MINI-REVIEW

MicroRNAs might be Promising Biomarkers of Human Gliomas

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Abstract

Recently, altered expression levels of several microRNAs have been observed in gliomas, the most frequent primary brain tumor in adults. To review whether microRNAs might be promising biomarkers of human gliomas, we comprehensively searched the Cochrane Library, Medline and EMbase from 1966 to 2010 with the language limitation of English. We found that further understanding of the functions of miRNAs in specific cellular events is needed; the continuous technological advances in accurate and cost-effective miRNAs detection provide the prospect of a very promising role for miRNAs as novel diagnostic biomarkers of gliomas.

Keywords: Gliomas - miRNAs - biomarkers

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Introduction

The glioma is one of the most devastating and lethal forms of human cancer despite the significant efforts that have been made to understand its molecular etiology and to improve treatment regimens. In Europe and North America, the incidence is three new cases per 100,000 inhabitants per year (Central Brain Tumor Registry of the United States, CBTRUS, www.cbtrus.org). Although gliomas can manifest itself at any age, it preferentially occurs in adults, with a peak age of incidence between 45 and 70 years (Aldape et al., 2003). It most frequently involves the brain hemispheres, but it can also affect basal ganglia and the brain stem. With the development of technologies, many of the major genetic aberrations in gliomas are known and result in the activation of characteristic signaling pathways underlying these biological hallmarks (Furnari et al., 2007). Several recent molecular profiling studies have revealed distinct patterns of microRNAs(miRNAs) expression in gliomas compared with lower-grade astrocytomas, adjacent tissue, or normal brain.

MiRNAs are approximately 23-nucleotide-long RNA molecules that typically act by suppressing the translation of messenger RNAs into protein, through binding to complementary sequences in their 3' untranslated regions (Esquela-Kerscher et al., 2006). They are potent regulators of cell behavior and show distinct patterns of expression during development, in different tissues, and in diseases including cancer. Characteristic miRNAs alterations have been identified in gliomas, and these play key roles in the biology of this tumor. MiRNAs are quite stable and readily detectable through polymerase chain reaction-based methods. It has been reported that miRNAs can be detected in circulating exosomes in the serum of glioma patients (Skog et al., 2007). Furthermore, Huang et al (2010) have proposed that miRNAs could be used to diagnose human cancer in a letter to the editor. Therefore, we want to know whether microRNAs might be promising biomarkers of human gliomas.

Search Strategy and Selection Criteria

We comprehensively searched the Cochrane Library, Medline and EMbase from 1966 to Dec 2010 for the following terms: ("miRNA" or "microRNA") and ("glomas" or "globlastomas") and ("diagnose*" or "prodiagnose"). Detailed information was extracted from studies that met the inclusion criteria: miRNAs in human gliomas diagnose or prodiagnose and studies published in the English literature.

MiRNA Alterations in Gliomas

Glioblastomas are characterized by multiple genetic alterations. Epidermal growth factor receptor (EGFR) amplification and PTEN mutations are typical for primary gliomas developing rapidly de novo, whereas P53 mutations are frequent in the pathway leading to secondary gliomas developing usually from lower grade astrocytomas. The prognosis for patients with high-grade gliomas, which include anaplastic astrocytoma (WHO III) and glioblastoma multiforme (GBM, WHO III), remains dismal. MiRNA, the regulation gene of RNA, which has

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profound effects on cell biology through targeting multiple components of a single cellular pathway, or components of multiple pathways is coming. Like other cancer-associated genetic changes, miRNAs alterations can be due to down-regulated and up-regulated.

Down-regulated miRNAs in Gliomas

MiRNA-7 was one of the first described downregulated miRNAs in glioblastoma, where it plays a role by targeting the epidermal growth factor receptor (EGFR) among other genes. MiRNA-7 expression reduced proliferation and invasion in gliomas cell lines (Kefas et al., 2008). While, PKM2 is a direct and functional target of miRNA-326, suggesting that miRNA-326 could regulate the glioma metabolism through its downregulation (Kefas et al., 2009).

MiRNA-124 and MiRNA-137, by preventing neuronal differentiation and allowing cell cycle progression to increase tumorigencity, is the most downregulated miR in glioblastoma comparing tumor and normal brain (Godlewski et al., 2008; Silber et al. 2008). Like miR-124, miR-128 is downregulated in glioblastoma, and miR-128 expression reduces glioma proliferation in vitro and in vivo (Godlewski et al. 2008). MiRNA-128 belongs to brain specific miRNAs (Sempere et al. 2004) which are scattered in other organs. However, this miRNA is downregulated in glioblastomas (Ciafrè et al., 2005; Godlewski et al., 2008) and to a lesser extent also in lower grade gliomas (Zhang et al., 2009). MiRNA-451 was identified in a microarray screen as a result of its downregulation in migrating glioma cells (Godlewski et al., 2010). Thus miRNA-451 acts as a switch that regulates glioma growth, invasion, and survival under metabolic stress. Shi et al (2008) reported downregulation of miRNA-181a and miRNA-181b in both human gliomas and glioma cell lines.

