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REVIEW

Glioblastoma: exosome and microRNA as novel diagnosis biomarkers

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Glioblastoma (GBM) is known as a tumor type, which arises from astrocytes. Several studies indicated that GBM tumor cells are malignant. This is because of the fact that they consist of different cell types, which are reproducing very quickly and are also supported by a large network of blood vessels. The correct identification of various stages of GBM could help to better treat the patients with this disease. Therefore, new biomarkers such as exosomes and microRNAs (miRNAs) may help us to learn more about GBM and they may also lead to a more effective treatment for patients with GBM. Exosomes have emerged as biological vehicles, which can perform various tasks in carcinogenesis pathways such as PI3K/AKT, SOX2, PTEN, ERK, and STAT3. The miRNAs are known as small noncoding RNAs that are involved in several GBM pathogenic events. These molecules have key roles in various biological processes such as angiogenesis, metastasis and tumor growth. In this study, we highlighted various exosomes and miRNAs that could be used for diagnosis and/or prognosis biomarkers in patients with GBM.

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INTRODUCTION

Glioblastoma is known to be one of the primary brain tumors. Many studies revealed that few available therapies could significantly improve survival chances of patients who have this disease.[1–3] These studies indicated that several molecular/cellular pathways such as SOX2, STAT3, and AKT are involved in GBM pathogenesis.[1,3] Hence, GBM is a complex disease that could grow rapidly. The most common symptoms are nausea, drowsiness, vomiting, and headaches, which are usually caused by increased blood pressure in the brain. The GBM tumors represent almost 15.4% of all primary brain tumors and almost 60–75% of all astrocytomas.[3,4] Glioblastomas consist of various cell types, which makes it difficult to treat, and also existing therapies are difficult to tolerate. Therefore, various studies suggested that a combination of several approaches can be suitable to treat this disease.[4] The identification of new biomarkers and a combination of therapies are new strategies to deal with GBM. Biomarkers are sometimes used to monitor the patients in different stages of treatment.[5–7] The monitoring of GBM with suitable biomarkers can be very important to choose a suitable treatment.[8] On the other hand, finding novel biomarkers can help increasing the efficiency of treatments for GBM. Several studies showed that exosomes and their cargos (including proteins, mRNA and miRNA) have key roles in different stages of cancer. Exosomes released from tumor cells could induce/inhibit various cellular and molecular pathways in the recipient cells and lead to the development and growth of various types of cancer. The miRNAs as biomarkers could have an effect on different pathways that are involved in cancers (for example, GBM). Thus, these molecules could be suggested as diagnosis, prognosis and therapeutic biomarkers. Here, we summarized various aspects of exosomes and miRNAs as diagnostic/prognostic biomarkers and their clinical application in GBM.

EXOSOME AND GLIOBLASTOMA

Various cell types including cancer and normal cells enable the exchange of information via chemical and electronic signals in human body. In addition, some nano-size particles such as exosomes could exchange information between various cells. Exosomes have been known as biological tools that carry various cargos such as proteins, mRNAs and miRNAs.[9–12] Note that these molecules are released from various cells for example, tumor cells and mesenchymal stem cells and so on. Therefore, the exosomes could carry various molecules to recipient cells leading to the development of tumors in different stages of cancer.[13–15] These circulating exosomes and their cargos enable to (de)-activate various cellular/molecular targets in tumor and normal cells (Figure 1). It is found that exosomes can be used as biological vehicles for targeting various molecules such as siRNA, curcumin.[16–18] There are few studies showing the importance of exosomes and their cargos that contribute to tumor growth in different stages of GBM disease.[19–23] As an example, Skog *et al.*, have shown that exosomes released from GBM cells containing

