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Mini Review

MicroRNA involvement in glioblastoma pathogenesis

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ABSTRACT

MicroRNAs are endogenously expressed regulatory noncoding RNAs. Altered expression levels of several microRNAs have been observed in glioblastomas. Functions and direct mRNA targets for these microRNAs have been relatively well studied over the last years. According to these data, it is now evident, that impairment of microRNA regulatory network is one of the key mechanisms in glioblastoma pathogenesis. MicroRNA deregulation is involved in processes such as cell proliferation, apoptosis, cell cycle regulation, invasion, glioma stem cell behavior, and angiogenesis. In this review, we summarize the current knowledge of miRNA functions in glioblastoma with an emphasis on its significance in glioblastoma oncogenic signaling and its potential to serve as a disease biomarker and a novel therapeutic target in oncology.
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Introduction

Glioblastoma is the most frequent and the most malignant brain tumor, with an incidence 3.55 new cases per 100,000 Caucasians per year [1]. Despite progress in surgical techniques, radiotherapy and chemotherapy, the prognosis remains poor, with a median survival less than one year [1,2]. Glioblastoma is characterized by rapid diffusely infiltrative growth and high level of cellular heterogeneity associated with therapeutic resistance. Glioblastomas are also characterized by multiple genetic alterations. Epidermal growth factor receptor (EGFR) amplification and PTEN mutations are typical for primary glioblastomas developing rapidly de novo, whereas TP53 mutations are frequent in the pathway leading to secondary glioblastomas developing usually from lower grade astrocytomas. Loss of heterozygosity (LOH) 10q is the most frequent abberation in both primary and secondary glioblastomas [3,4]. Recent knowledge of glioblastoma molecular pathology, however, is not sufficient to enable significant progress in individualized and targeted therapy of glioblastoma patients.

One of the novel approaches for molecular characterization of tumors is based on the expression profiling of microRNAs (miRNAs). miRNAs are endogenously expressed short noncoding RNAs, 18–25 nucleotides in length, that repress protein translation through binding to target mRNAs [5]. Until recently, more than 700 miRNAs were discovered in human cell [6]. Bioinformatics and cloning studies estimated that miRNAs regulate up to one-third of human genes [7]. By regulating translation of oncogenes and tumor suppressors, they participate also in processes involved in molecular pathology of cancer [8]. Moreover, miRNAs are frequently located in cancer-associated genomic regions or in fragile sites [9,10].

Physiological roles of only a small fraction of identified miRNAs have been elucidated to date. miRNAs play an important role in cell cycle control, cell proliferation, differentiation, and apoptosis [5]. Impaired miRNA expression levels, consequently, were identified in most solid cancers and hematological malignancies [5]. In this paper, we review and summarize the studies analyzing miRNA expression levels and their role in the pathogenesis of glioblastomas.

Specific microRNA candidates for glioblastoma pathogenesis

miR-21

In the first study exploring expression levels of miRNAs in glioblastomas, Chan et al. identified miR-21 upregulation [11]. The authors also demonstrated that knockdown of miR-21 in cultured glioblastoma cell lines triggered the caspase activation and associated apoptotic cell death, suggesting an anti-apoptotic function of miR-21. Many other following studies confirmed overexpression of this miRNA in glioblastomas [12–15]. miR-21 was overexpressed even in less malignant gliomas [12], low grade astrocytomas (WHO gr. II) that are characterized by a low proliferation rate and prolonged life-span. It suggests that defective apoptotic

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pathways that are associated with miR-21 overexpression may play a prominent role in the pathogenesis of such tumors. The overexpression of miR-21 was demonstrated in a wide range of other malignancies including breast, lung, colon, prostate, pancreas, and gastric cancer [16]. Tumor suppressors PTEN, TPM1 (Tropomyosin 1) and maspin were previously described as targets of miR-21 in tumor cell lines [17,18], however, these molecules were not confirmed to be targets of miR-21 in glioblastomas. miR-21 has been implicated in various aspects of carcinogenesis, including apoptosis, cell proliferation, invasiveness and migration.

