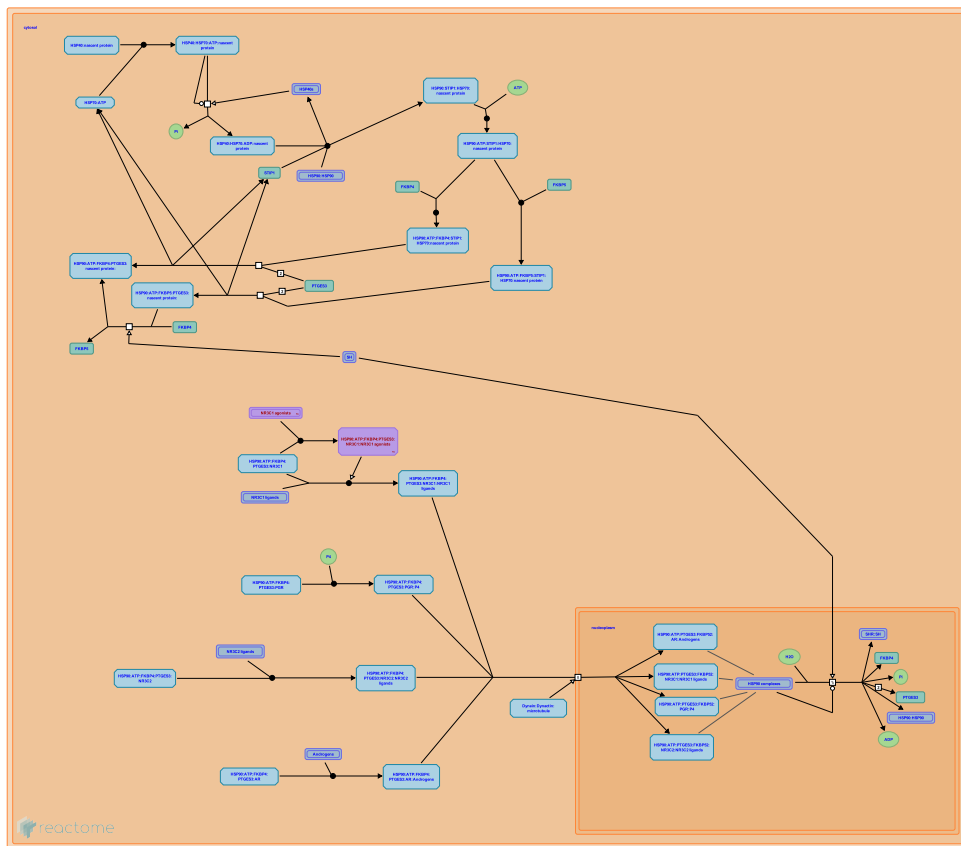


HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of ligand



Echeverria, PC., Jassal, B., Picard, D., Rothfels, K., Shamovsky, V., Shoichet, BK.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of [Creative Commons Attribution 4.0 International \(CC BY 4.0\) License](https://creativecommons.org/licenses/by/4.0/). For more information see our [license](https://creativecommons.org/licenses/by/4.0/).

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.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

- Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics*, 18, 142. [↗](#)
- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics*, 33, 3461-3467. [↗](#)
- Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res*, 46, D649-D655. [↗](#)
- Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology*, 14, e1005968. [↗](#)

