Recent Advances in Glioma Cancer Treatment

Subjects: Cell Biology

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Gliomas are the brain's most frequent and deadly tumors, accounting for roughly 30% of all brain malignancies. Glioblastoma (GBM) is characterized by changes in cell metabolism, including an increased Warburg effect, dysfunctional oxidative phosphorylation (OXPHOS), disrupted lipids metabolism, and other metabolic changes. Targeting epigenetic variables, immunotherapy, gene therapy, and different vaccine- and peptide-based treatments are some innovative approaches to improve anti-glioma treatment efficacy. Following the identification of lymphatics in the central nervous system, immunotherapy offers a potential method with the potency to permeate the blood-brain barrier.

glioblastoma cancer brain tumor epigenetic

1. Epigenetics in the Pathogenesis of Glioma

1.1. DNA Methylation

DNA methylation patterns in glioma cells are reported to differ from normal cells [1][2]. Most significantly, tumor cells are characterized to have widespread hypomethylation and CpG island hypermethylation. Therefore, the methylation status of glioma-related genes could be a useful diagnostic factor. Given the differences in methylation patterns and the prognostic G-CIMP index of gliomas in adults and children, adult-specific indicators of glioma must be identified. Most CpG islands are hypomethylated under normal physiological conditions [3]. However, a tumor suppressor and DNA repair genes often cause hypermethylation in tumor-related tissues [4]. These genes are associated with glioma development, due to the activity of DNA-5-hydroxymethylcytosine (5hmC). Recent evidence has revealed that 5hmC is negatively correlated with the tumor level. Moreover, p16INK4a [5], p14ARF MLH1 [6], and NDRG2 [6] are other tumor-repressor genes that are correlated with glioma. The p16INK4a gene keeps the retinoblastoma tumor-suppressor protein (pRb) in the active form (dephosphorylated) in the normal cyclinD-Rb pathway. The active form of this protein controls the cell cycle's progress [5]. GBM tissue shows a high incidence (greater than 50%) of deletion for the p16INK4a homozygous gene. Moreover, p16INK4a is changed in 80% of glioma cell lines. Thus, restoring the p16INK4a gene could decrease growth arrest and eliminate proliferation.

Steller et al. reported the hypermethylation of the MGMT promoter in approximately 40% of glioma tissues. The rate of methylation levels is dependent upon the zone in which the cells thereof have been cancerous [7].

Furthermore, the level of MGMT methylation is the critical index to determine TMZ susceptibility in glioma treatment. Low-adjusted MGMT can dramatically restore the in vitro and in vivo chemical sensitivity of TMZ [8]. A recurrent point mutation in isocitrate dehydrogenase 1 (IDH1) is frequently seen in adult diffuse gliomas. Mutant IDH1 gliomas are classified as mutant IDH1-1p/19q-codel or mutant IDH1-noncodel, based on the deletion of 1p/19q chromosomal regions [9][10][11]. IDH1 is the main source of NADPH in the human brain. It also can be found in other tissues of the body [12]. Most low-grade scattered astrocytomas (with a 75 percent mutation rate), anaplastic astrocytomas (with a 66 percent mutation rate), oligodendroglioma, promyelocyte, and secondary sex polymorphism include mutations in their IDH1/2 methylation regulatory protein [13]. The platelet-derived growth factor receptor alpha (PDGFRA) is a protein-coding gene that can reduce the growth of IDH mutant astrocytoma cells via the employment of demethylation medicines. This leads to the restoration of the normal function of such proteins [14][15]. Moreover, these medicines have a noticeable linkage to changes in NF1 and PDGFRA\IDH1, thus providing a practical treatment method [16].

The MAPK pathway or its downstream effectors contribute to carcinogenesis and proliferation in many types of malignancies. They can be activated in juvenile gliomas as a result of NF1 and BRAF gene alterations [17]. In addition, BMP signaling is activated in HGG tumor cells in children [18]. Activin A receptor type I (ACVR1) encodes for the type I BMP receptor ALK2. Its *somatic mutations, which are found in about 25% of pediatric brainstem gliomas, trigger BMP pathway activation [19]. Changes in the signaling pathways caused by specific genetic abnormalities in gliomas are promising targets for developing novel targeted gene therapies [20].

