Chapter

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 Kreb 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

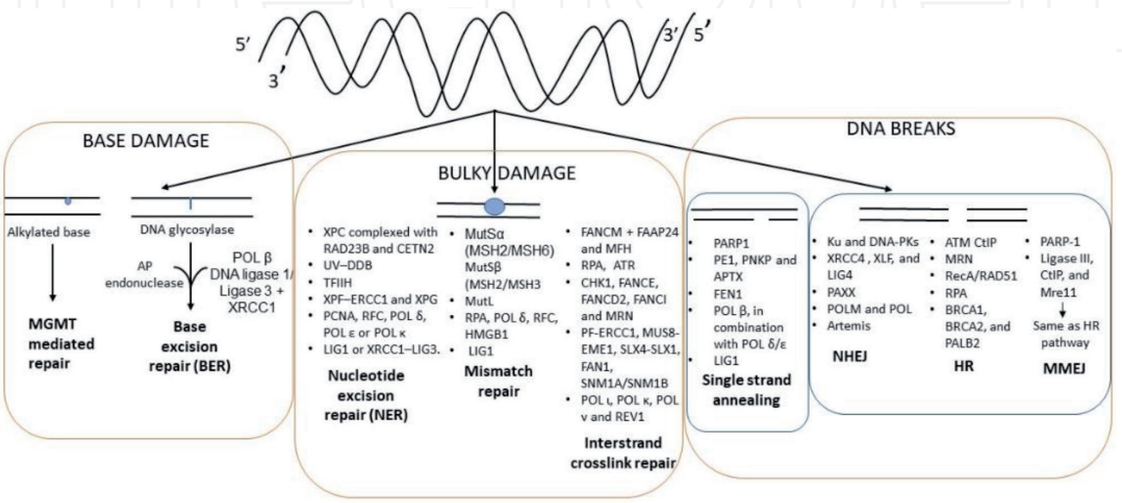

Figure 1.
Genes involved in the various types of DDR.

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 MutSα heterodimer (MSH2/MSH6) or MutSβ 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

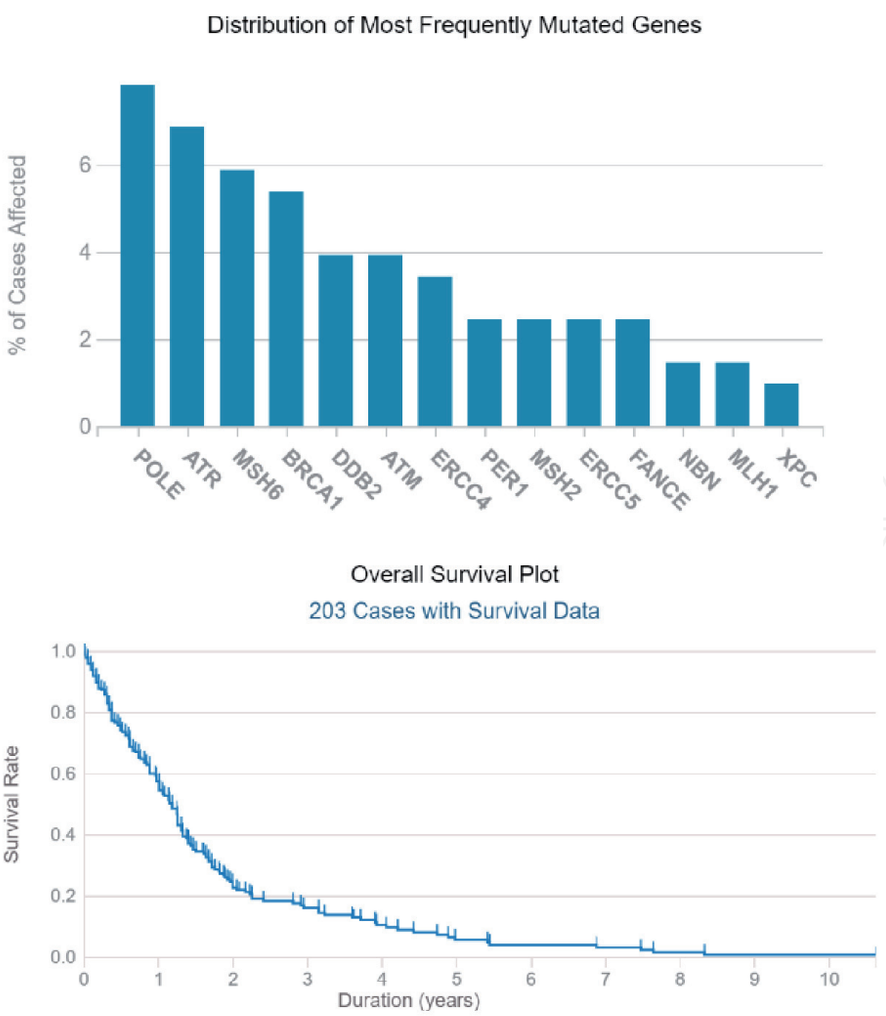

Figure 2.
Frequently mutated genes of DDR pathway in glioblastomas obtained from GEPIA database.

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].

