IDENTIFICATION OF POTENTIAL INHIBITORS OF HSP70-HSP90 ORGANIZING PROTEIN (HOP), A MULTIFACETED CO-CHAPERONE INVOLVED IN MULTIPLE DISEASES

Abstract

HSP70-HSP90 organizing protein (HOP), also identified as Stress-induced phosphoprotein (STIP1) is a 62.639 kDa eukaryotic co-chaperone that plays a crucial role in the transfer of substrate protein from HSP70 to HSP90 for their folding and functional activation. Some of the major interacting proteins of HOP are molecular chaperones (HSPA4, HSP90AA1, HSP90AB1, HSPA8, AHSA1, DNAJB1, CDC37 and HSPA1L), Prostaglandin E synthase 3 (PTGES3) and major prion protein (PRNP). Apart from acting as the co-chaperone, the overexpressed and secreted form of HOP is known for mediating autocrine and paracrine signalling, promoting tumor growth and metastasis in renal carcinoma and hepatocellular carcinoma. The secreted HOP interacts with cellular prion protein (PRPC) and ALK2-SMAD15 on the surface of glioblastoma stem-like cells and ovarian cancer cells and thereby signalling them for proliferation. Inhibiting / neutralizing extracellular HOP or knocking down of intracellular HOP has been shown to reduce the tumor growth in xenograft mouse models. Following this approach, some groups have identified a few inhibitors that target the interactions between HOP and HSP90, however, targeting this complex as a therapeutic approach is largely less explored. Here, in this study, we have modeled the structure of HOP using various computational tools. HOP is known to promote the ATPase activity of HSP70 and inhibit the ATPase of HSP90 during the substrate transfer. However, HOP itself has a weak ATPase activity, though the exact mode of ATP binding and the activity thereof is less known. We tried to identify the ATP binding site on HOP using structure and sequence-based approaches and compared the ATP binding site on HOP with AMP-PNP and GTP binding as well using molecular docking, and molecular dynamics simulations. Thereafter, we tried to screen the library of 3500 FDA approved drugs for repurposing against different domains of HOP, from which we identified top 10 candidates Atovaquone, Bicalutamide, Celecoxib, Dexamethasone, Glimepiride, Imipenem, Indinavir, Saxagliptin, Tadalafil and Tarceva (Erlotinib) out of which Indinavir and Tarceva were

of more interest. These compounds were further subjected to network pharmacology where around 321 common gene targets were identified which are involved in cancer. In addition to that, we tried to elucidate the role of different domains of HOP in interaction with prion protein and identified key residues mediating the binding between HOP and Prion protein. Previous studies have reported the interaction of prion with the TPR1, DP1 and TPR2A domain of HOP. This study identified the role of TPR2B and DP2 domains of HOP in stabilizing the interactions of HOP with the Prion protein. The prion peptide was binding to the TPR2A domain while prion protein interacted with TPR2A and TPR2B-DP2 domain as well. The presence of Tarceva restricted the interaction of Prion with TPR2A domain of HOP while addition of Indinavir along with Tarceva favoured the interaction of Prion protein with TPR2A and TPR2B-DP2 domain of HOP. The effect of Melittin binding was observed on the interactions between HOP and prion peptide/prion protein. While Melittin binding to TPR1 domain of HOP resulted in complete detachment of prion peptide with HOP, it also reduced the affinity between HOP and Prion protein and restricted the interaction of Prion with the TPR2B-DP2 domain of HOP. Hence, further experimental validations are required to validate the inhibitory role of Tarceva and Melittin in preventing the protein-protein interactions between HOP and Prion protein.