miR-21 targets signaling pathways of p53, TGF-β and mitochondrial apoptotic pathway [14] (Fig. 1). Direct targets of miR-21 are p63 (a homolog of p53), p53 activators JMY, TOPORS, TP53BP2, DAXX, and HNRNPK [14] that can stabilize p53 protein levels by interfering with MDM2 and/or act as p53 transcriptional cofactors, assisting p53 in transactivating genes that induce apoptosis and growth arrest. These proteins are necessary for proper function of the tumor suppressor p53, therefore, by targeting these genes, miR-21 can impair p53 response to stimuli such as DNA damage [14]. miR-21 repressed p53-mediated apoptosis in response to chemotherapeutic agents such as doxorubicin and induced DNA damage, therefore contributing to drug resistance in glioblastoma cells [14]. miR-21 suppression of the p53 response may take place in most cancers where miR-21 is upregulated, and this may be even more significant in tumors as primary glioblastoma with wild-type p53. In addition, miR-21 regulates the TGF-β pathway by direct targeting of TGFBR2/3 receptors and the apoptotic mediator DAXX. DAXX can stabilize p53 in addition to mediating TGF-β apoptosis, thus it may be a key target in disrupting crosstalk between these two pathways [14].

miR-21 contributes to invasiveness of glioma cells by targeting inhibitors of matrix metalloproteinases (MMPs). MMPs are a group of peptidases involved in degradation of the extracellular matrix. Their levels are significantly elevated in human gliomas and it correlates with tumor cell invasiveness [19]. miR-21 regulates the activity of MMPs through their inhibitors RECK and TIMP3. The di-

