Overexpression of EZH2 in 83.3% of benign lesionsPositive association with tumor stage	[54]
Upregulation	Ovarian cancer	Upregulation of lncRNA SNHG7 by Sp1Enhancing EZH2 expression and mediating KLF2 expressionExerting tumor-promoting activity	[55]

For instance, LINP1 recruits EZH2 and its partners LSD1 and DNMT1 to diminish expression levels of KLF2 and PRSS8, enhancing cervical tumor growth and preventing apoptotic cell death [40]. To decrease expression of target gene, EZH2 utilizes its H3K27 trimethylation activity [41]. Besides, upregulation of EZH2 in tumor leads to undesirable prognosis and showing it as promising target [42]. EZH2 inhibitors can reduce tumor malignancy and sensitize tumor to cell death [43,44]. In addition to synthetic inhibitors, there have been efforts in developing phytochemicals with capacity in decreasing EZH2 expression. It has been reported that emodin prevents the interaction of androgen receptor (AR) and EZH2 to interfere with growth and invasion of hepatocellular tumor [45]. Table 1 provides an overview of EZH2 upregulation and down-regulation in different tumors.

3. EZH2 inhibitors: pharmacological and genetic interventions

As EZH2 signaling causes cancer progression and can interfere with anti-tumor immunity, attention has been directed towards its inhibition in effective cancer therapy. To date, various nucleic acid drugs have been applied in EZH2 regulation. The small interfering RNA (siRNA) is one of them that its co-delivery with etoposide using polymeric nanoparticles, exerts synergistic cancer therapy and sensitizes lung cancer cells to etoposide [56]. The delivery of EZH2-siRNA by iron nanostructures elevates sensitivity of ovarian cancer cells to cisplatin chemotherapy [57]. The short hairpin RNA (shRNA) is another genetic tool capable of reducing EZH2 expression in cancer therapy. The proliferation and metastasis rates of prostate cancer cells undergo down-regulation by EZH2-shRNA [58]. The HIF-1α is silenced epigenetically using EZH2-CRISPR/Cas9 and prevents immunosuppression in cancer [59]. Therefore, genetic tools are promising candidates in targeting EZH2 and regulating its expression profile for effective cancer therapy [60].

In addition to gene therapy, pharmacological compounds can be utilized for targeting EZH2 signaling in cancer therapy. The first report of EZH2 inhibitor returns to 2007 that Tan and colleagues discovered 3-deazaneplanocin A (DZNep) that reduces EZH2 expression and diminishes H3K27me3 levels to stimulate apoptosis in breast and colon tumor cells [61]. However, there were some concerns about specificity of DZNep in targeting EZH2, as this inhibitor indirectly affects EZH2 and its capacity in apoptosis induction is attributed to PRC2 pathway suppression [62]. Therefore, efforts were performed to discover other EZH2 inhibitors in disease treatment, particularly cancer therapy with high specificity. EPZ005687 was then used for targeting EZH2 and it targets EZH2 with more than 500-fold specificity compared to other protein methyltransferases [30]. EPZ005687 can reduce H3K27me3 levels in a concentration-dependent manner and shows cytotoxicity against various cancers including breast cancer, prostate cancer and lymphoma. The GSK126 is another EZH2 inhibitor that shows higher specificity compared to EPZ005687. Based on an experiment, GSK126 shows more than 1000 specificity for EZH2 compared to other protein methyltransferases [63,64]. Furthermore, in vivo application of GSK126 led to significant decrease in progression of lymphoma [64]. The first EZH2 inhibitor with oral bioavailability was UNC1999. However, it affects both EZH2 and EZH1, as specificity of UNC1999 is 10-fold higher for EZH2 compared to EZH1 that is not significant [65]. The down-regulation of EZH2 by salinomycin sensitizes colon cancer cells to apoptosis via upregulation of death receptor 4 (DR4) [66]. The proteolysis targeting chimeras (PROTACs) have been developed for degradation of EZH2 signaling and inducing anti-proliferative activity [67]. The YM181 and YM281 are other new emerging degraders of EZH2 that can effectively suppress lymphoma progression [68]. The embryonic ectoderm development (EED) promotes enzymatic activity of EZH2. Therefore, novel inhibitors for EED-EZH2 interaction have been developed [69,70]. The astemizole is able to suppress EED-EZH2 protein--protein interaction in triggering cell cycle arrest (G0/G1 phase) and impairing lymphoma growth [71]. The chidamide is suggested to reduce expression level of EZH2, leading to inhibition of Smo/Gli-1 axis. This EZH2 inhibitor impairs growth of leukemia cells and enhances their drug sensitivity [72]. A recent experiment has developed prodrugs based on pyridine-derived phosphate to suppress EZH2 signaling and to disrupt progression of leukemia in vivo [73]. To date, three catalytic EZH2 inhibitors are being utilized in phase I/II clinical trials including lirametostat, valemetostat and tazemetostat. After the approval of tazemetostat by FDA for application in treatment of sarcoma and lymphoma, this EZH2 inhibitor showed rise in market [74]. A phase I clinical trial used tazemetostat in lymphoma treatment and it was well-tolerated and showed high anti-tumor activity [75]. Recently, phase II clinical trial utilized tazemetostat for lymphoma and it again demonstrated high safety profile with meaningful results in cancer treatment [76]. Based on these findings, significant attempt should be made in introducing EZH2 inhibitors with high specificity and safety for treatment of cancer patients. Therefore, pharmacological inhibitors of EZH2 not only impair cancer progression, but also improve its drug sensitivity [77].

4. EZH2 in glioblastoma

Glioblastoma (GBM) is a primary brain tumor that patients with this malignant cancer have undesirable prognosis and low five-year survival rate of 5.5% [78]. The drug resistance, heterogeneity and infiltrative paradigms make it difficult to take complete resection of GBM [79]. GBM demonstrates abnormal methylation patterns and significant

changes occur in its genetic and epigenetic profiles [80,81]. Gene mutations play a significant role in GBM development and progression [82–85]. The management and treatment of GBM are of importance, as for instance, it causes 2500 deaths annually in UK [86]. Furthermore, up to 250,000 deaths worldwide result from tumors in central nervous system [87]. In addition to tumor resection, radiotherapy and chemotherapy are also commonly utilized in GBM therapy. However, no significant changes have been made in survival of GBM patients [2,88]. Therefore, novel strategies should be made in this case.

