PRPS1 Lactylation by p300 Drives Nucleotide de novo Synthesis and Chemotherapy Resistance in Glioblastoma

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Glioblastoma (GBM) is the most aggressive primary brain tumor. It is associated with poor survival and frequent development of resistance to the first-line chemotherapeutic agent temozolomide (TMZ). Rapidly proliferating cancer cells depend on de novo nucleotide synthesis controlled by the rate-limiting enzyme PRPS1, which often is hyperactivated in resistant tumors. I demonstrated the enzyme p300 drives PRPS1 activation through lactylation, elucidating a potential new drug target for GBM treatment. Protein lactylation is a lactate-derived post-translational modification, playing a key role in regulating chemotherapy resistance. Lactate levels are elevated in TMZ-resistant GBM, due to increased activity of LDHA, a key glycolytic enzyme. I hypothesized that p300 promotes de novo nucleotide biosynthesis by lactylating PRPS1, facilitating its hexamer formation and activation. Increased nucleotide availability may support both rapid DNA replication and the repair of TMZ-induced DNA damage, thereby contributing to resistance. To test this, U87 and U-251 MG cells were treated with p300 or LDHA inhibitors or p300 siRNA, and assessed for PRPS1 lactylation and hexamer formation, as well as DNA replication and TMZ sensitivity. I found that inhibiting p300 or LDHA reduced PRPS1 lactylation and hexamer assembly, decreased nucleotide synthesis, and impaired DNA replication. Inhibiting p300 or LDHA, or the generation of PRPS1-lactylation deficient mutants resensitized TMZ-resistant GBM cells to TMZ again in the laboratory setting. This research highlights the critical role of lactate-driven metabolic regulation in nucleotide biosynthesis and chemotherapy resistance and suggests targeting p300-mediated PRPS1 lactylation as a promising strategy to overcome TMZ resistance in GBM.

Awards Won:

Third Award of $1,200