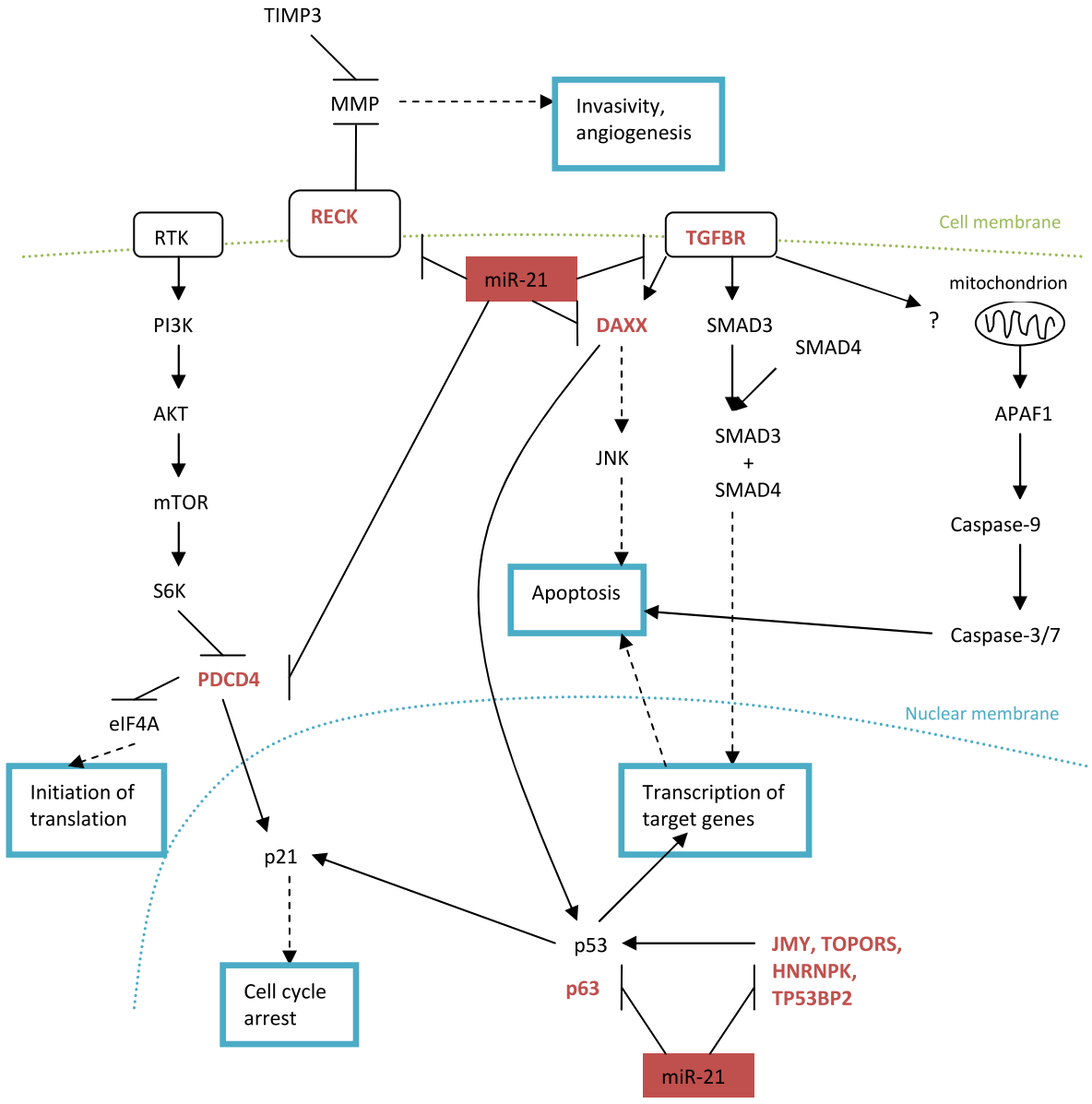

Fig. 1. Signaling pathways that are influenced by miR-21 in glioblastoma cells. miR-21 inhibits translation of molecules RECK, TGFBR, DAXX, PDCD4, p63, JMY, TOPORS, HNRNPK, and TP53BP2. This way, miR-21 regulates apoptosis, cell cycle and translation in glioblastoma cells.

rect target of miR-21 seems to be only RECK, however, the expression level of TIMP3 also decreases as the level of miR-21 increases [13].

miR-21 targets also a tumor suppressor PDCD4 (Programmed cell death 4). This protein inhibits translation by its interaction with a factor that initiates translation of eIF4A and eIF4G [20]. PDCD4 also inhibits proliferation via activation of p21 [20]. Chen et al. identified PDCD4 as a direct target in a glioblastoma cell line T98G [21]. PDCD4 was previously described as a target of miR-21 in colorectal cancer [22].

The oncogenic miR-21 negatively regulates a lot of specific molecules which function as tumor suppressors. Deregulation of these molecules has diverse biological effects connected with carcinogenesis. Therefore, miR-21 may play a key role in the pathogenesis of glioblastoma and other cancer types. Furthermore, targeted downregulation of miR-21 in human tumors, and particularly in glioblastoma with an extremely short median survival time, could have a great therapeutic impact.

miR-221/222

Another oncogenic miRNA which is overexpressed in glioblastoma is miR-221 [12,23,24]. Ciafrè et al. [24] demonstrated upregulation of this miRNA in glioblastoma tissue samples and in many glioblastoma cell lines. In contrast to miR-21, miR-221 is overexpressed only in high grade astrocytomas (WHO gr. III and IV) [12]. Its function was explored together with miR-222 because their expression is corregulated and they have the same target specificity. miR-221/222 represses the expression of a cell cycle regulator $p27^{Kip1}$ (Fig. 2) [25]. This protein is an inhibitor of cyclin-dependent protein kinases (CDK). It binds to a complex of CDK with a cyclin and triggers a cell cycle arrest in the G1 phase. le Sage et al. [26] demonstrated, using miRNA inhibitors, that some glioblastoma cell lines require high activity of miR-221/222 to maintain low $p27^{Kip1}$ levels and continuous proliferation, and that high levels of these miRNAs correlate with low levels of $p27^{Kip1}$ in glioblastoma [26].

According to bioinformatics analysis, CDK4 can serve as a possible activator of miR-221. Inhibition of CDK4 enhances translation of $p27^{Kip1}$ [27] which could be caused by decreased levels of miR-221 [25]. The activity of CDK4 is inhibited by a tumor suppressor $p16^{Ink4a}$ commonly deleted in glioblastoma [1], therefore, the deletion of $p16^{Ink4a}$ could lead to an upregulation of miR-221. The upregulation of miR-221/222 in glioblastomas may suggest a specific role in the defective cell cycle control and high proliferation rate of those tumors.

miR-181a and miR-181b

Shi et al. [28] reported downregulation of miR-181a and miR-181b in both human gliomas and glioma cell lines, confirming the data of Ciafrè et al. [24]. The expression level of miR-181a was negatively correlated with tumor grading whereas miR-181b showed significant differences in the expression only between high grade gliomas (WHO III and IV) and low grade gliomas [28].

