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Disulfiram as a Cytotoxic Agent and Radiosensitizer Against Medulloblastoma

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Introduction

Medulloblastoma, the most common pediatric brain tumor, is classified into 4 molecular subgroups: WNT, SHH, Group 3 and Group 4 (1). SHH tumors constitute 30% of all medulloblastomas, with TP53 mutation significantly worsening survival. Group 3 is particularly aggressive as a consequence of its tendency to metastasize. Disulfiram (DSF), a drug developed for chronic alcoholism, has been shown to be highly cytotoxic against many tumors, especially when combined with copper (Cu) (2).

Methods

Medulloblastoma cell lines, ONS-76 (SHH Group, TP53 wild-type), UW228 (SHH Group, TP53 mutated) and D425med (Group 3), were treated with increasing concentrations of DSF as monotherapy and in combination with Cu. Analyses included CCK8 cytotoxicity, proliferation (using DSF at 100nM and DSF+Cu at 80nM), and clonogenic assays (100nM DSF and DSF+Cu). UW228 cells were exposed to DSF alone, DSF+Cu, or in combination with radiation (at doses of 0.5, 1 or 2 Gy). Nu/Nu mice with intracranial D425med were treated with oral DSF (100mg/kg) and oral Cu (2mg/kg). Results were analyzed with GraphPad Prism® and ImageJ.

Results

The IC50 for DSF was 500nM at 48 hours, while the IC50 for DCF+Cu was < 300nM for all lines ($p<0.001$). DSF significantly decreased cell proliferation at a dose of 100nM, and combination therapy at 80nM ($p<0.001$). Clonogenic assays showed a synergistic reduction in colony formation in all samples with DSF+XRT and DSF+ Cu+XRT ($p=0.0002$). The in vivo experiment confirmed safety and tolerability of our proposed treatment, and an increase in median survival was observed in the group treated with DSF+Cu.

Conclusions

DSF and Cu, two orally bioavailable compounds, exhibited remarkable efficacy and safety against medulloblastoma both in vitro and in vivo. Studies are under way to assess DSF's role as a monotherapy and radiosensitizer, possibly paving the way for future clinical applications in medulloblastoma treatment.

Learning Objectives

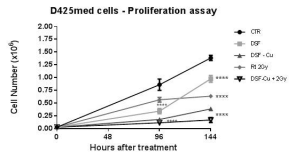
By the conclusion of this session, participants should be able to:1)understand the importance of repurposed drugs and of the combination of DSF-Cu, 2) Discuss the future implications of the data presented in this abstract, 3) Identify an effective combination of DSF-Cu and current strategies used for the treatment of medulloblastoma.

References

(1) Taylor MD. et al. Molecular subgroups of medulloblastoma: the current consensus. Acta Neuropathol., 123:465–472 (2012).

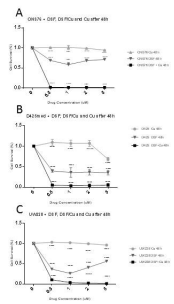
(2) Skrott, Z. et al. Alcohol-abuse drug disulfiram targets cancer via p97 segregase adaptor NPL4. Nature 552, 194–199 (2017).

D425med Proliferation assay



D425med cells were seeded at a density of 25000 cells/well and treated after 12 hours with DSF 0.1 uM, DSF + Copper 0.1 uM, Radiation 2Gy, DSF + Copper 0.1 uM + Radiation 2 Gy. Cells were counted at 96 and 144 hours post-treatment.

In Vitro Cytotoxicity assay



ONS76, D425med and UW228 cells treated with DSF, Cu and DSF + Cu for 48 hours.