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GENE-43. TARGETING GABPb1L INHIBITS IN VIVO GROWTH OF TERT PROMOTER MUTANT GLIOBLASTOMA

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Abstract

Understanding cancer cell immortality in primary glioblastoma (GBM) is essential for the development of more informed treatments. Multiple cancer types, including >80% of GBMs, undergo immortalization by reactivating Telomerase Reverse Transcriptase (*TERT*) through acquired mutations in the *TERT* promoter. *TERT,* the catalytically active and rate-limiting subunit of telomerase, functions to maintain telomeres, which cap and protect the ends of chromosomes. Our past work has demonstrated that the transcription factor GABP - and specifically its tetramer-forming isoform GABPb1L - binds and activates the mutant TERT promoter. The generation of CRISPR-induced indels in GABPb1L results in a gradual loss of cell viability in *TERT* promoter mutant but not *TERT* promoter wild type tumor cells in vitro, but the extent to which GABPb1L function is compromised in this setting is unclear. Thus, the potential for use of GABPb1L as an effective therapeutic target for *TERT* promoter mutant GBM requires further investigation. Here, we use CRISPR-based strategies to demonstrate that full knockout of GABPb1L is rapidly lethal in *TERT* promoter mutant cells *in vitro*, in association with a decrease in both *TERT* mRNA and telomerase activity. Heterozygous deletion of GABPb1L in the context of *TERT* promoter mutations leads to slowed growth of orthotopic xenograft tumors in mice, and prolonged survival. Additionally, inducible RNAi-mediated inhibition of GABPb1L in growing tumors is also capable of decreasing tumor burden and increasing survival, further strongly suggesting that targeting GABPb1L in patient tumors could be a viable treatment strategy. Finally, reduced GABPb1L synergizes with temozolomide (TMZ) therapy such that TMZ treatment in the context of low GABPb1L and low *TERT* leads to a complete ablation of orthotopic GBM xenografts. These results highlight the potential to improve disease outcomes by targeting *TERT* through inhibition of GABPb1L, particularly in conjunction with TMZ treatment.

Topic: mutation, cancer, glioblastoma, cell survival, chromosomes, genes, heterozygote, protein isoforms, rna messanger, telomerase, telomere, transplantation, heterologous, growth, mice, neoplasms, transcription factor, tumor cells, temozolomide, rna interference, ablation, binding (molecular function), tumor cells, malignant, primary glioblastoma, CRISPR

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