Effect of GRM1 Expression in Regulating HIF-1α Translation Rate and Stability

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Ectopically expressed Metabotropic Glutamate Receptor 1 (GRM1) has been previously linked to the neoplastic transformation of normal melanocytes into cancerous melanoma cells. Our group was the first to demonstrate the role of GRM1 in melanomagenesis via a transgenic mouse line, TG-3, that was prone to spontaneous melanoma development. We have hypothesized that GRM1 promotes melanocyte transformation through the formation of an autocrine loop which provides enhanced levels of extracellular glutamate to ensure constitutive activation of the GRM1 receptor. The metabolic pathways that are therefore activated through activation of GRM1 remain a topic of interest and potential research. It has been reported that GRM1 upregulates hypoxia inducible factors, including HIF-1α, which promote nutrient supply via formation of vasculature in tumors, known as angiogenesis. We studied both the stability and translation rate of HIF-1α using a pair of melanoma cell lines with differential GRM1 expression: a GRM1 expressing human melanoma cell line (C81-61 GRM1-6) and a non-GRM1 expressing cell line (C81-61). Both cell lines were treated with the following drugs to tease out the mechanism by which GRM1 upregulates HIF-1α: MG132, which blocks proteasome mediated HIF-1α degradation, was utilized to investigate HIF-1α translation rate; Cycloheximide (CHX), which blocks the translocation step during HIF-1α synthesis, was used to evaluate HIF-1α stability with and without HIF-1α stabilizer DMOG used as a positive control. It was found that for GRM1-expressing cells, the accumulation of HIF-1α protein upon MG132 treatment was marginally higher than what we saw in the GRM1-negative cells. Our preliminary results also suggest that the degradation rate and stability of HIF-1α were unaffected by the presence or lack thereof GRM1 in these cells. Another possibility may be that the concentrations of the drug treatments were not optimized enough. Supported by the ASPET SURF Program and NIH R25ES020721.