Micro RNA Molecules as Modulators of Treatment Resistance, Immune Checkpoints Controllers and Sensitive Biomarkers in Glioblastoma Multiforme

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Abstract: Based on genome sequencing, it is estimated that over 90% of genes stored in human genetic material are transcribed, but only 3% of them contain the information needed for the production of body proteins. This group also includes micro RNAs representing about 1%–3% of the human genome. Recent studies confirmed the hypothesis that targeting molecules called Immune Checkpoint (IC) open new opportunities to take control over glioblastoma multiforme (GBM). Detection of markers that indicate the presence of the cancer occupies a very important place in modern oncology. This function can be performed by both the cancer cells themselves as well as their components and other substances detected in the patients’ bodies. Efforts have been made for many years to find a suitable marker useful in the diagnosis and monitoring of gliomas, including glioblastoma.

Keywords: micro RNA; glioblastoma multiforme; immune checkpoints; glioma; tumor

1. Introduction

Only in the United States about 10,000 new cases of high grade glioma are detected annually [1]. Despite the relatively low prevalence due to high aggressiveness, the tumor is responsible for about 4% of cancer-related deaths [2]. Glioblastoma multiforme belongs to a group of primary nervous system tumors, characterized by high aggressiveness in terms of the histological as well as clinical aspect. It was described as IV grade glioma according to the World Health Organization (WHO) classification. GBM represents 10%–18% of all intracranial tumors and 50%–60% of all astrocytoma tumors. The annual occurrence of GBM is 5/100,000 persons, mostly diagnosed in the 5 th and 6 th decade. There are two forms of GBM-primary and secondary. The first one occurs most often in people over 55 years of age. It is characterized by rapid clinical manifestation and de novo occurrence, which already are typical for GBM. In the secondary form, usually diagnosed in people under 45 years of age, the tumor develops on the basis of low grade.

The 5-year survival rate is found to be below 20% in patients suffering from glioblastoma multiforme, while the median survival time after treatment reaches ca. 11–24 months [3].
Based on genome sequencing, it is estimated that over 90% of genes stored in human genetic material are transcribed, but only 3% of them contain the information necessary for the production of body proteins [4]. This group also includes micro RNAs (miRNA) representing about 1%–3% of the human genome [5].

About 40% of the micro RNA genes are located in the introns and exons of other genes, which may be associated with their basic function, i.e., regulation of the expression of other genes [6–8]. Furthermore, each micro RNA can control up to over 100 target points and each of which can be regulated by different miRNAs. The result of this is the creation of a complicated system of key dependences in the regulation of basic functions of the organism [5,9,10].

The first papers describing the presence of micro RNA were published in 1990s [11]. The role of miRNA was pointed out in many medical conditions such as kidney disease, diabetes, neurodegenerative disorder, arthritis, as well as cancer [12]. MiRNAs are also involved in studies on reproductive function and infertility [13,14].

In the 2000s, the first papers describing the importance of micro RNA in the pathophysiology of brain tumors, including glioblastoma, began to appear [15–17]. Since then, many authors have been analyzing the effects of these particles on various aspects of glioblastoma development. Numerous observations have shown the disturbances between the level of expression of micro RNA compared to normal brain tissue [18–23]. Analysis of the literature indicates that in the case of glioblastoma, the level of micro RNA (253 up-regulated vs. 95 down-regulated) is overexpressed more often [11]. Among the particles with increased expression, the authors most often mentioned: miR10b, miR17-92, miR21, miR26a, miR92 miR221/222, miR235, miR451, and miR486 while the low levels were often presented by: miR7, miR34a, miR106a, miR124, miR128, miR137, miR139, miR-181a, miR181b, miR218, miR323 and miR328, and miR342-3p [16,17,19,23–34]. The importance of many of these micro RNA in the pathogenesis of cancer is still unknown, but in recent years intensive research has been carried out to clarify this issue.

2. Immune Checkpoints vs. MirRNA

Recent studies confirmed the hypothesis that targeting molecules called Immune Checkpoint (IC) open new opportunities to take control over GBM. The cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) was the first particle with immunomodulatory properties, blocked with Ipilimumab (humanized antibody) in patients with metastatic melanoma [35]. CTLA-4 inhibits proper T cells co-stimulatory signaling by binding CD 86 and CD 80 on antigen-presenting cells. In patients suffering from GBM, there is a negative correlation with the expression of molecules on the CD8+ and CD4+ cells and the final outcome of the disease [36,37]. Programmed death ligand 1 (PD-L1) as a member of IC family plays a crucial role in immune modulation and immune adaptation of glioma cells. Activation of PD-1 receptor on T-cells results in significant reduction of its cytotoxicity and proliferation. Further signaling increases tumor evasion and leads to immune escape. Over-expression of PD-L1 is preceded by the stimulation of multiple receptors such as epidermal growth factor receptor (EGFR), interferon receptors (IFNAR, IFNGR) and toll like receptors (TLRs). Down-signaling of self-activated glioma cells takes place via several pathways such as: phosphatase and tensin homolog deleted on chromosome ten/the mammalian target of rapamycin (PTEN/mTOR), signal transducer and activator of transcription 3/mitogen-activated protein kinase/extracellular signal-regulated kinases (STAT3/MEK/ERK) or Janus-activated kinases/signal transducers and activators of transcription (JAK/STAT), which promote PD-1L mRNA transcription, translation and presentation on the surface of cell [38,39]. Micro RNA molecules have an ability to affect described processes. Wang et al. presented an analysis of various (49) miRNA particles regulating PD-L1 and PD-1 interplay in oncologic patients. The immunological variability of GBM harmonizes with IDH 1/2 mutations. Heiland et al. confirmed that PD-L1 is up-regulated in IDH1/2 wildtype contrary to the IDH1/2 mutated cells which hypermethylate the PD-L1 promoter region, resulting in lower levels of PD-L1 expression. Those findings could explain various responses to inhibition of PD-L1 in patients qualified in recruiting trials and point at molecules
interacting with ICs on the epigenetic level such as miRNAs. Moreover, miRNAs interfere with PD-1/PD-L1 and CTLA-4 pathways. Particular molecules interplay with precise IC: miR-28 (PD-1), miR-34a (PD-L1), mir-124 (PD-1), mir-138 (PD-1 and CTLA-4), miR-138-5p (PD-L1), mir-155 (CTLA4), miR-200 (PD-L1), miR-424 (PD-L1), and miR-513, (PD-L1) [36,37]. miRNAs could also interact with IC indirectly. Some of them induce IFN gamma secretion and control transcription, creating complicated connections. Studies over MiR-34a revealed an anti-tumor effect on glioma cells by modifying epidermal growth factor receptor (EGFR) and PD-L1 expression. MiR-34a silences FKBP51 (cochaperone molecule of PD-L1), interrupting the maturation of PD-L1. This action reduces resistance to treatment induced by the PD-L1/PD-1 axis. The expression of miR-34a correlates with better outcomes [40–42]. Epigenetic studies performed by Chen et al. concluded that the miR-200 particle represents a reciprocal connection with the expression of PD-L1 [43]. Wei et al. discovered the same relation between Pd-L1 and miR-138-5p. According to his study, MiR-138 targets also PD-1 and CTLA-4, and suppresses expression on the surface of CD4+ T cells. Studies carried out on mice models demonstrate tumor mass regression and significant elongation of median survival time. The regression of the tumor maintained after miR-138 intake discontinuation [44]. Moreover, miR-124 inhibits signal transducer and the activator of transcription 3 (STAT3) signaling, leading to down-regulation of immunosuppressive particles such as PD-1.

The expression of MiR-124 is limited in high-grade gliomas and in all types of malignant tumors. miR-124 affects glioma cancer stem cells (gCSC) modulated with immunosuppressive properties. Systemic management enhances anticancer properties and modulates glioma microenvironment to protect immunescape [45–47]. Up-regulation of miR-155 promotes the development of regional inflammation, which results in tumor invasion via CTLA-4 activation [48]. Mir-28 control replication processes reduce PD-1 expression attaching to 3’UTR. This causes T cells depletion by modulating cell cycles [49]. miR-424 and miR 513 inhibit PD-1L formation in glioma. miR 424 additionally inhibits CD80 molecule on antigen-presenting cell (APCs), resulting indirect inhibition of CTLA-4 signaling [46,47] (Figure 1).

**Figure 1.** APC, T cell and GBM interplay in activation of immune checkpoints resulting in immune escape of Glioma. The figure presents miRNA molecules developing an inhibitory influence on the presented axis. PD-1 and CTLA-4 on T cell interact with miR-138, inhibiting both. MiR-155 inhibits CTLA-4, and miR-28 inhibits PD-1 as well.

PD-1L in GBM is blocked by miR-513, miR 424, miR-200, miR-138-5p, miR-124, and miR 34a. Moreover, miR-424 blocks CD80 particle on APC, which is necessary to activate CTLA-4 receptor on T cell.

MHC—Major Histocompatibility Complex; NC-MHC—Non Classical Major Histocompatibility Complex; TCR—T Cell Receptor; CTLA—4 Cytotoxic T Cell Antigen 4; PD-1—Programmed Death Receptor-1; CD80—Cluster of Differentiation 80; PD-1L—Programmed Death-Ligand 1.
Moreover, IFN-gamma down-regulates MiR-513 and its restrictive activity on PD-1L expression in GBM cells. Despite promising results on animal models, further studies are required to explain and clarify the complicated interplay between miRNAs and ICs.

