

Dynamics Characterization of Tah1- a TPR Protein Interacting with HSP90.

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Tah1 contains two tetratricopeptide repeat (TPR) domains. TPR is a 34-amino-acid repeat motif that is found in many diverse proteins in all organisms and forms a helix-turn-helix structure. TPR family members usually bind specific peptide ligands and are thought to mediate protein-protein interactions in a variety of biological systems.¹ Tah1 is formed by two tandem TPR repeats and it has been shown to bind the C-terminal end of HSP90, which is a ubiquitous molecular chaperone found in eubacteria and all branches of eukaryotes. Considerable differences in the recognition mechanism between TPR domains and Hsp90 have been described.²

In this work, we have performed structural studies of Tah1, both free and in complex with a five-aminoacid peptide corresponding to the C-terminal end of HSP90. The aim of the project is to characterize the structural differences between the free and the bound forms of Tah1 and to translate this information to the design of compounds able to inhibit this interaction, thereby modulating epigenetic gene regulation. We have investigated the interaction between Tah1 and Hsp90 via 2D ¹⁵N-filtered, and 3D ¹H, ¹⁵N-HSQC NOESY experiments. We have also performed mobility studies of Tah1 protein interacting with the C-terminus of Hsp90. In our hands the protein has two different mobility motives and favors dimerization. It has been previously shown using chimeric proteins that the more domains TPR proteins have, the more stable they are.³ This tendency for dimerization is justified considering that Tah1 is the smallest TPR protein described to date. Additionally, it is expected, based on studies performed in chimeric proteins [3], that the mobility of the two structural domains would be similar in the free protein, while the binding to the MEEVD peptide should produce changes in dynamics between the two TPR motives as well as in the binding site.

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