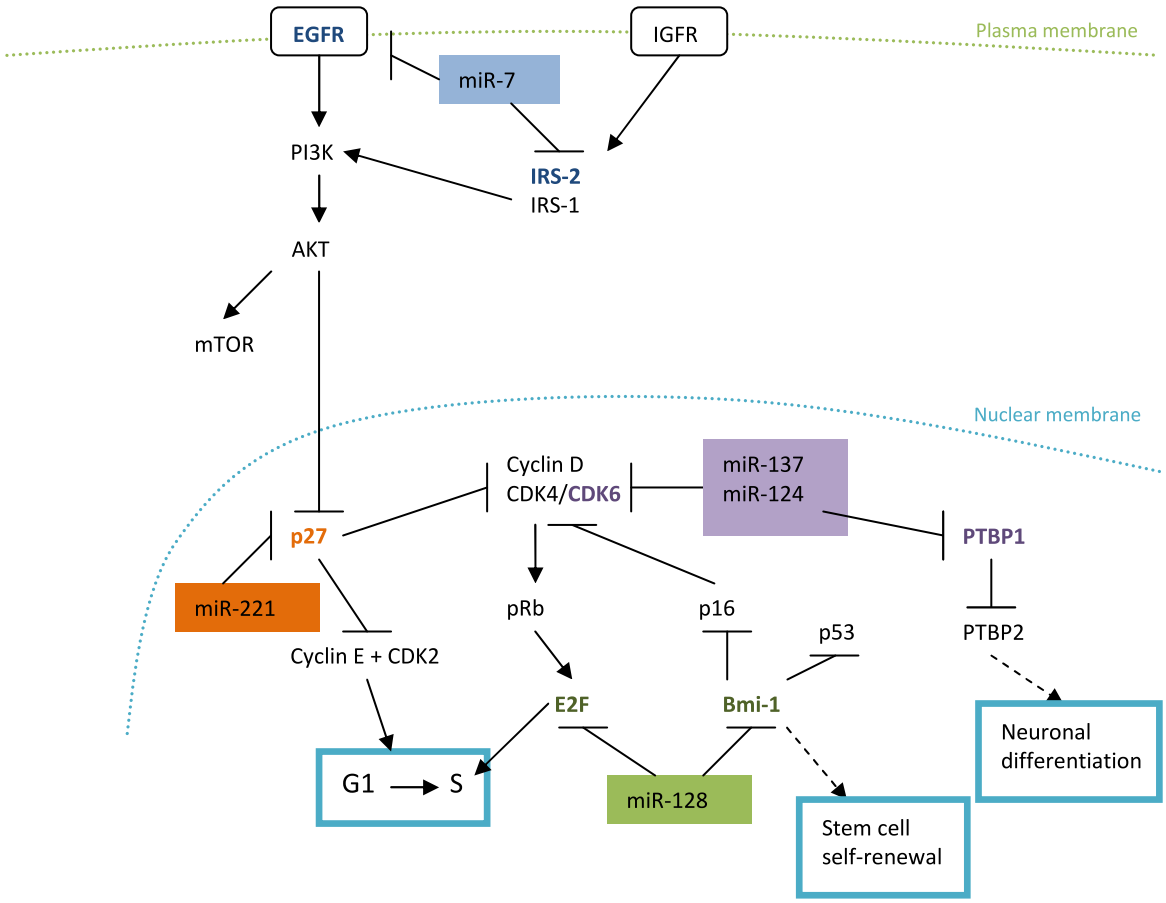

Fig. 2. Signaling pathways influenced by miRNAs in glioblastoma cells. miR-7 influences AKT pathway by targeting EGFR and IRS-2, and in consequence inhibits cell cycle progression. In contrast, oncogenic miR-221 promotes cell cycle progression by inhibiting translation of tumor supressor $p27^{Kip1}$. The cell cycle arrest is also caused by miR-128, miR-137, and miR-124. miR-128 and miR-124 affect neuronal stem cells by targeting Bmi-1 and PTBP1, respectively.

It was also shown that transfection of miR-181a and miR-181b triggered growth inhibition, apoptosis, and inhibited invasion [28]. miR-181a and miR-181b inhibited the proliferation of glioma cells *in vitro*. Cell lines with transfected miR-181a and miR-181b lost the ability of anchorage-independent growth, which is generally considered to be one of the *in vitro* properties associated with the malignancy of cells. Transfection of these miRNAs also increased the rate of apoptosis in glioma cells; however, miR-181b seemed to be more efficient in this process. This suggests that these miRNAs triggers apoptosis in cells by different mechanisms [28]. Despite the deregulation of these miRNAs in glioblastomas and observed biological effects in the cell lines, direct targets of miR-181a and miR-181b have not been identified yet.

miR-7

miR-7 is another potential tumor suppressor in glioblastoma targeting critical cancer signaling pathways. Kefas et al. [29] identified miR-7 downregulation in glioblastoma tissue compared to surrounding brain. It has been shown that the downregulation is a consequence of impaired processing of precursor miR-7 as the expression levels of pri-miR-7 were similar in glioblastoma and normal brain.

