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MicroRNA and Glial Tumors: Tiny Relation with Great Potential

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1. Introduction

MicroRNAs (miRNAs) are endogenously expressed small non-coding RNAs that act as post-transcriptional regulators of gene expression. Dysregulation of these molecules has been observed in many types of cancers. Altered expression levels of several miRNAs were identified also in gliomas. It was many times showed that miRNAs are involved in core signaling pathways, which play roles in crucial cellular processes, such as proliferation, apoptosis, cell cycle regulation, invasion, angiogenesis and stem cell behaviour. Therefore, miRNAs have a great potential for oncodiagnostic as well as could be promising therapeutic targets in gliomas.

2. MicroRNA: Function and biogenesis

MicroRNAs (miRNAs) comprise a numerous class of endogenous small non-coding RNAs, 18 – 25 nucleotides in length, which function as post-transcriptional regulators of gene expression. The regulation proceeds through binding of miRNAs to their mRNA targets (Bartel, 2004). Currently, the miRBase annotates over 800 verified miRNA sequences in the human genome and the number is still expanding (Griffiths-Jones et al., 2008). Bioinformatics and cloning studies have estimated that miRNAs may regulated more than 50% of all human genes and each miRNA can control hundreds of gene targets. This is possible among others due to the fact that the binding of miRNA to the mRNA doesn't require perfect complementarity. MiRNAs are highly conserved in sequence between distantly related organisms, indicating their participation in essential biological processes. It is well known today that miRNAs are involved in many signaling pathways playing crucial roles in such cellular processes as differentiation, proliferation, and apoptosis that affect biological processes including development and cancerogenesis (Alvarez-Garcia & Miska, 2005; Carthew & Sontheimer, 2009; Croce, 2009; Hatfield & Ruohola-Baker, 2008; Winter & Diederichs, 2011; Lakomy, 2011). A large fraction of miRNAs exhibits strict developmental stage-specific and tissue-specific expression patterns. Moreover, the levels of many miRNAs

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are altered in various disseses including many types of cancers (Krol et al., 2010; Siomi & Siomi, 2010; Winter et al., 2009).