1.2. miRNAs and Glioma

Some studies have recently revealed that miRNAs play a major role in the transcriptional control, growth, and proliferation of numerous tumor genes [21][22]. Therefore, miRNA-based personalized medicine and gene-editing techniques seem to be viable strategies in cancer therapy. Approximately half of the miRNA genes are thought to be found in glioma cancer genes or in their vulnerable locations. These miRNA genes can affect 3% of all glioma tumor genes and 30% of all coding genes [23]. A single miRNA can simultaneously alter 100 GBM-related mRNAs, and a single glioma mRNA can be controlled by one or more miRNAs [24].

In the course of glioma disorders, miRNAs perform a number of important roles in carcinogenesis, the expression of cancer-related genes, glioma stem cell development, and regulatory pathways [25][26]. MiR-221/222 was discovered to be positively linked with the level of glioma cell invasion and infiltration. Zhang C. et al. have shown that the knockdown of MiR-221/222 could reduce cell invasion by manipulating the levels of the TIMP3 target. In a xenograft model, the knockdown of MiR-221/222 has enhanced TIMP3 expression and significantly decreased tumor growth [27]. Moreover, the overexpression of miR221/222 lowers the p27kipl levels and vice versa, which inhibits tumor proliferation [28].

1.3. Chromatin Remodeling and Glioma

Mutations in the critical proteins of the regeneration complex are frequently found in human diseases [29]. These mutations are caused by aberrant chromatin remodeling [30][31][32]. Deficient chromatin remodeling can result in failed chromatin regeneration, in which the nucleosomes are unable to orient themselves properly, and the primary transcription machinery is prevented from acting [33][34][35]. These changes lead to aberrant gene expression [35]. Cancer develops when these mutations cause anomalies in tumor suppressor genes or cell-cycle regulatory proteins [36][37]. Drug-resistant tumor cells can be eliminated by targeting epigenetic and evolutionary processes [38][39]. This elimination could lead to avoiding disease recurrence [40][41]. Liu et al. have reported that targeting the GBM drug resistance stem cells (GSC) by kinase inhibitors can revert them to a slow-cycling, long-lasting state [40][41]. The notch signaling pathway is active in this state, and the histone demethylase KDM6A/B is considerably up-regulated [28][42]. This condition results in the removal of H3K27 trimethylation in the cis-regulatory region of the genome and higher levels of H3K27Ac [28][39]. This cellular transition was reported to be aided by chromatin remodeling [28]. The results of this study have identified a new target to develop effective anti-GBM treatments [43]. Moreover, according to a recent study [44], the expression of the controlled transcription factors E2F1 and GSK3 in astrocytomas and GBM was linked to glioma progression and LSH expression [42][44].

Glioma tissue also expresses the lipoprotein receptor protein (LRP6) 6, which is an upstream regulator of the GSK3 signaling cascade. LRP6 depletion decreases LSH expression by lowering the E2F1 engagement in the LSH promoter. These changes result in the suppression of cell growth. In light of these observations, the existing mechanical relationship between the activation of the LPR6/GSK3/E2F1 axis and LSH expression in glioblastoma could be interpreted as a key role in GBM. Understanding the role of LSH in the formation of gliomas adds to people's understanding of the disease and makes LSH a possible therapeutic candidate to treat these lethal brain malignancies [45][46][47].

1.4. Histone Modification and Gliomas

Glioma formation and progression can be accelerated by improper histone modifications [48]. These aberrant modifications could lead to transcriptional irregularities and changes in the expression of enzymes, including histone methyltransferases, histone deacetylases (HDACs), and acetyltransferases (HATs) [49][50]. Histone methyltransferases are the histone-modifying proteins that have garnered the most attention [51]. Histone methylation at the lysine and arginine residues of the N-terminal region occurs on the H3 and H4 histones and is regulated by histone methyltransferases [52][53][54]. The main role of histone methylation is that of transcriptional regulation [55][56]. It could either repress the transcription through H3K9, H3K27, and H4K20 histone methylation or activate it via H3K4 histone methylation [57]. KMTs can be categorized into two protein families, based on their catalytic domain [58][59]. The two classes of KMTs comprise the SET domain-containing family (SUV39, SET1, SET2, SMYD, SUV4-20, SET7/9, and SET8) and the DOT1 family [58][60][61].

