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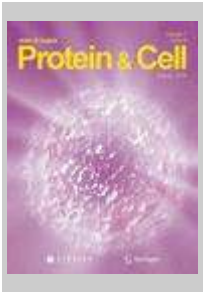

REVIEW

Cancer stem cells in glioblastoma—molecular signaling and therapeutic targeting

Zhi Huang, Lin Cheng, Olga A. Guryanova, Qiulian Wu and Shideng Bao

Abstract

Glioblastomas (GBMs) are highly lethal primary brain tumors. Despite current therapeutic advances in other solid cancers, the treatment of these malignant gliomas remains essentially palliative. GBMs are extremely resistant to conventional radiation and chemotherapies. We and others have demonstrated that a highly tumorigenic subpopulation of cancer cells called GBM stem cells (GSCs) promotes therapeutic resistance. We also found that GSCs stimulate tumor angiogenesis by expressing elevated levels of VEGF and contribute to tumor growth, which has been translated into a useful therapeutic strategy in the treatment of recurrent or progressive GBMs. Furthermore, stem cell-like cancer cells (cancer stem cells) have been shown to promote metastasis. Although GBMs rarely metastasize beyond the central nervous system, these highly infiltrative cancers often invade into normal brain tissues preventing surgical resection, and GSCs display an aggressive invasive phenotype. These studies suggest that targeting GSCs may effectively reduce tumor recurrence and significantly improve GBM treatment. Recent studies indicate that cancer stem cells share core signaling pathways with normal somatic or embryonic stem cells, but also display critical distinctions that provide important clues into useful therapeutic targets. In this review, we summarize the current understanding and advances in glioma stem cell research, and discuss potential targeting strategies for future development of anti-GSC therapies.

Keywords cancer stem cell - glioblastoma - therapeutic resistance - molecular targeting - tumor angiogenesis - hypoxia response - stem cell niche

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Cancer stem cells in glioblastoma — molecular signaling and therapeutic targeting

Zhi Huang, Lin Cheng, Olga A. Guryanova, Qiulian Wu, Shideng Bao ✉

Department of Stem Cell Biology and Regenerative Medicine, Lerner Research Institute, Cleveland Clinic, Cleveland, OH 44195, USA
✉ Correspondence: baos@ccf.org
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ABSTRACT

Glioblastomas (GBMs) are highly lethal primary brain tumors. Despite current therapeutic advances in other solid cancers, the treatment of these malignant gliomas remains essentially palliative. GBMs are extremely resistant to conventional radiation and chemotherapies. We and others have demonstrated that a highly tumorigenic subpopulation of cancer cells called GBM stem cells (GSCs) promotes therapeutic resistance. We also found that GSCs stimulate tumor angiogenesis by expressing elevated levels of VEGF and contribute to tumor growth, which has been translated into a useful therapeutic strategy in the treatment of recurrent or progressive GBMs. Furthermore, stem cell-like cancer cells (cancer stem cells) have been shown to promote metastasis. Although GBMs rarely metastasize beyond the central nervous system, these highly infiltrative cancers often invade into normal brain tissues preventing surgical resection, and GSCs display an aggressive invasive phenotype. These studies suggest that targeting GSCs may effectively reduce tumor recurrence and significantly improve GBM treatment. Recent studies indicate that cancer stem cells share core signaling pathways with normal somatic or embryonic stem cells, but also display critical distinctions that provide important clues into useful therapeutic targets. In this review, we summarize the current understanding and advances in glioma stem cell research, and discuss potential targeting strategies for future development of anti-GSC therapies.

KEYWORDS cancer stem cell, glioblastoma, therapeutic resistance, molecular targeting, tumor angiogenesis, hypoxia response, stem cell niche

INTRODUCTION

Glioblastomas (WHO grade IV gliomas) are the most common type of malignant tumors in central nervous system (CNS) in adults. Glioblastoma (GBMs) remains one of the most fatal and least successfully treated solid tumors (Furnari et al., 2007; Wen and Kesari, 2008). The median survival of GBM patients treated with multimodal therapies including surgical resection, radiation and chemotherapy is less than 16 months (Stupp et al., 2005; Furnari et al., 2007). This poor prognosis for GBM patients has not improved significantly over decades, underscoring the difficulties and challenges in effectively detecting and treating these lethal cancers. The fundamental problem of these malignancies is their highly infiltrative nature and extreme resistance to conventional treatments. Aggressive invasion of GBM cancer cells into the normal brain tissue and spinal cord often prevents complete removal of tumor cells through surgical resections. Invading cancer cells appear to be particularly resistant to current therapies and are often protected by the neurovascular niche (Furnari et al., 2007). In addition, the majority of patients suffer treatment failure within 2–3 cm of the original resection cavity, indicating that therapeutic resistance is a common feature of GBM tumors. Collectively, these difficulties have propelled the reevaluation of current treatments in order to achieve maximal efficacy with minimized toxicities or side-effects. While chemotherapy has been used for several decades in neuro-oncology, the oral DNA methylating agent temozolomide (TMZ) has shown effective when used concurrently with radiation and then as adjuvant chemotherapy such that it is now a standard practice (Stupp et al., 2005; Wen and Kesari, 2008). Several targeted therapies have been tested in trials of malignant gliomas, but to date only bevacizumab (Avastin) has been approved by the FDA to treat GBMs (Vredenburgh et al., 2007a, b; Friedman et al., 2009). Immunotherapies and