Notification No: **575/2025**
Date of Award: **11/02/2025**

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Topic of Research: **Role of PIH1D1 component of R2TP complex in Cell Cycle**

Findings

The R2TP complex is a highly conserved Hsp90 co-chaperone complex composed of RUVBL1, RUVBL2, PIH1D1, and RPAP3, known for its critical role in the assembly and stabilization of several multi-protein complexes. In this study, we investigated the interaction between PIH1D1 and p53, a key tumor suppressor frequently mutated in cancer. Our findings demonstrate, for the first time, that PIH1D1 directly interacts with and stabilizes both wild-type and mutant p53 proteins, thereby influencing cell cycle regulation and p53-mediated signaling pathways. Although PIH1D1 typically recognizes CK2-phosphorylated DpSDD/E motifs, our results revealed that p53 interaction occurs independently of its C-terminal CK2 phosphorylation site, suggesting broader substrate specificity of PIH1D1. Knockdown of PIH1D1 in MCF7 and T98G cells significantly reduced p53 and p21 expression and caused accumulation of cells in G1 and S phases, indicating impaired cell cycle progression. Furthermore, mutant p53 displayed enhanced stability compared to wild-type p53. In-silico analyses revealed elevated PIH1D1 expression across multiple cancers and significant associations with immune cell infiltration and clinical parameters, highlighting its potential prognostic and therapeutic relevance in cancer biology.