In order to ensure progression of GBM cells, EZH2 is modulated by various factors and it also affects different targets. The phosphatase and tensin homolog (PTEN) are tumor-suppressor undergoing mutations, deletions and down-regulation in carcinogenesis. PTEN negatively affects cancer progression via suppressing PI3K/Akt axis [89–91]. Recent experiments have confirmed anti-tumor activity of PTEN signaling in GBM. PTEN ubiquitylation by Smurf1 as oncogenic factor, leads to cancer proliferation and viability [92]. LINC00470 recruits DNMT3a via binding to MYC to induce PTEN methylation, resulting in GBM proliferation and migration [93]. Glycolysis is responsible for malignant and abnormal growth of GBM cells. PTEN signaling suppresses glycolysis via PGK1 down-regulation to impair GBM progression [94]. A recent experiment has revealed association between EZH2 and PTEN in GBM. In this case, E2F7 undergoes upregulation in GBM cells and enhances EZH2 expression by binding to its promoter. Then, H3K27me3 diminishes PTEN expression, resulting in PI3K/Akt signaling activation and subsequent increase in proliferation and migration of GBM cells [95]. In addition to PTEN, STAT3 plays a significant role in regulating progression of GBM cells. STAT3 enhances Bcl-2 expression to suppress apoptosis in GBM cells. As a tumor-suppressor, miRNA-519a reduces Bcl-2 expression via STAT3 signaling inhibition to promote GBM sensitivity to temozolomide [96]. STAT3 inhibition promotes survival of xenograft model of GBM [97]. Therefore, attention has been directed towards targeting STAT3 signaling in GBM and identification of molecular pathways involved in its regulation [98,99]. EZH2 phosphorylation occurs in GBM and it increases STAT3 expression via inducing its methylation. Then, STAT3 signaling exerts its oncogenic activity and promotes progression of GBM cells [100].

miRNAs are short ncRNAs with implication in various tumors [101–104]. miRNA-758-5p decreases expression level of ZBTB20 to impair proliferation and invasion of GBM cells [105]. Furthermore, upregulation of miRNA-221 ensures resistance of GBM cells to temozolomide and radiotherapy [106]. A recent experiment has focused on miRNA and EZH2 interaction in GBM. In this case, EZH2 binds to miRNA-9 and reduces its expression. Then, an increase occurs in expression level of CXCR4 to enhance proliferation and invasion rates of GBM cells [107]. On the other hand, miRNAs can regulate EZH2 signaling in GBM. miRNA-137 is considered as a tumor-promoting factor in GBM where down-regulation of miRNA-137 occurs in hypoxia to promote drug resistance and malignancy of GBM cells [108]. LncRNA HAS2-AS1 reduces miRNA-137 expression via sponging to ensure GBM progression [109]. EZH2 upregulation in GBM results in angiogenesis and increased proliferation. miRNA-137 impairs growth of GBM cells and suppresses angiogenesis via EZH2 down-regulation [110]. miRNA-101 is another tumor-suppressor factor that its expression shows down-regulation in GBM to pave the way for overexpression of EZH2, leading to growth, metastasis and angiogenesis [111]. A well-known pathway for reducing miRNA expression level by EZH2 is inducing methylation. DNMT1 and EZH2 jointly cooperate in methylation of miRNA-200b and miRNA-429 to diminish their expression and to elevate GBM progression [112].

In addition to miRNAs, lncRNAs are involved in modulating progression of tumor cells [113]. LncRNA XIST is suggested to promote growth and metastasis of GBM cells via down-regulating miRNA-448 and subsequent upregulation of ROCK1 [114]. Down-regulation of let-7 g-5p by lncRNA NEAT1 results in temozolomide resistance of GBM cells [115]. Most experiments demonstrate that lncRNAs regulate GBM progression via affecting miRNAs [116]. By sequestering away EZH2, G9a and Dnmts from promoter of HOXA1, lncRNA HOTAIRM1 increases growth and migration rates of GBM cells [117]. The epidermal growth factor receptor (EGFR) can function as upstream mediator in triggering lncRNA expression in GBM cells. For this purpose, EGFR stimulates STAT3 and nuclear factor-kappaB (NF-κB) pathway to enhance expression level of lncRNA NEAT1. Then, NEAT1 binds to EZH2 and induces trimethylation of H3K27, resulting in activation of Wnt/β-catenin axis and subsequent increase in GBM malignancy [118]. LncRNA H19 is a new emerging lncRNA in GBM where its overexpression mediates poor prognosis and increases proliferation, migration and angiogenesis [119–121]. In promoting GBM progression, lncRNA H19 recruits EZH2 to promoter of NKD1 to reduce its expression, resulting in an increase in tumorigenesis and viability of tumor cells [122]. In fact, EZH2 helps the lncRNAs to epigenetically affect their target genes in modulating GBM progression. LncRNA AGAP2-AS1 undergoes overexpression in GBM and is correlated with undesirable prognosis in cancer patients. TFPI2 functions as tumor-suppressor and reduces proliferation of GBM cells, while it induces apoptosis. Mechanistically, lncRNA AGAP2-AS1 enhances GBM progression via recruiting EZH2 and epigenetic silencing of TFPI2 [123]. Therefore, inhibition of lncRNA/EZH2 axis promotes apoptosis in GBM cells and suppresses their cell cycle progression [124,125]. Notably, expression level of lncRNAs can be modulated by other molecular pathways in GBM. SOX transcription factors are a well-known family in regulating cancer progression by affecting their growth, cell cycle progression, apoptosis and therapy response. Targeting and regulating expression level of SOX transcription factors are of importance in cancer therapy [126–130]. SOX9 is considered as tumor-promoting factor in GBM and its down-regulation by miRNA-30c and miRNA-101 leads to GBM progression disruption [131–133]. A recent experiment has shown that SOX9 is able to promote expression level of lncRNA PXN-AS1 in GBM. Then, overexpressed PXN-AS1 recruits EZH2 to promoter of DKK1 to induce its methylation and pave the way for GBM carcinogenesis [134].