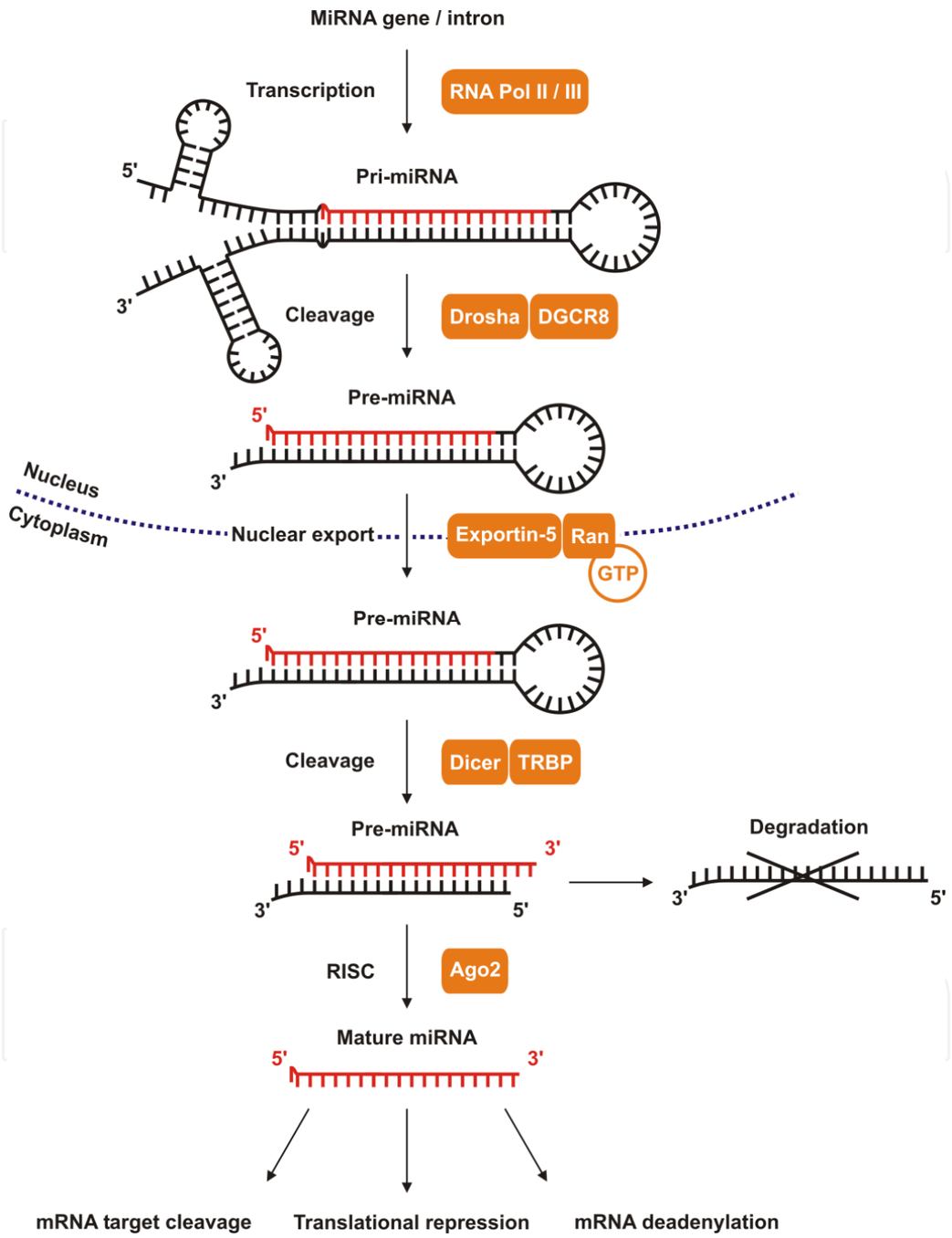


Fig. 1. Linear "canonical" pathway of miRNA processing

Most miRNA genes have own promoters and are transcribed as autonomous transcription units (Carthew & Sontheimer, 2009). Primary transcripts (pri-miRNAs) are generated by RNA polymerase II. These are processed to short 70-nucleotide stem-loop structures known

as pre-miRNAs by the ribonuclease called Drosha and the double-stranded-RNA-binding protein known as Pasha. The pre-miRNAs are transported to the cytoplasm where they are processed to mature miRNA duplexes by their interaction with the endonuclease enzyme Dicer in complex with dsRNA binding protein TRBP (Siomi & Siomi, 2010). One strand of the mature miRNA duplex ultimately gets integrated into the miRNA-induced silencing complex (miRISC), whereas the second strand is released and degraded. The resulting complex of mature miRNA and miRISC exerts regulatory effect by binding to its target site in the 3′ untranslated region (3′UTR) of mRNA that controls many aspects of mRNA metabolism, such as transport, localization, efficiency of translation and stability (Chiang et al., 2010; Krol et al., 2010) (summarized in Fig. 1).

3. MicroRNAs as potential biomarkers for diagnostic, prediction of therapy response, and prognosis of patients

As described above, the expression levels of many miRNAs are altered in various types of cancers. Thus, specific tissue miRNA signature could be an useful tool for diagnostic oncology. Among all gliomas, miRNAs are the most studied in glioblastomas that is associated with the very poor prognosis. Global analysis of miRNA expression profiles of glioblastoma tissues allowed to identify a group of miRNAs with significantly altered expression levels compared to non-malignant brain tissues (Sana et al., 2011). Two independent research groups described significant up-regulation of miR-21 in glioblastomas what fully corresponds to the expression levels of miR-21 observed in other cancers (Chan et al., 2005; Esquela-Kerscher & Slack, 2006; Zhang & Farwell, 2008). Furthermore, miR-125b was over-expressed, and miR-128a and miRNA-181 family were significantly down-regulated in both studies. On the other hand, miR-221 generates conflict between these studies. Ciafré described this miRNA as up-regulated in glioblastoma, whereas, Slaby showed lower level in comparison to the adult brain tissue (Ciafre et al., 2005; Slaby et al., 2010). The last-named autor speculated this discrepancy and concluded that it is likely that the brain tissues used as control samples in their study, though excised from the margin of resection materials, contained traces of micro-capillaries from around the arteriovenous malformation. This could be responsible for the relatively low levels of miR-221 and miR-222 in glioblastomas despite their absolute levels because it is generally known that endothelial cells are characterized by highest expression levels of these miRNAs (Slaby et al., 2010) (Tab. 1). Furthermore, Ciafré performed miRNA expression analysis of several glioblastoma cell lines and has come to the conclusion that miRNAs underexpressed in glioblastoma cell lines generally confirmed primary tumour data, whereas only miR-21 and miR-221 that were overexpressed in tumours were deregulated also in the cell lines (Ciafre et al., 2005). Taken together, only miR-21 and miR-181 family were significantly and consistently altered in all three studies.