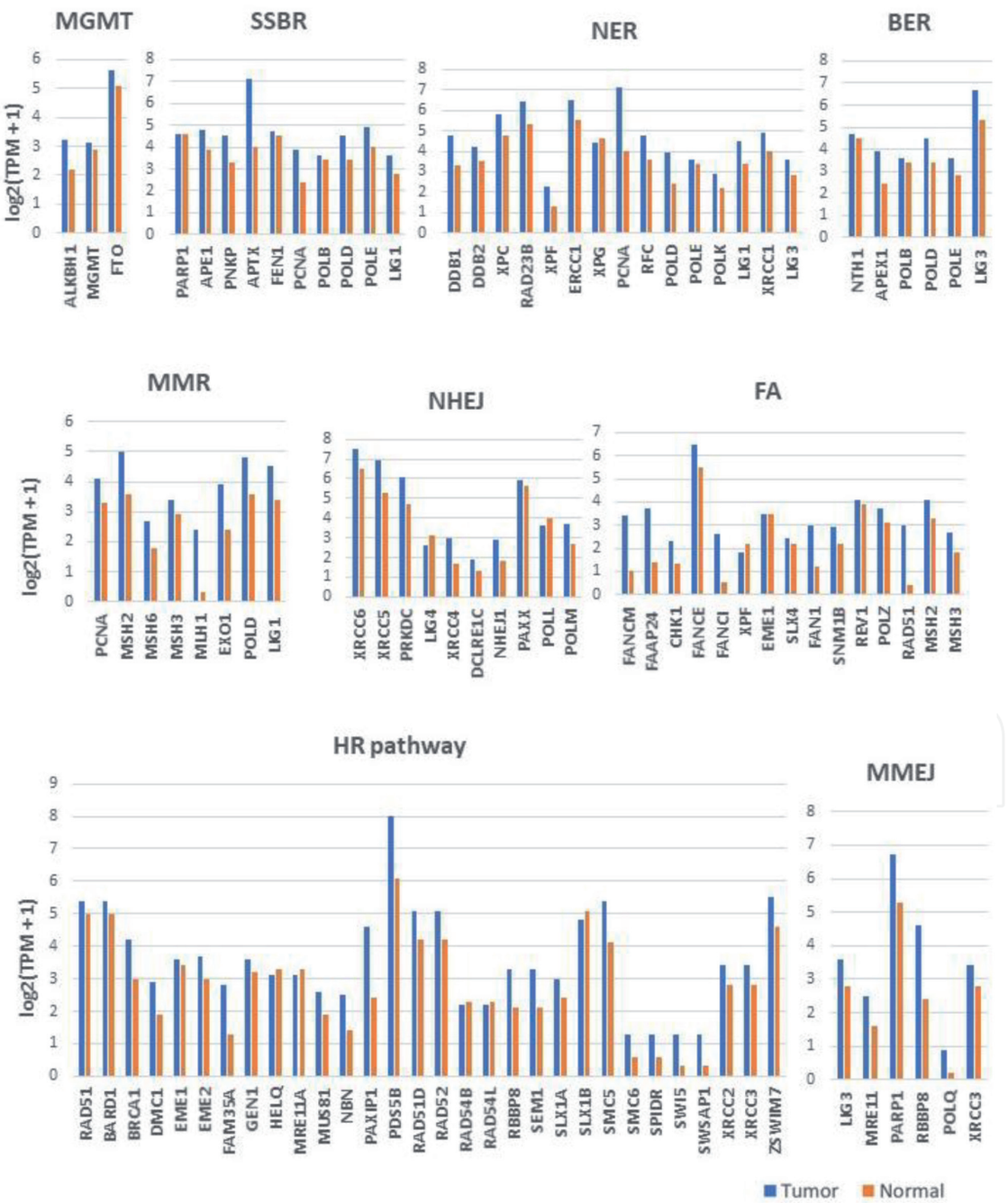

Figure 3.
Altered gene expressions in the various DDR pathway in glioblastoma.

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	HIF1α, 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	HIF1α/HIF2α	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-1α	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	αvβ3 and αvβ5 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.

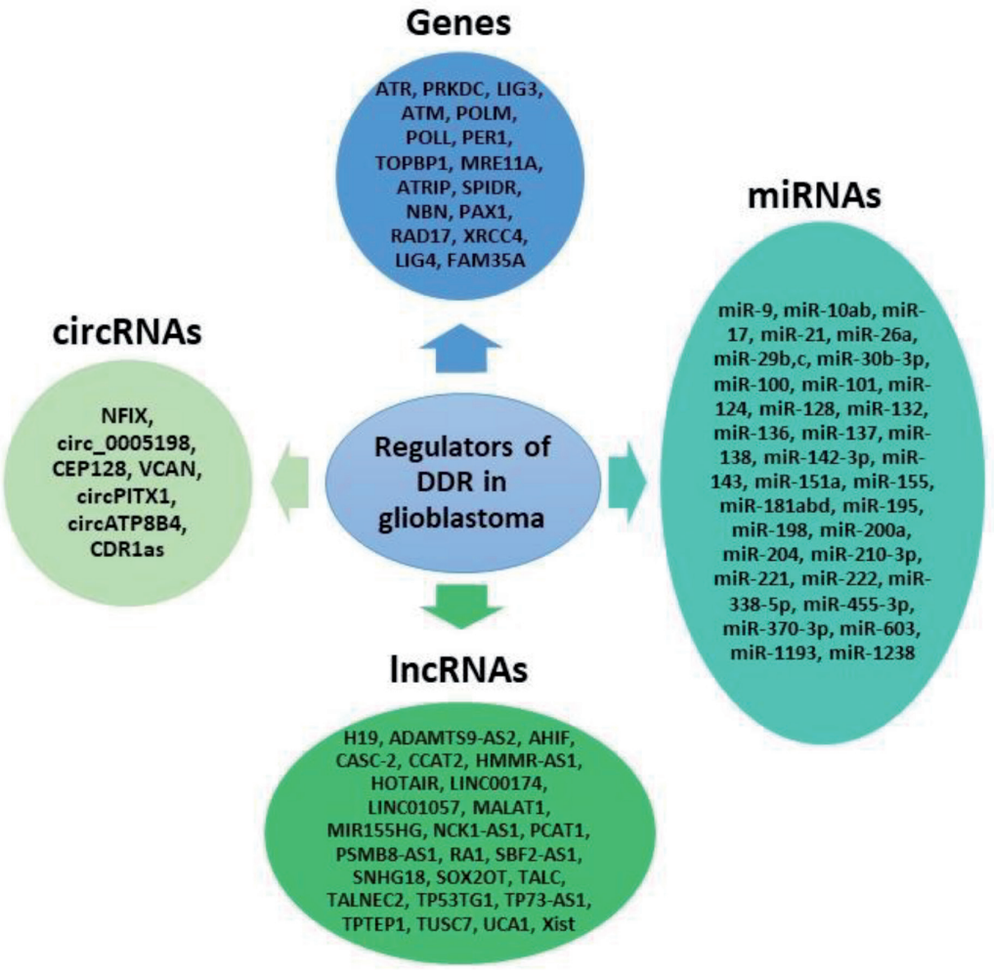

Figure 4.
Representative genes and non-coding RNAs in glioblastomas.

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References

[1] Cancer today [Internet]. [cited 2021 Feb 16]. Available from: http://gco.iarc.fr/today/home

[2] de Groot JF. High-grade gliomas. Continuum. 2015 Apr;21(2 Neuro-oncology):332-44.

[3] Wrensch M, Fisher JL, Schwartzbaum JA, Bondy M, Berger M, Aldape KD. The molecular epidemiology of gliomas in adults [Internet]. Vol. 19, Neurosurgical Focus. 2005. p. 1-11. Available from: http://dx.doi.org/10.3171/foc.2005.19.5.6

[4] Nayak L, Reardon DA. High-grade Gliomas [Internet]. Vol. 23, CONTINUUM: Lifelong Learning in Neurology. 2017. p. 1548-63. Available from: http://dx.doi.org/10.1212/con.0000000000000554

[5] Michaeli O, Tabori U. Pediatric High Grade Gliomas in the Context of Cancer Predisposition Syndromes. J Korean Neurosurg Soc. 2018 May;61(3):319-332.

[6] Vijapura C, Saad Aldin E, Capizzano AA, Policeni B, Sato Y, Moritani T. Genetic Syndromes Associated with Central Nervous System Tumors. Radiographics. 2017 Jan;37(1):258-280.

[7] Rice T, Lachance DH, Molinaro AM, Eckel-Passow JE, Walsh KM, Barnholtz-Sloan J, et al. Understanding inherited genetic risk of adult glioma – a review. Neurooncol Pract. 2015 Aug 25;3(1):10-16.

[8] Holland EC. Gliomagenesis: genetic alterations and mouse models. Nat Rev Genet [Internet]. 2001 Feb [cited 2021 Feb 16];2(2). Available from: https://pubmed.ncbi.nlm.nih.gov/11253051/

[9] Rajesh Y, Pal I, Banik P, Chakraborty S, Borkar SA, Dey G, et al. Insights into molecular therapy of glioma: current challenges and next generation blueprint [Internet]. Vol. 38, Acta Pharmacologica Sinica. 2017. p. 591-613. Available from: http://dx.doi.org/10.1038/aps.2016.167

[10] Wang R-J, Shen G-Q, Shiroishi MS, Gao B. Current concepts of imaging genomics in glioma. Glioma. 2018 Jan 1;1(1):9.

