



Review

MicroRNA as potential modulators in chemoresistant high-grade gliomas

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ABSTRACT

Gliomas account for 70% of human malignant primary brain tumours. The most common form is glioblastoma multiforme, World Health Organization grade IV. Despite the implementation of post-operative adjuvant radiotherapy with concurrent temozolomide (TMZ), the disease's overall prognosis remains dismal. TMZ is currently the only mono-chemotherapeutic agent for newly-diagnosed high-grade glioma patients and acquired resistance inevitably occurs in the majority of such patients, further limiting treatment options. Therefore, there is an urgent need to better understand the underlying mechanisms involved in TMZ resistance, a critical step to developing effective, targeted treatments. An emerging body of evidence suggests the intimate involvement of a novel class of nucleic acid, microRNA (miRNA), in tumorigenesis and disease progression for a number of human malignancies, including primary brain tumours. miRNA are short, single-stranded, non-coding RNA (~22 nucleotides) that function as post-transcriptional regulators of gene expression. This review provides an overview of the key treatment obstacles faced in patients with high-grade gliomas, especially in the context of recurrent, chemoresistant tumours and the potential roles of miRNA in chemoresistance and management of this disease.

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1. Introduction

Gliomas account for 70% of human malignant primary brain tumours [1]. In this group, glioblastoma multiforme (GBM) has the highest grade (World Health Organization grade IV) and is unfortunately the most common. The accepted treatment consists of surgical resection followed by adjuvant treatment with temozolomide (TMZ) and radiation therapy, which has been shown to confer survival benefit in GBM patients [2]. However, the disease prognosis remains dismal, with a median survival of 12–18 months [2]. Histopathologically, GBM cells tend to deeply invade the dense network of brain structures. This diffuse infiltrative nature of GBM is believed to be responsible for tumour recurrence and resistance to treatment [3]. Despite advances in the understanding of glioma biology, the molecular mechanisms underlying therapeutic failure are yet to be fully explored. Acquired TMZ chemoresistance occurs in more than 90% of recurrent high-grade gliomas [4], hence deciphering the underlying mechanisms involved in chemoresistance is critical in the development of effective treatments [5].

MicroRNA (miRNA) are short, single-stranded non-coding RNA (~22 nucleotides) that function as post-transcriptional regulators

of gene expression, and are important in regulating various cellular events [6]. Recently, there has been an upsurge in interest in miRNA involvement in tumorigenesis and progression of various cancers, including GBM. This paper aims to provide an overview of the potential roles of miRNA in the management of recurrent GBM, and more importantly to elucidate if miRNA may aid therapeutic agents in defeating chemoresistance.

2. miRNA in gliomas: The missing link?

miRNA are a diverse family of small RNA molecules generated from larger precursor RNA. They have approximately 22 non-coding nucleotides and are endogenous stem-loop structures encoded by a cell's own genome [6]. One strand of the mature double-stranded miRNA is incorporated into the RNA-induced silencing complex, which downregulates target mRNA by degrading them, or by inhibiting their translation [6]. Their main function is to silence the cell's own message by translational repression, mRNA cleavage and/or deadenylation [7,8]. The mechanism by which they regulate mRNA is to some degree dependant on the extent of miRNA complementarity with the mRNA molecule [6], and since perfect complementarity to the target is not required for regulation, a single miRNA may regulate a number of target genes via the interaction of the miRNA/RNA-induced silencing complex and

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its target mRNA [9]. As one specific miRNA can target the mRNA of various genes, this implies that by inhibiting one miRNA, there is a possibility of suppressing numerous genes and/or the silencing of cellular pathway(s) [10].

Alterations in miRNA expression have been implicated in a variety of pathological processes, including carcinogenesis [8]. An appreciation of aberrant miRNA expression in cancer-related and neoplastic pathogenesis has begun to emerge over the last decade [8,11]. The evidence has so far shown that miRNA profiles appear to be cell-type and disease specific [12]. Moreover, differential expressions of miRNA have been demonstrated to be reliable biomarkers of features such as cancer stage, proliferation capacity and vascular invasion in tumours, including breast and lung carcinomas [9].

In accordance with this, Dong et al. identified that the expression of a specific group of miRNA was significantly altered in human GBM samples. Their functional analyses of target genes suggested that these miRNA have frequently targeted genes associated with cell signalling in the central nervous system (CNS) [13]. Owing to the increasing number of miRNA that have been implicated in cancer-related disease, miRNA have been touted as predictors of glioma gene expression. For example, Wuchty et al. reported that physical interactions of miRNA with mRNA allow prediction of corresponding changes in target mRNA expression profiles in gliomas [14]. Therefore, successful phenotyping of GBM subtypes may help to identify therapeutic obstacles. Drug resistance remains one of the most difficult obstacles in cancer treatments [15], especially in GBM. Recent evidence has shown miRNA to be implicated in modulating sensitivity and/or resistance to other cancer treatments [16]. Based on these observations, miRNA may serve as potential agents in altering sensitivity to cytotoxic therapy [17]. The applications of miRNA as potential therapeutic tools will be discussed in this paper (Fig. 1).