The clinical significance of miRNA expression profiles in malignant gliomas is not yet much explored. Nevertheless, Guan published a set of 16 candidate miRNAs associated with the malignant progresiion from anaplastic astrocytomas to glioblastomas. Among these miRNAs, the members of miR-196 family, indicated the highest level of significance. MiR-196 expression levels significantly correlated with poor survival by Kaplan-Meier method ($p = 0.0073$) and, moreover, multivariate analysis showed that its expression levels were an

independent predictor of overall survival in glioblastoma patients (p = 0.021; HR 2.81) (Guan et al., 2010). Another research group investigated the miRNA expression profiles in four patients with primary WHO grade II gliomas that spontaneously progressed to WHO grade IV secondary glioblastomas. They identified 12 miRNAs (miR-9, miR-15a, miR-16, miR-17, miR-19a, miR-20a, miR-21, miR-25, miR-28, miR-130b, miR-140, and miR-210) showing increased expression, and two miRNAs (miR-184 and miR-328) with reduced expression upon progression (Malzkorn et al., 2010). Validation experiments on an independent series of primary low-grade and secondary high-grade astrocytomas confirmed miR-17 and miR-184 as interesting candidates contributing to glioma progression. Taken together, only miR-184 was significantly altered in all three studies. However, miR-21, which was identified in two independent studies but not confirmed by validation study, could also probably play an important role in progression of glioma tumors with respect to its oncogene function described in many other cancers.

Treatment of malignant gliomas remains one of the greatest challenges facing oncologists today through a frequent resistance to both chemo- and radiotherapeutics and short survival (Ziegler et al., 2008). Important question for management of glioblastoma patients is the possibility of predicting therapeutic outcome. MiRNA expression could have a great potential in prediction of therapeutic outcome after treatment by temozolomide (TMZ) that is an oral alkylating agent frequently used for the treatment of glioblastoma. Slaby showed that expression levels of miR-181b and miR-181c in glioblastoma tissued was successfully associated with response to concomitant chemoradiotherapy with temozolomide (RT/TMZ). MiR-181b and miR-181c were significantly down-regulated in patients who responded to RT/TMZ (p = 0.016; p = 0.047, respectively) in comparison to patients with progredient disease (Slaby et al., 2010). In other study, Ujifuku described miR-195, miR-455-3p, and miR-10a* as the three most up-regulated miRNAs in the TMZ-resistant cell lines. Moreover, knockdown of miRNA-195 in the TMZ-resistant cell line led to overcome of TMZ resistance and increase the cell killing effect of TMZ (Ujifuku et al., 2010).

4. MicroRNAs involved in drug resistance

It was many time showed that miRNAs play important role in drug resistance many cancers, including glioblastoma. Shi described that overexpression of miR-21 in glioblastoma cells could significantly reduce TMZ-induced apoptosis by decreasing Bax/Bcl-2 ratio and caspase-3 activity (Shi et al., 2010). The miR-21 inhibitor also enhances the chemosensitivity of human glioblastoma cells to paclitaxel via inhibition of STAT3 expression and phosphorylation. Moreover, the same treatment by miR-21 antisense oligonucleotides led to enhanced cytotoxicities of vepesid because miR-21 likely contributes to resistance through depression of LRRFIP1 expression, leading to the reduction of cytotoxicity of chemotherapeutic drugs through activation of the NF-κB pathway (Li et al., 2009b; Papagiannakopoulos et al., 2008; Ren et al., 2010). Li observed that miR-328 is in glioblastoma poorly expressed and contributes to tumour chemoresistance through multidrug resistance protein ABCG2 (Li et al., 2010). Finally, it was reported the possible impact on the therapeutic effect by transfection of miR-451 in combination with imatinib mesylate treatment. Up-regulation of miR-451 led to differentiation of glioblastoma stem cells (Gal et al., 2008).