HATs participate in various biological processes, including cell-cycle progression, DNA damage repair, cellular senescence, and hormone signaling. HATs are among the bi-substrate enzymes that use the Ac-CoA cofactor and the histone lysine residue as substrates.

HDAC, HDAC1, HDAC2, HDAC3, HDAC5, and HDAC9 are among the HDACs that showed substantial alterations in glioma cells [62]. The histone acetylation of lysine residues in H2A, H2B, H3, and H4 typically drives gene transcription, while histone methylation can either activate (H3K4, H3K36, and H3K79) or repress (H3K9, H3K27, and H4K20) gene transcription [63]. HDAC5 and HDAC9 expression rise in high-grade medulloblastoma, compared to low-grade medulloblastoma and abnormal tissues [64].

2. Glioma Treatment Strategies

2.1. Glioma Epigenetic Therapy

2.1.1. DNA Methylation Inhibitors (DNMTi)

The compressor tumor genes become silent by DNMT-mediated DNA methylation. Therefore, DNMT inhibition can restore the transcription of these important genes [65]. Thus, finding DNMT inhibitors could be deemed as a novel approach in glioma therapy. Aza-20-deoxycytidine 5 phosphate is the most common DNMT inhibitor, which is now in clinical trials. In tumor cells, aza-20 deoxycytidine-5 phosphate interacts with DNA and suppresses DNMT activity, which results in a favorable methylation state for anticancer activities [66].

2.1.2. Histone Deacetylase Inhibitors (HDACi)

HDACis have been shown to suppress transcription and end cell division in G1 and G2 phases, promote cell differentiation and apoptosis, reverse the heat shock protein-substrate protein interaction, enhance oncoprotein degradation, and limit tumor growth and angiogenesis [67]. Individually or in combination, DNMT inhibitors and HDACis can be used to treat various tumors [68]. HDACi, as a novel therapeutic agent for glioblastoma, opens up new avenues for glioma treatment. Many HDACis have now entered stage I/II clinical studies to treat various kinds of glioma, including diffuse intrinsic pontine glioma (DIPG) and progressive or recurrent GB. HDACis can be used alone or in conjunction with other chemotherapeutic drugs, such as TMZ and radiation therapy [69].

Vorinostat and TMZ were tested in primary recurrent or refractory CNS malignancies, in a study conducted by the Department of Pediatric Oncology (COG) [70]. In children with recurrent CNS malignancies, five-day cycles of vorinostat in conjunction with TMZ were well tolerated. Vorinostat treatment resulted in the aggregation of acetylated H3 in peripheral blood mononuclear cells (PBMC). In a phase II study of verinavastat monotherapy, conducted by North Central Cancer Treatment, good tolerance in recurrent GBM patients was recorded. Moreover, an obvious increase in H2B and H4 acetylation levels was observed after treatment [71].

A phase II research study of Panobinostat, in conjunction with bevacizumab (BEV), in anaplastic glioma and recurrent GBM patients, was conducted [72]. Treatment was acceptable in both groups prior to closure. However, adding panobinostat to BEV did not increase the 6-month progression-free survival (PFS6) rate in either group when compared to BEV monotherapy controls. According to the additional preclinical studies, Panobinostat may serve as a sensitive agent. A phase-I study of stereotactic re-irradiation in combination with panobinostat has been reported in patients with recurrent HGG [73].