3. Biomarkers

The detection of markers that indicate the presence of cancer plays a very important role in modern oncology. This property can be presented by both the cancer cell itself as well as their components and other substances detected in the patients bodies [50,51]. Efforts have been made for many years to find a suitable marker useful in the diagnosis and monitoring of gliomas, including glioblastoma [52,53]. However, to this day, it has not been possible to identify a substance that would fulfill this role properly [54]. In the case of GMB, monitoring the level of biochemical markers would be particularly important because of the difficulties linked to imaging diagnostics. Under the influence of the applied treatment, the tumor cells absorb larger amounts of administered contrast, thus leading to an adulterated radiosensitive image acquisition, significantly impeding the control of therapy [55]. For this reason, a great contribution is required to discover new markers such as micro RNAs.

The importance of miRNA playing a role as a marker of the different pathologies has already been suggested in Alzheimer’s disease as well as other cancers such as: papillary thyroid carcinoma, breast cancer, metastasis in gastric cancer, Hodgkin lymphoma, and pancreatic ductal adenocarcinoma [56–61]. One of the first studies on the importance of miRNA in the diagnosis of gliomas was conducted on astrocytoma samples. Zhi et al. indicated seven miRNA particles, in which levels were significantly different from healthy brain tissue [62]. Likewise, many other studies were conducted, including high-grade glioma [63]. Observations by Chen et al. indicated another seven examples of micro RNA with potential use as markers. The group consisted of: miR7, miR15b, miR21, miR124a, miR129, miR139, and miR218 [64]. In a large meta-analysis carried out by Sirnivasan et al., the role of 10 miRNAs that could be used as a predictor of the disease progression in patients with GBM was highlighted. Moreover, a great number of them were associated with a worse course of the disease, while others indicated a good prognosis. The first group included: miR31, miR146b, miR148a, miR193a, miR200b, and miR221 [65]. A similar relationship in the case of miR146b was also observed in the case of squamous cell lung cancer and papillary thyroid carcinoma [66]. Interestingly, some researchers emphasize the importance of this molecule in suppressing metastatic changes [67,68]. Similar observations have been made regarding breast cancer and miR31 [69]. Likewise, the role of miR221 in tumors pathogenesis, including GBM, has been confirmed in studies by other authors. Particular attention was paid to the participation of p27, p53, PTEN, and p27Kip1 particles in this mechanism [70–76]. In the case of miR193a, correlations with adverse prognosis were observed regarding melanoma [77]. Sirnivasan et al. included miR17-5p, miR20a and miR106a as substances that could potentially have protective properties [67]. A similar relationship to miR106a has been found in other studies on glioblastomas and colorectal cancer [64,78]. On the other hand, in the case of T-cell leukemia, the oncogenic potential of this particle has been demonstrated [79]. Similar conclusions regarding the positive prognostic significance of miR17 and miR20a (together included in the miR17-92 cluster) in gliomas were suggested in studies of the goals of these particles (cyclin D1, E2F1) [80–82]. Moreover, in observations carried out on various types of cancers, it was found that they can perform both oncogenic and suppressor functions in the cell [83–89]. Many researchers also pointed out other miRNAs in which presence may be associated with better prognosis and longer survival of patients with glioma and glioblastoma. Thanks to this, these can potentially be used as biomarkers of the course of the disease. This group includes, among others (Table 1): miR29c, miR101, miR107, miR144-3p, mir181d, miR203, miR205, and miR328 [30,90–94].
In another large analysis conducted by Qiu et al. on 480 GMB samples, it was noted that patients with longer survival rates showed high levels of miR130a and miR326, as well as low levels of miR155, miR210, miR323, and miR329. Moreover, in the case of miR155, miR210, miR130a, and miR326, this was also associated with progression-free survival (PFS) [95]. These data remain consistent with the observations of Schiesser et al. They confirmed that low levels of miR155 and miR210 reflect worse prognosis. In their analysis, 29 miRNA regions differing in methylation emphasized that only miR155 was a prognostic marker independent of other patient characteristics such as MGMT methylation, IDH1/IDH2 mutation and histology [96].

The correlation of the presence of some miRNAs with patients life expectancy is often associated with the degree of histological staging of the tumor. In the work carried out by Regazzo et al., it has been shown that testing the level of expression of some miRNAs (miR125b, miR497) can provide information on whether the examined tumor belongs to high-grade glioma or low grade [97]. Similar conclusions were made by Wang et al. stating that the level of miR342-3p in the serum of patients with gliomas is lowered, while the level of this decrease is different for tumors with grade II, III and IV [24]. The existence of similar correlations has been demonstrated by many other researchers, including: miR19, miR137, miR144-3p, and miR182 [98–101]. It was also found that the relationship between the stage of tumor histology is positive for miR19 and miR182, and negative for le7e, miR145 and miR181a [102,103]. This would provide valuable guidance on the characteristics of the tumor before surgery and histopathological examination of the slice, giving the chance for better planning of the procedure. Observing the level of markers in the form of miRNA could thus capture the moment of progression of low-grade gliomas in high-grade glioma. Malkorn et al. conducted research on WHO grade II gliomas that progressed to GBM (WHO IV). They indicated a number of markers helpful in determining the moment of histological progression. They included: miR9, miR15a, miR16, miR17, miR19a, miR20a, miR21, miR25, miR28, miR130b, and miR140; miR210 (elevated level); and miR184 and miR328 (reduced level) [104]. In their study, Wang et al. also found that the levels of miR21, miR128 and miR342-3p change under the influence of anti-cancer treatment (returns to levels characteristic of healthy tissue) [24]. In the case of miR128, similar trends were also reported in other studies [93]. This indicates the possibility of using miRNA as markers of treatment effectiveness.

| Increased | Increased Increased | Fold | Decreased | Decreased | Decreased Decreased |
|-----------|---------------------|------|-----------|-----------|---------------------|
| miR15b    | miR17-5p            |      | miR26a    | miR221/222 | miR33               |
| miR23a    | miR21               |      | miR25     | miR104    | miR105              |
| miR21     | miR106b             |      | miR122a   | miR128b   | miR129              |
| miR26a    |                    |      | miR124    | miR10a    | miR154              |
| miR221/222| miR148a             |      | iR30a-3p  | miR106a   | miR130              |
| miR335    | miR182              |      | miR143    | miR181a   | miR190              |
| miR210b   | miR18b              |      | miR186    | miR181b   | miR219              |
| miR324-3p | miR96               |      | miR324-3p | miR448    | miR221              |
| miR199a   | miR337              |      | miR337    | miR490    | miR299              |
| miR199b   | miR355              |      | miR876-3p | miR321    | miR317              |
| miR199s   |                    |      |           | miR323    | miR184              |
| miR200cN  |                    |      |           | miR323    | miR154              |
| miR210N   |                    |      |           | miR328    | miR184              |
| miR224    |                    |      |           | miR331    | miR203              |
| miR368    |                    |      |           | miR332    | miR203              |
| miR373    |                    |      |           | miR370    | miR326              |
|           | miR338              |      |           | miR370    | miR326              |

Table 1. Level of expression of particular mRNA molecules in Glioblastoma Multiforme.
4. Resistance to Treatment

Treatment of glioblastoma, due to the dynamics of its development, is a big challenge for modern medicine. Currently, the commonly accepted standard of treatment includes a combination of cytoreductive surgery, chemotherapy and radiotherapy. Not every patient will respond equally to the implemented treatment. It is caused, among others, by chemoresistance associated with: repair mechanisms, apoptosis, epigenetic regulations, and different accumulations of drugs in cells [105]. Micro RNA can play an important role in regulating these phenomena. In recent years, numerous observations have been made in this field [106–112].

Temozolomide (TMZ) is a cytostatic agent commonly used in the therapy of patients with GBM. It has been shown to be highly effective in reducing tumor growth, having a positive effect on patient survival [113,114]. Also in this case, there were observations describing the cell resistance to the drug. Micro RNA can also participate in this mechanism [115]. The cytostatic properties of TMZ are associated with alkylation of the guanine bases in DNA, consequently leading to impaired DNA replication and cell death [116–118]. However, in the case of neoplasm, some cells have developed mechanisms to avoid this scenario. An example of this is the O6-methylguanine-DNA methyl-transferase (MGMT). It is an enzyme involved in DNA repair by removing alkylated groups from the O6 guanine position, preventing mispairing in the process of DNA replication. The effect is a reversal of the cytostatic and lack of effectiveness of the therapy [119,120]. Despite the existence of other mechanisms conditioning chemoresistance, such as DYNC2H1 (DHC2) activity, MGMT is considered to be a critical regulator of temozolomide insensitivity [121].

Inactivation of O6-methylguanine-DNA methyl-transferase would allow blocking repair processes, thereby increasing the effectiveness of temozolomide [122]. This can be achieved by epigenetic mechanisms such as methylation. The first studies regarding silencing of MGMT in gliomas date back to 2005 [115]. In observations carried out by Hegi et al., the relationship between MGMT methylation determined by methylation-specific polymerase-chain-reaction and the survival of glioblastoma patients was examined. The results indicated that the methylation of the O6-methylguanine-DNA methyl-transferase promoter predicted a positive response to treatment regardless of other factors [115]. For this reason, many research facilities are trying to find an effective method to weaken MGMT activity.

