Glioma-Associated Mesenchymal Stem Cells Promote Glioma Growth via Delivery of Exosomal MicroRNA

Javier Miguel Figueroa MD, PhD; Tal Shahar MD; Anwar Hossain PhD; Joy Gumin BS; Frederick F. Lang MD

Introduction

Evidence indicates that human cancers are maintained by a population of cells with stem-like properties called cancer stem cells (CSCs). However, the influence of the surrounding stromal cells on the behavior of the CSCs remains poorly understood. We have recently shown that the micro-environment of human gliomas, the most aggressive human brain tumors, contains both glioma stem cells (GSCs) and cells that resemble human bone marrow-derived mesenchymal stem cells (BM-MSCs), called Glioma Associated-MSCs (GA-MSCs). We have also shown that GA-MSCs generate a cytokine-mediated increase in the growth and self-renewal (clonogenicity) of GSCs. However, other paracrine interactions between GA-MSCs and GSCs have not been fully explored. Recent studies have suggested that nano-sized vesicles, termed exosomes, may contribute to intercellular communication within the tumor niche. Therefore, we hypothesized that GA-MSC-derived exosomes increase the tumorigenicity GSCs.

Methods

GA-MSC-derived exosomes were isolated by differential ultra-centrifugation of GA-MSC-derived conditioned medium. MicroRNA profiling of GA-MSC-derived exosomes was performed utilizing micro-array hybridization. Specified target miRNA were over-expressed in GSCs by lentiviral transduction. In vivo experiments were conducted by co-culture of GSCs with GA-MSC-derived exosomes, and subsequent implantation into the brains of nude mice.

Results

We show for the first time that exosomes can be isolated from patient-derived GA-MSCs and that these exosomes contain oncogenic microRNAs. Importantly, in vitro delivery of exosomes isolated from GA-MSCs significantly increased both the proliferation and clonogenicity of GSCs. Furthermore, GSC xenografts, treated with GA-MSC-derived exosomes, in the brains of nude mice resulted in a greater tumor burden and significantly decreased animal survival. Lastly, delivery of specific microRNA identified as both highly expressed and highly enriched in GA-MSC-derived exosomes, altered gene expression in recipient GSCs resulting in the glioma-enhancing effects described.

Conclusions

We conclude that GA-MSC-derived exosomes represent an alternative intercellular communication mechanism for the transfer of specific microRNAs which enhance the aggressive nature of gliomas.

Learning Objectives

By the conclusion of this session, participants should be able to:

1) Describe the importance of exosome communication in the glioma microenvironment.

2) Discuss other properties of stroma-derived exosomes in glioma progression.

3) Identify possible adjunct therapeutic strategies that target exosome-mediated tumor promotion.