CHIR99021

Twenty clinical glioma samples were collected to obtain primary low-grade tumor cells. The cells were either maintained in serum-free medium as primary glioma-based cells (PGBCs) or cultured in the same medium with CHIR99021 as glioma stem-like cells (GSLCs). Then, the molecular and ultrastructural differences between the two cell groups were determined. Furthermore, the proliferation and migration of the GSLCs were examined and the potential mechanisms were investigated. Finally, temozolomide resistance in vitro and in the mouse model was assessed to study the properties of the induced GSLCs. The primary low-grade tumor cells extracted from surgical samples were enriched with GSLC properties, with high expression levels of CD133 and Nestin in 100 nM CHIR99021. The GSLCs exhibited high proliferation and migration. Furthermore, the expression of the PI3K/AKT signaling pathway and that of related genes and proteins were significantly enhanced by CHIR99021. The animal study also revealed high levels of STAT3, mTOR, NF-κB, and VEGF in the GSLC-transplanted mice. CHIR99021 could stably enhance GSLC properties in patient-derived glioma samples. It may provide a useful model for further study, helping to understand the pathogenesis of therapeutic resistance and to screen drug candidates [1)].

Pharmacological inhibition of GSK-3β with CHIR-99021 or overexpression of β-catenin reversed cordycepin-induced reduction of cell viability, downregulation of β-catenin and MGMT, increase of apoptosis and reduction of TMZ resistance. Furthermore, we found that β-catenin regulated cordycepin-induced overproduction of ROS by decreasing GSH. Inhibition of ROS production with N-acetyl-l-cysteine (NAC) not only rescued the reduction of cell viability but also eliminated β-catenin and MGMT inhibition, prevented glioma cells apoptosis and reversed the synergistic effect of cordycepin and TMZ. Taken together, we demonstrated that β-catenin contributed to cordycepin-induced MGMT inhibition and reduction of TMZ resistance in glioma cells via increasing intracellular ROS. These results indicate that cordycepin may be a novel agent to improve GBM treatment, especially in TMZ-resistant GBM with high MGMT expression [2)].

1)
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2)
Bi Y, Li H, Yi D, Bai Y, Zhong S, Liu Q, Chen Y, Zhao G. β-catenin contributes to cordycepin-induced MGMT inhibition and reduction of temozolomide resistance in glioma cells by increasing intracellular reactive oxygen species. Cancer Lett. 2018 Oct 28;435:66-79. doi: 10.1016/j.canlet.2018.07.040. Epub 2018 Aug 4. Erratum in: Cancer Lett. 2019 Oct 1;461:157-158. PubMed PMID: 30081068.