The Emerging Role of Exosomes and MicroRNA in Glioma

Mehdi Mohamad Zreik[1], Zhenggang Zhang[1] MD PhD, Michael Chopp[1,2] PhD

[1]Department of Neurology- Henry Ford Hospital, Detroit MI, USA

[2]Department of Physics- Oakland University, Rochester Hills MI, USA

MZreik1@hfhs.org

Abstract

Glioma ordains highly malignant forms of brain cancer that originate from the glial cells. As grade level of glioma increases, the cancer will transpire a poorer prognosis for the majority sum of affected patients. Despite the classical combination of therapies such as chemotherapy, radiation therapy, surgical resection; patients tend to become lifeless in a matter of months. Nevertheless, over recent years, membrane-bound lipid nanovesicles called exosomes and there encapsulated regulatory microRNAs, as well as circulatory microRNAs, have proven their significant role in glioma progression, migration, proliferation, invasion, etc. These nanosized lipid pieces of machinery carry astounding promise for diagnostic and prognostic applications for glioma treatment. All owing to their content catalog of short ribonucleic acids in the form of microRNAs that orchestrate revolutionary gene regulation processes in glioma cell lines. Therefore, a deep appreciation of the nature and content of exosomes and microRNAs is fundamental. Here we highlight the overall role of exosomes and microRNAs in glioma and their potential therapeutic applications for glioma treatment, prognostics, and diagnostics in the clinical setting.

Background

Patients with either low or high-grade glioma may undergo a series of treatments such as surgical resection, chemotherapy, radiation therapy, targeted therapy; however overall median survival rate remains between 12-15 months. The danger of glioma stems from the aggressive nature that it ordains, hence the reason for its poor prognosis of patients. Glioma tumor cells possess the capability of forming angiogenic structures amongst glial cells via carcinogenic pathways such as PI3K/AKT through the use of exosome and microRNAs; which can aid in gliomagenesis and provide insight for diagnostic and prognostic purposes. These glioma cell types have been shown to utilize exosomes and microRNAs as cellular cross-talk mechanisms in correspondence with other cancerous and normal cells, thus imposing a more potent tumor microenvironment implicating higher therapy and treatment resistance. In turn, multiple therapies have been and continue to be studied for glioma, but the most interesting is the use of nanotechnology therapy in the form of exosomes as well as master regulatory microRNAs.

Exosomes are 30-100nm bi-lipid layer molecules that are secreted by both normal and cancerous cells from the budding of multivesicular body cells. Within exosomes are biomolecules in the form of proteins, microRNAs, and messenger RNAs that can be transferred between cells via intercellular communication. Secretion of exosomes has been found to increase as cells undergo cellular senescence in response to stress-induced conditions such as DNA damage, oncogenic stress, irradiation, hypoxia, etc. Post secretion, they are taken up by cells via fusion with the target cell membrane, receptor-dependent endocytosis, as well as direct signaling via surface molecules. The content of exosomes that are most desirable for clinical application is there internal composition of specialized microRNAs that determine recipient cell fate after uptake. Depending on the nature and source of the exosome, there packaged microRNAs tend to concurrently regulate recipient cell types to either turn on and or off vital post-transcriptional degradation and or activation activity.

When specialized microRNAs make there way to recipient glioma cells and or normal brain parenchyma via exosome transportation, they can trigger a cascade of perpetual pathogenic abnormalities or immediate cell apoptosis. Given the fact that microRNAs regulate gene expression for more than one-third of the human genome, it comes at no surprise for both there positive and negative regulatory effects on glioma malignancy, proliferation, migration, angiogenesis, and apoptosis. Findings indicate that a number of microRNA to this caliber are present in stable forms all throughout the serum-plasma of humans and animals such as rats. The residency of these master gene regulators in the serum-plasma of patients is of great importance, in that they may serve as prognostic and diagnostic indicators of cancer infringements.

Figures

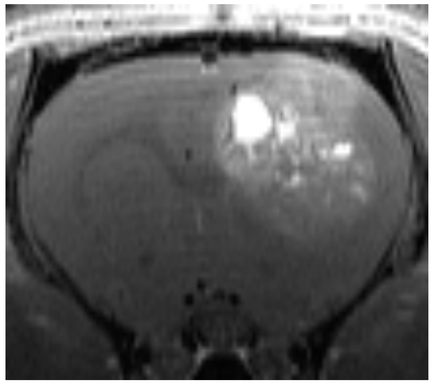

Figure 1. Post MRI imaging of Animal Model Post Right Intracranial Glioma implantation