	Ciafre et al., 2005		Slaby et al., 2010	
	miRNA	**C/P ratio†**	**miRNA**	**Fold change (P)‡**
Up-regulated	miR-9-2	1.88 - 10.16		
	miR-10b	1.97 - 13.6		
	miR-21	**1.81 - 9.3**	**miR-21**	**8.35 (<0.001)**
	miR-25	1.99 - 3.6		
	miR-123	1.9 - 2.45		
	miR-125b-1	**2.19 - 2.73**	**miR-125b**	**1.45 (0.502)**
	miR-125b-2	**1.95 - 2.88**		
	miR-130a	2.11 - 5.3		
	miR-221	1.84 - 4.8		
Down-regulated	**miR-128a**	**0.34 - 0.56**	**miR-128a**	**0.03 (<0.001)**
	miR-181a	**0.082 - 0.56**	**miR-181a**	**0.4 (0.073)**
	miR-181b	0.098 - 0.56	miR-181b	0.28 (0.036)
	miR-181c	0.096 - 0.56	miR-181c	0.29 (0.043)
			miR-221	0.25
			miR-222	0.22

Table 1. miRNAs significantly deregulated in human glioblastoma tissues

5. MicroRNAs and invasion

Invasion of malignant glioma is a highly complex phenomenon involving molecular and cellular processes, whose precise interplay is still not fully understood (Tektonidis et al., 2011). Several studies indicate that one of the possible players in this tumor feature are miRNAs (Sana et al., 2011). These observations are highlighted by the recently demonstrated relation of some miRNAs with molecules considered key in tumor invasion. Among these molecules belongs matrix metalloproteinases (MMPs). MMPs are zinc-containing endopeptidases, which degrade the extracellular matrix and basement membrane, and process bioactive mediators involved in promoting aspects of tumor growth, including gliomas (Badiga et al., 2011; Chetty et al., 2011). The activity of MMPs is regulated at several levels, including posttranscriptional regulation through miRNAs (Hadler-Olsen et al., 2011; Sana et al., 2011). Sun et al. found that miR-10b induced glioma cell invasion by modulating tumor invasion factors MMP-14 and urokinase-type plasminogen activator receptor (uPAR) espression via the direct target HOXD10 (Sun et al., 2011). Sasayama et al. came to the same conclusion in the study including 43 glioma samples of various grade and 6 glioma cell lines. Therefore, the miR-10b/HOXD10/MMP-14/uPAR signaling pathway might contribute to the invasion of glioma (Sasayama et al., 2009; Sun et al., 2011). Accordingly, glioma cells lost their invasive ability when treated with miR-10b inhibitors, suggesting that miR-10b could be used as a new bio-target to cure glioma (Sun et al., 2011). Another group established miRNA expression profile (14 positively and 31 negatively correlated miRNAs with MMP-9) in 60 GBM samples. Among them, two miRNAs: miR-885-5p and miR-491-5p,

† C/P ratio represents the range of ratio between tumour samples values (C, centre of the tumour) and the control samples values (P, peripheral brain area from the same patient)
‡ P value is presented (Mann-Whitney U-test)

were chosen for functional validation for their high positive correlation with MMP-9 expression. Both miRNAs were demonstrated to reduce the levels of MMP-9 expression and inhibit cellular invasion in glioma cells. Furthermore, miR-491-5p suppressed glioma cell invasion via targeting MMP-9 directly (Yan et al., 2011). Xia et al. observed that miR-146b overexpression by transfection with the precursor miR-146b, or knock-down by LNA-anti-miR-146b, has no effect on the growth of human glioblastoma cells. However, precursor miR-146b transfection significantly reduced the migration and invasion of these cells, while LNA-anti-miR-146b transfection generated the opposite result. Furthermore, they discovered that MMP16 is one of the downstream targets of miR-146b (Xia et al., 2009). Moreover, miR-146-5p supresses translation of EGFR and introduction of miR-146b-5p decreases cell invasion, migration, and phosphorylation of protein kinase B (AKT) (Katakowski et al., 2010). Another group described regulation of podoplanin membrane sialo-glycoprotein (PDPN) through direct targeting of PDPN gene by miR-29b and 125a in GBM. Earlier, it was demonstrated that PDPN is over-expressed and related to cellular invasion in astrocytic tumors. The similar findings, but in GBM, were published by Cortez et al. (Cortez et al., 2010). With GBM invasion are also related miR-124a and miR-34a whose targeted over-expression may be novel approach in GBM treatment (Fowler et al., 2011; Li et al., 2009a).

