OFFICIAL ABSTRACT and CERTIFICATION

Enhanced Mitochondrial Reductive Stress and Cell Death Observed Via the Synergistic Effect of Glucose Starvation and Ceftriaxone/N-acetylcysteine Treatment on Human Glioma Cells

Sumaiyah Khwaja
Half Hollow Hills High School East, Dix Hills NY, United States of America

Ceftiraxone (CTX) and N-Acetylcysteine (NAC) are regarded as generally harmless substances that are commonly utilized by physicians and healthcare professionals. Both have been found to contribute to increasing intracellular concentrations of precursors of the antioxidant glutathione in glial cells. Namely, glutamate and cysteine, where CTX has the ability to upregulate Glutamate transporter protein 1, the main glutamate reuptake protein in glial cells, and NAC as the precursor to cysteine. Previous studies have shown the necessity of antioxidants in cancer cells, as the form of metabolism exhibited with oncogenic onset forces cancer cells to rely on antioxidants to alleviate stress. It has long been hypothesized that this vulnerability of cancer cells be exploited. In this study, I examined this vulnerability by increasing antioxidant concentrations within the 667 Human glioma cell line under glucose deprivation in order to induce cell death via enhanced mitochondrial reductive stress. To visualize this, I used Western blotting, L-lactate assays and a Seahorse Assay. By utilizing Seahorse Assays to visualize extracellular fluxes in oxygen concentration and pH, I viewed changes in oxygen consumption rate (OCR) and extracellular acidification rate (ECAR). By utilizing Western blots to visualize protein abundance at different locations within the cell, I looked towards increases in the glioma cell' s main glucose transporter: Glut1. Lastly, by employing a lactate assay I viewed increased glycolysis. A quantified growth model indicated the stark effects of CTX/NAC and GD on glioma cell growth, confirming my hypothesis that CTX/NAC will work synergistically with GD to cause mitochondrial reductive stress-induced cell death in glioma, as shown by the <.1% growth indicated in the model. My findings reveal the potential of CTX/NAC to become a novel therapy against glioma cells when under GD.

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