

STIP1(HOP) binds HSP90 and HSP70:HSP40:nascent protein

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references

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Reactome database release: 88

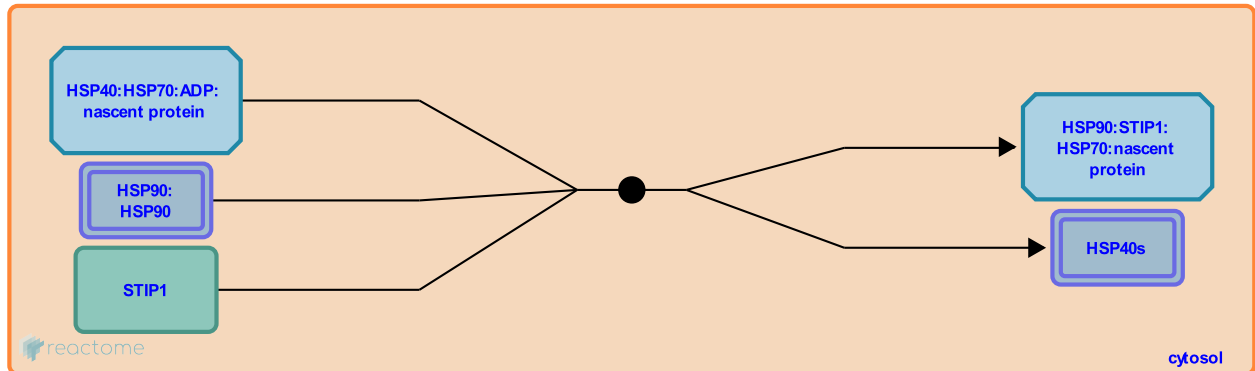
This document contains 1 reaction ([see Table of Contents](#))

STIP1(HOP) binds HSP90 and HSP70:HSP40:nascent protein ↗

Stable identifier: R-HSA-3371503

Type: binding

Compartments: cytosol



Stress-induced phosphoprotein 1 (STIP1, also known as HSP70-HSP90-organizing protein or HOP) functions as a mediator of interaction between heat shock protein (HSP)70 and HSP90 as part of the cellular assembly machine. It also modulates the ATPase activity of both HSP70 and HSP90, thus facilitating client protein transfer between the two. STIP1 is a monomeric protein composed of three tetratricopeptide repeat domains (TPR1, TPR2A, TPR2B) involved in protein-protein interactions, and two small aspartic acid-proline repeat domains (DP1, DP2) involved in client activation (Scheufler C et al. 2000; Nelson GM et al. 2003; Yi F et al. 2010; Schmid AB et al. 2012). A flexible linker of STIP1 (HOP) connects TPR1-DP1 and TPR2A-TPR2B-DP2 modules arranging it as TPR1-DP1-TPR2A-TPR2B-DP2 (Scheufler C et al. 2000). Biochemical and crystallographic analysis revealed that TPR domains of STIP1 interact specifically with C-terminal MEEVD motifs of HSP70 or HSP90 chaperones; TPR2A binds preferentially to HSP90, whereas TPR1 and TPR2B bind to HSP70 (Scheufler C et al. 2000; Carrigan PE et al. 2006; Schmid AB et al. 2012). Furthermore, cryoelectron microscopy (cryo-EM) reconstruction of the human HSP90:STIP1 complex revealed that STIP1 may also form interactions in several other parts of HSP90, pre-organizing N-terminal domains (NTDs) of HSP90 and thus increasing accessibility of the nucleotide-binding pocket (Southworth DR & Agard DA 2011). STIP1 stabilizes an alternate HSP90 open state where hydrophobic client-binding surfaces of HSP90 monomers have converged remaining accessible for client loading (Southworth DR & Agard DA 2011). STIP1 is positioned with a TPR1 domain extending from the HSP90 dimer cleft remaining available for an interaction with HSP70. In the STIP1-stabilized HSP90 conformation the N-terminal domains have rotated to match the closed ATP conformation. However, the arrangement of the STIP1 domains in the complex seems to prevent the NTDs dimerization of HSP90 monomers and total closure of the HSP90 dimer that is required for an efficient HSP90-mediated ATP hydrolysis (Southworth DR & Agard DA 2011; Alvira S et al. 2014). HSP70, in the ADP state, readily binds HSP90:STIP1, forming a client-loading complex HSP90:STIP1:HSP70:client protein (Hernández MP et al. 2002). Structural studies of GR-LBD (the ligand-binding domain of the glucocorticoid receptor) bound to HSP90:STIP1:HSP70 complex showed that one STIP1 molecule binds to the HSP90 dimer and through domain rearrangement, gives rise to two main conformations, an extended structure that recognizes and interacts with HSP70, and a compact one in which HSP70 is in contact with one HSP90 monomer (Alvira S et al. 2014). Movement between these two modes is thought to deliver the HSP70-bound substrate to the side of the HSP90 dimer opposite the site of STIP1 binding (Alvira S et al. 2014). Following client delivery by HSP70 and STIP1 release, HSP90:ATP converts to the closed ATP hydrolysis-active state to complete the chaperone cycling.

Literature references

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Editions

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