6. MicroRNAs involved in core signaling pathways: Possible therapeutic potential

The involvement of miRNAs in core signaling patways that regulate important cell processes of glioblastoma, led to the suggestion that miRNAs could serve as a potential therapeutic targets (Novakova et al., 2009; Sana et al., 2011). The most frequently explored miRNA is the miR-21, which has been found to act as an oncogene. It is evident that miR-21 influences multiple important components of oncogenic signaling pathways in glioblastoma. MiR-21 was revealed as post-transcriptional regulator involved in NF-κB signaling pathway. Aberrant activation of NF-κB signaling pathway has been proved to be important for invasiveness and metastatic capacity of tumors through up-regulation of matrix metalloproteinases (MMPs) and transcription factors regulating E-cadherin. Li et al. identified LRRFIP1 gene, which was remarkably up-regulated in miR-21-knockdown cells, as a candidate target gene of miR-21. Further, they found that LRRFIP1 mRNA carried a putative miR-21 binding site. Further analyses confirmed LRRFIP1 as a direct target of miR-21 (Li et al., 2009b). In connection with this signaling pathway, it was also identified miR-218 that in vitro dramatically reduced the migratory speed and invasive ability of analysed cells. Ectopic expression of miR-218 down-regulated matrix MMP-9 and reduced NF-κB transactivity at transcriptional level, whereas inhibition of miR-218 enhanced the expression of MMP-9 and transcriptional activity of NF-κB. Authors demonstrated that miR-218 could inactivate NF-kB/MMP-9 signaling by directly targeting the 3′-UTR of the IKK-κ which is a critical component in NF-κΥΥB regulation (Song et al., 2010).

PI3K/AKT and EGFR are in term of tumor biology other very important signaling pathways that are regulated by miR-21. Mechanistic studies identified mRNA targets of miR-21 among important components of the PI3K/AKT and EGFR signaling pathways. Glioblastoma cell lines U251 (mutant PTEN) and LN229 (wild-type PTEN) showed a decreased expression of EGFR, activated AKT, Cyclin D and Bcl-2 after treatment by miR-21-specific antisense

oligonucleotide (Zhou et al., 2010a). Although miR-21 is known to regulate PTEN and down-regulation of miR-21 led to increased PTEN expression, the glioblastoma suppressor effect of antisense-miR-21 is most likely independent of PTEN status because U251 has mutated PTEN (Ren et al., 2010; Zhou et al., 2010a). PTEN down-regulation followed by AKT activation was described after transfection of glioblastoma cells with the primary transcript of miR-26a-2. Similarly, the miR-26a mimics decreased PTEN protein levels and increased AKT phosphorylation (Huse et al., 2009; Kim et al., 2010). Modulation of expression levels of AKT signaling cascade components such as Akt1, Cyclin D1, MMP-2, MMP-9, and Bcl-2 in glioblastoma cell lines after transfection of miR-451 mimicked was described also by Nan. By contrast, miR-451 down-regulation led to increase in p27 levels. According to phenotypic experiments, miR-451 inhibited invasive ability, induced cell cycle arrest in the G0/G1 phase, delayed the progression of cell cycle, inhibited cell proliferation and induced apoptosis in glioblastoma cells in vitro (Nan et al., 2010). Furthermore, miR-451 affects downstrem members of PI3K/AKT signaling pathway via targeting of CAB39 (MO25α), which is binding partner of LKB1. LKB1 is upstream kinase of the major energy biosensor AMPK. Godlewski published that miR-451 levels are regulated by glucose; under conditions of abundant energy miR-451 expression is high, and the suppression of AMPK signaling allows cells to maintain elevated proliferation rates via unrestrained mTOR activation. Under conditions of glucose withdrawal, miR-451 downregulation is necessary for AMPK pathway activation, leading to suppressed proliferation rates, increased cell survival and migration. Thus, miR-451 is a regulator of the LKB1/AMPK pathway, and this may represent a fundamental mechanism that contributes to cellular adaptation in response to altered energy availability (Godlewski et al., 2010a; Godlewski et al., 2010b). MiR-128 is another miRNA that significantly reduced glioma cell proliferation in vitro and glioma xenograft growth through PI3K/AKT signaling pathway. Godlewski explained this effect by binding of mentioned miRNA to the 3'UTR of Bmi-1 mRNA that is significantly up-regulated in gliomas, wheares miR-128 is down-regulated compared to normal brain. In addition, miR-128 expression leads to a decrease in H3K27 methylation and modulation of cellular pathways, especially p21CIP1 and Akt, involved in cell cycle arrest and survival (Godlewski et al., 2008). Modulation of p21 was described also in context with another miRNAs. Gabriely showed that BCL2L11/Bim, TFAP2C/AP-2gamma, CDKN2A/p16, and CDKN1A/p21 are direct targets of miR-10b. Inhibition of miR-10b reduced glioma cell growth by cell cycle arrest and apoptosis, and, furthermore, survival of glioblastoma patients expressing high levels of miR-10 family members is significantly reduced in comparison to patients with low miR-10 levels, indicating that miR-10 may contribute to glioma growth in vivo (Gabriely et al., 2011). MiR-221 and miR-222 were also revealed as potential regulators of many target genes involved in AKT signaling pathway. Up-regulation of these miRNAs resulted in remarkable increase of p-Akt and significant changes in expression of Akt-related genes in glioma cells. Consequently, miR-221 and miR-222 overexpression increased glioma cell proliferation and invasion in vitro and induced glioma growth in a subcutaneous mouse model (Zhang et al., 2010c). EGFR signaling network contributes to promotion and progression of a broad spectrum of solid tumors, and it is a promising target for anticancer therapy. Stimulation of the EGFR and, subsequently, KRAS signaling, lead to activation of numerous signal transduction molecules initiating a cascade of downstream effectors that mediate tumour growth, survival, angiogenesis and metastasis (Jancik et al., 2010). Kefas published that miR-7 directly inhibited EGFR expression via its 3'-UTR and independently suppressed the AKT pathway via targeting

