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Tumor Biology 4: Stem Cells in Cancer 1 Abstract #320

Chemoresistance of stem-like cells isolated from glioblastoma

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Glioblastoma multiforme (GBM) is the most common adult primary brain tumor and is comprised of a heterogeneous population of cells. Recently, we and other groups identified a small population of cancer stem cells in adult and pediatric brain tumor. These tumor stem cells form neurospheres and possess the capacity for self-renewal. They can express genes associated with neural stem cells (NSCs) and, differentiate into phenotypically diverse populations, including neural, astrocytic and oligodendritic cells. CD133 has been identified as a marker of the subset of both leukemia and glioblastoma cancer stem cells. We sought to examine the drug resistance of CD133 positive cancer stem cells and delineate the gene expression. We further investigate whether these properties would affect the survival of these cancer stem cells after clinical therapeutic interventions. In this study, CD133 expression on three primary cell lines established from glioblastoma patient, was 10.2%, 69.7% and 27.5%, respectively. CD133 positive cells were successfully isolated by FACS sorting from the above three primary tumor cell lines. Then, we found that average expression levels of stem-like cell markers such as CD90, CD44, CXCR4, Nestin, Msi1, and MELK mRNA on CD133 positive cancer stem cells increased to 15.6, 5.7, 337.8, 2.14, 84 and 1351 times, respectively, compared to the levels found on autologous CD133 negative cells. In the mean time, CD133 positive cells not only expressed higher BCRP1 mRNA, but also expressed significantly higher levels mRNA on genes related to inhibiting cell apoptosis. Furthermore, CD133 positive cells were significantly resistant to chemotherapeutic drugs including temozolomide, carboplatin, etoposide (VP16) and paclitaxel (Taxol) as compared to the autologous CD133 negative cells. Finally, we found that CD133 expression was significant higher in the recurrent GBM tissue from five patients as compared to their respective newly diagnosed tumors which suggests that CD133 positive cancer stem cells are resistant to current chemotherapy. Our study demonstrates that CD133 positive cancer stem cells from glioblastoma displayed significantly higher resistance to chemotherapeutic drugs *in vitro* and *in vivo*. These features may be contributed by overexpressing genes functioning in multi-drug resistance genes such as BCRP1 and genes related to inhibiting cell apoptosis. These data demonstrate therapies targeting this small population of CD133 positive cancer stem cells may improve the survival of patients with glioblastoma.

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