3. Overcoming GBM chemoresistance with miRNA modulation

3.1. DNA repair mechanisms

3.1.1. MGMT: A key repair gene

Since its approval for use in newly-diagnosed GBM patients in 2005, TMZ, an oral alkylating agent, has proven to be an effective chemotherapy drug with tolerable side effects. Owing to its small size and lipophilic properties, it is able to cross the blood–brain barrier (BBB). Although CNS concentrations are approximately 30% of its plasma counterpart, this value is more efficacious than most other chemotherapeutic agents. These pharmacologic properties make it an ideal agent for treating CNS malignancies [18,19]. So far, TMZ remains the only recommended first-line mono-chemotherapeutic agent for malignant gliomas, and according to Stupp et al. TMZ is most effective when administered concomitantly with radiotherapy [2]. Once it enters the CNS, TMZ is spontaneously converted to the active metabolite, methyl-triazene-1-yl-imidazole-4-carboxamide (MTIC). MTIC further reacts with water to liberate 5-aminoimidazole-4-carboxamide and the highly reactive methyl diazonium. The active methyl diazonium cation then methylates DNA at N7 positions (N7-MeG) of guanine-rich regions, N3 adenine (N3-MeA) and O6 guanine (O6-MeG) residues [20]. Any resultant methyl adducts are removed by a DNA repair enzyme, O6-methyl-guanine-methyltransferase (MGMT) [20,21]. Building on this knowledge, innately high levels of MGMT expression will hence confer a resistant phenotype by blunting TMZ-related effects. Corroboratively, Heigi et al. demonstrated that epigenetic silencing of the MGMT gene by promoter methylation is associated with longer survival in GBM patients who received DNA alkylating treatments, such as TMZ [22].

Thus far, MGMT is the best characterised modulator of chemoresistance in GBM [22–24]. The main damage effected by TMZ is

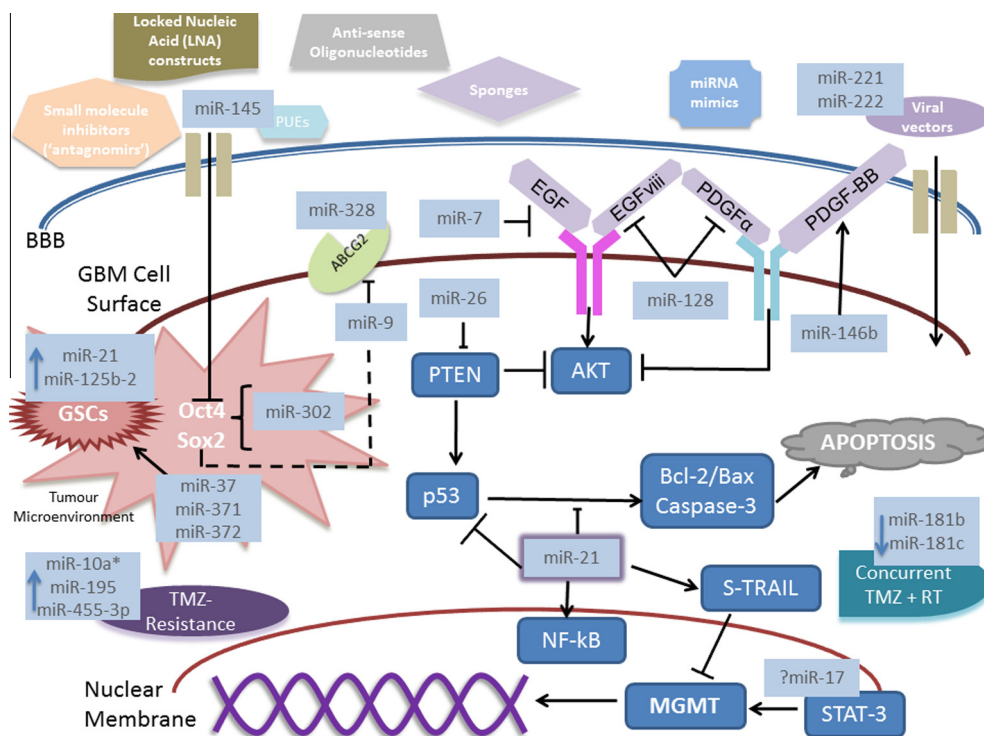


Fig. 1. Schematic diagram of the discussed microRNA and their associated cellular pathways or mechanisms involved in therapeutic resistance, as illustrated at the level of the blood–brain barrier, glioblastoma multiforme tumour cell surface and nuclear membrane. ABC = adenosine triphosphate binding cassette, BBB = blood–brain barrier, EGF = epidermal growth factor, GBM = glioblastoma multiforme, GSC = glioma stem cell, MGMT = O6-methyl-guanine-methyltransferase, PDGF = platelet-derived growth factor, PTEN = phosphatase and tensin homolog, RT = radiotherapy, S-TRAIL = S-tumor necrosis factor-related apoptosis-inducing ligand, STAT = signal transducer and activator of transcription, TMZ = temozolomide.

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