upstream regulators, such as IRS-1 and IRS-2. Moreover, transfection with miR-7 oligonucleotides decreased viability and invasiveness of primary glioblastoma cell lines (Kefas et al., 2008). Down-regulation of EGFR mRNA and protein expression in glioblastoma cell lines via two predicted sites of miR-7 was confirmed by Webster. This led to the induction of cell cycle arrest and apoptosis. Furthermore, the same author also described Raf1, another member of the EGFR signaling pathway, as a direct target of miR-7 in cancer cells (Webster et al., 2009). Katakowski have declared that EGFR is also direct target of miR-146b-5p. Its introduction decreased cell invasion, migration, and phosphorylation of Akt in glioma cells (Katakowski et al., 2010). Mir-21 is responsible for glioma cell invasiveness by disrupting the negative feedback circuit of EGFR components Ras/MAPK through post-transcriptional regulation of Spry2. Consistently with these results, Spry2 protein levels were significantly decreased in invasive WHO grade II-IV human glioma tissues, but not in non-invasive grade I and normal tissues (Kwak et al., 2011) (summarized in Fig. 2).

Other targets of miR-21 are p53, TGF-β, and mitochondrial apoptotic signaling networks. Papagiannakopoulos reported that these pathways are de-repressed in response to miR-21 knockdown. As direct targets of this miRNA were predicted proteins p63, JMY, TP53BP2, HNRPK, TOPORS, IGFB3, APAF1, PPIF, TGFBR2/3, DAXX, and HNRNPK. MiR-21 can also stabilize p53 protein levels by interfering with MDM2 and/or act as p53 transcriptional cofactors (Papagiannakopoulos et al., 2008). Inhibition of miR-21 increased also endogenous levels of PDCD4 in human glioma cell lines and activated caspases 9 and 3 (Chen et al., 2008; Zhou et al., 2010b). Protein PDCD4 inhibits translation by its interaction with the initiation translation factors, and proliferation via activation of $p21^{CIP1}$ (Kwak et al., 2010). In addition, specific inhibition of miR-21 led to reduced MMP activities in vitro and in model of gliomas in nude mice. Consequently, down-regulation of miR-21 decreased migratory and invasive abilities in glioma cells (Gabriely et al., 2008). Influence on glioma cell invasion by modulating MMP was observed also after treatment with miR-10b. This miRNA was overexpressed in glioma samples and directly associated with the glioma's pathological grade and malignicy. Sun found that miR-10b affected tumor invasion factors MMP-14 and uPAR expression via the direct target HOXD10 (Sun et al., 2011). Finally, it was shown that miR-221 and miR-222 directly regulated apoptotic pathway in glioblastoma through direct targeting an apoptotic gene PUMA (Zhang et al., 2010b) (summarized in Fig. 2).

