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DNA Damage Repair Genes and Noncoding RNA in High-Grade Gliomas and Its Clinical Relevance

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Abstract

Gliomas are the most common malignant tumors originating from the glial cells in the central nervous system. Grades III and IV, considered high-grade gliomas occur at a lower incidence (1.5%) but have higher mortality. Several genomic alterations like IDH mutation, MGMT mutation, 1p19q Codeletion, and p53 mutations have been attributed to its pathogenicity. Recently, several noncoding RNAs have also been identified to alter the expression of crucial genes. Current chemotherapeutic drugs include temozolomide targeting hypermethylated MGMT, a DNA repair protein; or bevacizumab, which targets VEGF. This book chapter delves deeper into the DNA damage repair pathway including its correlation with survival and the regulation of these genes by noncoding RNAs. Novel therapeutic drugs being developed are also highlighted.

Keywords: DDR in glioblastoma, noncoding RNA in gliomas, targeted therapy

1. Introduction and epidemiology

Gliomas are the brain's solid tumors that arise from the glial cells, which are the non-neuronal cells of the central nervous system (CNS). Neurons function in synaptic interactions, whereas glial cells provide protective and structural support to the neurons. According to the 2020 GLOBOCAN, cancer of the brain and central nervous system rank at 19th and 12th, respectively [1]. The age-standardized incidence of these tumors is 3.9 per 100,000 in males and 3.0 in females globally. In comparison, the mortality is 3.5 per 100,000 in males vs. 2.8 in females worldwide. These cancers are prevalent in countries with a high human development index [1]. In 2020 alone, 308102 worldwide brain and central nervous system cases were reported. More than half were reported from Asia (54.2%) [1]. The number of deaths reported in the same year was 251329 worldwide, pushing the mortality rate to 81.57% [1]. The survival rate of gliomas vary based on their grade; the median survival time for high-grade glioma is 14 to 16 months. It ranges from 3–15 years for low-grade gliomas [2].

One of the only risk factors identified for the development of high-grade gliomas is exposure to high-dose of ionizing radiation [3]. However, environmental factors, toxins, infections, cell phone usage, or head trauma have not been correlated to the development of gliomas. Only 5% of cases of brain tumors have been linked to

hereditary genetic syndromes [4]. Some of which are Li-Fraumeni cancer syndrome (associated with a germline mutation in the TP53 gene), neurofibromatosis, Turcot syndrome, and Lynch syndrome (constitutional mismatch repair deficiency), tuberous sclerosis, melanoma-neural system tumor syndrome, Ollier disease and Rubinstein-Taybi syndrome [4–7].

Gliomas are diagnosed when the patients become symptomatic, exhibiting recurrent headaches, the onset of seizures, personality changes, weakness in limbs, or language disturbances [8]. Elevated intracranial pressure is also a common feature in gliomas [9]. Infantile spasms and seizures have also been noted in infants [9]. Gliomas are generally diagnosed by computed tomography (CT), and Magnetic Resonance Imaging (MRI) scans [10]. The current treatment regimen is based on the tumor grade and includes either or combinations of surgical resection, radiation, and chemotherapy [11]. The chemotherapeutic drugs used for glioma treatment fall under the category of alkylating agents that induce double-stranded breaks in the DNA, thereby inhibiting tumor proliferation [12]. The standard chemotherapeutic drug used for high-grade glioma is temozolomide (TMZ), and for low-grade gliomas are carmustine, procarbazine, and lomustine [13]. Metastasis of malignant gliomas is rare, primarily due to the low survival of the patients and also due to the blood–brain barriers [14]. However, in certain rare cases of high-grade gliomas, metastasis to the lung, pleura, lymph nodes, bone, and liver have been reported [15]. Recurrence post-treatment is reported in most gliomas and can be attributed mainly to surgical brain injury (SBI) and TMZ chemoresistance [16].

The following sections describe the glioma subtypes, their molecular characterization, and their deregulated signaling pathways. This chapter's primary focus is on the DNA damage response (DDR) pathway, and noncoding RNAs in high-grade glioma called glioblastoma multiforme (GBM). The role of noncoding RNAs affecting chemosensitivity and other novel therapeutic drugs being developed for gliomas are also highlighted.

