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Review

REVIEW

Novel therapies hijack the blood–brain barrier to eradicate glioblastoma cancer stem cells

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Abstract

Glioblastoma (GBM) is amongst the most aggressive brain tumors with a dismal prognosis. Despite significant advances in the current multimodality therapy including surgery, postoperative radiotherapy (RT) and temozolomide (TMZ)-based concomitant and adjuvant chemotherapy (CT), tumor recurrence is nearly universal with poor patient outcomes. These limitations are in part due to poor drug penetration through the blood–brain barrier (BBB) and resistance to CT and RT by a small population of cancer cells recognized as tumor-initiating cells or cancer stem cells (CSCs). Though CT and RT kill the bulk of the tumor cells, they fail to affect CSCs, resulting in their enrichment and their development into more refractory tumors. Therefore, identifying the mechanisms of resistance and developing therapies that specifically target CSCs can improve response, prevent the development of refractory tumors and increase overall survival of GBM patients. Small molecule inhibitors that can breach the BBB and selectively target CSCs are emerging. In this review, we have summarized the recent advancements in understanding the GBM CSC-specific signaling pathways, the CSC–tumor microenvironment niche that contributes to CT and RT resistance and the use of novel combination therapies of small molecule inhibitors that may be used in conjunction with TMZ-based chemoradiation for effective management of GBM.

Introduction

Glioblastoma (GBM) is the most common malignant brain tumor in adults (1) with a 5-year survival rate ranging from 4 to 5% (2). The standard treatment options for newly diagnosed GBM include maximal feasible surgical resection, followed by radiotherapy (RT) and temozolomide (TMZ)-based concomitant and adjuvant chemotherapy (CT) (3). Despite this multimodality therapeutic intervention, GBM is universally fatal (4). Several recent studies have demonstrated that GBM is relatively resistant to CT and RT (5–7), in part due to the presence of small subset of malignant cells called cancer initiating cells or cancer stem cells (CSCs) (6,7).

CSCs are known to have indefinite ability for self-renewal, tumor initiation and propagation (8,9). Identified in 2002 by Ignatova *et al.* (10), in surgically resected GBM, these CSCs differ from neuronal stem cells (NSCs) in the expression of specific mRNA's, such as Notch-signaling ligands Jagged-2, Delta (10), bone marrow X-linked kinase (11), nitric oxide synthase-2 (12) and genetic or karyotypic alterations (13). Furthermore, these GBM CSCs are more proliferative than NSCs and will form tumors upon orthotopic transplantation (14). In addition, GBM CSCs are resistant to CT and RT (7,15–17) and have greater oncogenic potential than differentiated tumor

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