[11] Turek G, Pasterski T, Bankiewicz K, Dzierzęcki S, Ząbek M. Current strategies for the treatment of malignant gliomas – experience of the Department of Neurosurgery, Brodno Masovian Hospital in Warsaw [Internet]. Vol. 92, Polish Journal of Surgery. 2020. p. 1-5. Available from: http://dx.doi.org/10.5604/01.3001.0014.2473

[12] Ferri A, Stagni V, Barilà D. Targeting the DNA Damage Response to Overcome Cancer Drug Resistance in Glioblastoma [Internet]. Vol. 21, International Journal of Molecular Sciences. 2020. p. 4910. Available from: http://dx.doi.org/10.3390/ijms21144910

[13] McDuff SGR, Dietrich J, Atkins KM, Oh KS, Loeffler JS, Shih HA. Radiation and chemotherapy for high-risk lower grade gliomas: Choosing between temozolomide and PCV [Internet]. Vol. 9, Cancer Medicine. 2020. p. 3-11. Available from: http://dx.doi.org/10.1002/cam4.2686

[14] Wirsching H-G, Galanis E, Weller M. Glioblastoma [Internet]. Handbook of Clinical Neurology. 2016. p. 381-97. Available from: http://dx.doi.org/10.1016/b978-0-12-802997-8.00023-2

[15] Schweitzer T, Vince GH, Herbold C, Roosen K, Tonn JC. Extraneural metastases of primary brain tumors. J Neurooncol [Internet]. 2001 Jun [cited 2021 Feb 16];53(2). Available

from: https://pubmed.ncbi.nlm.nih.gov/11716064/

[16] Hamard L, Ratel D, Selek L, Berger F, van der Sanden B, Wion D. The brain tissue response to surgical injury and its possible contribution to glioma recurrence. J Neurooncol. 2016 May;128(1):1-8.

[17] Jessen KR. Glial cells [Internet]. Vol. 36, The International Journal of Biochemistry & Cell Biology. 2004. p. 1861-7. Available from: http://dx.doi.org/10.1016/j.biocel.2004.02.023

[18] Yao Y, Mack SC, Taylor MD. Molecular genetics of ependymoma [Internet]. Vol. 30, Chinese Journal of Cancer. 2011. p. 669-81. Available from: http://dx.doi.org/10.5732/cjc.011.10129

[19] Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al. The 2007 WHO Classification of Tumours of the Central Nervous System. Acta Neuropathol. 2007 Aug;114(2):97.

[20] Wen PY, Kesari S. Malignant gliomas in adults. N Engl J Med [Internet]. 2008 Jul 31 [cited 2021 Feb 16];359(5). Available from: https://pubmed.ncbi.nlm.nih.gov/18669428/

[21] International Agency for Research on Cancer, Wiestler OD. WHO Classification of Tumours of the Central Nervous System. International Agency for Research on Cancer; 2016. 408 p.

[22] Han S, Liu Y, Cai SJ, Qian M, Ding J, Larion M, et al. IDH mutation in glioma: molecular mechanisms and potential therapeutic targets. Br J Cancer. 2020 Apr 15;122(11):1580-1589.

[23] Cohen A, Holmen S, Colman H. IDH1 and IDH2 Mutations in Gliomas. Curr Neurol Neurosci Rep. 2013 May;13(5):345.

[24] Huang J, Yu J, Tu L, Huang N, Li H, Luo Y. Isocitrate Dehydrogenase Mutations in Glioma: From Basic Discovery to Therapeutics Development. Front Oncol [Internet]. 2019 [cited 2021 Feb 15];9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6584818/

[25] Yao J, Hagiwara A, Raymond C, Shabani S, Pope WB, Salamon N, et al. Human IDH mutant 1p/19q co-deleted gliomas have low tumor acidity as evidenced by molecular MRI and PET: a retrospective study. Sci Rep. 2020 Jul 17;10(1):1-12.

[26] Felsberg J, Erkwoh A, Sabel MC, Kirsch L, Fimmers R, Blaschke B, et al. Oligodendroglial tumors: refinement of candidate regions on chromosome arm 1p and correlation of 1p/19q status with survival. Brain Pathol [Internet]. 2004 Apr [cited 2021 Feb 15];14(2). Available from: https://pubmed.ncbi.nlm.nih.gov/15193024/

[27] Bell RJA, Rube HT, Xavier-Magalhães A, Costa BM, Mancini A, Song JS, et al. Understanding TERT Promoter Mutations: A Common Path to Immortality. Mol Cancer Res. 2016 Apr;14(4):315-323.

[28] Nonoguchi N, Ohta T, Oh J-E, Kim Y-H, Kleihues P, Ohgaki H. TERT promoter mutations in primary and secondary glioblastomas. Acta Neuropathol. 2013 Dec;126(6):931-937.

[29] Clinical implications of TERT promoter mutation on IDH mutation and MGMT promoter methylation in diffuse gliomas. Pathology - Research and Practice. 2018 Jun 1;214(6):881-8.

[30] Wick W, Weller M, van den Bent M, Sanson M, Weiler M, von Deimling A, et al. MGMT testing--the challenges for biomarker-based glioma treatment. Nat Rev Neurol. 2014 Jul;10(7):372-385.

[31] Wang K, Wang Y-Y, Ma J, Wang J-F, Li S-W, Jiang T, et al. Prognostic value of

MGMT promoter methylation and TP53 mutation in glioblastomas depends on IDH1 mutation. Asian Pac J Cancer Prev. 2014;15(24):10893-10898.

[32] Oppel F, Tao T, Shi H, Ross KN, Zimmerman MW, He S, et al. Loss of atrx cooperates with p53-deficiency to promote the development of sarcomas and other malignancies. PLoS Genet. 2019 Apr 10;15(4):e1008039.

[33] Haase S, Garcia-Fabiani MB, Carney S, Altshuler D, Núñez FJ, Méndez FM, et al. Mutant ATRX: uncovering a new therapeutic target for glioma. Expert Opin Ther Targets. 2018 Jul;22(7):599.

[34] Adult H3K27M-mutant diffuse midline glioma with gliomatosis cerebri growth pattern: Case report and review of the literature. Int J Surg Case Rep. 2020 Jan 1;68:124-128.

[35] Mohammad F, Weissmann S, Leblanc B, Pandey DP, Højfeldt JW, Comet I, et al. EZH2 is a potential therapeutic target for H3K27M-mutant pediatric gliomas. Nat Med. 2017 Feb 27;23(4):483-492.

[36] Ghasimi S, Wibom C, Dahlin AM, Brännström T, Golovleva I, Andersson U, et al. Genetic risk variants in the CDKN2A/B, RTEL1 and EGFR genes are associated with somatic biomarkers in glioma. J Neurooncol. 2016 Feb 2;127(3):483-492.

[37] Ohgaki H, Dessen P, Jourde B, Horstmann S, Nishikawa T, Di Patre PL, et al. Genetic pathways to glioblastoma: a population-based study. Cancer Res [Internet]. 2004 Oct 1 [cited 2021 Feb 16];64(19). Available from: https://pubmed.ncbi.nlm.nih.gov/15466178/

[38] Cancer Genome Atlas Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature. 2008 Oct 23;455(7216):1061-1068.

