Regulation of Glutaminase in GRM1-Expressing Melanoma Cells

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Melanoma is the most aggressive type of skin cancer and it begins in the transformation of melanocytes. Our lab has described that the ectopic expression of metabotropic glutamate receptor 1 (GRM1) in melanocytes can transform cells in vitro and induce spontaneous melanoma formation in mice. Glutamate is the natural ligand of GRM1. Overexpression or ectopic expression of GRM1 led to excess extracellular glutamate that promotes cell proliferation in vitro and tumor progression in vivo. Recent interest in the reprogramming of tumor cell metabolisms particularly glutamine metabolism showed elevated expression of glutaminase (GLS), an enzyme responsible for conversion of glutamine to glutamate. c-Myc and c-Jun are transcription factors known to promote glutamine metabolism in many cancer cells by up-regulating GLS. We hypothesized that GLS overexpression produces excess glutamate to activate GRM1 which then induces downstream signaling cascades ultimately leading to increased tumor cell proliferation. By using western immunoblotting methods, c-Myc/c-Jun and GLS levels were found to be directly proportional to GRM1 expression. In this study, we strive to investigate whether both c-Myc/c-Jun or just one of them can alter GLS in GRM1-expressing melanoma cells. We utilized lentiviral particles (shRNA) to knockdown c-Myc expression and a JNK inhibitor (JNK-IN-8) that inhibits phosphorylation of c-Jun. Western blot analysis showed that when infecting C8161 and 1205Lu cells (GRM1+ human melanoma cells) with shMyc lentiviral particles the expression of c-Myc significantly reduced, but the GLS expression was unchanged suggesting that GLS is not under the regulation of c-Myc. Consequently, after treating 1205Lu cells with 5µM JNK-IN-8, we observed a robust decrease in c-Jun phosphorylation and a subsequent decrease in GLS expression. The experiments to confirm this observation in other melanoma cell lines are ongoing.