Another study revealed miRNAs as possible regulators of IFN pathways. It was showed that STAT1 and STAT2 expression and phosphorylation were up-regulated in cells with silenced miR-221 and miR-222. Tyrosine phosphorylation of STAT1 and STAT2 was present in the nucleus after repression of the same miRNAs. These data illustrate a mechanism of STAT1/2 up-regulation under the transcriptional control of IFN-γ signaling after knockdown of miR-221 and miR-222 in glioma cells (Fig. 2) (Zhang et al., 2010a). Interestingly, Ohno investigated the possibility that IFN-γ may induce or down-regulate cellular miRNAs in human gliomas. They analysed the effect of IFN-γ treatment on miR-21 expression in glioma cells and intracranial glioma xenografts. Systematic delivery of IFN-γ markedly reduced the level of miR-21 in all glioma cells. The results indicate that decrease in the levels of miR-21 is the result of transcriptional suppression. In contrast, the addition of the STAT3-specific inhibitor increased the level of miR-21 and inhibited IFN-γ–mediated suppression of miR-21, suggesting that miR-21 expression is negatively regulated by STAT3 (Ohno et al., 2009).

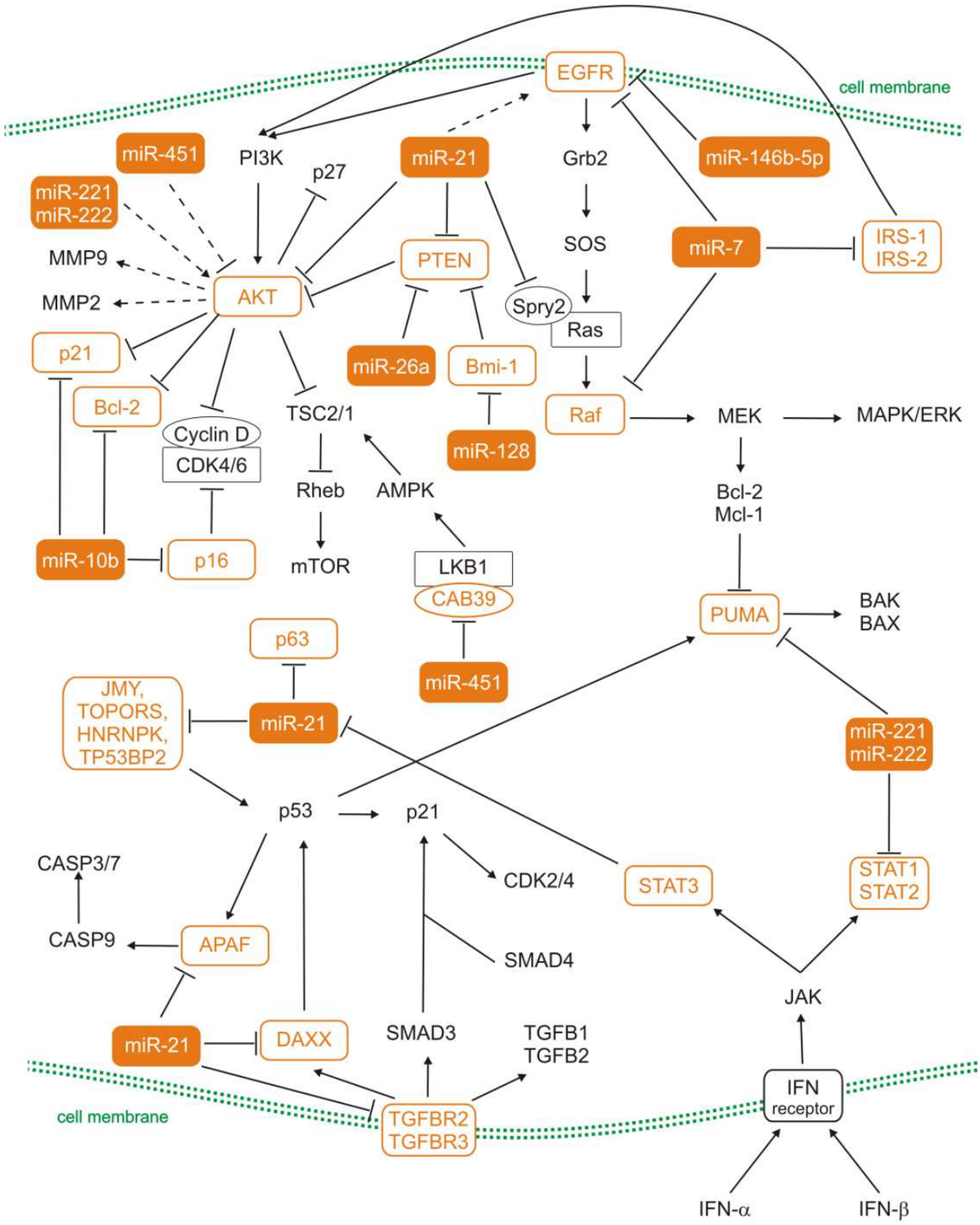


Fig. 2. MiRNAs involved in core signaling pathways

Notch signaling is critical in cell fate decisions such as neuronal versus glial fate in the developing nervous system. This pathway play also key role in stem-like phenotype maintenance and survival of normal stem cells as well as cancer stem cells that are often discussed in context with tumor initiation, progression, and metastasis. Therefore, it is not