In respect to the role of EZH2 in affecting GBM progression, it can be considered as a reliable biomarker in clinical studies. EZH2 is an oncogenic factor in GBM and its upregulation mediates undesirable prognosis [135]. The overexpression of EZH2 occurs in 69.2% of GBM cases and it is an independent prognostic factor [136]. The simultaneous suppression of EZH2 and PI3K pathways diminishes angiogenesis and metastasis in GBM and exerts synergistic impact [34]. EMT commonly occurs in GBM via reducing E-cadherin levels and enhancing vimentin and N-cadherin levels to promote metastasis and invasion [137–140]. The n-butylidenephthalide (BP) is a small molecule that reduces expression level of AXL. Then, EZH2 expression reduces and transforming growth factor-beta (TGF-β) signaling inhibition occurs, leading to reversing EMT and decreasing metastasis of GBM cells [141].

The mammalian target of rapamycin (mTOR) has two subunits including mTOR complex 1 (mTORC1) and mTORC2. The mTOR signaling is suggested to have a tumor-promoting role in GBM and its inhibition by anti-tumor compounds including arctigenin and galbanic acid significantly impairs GBM progression [142–144]. A recent experiment has revealed a novel signaling network in which mTORC1 and mTORC2 cooperate to regulate EZH2 and GBM progression. The mTORC1 involves in increasing expression level of EZH2, while mTORC2 controls S-adenosylmethionine generation in affecting histone methylation. The mTORC1 and mTORC2 jointly cooperate in triggering H3K27 trimethylation and enhancing GBM survival both in vitro and in vivo [145]. According to these tumor-promoting functions of EZH2, there have been efforts in targeting EZH2 in GBM therapy. A recent experiment designed two EZH2 inhibitors including UNC1999 and GSK343 to reduce activity of H3K27me3 in a time- and dose-dependent manner. These two small molecule inhibitors of EZH2 demonstrated higher anti-tumor activity compared to temozolomide and were able to suppress growth and EMT in GBM [146]. EZH2 can even regulate metabolism of GBM cells and their DNA damage responses. It has been

Table 2
EZH2 signaling as an oncogenic pathway in GBM.

Signaling network	Remarks	Refs
miRNA-138/EZH2/ CDK4/6/pRb-E2F1	Inhibiting progression of GBM Presence of feedback loopInducing cell cycle arrest at G1/S phaseSuppressing EZH2 and downstream targets by miRNA-138	[160]
–	Sustained inhibition of EZH2 signaling exerts an oncogenic role and changes cell fate, leading to increase in proliferation, DNA damage repair and stimulation of pluripotency network	[161]
EZH2/c-Myc	Preserving cancer stem cell features of GBM cellsOverexpression of c-Myc by EZH2	[162]
Akt/EZH2/STAT3	Induction of Akt/EZH2/STAT3 axis enhances cancer stem cell features in GBMMelatonin functions as tumor-suppressor and reduces GBM progression via suppressing EZH2	[163]
EZH2/EAF2/HIF-1α	Enhancing GBM progression via triggering glycolysisInducing metabolic reprogrammingDown-regulation of EAF2 by EZH2Upregulation of HIF-1α	[164]
EZH2/NOTCH1	Inducing NOTCH1 signaling by EZH2Melatonin suppresses cancer stem cell features in GBM via EZH2 down-regulation	[165]
E2F7/EZH2/PTEN/ Akt/mTOR	Overexpression of E2F7 in GBMAssociation with undesirable prognosis of GBM patientsOverexpression of EZH2 by E2F7 and subsequent PTEN signaling inhibitionTriggering Akt/mTOR signaling to increase GBM progression	[95]
HOTAIRM1/EZH2/ HOXA1	Increasing GBM progressionLncRNA HOTAIRM1 enhances HOXA1 expression via sequestering EZH2 away from its promoter	[117]
EZH2/STAT3	EZH2 phosphorylation in GBM enhances carcinogenesis and cancer stem cell like featuresActivation of STAT3 signaling by phosphorylated EZH2	[100]
EGFR/NEAT1/EZH2/ Wnt	Increased GBM progressionEGFR promotes expression of lncRNA NEAT1Inducing Wnt signaling via EZH2	[118]
EZH2/miRNA-9/ CXCR4	Down-regulation of miRNA-9 by EZH2Enhancing GBM progression via CXCR4 upregulation	[107]
HOTAIR/EZH2	Enhancing cancer proliferationMediating cell cycle progressionLncRNA HOTAIR exerts its oncogenic role via activating EZH2 signaling	[166]
EZH2/AXL	Upregulation of AXL by EZH2 to increase growth and metastasis of GBM cells	[167]
EZH2/miRNA-206/ Twist	Down-regulation of miRNA-206 by EZH2Enhancing progression and migration of GBM cells via Twist upregulation	[168]

reported that telomerase reverse transcriptase (TERT) functions as upstream mediator and enhances EZH2 expression in GBM. Ataxia-telangiectasia-mutated (ATM) phosphorylation undergoes a decrease by TERT/EZH2 axis and elevates lipid accumulation GBM [147]. Microglia involve in immune system and their transformation to M1 phenotype in tumor microenvironment can suppress GBM progression. In triggering immunosuppression, EZH2 prevents remodeling of microglia in GBM [148]. TMZ is a well-known chemotherapeutic agent in GBM therapy. However, GBM cells have obtained resistance to its anti-tumor activities [149,150]. It has been reported that EZH2 upregulation in GBM prevents TMZ-mediated apoptosis in GBM cells and inhibits cell cycle arrest [151]. Overall, studies highlight tumor-promoting and prognostic roles of EZH2 in GBM and its inhibition as a promising strategy in GBM therapy [152–159]. Table 2 summarizes EZH2 signaling and related molecular pathways in GBM progression. Fig. 2 shows the role of EZH2 signaling in GBM.