D’Atri et al. suggested that this effect could be achieved using combined TMZ therapy with cisplatin [123]. Unfortunately, further observations indicated a relatively low effectiveness of this combination in patients with glioblastoma [124]. Similar conclusions were received in the case of radiation therapy [125]. Many authors have tried to explain the mechanism of this type of resistance. Interestingly, Chen et al. and Guo et al. suggested that a certain group of micro RNAs could be good markers of patients’ poor response to cisplatin treatment. This concerned, among others, miR873 and Let7b [126–128].

Recent observations show that micro RNA can condition the chemosensitivity of cancer cells also by acting on MGMT. In their work, Berthois et al. noted the inverse correlation between miR200a levels and O6-methylguanine methyltransferase (MGMT) expression. They also showed that over-expression of miR200a causes sensitization of glioblastoma cells to TMZ and that it can serve as a good marker of tumor chemosensitivity [129]. In another work by Kushwah et al., the role of micro RNA in increasing the chemosensitivity of the tumor was also described. In this case, the observations concerned miR603. The authors pointed out that miR-603 binds to the MGMT 3’UTR resulting in a decrease in O6-methylguanine-DNA methyl-transferase activity. Interestingly, they also emphasized the role of miR603 and miR181d cooperation in the regulation of MGMT activity [130]. This coincided with their earlier work, which highlighted the role of miR181d in the mechanism of glioblastoma chemosensitivity [131] (Figure 2).
Figure 2. Presentation of MGMT-dependent mechanism leading to the development of resistance to TMZ treatment. TMZ administration intensifies alkylation processes concerning guanine nucleotides in glioblastoma cells. MGMT mRNA is translated to active MGMT enzyme, resulting in intensive dealkylation of guanine. Reverse effect of guanine alkylation leads to promotion of treatment resistance. MiR 767-3p and miR-181d-5p/miR 603 complex inhibit MGMT translation to prevent dealkylation. MiR-200A, miR-648, miR-124-3p, and miR 127-3p inhibit removing alkylated groups from guanine performed by MGMT enzyme. MiR-29c inhibits indirect dealkylation of guanine through Sp-1 protein.

Sp-1 - Specificity Protein-1

Other authors also pointed to the role of the aforementioned miR29c in regulating MGMT activity (Table 2). However, in this case, the micro RNA acts on the enzyme through specificity protein 1 (Sp1). It contributes to inhibition of O6-methylguanine-DNA methyl-transferase and an increase in the sensitivity of glioblastoma cells to TMZ [90].

Table 2. Presentation of miRNA, responsible for the resistance of glioblastoma cells to treatment.

| MiRNA.     | Target                                                                 |
|------------|------------------------------------------------------------------------|
| miR-29c    | Through specificity protein 1 (Sp1), it contributes to inhibition of    |
|            | O6-methylguanine-DNA methyl-transferase                                 |
| miR-143    | the reduction of RAS viral oncogene homolog (N-RAS)                    |
| miR-182    | Repression of Bcl2-like12 (Bcl2L12), c-Met, and hypoxia-inducible factor |
|            | 2α (HIF2A)                                                             |
| miR-139    | targeting MDA-9/syntenin                                               |
| miR-200a   | Direct transcriptional repressor of zipper containing kinase (ZAK)      |
| miR-648    | Represses luciferase activity                                           |
| miR-124-3p | Suppresses the expression of endothelia receptor type B                |
| miR-127-3p | Target the tumor-suppressor gene SEPT7                                 |
| miR-767-3p | Degradation of the MGMT mRNA                                           |
| miR-603    | inhibiting Wnt inhibitory factor 1 (WIF1) and β-catenin-interacting     |
|            | protein 1 (CTNNBIP1)                                                   |
| miR-181d-5p| Degradation of the MGMT mRNA                                           |
On the other hand, research by Slaby et al. conducted on 22 patients with primary glioblastoma suggested that there was no correlation between the survival rate of chemoradiotherapy-treated patients and MGMT methylation status. However, the authors found that miR181b and miR181c levels may serve as a marker of a positive response of glioblastoma patients to chemoradiotherapy with TMZ. Patients who had good sensitivity to the applied treatment showed lower levels of these micro RNAs. The lack of association with MGMT activity suggests the involvement of other mechanisms in regulating cell response to cytostatic [132]. Also, Ujifuku et al. in their research on acquired resistance to TMZ in glioblastoma multiforme cells, indicated the independence of this parameter from the methylation status of O6-methylguanine-DNA methyl-transferase [133]. Auger et al. also received similar results in previous observations of glioma cell lines [134]. This indicates the need for further research to fully understand the differences in glioblastoma sensitivity to treatment.

One of the mechanisms that can affect the chemoresistance of cells independent of MGMT is apoptosis. Wang et al. showed that miR143 overexpression is associated with a greater sensitivity of gliomas to TMZ treatment. The authors stated that the reason for this phenomenon is the reduction of RAS viral oncogene homolog (N-RAS) neuroblastoma expression, which is the direct target of micro RNA [135]. The relationship between proapoptotic mechanisms (regulation of Bcl genes) and sensitivity of glioblastoma cells to temozolomide has also been shown in studies by Kouri et al. and Li et al. In these cases, miR182 and miR139 were involved in the regulation of apoptosis [136]. In the research of Shi et al., the opposite correlation was described for miR21 activity. Overexpression of this micro RNA was associated with inhibition of the sensitivity of GBM cells to TMZ [137]. An analogous effect of miR21 was also seen in the observations of other authors, also in the case of resistance to other drugs such as doxorubicin, paclitaxel, carmustine, VM-26, and sunitinib [138–143].

The sensitivity of tumor cells to cytostatics is also influenced by the activity of metadherin (MTDH), also known as astrocyte elevated gene-1 protein (AEG-1). It is a protein involved in the process of angiogenesis [144]. It has been shown that it also plays a large role in the induction of chemoresistance in cancer cells [145]. For gliomas, lowering its level increases the sensitivity of cells to temozolomide [146]. Wu et al. research showed that this occurs with the increase in expression of miR136, whose direct target is MTDH [147]. This indicates the potential role of miR136 as a marker of glioma cell sensitivity to cytostatics.

In recent years, the potential role of several further micro RNAs in the induction of chemoresistance has been discovered. In the aforementioned work of Ujifuku et al., the authors pointed to miRNAs whose titters were particularly increased in resistant cells. They included miR10a, miR195 and miR455-3p. At the same time, they noted that reducing miR195 levels contributed most to increased tumor sensitivity to temozolomide therapy. Other researchers also mentioned in this group: miR17-5p, miR101, miR155, miR193a-5p, miR203, miR204, miR221, miR222, and miR328. This effect was determined by the impact on a number of metabolic pathways as well as cellular transporters as in the case of miR328 [148–155].

Furthermore, micro RNA can condition resistance not only to cytostatics but also to radiation therapy. This happens, among others, by affecting ATM (ATM serine/threonine kinase). It is a protein involved in the mechanisms of apoptosis, DNA repair and cell cycle arrest [156]. Tribius et al. studies have shown that it also plays an important role in regulating radiosensitivity in primary glioblastoma. The authors noted that the sensitivity of cells to radiation therapy is inversely correlated with the ATM level [157]. In another study by Ng et al., it has been shown that miR100 can negatively affect the ATM level, thereby affecting the radiosensitivity of glioma cells [158].

5. Conclusions

MicroRNA has great variety of applications both in the diagnostic processes as a potential tumor biomarker as well as in the treatment of glioblastoma multiforme. The immunological checkpoints encoded by microRNA can be a target of therapy, supporting commonly used methods such as radiochemotherapy and classical surgery.
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References
1. Ostrom, Q.T.; Gittleman, H.; Liao, P.; Rouse, C.; Chen, Y.; Dowling, J.; Wolinsky, Y.; Kruchko, C.; Barnholtz-Sloan, J. CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2007-2011. Neuro. Oncol. 2014, 16, 1–63. [CrossRef]
2. Romani, M.; Pistillo, M.P.; Banelli, B. Epigenetic Targeting of Glioblastoma. Front Oncol. 2018, 8, 448. [CrossRef]
3. Pollack, I.F.; Hamilton, R.L.; James, C.D.; Finkelstein, S.D.; Burnham, J.; Yates, A.J.; Holmes, E.J.; Zhou, T.; Finlay, J.L.; Children’s Oncology Group. Rarity of PTEN deletions and EGFR amplification in malignant gliomas of childhood: Results from the Children’s Cancer Group 945 cohort. J. Neurosurg. 2006, 105, 418–424. [PubMed]
4. Lander, E.S.; Linton, L.M.; Birren, B.; Nusbaum, C.; Zody, M.C.; Baldwin, J.; Devon, K.; Dewar, K.; Doyle, M.; FitzHugh, W.; et al. Initial sequencing and analysis of the human genome. Nature 2001, 409, 860–921. [CrossRef] [PubMed]
5. Zhang, Y.; Yang, P.; Sun, T.; Li, D.; Xu, X.; Rui, Y.; Li, C.; Chong, M.; Ibrahim, L.; Amadori, D.; et al. miR-126 and miR-126 repress recruitment of mesenchymal stem cells and inflammatory monocytes to inhibit breast cancer metastasis. Nat. Cell Boil. 2013, 15, 284–294. [CrossRef] [PubMed]
6. Lee, Y.; Kim, M.; Han, J.; Yeom, K.H.; Lee, S.; Baek, S.H.; Kim, V.N. MicroRNA genes are transcribed by RNA polymerase II. EMBO J. 2004, 23, 4051–4060. [CrossRef] [PubMed]
7. Pasquariello, R.; Manzoni, E.F.M.; Fiandanese, N.; Viglino, A.; Pocar, P.; Brevini, T.A.L.; Williams, J.L.; Gandolfi, F. Implications of miRNA expression pattern in bovine oocytes and follicular fluids for developmental competence. Theriogenology 2020, 145, 77–85. [CrossRef] [PubMed]
17. Shi, L.; Cheng, Z.; Chijioke, J.; Kedir, H.; Dusmatova, S.; Roy, A.; Ramalinga, M.; Harris, B.; Blancto, J.; et al. MicroRNAs in glioblastoma multiforme pathogenesis and therapeutics. *Cancer Med.* 2016, 5, 1917–1946. [CrossRef]

