Cytocidal effects of active bufadienolide compounds against human glioblastoma cell line U-87

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Glioblastoma is the most common and lethal intracranial tumor type, characterized by high angiogenic and infiltrative capacities. To provide a novel insight into therapeutic strategies against glioblastoma, the cytotoxicity of arenobufagin and hellebrigenin, two active bufadienolide compounds, was investigated in the human glioblastoma cell line, U-87. Similar dose-dependent cytotoxicity of two drugs was observed in the cells, whereas no detectable toxicity was confirmed in mouse primary astrocytes. Treatment with each drug downregulated the expression levels of Cdc25C, Cyclin B1 and survivin, which occurred in parallel with G_2/M phase arrest. Necrotic-like cell death was only observed in the cells treated with a relatively high concentration (>100 ng/ml). These results indicate that the two drugs exhibited distinct cytotoxicity against cancerous glial cells with high potency and selectivity, suggesting that growth inhibition associated with G_2/M phase arrest and/or necrosis were attributed to their toxicities. Activation of the p38 mitogen activated protein kinase (MAPK) signaling pathway was also observed in treated cells. Notably, a specific inhibitor of p38 MAPK itself caused a significant decrease in cell viability, and further enhanced the cytotoxicity of the two drugs, suggesting an important pro-survival role for p38 MAPK. Given that p38 MAPK serves an essential role in promoting glioblastoma cell survival, developing a novel combination regimen of arenobufagin/hellebrigenin plus a p38 MAPK inhibitor may improve the efficacy of the two drugs, and may provide more therapeutic benefits to patients with glioblastoma.