The COG has completed another phase of Valproic acid (VPA) research in children with refractory or CNS malignancies. At a steady state, half of the patients showed hyperacetylation of their histones. Krause et al. recently published a phase-II trial on simultaneous TMZ and VPA radiation therapy for GBM patients. Their findings revealed that the simultaneous administration of VPA and RT/TMZ is well tolerated in individuals with newly diagnosed GBM [74]. In general, HDACis appear to be promising therapies to improve the prognosis of malignant gliomas, when used as a monotherapy or combination therapy [75]. Improving or inventing novel epigenetic medicines or learning how to coordinate them with other treatments are viable options to reduce the damaging effect of epigenetic drug poisoning during treatment. HDAC, Vorinostat, and Valproic acid inhibitors have all had good clinical outcomes when paired with TMZ or RT in treating children with resistant or recurrent adult CNS or GBM cancers [74]. This could be a promising direction for future clinical investigations. Nonetheless, Vorinostat, in combination with erlotinib, or panobinostat in combination with BEV had no discernible effects [72]. Although these findings are not encouraging, they provide useful information for further studies.

Contemporary immunotherapy has become a popular strategy in cancer treatment. Even though few clinical trials on the combination of HDACis and the cytotoxic-mediated immunotherapy gene have been reported, most G-MCIs are recommended to be paired with TMZ. Most G-MCIs are recommended to be paired with TMZ. This strategy dramatically improved survival rates in individuals with minimal residual disease [76]. Tumor cells employ epigenetic processes to change autoimmune genesis and impair the process of tumor cell detection by the immune system. Tumor cells can kill themselves by lowering the expression levels of critical molecules in the tumor immune response process. They exploit DNA methylation or histone modification to exert these functions [77]. Immunosuppressive medications, such as cytokines and polypeptide vaccines, are currently the most common immunosuppressive drugs that can be applied in combination with epigenetic therapies [78][79]. This approach has become an increasingly popular strategy for the treatment of malignancies such as gliomas (**Table 1**).

Table 1. Treatment strategies for glioblastoma therapy.

Standard Management			
Category	**Therapy**	**Mechanisms of Action**	**References**
Current treatments	Surgical resection	Removing the possible amount of tumor in almost all types of gliomas.	[80]
	Radiation	Using high-energy beams after surgery, mainly in high-grade gliomas.	[81]
	Chemotherapy with Temozolomide (TMZ)	Binding to the genome, preventing the tumor cell growth and division.	[82]
	Tumor-treating fields (TTF) with bevacizumab	Selectively using an electromagnetic field with bevacizumab targeting	[83]

Standard Management			
Category	**Therapy**	**Mechanisms of Action**	**References**
		vascular endothelial growth factor (VEGF).	
	Future Directions		
	Therapy *(Study Numbers)*	**Mechanisms of Action**	**References**
Checkpoint inhibitors	**Immune checkpoint inhibitors** Programmed cell death protein 1 (PD-1/CD279) • Nivolumab (*NCT02335918*) • Bevacizumab (*NCT03743662*) • Pembrolizumab (*NCT03899857*) Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4/ CD152) • Ipilimumab (*NCT02311920*) • Durvalumab (*NCT02794883*) Tremelimumab Indoleamine 2,3-dioxygenase (IDO)	• Decreasing the level, and cumulation of regulatory T (Treg) cells • Increasing the survivorship • Promoting the immune-mediated tumor destruction	[84][85][86][87][88][89][90]
Immunostimulatory gene therapy	**Oncolytic viral (OV) therapy** • G207 (*NCT00028158 and NCT03911388*) • M032 (*NCT02062827*) • sh-SirT1 lentivirus (genetically engineered Lentivirus) • miR-100 lentivirus (genetically engineered Lentivirus) • DNX-2401 (modified adenovirus) (*NCT02798406, NCT02197169*) • PVSRIPO • ONYX-015 (Genetically modified adenoviral vector)	• Inducing the secretion of IL-12 by tumor cells, increasing the antitumor efficiency of the therapy • Targeting highly expressed receptors in solid tumors (e.g., CD155 by PVSRIPO). • Replication in p53-deficient tumor cells (e.g., ONYX-015) • Improving radiotherapeutic sensitivity by silencing SirT1 (e.g., sh-SirT1 lentivirus)	[91][92][93]

