Targeting glucocorticoid receptor eliminate dormant chemoresistant cancer stem cells in glioblastoma

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***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.

Glucocorticoids (GCs) are used to treat GBM-associated edema. However, glucocorticoids participate in the physiological response to psychosocial stress, linked to poor cancer prognosis. This raises concern that glucocorticoids affect the tumor and BTSCs.

Identifying markers specifically expressed by brain tumor stem cells (BTSCs) may enable specific therapies that spare their regular tissue-resident counterparts. By ribosome profiling analysis, we have identified that glycerol-3-phosphate dehydrogenase 1 (GPD1) is expressed by dormant BTSCs but not by NSCs. Through different stress-induced experiments in vitro, we found that only dexamethasone (DEXA) can significantly increase the expression of GPD1 in NSCs. Adversely, mifepristone (MIFE) which is classified as glucocorticoid receptors antagonists, could decrease GPD1 protein level and weaken the proliferation and stemness in BTSCs. Furthermore, DEXA can induce GPD1 expression in tumor-bearing mice brains and shorten animal survival, whereas MIFE has a distinct adverse effect that prolonged mice lifespan. Knocking out GR in NSC can block the upregulation of GPD1 inducing by DEXA, and we find the specific sequences on GPD1 promotor combined with GR, thus improving the efficiency of GPD1 transcription from CHIP-Seq. Moreover, GR and GPD1 are highly co-stained on GBM sections obtained from patients and mice. All these findings confirmed that GR could regulate GPD1 and loss of GPD1 Impairs Multiple Pathways Important for BTSCs Maintenance

GPD1 is also a critical enzyme regulating glycolysis and lipid synthesis. We observed that DEXA and MIFE could change the metabolic profiles of BTSCs by regulating GPD1 to shift the transition of cell dormancy. Our transcriptome and lipidomics analysis demonstrated that cell cycle signaling and phosphoglycerides synthesis pathways contributed a lot to the inhibition of GPD1 caused by MIFE.

In conclusion, our findings raise concern that treatment of GBM with GCs may compromise the efficacy of chemotherapy and contribute to BTSC dormancy. Inhibition of GR can dramatically reduce GPD1 and extend the survival duration of GBM-bearing mice. The molecular link between GPD1 and GR may give us an attractive therapeutic target for glioblastoma.

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

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