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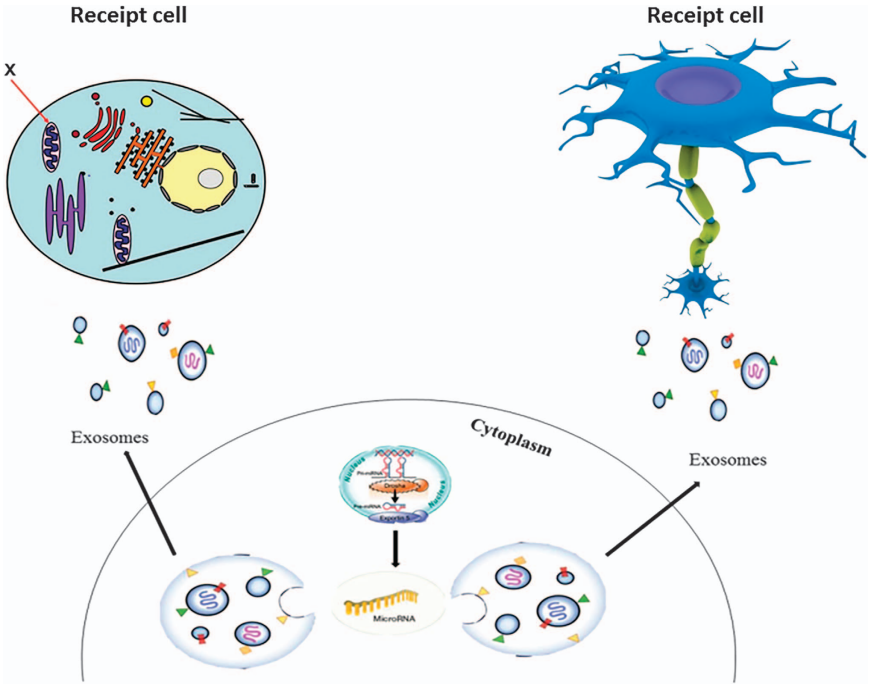

Figure 1. Schema of exosomes released from tumor cells.

RNA and angiogenic proteins could induce tumor growth.[24] Exosomes released from GBM cells are taken up by recipient normal cells. These molecules can induce tubule formation by endothelial cells. Their results indicated that exosomes derived from tumor cells are able to promote proliferation of a human glioma cell line. Moreover, they revealed that mRNA and various miRNAs of gliomas could be detected in serum exosomes of GBM patients. Their study was done on 25 GBM patients, of which 7 had exosomes containing EGFRvIII. These findings suggested that exosomes derived from tumor cells may be used as diagnostic biomarkers in GBM patients. Akers et al.,[25] have found that exosomes containing miR-21 could be used as diagnostic biomarkers for GBM patients. Their results showed that miR-21 levels in exosomes of GBM patients were upregulated (10-fold higher than exosomes isolated from control group).[25] Moreover, exosomes may also be suitable for monitoring patients with GBM in response to various drug treatments.[26] In conclusion, exosomes released from tumor cells and their cargos may be used as diagnosis and prognosis biomarkers for monitoring of patients with GBM.

GLIOBLASTOMA AND MIRNAS

The microRNAs (miRNAs) are known as a class of small noncoding RNAs, which approximately consist of 21–25 nucleotides in length.[27–29] miRBase has been recorded in almost 1921 mature *Homo sapiens* miRNAs. These molecules have central roles in many biological processes such as cell growth, cell development and regulation of many cellular functions.[30–32] Numerous studies indicated that aberrant of miRNAs expression could be involved in various pathogenesis events in GBM. The miRNAs have several molecular and cellular targets such as PTEN, Mdm2, TSC1, POLD2, TGFβ-RII, CTGF and CAMTA1 in GBM.[1,8,33] Qiu et al.[1] have shown that the upregulated miRNAs such as miRNA-326 and miRNA--130a, and down regulated miRNAs such as miRNA-323, miRNA-329, miRNA-155 and miRNA-210 could be associated with long overall survival in GBM patients. They also indicated that miRNA-326, miRNA-130a upregulated and miRNA-155, miRNA-210 down-regulated could be related to extended progression free survival (PFS).[1] It has been observed that miRNA-328 was downregulated in 20 anaplastic and 60 GBM tumor samples.[33] The downregulation of miRNA-328 conferred poor survival in patients with primary GBM.[33] In another study, Lakomy et al.[8] assessed 38 patients with primary GBM. They showed that miRNA-196b and miRNA-195 could positively correlate with overall survival. Moreover, the combination of these miRNAs with miRNA-181c and miRNA-21 could predict time-to-progression within 6 months of diagnosis with 92% sensitivity and 81% specificity. These findings suggested that these miRNAs could identify patients at high risk of early progression after surgery.[8] Circulating miRNA-128, miRNA-21 and miRNA-342-3p were also observed to be changed in 50 patients with GBM compared with a control group.[34] It is found that circulating miRNA-128 and miRNA-342-3p were positively correlated with histopathological grades of GBM.