Standard Management			
Category	**Therapy**	**Mechanisms of Action**	**References**
	• H-1PV (wild-type parvovirus) • Toca 511(a retroviral OV based on the murine leukemia virus) (*NCT02414165*)	• Increasing sensitivity to chemotherapy (e.g., miR-100 lentivirus) • Converting the prodrug,5-fluorocytosine, into the antimetabolite by cytosine deaminase leads to tumor cell death 9, e.g., toca 511) • Damaging genome and attesting the cell cycle (e.g., H-1PV) • Reducing the number of tumor-associated macrophages • Increasing the survivorship	
	Suicide gene therapy • Ad-TK (genetically engineered Adenoviral vectors encoding HSV thymidine kinase) • Ad-Flt3L	• Introducing thymidine kinase into the tumor • Converting ganciclovir into an active form • Inducing apoptosis in dividing tumor cells and releasing tumor antigens	[94][95]
	Cytokine therapy • (HSVTK) genes and IL-2/ 4-encoding genes • of IL-4/13 and Pseudomonas exotoxin (IL-4-PE)	• Prolonging the survival of patients	[96][97][98]

Standard Management			
Category	**Therapy**	**Mechanisms of Action**	**References**
	• IFN-β with TMZ		
Adjuvant therapy	**Tumor-associated macrophages (TAMs) therapy** • Anti-CCL-2 antibody • BLZ945 • PLX3397(*NCT01790503*) • Minocycline(*NCT02272270, NCT01580969*) • Cyclosporine (*NCT00003625*)	• Formation and retention of tumor cell migration • Promoting angiogenesis • Increasing the survivorship • Inhibition of colony-stimulating factor • Reducing the amount of the M2 macrophage • Debilitating the expression of microglial secreting matrix metalloproteinases	[99][100][101][102][103]
Passive immunotherapy	**Chimeric antigen receptors (CARs) therapy** • EGFRvIII(*NCT03283631, NCT03389230*) • IL-13Rα2 (*NCT02208362*) • HER2 (*NCT01109095*) • CD70 • Cd147 (*NCT04045847*) • GD2 (*NCT03252171*) • EphA2(*NCT02575261*) • B7-H3(*NCT04077866*)	• Inhibition of tumor growth via IFN-γ and IL-2 Secretion • Receding CD70+ glioblastoma in xenograft models	[104][105][106][107][108][109]

Standard Management			
Category	**Therapy**	**Mechanisms of Action**	**References**
	Antibodies • Daclizumab (selective antibody for the high-affinity IL-2Rα)	• Decreasing the amount of Tregs without affecting the T cells	[110]
Active immunotherapy	**EGFRvIII-mediated vaccine** • Rindopepimut(CDX-110) (*NCT00458601*) • MAb806 (ABT-806) (*NCT01472003*)	• Targeting EGFRvIII tumor and increasing the immune response	[111]
	Tumor cell vaccines • Temozolomide • HSPPC-96 (*NCT01814813*)	• Increasing efficacy using autologous tumor lysates • Activating DCs (e.g., heat shock protein chaperon gp96)	[112][113]
	Dendritic cell vaccines (DCVs) • ICT-107 • DCVax-L • Fusions of DC and glioma cells • DCVax-L + GBM Pvax • Pp65-DCs + GM-CSF1	• Inducing strong anti-tumor immunity by activation of NKT, CD4, and CD8 cells	[114][115][116]
Epigenome therapy	**Inhibitors of mutant IDH (mtIDHi)** • IDH305 (*NCT02381886*) • AG-221 (*NCT02273739*) • AG-120 (Ivosidenib) (*NCT02073994*)	• Normalizing the function of α-ketoglutarate-dependent enzymes • Inhibiting polycomb repressor complex 2 (PRC2)	[117][118]