[39] Eléonore Toufektchan FT. The Guardian of the Genome Revisited: p53 Downregulates Genes Required for Telomere Maintenance, DNA Repair, and Centromere Structure. Cancers [Internet]. 2018 May [cited 2021 Feb 15];10(5). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5977108/

[40] Toshinori Ozaki AN. Role of p53 in Cell Death and Human Cancers. Cancers. 2011 Mar;3(1):994.

[41] Aubrey BJ, Strasser A, Kelly GL. Tumor-Suppressor Functions of the TP53 Pathway. Cold Spring Harb Perspect Med [Internet]. 2016 May 2;6(5). Available from: http://dx.doi.org/10.1101/cshperspect.a026062

[42] Takami H, Yoshida A, Fukushima S, Arita H, Matsushita Y, Nakamura T, et al. RevisitingTP53Mutations and Immunohistochemistry-A Comparative Study in 157 Diffuse Gliomas [Internet]. Vol. 25, Brain Pathology. 2015. p. 256-65. Available from: http://dx.doi.org/10.1111/bpa.12173

[43] Ohgaki H, Kleihues P. Genetic pathways to primary and secondary glioblastoma. Am J Pathol. 2007 May;170(5):1445-1453.

[44] Biasoli D, Kahn SA, Cornélio TA, Furtado M, Campanati L, Chneiweiss H, et al. Retinoblastoma protein regulates the crosstalk between autophagy and apoptosis, and favors glioblastoma resistance to etoposide. Cell Death Dis. 2013 Aug 15;4(8):e767–e767.

[45] Christmann M, Verbeek B, Roos WP, Kaina B. O(6)-Methylguanine-DNA methyltransferase (MGMT) in normal tissues and tumors: enzyme activity, promoter methylation and immunohistochemistry. Biochim Biophys Acta. 2011 Dec;1816(2):179-190.

[46] Krokan HE, Bjørås M. Base excision repair. Cold Spring Harb Perspect Biol. 2013 Apr 1;5(4):a012583.

[47] Schärer OD. Nucleotide excision repair in eukaryotes. Cold Spring Harb Perspect Biol. 2013 Oct 1;5(10):a012609.

[48] The Cancer Genome Atlas program [Internet]. 2018 [cited 2021 Mar 6]. Available from: https://www.cancer.gov/tcga

[49] Li G-M. Mechanisms and functions of DNA mismatch repair. Cell Res. 2007 Dec 24;18(1):85-98.

[50] Lieber MR. The mechanism of human nonhomologous DNA end joining. J Biol Chem. 2008 Jan 4;283(1):1-5.

[51] San Filippo J, Sung P, Klein H. Mechanism of eukaryotic homologous recombination. Annu Rev Biochem. 2008;77:229-257.

[52] McVey M, Lee SE. MMEJ repair of double-strand breaks (director's cut): deleted sequences and alternative endings. Trends Genet. 2008 Nov;24(11):529-538.

[53] Jackson SP, Bartek J. The DNA-damage response in human biology and disease. Nature. 2009 Oct 22;461(7267):1071-1078.

[54] Golding SE, Rosenberg E, Valerie N, Hussaini I, Frigerio M, Cockcroft XF, et al. Improved ATM kinase inhibitor KU-60019 radiosensitizes glioma cells, compromises insulin, AKT and ERK prosurvival signaling, and inhibits migration and invasion. Mol Cancer Ther. 2009 Oct;8(10):2894-2902.

[55] Charrier J-D, Durrant SJ, Golec JMC, Kay DP, Knegtel RMA, MacCormick S, et al. Discovery of potent and selective inhibitors of ataxia telangiectasia mutated and Rad3 related (ATR) protein kinase as potential anticancer agents. J Med Chem. 2011 Apr 14;54(7):2320-2330.

[56] Foote KM, Blades K, Cronin A, Fillery S, Guichard SS, Hassall L, et al. Discovery of 4-{4-[(3R)-3-Methylmorpholin-4-yl]-6-[1-(methylsulfonyl)cyclopropyl] pyrimidin-2-yl}-1H-indole (AZ20): a potent and selective inhibitor of ATR protein kinase with monotherapy in vivo antitumor activity. J Med Chem. 2013 Mar 14;56(5):2125-2138.

[57] Ning J, Wakimoto H, Martuza RL, Rabkin SD. Abstract 1122: ATR inhibitors synergize with PARP inhibitors in killing glioblastoma stem cells and treating glioblastoma. Cancer Res. 2017 Jul 1;77(13 Supplement):1122-1122.

[58] Munster P, Mita M, Mahipal A, Nemunaitis J, Massard C, Mikkelsen T, et al. First-In-Human Phase I Study Of A Dual mTOR Kinase And DNA-PK Inhibitor (CC-115) In Advanced Malignancy. Cancer Manag Res. 2019 Dec 13;11:10463-10476.

[59] Jobson AG, Lountos GT, Lorenzi PL, Llamas J, Connelly J, Cerna D, et al. Cellular inhibition of checkpoint kinase 2 (Chk2) and potentiation of camptothecins and radiation by the novel Chk2 inhibitor PV1019 [7-nitro-1H-indole-2-carboxylic acid {4-[1-(guanidinohydrazone)-ethyl]-phenyl}-amide]. J Pharmacol Exp Ther. 2009 Dec;331(3):816-826.

[60] Alexander B, Supko J, Agar N, Ahluwalia M, Desai A, Dietrich J, et al. ACTR-14. PHASE I STUDY OF AZD1775 WITH RADIATION THERAPY (RT) AND TEMOZOLOMIDE (TMZ) IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA (GBM) AND EVALUATION OF INTRATUMORAL DRUG DISTRIBUTION (IDD) IN PATIENTS

WITH RECURRENT GBM. Neuro Oncol. 2018 Nov;20(Suppl 6):vi13.

[61] Anderson VE, Walton MI, Eve PD, Boxall KJ, Antoni L, Caldwell JJ, et al. CCT241533 is a potent and selective inhibitor of CHK2 that potentiates the cytotoxicity of PARP inhibitors. Cancer Res. 2011 Jan 15;71(2):463-472.

[62] Grossman RL, Heath AP, Ferretti V, Varmus HE, Lowy DR, Kibbe WA, et al. Toward a Shared Vision for Cancer Genomic Data. N Engl J Med. 2016 Sep 22;375(12):1109-12.

[63] Tang Z, Li C, Kang B, Gao G, Li C, Zhang Z. GEPIA: a web server for cancer and normal gene expression profiling and interactive analyses. Nucleic Acids Res. 2017 Jul 3;45(W1):W98-102.

[64] Gobin M, Nazarov PV, Warta R, Timmer M, Reifenberger G, Felsberg J, et al. A DNA Repair and Cell-Cycle Gene Expression Signature in Primary and Recurrent Glioblastoma: Prognostic Value and Clinical Implications. Cancer Res. 2019 Mar 15;79(6):1226-1238.

[65] Brown JS, O'Carrigan B, Jackson SP, Yap TA. Targeting DNA Repair in Cancer: Beyond PARP Inhibitors. Cancer Discov. 2017 Jan;7(1):20-37.

[66] Rainey MD, Charlton ME, Stanton RV, Kastan MB. Transient inhibition of ATM kinase is sufficient to enhance cellular sensitivity to ionizing radiation. Cancer Res. 2008 Sep 15;68(18):7466-7474.