5. EZH2 in glioma

Similar to GBM, EZH2 signaling plays an oncogenic role in glioma and reducing its expression interferes with progression of tumor cells. Glioma stem cells enhance expression level of EZH2 to ensure their progression. Inhibiting EZH2 signaling impairs growth and progression of glioma stem cells [169]. HK27M-expressing glioma cells need PCR2 to promote their growth. The application of small molecule inhibitors of EZH2 impairs glioma progression via enhancing expression level of p16, as tumor-suppressor factor [170]. The TMZ resistance also occurs in glioma and EZH2 signaling involves in this condition. The mechanism for inducing TMZ resistance by EZH2 in glioma is based on DNA repair. Alpha thalassemia/mental retardation syndrome X-linked (ATRX) shows upregulation in glioma cells and mediates their resistance to TMZ chemotherapy. STAT5b/TET2 induces DNA methylation to enhance ATRX expression in glioma cells. Then, ARTX recruits EZH2 and mediates H3K27me3 enrichment to decrease FADD expression, leading to PARP1 stabilization and subsequent resistance in glioma cells that has been confirmed in vitro and in vivo (pre-clinical stage) [171]. A clinical study has shown that changes in EZH2 expression at protein and mRNA levels can provide condition for malignant transformation of glioma cells [172]. Hence, future experiments can be directed towards targeting EZH2 signaling in glioma therapy.

In previous section, we highlighted that non-coding RNAs participate in progression of brain tumors. Recent experiments also showed abnormal expression of miRNAs in glioma [173–175]. miRNA-935 functions as tumor-suppressor factor and reduces expression level of HIF-1α to suppress proliferation, invasion and angiogenesis of glioma cells [176]. miRNA-525-5p suppresses EMT mechanism to impair metastasis of glioma cells [177]. In contrast, there are tumor-promoting miRNAs such as miRNA-5188 that induce PI3K/Akt axis to enhance progression of glioma cells [178]. miRNA and EZH2 interaction determines progression of glioma cells. miRNA-32 undergoes down-regulation in glioma, while EZH2 demonstrates an increase in expression. Restoring miRNA-32 expression impairs migration and growth of glioma cells via binding to 3′-UTR of EZH2 and decreasing its expression [179]. miRNA/EZH2 axis can be considered as a prognostic factor in glioma patients. miRNA-524-5p and miRNA-324-5p function as tumor-suppressor factors in glioma. Increasing expression level of these miRNAs suppresses EZH2 signaling to diminish proliferation rate of glioma cells and enhance their sensitivity to temozolomide chemotherapy [180]. One of the interesting points is the transfer of miRNAs by exosomes to modulate cancer progression. Briefly, exosomes have an average particle size of 100 nm and can transport lipids, proteins and nucleic acids between cells [181–184]. A recent experiment has shown that exosomes derived from mesenchymal stem cells are able to deliver miRNA-133b to glioma cells. In this case, exosomal miRNA-133b reduces expression level of EZH2 to suppress Wnt/β-catenin axis, leading to a decrease in growth and invasion of glioma cells [185]. Therefore, inhibiting EZH2 hyperactivation by miRNAs can result in a significant decrease in progression of glioma cells [186]. On the other hand, EZH2 is able to regulate miRNA expression to affect tumor microenvironment of glioma cells. The macrophages are abundantly found in tumor microenvironment and they have two phenotypes including M1 and M2. Macrophages with M2 polarization have tumor-promoting role and can enhance proliferation and invasion of cancer cells [187–189]. EZH2 upregulation in glioma cells is in favor of miRNA-454-3p down-regulation to inhibit PTEN signaling, leading to M2 polarization of macrophages and enhancing glioma progression [190].

Similar to miRNAs, lncRNAs can regulate proliferation, invasion and therapy response of glioma cells via targeting various molecular pathways such as PTEN, Akt, miRNAs and p21 [191–196]. LncRNA Prader Willi/Angelman region RNA 5 (PAR5) undergoes down-regulation in glioma cells and tissues. Low expression of PAR5 determines reduced survival of patients with glioma. The anti-tumor activity of PAR5 in glioma is related to down-regulating EZH2 expression to suppress growth and metastasis [197]. In contrast, the expression level of lncRNA PVT1 undergoes overexpression in glioma cells. LncRNA PVT1 upregulation leads to undesirable prognosis in glioma and enhances growth and metastasis of cancer cells via EZH2 upregulation [198]. miRNA-137 is considered as a tumor-suppressor factor and reduces EZH2 expression

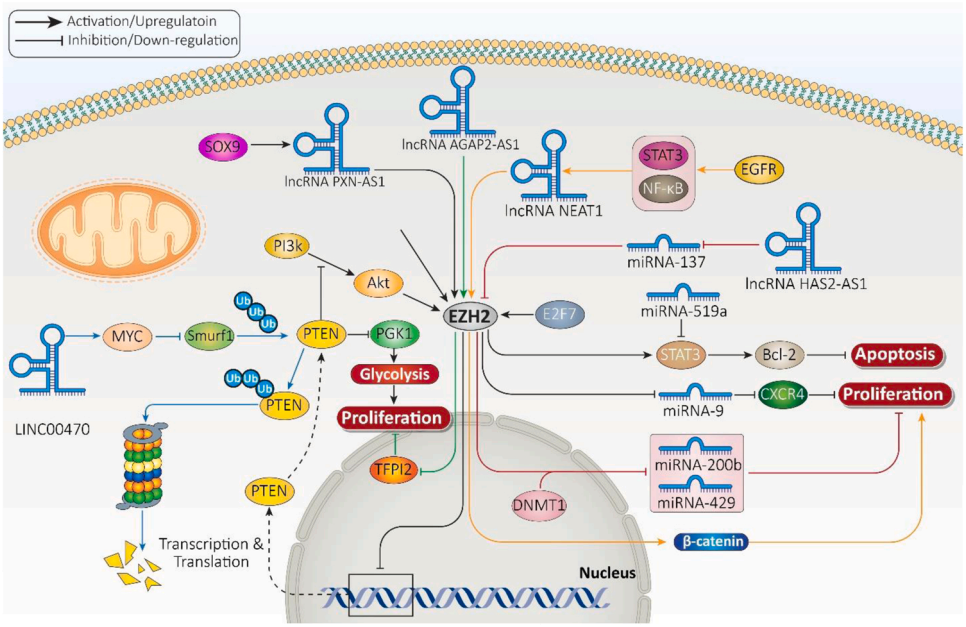

Fig. 2. The role of EZH2 signaling in GBM. The proliferation, apoptosis and glycolysis in GBM cells are tightly modulated by EZH2 signaling. The miRNAs and lncRNAs are the most-well known upstream mediators of EZH2 signaling in GBM. Furthermore, EZH2 has capacity in regulating miRNA expression such as miRNA-9, − 200b and − 429 to affect growth and apoptosis in GBM. Other molecule pathways such as STAT3 and TFPI2 are affected by EZH2 in GBM.