2. Glioma classification

The Glial cells are classified as astrocytes, oligodendrocytes, and ependymal cells [17]. The astrocytes function in providing mechanical support to the neurons; oligodendrocytes are involved in myelin production, a component of the myelin sheath and ependymal cells play essential roles in the transport of CSF and brain homeostasis [18]. Based on the cellular origins, gliomas are classified as astrocytoma (derived from astrocytes), oligodendrogliomas (derived from oligodendrocytes), and ependymoma [2].

Until 2016, the World Health Organization (WHO) had categorized gliomas entirely based on histological features and graded them according to their malignancy profile [19]. **Table 1** represents this WHO grading of gliomas where grades I and II are considered low-grade gliomas (LGGs) that are slow-growing with a better prognosis. The Grade I tumors are mainly diagnosed in children and curable with just surgical resection. On the contrary, the most aggressive tumors are referred to as high-grade gliomas (grade III and IV). Grade III tumors are termed 'anaplastic' as they have lost their characteristic cellular features to become malignant. The grade IV in this category, which accounts for 90% of gliomas, is GBM, the most aggressive and deadly tumor of all gliomas, with an abysmal survival rate. About 90% of GBM cases are de novo and develop in older patients [20]. On the contrary, secondary GBM, which arises from LGG, manifests mostly in younger patients and has a better prognosis [20].

WHO grade		Astrocytoma	Oligodendroglioma	Oligoastrocytoma	Prognosis	Incidence
Low grade	I	Pilocytic astrocytoma, subependymal giant cell astrocytoma			Good	Predominant in children <1 year
	II	Low-grade astrocytoma	Low-grade oligoastrocytoma	Low-grade oligodendroglioma	Favorable	Median age of 35
High grade	III	Anaplastic astrocytoma	Anaplastic oligoastrocytoma	Anaplastic oligodendroglioma	Poor	Predominant in adults
	IV	Glioblastoma			Very poor	Predominant in adults

Table 1.
Glioma classification based on histology and malignancy scale.

2.1 Molecular classification of gliomas

A more recent WHO classification in 2016 includes genetic screening to histopathological analysis, which integrates the tumor’s morphological and genetic considerations [21]. The status of the following molecular alterations has been incorporated in this classification and are critical to diagnosis and further treatment.

IDH mutation: The most prevalent genetic mutation is the Isocitrate dehydrogenase (IDH) mutation accounting for a single point mutation in around 80% of glioma cases [22]. It is identified to be one of the earliest mutations for gliomagenesis and has been implemented primarily to classify gliomas as either IDH mutant or IDH wildtype. IDH mutation is considered to be a favorable prognostic marker with increased survival [23]. It is a metabolic enzyme that catalyzes the oxidative decarboxylation of isocitrate to α -ketoglutarate (α -KG) and produces NADPH from NADP without the Krebs cycle’s involvement. This mutated IDH produces high levels of 2-hydroxyglutarate (2-HG) instead of the α -KG which is implicated in glioma invasion as well in epigenetic alterations leading to a glioma CpG island methylator (G-CIMP) phenotype (G-CIMP) [24].

Codeletion 1p19q: Post IDH mutation status, the gliomas are further classified based on this chromosomal co-deletion of 1p19q where the short arm chromosome 1 (1p) and the long arm of chromosome 19 (19q) are lost. It is observed in more than 70% oligodendrogliomas and 50% mixed oligoastrocytomas [25]. Clinically, IDH mutants with co-deletion 1p19q are linked to better prognosis and chemotherapy response [26].

TERT promoter mutations: Telomerase reverse transcriptase (TERT) promoter mutations are reported in several cancers leading to enhanced activity of TERT resulting in tumor cell survival and its progression [27]. It is present in 55% GBM and its prevalence is inversely correlated with IDH mutation [27, 28]. This TERT mutation serves as a prognostic biomarker and is associated with poor survival [29].

MGMT promoter methylation: MGMT (O[6]-methylguanine-DNA methyltransferase) is a DNA damage repair protein that removes alkyl groups added to nucleotides preventing mutation. Chemotherapeutic drugs like TMZ blocks cell growth by alkylating DNA. Hypermethylation of MGMT promoter regions renders this enzyme inactive and is reported in 40% GBM cases [30]. IDH mutant-MGMT promoter methylation cases are associated with increased PFS (Progression-free

survival) whereas MGMT promoter methylation with TP53 mutation has favorable outcome irrespective of IDH status [31].