[67] Karlin J, Allen J, Ahmad SF, Hughes G, Sheridan V, Odedra R, et al. Orally Bioavailable and Blood-Brain Barrier-Penetrating ATM Inhibitor (AZ32) Radiosensitizes Intracranial Gliomas in Mice. Mol Cancer Ther. 2018 Aug;17(8):1637-1647.

[68] Durant ST, Zheng L, Wang Y, Chen K, Zhang L, Zhang T, et al. The brain-penetrant clinical ATM inhibitor AZD1390 radiosensitizes and improves survival of preclinical brain tumor models. Sci Adv. 2018 Jun;4(6):eaat1719.

[69] Sun K, Mikule K, Wang Z, Poon G, Vaidyanathan A, Smith G, et al. A comparative pharmacokinetic study of PARP inhibitors demonstrates favorable properties for niraparib efficacy in preclinical tumor models. Oncotarget. 2018 Dec 14;9(98):37080-37096.

[70] Gupta SK, Kizilbash SH, Carlson BL, Mladek AC, Boakye-Agyeman F, Bakken KK, et al. Delineation of MGMT Hypermethylation as a Biomarker for Veliparib-Mediated Temozolomide-Sensitizing Therapy of Glioblastoma. J Natl Cancer Inst [Internet]. 2016 May;108(5). Available from: http://dx.doi.org/10.1093/jnci/djv369

[71] Hanna C, Kurian KM, Williams K, Watts C, Jackson A, Carruthers R, et al. Pharmacokinetics, safety, and tolerability of olaparib and temozolomide for recurrent glioblastoma: results of the phase I OPARATIC trial. Neuro Oncol. 2020 Dec 18;22(12):1840-1850.

[72] Zhang Y, Cruickshanks N, Pahuski M, Yuan F, Dutta A, Schiff D, et al. Noncoding RNAs in Glioblastoma. Exon Publications. 2017 Sep 20;95-130.

[73] O'Brien J, Hayder H, Zayed Y, Peng C. Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation. Front Endocrinol [Internet]. 2018 [cited 2021 Feb 16];9. Available from: https://www.frontiersin.org/articles/10.3389/fendo.2018.00402/pdf

[74] Peng Y, Croce CM. The role of MicroRNAs in human cancer. Signal Transduction and Targeted Therapy. 2016 Jan 28;1(1):1-9.

[75] Besse A, Sana J, Lakomy R, Kren L, Fadrus P, Smrcka M, et al. MiR-338-5p

sensitizes glioblastoma cells to radiation through regulation of genes involved in DNA damage response. Tumour Biol. 2016 Jun;37(6):7719-7727.

[76] Zhen L, Li J, Zhang M, Yang K. MiR-10b decreases sensitivity of glioblastoma cells to radiation by targeting AKT. J Biol Res. 2016 Dec;23:14.

[77] Guo P, Lan J, Ge J, Nie Q, Guo L, Qiu Y, et al. MiR-26a enhances the radiosensitivity of glioblastoma multiforme cells through targeting of ataxia-telangiectasia mutated. Exp Cell Res. 2014 Jan 15;320(2):200-208.

[78] Yin J, Ge X, Shi Z, Yu C, Lu C, Wei Y, et al. Extracellular vesicles derived from hypoxic glioma stem-like cells confer temozolomide resistance on glioblastoma by delivering miR-30b-3p. Theranostics. 2021 Jan 1;11(4):1763-1779.

[79] Zhang J, Jing L, Tan S, Zeng E-M, Lin Y, He L, et al. Inhibition of miR-1193 leads to synthetic lethality in glioblastoma multiforme cells deficient of DNA-PKcs. Cell Death Dis. 2020 Jul 30;11(7):602.

[80] Guo P, Yu Y, Tian Z, Lin Y, Qiu Y, Yao W, et al. Upregulation of miR-96 promotes radioresistance in glioblastoma cells via targeting PDCD4. Int J Oncol. 2018 Oct;53(4):1591-1600.

[81] Comincini S, Allavena G, Palumbo S, Morini M, Durando F, Angeletti F, et al. microRNA-17 regulates the expression of ATG7 and modulates the autophagy process, improving the sensitivity to temozolomide and low-dose ionizing radiation treatments in human glioblastoma cells. Cancer Biol Ther. 2013 Jul;14(7):574-586.

[82] Wong STS, Zhang X-Q, Zhuang JT-F, Chan H-L, Li C-H, Leung GKK. MicroRNA-21 inhibition enhances in vitro chemosensitivity of temozolomide-resistant glioblastoma cells. Anticancer Res. 2012 Jul;32(7):2835-2841.

[83] Wang L, Shi Z-M, Jiang C-F, Liu X, Chen Q-D, Qian X, et al. MiR-143 acts as a tumor suppressor by targeting N-RAS and enhances temozolomide-induced apoptosis in glioma. Oncotarget. 2014 Jul 30;5(14):5416-5427.

[84] Berthois Y, Delfino C, Metellus P, Fina F, Nanni-Metellus I, Al Aswy H, et al. Differential expression of miR200a-3p and miR21 in grade II-III and grade IV gliomas: evidence that miR200a-3p is regulated by O6-methylguanine methyltransferase and promotes temozolomide responsiveness. Cancer Biol Ther. 2014 Jul;15(7):938-950.

[85] miR-195, miR-455-3p and miR-10a∗ are implicated in acquired temozolomide resistance in glioblastoma multiforme cells. Cancer Lett. 2010 Oct 28;296(2):241-8.

[86] Huang H, Jiang R, Lian Z, Zhang W, Hu Z, Hu D. miR-222/GAS5 is involved in DNA damage and cytotoxic effects induced by temozolomide in T98G cell line. J Appl Toxicol. 2019 May;39(5):726-734.

[87] Xiao S, Yang Z, Qiu X, Lv R, Liu J, Wu M, et al. miR-29c contribute to glioma cells temozolomide sensitivity by targeting O6-methylguanine-DNA methyltransferases indirectely. Oncotarget. 2016 Aug 2;7(31):50229-50238.

[88] Mueller AC, Sun D, Dutta A. The miR-99 family regulates the DNA damage response through its target SNF2H. Oncogene. 2013 Feb 28;32(9):1164-1172.

[89] Wang P, Yan Q, Liao B, Zhao L, Xiong S, Wang J, et al. The HIF1α/HIF2α-miR210-3p network regulates glioblastoma cell proliferation, dedifferentiation and chemoresistance

through EGF under hypoxic conditions. Cell Death Dis. 2020 Nov 18;11(11):992.

[90] Wu H, Liu Q, Cai T, Chen Y-D, Liao F, Wang Z-F. MiR-136 modulates glioma cell sensitivity to temozolomide by targeting astrocyte elevated gene-1. Diagn Pathol. 2014 Sep 30;9:173.

[91] Liu Q, Zou R, Zhou R, Gong C, Wang Z, Cai T, et al. miR-155 Regulates Glioma Cells Invasion and Chemosensitivity by p38 Isforms In Vitro. J Cell Biochem. 2015 Jul;116(7):1213-1221.

[92] Wang J, Sai K, Chen F-R, Chen Z-P. miR-181b modulates glioma cell sensitivity to temozolomide by targeting MEK1. Cancer Chemother Pharmacol. 2013 Jul;72(1):147-158.

