Involvement of DNA Damage and Oxidative Stress in Differential Sensitivities to Glutamatergic Signaling Inhibitor

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Melanoma is the most threatening type of skin cancer, as it has high potential for developing metastasis resulting in poor patient outcomes. In our lab, metabotropic glutamate receptor 1 (mGluR1) has been demonstrated as a driver of melanocytic transformation in vitro and melanoma tumorigenesis in vivo. mGluR1 expression in melanocytes leads to hyperactivation of MAPK and PI3K/AKT pathways, resulting in anti-apoptotic signals and increased proliferation rates. Riluzole, an FDA approved drug for amyotrophic lateral sclerosis (ALS) and an inhibitor of glutamatergic signaling, was shown to decrease extracellular levels of glutamate, melanoma cell proliferation in vitro and tumor growth in vivo. Based on these results, several clinical trials have demonstrated that mGluR1 is a potential target for further development in melanoma therapeutic. We propose a potential mechanism of action for riluzole is by blocking xCT antiporter activity. xCT exports glutamate out of the cell in exchange for import of cystine, which is then reduced to cysteine and contributed to the synthesis of glutathione (GSH), a major antioxidant in cells. By blocking xCT, riluzole decreases available levels of cysteine, reduces GSH levels, elevates reactive oxygen species (ROS), increases DNA damage, ultimately in cell transformation and/or cell death. Previous studies showed onset of resistance to riluzole. Therefore, the current project is aiming at elucidating the mechanisms that mediate resistance to riluzole. We begin to investigate the involvement of NRF2—a regulator of oxidative homeostasis—in the onset of treatment resistance. We perform Western blots using tumor protein lysates collected from an allograft mouse model inoculated with an mGluR1-positive murine cell line and treated with different concentrations of troriluzole, a prodrug of riluzole. We also monitor levels of □H2AX—a marker of double-stranded DNA damage—to confirm if onset of riluzole treatment responses is mediated through individual's reaction to oxidative stress and DNA damage.