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Editorial Open Access

Structure Based Drug Design for Heat Shock Proteins

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Editorial

Structure-activity relationships derived researchers to perturb conformational alteration mechanisms of proteins. Determining structure of a protein by NMR or X-Ray is not feasible all the time; physical barriers such as higher molecular weight of the proteins, crystallization problems, aggregation of proteins may prevent determining structure of a protein. However, expression of partial structure of a particular protein (a subdomain or allosteric region) of interest may also provide essential structural information including conformational changes, binding, inhibition constant, and stability.

Alternatively, transformation of proteins from primary sequence to three dimensional structure provides some insights to structural biologist. Conserved sequence of proteins may yield similar structure and deposition of protein structures to databases helps computer based structural determinations to build algorithms and to predict three dimensional structures from primary sequences.

In silico analysis of the proteins not only predicts three dimensional structures but also provides protein-protein and protein-drug interactions. Structural information and in silico analysis data provides a starting point to drug design research and several thousands of drug candidates may be reduced to manageable quantities for further evaluations and tests.

Protein structure is a key to drug design and Heat Shock Proteins (Hsps) chaperone structure of a protein. Hsps maintain substrate protein structure in a properly folded state so that the substrate protein can perform its function [1]. Several stress factors including heat, drugs, parasites, malignancy, infectious factors, and oxidative stress may disrupt protein structure and Hsps maintain substrate proteins in their native state [2]. If Hsps chaperoning activity fails, then cells go to apoptosis. This unique information can be used to design innovative drugs and drug designers have been used to build innovative drugs just because of this strategy.

In spite of this information, Hsps consist of diverging set of subclass proteins. The subclass of Hsps are namely Hsp27, Hsp40, Hsp60, Hsp70, Hsp90, Hsp100, and small Hsps. These Hsps coordinate and cooperate to form different cellular functions. Hsps have several biochemical roles besides their protein folding function [3]. So, how researchers pick an Hsp to design an inhibitor? Hsp network has key components and these are located at the heart of substrate protein folding machinery namely Hsp70 and Hsp90. Both of them have ATPase domain where they hydrolyze ATP and substrate binding domain to fold substrate proteins to their native state. But Hsp70 only process seven residues at a time and Hsp90 can process a relatively big unfolded protein at time [4]. Hsp70 locally fold substrate protein and submit it to Hsp90 for an overall folding.

Thus, Hsps coordinate and cooperate via Hop protein. Nucleotide exchange factors take ADP from ATPase pocket to regenerate another cycle and this help another ATP hydrolysis. ATP hydrolysis provides energy for entrapping the substrate. Since Hsp70 and Hsp90 are key components of the folding machinery, several researchers designed Hsp90 inhibitors and most of them are in clinical trials. Hsp90 ATPase domain is an easy target to hold and stop Hsp90 function.

To stop Hsp90 function several ATPase inhibitors were designed. Geldanamycin is the first inhibitor in the drug market but has solubility problems. Therefore, derivatives of this compound generated and clinical trials are underway [4]. Hsp inhibitors especially in anticancer agents draw attention of the researchers [5].

Our lab designed C-terminal inhibitor rather than and ATPase inhibitor for Hsp90. This inhibitor basically prevents Hsp90 dimer formation. The dimer cavity holds the substrate protein in and hydrophobic nature of this cavity provide an environment to substrate protein to fold properly. Inhibition of dimer formation by our inhibitor at the hinge region of Hsp90 per turb dimer formation and disrupt Hsp90 function.

Recently it was determined that, inhibition of Hsp90 induces Hsp70 expression and Hsp70 complements Hsp90 substrate protein folding function. Therefore, researchers decided to inhibit Hsp70 function as well.

The first target was thought to be ATPase domain but compared to Hsp90, Hsp70 ATPase domain is deeper and has hydrophilic character. Drug candidates for this region were not promising yet and does not meet Weber-Lipinski criteria. In our lab, we decided to target HSP70 substrate protein domain and designed an inhibitor for this region explicitly. The inhibitor efficiently inhibits Hsp70 as evidenced by several biochemical and biophysical experiments. Combination of both Hsp90 and Hsp70 inhibitors provided superior results compared to the competitors.

Hsp70 inhibitor not only binds to Hsp70 substrate binding region but also binds to the interface of Hsp70 interacting proteins. This is way our Hsp70 inhibitor completely kills cancer cells and patent pending for the Hsp70 compound as anticancer-agent.

In conclusion, Hsp90 and Hsp70 display different character for inhibition due to their unique structures. ATPase domains of each protein differ and designing an inhibitor requires strict knowledge of protein structure.

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