Standard Management			
Category	**Therapy**	**Mechanisms of Action**	**References**
	• DS-1001b (*NCT03030066*) • etc. **EZH2 inhibitors (EZH2i)** • Tazemetostat (NCT03155620) **DNA methylation inhibitors (DNMTi)** • 5-Azacytidine (Vidaza) (NCT02223052) • 5-Azacytidine (Vidaza) (NCT03206021) **Histone deacetylase inhibitors (HDACi)** • Valproic acid (*NCT03243461*) • Vorinostat (SAHA) (*NCT01189266*) • Belinostat (*NCT02137759*) • Panobinostat(LBH589) (*NCT02717455*) • Et	• Inducing innate immune response by reactivating retroviruses • Modulating histone acetylation marks	
Combinational therapy	**Combinations of multiple checkpoint inhibitors** • Anti-CTLA4 (ipilimumab, tremelimumab) and anti-PDL1 (nivolumab, durvalumab, pembrolizumab) monoclonal antibodies • Nivolumab in combination with the anti-LAG3	• Increasing the survivorship	[119][120]

Standard Management			
Category	**Therapy**	**Mechanisms of Action**	**References**
	Checkpoint inhibitors combined with other immunotherapies • Vaccination with GM-CSF-expressing glioma cells and treatment with anti-CTLA4 antibodies • Nivolumab with and without DC vaccine therapy • PD-1 antibody blockade in combination with CD28-targeted CAR T cell • Combination of a PD-1 inhibitor and VEGF inhibitor	• Resulting in a higher antigen-specific immune response	[121][122][123][124]
	Targeting immunosuppression in the tumor microenvironment • Combination therapy with the CD40 mAb and celecoxib • Combination of a CD200R antagonist with tumor lysate vaccination	• Activating myeloid cells toward a tumor-killing feature • Inhibiting immunosuppressive functions	[125][126]
	Combinations of multiple immunostimulatory gene therapies • Herpes simplex virus 1-thymidine kinase (HSV1-TK), and immune stimulation with Flt3L • A cytokine that recruits DCs into the tumor microenvironment	• Killing the remained proliferating tumor cells • Releasing proinflammatory cytokines • Stimulating DCs movement toward the tumor cells	[127]
	Immunostimulatory gene therapy combined with other	• Increasing the survivorship	[128][129]

Standard Management			
Category	Therapy	Mechanisms of Action	References
	immunotherapies • Ad-TK/Flt3L in combination with subcutaneous vaccination with DCs, • MDSC depletion with the anti-Gr-1 antibody following TK/Flt3L gene therapy • PDL1 blockade combined with TK/Flt3L gene therapy • CTLA-4 blockade combined with TK/Flt3L gene therapy		
	Vaccination combined with immune stimulatory adjuvants • Peptide vaccine containing 11 GBM-associated peptides, with GM-CSF • Peptide vaccine containing 11 GBM-associated peptides, with poly-ICLC • An agonist of TLR3 • An IDH1 mutant peptide vaccine in combination with imiquimod (the TLR7 ligand) • mTOR inhibition with rapamycin to enhance DC vaccine	• Stimulating DCs maturation	[130][131]
	Vaccination combined with other immunotherapies • Vaccination with CEApeptide pulsed DCs	• Normalizing the tumor vasculature • Increasing better infiltration of immune cells	[132]

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Standard Management			
Category	**Therapy**	**Mechanisms of Action**	**References**
	• Anti-angiogenic therapy with immune-based therapies	into the tumor cells	
Miscellaneous	**Nanoparticle formulations** • PLGA microparticles encapsulated with nicotinamide phosphoribosyltransferase inhibitor (GMX-1778) • lipopolymeric NP • NU-0129 (*NCT03020017*)	• Selectively antagonizing NAD+ biosynthesis • Targeting transcription factors, such as SOX2, OLIG2, SALL2, etc. • Targeting Bcl-2-like protein by siRNA gold nanoparticles	[133][134]
	BBB disruptive therapies • SonicCould (*NCT02253212*)	• Using pulsed ultrasound to open the blood-brain barrier	[135]
	Exosomes • miR-21sponge construct • miR-199a • miR-34a • Long-noncoding RNA PTENP1 • miR-146b	• Inhibiting EGFR expression • Compelling cell apoptosis • Inhibiting cell proliferation and invasion	[136][137]

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