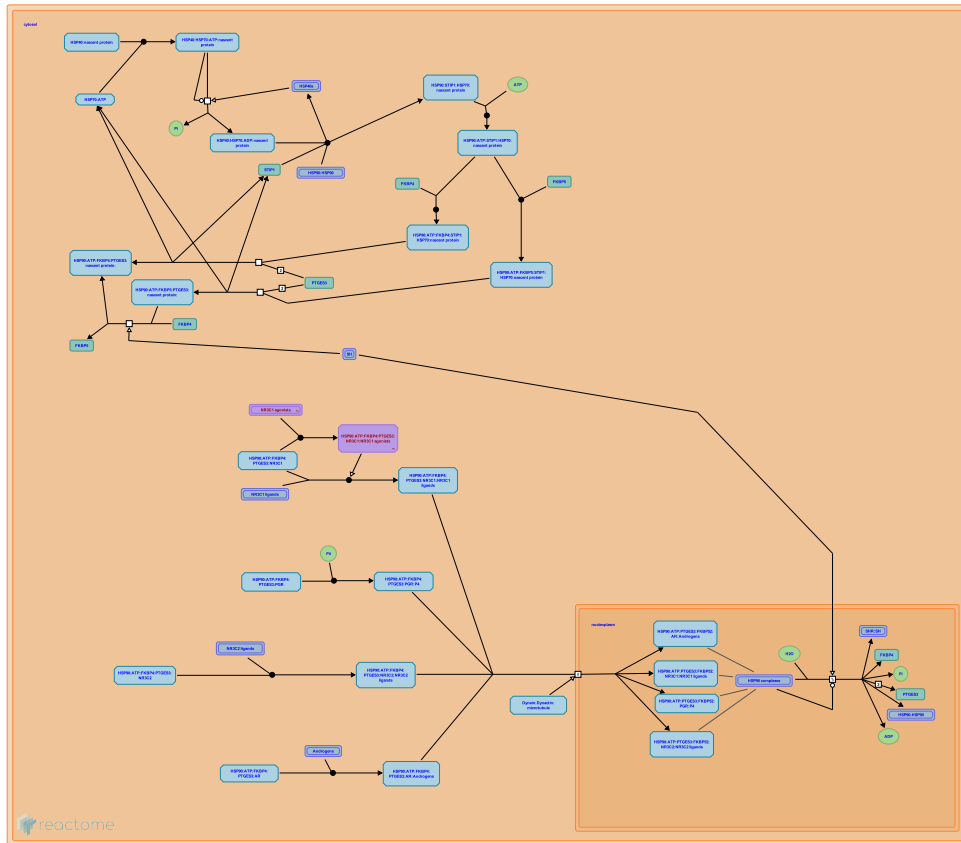
Reactome database release: 77

This document contains 1 pathway and 16 reactions ([see Table of Contents](#))

HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of ligand ↗

Stable identifier: R-HSA-3371497

Compartments: cytosol



Steroid hormone receptors (SHR) are transcription factors that become activated upon sensing steroid hormones such as glucocorticoids, mineralocorticoids, progesterone, androgens, or estrogen (Escriva et al 2000; Griekspoor A et al. 2007; Eick GN & Thornton JW. 2011). Depending on SHR type and the presence of ligand, they show different subcellular localizations. Whereas both unliganded and liganded estrogen receptors (ERalpha and ERbeta) are predominantly nuclear, unliganded glucocorticoid (GR) and androgen receptors (AR) are mostly located in the cytoplasm and completely translocate to the nucleus only after binding hormone (Htun H et al. 1999; Stenoien D et al. 2000; Tyagi RK et al. 2000; Cadepond F et al. 1992; Jewell CM et al. 1995; Kumar S et al. 2006). The unliganded mineralocorticoid receptor (MR) is partially cytoplasmic but can be found in nucleus in the ligand-bound or ligand-free form (Nishi M & Kawata M 2007). The progesterone receptor (PR) exists in two forms (PRA and PRB) with different ratios of nuclear versus cytoplasmic localization of the unliganded receptor. In most cell contexts, the PRA isoform is a repressor of the shorter PRB isoform, and without hormone induction it is mostly located in the nucleus, whereas PRB distributes both in the nucleus and in the cytoplasm (Lim CS et al. 1999; Griekspoor A et al. 2007). In the absence of ligand, members of the steroid receptor family remain sequestered in the cytoplasm and/or nucleus in the complex with proteins of HSP70/HSP90 chaperone machinery (Pratt WB & Dittmar KD1998). The highly dynamic ATP-dependent interactions of SHRs with HSP90 complexes regulate SHR cellular location, protein stability, competency to bind steroid hormones and transcriptional activity (Echeverria PC & Picard D 2010). Understanding the mechanism of ATPase activity of HSP90 is mostly based on structural and functional studies of the *Saccharomyces cerevisiae* Hsp90 complexes (Meyer P et al. 2003, 2004; Ali MM et al. 2006; Prodromou C et al. 2000; Prodromou C 2012). The ATPase cycle of human HSP90 is less well understood, however several studies suggest that the underlying