ATRX mutation: The alpha thalassemia/mental retardation syndrome X-linked (ATRX) is a chromatin remodeling enzyme involved in incorporating histone H3.3 at telomeres and pericentromeric heterochromatin. Loss of function mutations of ATRX is reported in gliomas which correspond to alternative lengthening of telomeres (ALT) phenotype [32]. ATRX and TERT mutations occur in 90% diffuse IDH mutant gliomas with both being mutually exclusive which confer better progression-free and overall survival [33].

H3K27M mutations: H3K27M (methionine substitution of lysine at residue 27 of histone H3) are mutations that occur in Histone 3 of H3F3A or HIST1H3B/C gene. These mutations are predominantly present in pediatric cases with IDH-wildtype and lack 1p/19q co-deletion and are associated with poor prognosis [34]. The H3K27M mutant protein has a dominant-negative effect on EZH2 protein, a histone methyltransferase impacting the epigenetic landscape of tumor genes [35].

Besides the above, other somatic and germline mutations are also reported in gliomas. More than 25 gene loci are linked to an increased risk of development of gliomas. Somatic mutations of cyclin-dependent kinase inhibitor 2A and B (CDKN2A, CDKN2B), epidermal growth factor receptor (EGFR), pleckstrin homology-like domain family B member 1 (PHLDB1), and regulator of telomere elongation helicase 1 (RTEL1) are reported in gliomas [36]. In case of GBM, the frequent genetic alterations in the decreasing order are LOH 10q (69%), EGFR amplification (34%), TP53 mutations (31%), p16INK4a deletions (31%) and PTEN mutations (24%) [37].

3. Deregulated pathways in glioblastomas

GBMs are the most fatal of all glial cancers. Secondary GBMs arising from LGG constitute 10% whereas the remaining 90% GBMs arise de novo. The genomic alterations of oncogenes and tumor suppressors are the fundamental cause of cancer development. These alterations further lead to deregulation of several signaling pathways aiding in tumor progression manifesting in metastasis and chemoresistant cancers. GBMs were one of the first tumors to be studied by the TCGA [38] and some of the key signaling pathways reported to be deregulated are as follows:

RTK/RAS/PI3K pathway: This pathway is majorly involved in growth and proliferation and is dysregulated in 88% of GBM cases. This dysregulation occurs by amplification and mutational activation of receptor tyrosine kinase (RTK) genes – EGFR, ERBB2, PDGFRA, MET. A variant of the protein – EGFRvIII that occurs due to intragenic deletions is also a common feature. Activation of the phosphatidylinositol 3-kinase (PI3K) pathway are achieved by PTEN deletion, activating mutations in PIK3CA or PIK3R, AKT3 amplification, NF1 mutation, RAS mutation, FOXO mutation.

p53 pathway: Inactivation of the p53 pathway occurs in about 87% of the GBM cases. TP53, termed as “the guardian of the genome”, is a tumor suppressor gene and is frequently mutated or deleted in most cancers [39, 40]. The pathway is involved in several processes like cell cycle arrest, DNA repair, apoptosis, autophagy, differentiation, senescence, and self-renewal [41]. Mutations in the TP53 gene lead to nonfunctional proteins. Several missense mutations, particularly in IDH-wildtype GBM (primary GBM), have been reported, resulting in accumulating the protein in the nucleus [42]. Additionally, deletions in ARF (ADP-ribosylation factor) at 55%, amplification of MDM2 (Mouse double minute 2 homolog) at 11%, and amplification of MDM4 (Double minute 4 protein) at 4% contribute to the inactivation of the P53 pathway [38]. TP53 is the most frequent and the earliest detectable alteration in the transition from low grade to high-grade [43].

Rb pathway: This retinoblastoma (Rb) pathway is dysregulated in 78% of GBM cases and is a vital regulator of the cell cycle and controls progression through the G1 to S phase of the cell cycle at the G1 checkpoint [44]. The Rb gene promoter is methylated frequently in secondary than primary GBMs and is associated with its low gene expression. There are two significant genetic alterations seen in the pathway– deletion of the CDKN2A/CDKN2B locus on chromosome 9p21 and the amplification of the CDK4 locus [38]. Such a loss of CDKN2A, RB or CDK4 amplification disrupts the p16INK4A-CDK4-RB tumor suppressor pathway. It has been shown to correlate with decreased expression and survival.