to impair progression of glioma cells. As upstream mediator, lncRNA HAS2-AS1 reduces miRNA-137 expression via sponging to induce EZH2 signaling, promoting glioma growth and metastasis [199]. The down-regulation of PTEN in glioma can be performed by lncRNAs, miRNAs and other upstream mediators [200–202]. EZH2 is able to bind to promoter of PTEN and diminish its expression. The upregulation of EZH2 in glioma occurs by lncRNA ANCR to suppress PTEN signaling and pave the way for apoptosis inhibition in glioma cells [203]. Similar to miRNAs, EZH2 modulates lncRNA expression by binding to its promoter. LncRNA MEG3 possesses a tumor-suppressor role in glioma and its expression demonstrates down-regulation, while EZH2 and miRNA-21-3p show an increase in expression. EZH2 binds to MEG3 promoter and enriches H3K27me3 to reduce MEG3 expression, resulting in miRNA-21-3p overexpression and increased glioma progression [204]. As more experiments are performed, more lncRNAs involved in regulating EZH2 expression are identified [205].

Both EZH2 and BET pathways are responsible for glioma progression and utilization of their inhibitors paves the way for suppressing cancer proliferation and inducing apoptosis [206]. EZH2 overexpression is associated with advanced stage in glioma and reduces overall survival of glioma patients. Therefore, it can be considered as an independent prognostic factor [207]. The overexpression of EZH2 occurs in 39.4% of glioma cases and suppressing EZH2 signaling diminishes capacity of glioma cells in colony formation and proliferation. The investigation of molecular pathways revealed that EZH2 down-regulation significantly reduces expression level of Akt and c-Myc as downstream targets to impair glioma progression [208]. It seems that EZH2 induces PIK3-K/Akt/mTOR axis to mediate resistance of glioma cells to apoptosis. As potent anti-tumor agent, PCI-24781 administration (0, 0.25, 0.5, 1, 2.5 and 5 μM) diminishes glioma proliferation and induces apoptosis via down-regulating EZH2 and subsequent suppression of PIK3K/Akt/mTOR axis [209].

The experiments obviously demonstrated that EZH2 is an independent prognostic factor in glioma and its inhibition by anti-tumor agents can suppress proliferation and invasion. Now, this question comes into mind that is there any possibility for EZH2 targeting using gene therapy? The answer is positive, but just one experiment has evaluated this possibility, showing that we still have a long way in targeting EZH2 by genetic tools in glioma therapy. Briefly, siRNA can be synthesized in laboratory and without undergoing DICER processing, it can be incorporated in RNA-induced silencing complex (RISC) to obtain its proper function. Then, it mediates mRNA cleavage and degradation to reduce expression of target gene. siRNAs have been extensively applied in cancer therapy in recent years and for promoting its potential in gene silencing, various nanoparticles have been developed for its targeted delivery to tumor site [22,210–213]. A recent experiment has developed self-assembled DMC nanoparticles for delivery of EZH2-siRNA. The nanostructures had particle size and zeta potential of 36.7 mV and 35.6 nm, respectively with high encapsulation efficiency (98%). The siRNA-loaded nanostructures effectively reduced expression level of siRNA to induce apoptosis and impair growth of glioma cells. The in vivo experiment also demonstrated potential of siRNA-loaded nanoparticles in retarding glioma growth and inducing apoptosis [214]. Hence, EZH2 is an oncogenic factor in glioma and its related molecular pathways should be highlighted in next experiments to provide new insight for developing novel therapeutics (Table 3) [215–217]. Fig. 3 provides a summary of EZH2 signaling in glioma.

6. EZH2 in astrocytoma

Astrocytoma is another brain tumor that its management and treatment should be considered to save lives of many people around the world. Astrocytoma is divided into two major kinds including low-grade astrocytoma and anaplastic astrocytoma. The low-grade astrocytoma demonstrates PDGF/PDGFR upregulation and up to 69% of astrocytoma cases show *TP53* gene mutation. These genetic alterations are also observed in anaplastic astrocytoma, but *TP53* gene mutation occurs in 53% of cases. One of the interesting points is that astrocytoma can develop into secondary GBM. Both low-grade and anaplastic astrocytoma can drive to secondary GBM and it has unique molecular features including *EGFR* amplification (8%), *TP53* mutation (65%), *PTEN* mutation (4%), *P16* deletion (19%) and PDGF/PDGFR upregulation [232]. Studies have focused on identification of molecular pathways involved in astrocytoma progression and finding related therapeutics. The induction of Hedgehog signaling is responsible for astrocytoma progression. As an upstream mediator, nucleolar and spindle associated protein

Table 3
EZH2 and related molecular pathways in glioma.

Signaling network	Remarks	Refs
miRNA-137/EZH2	Down-regulation of miRNA-137 in glioma cells and tissues Enhancing miRNA-137 expression impairs growth and metastasis of cancer cellsmiRNA-137 down-regulates EZH2 expression in glioma suppression	[218]
MELK/EZH2/NF-κB	Promoting self-renewal capacity of glioma stem cellsEZH2 phosphorylation leads to NF-κB methylation to increase growth and stemness of glioma cellsPhosphorylation of EZH2 occurs by MELK	[219]
EZH2	EZH2 suppression by RNA interference leads to cell cycle arrest at G0/G1 phaseDown-regulation of Bcl-2 and upregulation of Bax	[220]
EZH2	EZH2 upregulation predicts undesirable prognosis in glioma patients	[221]
EZH2/LINC00963/p21	Upregulation of LINC00963 by EZH2Acting as tumor-promoting factor and increasing glioma growth and progressionDown-regulation of p21	[222]
TTBK2/miRNA-520b/EZH2	Enhancing progression of glioma cellsDown-regulation of miRNA-520b by circRNA TTBK2Elevating EZH2 expression	[223]
EZH2/miRNA-1224-3p/− 328/− 214/β-catenin	Down-regulation of miRNA-1224-3p, − 328 and − 214 by EZH2Increasing glioma progression via inducing β-catenin signaling	[224]
β-catenin/USP1/EZH2	Increasing glioma carcinogenesisβ-catenin mediates transcription of USP1Increasing EZH2 stability	[225]
SNHG7/miRNA-138-5p/EZH2	Tumor-promoting role of SNHG7 in gliomaReducing miRNA-138-5p expression via spongingIncreasing EZH2 stability	[226]
NNT-AS1/miRNA-582-5p/EZH2	Overexpression of lncRNA NNT-AS1 in glioma to promote cancer progressionMiRNA-582-5p down-regulation by NNT-AS1Inducing EZH2 signaling	[227]
EZH2/MELK/FOXM1	EZH2/MELK axis leads to glioma progression, cancer stem cell features and resistance to radiotherapy	[228]
EZH2	Overexpression of EZH2 reduces overall survival of glioma patients	[229]
TUG1/EZH2	Suppressing cancer stem cell like features in gliomaDown-regulation of TUG1 in gliomaReducing EZH2 expression	[230]
HOXB13-AS1//EZH2/HOXB13	Down-regulation of HOXB13 by HOXB13-AS1 via binding to EZH2 and mediating methylationIncreasing progression of glioma cells	[231]