ing enzymatic mechanisms and a set of conformational changes that accompany the ATPase cycle are highly similar in both species (Richter K et al. 2008; Vaughan CK et al. 2009). Nascent SHR proteins are chaperoned by HSP70 and HSP40 to HSP90 cycle via STIP1 (HOP) (and its TPR domains) (Hernández MP et al. 2002a,b; EcheverriaPC & Picard D 2010; Li J et al. 2011). The ATP-bound form of HSP90 leads to the displacement of STIP1 by immunophilins FKBP5 or FKBP4 resulting in conformational changes that allow efficient hormone binding (Li J et al. 2011). PTGES3 (p23) binds to HSP90 complex finally stabilizing it in the conformation with a high hormone binding affinity. After hydrolysis of ATP the hormone bound SHR is released from HSP90 complex. The cytosolic hormone-bound SHR can be transported to the nucleus by several import pathways such as the dynein-based nuclear transport along microtubules involving the transport of the entire HSP90 complex or nuclear localization signals (NLS)-mediated nuclear targeting by importins (Tyagi RK et al. 2000; Cadepond F et al. 1992; Jewell CM et al. 1995; Kumar S et al. 2006). It is worth noting that GR-importin interactions can be ligand-dependent or independent (Freedman & Yamamoto 2004; Picard & Yamamoto 1987). In the nucleus ligand-activated SHR dimerizes, binds specific sequences in the DNA, called Hormone Responsive Elements (HRE), and recruits a number of coregulators that facilitate gene transcription. Nuclear localization is essential for SHRs to transactivate their target genes, but the same receptors also possess non-genomic functions in the cytoplasm.

The Reactome module describes the ATPase-driven conformational cycle of HSP90 that regulates ligand-dependent activation of SHRs.

Literature references

Li, J., Buchner, J. (2013). Structure, function and regulation of the hsp90 machinery. *Biomed J*, 36, 106-17. [↗](#)

Echeverria, PC., Picard, D. (2010). Molecular chaperones, essential partners of steroid hormone receptors for activity and mobility. *Biochim. Biophys. Acta*, 1803, 641-9. [↗](#)

Jackson, SE. (2013). Hsp90: structure and function. *Top Curr Chem*, 328, 155-240. [↗](#)

Editions

2016-09-17	Reviewed	Rothfels, K.
2016-11-19	Authored	Shamovsky, V.
2017-02-22	Reviewed	Picard, D., Echeverria, PC.
2017-02-25	Edited	Shamovsky, V.

