Elucidating the Mechanisms of Riluzole in GRM1+ Melanoma Cells

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Melanoma is the deadliest form of skin cancer that arises from the uncontrolled growth of transformed melanocytes. Our lab has shown that the ectopic expression of a normal neuronal receptor, metabotropic glutamate receptor 1(mGluR1/GRM1), in melanocytes leads to cellular transformation in vitro and tumor formation in vivo. GRM1 is mediated by active glutamatergic signaling upon binding of the natural ligand, glutamate, to GRM1. Previous studies have shown that treatment of GRM1+ melanoma with riluzole decreases cell proliferation and viability. Riluzole is an FDA-approved drug used to treat amyotrophic lateral sclerosis (ALS) and one of its functions is to reduce the export of glutamate to extracellular space thus decreasing the availability of glutamate to activate the GRM1 receptor. Here, we explore if riluzole inhibits the release of glutamate via the xCT antiporter. xCT exchanges intracellular glutamate for extracellular cystine at a 1:1 ratio. Cystine enters the cells and reduces to cysteine to participate in glutathione synthesis (GSH). Glutathione consists of cysteine, glycine, and glutamate and is a powerful antioxidant and prevents damage to cellular components caused by reactive oxygen species (ROS). If riluzole functions through xCT, then any modulation of xCT expression/function results in a decrease in cystine and less cysteine for GSH and therefore an increase in ROS. Results from previous findings showed an increase in ROS levels in riluzole-treated cells. In order to test whether riluzole is mediated through xCT, we used a CRISPR/CAS9 system via stable transfection to knock out the expression of xCT in both melanoma and melanocyte cell lines. The expression of xCT was verified by western blots. We will continue to assess the consequences of the xCT-null cells lines by measuring levels of glutathione, ROS, cystine/cysteine, and glutamate. Supported by the ASPET SURF Program, the Rutgers Office of Research and Economic Development, and R25ES020721.