[93] Xu J-X, Yang Y, Zhang X, Luan X-P. MicroRNA-29b promotes cell sensitivity to Temozolomide by targeting STAT3 in glioma. Eur Rev Med Pharmacol Sci. 2020 Feb;24(4):1922-1931.

[94] Yan D, Ng WL, Zhang X, Wang P, Zhang Z, Mo Y-Y, et al. Targeting DNA-PKcs and ATM with miR-101 sensitizes tumors to radiation. PLoS One. 2010 Jul 1;5(7):e11397.

[95] Wang Y, Chen R, Zhou X, Guo R, Yin J, Li Y, et al. miR-137: A Novel Therapeutic Target for Human Glioma. Mol Ther Nucleic Acids. 2020 Sep 4;21:614-622.

[96] Yang Y-N, Zhang X-H, Wang Y-M, Zhang X, Gu Z. miR-204 reverses temozolomide resistance and inhibits cancer initiating cells phenotypes by degrading FAP-α in glioblastoma. Oncol Lett. 2018 May;15(5):7563-7570.

[97] Chen G, Zhu W, Shi D, Lv L, Zhang C, Liu P, et al. MicroRNA-181a sensitizes human malignant glioma U87MG cells to radiation by targeting Bcl-2. Oncol Rep. 2010 Apr;23(4):997-1003.

[98] Cheng Z-X, Yin W-B, Wang Z-Y. MicroRNA-132 induces temozolomide resistance and promotes the formation of cancer stem cell phenotypes by targeting tumor suppressor candidate 3 in glioblastoma. Int J Mol Med. 2017 Nov;40(5):1307-1314.

[99] Stojcheva N, Schechtmann G, Sass S, Roth P, Florea A-M, Stefanski A, et al. MicroRNA-138 promotes acquired alkylator resistance in glioblastoma by targeting the Bcl-2-interacting mediator BIM. Oncotarget. 2016 Mar 15;7(11):12937-12950.

[100] Li W, Guo F, Wang P, Hong S, Zhang C. miR-221/222 confers radioresistance in glioblastoma cells through activating Akt independent of PTEN status. Curr Mol Med. 2014 Jan;14(1):185-195.

[101] Yin J, Zeng A, Zhang Z, Shi Z, Yan W, You Y. Exosomal transfer of miR-1238 contributes to temozolomide-resistance in glioblastoma. EBioMedicine. 2019 Apr;42:238-251.

[102] Ge X, Pan M-H, Wang L, Li W, Jiang C, He J, et al. Hypoxia-mediated mitochondria apoptosis inhibition induces temozolomide treatment resistance through miR-26a/Bad/Bax axis. Cell Death Dis. 2018 Nov 13;9(11):1128.

[103] Munoz JL, Rodriguez-Cruz V, Ramkissoon SH, Ligon KL, Greco SJ, Rameshwar P. Temozolomide resistance in glioblastoma occurs by miRNA-9-targeted PTCH1, independent of sonic hedgehog level. Oncotarget. 2015 Jan 20;6(2):1190-1201.

[104] Bhaskaran V, Nowicki MO, Idriss M, Jimenez MA, Lugli G, Hayes JL, et al. The functional synergism of microRNA clustering provides therapeutically relevant epigenetic interference in glioblastoma. Nat Commun. 2019 Jan 25;10(1):442.

[105] Zeng A, Wei Z, Yan W, Yin J, Huang X, Zhou X, et al. Exosomal transfer of miR-151a enhances chemosensitivity to temozolomide in drug-resistant glioblastoma. Cancer Lett. 2018 Nov 1;436:10-21.

[106] Rynkeviciene R, Simiene J, Strainiene E, Stankevicius V, Usinskiene J, Kaubriene EM, et al. Non-Coding RNAs in Glioma [Internet]. Vol. 11, Cancers. 2018. p. 17. Available from: http://dx.doi.org/10.3390/cancers11010017

[107] Stackhouse CT, Gillespie GY, Willey CD. Exploring the Roles of lncRNAs in GBM Pathophysiology and Their Therapeutic Potential. Cells [Internet]. 2020 Oct 28;9(11). Available from: http://dx.doi.org/10.3390/cells9112369

[108] Quinn JJ, Chang HY. Unique features of long non-coding RNA biogenesis and function. Nat Rev Genet. 2016 Jan;17(1):47-62.

[109] Kiang K, Zhang X-Q, Leung G. Long Non-Coding RNAs: The Key Players in Glioma Pathogenesis [Internet]. Vol. 7, Cancers. 2015. p. 1406-24. Available from: http://dx.doi.org/10.3390/cancers7030843

[110] Yan Y, Xu Z, Chen X, Wang X, Zeng S, Zhao Z, et al. Novel Function of lncRNA ADAMTS9-AS2 in Promoting Temozolomide Resistance in Glioblastoma via Upregulating the FUS/MDM2 Ubiquitination Axis. Front Cell Dev Biol. 2019 Oct 2;7:217.

[111] Dai X, Liao K, Zhuang Z, Chen B, Zhou Z, Zhou S, et al. AHIF promotes glioblastoma progression and radioresistance via exosomes. Int J Oncol. 2019 Jan;54(1):261-270.

[112] Liao Y, Shen L, Zhao H, Liu Q, Fu J, Guo Y, et al. LncRNA CASC2 Interacts With miR-181a to Modulate Glioma Growth and Resistance to TMZ Through PTEN Pathway. J Cell Biochem. 2017 Jul;118(7):1889-1899.

[113] Ding J, Zhang L, Chen S, Cao H, Xu C, Wang X. lncRNA CCAT2 Enhanced Resistance of Glioma Cells Against Chemodrugs by Disturbing the Normal Function of miR-424. Onco Targets Ther. 2020 Feb 17;13:1431-45.

[114] Jiang P, Wang P, Sun X, Yuan Z, Zhan R, Ma X, et al. Knockdown of long noncoding RNA H19 sensitizes human glioma cells to temozolomide therapy. Onco Targets Ther. 2016 Jun 13;9:3501-3509.

[115] Li J, Ji X, Wang H. Targeting Long Noncoding RNA HMMR-AS1 Suppresses and Radiosensitizes Glioblastoma. Neoplasia. 2018 May;20(5):456-466.

[116] Yuan Z, Yang Z, Li W, Wu A, Su Z, Jiang B. Exosome-Mediated Transfer of Long Noncoding RNA HOTAIR Regulates Temozolomide Resistance by miR-519a-3p/RRM1 Axis in Glioblastoma. Cancer Biother Radiopharm [Internet]. 2020 Jul 24; Available from: http://dx.doi.org/10.1089/cbr.2019.3499

[117] Li B, Zhao H, Song J, Wang F, Chen M. LINC00174 down-regulation decreases chemoresistance to temozolomide in human glioma cells by regulating miR-138-5p/SOX9 axis. Hum Cell. 2020 Jan;33(1):159-174.

[118] Tang G, Luo L, Zhang J, Zhai D, Huang D, Yin J, et al. lncRNA LINC01057 promotes mesenchymal differentiation by activating NF-κB signaling in glioblastoma. Cancer Lett. 2021 Feb 1;498:152-164.

