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The Effects of Apigenin on Cell Proliferation and Apoptosis in Glioblastoma Multiforme

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Glioblastoma multiforme (GBM) is a WHO grade IV brain tumor. These tumors are highly proliferative, infiltrative, necrotic, angiogenic, and resistant to apoptosis. One major characteristic of GBM is the overexpression of epidermal growth factor receptor (EGFR), which leads to cell growth and proliferation when activated. GBM is very difficult to treat due to its location, heterogeneity, and invasiveness; an effective treatment is therefore needed. The use of flavonoids, which are natural compounds found in many fruits and vegetables, has been studied in the treatment of many different tumor types. Apigenin is a specific flavonoid that has previously been shown to have antitumor activity in a number of cancer cells. Our study set out to investigate the molecular effects of apigenin treatment on glioblastoma cell proliferation and viability using the trypan blue exclusion assay, MTT assay, and an LDH assay. In addition, Western blot analyses were utilized out to determine the signaling pathways through which apigenin treatment exerts its effects on cell proliferation and apoptosis. Finally, hoechst-propidium iodide staining and flow cytometry were used to examine the extent of apoptosis and the cell cycle context of these effects. Our results show that apigenin reduces cell viability and proliferation in a dose and time dependent manner while increasing cytotoxicity in GBM cells. Additionally, apigenin inhibits the EGFR mediated phosphorylation in the presence of EGF treatment of AKT, mTOR, and s6k resulting in decreased cell survival, growth and proliferation. It also inhibits the MAPK pathways in one cell line thereby reducing cell growth and proliferation. It also inhibits the anti-apoptotic effects of BCL-XL and increases PARP cleavage, which leads to increased apoptosis. Finally, apigenin induced cycle arrest at the G2M checkpoint, meaning that apoptosis primarily occurred at the DNA repair checkpoint in the cell cycle. In conclusion, apigenin has demonstrated some in vitro biological effects on glioblastoma cell lines that show promises in limiting the growth, proliferation and survival of these cell lines. Future research should look to identify means through which apigenin can be administered in clinically significant concentrations to the brain.