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miRNAs in Glioblastoma Multiforme: A Brief Review

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ABSTRACT

miRNAs are endogenous small noncoding RNAs that can regulate many cellular processes. Different expression levels of several miRNAs have been detected in glioblastomas. Function of miRNAs and targets have been well studied in recent years. According to these studies, the role of miRNAs in glioblastoma pathogenesis have been defined. miRNAs have affected many processes in GBM such as apoptosis, proliferation, angiogenesis, invasion and cell cycle regulation. In this review, we summarize the information of different miRNAs functions in glioblastoma.

Keywords: miRNAs; Glioblastoma Multiforme, Glioma; Systematic Review; Cancer

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INTRODUCTION

Glioblastoma multiforme (GBM) is a most aggressive cancer that occur in the brain. Clinically, gliomas are divided into four grades: in the grade I tumors are benign and can be surgically resected; in the grade II tumors are low-grade malignancies that have long clinical options; in the grade III tumors show increased anaplasia and proliferation and are more quickly fatal; the grade 4 is GBM that is also common in humans. The most length of survival following diagnosis for patients with GBMs is less than a year. Lacking of treatment survival is usually 3 months and essentially these tumors have drawn considerable attention [1-5].

The reason of this cancer is uncertain. The study shown that Li Fraumeni syndrome, neurofibromatosis, genetic disorders and radiation therapy are risk factors for GBM. For diagnosis a combination of MRI scan CT scan and tissue biopsy are done [6].

Totally treatment of GBM involves tumor resection and following chemo- and radiotherapy. Temozolomide, as an alkylating agents, is often used for chemotherapy. Despite of discover new therapeutic targets and exhaustive efforts to progress recent treatment, clinical improvement has remained absent during the last decade. The discovery of molecular mechanisms of GBM can be used for molecularly targeted therapies [7-10]. Many genetic alterations have been defined in glioblastoma. MicroRNA-screening of plasma is used to define the prediction of glioblastoma. The study demonstrated that several miRNAs are expressed in a different malignancies compared to healthy tissue. In GBM, some of these miRNAs can modulate tumor suppressors and oncogenes [11-13]. For instance, JA Chan et.al demonstrated that in human glioblastoma cells microRNA-21 has an antiapoptotic role. Increasing of apoptotic cell death and activation of caspases have been shown with knockdown of miR-21 in glioblastoma cells [14]. Benjamin Kefas et.al indicated that miR-7 has therapeutic potential for glioblastoma because of it is regulator of major cancer pathways [15].

miR-137 has been reported to act as a tumor suppressor miRNA in various types of tumors and is downregulated in GBM and could be used for the treatment of GBM [16].

Biogenesis of miRNA

MicroRNAs (miRNAs) are a class of small RNA molecules (~22 nucleotides) that found in various organisms. They downregulate the translation of

definite messenger RNAs (mRNAs) by binding partly or fully to complementary sequences in target mRNAs. mRNA molecules are silenced by cleavage of mRNA or destabilization of hat through shortening of its poly(A) tail. miRNAs genes transcribed by RNA polymerase II/III, creating a primary transcript (pri-miRNA) that is both polyadenylated and capped. Through intramolecular base-pairing, the transcript folds into a stem-loop structure. After that by the Drosha/DGCR8 complex, the stem loop structure is cut to pre-miRNA and transported to cytoplasm by Exportin-5. In the cytoplasm, a second RNase-III enzyme named Dicer makes final cleavage to create double-stranded miRNA. Then one strand is incorporated into the large protein complex recognized as RNA-induced silencing complex (RISC). Another strand is degraded. The miRNA guides the RISC complex to the mRNA, resulting in mRNA cleavage, mRNA decay or inhibition of translational regarding to the amount of sequence complementarity of the target mRNA with miRNA. MiRNAs affecting many of cellular processes, e.g. apoptosis, migration, proliferation and stem cell differentiation [17-21].

MicroRNAs expression in GBM

The studies show that 256 miRNAs remarkably overexpressed in GBM. For instance, miR-21 is the most extensively miRNA that investigated to be overexpressed in GBM. miR-21 inhibition is a leading cause of an increase in apoptosis and significantly improved levels of caspases. Also, transfection with antisense-miR-21 has been evaluated to increase GBM cell line sensitivity to both chemo- and radio therapy. Therefore, this feature of miR-21 function makes it suitable for molecular therapy [14, 22, 23].

Nearly 8 studies demonstrated that miR-10b overexpressed in GBM. This miRNA has oncogenic effects on glioblastoma cells and associated with tumor invasive factors [22, 24, 25]. The expression of the miR-17~92-cluster is upregulated in GBM tumor samples and cell lines [26]. Several studies have proven that miR-93 can increase angiogenesis, proliferation and in vivo tumor volume in GBM [27]. In summary, many miRNAs upregulated in GBM and show that miRNAs are critical regulator of GBM.

The reviewed literature show that compared to normal brain tissue, 95 miRNAs were downregulated in GBM [10]. Therefore, further study of these miRNAs could make knowledge on appreciated therapeutic targets. For example, lack of miR-7 function in glioma cells, resulting in metastases, invasion and glioma increase and thus may be used for therapeutic of malignant glioma [28] . miR-34a, miR-181, miR-137, miR-153 and miR-128 decreased proliferation and in vivo tumor volume in GBM [10]. WL Ng et al reported that miR-100 can increase radio-sensitivity [29]. Zhang et al demonstrated that target of miR-185 is DNMT1 and decrease DNA methylation [30]. Barciszewska et al reported that microRNAs have many potentials that used as biomarkers in high-grade gliomas due to their simple identification [31]. In addition Saadatpour and colleagues proved that microRNAs could be used as novel prognosis and/or diagnosis biomarkers in GBM patients and have critical roles in many biological processes [32].

CONCLUSION

The miRNAs are one of the most growing fields in molecular biology. With respect to the role of miRNAs in the regulation of several biological processes it is receiving the necessary attention. Results of different studies indicate that miRNAs have essential role in diseases such as cancer. In this brief review we have summarized the role of miRNAs in GBM. Due to its role in GBM, has proven to have greater potential in future therapeutics.

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