Abstract

Glioblastoma is the most aggressive primary brain tumor and is characterized by rapid proliferation, diffuse invasion, and resistance to current therapies. Increasing evidence suggests that aberrant reactivation of developmental transcription factors contributes to GBM progression. This study investigated the role of Transcription Factor 241 (TF241) and its conserved TFH1 and TFH5 domains in transcriptional regulation within U87-MG GBM cells, with particular focus on identifying potential downstream target genes and determining the contribution of these domains to TF241 regulatory activity. Wild-type TF241 and TFH1/TFH5 deletion constructs were generated and transiently expressed in U87-MG cells, followed by quantitative PCR analysis of candidate target genes associated with cell fate regulation, tumor invasion, and tumor microenvironment/metabolic regulation. Among the genes analyzed, CCN4, CDKN1A, and PLEKHN1 demonstrated the most notable expression trends. TF241 overexpression strongly increased CCN4 expression, whereas deletion of either TFH1 or TFH5 reduced CCN4 expression, suggesting that these domains contribute to TF241-mediated transcriptional regulation and may be required for full activation of invasion-associated target genes. Increased CDKN1A expression following TFH deletion suggested reduced repression of p21-mediated growth arrest pathways, while altered PLEKHN1 and CCN4 expression patterns indicated that TF241 may exert context-dependent regulatory effects depending on target gene and domain integrity. Collectively, these findings suggest that TF241 does not function exclusively as either a transcriptional activator or repressor, but rather exhibits transcriptional duality, with the TFH1 and TFH5 domains contributing to both activation- and repression-associated regulatory activities. The findings provide preliminary evidence that the TFH1 and TFH5 domains contribute to TF241-dependent transcriptional regulation and support a role for these domains in modulating gene networks relevant to glioblastoma progression.

Keywords: *glioblastoma, transcriptional regulation, TF241, downstream signaling*