Abstract 39

Temozolomide Resistant Glioblastoma Derived Exosomes Mediate Hematopoietic Changes: Expansion of Myeloid-Derived Suppressors Cells

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\textbf{Background:} Glioblastoma multiforme (GBM) is the most common and aggressive form of glioma with the average survival, <15 months. Current treatment includes surgical resection followed by radiotherapy and chemotherapy, with temozolomide (TMZ) as the frontline treatment. Similar to other solid tumors, GBM is associated with immune dysfunction, including increase of local and systemic myeloid-derived suppressor cells (MDSCs). These cells are heterogeneous population of myeloid origin from bone marrow (BM). The over\textbf{arching hypothesis} states that GBM pathology is in part due to a bidirectional communication with BM. The specific \textbf{hypothesis} states that GBM cells release exosomes (GDEs) that enter the BM to induce the differentiation of MDSC, leading to increased tumor growth and chemoresistance.

\textbf{Methods:} A transwell co-cultures of GBM in the inner wells and BM cells from healthy donors in the outer wells established indirect cellular communication via exosomal secretome. Loss of function studies transfected GBM cells with Rab27a shRNA lentivirus to prevent the release of exosomes, and gain of function assay added GDEs directly to BM cells. The responding hematopoietic cells were analyzed by viability, clonogenic assay and flow cytometry for stem (HSC), progenitor and MDSC. Parallel studies used TMZ resistant GBM cells that were established by treatment with 200 μM for 72 h.

\textbf{Results:} GDEs showed a bias towards myelopoiesis as indicated by flow cytometry and clonogenic assay. Further, GDE-treated BM cells (5 days), in the absence of growth factor supplement, increased MDSCs. Interestingly, chemoresistant GBMs secreted significantly more exosomes/cell, suggesting a mechanism for enhanced MDSCs during treatment. Gain and loss of function studies indicated that GDEs are indeed responsible for increased myelopoiesis.

\textbf{Conclusion:} GDEs increased MDSCs in BM cells, indicating a feedback to the brain to exacerbate GBM physiology. More importantly, enhanced exosomes in TMZ resistant GBM suggested that treatment while benefiting the subject could also worsen the GBM outcome. These findings provide insights into how a filtration system might be useful to eliminate exosomes in GBM patients.