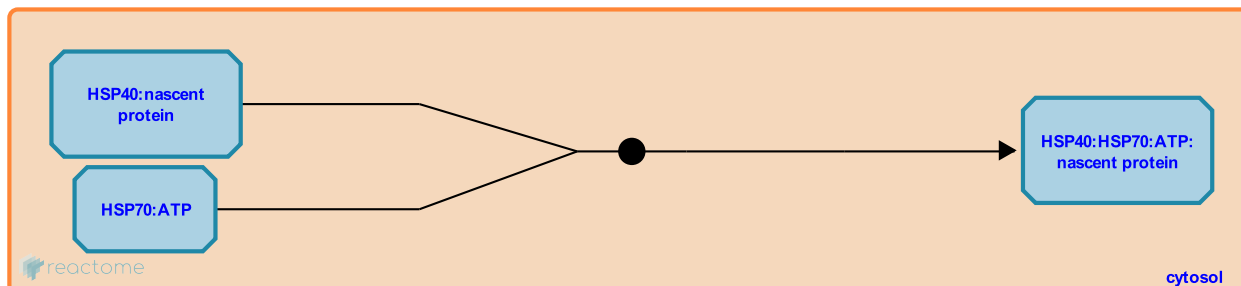
HSP70 binds to HSP40: nascent protein ↗

Location: HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of ligand

Stable identifier: R-HSA-3371590

Type: binding

Compartments: cytosol



The human HSP70 family comprises at least eight unique gene products that differ from each other by amino acid sequence, expression level and sub-cellular localization (Daugaard M et al. 2007). HSP70 family members display highly conserved amino acid sequences and domain structures consisting of: the ATPase N-terminal domain that binds and hydrolyzes ATP (NBD), the substrate domain (SBD) that binds to exposed hydrophobic segments of client polypeptides and promote their solubility and/or folding in a dynamic ATP-dependent manner, and the C-domain that provides a “lid” for the substrate domain (Zhang P et al. 2014; Brocchieri L et al. 2008; Wisniewska M et al. 2010). The conserved domain structure consolidates the chaperone function of the Hsp70 proteins and enables them to bind and release extended stretches of hydrophobic amino acids, exposed by incorrectly folded globular proteins in an ATP-dependent manner (Takayama S et al. 1999; Mayer MP 2013; Daugaard M et al. 2007). The initial binding of an unfolded client protein by a heat shock protein 40 (HSP40) prevents its aggregation and 'delivers' it to HSP70. The substrate binding ability of HSP70 is dependent on its bound state to either ATP or ADP (Kityk R et al. 2012; Qi R et al. 2013). Client substrates enter the HSP70 functional cycle by binding the ATP form of the chaperone, which has lower substrate affinity but faster binding and release rates compared with the ADP state. Interaction of the client in the cleft results in conformational changes in NBD that modestly increase ATP hydrolysis. Second, a transient interaction of HSP70 with J-protein co-chaperone HSP40, which has a higher affinity to ATP-bound HSP70 than ADP-bound HSP70, also stimulates the ATPase activity of HSP70 (Wittung-Stafshede P et al. 2003).

Followed by: [ATP hydrolysis by HSP70](#)

Literature references

Mayer, MP. (2013). Hsp70 chaperone dynamics and molecular mechanism. *Trends Biochem. Sci.*, 38, 507-14. ↗

Brocchieri, L., Conway de Macario, E., Macario, AJ. (2008). hsp70 genes in the human genome: Conservation and differentiation patterns predict a wide array of overlapping and specialized functions. *BMC Evol. Biol.*, 8, 19. ↗

Editions

2016-09-17	Reviewed	Rothfels, K.
2016-11-19	Authored	Shamovsky, V.
2017-02-22	Reviewed	Picard, D., Echeverria, PC.
2017-02-25	Edited	Shamovsky, V.