18. Møller, H.G.; Rasmussen, A.P.; Andersen, H.H.; Johnsen, K.B.; Henriksen, M.; Durox, M. A systematic review of microRNA in glioblastoma multiforme: Micro-modulators in the mesenchymal mode of migration and invasion. *Mol. Neurobiol.* 2013, 47, 131–144. [CrossRef]

19. Ahir, B.K.; Ozer, H.; Engelhard, H.H.; Lakka, S.S. MicroRNAs in glioblastoma pathogenesis and therapy: A comprehensive review. *Crit. Rev. Oncol. Hematol.* 2017, 120, 22–33. [CrossRef]

20. Godlewski, J.; Nowicki, M.O.; Bronisz, A.; Williams, S.; Otsuki, A.; Nuovo, G.; Raychaudhury, A.; Newton, H.B.; Chiocca, E.A.; Lawler, S. Targeting of the Bmi-1 oncogene/stem cell renewal factor by miR-128 inhibits glioma proliferation and self-renewal. *Cancer Res.* 2008, 68, 9125–9130. [CrossRef]

21. Lawler, S.; Chiocca, E.A. Emerging functions of microRNAs in glioblastoma. *J. Neurooncol.* 2009, 92, 297–306. [CrossRef]

22. Silber, J.; Lim, D.A.; Petritsch, C.; Persson, A.I.; Maunakea, A.K.; Yu, M.; Vandenberg, S.R.; Ginzinger, D.G.; James, C.D.; Costello, J.F.; et al. miR-124 and miR-137 inhibit proliferation of glioblastoma multiforme cells and induce differentiation of brain tumor stem cells. *BMC Med.* 2008, 6, 14. [CrossRef]

23. Chan, J.A.; Krichevsky, A.M.; Kosik, K.S. MicroRNA-21 is an antiapoptotic factor in human glioblastoma cells. *Cancer Res.* 2005, 65, 6029–6033. [CrossRef]

24. Wang, Q.; Li, P.; Li, A.; Jiang, W.; Wang, H.; Wang, J.; Xie, K. Plasma specific miRNAs as predictive biomarkers for diagnosis and prognosis of glioma. *J. Exp. Clin. Cancer Res.* 2019, 31, 97. [CrossRef]

25. De Smaele, E.; Ferretti, E.; Gulino, A. MicroRNAs as biomarkers for CNS cancer and other disorders. *Brain Res.* 2010, 1338, 100–111. [CrossRef]

26. Yang, G.; Zhang, R.; Chen, X.; Mu, Y.; Ai, J.; Shi, C.; Liu, Y.; Shi, C.; Sun, L.; Rainov, N.G.; et al. MiR-106a inhibits glioma cell growth by targeting E2F1 independent of p53 status. *J. Mol. Med.* 2011, 89, 1037–1050. [CrossRef]

27. Huse, J.T.; Brennan, C.; Hambardzumyan, D.; Wee, B.; Penia, J.; Rouhanifard, S.H.; Sohn-Lee, C.; Agami, R.; Tuschl, T.; Holland, E.C.; et al. The PTEN-regulating microRNA miR-26a is amplified in high-grade glioma and facilitates gliomagenesis in vivo. *Genes Dev.* 2009, 23, 1327–1337. [CrossRef]

28. Hermansen, S.K.; Dahlrot, R.H.; Nielsen, B.S.; Hansen, S.; Kristensen, B.W. MiR-21 expression in the tumor cell compartment holds unfavourable prognostic value in gliomas. *J. Neurooncol.* 2013, 111, 71–81. [CrossRef]

29. Corsten, M.F.; Miranda, R.; Kasmieh, R.; Krichevsky, A.M.; Weissleder, R.; Shah, K. MicroRNA-21 knockdown disrupts glioma growth in vivo and displays synergistic cytotoxicity with neural precursor cell delivered S-TRAIL in human gliomas. *Cancer Res.* 2007, 67, 8994–9000. [CrossRef]

30. Wu, Z.; Sun, L.; Wang, H.; Yao, J.; Jiang, C.; Xu, W.; Yang, Z. MiR-328 expression is decreased in high-grade gliomas and is associated with worse survival in primary glioblastoma. *PLoS ONE* 2012, 7, e47270. [CrossRef]

31. Jiang, J.; Sun, X.; Wang, W.; Jin, X.; Bo, X.; Li, Z.; Bian, A.; Jiu, J.; Wang, X.; Liu, D.; et al. Tumor microRNA-335 expression is associated with poor prognosis in human glioma. *Med. Oncol.* 2012, 29, 3472–3477. [CrossRef]

32. Conti, A.; Aguennouz, M.; La Torre, D.; Tomasello, C.; Cardali, S.; Angileri, F.F.; Cama, A.; Germano, A.; Vita, G.; et al. miR-21 and 221 upregulation and miR-181b downregulation in human grade II-IV astrocytic tumors. *J. Neurooncol.* 2009, 93, 325–332. [CrossRef] [PubMed]

33. Kefas, B.; Godlewski, J.; Comeau, L.; Li, Y.; Abounader, R.; Hawkinson, M.; Lee, J.; Fina, H.; Chiocca, A.; Lawler, S.; et al. MicroRNA-7 inhibits the epidermal growth factor receptor and the Akt pathway and is down-regulated in glioblastoma. *Cancer Res.* 2008, 68, 3566–3572. [CrossRef] [PubMed]

34. Shi, L.; Cheng, Z.; Zhang, J.; Li, R.; Zhao, P.; Fu, Z.; You, Y. hsa-mir-181a and hsa-mir-181b function as tumor suppressors in human glioma cells. *Brain Res.* 2008, 1236, 185–193. [CrossRef] [PubMed]

35. Hodi, F.S.; O’Day, S.J.; McDermott, D.F.; Weber, R.W.; Sosman, J.A.; Haanen, J.B.; Gonzalez, R.; Robert, C.; Schadendorf, D.; Hassel, J.C.; et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N. Engl. J. Med.* 2010, 363, 711–723. [CrossRef] [PubMed]

