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Persistence of CD133⁺ Cells in Human and Mouse Glioma Cell Lines: Detailed Characterization of GL261 Glioma Cells with Cancer Stem Cell-Like Properties

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The concept of cancer stem cells suggests that there are malignant stem-like cells within a tumor that are responsible for tumor renewal and resistance to cytotoxic therapies. Studies have identified glioma stem-like cells that extrude Hoechst 33342 dye, representing a double-negative "side population" (SP) thought to be selectively resistant to drug therapy. A CD133⁺ stem cell-like subpopulation has been isolated from a human glioma that was enriched for tumor-initiating cells. It is unknown whether CD133⁺ cells with similar phenotype persist in established glioma cell lines, or if CD133 is a marker of glioma stem-like cells in rodents. We investigated whether CD133⁺ and SP cells existed in the GL261 cell line, a syngeneic mouse glioma model that is widely used for preclinical and translational research. Intracerebral injection of less than 100 CD133⁺ GL261 cells formed tumors, whereas it required 10,000 CD133⁻ cells to initiate a tumor. CD133⁺ GL261 cells expressed nestin, formed tumor spheres with high frequency, and differentiated into glial and neuronal-like cells. Similar to GL261, seven human glioma cell lines analyzed also contained a rare CD133⁺ population. Surprisingly, we found that CD133⁺ GL261 cells did not reside in the SP, nor did the majority (~94%) of CD133⁺ human glioma cells. These results demonstrate that the expression of CD133 in murine glioma cells is associated with enhanced tumorigenicity and a stem-like phenotype. This study also reveals a previously unrecognized level of heterogeneity in glioma cell lines, exposing several populations of cells that have characteristics of cancer stem cells.

Original Research Report

Persistence of CD133⁺ Cells in Human and Mouse Glioma Cell Lines: Detailed Characterization of GL261 Glioma Cells with Cancer Stem Cell-Like Properties

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ABSTRACT

The concept of cancer stem cells suggests that there are malignant stem-like cells within a tumor that are responsible for tumor renewal and resistance to cytotoxic therapies. Studies have identified glioma stem-like cells that extrude Hoechst 33342 dye, representing a double-negative "side population" (SP) thought to be selectively resistant to drug therapy. A CD133⁺ stem cell-like subpopulation has been isolated from a human glioma that was enriched for tumor-initiating cells. It is unknown whether CD133⁺ cells with similar phenotype persist in established glioma cell lines, or if CD133 is a marker of glioma stem-like cells in rodents. We investigated whether CD133⁺ and SP cells existed in the GL261 cell line, a syngeneic mouse glioma model that is widely used for pre-clinical and translational research. Intracerebral injection of less than 100 CD133⁺ GL261 cells formed tumors, whereas it required 10,000 CD133⁻ cells to initiate a tumor. CD133⁺ GL261 cells expressed nestin, formed tumor spheres with high frequency, and differentiated into glial and neuronal-like cells. Similar to GL261, seven human glioma cell lines analyzed also contained a rare CD133⁺ population. Surprisingly, we found that CD133⁺ GL261 cells did not reside in the SP, nor did the majority (~94%) of CD133⁺ human glioma cells. These results demonstrate that the expression of CD133 in murine glioma cells is associated with enhanced tumorigenicity and a stem-like phenotype. This study also reveals a previously unrecognized level of heterogeneity in glioma cell lines, exposing several populations of cells that have characteristics of cancer stem cells.

INTRODUCTION

GLIOMASTOMA MULTIFORME (GBM) is a lethal primary brain tumor that is comprised of a phenotypically diverse population of cells [1]. The exact mechanisms responsible for the heterogeneity of GBM are poorly understood. The cancer stem cell hypothesis suggests that the bulk tumor mass contains a population of cells with stem-like characteristics that give rise to a di-

verse mixture of more differentiated tumor cells [2]. Recently, a CD133⁺ (prominin-1) stem cell-like population was identified in GBM [3,4]. This subpopulation of cells is multipotent, has the property of self-renewal, and can recapitulate the heterogeneity of the patient's original tumor when injected intracerebrally into immunodeficient mice [4]. Interestingly, the CD133⁺ population of GBM has been found to be selectively resistant to radiation [5] and chemotherapy [6] relative to the CD133⁻ bulk tu-

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