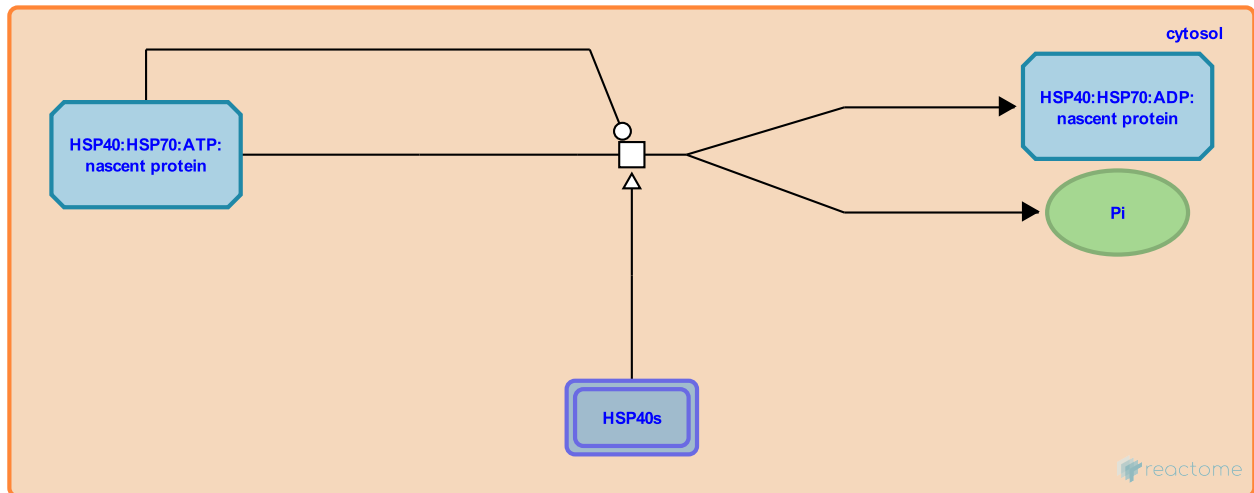
ATP hydrolysis by HSP70 ↗

Location: HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of ligand

Stable identifier: R-HSA-3371422

Type: transition

Compartments: cytosol



Heat shock protein 70 (HSP70) proteins bind and release client polypeptides in a cycle of cochaperone-mediated conformational changes that is coupled to ATP binding and hydrolysis (Mayer MP 2013). The overall domain structure of all HSP70 chaperone proteins is evolutionary conserved: the N-terminal nucleotide-binding domain (NBD) with ATPase activity is joined by a flexible linker to the C-terminal polypeptide substrate-binding domain (SBD). Most of our mechanistic understanding of HSP70 structure and function has come from analyses of *Escherichia coli* HSP70 family member, DnaK (Pellecchia M et al. 2000; Schuermann, JP et al. 2008; Bertelsen EB et al. 2009; Kityk R et al. 2012; Qi R et al. 2013). Chaperone function of bacterial DnaK involves an allosteric control mechanism between its two functional domains NBD and SBD. ATP binding and hydrolysis modulates the affinity of bacterial HSP70 protein for polypeptides, and polypeptide binding stimulates ATP hydrolysis (Mayer MP et al. 2000; Kityk R et al. 2012; Qi R et al. 2013). Also in the ATP-bound form, the lid domain remains open, which facilitates transient interactions with substrates. Following ATP hydrolysis, a conformational change releases the SBD, resulting in closure of the lid and a ~10-fold increase in the affinity for substrate (Wittung-Stafshede P et al. 2003; Slepnev SV & Witt SN 2002). The conformation change associated with ATP hydrolysis is communicated through a key proline switch and involves the conserved, hydrophobic linker that connects the NBD to the SBD (Vogel M et al. 2006; Swain JF et al. 2007). ATP hydrolysis is essential for HSP70 chaperones, but the intrinsic ATPase rate is very low (Chang L et al. 2008). This ATPase activity of HSP70 is stimulated by protein substrates in synergism with J domain cochaperones (HSP40s) (Karzai AW & McMacken R 1996; Russell R et al. 1999; Laufen T et al. 1999; Landry SJ 2003; Wittung-Stafshede P et al. 2003).

