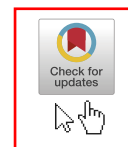


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Engineering prodrug nanoparticles for targeted therapy in heterogeneous glioblastoma

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ABSTRACT

Glioblastoma (GBM) microenvironment heterogeneity poses a major challenge to GBM therapy. Glioma stem cells (GSCs) and tumor-associated macrophages (TAMs) are important elements in the GBM microenvironment and are crucial for malignant progression. Here, we constructed prodrug nanoparticles (A-PER-p(TMZ)₂₉/Clo) containing perifosine (Akt inhibitors), an ester bond-linked poly-temozolomide (poly(TMZ)₂₉) prodrug, and clodronate (Clo) for combined approach to TAMs depletion, GSCs eradication, and activation inhibition of GBM. A-PER-p(TMZ)₂₉/Clo treatment in a mouse model of intracranial GBM significantly inhibited tumor growth and markedly extended survival. These findings suggest that A-PER-p(TMZ)₂₉/Clo provides a new strategy for therapeutic targeting of the heterogeneous glioma microenvironment.

1. Introduction

Glioblastoma (GBM) remains the most aggressive and devastating primary brain tumor that is highly resistant to conventional therapies [1,2]. Studies have shown that tumor microenvironment heterogeneity plays a key role in supporting the malignant growth and progression of GBM [3–6]. Single therapies for GBM are less effective than combined therapies. Glioma stem cells (GSCs) and tumor-associated macrophages (TAMs) are important elements in the GBM microenvironment and are a major source of relapse and chemoresistance [7]. Therefore, there is an urgent need to develop novel and effective therapeutic strategies for GBM.

About 30–50% of the cells in gliomas are TAMs, which facilitate neoplastic cell proliferation, survival, and migration [8]. Many studies have shown that TAMs promote glioma growth and invasion. In GBM, increased TAM numbers are related to poor patient prognosis [9]. TAMs can polarize to proinflammatory M1 macrophages or anti-inflammatory and immunosuppressive M2 phenotype macrophages. Reducing the density of TAMs in gliomas resulted in attenuated glioma invasion and growth [10,11]. These studies suggest that decreasing the number of


TAMs could be an effective therapeutic strategy to inhibit glioma growth [12].

GSCs are a subpopulation of glioma cells that are capable of self-renewal and differentiation [13]. Though GSCs represent a small proportion of the total tumor volume, they are thought to play a significant role in resistance and recurrence [13]. Conventional treatment with surgery, radiation, and chemotherapy may not efficiently eliminate GSCs. Indeed, the crosstalk between GSCs and TAMs makes gliomas difficult to treat by conventional therapies and exacerbates disease progression [14]. GSCs release periostin (a member of the fasciclin family and a disulfide-linked cell adhesion protein) to recruit TAMs [15]. GSCs secrete chemokines and growth factors [vascular endothelial growth factor, stromal cell-derived factor-1 (SDF1), and transforming growth factor- β 1 (TGF- β 1)] to recruit TAMs to the tumor site where they polarize into immunosuppressive M2 phenotype [16]. TAMs release a variety of cytokines and signaling molecules such as TGF- β to enhance GSC invasiveness and promote the GSC phenotype [16]. After decades of glioma cell-targeted therapies, the overall survival rate of patients with GBM has not been significantly improved. Therapies targeting GSCs therapy may improve the efficacy of glioma treatment [17].

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