1 (NUSAP1) stimulates Hedgehog signaling to enhance invasion and migration of astrocytoma cells [233]. *BRAF-FGFR* genes and MAP-K/ERK/mTOR signaling demonstrate high mutation in adult pilocytic astrocytoma and demonstrate tumor-promoting role [234]. The expression level of caspase-9 undergoes down-regulation by caveolin-1 to increase viability and progression of astrocytoma cells [235]. Eya2 is able to increase expression level of matrix metalloproteinases 9 (MMP9), resulting in enhanced astrocytoma cell metastasis [236].

EZH2 is involved in progression of astrocytoma, and various upstream mediators are able to regulate its expression. miRNA-144 is suggested to function as tumor-suppressor in astrocytoma and impairs growth and invasion. miRNA-144 can be considered as a prognostic factor in astrocytoma where its low expression is correlated with undesirable prognosis. Mechanistically, miRNA-144 reduces expression level of EZH2 to suppress astrocytoma progression. Reducing miRNA-144 expression and increasing EZH2 expression promote both proliferation and metastasis of astrocytoma cells. The combined expression of EZH2 and miRNA-144 (miRNA-144/EZH2) can be considered as reliable prognostic tools in astrocytoma [237]. The interesting point about EZH2 signaling in astrocytoma is the clinical application of its expression. The expression profile of EZH2 undergoes upregulation in astrocytoma and is associated with high grade [238]. There is a positive association between EZH2 transcript level and astrocytoma grade. Noteworthy, EZH2 has higher expression in GBM compared to astrocytoma. Furthermore, enhanced expression level of EZH2 in GBM results from post-transcriptional modification, probably mediated by miRNAs. miRNA-26a-5p, miRNA-27a-3p and miRNA-498 are able to regulate EZH2 expression. miRNA-26a-5p expression decreases with tumor grade. Furthermore, EZH2 can form feedback loop with miRNA-26 and regulating its expression by affecting promoter [239]. Another experiment has examined forty patients including 22 males and 18 females. EZH2 overexpression reduces overall survival of patients and its upregulation is observed in stages I to IV [240]. An experiment demonstrates EZH2 function in impairing differentiation of neurons. The down-regulation of EZH2 is vital for differentiation into astrocytes and its expression disrupts differentiation of astrocytes to neural stem cells [241]. Although a few studies have examined EZH2 role in astrocytoma, they are in line with oncogenic role of EZH2 in astrocytoma and its association with advanced stages. Besides, EZH2 prevents normal functions in neurons and paves the way for astrocytoma development. Future experiments can focus on revealing related molecular pathways to EZH2 in astrocytoma and providing insight towards its targeting in astrocytoma therapy.

7. EZH2 in medulloblastoma

The localization of medulloblastoma is suggested to be in cerebellum and it is considered as a solid tumor [242,243]. Medulloblastoma has a heterogenous nature and is commonly diagnosed in young children with ages below 10. Both classical and non-classical therapeutic strategies are performed for medulloblastoma patients [244–246]. Overall, medulloblastoma is divided into four subcategories including Wnt type, Sonic Hedgehog type, group 3 and group 4 [247]. Medulloblastoma patients demonstrate abnormalities including high intracranial pressure and cerebellar dysfunction [248]. These alterations result in emergence of a number of symptoms in clinical course such as nausea, headache, vomiting, dizziness and difficult walking. Surgery, chemotherapy and radiotherapy are applied for the treatment of medulloblastoma patients [249]. Recent experiments have revealed crucial role of epigenetic and genetic changes in medulloblastoma progression and development [250–254]. It is suggested that Wnt signaling activation can be considered as a promising strategy in medulloblastoma treatment. In xenografts with medulloblastoma, application of Wnt agonist demonstrates therapeutic prospects and impairs tumor progression [255]. Besides, medulloblastoma cells stimulate Sonic Hedgehog signaling to increase their capacity in tumor spheroid formation [256]. The following statements focus on the role of EZH2 signaling in medulloblastoma progression/inhibition.

Compared to astrocytoma, more experiments have evaluated the role of EZH2 signaling in medulloblastoma progression, therapy response and cancer stem cells (CSC) features. At the first step, EZH2 signaling regulates CSC features of medulloblastoma. EZH2 interacts with maternal embryonic leucine-zipper kinase (MELK) to affect progression of medulloblastoma. Both MELK and EZH2 expressions undergo upregulation in medulloblastoma and are responsible for reduced survival. MELK phosphorylates EZH2 and in turn, EZH2 stimulates MELK methylation in medulloblastoma to increase growth rate of medulloblastoma cells. The in vivo experiment on xenografts demonstrates that differentiation increases, while tumor growth decreases upon inhibition of EZH2 or MELK. Therefore, MELK and EZH2 interaction is vital for self-renewal capacity and CSC features of medulloblastoma [257]. EZH2 inhibition results in decreased proliferation rate and self-renewal capacity of medulloblastoma and diminishes H3K27me3 level. Notably, EZH2 is a druggable target and its expression level can be affected by pharmacological compounds. An experiment has synthesized small molecule inhibitor of EZH2 with similarity to EPZ005687, GSK2816126 and MC3629 agents. EZH2 inhibition by this small molecule suppresses