36. Lee, K.M.; Chuang, E.; Griffin, M.; Khattri, R.; Hong, D.K.; Zhang, W.; Straus, D.; Samelson, L.E.; Thompson, C.B.; Bluestone, J.A. Molecular basis of T cell inactivation by CTLA-4. *Science* 1998, 282, 2263–2266. [CrossRef]
37. Fong, B.; Jin, R.; Wang, X.; Safaee, M.; Lisiero, D.N.; Yang, I.; Li, G.; Liau, L.M.; Prins, R.M. Monitoring of regulatory T cell frequencies and expression of CTLA-4 on T cells, before and after DC vaccination, can predict survival in GBM patients. *PLoS ONE* **2012**, *7*, e32614. [CrossRef]  
38. Banelli, B.; Forlani, A.; Allemanni, G.; Morabito, A.; Pistillo, M.P.; Romani, M. MicroRNA in glioblastoma: An overview. *Int. J. Genomics* **2017**, 1, 1–16. [CrossRef]  
39. Romani, M.; Pistillo, M.P.; Carosio, R.; Morabito, A.; Banelli, B. Immune Checkpoints and Innovative Therapies in Glioblastoma. *Front. Oncol.* **2018**, *8*, 464. [CrossRef]  
40. Wang, Y.; Wang, H.; Yao, H.; Li, C.; Fang, J.Y.; Xu, J. Regulation of PD-L1: Emerging routes for targeting tumor immune evasion. *Front. Pharmacol.* **2018**, *9*, 536. [CrossRef]  
41. Wang, Y.; Wang, L. miR-34a attenuates glioma cells progression and chemoresistance via targeting PD-L1. *Biotecnol. Lett.* **2017**, *39*, 1485–1492. [CrossRef] [PubMed]  
42. Wang, Z.; Zhang, C.; Liu, X.; Wang, Z.; Sun, L.; Li, G.; Li, H.; Liu, Y.; Zhang, W.; et al. Molecular and clinical characterization of PD-L1 expression at transcriptional level via 976 samples of brain glioma. *Oncoimmunology* **2016**, *5*, e1196310. [CrossRef] [PubMed]  
43. Chen, L.; Gibbons, D.L.; Goswami, S.; Cortez, M.A.; Ahn, Y.H.; Byers, L.A.; Zhang, X.; Yi, X.; Dwyer, D.; Lin, W. Metastasis is regulated via microRNA-200/ZEB1 axis control of tumour cell PD-L1 expression and intratumoral immunosuppression. *Nat. Commun.* **2014**, *5*, 524. [CrossRef] [PubMed]  
44. Wei, J.; Nduom, E.K.; Kong, L.Y.; Hashimoto, Y.; Xu, S.; Gabrusiewica, K.; Ling, X.; Huang, N.; Qiao, W.; Zhou, S.; et al. MiR-138 exerts anti-glioma efficacy by targeting immune checkpoints. *Neuro-Oncology* **2016**, *18*, 639–648. [CrossRef]  
45. Wei, J.; Wang, F.; Kong, L.Y.; Xu, S.; Doucette, T.; Ferguson, S.D.; Yang, Y.; McEnery, K.; Jethwa, K.; Gjyshi, O.; et al. miR-124 inhibits STAT3 signaling to enhance T cell-mediated immune clearance of glioma. *Cancer Res.* **2013**, *73*, 3913–3926. [CrossRef]  
46. Xu, S.; Tao, Z.; Hai, B.; Liang, H.; Shi, Y.; Wang, T.; Song, W.; Chen, Y.; Ouyang, J.; Chen, J.; et al. MiR-424(322) reverses chemoresistance via T-cell immune response activation by blocking the PD-L1 immune checkpoint. *Nat. Commun.* **2016**, *7*, 11406. [CrossRef] [PubMed]  
47. Gong, A.Y.; Zhou, R.; Hu, G.; Liu, J.; Sonnowska, D.; Drescher, K.M.; Dong, H.; Chen, X.M. Cryptosporidium parvum Induces B7-H1 Expression in Cholangiocytes by Downregulating MicroRNA-513. *J. Infect. Dis.* **2010**, *201*, 160–169. [CrossRef]  
48. Dunand-Sauthier, I.; Santiago-Raber, M.L.; Capponi, L.; Vejnarn, C.E.; Schaad, O.; Irla, M.; Seguin-Estèvez, Q.; Descombes, P.; Zdobnov, E.M.; Acha-Orbea, H.; et al. Silencing of c-Fos expression by microRNA-155 is critical for dendritic cell maturation and function. *Blood* **2011**, *117*, 4490–4500. [CrossRef]  
49. Li, Q.; Johnston, N.; Zheng, X.; Wang, H.; Zhang, X.; Gao, D.; Min, W. MiR-28 modulates exhaustive differentiation of T cells through silencing programmed cell death-1 and regulating cytokine secretion. *Oncotarget* **2016**, *7*, 53735–53750. [CrossRef]  
50. Litak, J.; Mazurek, M.; Grochowski, C.; Kamieniak, P.; Rolﬁ´ski, J. PD-L1/PD-1 Axis in Glioblastoma Multiforme. *Int. J. Mol. Sci.* **2019**, *20*, 5347. [CrossRef] [PubMed]  
51. Liang, S.B.; Fu, L.W. Application of single-cell technology in cancer research. *Biotecnol. Adv.* **2017**, *35*, 443–449. [CrossRef] [PubMed]  
52. Han, X.; Wang, J.; Sun, Y. Circulating tumor DNA as biomarkers for cancer detection. *Genom. Proteomics Bioinform.* **2017**, *15*, 59–72. [CrossRef] [PubMed]  
53. Palanchamy, K.; Erkkinen, M.; Chakravarti, A. Predictive and prognostic markers in human glioblastomas. *Curr. Treat Options Oncol.* **2006**, *7*, 490–504. [CrossRef] [PubMed]  
54. Capper, D.; Simon, M.; Langhans, C.D.; Okun, J.G.; Tonn, J.C.; Weller, M.; von Deimling, A.; Hartmann, C. 2-hydroxyglutarate concentration in serum from patients with gliomas does not correlate with IDH1/2 mutation status or tumor size. *Int. J. Cancer* **2012**, *131*, 766–768. [CrossRef]  
55. Ellingson, B.M.; Chung, C.; Pope, W.B.; Bozeman, J.L.; Kaufmann, T.J. Pseudoprogression, radionecrosis, inflammation or true tumor progression? Challenges associated with glioblastoma response assessment in an evolving therapeutic landscape. *J. Neuro-Oncol.* **2017**, *134*, 495–504. [CrossRef]  
56. Hara, N.; Kikuchi, M.; Miyashita, A.; Hatsuta, H.; Saito, Y.; Kasuga, K.; Murayama, S.; Ikeuchi, T.; Kuwano, R. Serum microRNA miR-501-3p as a potential biomarker related to the progression of Alzheimer’s disease. *Acta Neuropathol. Commun.* **2017**, *5*, 10. [CrossRef]
57. Huang, Y.; Liao, D.; Pan, L.; Ye, R.; Li, X.; Wang, S.; Ye, C.; Chen, L. Expressions of miRNAs in papillary thyroid carcinoma and their associations with the BRAFV600E mutation. *Eur. J. Endocrinol.* 2013, 168, 675–681. [CrossRef]
58. Ma, L.; Teruya-Feldstein, J.; Weinberg, R.A. Tumour invasion and metastasis initiated by microRNA-10b in breast cancer. *Nature* 2007, 449, 682–688. [CrossRef]
59. Jiang, X.; Wang, W.; Yang, Y.; Du, L.; Yang, X.; Wang, L.; Zheng, G.; Duan, W.; Wang, R.; Zhang, X.; et al. Identification of circulating microRNA signatures as potential noninvasive biomarkers for prediction and prognosis of lymph node metastasis in gastric cancer. *Oncotarget* 2017, 8, 65132–65142.
60. Paydas, S.; Acikelin, A.; Ergin, M.; Celik, H.; Yavuz, B.; Tanriverdi, K. Micro-RNA (miRNA) profile in Hodgkin lymphoma: Association between clinical and pathological variables. *Med. Oncol.* 2016, 33, 34. [CrossRef]
61. Ling, Q.; Xu, X.; Ye, P.; Xie, H.; Gao, F.; Hu, Q.; Liu, Z.; Wei, X.; Roder, C.; Trauzold, A.; et al. The prognostic relevance of primary tumor location in patients undergoing resection for pancreatic ductal adenocarcinoma. *Oncotarget* 2017, 8, 15159–15167. [CrossRef] [PubMed]
62. Zhi, F.; Chen, X.; Wang, S.; Xiu, X.; Shi, Y.; Guan, W.; Shao, N.; Qu, H.; Yang, C.; Yang, C.; et al. The use of hsa-miR-21, hsa-miR-181b and hsa-miR-106a as prognostic indicators of astrocytoma. *Eur. J. Cancer* 2010, 46, 1640–1649. [CrossRef] [PubMed]
63. Sasayama, T.; Nishihara, M.; Kondoh, T.; Hosoda, K.; Kohmura, E. MicroRNA-10b is overexpressed in malignant glioma and associated with tumor invasive factors, uPAR and RhoC. *Int. J. Cancer* 2009, 125, 1407–1413. [CrossRef] [PubMed]
64. Chen, W.; Yu, Q.; Chen, B.; Lu, X.; Li, Q. The prognostic value of a seven-microRNA classifier as a novel biomarker for the prediction and detection of recurrence in glioma patients. *Oncotarget* 2016, 7, 53392–53413. [CrossRef] [PubMed]
65. Srinivasan, S.; Patric, I.R.; Somasundaram, K. A ten-microRNA expression signature predicts survival in glioblastoma. *PLoS ONE* 2011, 6, e17438. [CrossRef] [PubMed]
66. Raponi, M.; Dossey, L.; Jatkoe, T.; Wu, X.; Chen, G.; Fan, H.; Beer, D.G. MicroRNA classifiers for predicting prognosis of squamous cell lung cancer. *Cancer Res.* 2009, 69, 5776–5783. [CrossRef]
67. Hurst, D.R.; Edmonds, M.D.; Scott, G.K.; Benz, C.C.; Vaidya, K.S.; Welch, D.R. Breast cancer metastasis suppressor 1 up-regulates miR-146, which suppresses breast cancer metastasis. *Cancer Res.* 2009, 69, 1279–1283. [CrossRef]
68. Xia, H.; Qi, Y.; Ng, S.S.; Chen, X.; Li, D.; Chen, S.; Ge, R.; Jiang, S.; Li, G.; Chen, Y.; et al. microRNA-146b inhibits glioma cell migration and invasion by targeting MMPs. *Brain Res.* 2009, 1269, 158–165. [CrossRef]
69. Valastyan, S.; Reinhardt, F.; Benach, N.; Calogrias, D.; Szasz, A.M.; Wang, Z.C.; Jane, E.B.; Richardson, A.L.; Weinberg, R.A. A pleiotropically acting microRNA, miR-31, inhibits breast cancer metastasis. *Cell* 2009, 137, 1032–1046. [CrossRef]
70. Mizumatsu, S.; Tamiya, T.; Ono, Y.; Abe, T.; Matsumoto, K.; Furuta, T.; Ohmoto, T. Expression of cell cycle regulator p27Kip1 is correlated with survival of patients with astrocytoma. *Clin. Cancer Res.* 1999, 5, 551–557.
71. Kirla, R.M.; Haapasalo, H.K.; Kalimo, H.; Salminen, E.K. Low expression of p27 indicates a poor prognosis in patients with high-grade astrocytomas. *Cancer* 2003, 97, 644–648. [CrossRef] [PubMed]
72. Gillies, J.K.; Lorimer, I.A. Regulation of p27Kip1 by miRNA 221/222 in glioblastoma. *Cell Cycle* 2007, 6, 2005–2009. [CrossRef]
73. Pu, X.X.; Huang, G.L.; Guo, H.Q.; Guo, C.C.; Li, H.; Ye, S.; Ling, S.; Jiang, L.; Tian, Y.; Lin, T. Circulating miR-221 directly amplified from plasma is a potential diagnostic and prognostic marker of colorectal cancer and is correlated with p53 expression. *J. Gastroenterol. Hepatol.* 2010, 25, 1674–1680. [CrossRef] [PubMed]
74. Medina, R.; Zaidi, S.K.; Liu, C.G.; Stein, J.I.; van Wijnen, A.J.; Croce, C.M.; Stein, G.S. MicroRNAs 221 and 222 bypass quiescence and compromise cell survival. *Cancer Res.* 2008, 68, 2773–2780. [CrossRef]
75. Chun-Zhi, Z.; Lei, H.; An-Ling, Z.; Yan-Chao, F.; Xiao, Y.; Huang, G.L.; Guo, H.Q.; Li, H.; Ye, S.; Ling, S.; Jiang, L.; Tian, Y.; Lin, T. Circulating miR-221 directly amplified from plasma is a potential diagnostic and prognostic marker of colorectal cancer and is correlated with p53 expression. *J. Gastroenterol. Hepatol.* 2010, 25, 1674–1680. [CrossRef] [PubMed]
76. Chun-Zhi, Z.; Lei, H.; An-Ling, Z.; Yan-Chao, F.; Xiao, Y.; Huang, G.L.; Guo, H.Q.; Li, H.; Ye, S.; Ling, S.; Jiang, L.; Tian, Y.; Lin, T. Circulating miR-221 directly amplified from plasma is a potential diagnostic and prognostic marker of colorectal cancer and is correlated with p53 expression. *J. Gastroenterol. Hepatol.* 2010, 25, 1674–1680. [CrossRef] [PubMed]
77. Chun-Zhi, Z.; Lei, H.; An-Ling, Z.; Yan-Chao, F.; Xiao, Y.; Huang, G.L.; Guo, H.Q.; Li, H.; Ye, S.; Ling, S.; Jiang, L.; Tian, Y.; Lin, T. Circulating miR-221 directly amplified from plasma is a potential diagnostic and prognostic marker of colorectal cancer and is correlated with p53 expression. *J. Gastroenterol. Hepatol.* 2010, 25, 1674–1680. [CrossRef] [PubMed]
77. Caramuta, S.; Egyhazi, S.; Rodolfo, M.; Witten, D.; Hansson, J.; Larsson, C.; Lui, W.O. MicroRNA expression profiles associated with mutational status and survival in malignant melanoma. *J. Investig. Dermatol.* **2010**, *130*, 2062–2070. [CrossRef]