4. Significance of DDR pathway in glioblastoma

Recent studies have implicated the DNA damage response (DDR) pathway in modulating GBM chemoresistance. GBMs being the most aggressive gliomas with the least survival rate with treatment options being only radiation and chemotherapy using TMZ. These tumors ultimately gain resistance, leading to cancer relapse. This chemoresistant phenotype is attributed to enhanced DDR with alterations in DNA-repair and cell-cycle genes [12]. DNA repair mechanisms have evolved to counteract this damage based on the type of damage the DNA experiences (Figure 1). Some of the commonly observed damage and repair mechanisms are:

1. Methylated O6 or N7 Guanine is repaired directly by MGMT (O-6-Methylguanine-DNA Methyltransferase)
2. Oxidized/Deaminated bases by Base excision repair
3. Bulky DNA lesions or DNA-protein adducts by Nucleotide excision repair
4. Mismatched bases by Mismatch repair
5. Double-strand breaks by Homologous recombination or Nonhomologous end-joining or Alternate End Joining or Single-strand annealing
6. Inter-strand crosslinks by Fanconi Anemia pathway

Figure 1.
Genes involved in the various types of DDR.

4.1 Frequently mutated genes of DDR pathway in glioblastoma

Besides mutations in IDH, TP53, and TERT promoter in GBMs, the mutation in genes that function in various DDR pathways have been reported:

MGMT-mediated DNA repair: As previously explained, MGMT is a DNA repair enzyme involved in DNA damage repair induced by alkylating drugs like TMZ. It is involved in the repair of DNA lesions. MGMT enzyme reverses O-alkylated DNA lesions of the alkylated bases [45]. MGMT is mostly hypermethylated in GBM; ~1.6% of the patient's mutation is observed (The results are in whole or part based upon data generated by the TCGA Research Network: <https://www.cancer.gov/tcga>).

Base excision repair: BER corrects base damage that does not cause significant distortions to the DNA helix. The enzymes involved in repair are DNA glycosylase, AP endonuclease, POL β , DNA ligase 1, or a complex of DNA ligase 3 and XRCC1 [46]. Unlike direct repair by MGMT, there are very few BER machinery components that showed a mutation in GBM.

Nucleotide excision repair: NER is the pathway chosen to remove bulky lesions. The damage is sensed by XPC complexed with RAD23B and CETN2. The other pathway proteins are the UV-DDB complex consisting of DDB1, DDB2, and TFIIH complex. Endonuclease XPF-ERCC1 and XPG, the replicative proteins PCNA, RFC, POL δ , POL ϵ or POL κ , and LIG1, XRCC1-LIG3 [47]. Of these genes, 5.6% of the cases had a mutation in POLE [48].

Mismatch repair (MMR): The mismatches incorporated during replication are recognized by MutS α heterodimer (MSH2/MSH6) or MutS β heterodimer (MSH2/MSH3). The other proteins involved are POL δ , RFC, HMGB1, and LIG1 [49]. Of these, 3.8% of patients had a mutation in MSH6 and 1.6% in the MSH2 gene [48].

Double-strand breaks repair: The Double-Stranded Breaks (DSBs) are majorly repaired by nonhomologous end-joining (NHEJ) [50] and homologous recombination (HR) [51]. The alternate less-characterized pathway is microhomology-mediated end joining (MMEJ) or alternative end-joining (AEJ) [52]. While HR is restricted to the cell-cycle S and G2 phases, NHEJ and MMEJ are free to get employed in any cell cycle phase [53]. In response to DSBs, three proteins of the phosphoinositide 3-kinase-related kinase (PIKK) family are activated – ATM, ATR, and DNA-PK, downstream they phosphorylate other substrates, activating them [12]. The additional factors that are subsequently recruited include XRCC4, XLF, DNA ligase IV (LIG4), ARTEMIS, and PAXX which plays a key role in stabilizing the complex chromatin [54]. Other proteins that facilitate the pathway are DNA polymerases like POLM and POLL. Multiple proteins in this pathway are mutated in GBM. The ATR gene is mutated in 4.5% patients followed by 2.9% in PRKDC (DNA-PK), 2.5% in ATM, 1.9% ARTEMIS, 1.94% in XRCC5 (Ku80) and POLL [48].

The HR preferentially repairs the DSBs, which occur at the replication fork [55]. The pre-requisite for the homologous recombination repair pathway is the end-processing of DSBs by helicases and nucleases to produce single-stranded DNA. ATM, CtIP, MRN complex (MRE11-RAD50-NBS1) is involved in generating ssDNA [56]. This ssDNA binds with the RecA/RAD51 complex, stimulated by RPA, promotes DNA pairing and strand exchange in an ATP-dependent fashion [57]. Additionally, the tumor suppressor proteins – BRCA1, BRCA2, and PALB2 are involved in HR [58]. In GBM patients, 3.55% BRCA1, 1.86% MRE11A and RAD50, 1.4% NBN, and ~ 1% RPA1 mutations have been reported [48].

