

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

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**KUSUMA SCHOOL OF BIOLOGICAL SCIENCES
INDIAN INSTITUTE OF TECHNOLOGY DELHI**

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Protein (Hop), A Multifaceted Co-Chaperone Involved In Multiple
Diseases**

by

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KUSUMA SCHOOL OF BIOLOGICAL SCIENCES

Submitted

in fulfillment of the requirements of the degree of Doctor of Philosophy
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CERTIFICATE

This is to certify that the thesis entitled “Identification of Potential Inhibitors of HSP70-HSP90 Organizing Protein (HOP), a multifaceted co-chaperone involved in multiple diseases” being submitted by Mr. Gagandeep Singh to the Kusuma School of Biological Sciences, Indian Institute of Technology Delhi for the award of the degree of “Doctor of Philosophy” is a record of the bonafide research work carried out by him, prepared under my supervision, in conformity with the rules and regulations of the ‘Indian Institute of Technology Delhi’. The research report and the results present in the thesis have not been submitted to any other University or Institute for the award of any other degree or diploma.

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"The journey of a thousand miles begins with one step." - Lao Tzu

This ancient wisdom aptly describes the PhD journey - a long and challenging path that starts with a single question and unfolds into years of discovery, perseverance, and growth.

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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.

सार

HSP70-HSP90 ऑर्गनाइजिंग प्रोटीन (HOP), जिसे स्ट्रेस-इंड्यूस्ड फॉस्फोप्रोटीन (STIP1) के रूप में भी पहचाना जाता है, एक 62.639 kDa यूकेरियोटिक सह-संरक्षक है जो HSP70 से HSP90 तक सबस्ट्रेट प्रोटीन के हस्तांतरण में उनकी तह और कार्यात्मक सक्रियण के लिए महत्वपूर्ण भूमिका निभाता है। HOP के कुछ प्रमुख इंटरैक्टिंग प्रोटीन आणविक चैपरोन (HSPA4, HSP90AA1, HSP90AB1, HSPA8, AHSA1, DNAJB1, CDC37 और HSPA1L), प्रोस्टाग्लैंडीन ई सिंथेस 3 (PTGES3) और प्रमुख प्रियन प्रोटीन (PRNP) हैं। सह-संरक्षक के रूप में कार्य करने के अलावा, HOP का अति-अभिव्यक्त और स्रावित रूप ऑटोक्राइन और पैराक्राइन सिग्नलिंग की मध्यस्थता के लिए जाना जाता है, जो रीनल कार्सिनोमा और हेपेटोसेलुलर कार्सिनोमा में ट्यूमर के विकास और मेटास्टेसिस को बढ़ावा देता है। स्रावित HOP ग्लियोब्लास्टोमा स्टेम जैसी कोशिकाओं और डिम्बग्रंथि के कैंसर कोशिकाओं की सतह पर सेलुलर प्रियन प्रोटीन (PRPC) और ALK2-SMAD15 के साथ परस्पर क्रिया करता है और इस प्रकार उन्हें प्रसार के लिए संकेत देता है। बाह्य कोशिकीय HOP को रोकना / बेअसर करना या अंतःकोशिकीय HOP को खत्म करना ज़ेनोग्राफ़्ट माउस मॉडल में ट्यूमर के विकास को कम करने के लिए दिखाया गया है। इस दृष्टिकोण का अनुसरण करते हुए, कुछ समूहों ने कुछ अवरोधकों की पहचान की है जो HOP और HSP90 के बीच की अंतःक्रियाओं को लक्षित करते हैं, हालांकि, इस परिसर को एक चिकित्सीय दृष्टिकोण के रूप में लक्षित करना काफी हद तक कम खोजा गया है। यहां, इस अध्ययन में, हमने विभिन्न कम्प्यूटेशनल उपकरणों का उपयोग करके HOP की संरचना का मॉडल तैयार किया है। HOP को HSP70 की ATPase गतिविधि को बढ़ावा देने और सबस्ट्रेट स्थानांतरण के दौरान HSP90 के ATPase को बाधित करने के लिए जाना जाता है हमने संरचना और अनुक्रम-आधारित तरीकों का उपयोग करके HOP पर एटीपी बंधन स्थल की पहचान करने की कोशिश की और आणविक डॉकिंग और आणविक गतिशीलता सिमुलेशन का उपयोग करके HOP पर एटीपी बंधन स्थल की तुलना AMP-PNP और GTP बंधन से की। इसके बाद हमने HOP के