78. Diaz, R.; Silva, J.; Garcia, J.M.; Lorenzo, Y.; Garcia, V.; Pena, C.; Rodriguez, R.; Munoz, C.; Garcia, F.; Bonilla, F.; et al. Deregulated expression of miR-106a predicts survival in human colon cancer patients. *Genes Chromosom. Cancer.* **2008**, *47*, 794–802. [CrossRef]

79. Landais, S.; Landry, S.; Legault, P.; Rassart, E. Oncogenic potential of the miR-106-363 cluster and its implication in human T-cell leukemia. *Cancer Res.* **2007**, *67*, 5699–5707. [CrossRef]

80. Sallinen, S.L.; Sallinen, P.K.; Kononen, J.T.; Syrjakoski, K.M.; Nupponen, N.N.; Rantala, I.S.; Pauli, T.H.; Helin, H.J.; Haapasalo, H.K. Cyclin D1 expression in astrocytomas is associated with cell proliferation activity and patient prognosis. *J. Pathol.* **1999**, *188*, 289–293. [CrossRef]

81. Alonso, M.M.; Fueyo, J.; Shay, J.W.; Aldape, K.D.; Jiang, H.; Lee, O.H.; Johnson, D.G.; Xu, J.; Kondo, Y.; Kanzawa, T.; et al. Expression of transcription factor E2F1 and telomerase in glioblastomas: mechanistic linkage and prognostic significance. *J. Natl. Cancer Inst.* **2005**, *97*, 1589–1600. [CrossRef] [PubMed]

82. Liu, C.; Tu, Y.; Sun, X.; Jiang, J.; Jin, X. Wnt/beta-Catenin pathway in human glioma: expression pattern and clinical/prognostic correlations. *Clin. Exp. Med.* **2011**, *1*, 105–112. [CrossRef] [PubMed]

83. Cloonan, N.; Brown, M.K.; Steptoe, A.L.; Wani, S.; Chan, W.L.; Forrest, A.R.; Kolle, G.; Gabrielli, B.; Grimm, S.M. The miR-17-5p microRNA is a key regulator of the G1/S phase cell cycle transition. *Genome Biol.* **2008**, *9*, 127. [CrossRef] [PubMed]

84. Takakura, S.; Mitsutake, N.; Nakashima, M.; Namba, H.; Saenko, V.A.; Rogounovitch, T.I.; Nakazawa, Y.; Hayashi, T.; Ohtsuru, A.; Yamasita, S. Oncogenic role of miR-17-92 cluster in anaplastic thyroid cancer cells. *Cancer Sci.* **2008**, *99*, 1147–1154. [CrossRef]

85. Sun, J.; Xue, G.; Puro, B.; Zhao, Z. Uncovering microRNA and transcription factor mediated regulatory networks in glioblastoma. *PLoS Comput. Biol.* **2012**, *8*, e1002488. [CrossRef] [PubMed]

86. Yu, Z.; Wang, C.; Wang, M.; Li, Z.; Casimiro, M.C.; Liu, M.; Wu, K.; Whittle, J.; Ju, X.; Hyslop, T.; et al. A cyclin D1/microRNA 17/20 regulatory feedback loop in control of breast cancer cell proliferation. *J. Cell Biol.* **2008**, *182*, 509–517. [CrossRef]

87. O’Donnell, K.A.; Wentzel, E.A.; Zeller, K.I.; Dang, C.V.; Mendell, J.T. c-Myc-regulated microRNAs modulate E2F1 expression. *Nature* **2005**, *435*, 839–843. [CrossRef]

88. Scherr, M.; Venturini, L.; Battmer, K.; Schaller-Schoenitz, M.; Schaefer, D.; Dallmann, I.; Ganser, A.; Eder, M. Lentivirus-mediated antagomir expression for specific inhibition of miRNA function. *Nucleic Acids. Res.* **2005**, *33*, e142. [CrossRef] [PubMed]

89. Hossain, A.; Kuo, M.T.; Saunders, G.F. Mir-17-5p regulates breast cancer cell proliferation by inhibiting translation of AIB1 mRNA. *Mol. Cell Biol.* **2006**, *26*, 8191–8201. [CrossRef]

90. Xiao, S.; Yang, Z.; Qiu, X.; Lv, R.; Liu, J.; Wu, M.; Liao, Y.; Liu, Q. miR-29c contribute to glioma cells temozolomide sensitivity by targeting O6-methylguanine-DNA methyltransferases indirectly. *Oncotarget* **2016**, *7*, 50229–50238. [CrossRef]

91. Ji, Y.; Wei, Y.; Wang, J.; Ao, Q.; Gong, K.; Zuo, H. Decreased expression of microRNA-107 predicts poorer prognosis in glioma. *Tumour Biol.* J. Int. Soc. Oncodev. Biol. Med. **2015**, *36*, 4461–4466. [CrossRef]

92. Ho, K.H.; Chen, P.H.; Hsi, E.; Shih, C.M.; Chang, W.C.; Cheng, C.H.; Lin, C.W.; Chen, K.C. Identification of IGF-1-enhanced cytokine expressions targeted by miR-181d in glioblastomas via an integrative miRNA/mRNA regulatory network analysis. *Sci. Rep.* **2017**, *7*, 732. [CrossRef]

93. Sun, J.; Liao, K.; Wu, X.; Huang, J.; Zhang, S.; Lu, X. Serum microRNA-128 as a biomarker for diagnosis of glioma. *Int. J. Clin. Exp. Med.* **2015**, *8*, 456–463. [PubMed]

94. Yue, X.; Lan, F.; Hu, M.; Pan, Q.; Wang, Q.; Wang, J. Downregulation of serum microRNA-205 as a potential diagnostic and prognostic biomarker for human glioma. *J. Neurosurg.* **2015**, *124*, 122–128. [CrossRef]

95. Qiu, S.; Sheng, L.; Dan, H.; Yimin, F.; Yang, T.; Ying, P. Interactions of miR-323/miR-326/miR-329 and miR-130a/miR-155/miR-210 as prognostic indicators for clinical outcome of glioblastoma patients. *J. Transl. Med.* **2012**, *10*, 10–1186. [CrossRef] [PubMed]

96. Schliesser, M.G.; Claus, R.; Hielscher, T.; Grimm, C.; Weichenhan, D.; Blaes, J.; Wiestler, B.; Hau, P.; Schramm, J.; Sahm, F.; et al. Prognostic relevance of miRNA-155 methylation in anaplastic glioma. *Oncotarget* **2016**, *7*, 82028–82045. [CrossRef] [PubMed]
97. Regazzo, G.; Terrenato, I.; Spagnuolo, M.; Carosi, M.; Cognetti, G.; Cicchillitti, L.; Sperati, F.; Villani, V.; Carapella, C.; Piaggion, G.; et al. A restricted signature of serum miRNAs distinguishes glioblastoma from lower grade gliomas. *J. Exp. Clin. Cancer Res.* 2016, 35, 124. [CrossRef]

98. Shi, Y.; Tao, T.; Liu, N.; Luan, W.; Qian, J.; Li, R.; Hu, Q.; Wei, Y.; Zhang, J.; You, Y. PPARalpha, a predictor of patient survival in glioma, inhibits cell growth through the E2F1/miR-19a feedback loop. *Oncotarget* 2016, 7, 84623–84633. [CrossRef]

99. Sun, G.; Cao, Y.; Shi, L.; Sun, L.; Wang, Y.; Chen, C.; Wan, Z.; Fu, L.; You, Y. Overexpressed miRNA-137 inhibits human glioma cells growth by targeting Rac1. *Cancer Biother. Radiopharm.* 2013, 28, 327–334. [CrossRef]

100. Li, H.Y.; Li, Y.M.; Li, Y.; Shi, X.W.; Chen, H. Circulating microRNA-137 is a potential biomarker for human glioblastoma. *Eur. Rev. Med. Pharmacol. Sci.* 2016, 20, 3599–3604.

