Grand Theft Transcription Factor: Reversing Tumor Cell Immortality by Transcription Factor Relocalization

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Glioblastoma (GBM) is the most predominant malignant brain cancer in adults without prognosis improvement in decades (average survival interval of 14-17 months). Nevertheless, 83% of GBM cases have mutations in the Telomerase Reverse Transcriptase promoter (TERTp), responsible for maintaining telomeres. TERTp mutations create an ETS factor binding site, enabling the ETS transcription factor, GABP, to bind and reactivate TERT expression. While directly targeting telomerase has systematic toxicity, targeting GABP may allow for tumor-specific TERT silencing. Still, targeting transcription factors with small-molecule inhibitors is nearly impossible, so a novel approach is required. To address this, we engineered GABPB1L dominant negative (B1L-DN) transgenes by removing the transactivation (TAD-DEL) or both the TAD and the nuclear localization signal (TAD-NLS-DEL) domains. We hypothesized that with only TAD deleted, TERT expression would decrease, but the protein still could enter the nucleus. However, the DN with both NLS and TAD deleted would not enter the nucleus, ensuring the decrease of TERT expression. To test this hypothesis, we transduced GBM cells with either B1L-DN or an empty vector and measured TERT expression by RT-qPCR and protein subcellular localization with immunofluorescence staining. We observed a 70-80% decrease in TERT expression by cells expressing either dominant-negative. Furthermore, immunofluorescence staining showed that GABPA was bound to the TAD-NLS-DEL-DN and could not enter the nucleus, thus rendering GABPA futile. If we can deliver the modified TAD-NLS-DEL-DN with viruses specifically targeting cancer cells in a TERTp mutant patient, this could be a potential application to inhibit tumor growth and thereby reverse immortality.