The HSP70 family of chaperone proteins is one of the most conserved protein families in evolution (Takayama S et al. 1999; Boorstein WR et al. 1994; Brocchieri L et al. 2008). The sequence alignment of eukaryotic and bacterial HSP70 proteins revealed that the human HSP70 SBD is highly homologous to the DnaK SBD (51% sequence identity in the full-length protein and 47% identity in the SBD) (Zhang P et al. 2014). Moreover, the crystal structure of the substrate-bound human HSP70-SBD resembled the overall fold of the corresponding domain in the substrate-bound DnaK structures, confirming a similar overall architecture of the orthologous bacterial and human HSP70 proteins (Zhang P et al. 2014). Structures of nucleotide-binding domains of four human HSP70 isoforms: HSPA1L, HSPA2, HSPA6 and HSPA5 also

support the view that the NBDs of human HSP70 function by conserved mechanisms (Wisniewska M et al. 2014). Structural analysis of a functionally intact bovine Hsp70 family member Hsc70 together with analysis of mutants in the interdomain linker and interface support the allosteric mechanism of the mammalian HSP70 chaperones (Wilbanks SM & McKay DB 1998; Jiang J et al. 2005).

Preceded by: [HSP70 binds to HSP40:nascent protein](#)

Followed by: [STIP1\(HOP\) binds HSP90 and HSP70:HSP40:nascent protein](#)

Literature references

Wisniewska, M., Karlberg, T., Lehtiö, L., Johansson, I., Kotenyova, T., Moche, M. et al. (2010). Crystal structures of the ATPase domains of four human Hsp70 isoforms: HSPA1L/Hsp70-hom, HSPA2/Hsp70-2, HSPA6/Hsp70B', and HSPA5/BiP/GRP78. *PLoS ONE*, 5, e8625. [↗](#)

Mayer, MP. (2013). Hsp70 chaperone dynamics and molecular mechanism. *Trends Biochem. Sci.*, 38, 507-14. [↗](#)

Editions

2016-09-17	Reviewed	Rothfels, K.
2016-11-19	Authored	Shamovsky, V.
2017-02-22	Reviewed	Picard, D., Echeverria, PC.
2017-02-25	Edited	Shamovsky, V.

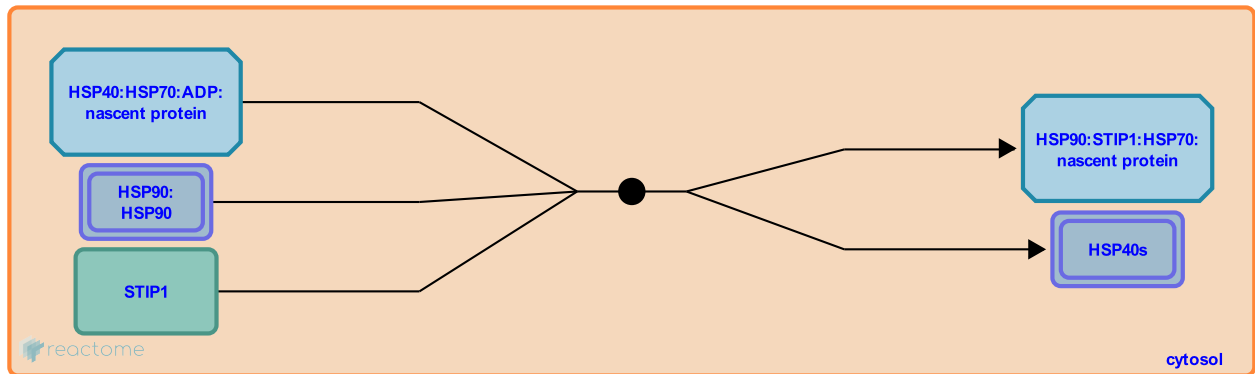
STIP1(HOP) binds HSP90 and HSP70:HSP40:nascent protein ↗

Location: HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of ligand

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.

Preceded by: [ATP hydrolysis by HSP70](#)

Followed by: [ATP binding to HSP90 triggers conformation change](#)

Literature references

Ebong, IO., Morgner, N., Zhou, M., Saraiva, MA., Daturpalli, S., Jackson, SE. et al. (2011). Heterogeneity and dynamics in the assembly of the heat shock protein 90 chaperone complexes. *Proc. Natl. Acad. Sci. U.S.A.*, 108, 17939-44.