EGFR/AKT pathway has an important role in developing of primary glioblastoma. Its downstream effects are inhibition of apoptosis, cellular proliferation and growth. EGFR (epidermal growth factor receptor) is overexpressed in more than 60% of primary glioblastomas [30], however, not all of them show also the EGFR gene amplification. miR-7 directly targets EGFR thus decreasing its levels in glioblastoma cells [29]. AKT is activated due to an upstream signal of EGFR or independently of this receptor by molecules IRS-1 and IRS-2. The latter was proved to be another direct target of miR-7 (Fig. 2) [29]. Furthermore, these authors have demonstrated that transfection of miR-7 reduced viability and invasiveness of glioblastoma cells.

miR-128

miR-128 belongs to brain specific miRNAs [31] which are scattered in other organs. However, this miRNA is downregulated in glioblastomas [24,32] and to a lesser extent also in lower grade gliomas [33]. Godlewski et al. [32] showed that miR-128 expression significantly reduced glioma cell proliferation *in vitro* and glioma xenograft growth *in vivo*. miR-128 directly targets a transcription factor E2F3a which activates genes necessary for progression of cell cycle [33]. miR-128 can inhibit proliferation of brain cells by negative regulation of E2F3a. Another direct target of miR-128 is an oncogene Bmi-1 (Fig. 2) [32], which regulates tumor suppressors like p53 and $p16^{Ink4a}$ [34]. Bmi-1 has also been shown to promote stem cell self-renewal [35]. miR-128 specifically blocked glioma self-renewal consistent with Bmi-1 downregulation [32]. By regulating Bmi-1, a neural stem cell self-renewal factor, brain specific miR-128a can regulate brain development.

miR-124 and miR-137

Expression levels of miR-124 and miR-137 are decreased in glioblastomas and anaplastic astrocytomas [15]. Silber et al. [15] have also found that these miRNAs promote G0/G1 cell cycle arrest in glioblastoma cell lines and induce neuronal-like differentiation of glioblastoma-derived stem cells in the absence of growth factor signaling.

miR-124 directly targets PTBP1(PTB/hnRNP I), a global repressor of alternative pre-mRNA splicing in non-neuronal cells. During neuronal differentiation, miR-124 reduces PTBP1 levels, resulting in the transition from non-neuronal to neuronal-specific alternative splicing patterns [36]. Both miR-124 and miR-137 directly target also cyclin-dependent kinase 6 (CDK6) [15] which regulates cell cycle progression and differentiation.

Other miRNAs

Gal et al. [37] demonstrated that transfection of glioblastoma cells by miR-451 inhibited their growth. It also inhibited neurosphere formation (neurosheres are structures generated by neural stem cells *in vitro*) [38].

miR-10b is upregulated in glioblastomas [24,15]. Increased levels of miR-10b have been observed in breast cancer cells and it correlated with disease progression [39]. However, the function of miR-10b has not yet been described in glioblastoma.

miR-129, miR-139 a miR-218 are downregulated in glioblastomas [15], but their function remains unknown.

Conclusions and future directions

The discovery of miRNAs has enabled deeper insight into regulation of gene expression and complexity of this process. Recent data demonstrated that deregulation of miRNA expression is an integral process of cancer pathogenesis. It is evident that miRNAs play a crucial role also in glioblastoma pathogenetic pathways. However, it is not known whether the deregulation of miRNAs is a reason or consequence of cancer transformation. A few smaller studies analyzed the expression levels of miRNAs in glioblastomas, but these results should be validated on larger, more representative cohorts of glioblastoma patients. To study these small molecules, miRNAs have an advantage to mRNA that they do not undergo a significant decay of tumor sample during fixation in formaline and archivation in paraffine blocks. This allows us to perform large retrospective studies. miRNAs have not been tested for correlation with clinicopathologic features of glioblastoma like therapy response or overall survival of patients. Regulatory RNAs may have therapeutic implications by which disease-related miRNAs could be antagonized or functional miRNAs restored. New knowledge about miRNA function may bring new possibilities and strategies in developing novel glioblastoma therapies.

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