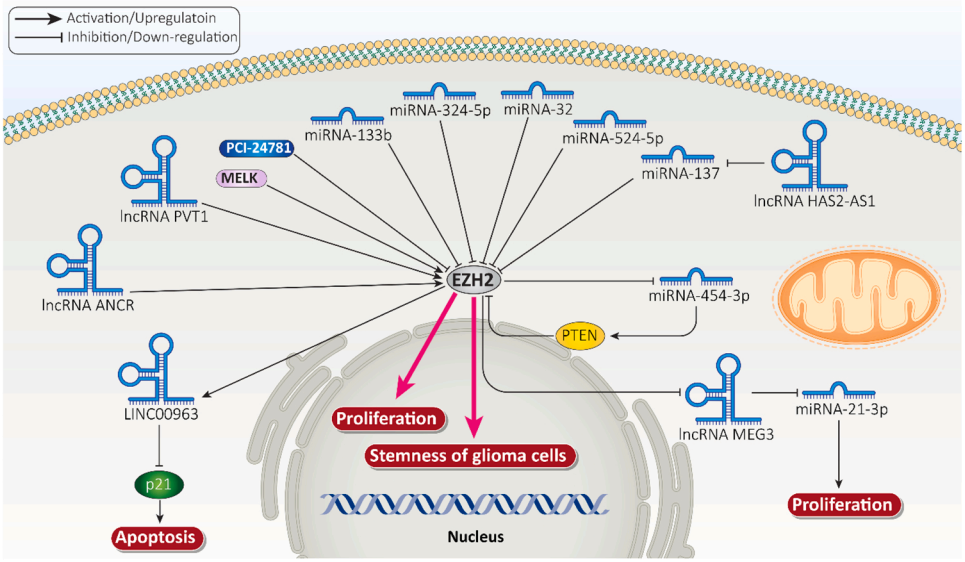

Fig. 3. EZH2 affects progression of glioma cells. The lncRNA PVT1 and ANCR are capable of inducing EZH2 signaling to increase growth rate and stemness of glioma cells. The EZH2 signaling can induce LINC00963 expression to prevent apoptosis in glioma cells. Moreover, miRNA-32, – 324-5p, – 133b, and – 137 regulate EZH2 expression. The lncRNA/miRNA/EZH2 axis has been also evaluated in glioma cells. These interactions that EZH2 is the central player, affect progression of glioma cells.

self-renewal ability and growth of medulloblastoma cells and triggers apoptosis. In vivo experiment on xenograft retards tumor growth, induces apoptosis and decreases stemness upon EZH2 inhibition in medulloblastoma [258]. Therefore, EZH2 signaling is vital for stemness and CSC features in medulloblastoma and future experiments should focus on this aspect of EZH2 in cancer treatment.

The interesting point about EZH2 is its double-edged sword role in medulloblastoma. Two different experiments have evaluated EZH2 targeting in medulloblastoma and they demonstrate both tumor-suppressor and tumor-promoting functions of this signaling pathway. EPZ-6438 (Tazemetostat) is small molecule inhibitor of EZH2 that has opened its way in clinical course for treatment of cancer patients. EPZ-6438 administration can inhibit medulloblastoma growth in vitro and in vivo. In medulloblastoma, ADGRB1 expression is silenced. It has binding site for H3K27me3 on its promoter that mediates its down-regulation. Upon EZH2 inhibition, ADGRB1 obtains an active chromatin status and enhances expression level of its downstream target BAI1. Then, Mdm2 activity is blocked and an increase occurs in stability and expression level of p53 [259]. However, another experiment demonstrates down-regulation of EZH2 as an opportunity for medulloblastoma progression. Gfi1 is a tumor-promoting factor in medulloblastoma that cooperates with Myc in cancer progression. EZH2 inhibition mediates Gfi1 upregulation in increasing medulloblastoma progression [260].

Similar to other brain tumors, miRNAs are able to regulate EZH2 signaling in medulloblastoma. Exosomes are a member of extracellular vesicles (EVs) that can provide communication between cells and transport a variety of molecules such as proteins, lipids and nucleic acids [102,261,262]. The exosomal miRNAs play a significant role in progression of medulloblastoma. miRNA-135b and miRNA-135a are transported by EVs in medulloblastoma and their suppression reduces cancer progression [263]. The exosomal miRNA-130b-3p down--regulates serine/threonine-protein kinase 1 (SIK1) expression to induce p53 signaling, resulting in reduced medulloblastoma progression [264]. The exosomal miRNA-101-3p functions as tumor-suppressor in medulloblastoma and prevents growth, colony-formation capacity and metastasis of cancer cells. Investigation of molecular pathways reveals that miRNA-101-3p is able to bind to 3′-UTR of EZH2 in reducing its expression and impairing medulloblastoma progression [265].

Clinically, EZH2 affects overall survival of medulloblastoma patients. EZH2 and DAB2IP expression levels undergo upregulation and down-regulation in medulloblastoma, respectively. EZH2 induces trimethylation of DAB2IP to decrease its expression. The low expression of DAB2IP is associated with undesirable prognosis. The low expression of DAB2IP mediates irradiation resistance in medulloblastoma and prevents apoptosis. Therefore, EZH2 overexpression negatively affects DAB2IP expression in medulloblastoma progression [266]. However, we are still at the beginning point and more experiments are required to demonstrate the role of EZH2 in drug resistance feature of medulloblastoma and its impact on other molecular pathways in regulating proliferation and invasion of cancer cells.

8. EZH2 in ependymomas

Ependymomas (EPNs) are malignant brain tumors that are observed in both children and adults. EPNs comprise 8–10% of brain tumors in children, while they have lower incidence rate in adults (4% of brain tumors) [267]. Originally, EPNs are derived from ependymal cells of cerebral ventricles and are considered as neuroepithelial tumors [268]. EPNs have three grades including subependymomas and myxopapillary ependymomas (grade I), ependymomas (grade II) and anaplastic ependymomas (grade III), based on WHO classification [267]. Besides, intracranial EPNs are more common compared to spinal EPNs. According to grade, a distinct strategy is applied for treatment of EPNs. For grade I tumors, surgery is effective and completely eradicates tumor [269,270]. For grade I and II tumors, surgery along with radiation is recommended [271]. When grade II tumors are eliminated with surgery, radiation is not recommended. Furthermore, radiation should be prohibited for patients with ages less than 3 [272,273]. When the tumor spreads via cerebrospinal fluid, radiotherapy is a great option for tumor eradication [272].