101. Jiang, L.; Mao, P.; Song, L.; Wu, J.; Huang, J.; Lin, C.; Yuan, J.; Qu, L.; Chen, S.Y.; Li, J. miR-182 as a prognostic marker for glioma progression and patient survival. *Am. J. Pathol.* 2010, 177, 29–38. [CrossRef]

102. Xiao, Y.; Zhang, L.; Song, Z.; Guo, C.; Zhu, J.; Li, Z.; Zhu, S. Potential Diagnostic and Prognostic Value of Plasma Circulating MicroRNA-182 in Human Glioma. *Med. Sci. Monit. Int. Med. J. Exp. Clin. Res.* 2016, 22, 855–862. [CrossRef] [PubMed]

103. Rani, S.B.; Rathod, S.S.; Karthik, S.; Kaur, N.; Muzumdar, D.; Shiras, A.S. MiR-145 functions as a tumor-suppressive RNA by targeting Sox9 and adducin 3 in human glioma cells. *Neuro-Oncology* 2013, 15, 1302–1316. [CrossRef] [PubMed]

104. Malzkorn, B.; Wolter, M.; Liesenberg, F.; Grzendowski, M.; Stuhler, K.; Meyer, H.E.; Reifenberger, G. Identification and functional characterization of microRNAs involved in the malignant progression of gliomas. *Brain Pathol.* 2010, 20, 539–550. [CrossRef] [PubMed]

105. Comincini, S.; Allavena, G.; Palumbo, S.; Morini, M.; Durando, F.; Angeletti, F.; Pirtoli, L.; Miracco, C. 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, 14, 574–586. [CrossRef]

106. He, L.; Hannon, G.J. MicroRNAs: Small RNAs with a big role in gene regulation. *Nat. Rev. Genet.* 2004, 5, 522–531. [CrossRef] [PubMed]

107. Croce, C.M. Causes and consequences of microRNA dysregulation in cancer. *Nat. Rev. Genet.* 2009, 10, 704–714. [CrossRef] [PubMed]

108. Shen, R.; Wang, Y.; Wang, C.X.; Yin, M.; Liu, H.L.; Chen, J.P.; Han, J.Q.; Wang, W.B. MiRNA-155 mediates TAM resistance by modulating SOCS6-STAT3 signalling pathway in breast cancer. *Am. J. Transl. Res.* 2015, 7, 2115–2126.

109. Blower, P.E.; Chung, J.H.; Verducci, J.S.; Lin, S.; Park, J.K.; Dai, Z.; Liu, C.G.; Schmittgen, T.D.; Reinhold, W.C.; Croce, C.M.; et al. MicroRNAs modulate the chemosensitivity of tumor cells. *Mol. Cancer Ther.* 2008, 7, 1–9. [CrossRef]

110. Munoz, J.L.; Walker, N.D.; Scotto, K.W.; Rameshwar, P. Temozolomide competes for P-glycoprotein and contributes to chemoresistance in glioblastoma cells. *Cancer Lett.* 2015, 367, 69–75. [CrossRef]

111. Dong, Z.; Ren, L.; Lin, L.; Li, J.; Huang, Y.; Li, J. Effect of microRNA-21 on multidrug resistance reversal in A549/DDP human lung cancer cells. *Mol. Med. Rep.* 2015, 11, 682–690. [CrossRef]

112. Sun, C.; Li, N.; Yang, Z.; Zhou, B.; He, Y.; Weng, D.; Fang, Y.; Wu, P.; Chen, P.; Yang, X.; et al. miR-9 regulation of BRCA1 and ovarian cancer sensitivity to cisplatin and PARP inhibition. *J. Natl. Cancer Inst.* 2013, 105, 1750–1758. [CrossRef] [PubMed]

113. Zhang, W.B.; Wang, Z.; Shu, F.; Jin, Y.H.; Liu, H.Y.; Wang, Q.J.; Wang, Y. Activation of AMP-activated protein kinase by temozolomide contributes to apoptosis in glioblastoma cells via p53 activation and mTORC1 inhibition. *J. Biol. Chem.* 2010, 285, 40461–40471. [CrossRef] [PubMed]

114. Hegi, M.E.; Diserens, A.C.; Gorlia, T.; Hamou, M.F.; de Tribolet, N.; Weller, M.; Kros, J.M.; Hainfellner, J.A.; Mason, W.; Mariani, L.; et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N. Engl. J. Med.* 2005, 352, 997–1003. [CrossRef] [PubMed]

115. Wong, S.T.; Zhang, X.Q.; Zhuang, J.T.; Chan, H.L.; Li, C.H.; Leung, G.K. MicroRNA-21 inhibition enhances in vitro chemosensitivity of temozolomide-resistant glioblastoma cells. *Anticancer Res.* 2012, 32, 2835–2841. [PubMed]

116. Wick, W.; Platten, M. Understanding and targeting alkylator resistance in glioblastoma. *Cancer Discov.* 2014, 4, 1120–1122. [CrossRef]
117. Strobel, H.; Baisch, T.; Fitzel, R.; Schiberg, K.; Siegelin, M.D.; Karpel-Massler, G.; Debatin, K.M.; Westhoff, M.A. Temozolomide and Other Alkylation Agents in Glioblastoma Therapy. *Biomedicines* 2019, 7, 69. [CrossRef]

118. Mansouri, A.; Hachem, L.D.; Mansouri, S.; Nassiri, F.; Laperriere, N.J.; Xia, D.; Lindeman, N.I.; Wen, P.Y.; Chakravarti, A.; Mehta, M.P.; et al. MGMT promoter methylation status testing to guide therapy for glioblastoma: refining the approach based on emerging evidence and current challenges. *Neuro Oncol.* 2018, 21, 167–178. [CrossRef]

119. Liu, C.J.; Tsai, M.M.; Hung, P.S.; Kao, S.Y.; Liu, T.Y.; Wu, K.J.; Chiou, S.H.; Lin, S.C.; Chang, K.W. miR-31 with carmustine alone and standard radiation therapy or accelerated radiation therapy in patients with glioblastoma multiforme cells is associated with regulation of DNA repair by DHCR2. *Brain* 2019, 142, 2352–2366. [CrossRef] [PubMed]

120. Baisch, T.; Fitzel, R.; Schiberg, K.; Siegelin, M.D.; Karpel-Massler, G.; Debatin, K.M.; Westhoff, M.A. Temozolomide and Other Alkylation Agents in Glioblastoma Therapy. *Biomedicines* 2019, 7, 69. [CrossRef]

121. Guo, Y.; Yan, K.; Fang, J.; Qu, Q.; Zhou, M.; Chen, F. Let-7b expression determines response to chemotherapy with O(6)-methylguanine-DNA methyltransferase activity and mRNA levels by cisplatin and temozolomide in Jurkat cells. *J. Pharmacol. Exp. Ther.* 2000, 294, 664–671. [PubMed]

122. Scheithauer, B.W.; Sandler, H.M.; Marks, R.S.; et al. Phase III trial of carmustine and cisplatin compared with carmustine alone and standard radiation therapy or accelerated radiation therapy in patients with glioblastoma multiforme: North Central Cancer Treatment Group 93-72-52 and Southwest Oncology Group 9503 Trials. *J. Clin. Oncol.* 2000, 18, 3871–3879.

