Inhibiting protein-protein interactions in HSP90 dimerization as a novel approach for targeting cancer

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HSP90 (heat shock protein of 90 kDa) is a molecular chaperone intervening in protein folding and in refolding processes taking place after stress stimuli. In eukaryotes, HSP90 is essential for cell viability and growth, tuning the function of several regulatory and signaling client proteins [1]. Several studies demonstrated an involvement of HSP90 in cancer, stabilizing oncogenic proteins and allowing malignant transformation [2]. Clinical studies on small molecules acting as HSP90 inhibitors established HSP90 as an attractive and validated target for cancer therapy [3, 4]. On a structural side, HSP90 is a homodimer, each monomer consisting of three domains: an N-terminal ATP binding domain, a middle domain, and a C-terminal dimerization domain, responsible for the permanent association of the two monomers [1]. Most of the known HSP90 inhibitors act by binding at the N-terminus, impeding ATP binding and hydrolysis, therefore blocking the chaperone activity. None of the inhibitors so far reported target the dimerization of the HSP90, however. Thus, the aim of this project is to characterize determinants of the dimerization of human HSP90 and to use this information to develop α-helix mimetics and non-peptidic small-molecules disrupting HSP90 dimerization. For this, we first generated a homology model of the human HSP90. The homology model obtained was subjected to molecular dynamics simulations, and the conformational ensemble generated was used for the identification of residues mostly involved in the dimer formation, (hot spots). For this purpose, *in silico* alanine scanning using DrugScore^{PPI} and binding energy decomposition on a per-residue level using MM-GBSA were performed. Remarkably, results from the two approaches were convergent, suggesting that eight amino-acids located at the dimer interface account for the highest contribution to the binding free energy. Utilizing this information, short peptides derived from the interface are currently being designed that should inhibit dimerization. Furthermore, the hot spot information is used to guide the design of α-helix mimetics and the screening of non-peptidic small molecules directed to the dimerization interface of the protein.

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