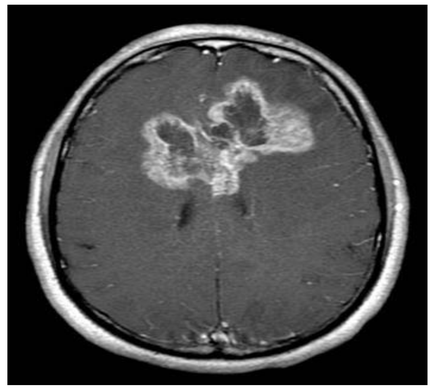

Figure 2. MRI imaging of Glioma Patient

Table 3. Overall and Progression-free Survival According to Treatment Group.*

Variable	Radiotherapy (N=286)	Radiotherapy plus Temozolomide (N=287)
	value (95% CI)	
Median overall survival (mo)	12.1 (11.2–13.0)	14.6 (13.2–16.8)
Overall survival (%)		
At 6 months	84.2 (80.0–88.5)	86.3 (82.3–90.3)
At 12 months	50.6 (44.7–56.4)	61.1 (55.4–66.7)
At 18 months	20.9 (16.2–26.6)	39.4 (33.8–45.1)
At 24 months	10.4 (6.8–14.1)	26.5 (21.2–31.7)
Median progression-free survival (mo)	5.0 (4.2–5.5)	6.9 (5.8–8.2)
Progression-free survival (%)		
At 6 months	36.4 (30.8–41.9)	53.9 (48.1–59.6)
At 12 months	9.1 (5.8–12.4)	26.9 (21.8–32.1)
At 18 months	3.9 (1.6–6.1)	18.4 (13.9–22.9)
At 24 months	1.5 (0.1–3.0)	10.7 (7.0–14.3)

Figure 3. Tabulated data of glioma patient percent and month survival rates for both Radiotherapy and Radiotherapy plus Temozolomide group.

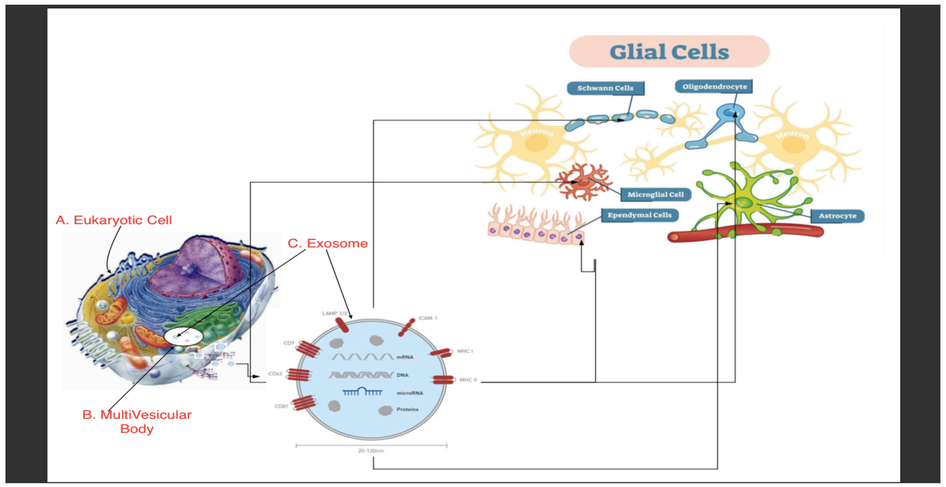

Figure 4. Overview of exosome production and transport scheme of content catalog to prospective recipient glial cells.

Importance of Exo-MiR in Clinical Applications

When recognizing exo-miR as potential therapeutics for glioma, we must gain a deeper appreciation for there endogenous origin and special surface composition. These features are what allow exo-miR inpatient circulation to be more stable than any other synthetic polymer-based nanoparticle. The Blood-Brain Barrier, for example, is known to be restrictive of biomolecules that try to enter into the brain complex; in specific to therapeutic drugs. Yang and colleagues, however, have revealed that anti glioma exo-miRs derived from brain endothelial cells can cross the BBB and enter into the brain; activating anti-tumorigenic events. In vitro studies have also revealed that Glioma Associated Stem cell-derived exo-miRs propagate malignant properties to glioma cell lines; thus providing an independent predictor l glioma patient prognosis via differential studies on HGG and LGG groups. GSC-derived Exo-miR-26a and GSC derived exo-miR-21, for example, promote the angiogenesis of HBMECs and endothelial cells via targeted activation of PI3K/AKT and VEGF signaling pathway. This approach holds great clinical importance in that it may exploit novel strategies that target tumor stroma of glioma patients.

A potential clinical diagnostic biomarker, CSF derived exo-miR-2, correlated findings of glioma metastasis and recurrence in 198 glioma tissue samples given increased expression levels. Interestingly, studies have been tailored to bioengineer MSCS to secrete anti-glioma exo-miRs; in vitro studies revealed, for example, that MSC derived Exo-miR-146b slows glioma growth. Findings of this magnitude suggest that engineering anti-glioma specific exo-miR in MSCs can potentially provide a clinical means for malignant glioma treatment. Similar in vivo studies on MSC derived Exo-mir-199a and MSC derived exo-miR-124, suggested overexpression inhibited glioma cell migration, migration, and proliferation.

Future Reservations?

Although there may be several clinical obstacles of introducing exo-miR for diagnostics, prognostics, and therapy for glioma. It is far from impossible to potentially utilize these intercellular cross-talk vesicles as novel therapeutic applications. These novel approaches mentioned in our review paper, hold great potential because of the minimal toxicity; target specificity; nanosized nature of the vesicle; specific expression levels of miR in glioma tissue, and ability to pass the BBB with ease. Highly dynamic characteristics like so, call for further investigative-specific in vivo and in vitro studies; in order to move these nanotherapuetic applications to the bedside.

Acknowledgements, Correspondence, References

- Zreik MM would like to thank Mohamad Amine Zreik for support. Zreik MM would also like to recognize all colleague researchers at the Henry Ford Hospital Department of Neurology for there efforts, specifically Dr. Zhang and Dr. Chopp for there mentorship.

- Correspondence to: Mehdi Mohamad Zreik, MZreik1@hfhs.org; orcid: 0000-0001-8794-9128

- Do to high reference count, references will be provided concurrently with presentation.