Molecular Arsonists: Degrading Oncogenic Transcription Factors to Reverse Tumor Cell Immortality

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Glioblastoma (GBM) is the most predominant malignant brain cancer in adults without prognosis improvement in decades. Nevertheless, 83% of GBM cases have Telomerase Reverse Transcriptase promoter (TERTp) mutations, enabling the GA-binding protein (GABP) transcription factor complex to bind and reactivate TERT expression, allowing the tumor to divide indefinitely. While directly targeting telomerase has systemic toxicity, targeting GABP may allow tumor-specific TERT silencing. Because targeting transcription factors with small-molecule inhibitors is nearly impossible, a novel approach is required. Last year, a GABPB1 dominant negative was designed, reducing TERT expression in glioma cells. Still, because GABPB has multiple isoforms, it could reactivate TERT. To improve this approach, a strategy for creating biologic-based Proteolysis-Targeting Chimeras (bioPROTACs) was devised to target GABP. Using GABPA, the binding partner of GABPB isoforms, we engineered a GABPA dominant-negative by mutating key DNA-binding residues. AlphaFold3.0 was then utilized to identify the smallest GABPA capable of binding to GABPB1/2 via in-silico modeling. Finally, this minimal GABPA-DN was functionalized by attaching a Ubiquitin degrader (SPOP) or a lysosomal degrader (CMA) domain, resulting in an 80-90% decrease in TERT expression and a near-complete degradation of all GABPB1 isoforms in tumor cells. Here, I present a strategy for the creation of biologic-based therapeutics targeting oncogenic transcription factors utilizing modern machine learning algorithms, using the master regulator of mutant TERT promoter-driven tumor immortality as a proof-of-concept, providing a powerful example for the potential applications it may have in other transcription factor-regulated diseases.

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