Enhancing Neuroendocrine (NET) Cancer Therapy Responses via Disruption of Peroxide Balance

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Background: Cancer cells relative to normal cells are believed to exist in a chronic state of oxidative stress characterized by increased steady-state levels super oxide and peroxide produced as by-products of dysfunctional mitochondrial metabolism. It has also been shown that cancer cells, compared to normal cells, have increased labile iron and copper. These metals can participate in oxidation reactions that result in highly toxic hydroxyl radicals. Our project takes advantage of these differences using drugs that are already deemed safe for human use [ascorbate (ASC), D-penicillamine (DPEN), and disulfiram (DSF)] for killing cancer cells and enhancing traditional therapy responses.

Methods: Peroxide flux after addition of ASC, DPEN or DSF was measured in lung cancer cells using the 3 aminotriazole method. NET cell lines DMS53 (lung small cell), BON and QGP-1 (pancreatic) and H727 (bronchial carcinoid) were treated with ASC, DPEN or DSF + Cu with and without traditional therapies and clonogenic assays were performed. BON cells were grown as xenografts and the mice treated with ASC, DPEN and/or everolimus daily. Tumor volumes were measured using calipers.

Results: Pharmacologically relevant dosing of DSF, DPEN, and ASC resulted in significantly elevated fluxes of H2O2 compared to control. DPEN and DSF combined with copper resulted in a significant decrease in clonogenic cell survival in all four NET cell lines. Traditional NET therapies, everolimus and sunitinib, were both enhanced by ASC in H727, BON and QGP-1 cell. ASC or DSF+Cu significantly increased clonogenic cell death when combined with IR in DMS53 cells. ASC+everolimus delayed xenograft tumor growth without causing toxicity to the mice.

Conclusion: These observations support the hypothesis that the differences in levels of reactive oxygen species and redox active metals in cancer versus normal cells can be exploited to develop effective NET therapy using ASC, DPEN and DSF to enhance responses to standard of care therapy.

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