The MMEJ pathway is promoted by PARP-1, Ligase III, CtIP, and Mre11. It uses the same machinery as the HR pathway to form a 3' single-stranded overhang at the

region of DSB [52, 59]. Mutations in Ligase III (3.49%) PARP1 (3.33%) and CtIP (2.5%) have been reported in GBM patients [48].

Single strand annealing (SSBR): The single-strand breaks are detected by PARP1, followed by end-processing by PE1, PNKP, and APTX. FEN1 acts as an endonuclease to create a gap. POL β , in combination with POL δ/ϵ , fills the gap and is ligated by LIG1 [60]. Mutations, although at a much lower frequency, have been reported in all the components of SSBR, APTX (1.17%), FEN1 and PNKP (0.78%), and POLB (0.39%) [48].

Inter-strand crosslink repair (ICL): ICLs are resolved by complex FANCM and FAAP24. MFH stimulates the remodeling of the replication fork. The RPA protein binds to ssDNA and activates ATR, CHK1, FANCE, FANCD2, FANCI, and MRN consecutively. Further, excision is carried out by PF-ERCC1, MUS8-EME1, SLX4-SLX1, FAN1, SNM1A/SNM1B. The polymerase which acts to repair includes POL ι , POL κ , POL ν , and REV1 [61]. 4.42% mutations in FANCD2, 2.26% in FANCI, 1.61% in FANCE, 2.7% and 1.91% in SNM1A and SNM1B, respectively have been reported in GBM patients [48].

Depending on the type of damage a cell encounters, any of these pathways can be activated to restore the damage sites. One of the most deleterious repairs found in cancer cells is MMEJ which results in large deletions and translocations, destabilizing the genome. In GBM, HR and c-NHEJ have higher mutation rates than in MMEJ, making MMEJ the preferred pathway for DNA repair. **Figure 2** represents the frequently mutated genes of the various DDR pathways along with their impact

Figure 2.
Frequently mutated genes of DDR pathway in glioblastomas obtained from GEPIA database.

on overall survival obtained from NCI - GDC Database [62]. As can be observed, the mutations in these genes reduce patients’ survival in GBM (14–16 months).

4.2 Altered gene expressions of DDR pathway genes in glioblastoma

The various genomic mutations like the overexpression of oncogenes and under expression of tumor suppressor genes lead to altered genomic and epigenomic changes favoring cancer growth. In GBM several genes that encode proteins in the DNA repair pathway have altered expression. **Figure 3** represents some of the altered gene expressions in the different DDR pathways in GBMs. This data is obtained from GEPIA database which compares normal patient samples with GBM tumor samples [63].

Figure 3. Altered gene expressions in the various DDR pathway in glioblastoma.

The DDR genes are significantly upregulated and include HR factors - RAD51 recombinase, the chromatin remodelers RAD54B and RAD54L, enzymes in the HOLLIDAY JUNCTION resolution (EME1/MUS81 complex), NER (ERCC3 (XPB), ERCC4 (XPF). Also, expression of genes encoding DNA glycosylase NEIL3, Fanconi Anemia factors (FANCD2, UBE2T), the ubiquitin-protein ligase UBE3B, and two specialized DNA polymerases POLM and POLQ in the NHEJ pathway are increased significantly [64]. Coincident with the least mutation, MMEJ transcripts show relatively higher expression than other pathways. Closer observation shows elevated MMR transcripts, but a higher mutation rate has been observed of some of the genes like MSH2 and MSH6 in GBM. Among HR gene expression, PDS5B is highly expressed, which is required for proper segregation.

Additionally, these signatures also suggest the sensitivity of the tumor to therapeutic drugs. Upregulation of the TOP2A gene, which encodes topoisomerase II, might be more sensitive to topoisomerase II inhibitors like etoposide. Similarly, the decreased expression of NER genes like ERCC3/XPB and ERCC4/XPF can be more sensitive to cisplatin. Cisplatin acts by causing inter-strand crosslinking, and its repair requires NER [64]. Targeting RAD51 is also a potential therapeutic option that can either target the HR pathway or sensitize the cancer cells to irradiation and chemotherapeutic agents that cause DSBs [65].

