

Biophysical characterization of the interaction between Forkhead Box O4 (FOXO4) and p53 transcription factors

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The transcription factor p53 controls numerous cellular processes including apoptosis, senescence, DNA repair, and tumor suppression [1]. The function of p53 is closely intertwined with Forkhead box O (FOXO) transcription factors and FOXO protein regulates cellular functions such as cellular homeostasis, oxidative stress resistance, metabolism, and longevity. FOXO protein family has four members: FOXO1, FOXO3, FOXO4, and FOXO6 wherein their activity is tightly regulated by post-translation modification (phosphorylation, acetylation, methylation, and ubiquitination) [2]. The previous study has demonstrated that the physical interaction between FOXO4 and p53 represses apoptosis of senescent cells by upregulating the transcription of p21 gene and maintain the viability of senescent cells [3]. However, the structural aspects of FOXO4:p53 complex formation remain unclear. Therefore, we designed several truncated constructs of FOXO4 and p53 to elucidate the structural details of this complex using analytical ultracentrifugation, NMR, chemical cross-linking, and molecular docking. Our data suggest that the transactivation domain (TAD) of p53 and DNA binding domain of FOXO4 provide overall stability of the complex along with the transient interaction from other regions of FOXO4 and p53. Furthermore, FOXO4:p53 complex formation does not affect the DNA binding affinity of FOXO4, thereby this interaction presumably allows co-localization of both FOXO4 and p53 transcription factors in the promoter region. Our finding further promotes future research for drug development aiming for the selective elimination of senescent cells.

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