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Targeting Glucocorticoid Receptor Eliminate Dormant Chemoresistant Cancer Stem Cells in Glioblastoma

Authors : Aoxue Yang, Weili Tian, Yonghe Wu, Haikun Liu

Abstract : Brain tumor stem cells (BTSCs) are resistant to therapy and give rise to recurrent tumors. These rare and elusive cells are likely to disseminate during cancer progression, and some may enter dormancy, remaining viable but not increasing. The identification of dormant BTSCs is thus necessary to design effective therapies for glioblastoma (GBM) patients. Little progress has been made in therapeutic treatment of glioblastoma in the last decade despite rapid progress in molecular understanding of brain tumors1. Here we show that the stress hormone glucocorticoid is essential for the maintenance of brain tumor stem cells (BTSCs), which are resistant to conventional therapy. The glucocorticoid receptor (GR) regulates metabolic plasticity and chemoresistance of the dormant BTSC via controlling expression of GPD1 (glycerol-3-phosphate dehydrogenase 1), which is an essential regulator of lipid metabolism in BTSCs. Genomic, lipidomic and cellular analysis confirm that GR/GPD1 regulation is essential for BTSCs metabolic plasticity and survival. We further demonstrate that the GR agonist dexamethasone (DEXA), which is commonly used to control edema in glioblastoma, abolishes the effect of chemotherapy drug temozolomide (TMZ) by upregulating GPD1 and thus promoting tumor cell dormancy in vivo, this provides a mechanistic explanation and thus settle the long-standing debate of usage of steroid in brain tumor patient edema control. Pharmacological inhibition of GR/GPD1 pathway disrupts metabolic plasticity of BTSCs and prolong animal survival, which is superior to standard chemotherapy. Patient case study shows that GR antagonist mifepristone blocks tumor progression and leads to symptomatic improvement. This study identifies an important mechanism regulating cancer stem cell dormancy and provides a new opportunity for glioblastoma treatment.

Keywords : cancer stem cell, dormancy, glioblastoma, glycerol-3-phosphate dehydrogenase 1, glucocorticoid receptor, dexamethasone, RNA-sequencing, phosphoglycerides.
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