[119] Chen W, Xu X-K, Li J-L, Kong K-K, Li H, Chen C, et al. MALAT1 is a prognostic factor in glioblastoma multiforme and induces chemoresistance to temozolomide through suppressing miR-203 and

promoting thymidylate synthase expression [Internet]. Vol. 8, Oncotarget. 2017. p. 22783-99. Available from: http://dx.doi.org/10.18632/oncotarget.15199

[120] Cai T, Liu Y, Xiao J. Long noncoding RNA MALAT1 knockdown reverses chemoresistance to temozolomide via promoting microRNA-101 in glioblastoma. Cancer Med. 2018 Apr;7(4):1404-1415.

[121] He X, Sheng J, Yu W, Wang K, Zhu S, Liu Q. LncRNA MIR155HG Promotes Temozolomide Resistance by Activating the Wnt/β-Catenin Pathway Via Binding to PTBP1 in Glioma. Cell Mol Neurobiol [Internet]. 2020 Jun 11; Available from: http://dx.doi.org/10.1007/s10571-020-00898-z

[122] Chen M, Cheng Y, Yuan Z, Wang F, Yang L, Zhao H. NCK1-AS1 Increases Drug Resistance of Glioma Cells to Temozolomide by Modulating miR-137/TRIM24 [Internet]. Vol. 35, Cancer Biotherapy and Radiopharmaceuticals. 2020. p. 101-8. Available from: http://dx.doi.org/10.1089/cbr.2019.3054

[123] Zhang P, Liu Y, Fu C, Wang C, Duan X, Zou W, et al. Knockdown of long non-coding RNA PCAT1 in glioma stem cells promotes radiation sensitivity. Med Mol Morphol. 2019 Jun;52(2):114-122.

[124] Hu T, Wang F, Han G. LncRNA PSMB8-AS1 acts as ceRNA of miR-22-3p to regulate DDIT4 expression in glioblastoma. Neurosci Lett. 2020 May 29;728:134896.

[125] Zheng J, Wang B, Zheng R, Zhang J, Huang C, Zheng R, et al. Linc-RA1 inhibits autophagy and promotes radioresistance by preventing H2Bub1/USP44 combination in glioma cells. Cell Death Dis. 2020 Sep 15;11(9):758.

[126] Zhang Z, Yin J, Lu C, Wei Y, Zeng A, You Y. Exosomal transfer of long non-coding RNA SBF2-AS1 enhances chemoresistance to temozolomide in glioblastoma. J Exp Clin Cancer Res. 2019 Apr 16;38(1):166.

[127] Zheng R, Yao Q, Ren C, Liu Y, Yang H, Xie G, et al. Upregulation of Long Noncoding RNA Small Nucleolar RNA Host Gene 18 Promotes Radioresistance of Glioma by Repressing Semaphorin 5A. Int J Radiat Oncol Biol Phys. 2016 Nov 15;96(4):877-887.

[128] Liu B, Zhou J, Wang C, Chi Y, Wei Q, Fu Z, et al. LncRNA SOX2OT promotes temozolomide resistance by elevating SOX2 expression via ALKBH5-mediated epigenetic regulation in glioblastoma. Cell Death Dis. 2020 May 21;11(5):384.

[129] Wu P, Cai J, Chen Q, Han B, Meng X, Li Y, et al. Lnc-TALC promotes O6-methylguanine-DNA methyltransferase expression via regulating the c-Met pathway by competitively binding with miR-20b-3p [Internet]. Vol. 10, Nature Communications. 2019. Available from: http://dx.doi.org/10.1038/s41467-019-10025-2

[130] Brodie S, Lee HK, Jiang W, Cazacu S, Xiang C, Poisson LM, et al. The novel long non-coding RNA TALNEC2, regulates tumor cell growth and the stemness and radiation response of glioma stem cells. Oncotarget. 2017 May 9;8(19):31785-31801.

[131] Gao W, Qiao M, Luo K. Long Noncoding RNA TP53TG1 Contributes to Radioresistance of Glioma Cells Via miR-524-5p/RAB5A Axis. Cancer Biother Radiopharm [Internet]. 2020 Aug 6; Available from: http://dx.doi.org/10.1089/cbr.2020.3567

[132] Mazor G, Levin L, Picard D, Ahmadov U, Carén H, Borkhardt A, et al. The lncRNA TP73-AS1 is linked to aggressiveness in glioblastoma and

promotes temozolomide resistance in glioblastoma cancer stem cells. Cell Death Dis. 2019 Mar 13;10(3):246.

[133] Tang T, Wang L-X, Yang M-L, Zhang R-M. lncRNA TPTEP1 inhibits stemness and radioresistance of glioma through miR-106a-5p-mediated P38 MAPK signaling. Mol Med Rep. 2020 Dec;22(6):4857-4867.

[134] Shang C, Tang W, Pan C, Hu X, Hong Y. Long non-coding RNA TUSC7 inhibits temozolomide resistance by targeting miR-10a in glioblastoma. Cancer Chemother Pharmacol. 2018 Apr;81(4):671-678.

[135] Zhang B, Fang S, Cheng Y, Zhou C, Deng F. The long non-coding RNA, urothelial carcinoma associated 1, promotes cell growth, invasion, migration, and chemo-resistance in glioma through Wnt/β-catenin signaling pathway [Internet]. Vol. 11, Aging. 2019. p. 8239-53. Available from: http://dx.doi.org/10.18632/aging.102317

[136] Du P, Zhao H, Peng R, Liu Q, Yuan J, Peng G, et al. LncRNA-XIST interacts with miR-29c to modulate the chemoresistance of glioma cell to TMZ through DNA mismatch repair pathway [Internet]. Vol. 37, Bioscience Reports. 2017. Available from: http://dx.doi.org/10.1042/bsr20170696

[137] Hao Z, Hu S, Liu Z, Song W, Zhao Y, Li M. Circular RNAs: Functions and Prospects in Glioma. J Mol Neurosci. 2019 Jan;67(1):72-81.

[138] Tay Y, Rinn J, Pandolfi PP. The multilayered complexity of ceRNA crosstalk and competition [Internet]. Vol. 505, Nature. 2014. p. 344-52. Available from: http://dx.doi.org/10.1038/nature12986

[139] Li Z, Huang C, Bao C, Chen L, Lin M, Wang X, et al. Exon-intron circular RNAs regulate transcription in the nucleus. Nat Struct Mol Biol. 2015 Mar;22(3):256-264.

[140] Schneider T, Hung L-H, Schreiner S, Starke S, Eckhof H, Rossbach O, et al. CircRNA-protein complexes: IMP3 protein component defines subfamily of circRNPs. Sci Rep. 2016 Aug 11;6:31313.

[141] Guarnerio J, Bezzi M, Jeong JC, Paffenholz SV, Berry K, Naldini MM, et al. Oncogenic Role of Fusion-circRNAs Derived from Cancer-Associated Chromosomal Translocations. Cell. 2016 Aug 11;166(4):1055-1056.

[142] Rybak-Wolf A, Stottmeister C, Glažar P, Jens M, Pino N, Giusti S, et al. Circular RNAs in the Mammalian Brain Are Highly Abundant, Conserved, and Dynamically Expressed. Mol Cell. 2015 Jun 4;58(5):870-885.