4.3 Drugs targeting DDR kinases

In tumors treated with DNA damaging agents, efficient DNA repair systems become the primary cause for treatment failure. GBM’s ability to resist DNA insults is directly attributable to its upregulation of DNA repair pathways. Hence, along with the standard care regimen, DDR kinase inhibitors are being investigated to overcome chemo- and radio-resistance. **Table 2** represents inhibitors that are being developed to target kinases in the DNA damage response pathway.

Kinase	Inhibitor	Phase	Reference
ATM	KU60019	Preclinical	[54]
	CP466722	Pre-clinical +temozolomide	[66]
	AZ32	Preclinical + IR	[67]
	AZD1390	Phase-I + IR	[68]
ATR	VE-821	Preclinical +cisplatin	[55]
	AZ20	Preclinical	[56, 57]
DNA-PK	CC-115	Phase-I + neratinib +temozolomide	[58]
Chk2	PV1019	Pre-clinical - + IR + topotecan	[59]
	CCT241533	Pre-clinical - bleomycin +olaparib +IR	[61]
Wee1	MK-1775	Phase-I monotherapy +IR + temozolomide	[60]
PARP	Niraparib	Phase II monotherapy +temozolomide +bevacizumab +carboplatin	[69]
	Veliparib	Phase III + IR + temozolomide	[70]
	Olaparib	Phase II monotherapy +bevacizumab +IR + temozolomide	[71]

Table 2.
List of drugs developed targeting DDR kinases in gliomas.

4.4 miRNAs involved in DDR

MicroRNAs are a group of noncoding RNAs ~18–22 nucleotides in length. miRNA regulates gene expression at both transcriptional and post-transcriptional levels. It modulates transcription by binding to the 5' UTR of the gene. The binding of miRNA at 3' UTR regions (untranslated regions) reduces mRNA stability or inhibits translation [72, 73]. Dysregulated miRNA expression is one of the hallmarks of cancer. They have been shown to affect several crucial processes like proliferation, invasion, and metastasis [74]. Hence, they are potential biomarkers and targets for therapeutic intervention. The aberrant expression of miRNAs in GBM is well documented. 256 upregulated miRNAs and 95 downregulated miRNAs are reported in GBM compared to normal brain tissue [72]. Here, we focus on the deregulated miRNAs involved in DDR pathways leading to chemoresistant or chemosensitive phenotype (**Table 3**).

miRNA	Target	Activity	Reference
MiR-338-5p	Ndfip1, Rheb, ppp2R5a	Radio sensitivity	[75]
MiR-10b	p-AKT	Decreases sensitivity to radiation	[76]
miR-26a, miR-100	ATM	Radio sensitivity	[77]
miR-30b-3p	HIF1 α , STAT3	Chemo resistance	[78]
miR-1193	FEN1	Chemo sensitivity	[79]
miR-96	PDCD4	Radio resistance	[80]
miR-17	ATG7	Chemo and radio sensitivity	[81]
miR-21	PDCD4, TPM1, PTEN	Chemoresistance	[82]
miR-143	N-RAS	Chemo sensitivity	[83]
miR200a, miR-603, miR-181d, miRNA-370-3p, miR-198, miR-142-3p	MGMT	Chemo sensitivity	[84]
miR195	SIAH1,WEE1 RANBP3	Chemoresistance	[85]
miR-455-3p	LTBR, EI24, SMAD2	Chemoresistance	
miR-10a	EPHX1 and BRD7	Chemoresistance	
miR-222	GAS5, MGMT	Increase the DNA damage effect induced by TMZ	[86]
miR-29c	Sp1, MGMT	Chemo sensitivity	[87]
miR-99	SNF2H/SMARCA5	Radio sensitivity	[88]
miR210-3p	HIF1 α /HIF2 α	Chemo resistance	[89]
miR-136	AEG-1	Chemo sensitivity	[90]
miR-155	p38	Chemo sensitivity	[91]
miR-181b	MEK1	Chemo sensitivity	[92]
miR-29b	STAT3	Chemo sensitivity	[93]
miR-101	DNA-PKcs, ATM	Radio sensitivity	[94]
miR-137	CAR, MDR1	Chemo sensitivity	[95]
miR-204	FAP- α	Reverses chemo resistance	[96]
MiR-181a	Bcl-2	Radio sensitivity	[97]
miR-132	TUSC3	Chemo resistance	[98]

miRNA	Target	Activity	Reference
miR-138	BIM	Chemo resistance	[99]
miR-221, miR-222	DNA-PKcs	Radio resistance	[100]
miR-1238	CAV1	Chemo resistance	[101]
miR-26a	Bax, Bad, HIF-1 α	Chemo resistance	[102]
miR-9	PTCH1	Chemo resistance	[103]
miR-124, miR-128, miR-137	EZH2, BMI1, LSD1	Chemo resistance	[104]
miR-151a	XRCC4	Chemo sensitivity	[105]

Table 3.
Deregulated miRNAs involved in DNA damage response in GBM.

