

REVIEW ARTICLE

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Brain tumor stem cells as research and treatment targets

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Abstract Glioblastoma multiforme (GBM) is one of the most malignant forms of human cancer. Despite intensive treatment, the mean survival of GBM patients remains about 1 year. Recent cancer studies revealed that cancer tissues are pathologically heterogeneous and only a small population of cells has the specific ability to reinitiate cancer. This small cell population is called cancer stem cells (CSCs); in brain tumors these are known as brain tumor stem cells (BTSCs). The identification of BTSCs yielded new insights into chemo- and radioresistance, by which BTSCs can survive selectively and initiate recurrence. Research focused on BTSCs as treatment targets may contribute to the discovery of new therapeutic strategies.

Key words Brain tumor stem cell · Cancer stem cell · CD133 · Side population

Introduction

After the identification of leukemia stem cells,¹ cancer stem cells (CSCs) from solid tumors, breast and brain tumors, were reported.^{2,3} CSCs are defined as cells with the ability for extensive proliferation, self-renewal, multilineage differentiation, and tumor initiation.⁴ They are concentrated in the fraction expressing specific antigen(s); however, only 0.01%–1.0% of cells even in this selected population from brain tumors can reinitiate tumors in immunodeficient mice.^{5–7} This finding suggests that the purity of brain tumor stem cells (BTSCs) is not sufficient to reveal the fine nature of bona fide BTSCs.

Clinical and basic research studies gradually led to improved outcomes in patients with brain tumors. Stupp et al.⁸ reported a mean survival of 14.6 months in glioblastoma multiforme (GBM) patients treated with radiotherapy plus temozolomide and 12.1 months in those subjected to radiotherapy alone. Earlier cancer therapies primarily targeted rapidly dividing cells but not minor populations of slowly dividing cells that contain BTSCs. Accumulating evidence suggests that BTSCs may represent an excellent tool for discovering new strategies to treat GBM patients.

In this review, we present evidence supporting the CSC model of tumor progression, and discuss difficulties encountered in CSC research and experimental and therapeutic implications.

Identification of CSCs in cancer tissues and cancer cell lines

CSCs have been identified in different types of malignancy^{1–3,5–7,9–15} and in long-term cultures of cancer cell lines^{14,16–21} (Table 1). There are two major techniques for separating CSCs from non-CSCs. One uses single or combinations of cell-surface antigens to purify CSCs from dissociated fresh cancer cells. CSCs from primary cancer samples are concentrated by cell sorting or on magnetic columns using specific immunoreactivities that are similar to those of normal stem cells found in individual somatic tissues. The other technique exploits their ability to efflux Hoechst 33342 dye; CSCs are thought to maintain their drug efflux ability, which makes it possible to separate CSCs in unstained cell fractions.^{16,22} As these cells appear on the lower left side of dot graphs analyzed by a cell sorter, they are called side population (SP) cells. In contrast, stained (non-SP) cells are viewed as non-CSCs. The drug efflux ability is neither tissue specific nor exclusive to CSCs; rather, it is considered a general function of all stem cells. Cancer cell lines maintain a small fraction of CSCs concentrated in the SP fraction.

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