[↗](#)

Southworth, DR., Agard, DA. (2011). Client-loading conformation of the Hsp90 molecular chaperone revealed in the cryo-EM structure of the human Hsp90:Hop complex. *Mol. Cell*, 42, 771-81. [↗](#)

Editions

2016-09-17	Reviewed	Rothfels, K.
2016-11-19	Authored	Shamovsky, V.
2017-02-22	Reviewed	Picard, D., Echeverria, PC.
2017-02-25	Edited	Shamovsky, V.

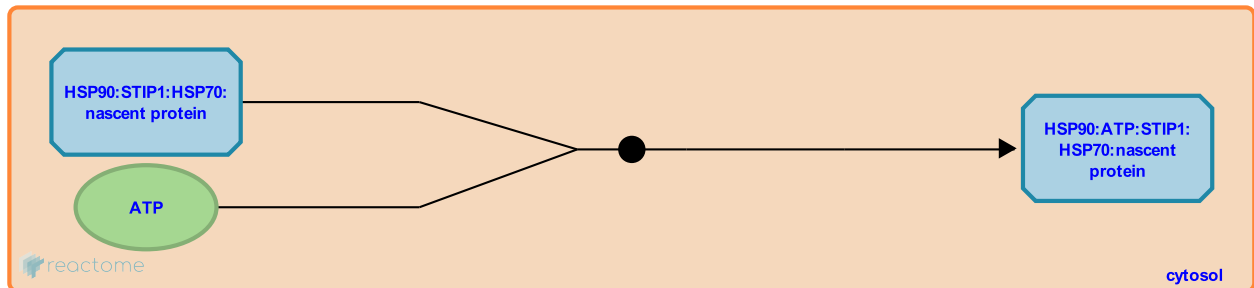
ATP binding to HSP90 triggers conformation change ↗

Location: HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of ligand

Stable identifier: R-HSA-5618107

Type: binding

Compartments: cytosol



The molecular chaperone heat-shock protein 90 (HSP90) functions as a homodimer. Each HSP90 protomer contains three flexibly linked regions, the N-terminal ATP-binding domain (NTD), the middle domain, and the C-terminal dimerization domain (Prodromou C et al. 1997; Pearl LH and Prodromou C 2006). HSP90 dimer is rather a dynamic molecule and ATP binding and hydrolysis are associated with conformational changes (Obermann WM et al. 1998; Krukenberg KA et al. 2011; Li J & Buchner J 2013; Prodromou C 2012). The structures of the isolated yeast and human N-terminal domain (NTD) of HSP90 bound to ATP, ADP and adenylylimidodiphosphate (AMP-PNP, a non-hydrolysable analogue of ATP) suggest that nucleotides bind deep in the cleft of NTD in open apo state of HSP90 (Prodromou C et al.1997; Meyer P et al. 2003, 2004; Colombo G et al. 2008; Li J et al. 2012). The structural studies of NTD of human HSP90 with antitumor agent geldanamycin (that acts as an ADP/ATP mimetic) support the polar interactions in the binding pocket described for yeast Hsp90 and ADP or ATP (Stebbins CE et al. 1997; Prodromou C et al.1997; Grenert JP et al. 1997). Once ATP is bound it helps to stabilize the closed ATP lid state, in which the gamma-phosphate of ATP provides a hydrogen bonding that promotes a stable association of the ATP lid with NTD. The association of ATP or AMP-PNP with NTD then stimulates structural changes in NTD. NMR analysis of human full-length HSP90 protein with and without ATP confirmed that ATP binding led to conformational changes in NTD (Karagöz GE et al. 2010). No structural changes were observed in the middle and C-terminal domains (Karagöz GE et al. 2010). However, other studies suggest that ATP-dependent conformational changes occur both in NTD and in the middle domain of HSP90 (Ali MM et al. 2006; Prodromou C et al. 2000; Chadli A et al. 2000; Meyer P et al. 2003). The changes are likely to involve movements of the ATP lid segment within each N-terminal domain that locates over the bound ATP (Ali MM et al. 2006; Prodromou C et al. 2000; Chadli A et al. 2000). The movement of the lids exposes surface residues that are subsequently involved in transient dimerization of the N-terminal domains of HSP90 (Ali MM et al. 2006; Prodromou C et al. 2000; Chadli A et al. 2000). The subsequent conformational changes upon ATP binding are regulated by co-chaperone activities. For example, 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). Thus, ATP binding coupled to co-chaperone-mediated loading of client protein to HSP90 complex regulates ATPase activity of HSP90.