4.5 lncRNAs in gliomas

The noncoding RNAs are a diverse group of transcribed RNAs, with long-non coding RNA or lncRNA being the largest sub-type in this category [106]. Long noncoding RNA can regulate gene expression by binding to the gene’s promoter and recruiting activators or repressors, or chromatin modifiers and activating or repressing transcription, respectively [106, 107]. Alternatively, they can work as antisense and bind to the transcripts, thereby inhibiting translation or destabilizing the transcript. They can also act as miRNA sponges, altering gene expression post-transcriptionally [108]. lncRNA deregulation is involved in cancer development, progression, and metastasis. It is a potential target for therapeutic interventions. Their expression pattern in response to chemotherapeutic treatment has prognostic value and serves as predictive biomarkers [106, 107].

lncRNAs are abundantly expressed in the brain as compared to other parts of the body [109]. Glioma subclassification has also been done based on the lncRNA profile into three groups: (i) astrocytic tumor with high EGFR amplification (ii) neuronal-type tumor (iii) oligodendrocytic tumor enriched with an IDH-1 mutation and 1p19q co-deletion. Such a classification has been shown to correspond to patient survival where lncRNAs like PART1, MGC21881, MIAT, GAS5, and PAR5 were correlated with prolonged survival. At the same time, KIAA0495 was associated with poor survival [109]. **Table 4** represents the lncRNAs studied in gliomas that are involved in chemoresistance or chemosensitivity.

4.6 Circular RNAs in gliomas

Circular RNA is yet another group of noncoding RNA produced from pre-mRNA back-splicing [137]. They inhibit miRNA and upregulate the expression of genes at the transcriptional and post-transcriptional levels [138, 139]. CircRNAs have also been shown to bind to different proteins to form circRNA-protein complexes (circRNPs) that regulate the action of associated proteins, the subcellular localization of proteins, and the transcription of parental or related genes [140]. circRNAs play significant roles in tumor growth, metastasis, EMT transformation, and therapy resistance [141]. circRNAs are the most abundant in the brain and play a crucial role in the brain’s functioning [142]. In glioma, they are expressed aberrantly and play a key role in tumor initiation and progression [143]. In GBM, several studies have identified the upregulated and the down-regulated circRNAs. Identifying these circRNAs is valuable for further understanding the molecular mechanism of glioma and developing novel targeted treatments [144]. **Table 5** represents the circRNAs studied in gliomas with their targets.

lncRNA	Target	Activity	Reference
ADAMTS9-AS2	FUS	Chemo-resistance	[110]
AHIF	HIF1a, p53	Radio-resistance	[111]
CASC-2	miR 181a, PTEN	Chemo-resistance	[112]
CCAT2	miR-424, CHK1	Chemo-resistance	[113]
H19	MDR, MRP, and ABCG2	Chemo-resistance, Stemness in GSCs	[114]
HMMR-AS1	HMMR mRNA stabilization, ATM, RAD51, BMI1	Radio-resistance	[115]
HOTAIR	miR-519a-3p, RRM1	Chemo resistance	[116]
LINC00174	miR-138-5, SOX9	Chemo resistance	[117]
LINC01057	IKKα	Radio resistance	[118]
MALAT1	miR-203, miR-101, Thymidylate synthase (TS)	Reduction of cell proliferation	[119, 120]
MIR155HG	PTBP1	Chemo-resistance	[121]
NCK1-AS1	miR-137, TRIM24	Chemo-resistance	[122]
PCAT1	miR-129-5p, HMGB1	Radio-resistance	[123]
PSMB8-AS1	MiRNA-22-3p, DDIT4	Radio resistance	[124]
RA1	H2B	Radio resistance	[125]
SBF2-AS1	miR-151a-3p, XRCC4	Chemo-resistance	[126]
SNHG18	Sema5A	Radio resistance	[127]
SOX2OT	ALKBH5, SOX2, Wnt5a/β-catenin	Chemo-resistance	[128]
TALC	miR-20b-3p, Stat3/p300 complex, MGMT	Chemo-resistance	[129]
TALNEC2	G1/S transition, mesenchymal transformation	Radio-resistance	[130]
TP53TG1	miR-524-5p, RAB5A	Radio-resistance	[131]
TP73-AS1	Metabolism related genes, ALDH1A1	Chemo-resistance	[132]
TPTEP1	miR-106a-5p, MAPK14	Radio-resistance	[133]
TUSC7	miR-10a MDR1	Chemo resistance	[134]
UCA1	Wnt/β-catenin	Chemo-resistance	[135]
Xist	miR-29c, SP1, MGMT	Chemo-resistance	[136]

