Research Paper: The Role of Protein Kinase B Signaling Pathway in Anti-Cancer Effect of Rolipram on Glioblastoma Multiforme: An In Vitro Study

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ABSTRACT

Introduction: The mechanism of putative cytotoxicity of 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidone (rolipram), a specific phosphodiesterase-4 (PDE4) inhibitor, on glioblastoma multiforme (GBM) is almost unknown. This study aimed to investigate the role of protein kinase B (Akt) pathway in the cytotoxic effect of rolipram on human GBM U87 MG cell line and Tumor-Initiating Cells (TICs) isolated from patient's GBM specimen.

Methods: TICs were characterized by using flow cytometry and quantitative real-time PCR. The cells were treated with rolipram at inhibitory concentration of 50% (IC50) in the presence or absence of SC79 (4µg/mL), a specific AKT activator, for 48 hours. The cell viability and apoptosis were measured by MTT assay and TUNEL staining, respectively. The relative expression of Phospho-Akt (Ser473), matrix metalloproteinase 2 (MMP2), and vascular endothelial growth factor A (VEGFA) were detected using Western blotting.

Results: The findings showed that rolipram could suppress cell viability in both U87MG and TICs, dose-dependently. Interestingly, the rolipram-induced cytotoxicity was significantly reduced in the presence of SC79. Nevertheless, in rolipram-treated cells, the pretreatment with SC79 significantly led to increase in U87 MG cells and TICs apoptosis and decrease in viability of U87 MG cells but not TICs relative to corresponding control. In U87 MG and TICs, rolipram-induced reduction of Phospho-Akt (Ser473) and MMP2 levels were significantly suppressed by SC79.

Conclusion: There is a cell type-specific mechanism of anti-proliferative action of rolipram on GBM cells. The reduction of intracellular level of MMP2 but not VEGFA by rolipram is conducted through the inhibition of Akt signal. Rolipram-induced apoptosis is mediated via Akt dependent/ independent mechanisms.

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