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Biophysical characterization of p53 regulation by the mRNA export factor-THOC4

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Background: The p53 tumour suppressor protein is a transcription factor (TF) and regulates the transcription of target genes involved in cellular processes like DNA damage repair, cell cycle arrest, apoptosis, and senescence. Its activity is regulated by cofactors including certain RNA-binding proteins (RBPs). Examples involve, RBPs like, SUMOylated hnRNP K, which regulates the transcriptional activity of p53 via direct interaction and CIRBP, which regulates p53 activity and to inhibit DNA damage-induced apoptosis. Previously, our lab found that the RG/RGG repeat region of CIRPB directly interacts with the transactivation domain (TAD) of p53. The RG/RGG region containing RBP, THOC4/ALYREF which is responsible for nuclear export of mRNA in the THO complex, is also known to interact with, and regulate the activity of multiple TFs like MYCN, E2F2, LEF-1 AND AML-1. Considering the proclivity of THOC4 towards regulation of TF activity, we aim to: 1) Unravel the molecular determinants and functional implications of the interaction between p53 and THOC4 2) Study the implications of post-translational modifications on this interaction Results/Methods: 1) NMR titration show that the N- and C-terminal RG/RGG regions of THOC4 and the TAD of p53 directly bind with each other. ITC experiments reveal that the THOC4 N-terminal RG/RGG region is the strongest binding site for p53 TAD. 2) Since RG/RGG regions are regulated by arginine methylation, we in-vitro arginine methylated both RG/RGG regions of THOC4 with PRMT1. Strikingly, and in contrast to the impact of arginine methylation in the context of RNA-binding, methylation of the THOC4 N-terminal region enhances binding to p53 TAD Conclusions: 1) Both RG/RGG regions of THOC4 bind to p53 TAD and arginine methylation enhances this interaction 2) As the TAD of p53 is essential for the transcriptional activation activity of p53, its interaction with THOC4 might affect the transcription of p53 targets in cells and in turn p53 function