Table 4.
lncRNAs in glioma involved in chemoresistance or chemosensitivity.

circRNA	Target	Activity	Reference
NFIX	miR-132	Chemo resistance	[145]
circ_0005198	miR-198 TRIM14	Chemo resistance	[146]
CEP128	miR-145-5p	Chemo resistance	[147]
VCAN	miR-1183	Radio resistance	[148]
circPITX1	MiR-329-3p NEK2	Radio resistance	[149]
CircATP8B4	miR-766-5p	Radio resistance	[150]
CDR1as	miR-7, p53	Protects from DNA damage	[151]

Table 5.
circRNAs involved in chemoresistance/chemosensitivity in gliomas.

5. Novel therapeutic drugs being developed for gliomas

The standard chemotherapeutic drugs used for gliomas are alkylating agents (TMZ, procarbazine, vincristine, carmustine). More recently, GLIADEL wafer containing carmustine is approved for GBM as an adjunct to surgery and radiation [152]. Humanized monoclonal IgG1 antibody Bevacizumab targeting VEGF is used for recurrent GBM [153]. Surpassing the blood–brain barrier makes treating gliomas difficult [154]. Several inhibitors targeting enzymes like topoisomerase II, [155], immunotherapeutic agents like α -type-1 dendritic cell vaccine [156], autologous cytokine-induced killer cell immunotherapy [157], autologous dendritic cell vaccine [158], and immunomodulatory drugs [159] are in clinical trials phases I and II. Additionally, many of these drugs in combination with the standard chemotherapeutic drug are also in trials, including Giladel wafers with dendritic cell vaccine [160], Lomustine-temozolomide [160, 161], Bevacizumab + radiation therapy + temozolomide [162], Irinotecan + bevacizumab + temozolomide [163]. The **Table 6** lists some of the drugs which are in phase 3 trial for glioma treatment.

Drug	Status	Activity	Reference
Cilengitide	Did not improve outcomes	α v β 3 and α v β 5 integrin inhibitor	[164]
Rindopepimut	Did not improve outcomes	Targets EGFRvIII	[165]
DCVax®-L	Feasible and safe, May extend survival	Autologous tumor lysate-pulsed dendritic cell vaccine	[166]
Nivolumab	Did not improve overall survival	PD-1 inhibitor	[167]
Lomustine (CCNU) -temozolomide	Might improve survival	Nitrosourea Alkylating agent	[161]
Tumor treating fields	Significantly improved OS and PFS (with TMZ)	Alternating electric fields targeting microtubules and septin fibers	[168]
Sitimagene ceradenovec	Can increase time to death or re-intervention but did not improve overall survival	Adenovirus-mediated gene therapy	[169]
CIK cell immunotherapy	Along with TMZ improves PFS, but not OS	Autologous cytokine-induced killer cell immunotherapy	[157]

Table 6.
Novel drugs in clinical trials for glioma treatment.

6. Conclusion

Gliomas are the most common malignant brain cancers constituting 80% of all brain & central nervous system cancers. Even though gliomas represent a small percentage of all cancers, they account for disproportionally high morbidity and mortality. Despite the emphasis on new therapeutic interventions, the standard care regimen has not changed drastically. However, there has been more emphasis on understanding molecular pathogenesis and its clinical relevance. Emerging preclinical and clinical data points to a shift towards more personalized therapies, and targeting the DDR pathway and its related noncoding genes is on the horizon. **Figure 4** summarizes the interplay of noncoding in DDR and drug resistance in gliomas.

Figure 4.
Representative genes and non-coding RNAs in glioblastomas.

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