[143] Shang Q, Yang Z, Jia R, Ge S. The novel roles of circRNAs in human cancer [Internet]. Vol. 18, Molecular Cancer. 2019. Available from: http://dx.doi.org/10.1186/s12943-018-0934-6

[144] Sun J, Li B, Shu C, Ma Q, Wang J. Functions and clinical significance of circular RNAs in glioma. Mol Cancer. 2020 Feb 15;19(1):34.

[145] Ding C, Yi X, Wu X, Bu X, Wang D, Wu Z, et al. Exosome-mediated transfer of circRNA CircNFIX enhances temozolomide resistance in glioma. Cancer Lett. 2020 Jun 1;479:1-12.

[146] Deng Y, Zhu H, Xiao L, Liu C, Meng X. Circ_0005198 enhances temozolomide resistance of glioma cells through miR-198/TRIM14 axis. Aging. 2020 Dec 9;13(2):2198-2211.

[147] Hua L, Huang L, Zhang X, Feng H, Shen B. Knockdown of circular RNA CEP128 suppresses proliferation and improves cytotoxic efficacy of temozolomide in glioma cells by regulating miR-145-5p. Neuroreport. 2019 Dec 18;30(18):1231-1238.

[148] Zhu C, Mao X, Zhao H. The circ_VCAN with radioresistance contributes

to the carcinogenesis of glioma by regulating microRNA-1183. Medicine. 2020 Feb;99(8):e19171.

[149] Guan Y, Cao Z, Du J, Liu T, Wang T. Circular RNA circPITX1 knockdown inhibits glycolysis to enhance radiosensitivity of glioma cells by miR-329-3p/NEK2 axis. Cancer Cell Int. 2020 Mar 14;20:80.

[150] Zhao M, Xu J, Zhong S, Liu Y, Xiao H, Geng L, et al. Expression profiles and potential functions of circular RNAs in extracellular vesicles isolated from radioresistant glioma cells. Oncol Rep. 2019 Mar;41(3):1893-1900.

[151] Lou J, Hao Y, Lin K, Lyu Y, Chen M, Wang H, et al. Circular RNA CDR1as disrupts the p53/MDM2 complex to inhibit Gliomagenesis. Mol Cancer. 2020 Sep 7;19(1):138.

[152] Xing W-K, Shao C, Qi Z-Y, Yang C, Wang Z. The role of Gliadel wafers in the treatment of newly diagnosed GBM: a meta-analysis. Drug Des Devel Ther. 2015 Jun 29;9:3341-3348.

[153] Cohen MH, Shen YL, Keegan P, Pazdur R. FDA drug approval summary: bevacizumab (Avastin) as treatment of recurrent glioblastoma multiforme. Oncologist. 2009 Nov;14(11):1131-1138.

[154] Arvanitis CD, Ferraro GB, Jain RK. The blood-brain barrier and blood-tumour barrier in brain tumours and metastases. Nat Rev Cancer. 2020 Jan;20(1):26-41.

[155] Chastagner P, Devictor B, Geoerger B, Aerts I, Leblond P, Frappaz D, et al. Phase I study of non-pegylated liposomal doxorubicin in children with recurrent/refractory high-grade glioma. Cancer Chemother Pharmacol. 2015 Aug;76(2):425-432.

[156] Mitsuya K, Akiyama Y, Iizuka A, Miyata H, Deguchi S, Hayashi N, et al. Alpha-type-1 Polarized Dendritic Cell-based Vaccination in Newly Diagnosed High-grade Glioma: A Phase II Clinical Trial. Anticancer Res. 2020 Nov 1;40(11):6473-6484.

[157] Kong D-S, Nam D-H, Kang S-H, Lee JW, Chang J-H, Kim J-H, et al. Phase III randomized trial of autologous cytokine-induced killer cell immunotherapy for newly diagnosed glioblastoma in Korea. Oncotarget. 2017 Jan 24;8(4):7003-7013.

[158] Liau LM, Ashkan K, Tran DD, Campian JL, Trusheim JE, Cobbs CS, et al. First results on survival from a large Phase 3 clinical trial of an autologous dendritic cell vaccine in newly diagnosed glioblastoma. J Transl Med. 2018 May 29;16(1):142.

[159] Hipp SJ, Goldman S, Kaushal A, Krauze A, Citrin D, Glod J, et al. A phase I trial of lenalidomide and radiotherapy in children with diffuse intrinsic pontine gliomas or high-grade gliomas. J Neurooncol. 2020 Sep;149(3):437-445.

[160] Rudnick JD, Sarmiento JM, Uy B, Nuno M, Wheeler CJ, Mazer MJ, et al. A phase I trial of surgical resection with Gliadel Wafer placement followed by vaccination with dendritic cells pulsed with tumor lysate for patients with malignant glioma. J Clin Neurosci. 2020 Apr;74:187-193.

[161] Herrlinger U, Tzaridis T, Mack F, Steinbach JP, Schlegel U, Sabel M, et al. Lomustine-temozolomide combination therapy versus standard temozolomide therapy in patients with newly diagnosed glioblastoma with methylated MGMT promoter (CeTeG/NOA-09): a randomised, open-label, phase 3 trial. Lancet. 2019 Feb 16;393(10172):678-688.

[162] Grill J, Massimino M, Bouffet E, Azizi AA, McCowage G, Cañete A, et al. Phase II, Open-Label, Randomized, Multicenter Trial (HERBY) of Bevacizumab in Pediatric Patients With

Newly Diagnosed High-Grade Glioma. J Clin Oncol. 2018 Apr 1;36(10):951-958.

[163] Hummel TR, Salloum R, Drissi R, Kumar S, Sobo M, Goldman S, et al. A pilot study of bevacizumab-based therapy in patients with newly diagnosed high-grade gliomas and diffuse intrinsic pontine gliomas. J Neurooncol. 2016 Mar;127(1):53-61.

[164] Stupp R, Hegi ME, Gorlia T, Erridge SC, Perry J, Hong Y-K, et al. Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC EORTC 26071-22072 study): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2014 Sep;15(10):1100-1108.

[165] Weller M, Butowski N, Tran DD, Recht LD, Lim M, Hirte H, et al. Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial. Lancet Oncol. 2017 Oct;18(10):1373-1385.

[166] Liau LM, Ashkan K, Tran DD, Campian JL, Trusheim JE, Cobbs CS, et al. Correction to: First results on survival from a large Phase 3 clinical trial of an autologous dendritic cell vaccine in newly diagnosed glioblastoma. J Transl Med. 2018 Jun 29;16(1):179.

[167] Reardon DA, Brandes AA, Omuro A, Mulholland P, Lim M, Wick A, et al. Effect of Nivolumab vs Bevacizumab in Patients With Recurrent Glioblastoma: The CheckMate 143 Phase 3 Randomized Clinical Trial. JAMA Oncol. 2020 Jul 1;6(7):1003-1010.

[168] Toms SA, Kim CY, Nicholas G, Ram Z. Increased compliance with tumor treating fields therapy is prognostic for improved survival in the treatment of glioblastoma: a subgroup analysis of the EF-14 phase III trial. J Neurooncol. 2019 Jan;141(2):467-473.

[169] Westphal M, Ylä-Herttuala S, Martin J, Warnke P, Menei P, Eckland D, et al. Adenovirus-mediated gene therapy with sitimagene ceradenovec followed by intravenous ganciclovir for patients with operable high-grade glioma (ASPECT): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013 Aug;14(9):823-33. g;14(9):823-33.