To date, one experiment has focused on EZH2 signaling in EPNs and more studies are required to clarify EZH2 role in this cancer. EZH2 overexpression occurs in 16% of EPN cases and is correlated with poor prognosis and low 5-year overall survival. EZH2 expression can be considered as an independent biomarker that enhances EPN progression and has high specificity [274].

9. EZH2 in rhabdoid tumors

Rhabdoid tumor is a rare complication in brain. Rhabdoid tumors occur in various organs of body including brain, kidney and soft tissues, but they have high prevalence in brain [275]. Children can develop rhabdoid tumors firstly in CNS and can be followed by development in others organs such as lung and liver [275]. Therefore, brain is considered as the primary and first organ affected by rhabdoid tumors in

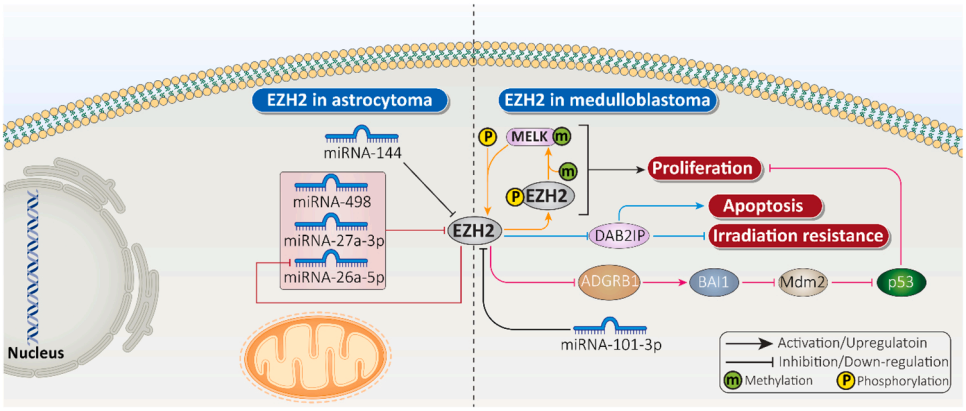

Fig. 4. EZH2 signaling in other brain tumors including astrocytoma and medulloblastoma. The focus in astrocytoma is on miRNAs regulating EZH2 and their interactions for regulating brain tumor progression. The EZH2 signaling induces DAB2IP expression for inhibiting radio-resistance and inducing apoptosis.

children and factors involved in its development and progression should be characterized.

Similar to EPNs, one study has examined EZH2 expression in rhabdoid tumors of CNS. Fourteen clinical cases of rhabdoid tumors of CNS were collected and they were investigated based on EZH2 on expression. Noteworthy, EZH2 upregulation was observed in all cases, showing that it can be considered as a biomarker and future experiments can focus on developing therapeutics for targeting this molecular signaling (Fig. 3) [276] (Fig. 4).

10. Conclusion and remarks

The present review focused on revealing the role of EZH2 in various brain tumors and its interaction with other signaling networks in regulating cancer malignancy. The EZH2 signaling induces EMT mechanism in promoting invasion and metastasis of GBM cells. Therefore, small molecule inhibitors of EZH2 can be utilized to reverse EMT and improve prognosis of GBM patients. EZH2 overexpression can prevent apoptosis in GBM cells that not only promotes their survival rate, but also mediates drug resistance. The GBM cells show high proliferation rate due to cell cycle progression and silencing EZH2 impairs GBM progression. Various upstream and downstream mediators of EZH2 signaling have been identified in GBM. miRNAs can regulate EZH2 expression in affecting brain tumor progression and in turn, EZH2 has capacity of binding to promoter of miRNAs in regulating their expression. LncRNAs are able to epigenetically target expression of target genes via recruiting EZH2. Similar to miRNAs, EZH2 signaling modulates lncRNA expression in brain tumors. mTOR signaling is another upstream mediator of EZH2. The identification of such signaling networks is of importance in GBM therapy, since they can be targeted in next experiments by pharmacological compounds or genetic tools to suppress cancer progression.

The EZH2 signaling also plays an oncogenic role in glioma. The overexpression of EZH2 prevents apoptosis in glioma cells and increases both growth and migration of tumor cells. EZH2 can promote cancer stem cell features in glioma cells and induces their resistance to chemotherapy and radiotherapy. Therefore, suppressing EZH2 signaling using pharmacological and genetic tools has been performed in glioma therapy. Furthermore, miRNAs and lncRNAs are able to regulate EZH2 signaling in glioma.

Most of the studies have focused on EZH2 signaling in glioma and GBM, and a few of them are about other kinds of brain tumors such as EPNs, rhabdoid tumors, astrocytoma and medulloblastoma. However, the interesting point is that clinical role of EZH2 signaling in these brain tumors, as for EPNs and rhabdoid tumors, high expression level of EZH2 has been observed in tumor cases. The expression level of EZH2 can be considered as a prognostic factor in brain tumors and then, small molecular inhibitors and gene therapy can be used for regulating EZH2 expression. The self-renewal capacity of medulloblastoma and astrocytoma mainly depends on EZH2 signaling. Hence, suppressing progression and CSC features of medulloblastoma and astrocytoma can be achieved via EZH2 signaling inhibition. Although there is no study about EZH2 and self-renewal capacity in EPNs and rhabdoid tumors, future experiments can focus on this aspect and pertain it to CSC features. The miRNA-EZH2-miRNA loop mainly affects astrocytoma and medulloblastoma progression and such axis has been also implicated in clinical course. Apart from challenges in reaching to brain tumors due to presence of BBB, chemoresistance is a major problem in treatment of these cancers [277]. The limitation of current works is lack of relating EZH2 signaling to drug resistance in EPNs, rhabdoid tumors, astrocytoma and medulloblastoma that can be the focus on future experiments. Although significant efforts have been made in investigating role of EZH2 signaling in brain tumors, the experiments have mainly focused on revealing EZH2 interaction with other signaling networks. However, there are different inhibitors of EZH2 signaling (discussed in Section 3) that can be used for brain tumor treatment. Furthermore, clinical application of EZH2 inhibitors may be limited due to their poor bioavailability. The nucleic acid drugs for targeting EZH2 such as siRNA also suffer from off-targeting and low accumulation at tumor site that their clinical application depends on using nanostructures for their delivery [22,210–213].

Conflict of interest statement

The authors declare no conflict of interest.

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