

[Index No.: 32/17/Life Sc./25]

Thesis title:

“The role of FKBP51 in P-TEFb mediated Transcriptional Regulation in Eukaryotes”

Abstract:

Although a number of recent studies have found a substantial link between FKBP51 (also known as FKBP5) functions and a variety of diseases including many cancer types, stress-related mental diseases etc., the overall mechanistic processes remain unknown. A few studies has been done revealing its participation in glucocorticoid receptor and AKT signaling pathways regulation but other functional activities contributing in its involvement in disease progression (if any) are unknown. We show that human FKBP51 has an anti proliferative effect via negatively regulating the expression of proliferation-related genes. We show that, due to the overlapping interaction site on CDK9, human FKBP51 competes directly with CyclinT1 for the formation of a functional positive transcription elongation factor b (P-TEFb) complex. *In vitro* biochemical experiments combined with cell-based studies revealed that FKBP51 has a substantial inhibitory effect on P-TEFb-mediated phosphorylation of a variety of substrates. FKBP51 knockdown resulted in increased P-TEFb complex formation, which led to increased phosphorylation of the global RNA polymerase II C-terminal domain (CTD), expression of proliferation-related genes, and consequent proliferation. As a consequence, our findings suggest that FKBP51 plays a crucial role in the negative control of P-TEFb activities in mammalian cells.

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