विभिन्न डोमेन के विरुद्ध पुनः प्रयोजन के लिए 3500 FDA अनुमोदित दवाओं की लाइब्रेरी की स्क्रीनिंग करने की कोशिश की, जिसमें से हमने शीर्ष 10 उम्मीदवारों एटोवाक्वोन, बिकालुटामाइड, सेलेकोक्सिब, डेक्सामेथासोन, ग्लिमैपिराइड, इमिपेनम, इंडिनवीर, सैक्सग्लिप्टिन, तडालाफिल और टारसेवा (एर्लोटिनिब) की पहचान की, जिनमें से इंडिनवीर और टारसेवा अधिक रुचि के थे। इन यौगिकों को आगे नेटवर्क फार्माकोलॉजी के अधीन किया गया जहां लगभग 321 सामान्य जीन लक्ष्यों की पहचान की गई जो कैंसर में शामिल हैं पिछले अध्ययनों में HOP के TPR1, DP1 और TPR2A डोमेन के साथ प्रियन की अंतःक्रिया की रिपोर्ट की गई है। इस अध्ययन ने HOP के TPR2B और DP2 डोमेन की भूमिका की पहचान की है, जो HOP के प्रियन प्रोटीन के साथ अंतःक्रिया को स्थिर करने में मदद करता है। प्रियन पेप्टाइड TPR2A डोमेन से जुड़ रहा था, जबकि प्रियन प्रोटीन TPR2A और TPR2B-DP2 डोमेन के साथ भी अंतःक्रिया कर रहा था। टारसेवा की मौजूदगी ने HOP के TPR2A डोमेन के साथ प्रियन की अंतःक्रिया को सीमित कर दिया, जबकि टारसेवा के साथ इंडिनवीर को शामिल करने से HOP के TPR2A और TPR2B-DP2 डोमेन के साथ प्रियन प्रोटीन की अंतःक्रिया को बढ़ावा मिला। HOP और प्रियन पेप्टाइड/प्रियन प्रोटीन के बीच अंतःक्रिया पर मेलिटिन बाइंडिंग का प्रभाव देखा गया। जबकि मेलिटिन के HOP के TPR1 डोमेन से जुड़ने से HOP के साथ प्रियन पेप्टाइड का पूर्ण पृथक्करण हुआ, इसने HOP और प्रियन प्रोटीन के बीच आत्मीयता को भी कम कर दिया और HOP के TPR2B-DP2 डोमेन के साथ प्रियन की अंतःक्रिया को सीमित कर दिया। इसलिए, HOP और प्रियन प्रोटीन के बीच प्रोटीन-प्रोटीन अंतःक्रिया को रोकने में टारसेवा और मेलिटिन की निरोधात्मक भूमिका को मान्य करने के लिए आगे के प्रयोगात्मक सत्यापन की आवश्यकता है।

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ABBREVIATIONS & SYMBOLS

~	Approximately
°C	Degree Celsius
3D	Three-dimensional
Å	Angstrom
ADP	Adenosine diphosphate
ATP	Adenosine triphosphate
AMP-PNP	Adenylyl-imidodiphosphate
AMBER	Assisted Model Building with Energy Refinement
ATP	Adenosine Triphosphate
CTD	Carboxy Terminal Domain
GROMACS	GRoningen Machine for Chemical Simulations
GTP	Guanosine Triphosphate
HCC	Hepatocellular Carcinoma
HS	Heat Shock
HSR	Heat Shock Response
Hsp90	Heat Shock Protein 90
hHsp90	Human Heat Shock Protein 90
kDa	KiloDalton
mg	Milligram
min	Minute
ml	Millilitre

mM	millimolar
mol. wt.	Molecular weight
Na ⁺	Sodium Ion
Cl ⁻	Chloride Ion
nM	nanomolar
nm	Nanometre
NTD	Amino-terminal domain
PDB	Protein data bank
RCSB	Research Collaboratory for Structural Bioinformatics
RMSD	Root Mean Square Deviation
RMSF	Root Mean Square Fluctuation
Rg	Radius of Gyration
SASA	Solvent Accessible Surface Area
T	Temperature in degree Celsius
ΔG	Free energy change
ΔH	Change in Enthalpy
ΔS	Change in Entropy
μM	micromolar