Characterization of Anti-Cancer properties of Fungal Metabolite Ophiobolin A

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Background: Ophiobolin A (Oph A) is a secondary metabolite and a phytotoxin produced by the pathogenic fungi *Cochliobolus heterostrophus* that causes “southern corn leaf blight” disease in maize via modulation of the calcium binding protein calmodulin. Numerous studies have found antiproliferative effects of Ophiobolin A against a variety of cells including bacteria and various cancers including melanoma, glioma and leukemia. Recent studies have shown that OphA induces paraptosis-like cell death in glioblastoma multiforme (GBM) cells via vacuolization of the cytoplasm and enlargement of the mitochondria and endoplasmic reticulum. Notably, unlike apoptosis, paraptosis cell death lacks DNA fragmentation and activation of caspases, creating a possible mechanism for targeted treatment of malignant brain tissue of GBM patients who have GBM cells that are highly resistant to pro-apoptotic treatments. This study aimed to further characterize the effects of this promising anti-cancer agent on glioblastoma (U118 and U87), breast cancer (MCF7 and T47D), neuroblastoma cells (SH-SY5Y) and rat pheochromocytoma cells (PC12). SH-SY5Y and rat PC12 commonly serve as two popular neuron models to test drug toxicity and viability.

Methods: The effects of Ophiobolin A were studied in six cancer cell lines from various tissue types including glioblastoma, breast cancer and rat pheochromocytoma cells: U87, MCF-7, T47D, U118, SH-SY5Y and PC12. Over 4 weeks, cell lines were recovered and cultured until adequate confluence was reached with subculturing and medium refreshing. Once adequate growth and attachment was confirmed with microscopy, cells were seeded in 6-well plates from 100k to 600k and treated with either DMSO or 1 µM of Ophiobolin A. Cell morphology was monitored using inverted microscope at 1 hour, 3 hours, and 6 hours following Ophiobolin A application. Cell survivability was measured using Countess at 6 hours post drug treatment.

Results: Similar to previous studies, OphA was found to induce cell apoptosis and decrease cell numbers in glioblastoma cell lines, U87 and U118. As expected, similar results were observed in the breast cancer line MCF7. The impact of Oph A on cell morphology changes demonstrated a time-dependent manner in both glioblastoma cell lines, showing elongated neuronal bodies and cell processes. In MCF7 cells, we observed increased vacuolization after drug treatment at 1 hour, 3 hours, and 6 hours. Cell survival rates were significantly reduced in all tested cancer cells in compared to the control groups.

Conclusions: Ophiobolin A has been shown to induce cell apoptosis in glioblastoma cells and breast cancer cells. The effect of OphA on healthy cells and the mechanisms underlying the OphA-induced cell apoptosis will be studied.

Citation:

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