Recent studies have indicated that p53 enters into miRNA world (Hermeking, 2007). He et al (2007) found that the miRNA-34 family is identified as the miRNA components of the p53 network. Hence, Luan et al (2010) demonstrated that miRNA-34a acts as a tumor suppressor in p53-mutantglioma cells U251, partially through regulating SIRT1. Reexpression of miRNA-34a slows intracranial tumor growth in vivo (Li et al., 2009)

Up-regulated miRNAs in Gliomas

MiRNA-21 has emerged as one of the most consistently highly expressed microRNAs in cancer. The authors also demonstrated that knockdown of miRNA-21 in cultured glioblastoma cell lines triggered the caspase activation and associated apoptotic cell death, suggesting an anti-apoptotic function of miRNA-21 (Chan et al., 2005). Thereafter, Many other following studies confirmed overexpression of this miRNA in glioblastomas (Papagiannakopoulos et al., 2008; Conti et al., 2009). Novakova et al (2009) thought targeted downregulation of miRNA-21 in human tumors, and particularly in glioblastoma with an extremely short median survival time, could have a great therapeutic impact. Another oncogenic miRNA which is overexpressed in glioblastoma is miRNA-221 (Conti et al. , 2009; Ciafrè et al., 2005). Ciafrè et al (2005) demonstrated upregulation of this miRNA in glioblastoma tissue samples and in many glioblastoma cell lines. In contrast to miRNA-21, miRNA-221 is overexpressed only in high grade astrocytomas (WHO gr. III and IV) (Conti et al., 2009).

Guan et al (2010) using TaqMan real-time quantitative PCR arrays, found miRNA-196 was upregualted in gliomas but not in anaplastic astrocytoma. The authors thought that miR-196 may play a role in the malignant progression of gliomas and may be a prognostic predictor in glioblastomas. With the same methods, Jiang et al (2010) reported that miRNA-182 was significantly increased by up to 32-fold in glioma tumors compared with the adjacent nontumor brain tissues obtained from the same patient. Elevated expression of miRNA-182 was further identified by in situ hybridization in 248 of 253 (98%) archived human glioma biopsies tested. Statistical analysis revealed a significant correlation between miRNA-182 expression and World Health Organization glioma grading ($P < 0.001$). They suggested that miR-182 could be a valuable marker of glioma progression and that high miRNA-182 expression is associated with poor overall survival in patients with malignant glioma. Furthermore, miRNA-10b is upregulated in glioblastomas (Ciafrè et al., 2005) MiRNA-26a is overexpressed in gliomas and contributes to growth by targeting PTEN expression (Huse et al. 2009). While, increased levels of miRNA-10b have been observed in breast cancer cells and it correlated with disease progression (Ma et al., 2007). However, the function of miRNA-10b has not yet been described in glioblastoma.

Circulating miRNAs as Promising Biomarkers

Biomarkers are objectively measurable biologic characteristics which can be used as indicators of normal or pathologic processes. Recent studies indicated that some, including gliomas, can secrete microvesicles that contain RNA, including miRNA (Skog et al. 2008). These microvesicles have been detected in biological fluids including blood, urine, and cerebral spinal fluid (Skog et al. 2008, Huttner et al. 2008). In 2010, Katakowski et al (2010) found functional miRNAs was transferred between gliomas cells. In addition, miRNA expression patterns of miRNAs in human cancer appear to be tissue specific; and miRNAs are stable, reproducible, and consistent among individuals of the same species (Huang et al. 2010). Hence, these data suggested the possibility to detect non-invasively microRNAs in patients affected by gliomas for diagnostic and therapeutic use.

Conclusions, Barriers and Perspectives of Diagnostic Application of miRNAs

MiRNAs play important roles in regulating a great variety of targets and, as a consequence, multiple pathways making their use in diagnostics a powerful tool to be exploited in the holistic evaluation of gliomas, early detection, risk assessment and innovative therapeutic strategies.

An important aspect that has to be underlined is

the limited utility of a single miRNA as molecular marker (because of the lack of sufficient specificity and sensitivity), while a "signature" derived fromaltered expression of a number of miRNAs is needed for the use of miRNAs as biomarkers in the detection of a disease (Keller et al., 2009; Kong et al., 2009). For example, miRNA-21 deregulation has been identified in many other types of human cancer.

As shown by the examples cited in this article, miRNAs may find applications in attacking each of the key hallmarks of malignancy in glioblastoma, through direct effects on growth, migration, differentiation, and treatment resistance. However, it is not known whether the deregulation of miRNAs is a reason or consequence of cancer transformation.

Another major challenge is represented by technological aspects of miRNA detection aiming to high throughput, sensitive and accurate analysis.

New knowledge about miRNAs function may bring new possibilities and strategies in developing novel glioblastoma diagnose. But, we should sure that with the current pace of development in these areas it is possible that in the near future we may be able to harness these activities for improved diagnose of gliomas as well as other diseases of the central nervous system.

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