123. Chen, X.; Zhang, Y.; Shi, Y.; Lian, H.; Tu, H.; Han, S.; Peng, B.; Liu, W.; He, X. MiR-873 acts as a novel sensitizer for glioblastoma. *J. Exp. Clin. Cancer Res.* 2013, 32, 41. [CrossRef] [PubMed]

124. Zhang, W.; Zhang, J.; Hoadley, K.; Kushwaha, D.; Ramakrishnan, V.; Li, S.; Kang, C.; You, Y.; Jiang, C.; et al. A genomewide miRNA screen revealed miR-603 as a MGMT-regulating miRNA in glioblastoma. *Cancer Biol. Ther.* 2014, 15, 938–950. [CrossRef] [PubMed]

125. Novakova, J.; et al. MicroRNA-181 family predicts response to concomitant chemoradiotherapy with temozolomide in glioblastoma patients. *Neoplasia* 2020, 2019, 69. [CrossRef]

126. Novakova, J.; et al. MicroRNA-181 family predicts response to concomitant chemoradiotherapy with temozolomide in glioblastoma patients. *Neoplasia* 2020, 2019, 69. [CrossRef] [PubMed]

127. Guo, Y.; Yan, K.; Fang, J.; Qu, Q.; Zhou, M.; Chen, F. Let-7b expression determines response to chemotherapy with O(6)-methylguanine-DNA methyltransferase activity and mRNA levels by cisplatin and temozolomide in glioblastoma patients. *Neoplasia* 2020, 20, 264–269. [CrossRef] [PubMed]

128. Slaby, O.; Lakomy, R.; Fadrus, P.; Hrstka, R.; Kren, L.; Lzicarova, E.; Smrcka, M.; Svoboda, M.; Dolezalove, H.; Novakova, J.; et al. MicroRNA-181 family predicts response to concomitant chemoradiotherapy with temozolomide in glioblastoma patients. *Neoplasia* 2020, 2019, 69. [CrossRef] [PubMed]

129. Chen, X.; Zhang, Y.; Shi, Y.; Lian, H.; Tu, H.; Han, S.; Peng, B.; Liu, W.; He, X. MiR-873 acts as a novel sensitizer for glioblastoma. *J. Exp. Clin. Cancer Res.* 2013, 32, 41. [CrossRef] [PubMed]

130. Kamada, K.; Nagata, I.; et al. miR-195, miR-455-3p and miR-10a(*) are implicated in acquired temozolomide resistance in glioblastoma multiforme cells. *Cancer Lett.* 2010, 296, 241–248. [CrossRef] [PubMed]

131. Takakura, S.; Matsuse, M.; Saenko, V.; Suzuki, K.; Hayashi, K.; Matsuo, T.; Kamada, K.; Nagata, I.; et al. miR-195, miR-455-3p and miR-10a(*) are implicated in acquired temozolomide resistance in glioblastoma multiforme cells. *Cancer Lett.* 2010, 296, 241–248. [CrossRef] [PubMed]
134. Auger, N.; Thillet, J.; Wanherdrick, K.; Idbaih, A.; Legrier, M.E. Genetic alterations associated with acquired temozolomide resistance in SNB-19, a human glioma cell line. Mol. Cancer Ther. 2006, 5, 2182–2192. [CrossRef] [PubMed]

135. Wang, L.; Shi, Z.; Jiang, C.; Liu, X.; Chen, Q.; Qian, X.; Li, D.; Ge, X.; Wang, X.; Liu, L.; et al. MiR-143 acts as a tumor suppressor by targeting N-RAS and enhances temozolomide-induced apoptosis in glioma. Oncotarget 2014, 5, 5416–5427. [CrossRef] [PubMed]

136. Li, R.Y.; Chen, L.C.; Zhang, H.Y.; Du, W.Z.; Feng, Y.; Wang, H.B.; Wen, J.Q.; Liu, X.; Li, X.F.; Sun, Y.; et al. MiR-139 inhibits Mcl-1 expression and potentiates TMZ-induced apoptosis in glioma. CNS Neurosci. Ther. 2013, 19, 477–483. [CrossRef]

137. Shi, L.; Chen, J.; Yang, J.; Pan, T.; Zhang, S.; Wang, Z. MiR-21 protected human glioblastoma U87MG cells from chemotherapeutic drug temozolomide induced apoptosis by decreasing Bax/Bcl-2 ratio and caspase-3 activity. Brain Res. 2010, 1352, 255–264. [CrossRef] [PubMed]

138. Li, Y.; Li, W.; Yang, Y.; Lu, Y.; He, C.; Hu, G.; Liu, H.; Chen, J.; He, J.; Yu, H. MicroRNA-21 targets LRRFIP1 and contributes to VM-26 resistance in glioblastoma multiforme. Brain Res. 2009, 1286, 13–18. [CrossRef] [PubMed]

139. Costa, P.M.; Cardoso, A.L.; Nobrega, C.; de Almeida, L.F.P.; Bruce, J.N.; Canoll, P.; de Lima, M.C.P. MicroRNA-21 silencing enhances the cytotoxic effect of the antiangiogenic drug sunitinib in glioblastoma. Hum. Mol. Genet. 2013, 22, 904–918. [CrossRef] [PubMed]

140. Wang, G.B.; Liu, J.H.; Hu, J.; Xue, K. MiR-21 enhanced glioma cells resistance to carmustine via decreasing Spry2 expression. Eur. Rev. Med. Pharmacol. Sci. 2017, 21, 5065–5071.

141. Zhang, S.; Han, L.; Wei, J.; Shi, Z.; Pu, P.; Zhang, J.; Yuan, X.; Kang, C. Combination treatment with doxorubicin and microRNA-21 inhibitor synergistically antagonizes anticancer activity through upregulation of tumor suppressing gene. Int. J. Oncol. 2015, 46, 1589–1600. [CrossRef] [PubMed]

142. Ren, Y.; Zhou, X.; Mei, M.; Yuan, X.B.; Han, L.; Wang, G.X.; Jia, Z.F.; Xu, P.; Pu, P.Y.; Kang, C.S. MicroRNA-21 inhibitor sensitizes human glioblastoma cells U251 (PTEN-mutant) and LN229 (PTEN-wild type) to taxol. BMC Cancer 2010, 10, 27. [CrossRef] [PubMed]

143. Barker, C.A.; Chang, M.; Chou, J.F.; Zhang, Z.; Beal, K.; Gutin, P.H.; Iwamoto, F.M. Radiotherapy and concomitant temozolomide may improve survival of elderly patients with glioblastoma. Int. J. Oncol. 2012, 391–397. [CrossRef] [PubMed]

144. Yoo, B.K.; Emdad, L.; Lee, S.G.; Su, Z.Z.; Santhekadur, P.; Chen, D.; Gredler, R.; Fisher, P.B.; Sarkar, D. Astrocyte elevated gene-1 (AEG-1): A multifunctional regulator of normal and abnormal physiology. Pharmacol. Ther. 2011, 130, 1–8. [CrossRef] [PubMed]

145. Wu, H.; Liu, Q.; Cai, T.; Chen, Y.; Liao, F.; Wang, Z.; Cai, T.; Chen, C.; He, J.; Yang, B.B. Stress response of glioblastoma cells mediated by miR-17-5p targeting PTEN and the GSK3beta in glioblastoma. Oncotarget 2015, 6, 904–918. [CrossRef] [PubMed]

146. Emdad, L.; Sarkar, D.; Lee, S.G.; Su, Z.Z.; Yoo, B.K.; Dash, R.; Yacoub, A.; Fuller, C.E.; Shah, K.; Dent, P.; et al. Astrocyte elevated gene-1: A multifunctional regulator of normal and abnormal physiology. Pharmacol. Ther. 2014, 138, 5416–5427. [CrossRef] [PubMed]

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

148. Li, H.; Yang, B.B. Stress response of glioblastoma cells mediated by miR-17-5p targeting PTEN and the passenger strand miR-17-3p targeting MDM2. Oncotarget 2012, 3, 1653. [CrossRef]

149. Tian, T.; Mingyi, M.; Qiu, X.; Qiu, Y. MicroRNA-101 reverses temozolomide resistance by inhibition of GSK3beta in glioblastoma. Oncotarget 2016, 7, 79584–79595. [CrossRef]

150. Liu, Q.; Kou, R.; Zhou, R.; Gong, C.; Wang, Z.; Cai, T.; Tan, C.; Fang, J. miR-155 Regulates Glioma Cells Invasion and Chemosensitivity by p38 Isforms In Vitro. J. Cell. Biochem. 2015, 116, 1213–1221. [CrossRef]

151. Chen, W.; Xu, X.K.; Li, J.L.; Kong, K.K.; Li, H.; Chen, C.; He, J.; Wang, F.; Li, P.; Ge, X.S.; et al. MALAT1 is a prognostic factor in glioblastoma multiforme and induces chemoresistance to temozolomide through suppressing miR-203 and promoting thymidylate synthase expression. Oncotarget 2017, 8, 22783–22799. [CrossRef] [PubMed]

152. 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, 15, 7563–7570. [CrossRef] [PubMed]
153. Jiang, C.; Shen, F.; Du, J.; Fang, X.; Li, X.; Su, J.; Wang, X.; Huang, X.; Liu, Z. Upregulation of CASC2 sensitized glioma to temozolomide cytotoxicity through autophagy inhibition by sponging miR-193a-5p and regulating mTOR expression. *Biomed. Pharmacother.* **2018**, *97*, 844–850. [CrossRef] [PubMed]

154. Anido, J.; Sáez-Borderísa, A.; González-Juncà, A.; Rodón, L.; Folch, G.; Carmona, M.A.; Prieto-Sánchez, R.M.; Barba, I.; Martínez-Sáez, E.; Prudkin, L.; et al. TGF-β receptor inhibitors target the CD44(high)/Id1(high) glioma-initiating cell population in human glioblastoma. *Cancer Cell* **2010**, *18*, 655–668. [CrossRef]

155. 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**, *14*, 185–195. [CrossRef]

156. Kurz, E.U.; Lees-Miller, S.P. DNA damage-induced activation of ATM and ATM-dependent signaling pathways. *DNA Repair* **2004**, *3*, 889–900. [CrossRef]

157. Tribius, S.; Pidel, A.; Casper, D. ATM protein expression correlates with radioresistance in primary glioblastoma cells in culture. *Int. J. Radiat. Oncol. Biol. Phys.* **2001**, *50*, 511–523. [CrossRef]

158. Ng, W.L.; Yan, D.; Zhang, X.; Mo, Y.Y.; Wang, Y. Overexpression of miR-100 is responsible for the low-expression of ATM in the human glioma cell line: M059J. *DNA Repair* **2010**, *9*, 1170–1175. [CrossRef]

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