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## Stem Cells and Development

### Tumorigenesis of Chemotherapeutic Drug-Resistant Cancer Stem-Like Cells in Brain Glioma

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**Glioblastoma multiforme (GBM) is the most frequently occurring brain cancer. Although the existence of cancer stem cells (CSCs) in GBM has been established, there is little evidence to explain the link between CSCs and chemoresistance. In this study, we developed a dissociated cell system of human GBM cells, A172 and established GBM2 cells, that have shown resistance to 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU). After exposure to a lethal dose of BCNU, the small population of GBM cancer cells survived and proliferated, as opposed to direct inhibition of the apoptosis and activation of the proliferation signal. Also, these cells contained subpopulations of stem-like cells, expressing CD133, CD117, CD90, CD71, and CD45 cell-surface markers, and had the capacity for multipotency. Moreover, we observed that BCNU-resistant subpopulations derived from GBM cancer cells can be grown to tumors when transplanted into severe combined immunodeficient (SCID) mouse brain. These results demonstrated that BCNU-resistant subpopulations derived from GBM have cancer stem-like cell properties. These findings provide further evidence that CSCs in GBM display chemotherapeutic drug resistance. Hopefully, it will be possible to improve the therapeutic outcome of GBM, leading to better anticancer strategies.**

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## Original Research Report

# Tumorigenesis of Chemotherapeutic Drug-Resistant Cancer Stem-Like Cells in Brain Glioma

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### ABSTRACT

Glioblastoma multiforme (GBM) is the most frequently occurring brain cancer. Although the existence of cancer stem cells (CSCs) in GBM has been established, there is little evidence to explain the link between CSCs and chemoresistance. In this study, we developed a dissociated cell system of human GBM cells, A172 and established GBM2 cells, that have shown resistance to 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU). After exposure to a lethal dose of BCNU, the small population of GBM cancer cells survived and proliferated, as opposed to direct inhibition of the apoptosis and activation of the proliferation signal. Also, these cells contained subpopulations of stem-like cells, expressing CD133, CD117, CD90, CD71, and CD45 cell-surface markers, and had the capacity for multipotency. Moreover, we observed that BCNU-resistant subpopulations derived from GBM cancer cells can be grown to tumors when transplanted into severe combined immunodeficient (SCID) mouse brain. These results demonstrated that BCNU-resistant subpopulations derived from GBM have cancer stem-like cell properties. These findings provide further evidence that CSCs in GBM display chemotherapeutic drug resistance. Hopefully, it will be possible to improve the therapeutic outcome of GBM, leading to better anticancer strategies.

### INTRODUCTION

**G**LIOMASTOMA MULTIFORME (GBM) is the most frequent brain tumor. Compared with other tumors, GBM has relatively aggressive variants in humans (1). Besides surgery, which is an important initial therapeutic measure in this malignant glioma, postoperative radiotherapy and chemotherapy have been effective in treating GBM (2,3). Despite constant efforts toward the prevention and treatment of GBM, GBM is particularly resistant to current strategies of surgery, radiation, and chemotherapy (2,3). Moreover, GBM contains subpopulations of cells with intrinsic resistance to therapy that can repopulate the tumor after treatment (4). Therefore, the identification of the cell types involved in this resistant phenomenon is critical from both the scientific and therapeutic standpoints of GBM.

Chloroethylnitrosourea and especially 1,3-bis(2-

chloroethyl)-1-nitrosourea (BCNU), have been the most commonly used pharmacological agents in chemotherapy of GBM following surgical resection and radiation (1). BCNU passes across the blood-brain barrier (5) and kills tumor cells via multiple cytotoxic actions, including carbamoylation and alkylation of DNA (6). However, BCNU does not appear to prolong median survival substantially, even though the proportion of patients living more than 18 months increases from 5% to 15% with adjunct BCNU chemotherapy (7,8). Moreover, GBM has shown resistance to BCNU chemotherapy, leading to subsequent tumor growth. Several investigators have demonstrated that variation in multidrug resistance genes (9), DNA repair activity (10), and glutathione *S*-transferase and intracellular glutathione content (11) have been speculated to cause BCNU chemoresistance in GBM.

In the last years, it has been reported that cancers are organized in a hierarchy of heterogeneous cell popula-

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