NMR reveals changes of Hsp90 dynamics upon ligand binding

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Hsp90 is a major cellular chaperone required to maintain cellular homeostasis and to buffer genetic variation. Hsp90 is a homodimer of 180kDa which stabilizes client proteins in an ATP dependent cycle. It was found to be important in stabilization of many signaling proteins such as kinases and nuclear hormone receptors, also implicated in cancerogenesis. Several pharmacophores were found to inhibit the hsp90 in an ATP competitive manner. The cellular efficacy of hsp90 inhibitors was found to be correlated with the inhibitor residence time, a lifetime of the protein-drug complex [1], which is related to the dissociation rate constant k_{off}.

The molecular determinants of the protein-ligand half time are not fully understood yet. Beside the ligand physico-chemical properties, the conformational dynamics of both, protein and ligand, play a role in protein-ligand lifetime [2, 3]. In our work, we focus on the comparison of dynamics of Hsp90-NTD in apo- and two ligand bound forms. We show that ligand binding modulates the dynamics of target protein residues located near the binding center, but we also identify sites distant from ligand binding site with dynamics modulated remotely by the binding of the ligand, suggesting presence of allosteric effects. Furthemore, while the two ligands are of similar structures and of comparable K_d, they differently modulate the dynamics relative to the apo- Hsp90. These results give a structural basis to understand how protein target motions can modulates kinetics and thermodynamic properties of potential drug candidates.

References

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