Journal of Cancer Stem Cell Research (2018), 6:e1009
 ISSN 2329-5872
DOI: 10.14343/JCSCR.2018.6e1009
http://cancerstemcellsresearch.com

Open Access

The Effect of CD133 Positive Stemness on the Exosomes Secreted by Glioma Cells

Oliver D. Mrowczynski[1,*], A. B. Madhankumar[1], Jeffrey M. Sundstrom[2], Yuanjun Zhao[2], Yuka Imamura Kawasawa[3], Becky Slagle-Webb[1], Ganesh Shenoy[1], Vagisha Ravi[1], Elias B. Rizk[1], Brad E. Zacharia[1], and James R. Connor[1,*]

[1]Department of Neurosurgery, Pennsylvania State University College of Medicine, Hershey, PA 17033.
[2]Department of Ophthalmology, Pennsylvania State University College of Medicine, Hershey, PA 17033.
[3]Department of Pharmacology, Biochemistry and Molecular Biology, Institute for Personalized Medicine, Pennsylvania State University College of Medicine, Hershey, PA 17033. [*]Corresponding author.

Abstract: Glioblastoma is the most common central nervous system malignancy in adults with a median survival of only 14 months. The current arsenal of treatment modalities including surgical resection and combination chemoradiation have been largely ineffective. One reason proposed for the ineffectiveness of our current therapeutic regimen is the resistance of glioma stem cells (GSCs) within the tumor and tumor borders. We investigated the hypothesis that the communication of GSCs to their microenvironment through exosomes is a key factor underlying the enhanced cellular proliferation and the development of resistance to therapeutics. Exosomes are nanometer sized vesicles released by cancer cells that contain DNA, RNA, and protein critical to the interaction of a cell with its microenvironment. Two properties of exosomes were analyzed: 1) exosome function and 2) exosome profile. Exosomes secreted by patient derived-glioma stem cells (GSC-exosomes) increased cellular proliferation, radiation resistance, temozolomide resistance, and doxorubicin resistance. We further profiled the GSC-exosomes to begin to probe the underlying mechanism of this phenomenon. Profiling showed specific changes to RNA and protein favoring therapeutic resistance and cellular proliferation. For example, GSC exosomes have increased expression of proteins involved in radiation and chemotherapeutic resistance (Ex. CDK4 and Notch), cellular proliferation (Ex. Cyclin B1 and Cyclin D2), angiogenesis (Ex. VEGF-A and EGFR), glioma cell stemness and de-differentiation (Ex. EPHA2, Cathepsin B), and cell invasion and metastasis (Ex. ITGA3, COL4A2). The results of our study suggest a novel exosome-based mechanism by which glioma stem cells alter therapeutic resistance and increase cellular proliferation.

Keywords: Exosomes, Radiation, Temozolomide, Resistance, Glioma stem cell, Glioblastoma.

ACKNOWLEDGMENTS

This study was supported by funds from Penn State Hershey Department of Neurosurgery. Research work was presented at the Cancer Stem Cell Conference (2018), Cleveland, Ohio, USA.

Received: November 6, 2018; Revised: November 6, 2018;
Accepted: November 6, 2018