Moreover, it was also indicated that miR-24 is over-expressed in glioma samples and glioma cells.[35] The miR-24 downregulated in glioma cell lines could induce apoptosis and thus inhibit invasion and cell proliferation.[35] By using a computational analysis it was found that ST7L is the main target for miR-24. These findings showed that the miR-24 could be an oncogene and it could be used as a diagnostic and therapeutic biomarker.[35] The miRNA-124 and miRNA-137 were found to be downregulated in GBM samples and cell lines.[36] Moreover, it was found that these miRNAs enable the induction of cell arrest in GBM cells, differentiation of adult mouse neural stem cells and mouse oligodendroglioma-derived stem cells. These results showed that these molecules could be used as new therapeutic and diagnostic biomarkers for treatment and monitoring of patients with this disease.[36]

Finally, several studies confirmed that miRNAs have key roles in various pathogenic events in GBM. Hence, these molecules may

Table 1. Various miRNAs as diagnostic/prognostic biomarkers in GBM

miRNA	*Expression in GBM*	*Target gene(s)*	*Ref*
miR-9	Upregulation	*CAMTA1, REST, TrkC*	37
miR-25	Upregulation	*Mdm2, TSC1*	6
miR-23	Upregulation	*Mdm2, TSC1*	38
miR-10b	Upregulation	*HOXD10, RhoC*	39
miR-15a	Upregulation	*BCL2*	40
miR-16	Upregulation	*BCL2*	40
miR-23a	Upregulation	*HOXD10*	41
miR-23b	Upregulation	*VHL*	42
miR-204	Upregulation	*SOX4, EphB2*	43
miR-222	Upregulation	*PUMA, P57, PTPμ, AKT*	44
miR-221	Upregulation	*PUMA*	44
miR-130a	Upregulation	-	1
miR-125b	Upregulation	*E2F2*	45
miR-92	Upregulation	*CTGF*	46
miR-28	Upregulation		47
miR-24	Upregulation	*ST7L*	35
miR-328	Downregulation	*SFRP1*	48,49
miR-19a	Downregulation	*CTGF*	50
miR-451	Downregulation	*PI3K/AKT*	51
miR-145	Downregulation	*Oct4, SOX2*	52
miR-106a	Downregulation	*SLC2A3*	53
miR-410	Downregulation	*MET*	54
miR-15b	Downregulation	*NRP-2, CCNE1*	55
miR-152	Downregulation	*MMP-3*	56
miR-195	Downregulation	*E2F3, CCND3*	57
miR-633	Downregulation	CXCR4	58
miR-136	Downregulation	*AGE1, Bcl2*	59
miR-148	Downregulation	*Npm1, Akt2*	60
miR-634	Downregulation	*CYR61, mTOR*	61
miR-491-5p	Downregulation	*MMP9*	62
miR-885-5p	Downregulation	*MMP9*	63
miR-483-5p	Downregulation	*ERK1*	64
miR-7	Downregulation	*AKT*	65
miR-31	Downregulation	*Radixin (RDX)*	66
miR-32	Downregulation	*MDM2, TSC1*	67
miR-101	Downregulation	*EZH2*	68
miR-34a	Downregulation	*SIRT1, c-Met, Notch1/2*	69
miR-128	Downregulation	*EGFR*	70
miR-124	Downregulation	*STAT3*	36,71
miR-137	Downregulation	*STAT3*	36
miR-330	Downregulation	*Endophilin-1*	72

Abbreviations: GBM, glioblastoma; miRNA, microRNA.

be a new candidate for monitoring and treatment of GBM. Table 1 illustrates some miRNAs that could use as biomarkers in GBM.

CONCLUSION

GBM is known to be one of the most important cancer types with a poor prognosis and could be resistant to various therapies. The main aspect for an efficient treatment is to identify potent biomarkers for monitoring patients with GBM. Monitoring patients could contribute to better and more efficient treatments for this disease. Among various biomarkers for monitoring patients with GBM, exosomes and miRNAs have emerged as suitable tools. These molecules are involved in various GBM pathogenic pathways including AKT, ERK, STAT, PTEN and SOX2. The accumulated evidence indicated that these molecules have key roles in various biological processes and therefore, could be used as potential diagnostic/prognostic biomarkers for GBM patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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