surprising that Notch pathway plays a crucial role in brain tumours, including glioblastoma (Kefas et al., 2009; Lathia et al., 2008; Sana et al., 2011). Kefas et al. performed miRNA microarray analysis of glioma tumour stem cells transfected with Notch-1 siRNA. In these Notch-1 knockdown cells, miR-326 was one of the miRNAs significantly increased. However, pre-miR-326 transfection caused substantial decrease in both Notch-1 and Notch-2 protein. Therefore, it was indicated that miR-326 is suppressed by Notch activity and regulates Notch pathway at the same time. It was observed that miR-326 induces apoptosis and decreases glioma cells proliferation, viability and invasiveness of glioblastoma stem cell-like lines. Furthermore, miR-326 transfection also reduced glioma cell tumourigenicity in vivo (Kefas et al., 2009). Another important target of miRNA-326 is pyruvate kinase type M2 (PKM2) that has recently been shown to play a key role in cancer cell metabolism (Hitosugi et al., 2009; Kefas et al., 2010). Further, it was studied the role of miR-34a in glioblastoma. MiR-34a inhibits Notch-1 and Notch-2 protein expression and 3'-UTR reporter activities as well as CDK6 and c-Met protein expression in glioma cells. In this study, Li observed for the first time that pre-miR-34a expression is down-regulated in human glioblastoma tissues compared to normal human brain (Li et al., 2009a). Other studies showed that miR-34a acts as a tumour suppressor in p53-mutant glioma cells, partially through regulating SIRT1 (Guessous et al., 2010). Transfection of miR-34a into tested glioblastoma cell lines strongly inhibited cell proliferation, cell cycle, cell survival, cell invasion and in vivo glioblastoma xenograft growth; however, the treatment did not affect human astrocyte cell survival and cell cycle (Luan et al., 2010).

At a glance

- MicroRNAs (miRNAs) are an abundant class of small non-coding RNAs able to posttranscriptionaly regulate gene expression.
- MiRNAs are involved in many signalling pathways that have been shown to control a wide range of biological processes such as cellular proliferation, differentiation and apoptosis.
- Many miRNAs are deregulated in gliomas and are associated with their biologic and clinicopathological features.
- Expression profiles of selected miRNAs could be used as novel diagnostic and prognostic biomarkers as well as possible predictors of therapy response.
- Targeted regulation of miRNAs in gliomas represents promising therapeutic approach leading to the improvement of unsatisfactory survival in glioma patients.

7. Conclusion

The discovery of miRNA function has markedly spread the view on regulation of gene expression. Its remarkable ability to regulate large number of genes, including oncogenes and tumor suppressor genes, has catapulted miRNAs into the centre of cancer molecular biology over the past few years. It is now evident that dysregulation of miRNAs is an important step in the development of many cancers, including gliomas. Some few studies based on expression profiling have proven there are significant changes of miRNA expression levels in gliomas compared to adult brain tissue; these expression levels

identified groups of miRNAs with potential of prognostic stratification and prediction of responses to chemoradiotherapy in glioma patients. But much more studies have been focused on the improvement our knowledge of role of miRNAs in glioma core signaling pathways. The results of these studies suggest a great potential and relevance of miRNAs as a novel class of therapeutic targets and possibly powerful intervention tools in glioblastoma.

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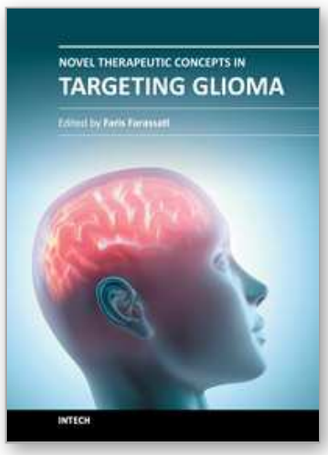
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