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

Followed by: FKBP4 binds HSP90:ATP:STIP1:HSP70: nascent protein, FKBP5 binds HSP90:ATP:STIP1:HSP70: nascent protein

Literature references

Li, J., Sun, L., Xu, C., Yu, F., Zhou, H., Zhao, Y. et al. (2012). Structure insights into mechanisms of ATP hydrolysis and the activation of human heat-shock protein 90. *Acta Biochim. Biophys. Sin. (Shanghai)*, 44, 300-6. [↗](#)

Editions

2016-09-17	Reviewed	Rothfels, K.
2016-11-19	Authored	Shamovsky, V.
2017-02-22	Reviewed	Picard, D., Echeverria, PC.
2017-02-25	Edited	Shamovsky, V.

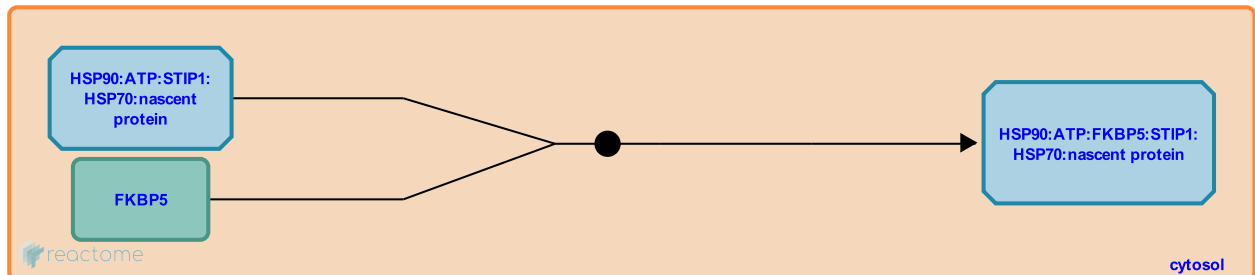
FKBP5 binds HSP90:ATP:STIP1:HSP70:nascent protein ↗

Location: HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of ligand

Stable identifier: R-HSA-5618105

Type: binding

Compartments: cytosol



FK506 binding protein 5 (FKBP51, also known as FKBP5) is a member of the immunophilin (IMM) protein family of intracellular proteins. The signature domain of the IMM family is the peptidyl-prolyl-cis/trans-isomerase (PPIase) domain, which is in turn the drug binding domain. IMMs are classified by their ability to bind immunosuppressant drugs – CyPs (cyclophilins) bind cyclosporine A (CsA), and FK-BPs (FK506-binding proteins) bind FK506 (Pratt and Toft 1997; Kang et al. 2008). In addition to the PPIase domain, there are three additional domains – the nucleotide-binding domain, (also called FKBD2 in FKBP proteins) where ATP binds, the calmodulin-binding domain, a poorly characterized domain able to interact with calmodulin, and tetratricopeptide repeat (TPR) domains, sequences of 34 amino acids repeated in tandem through which FKBP5s bind to the HSP90 C-terminal sequence MEEVD (Davies et al. 2005; Wu et al. 2004). Mass spectrometry analysis showed that FKBP51 (FKBP5) and FKBP52 (FKBP4) form analogous complexes with GR:HSP90:STIP1:HSP70:ATP (Ebong IO et al. 2016). Binding of FKBP51 (FKBP5) and other immunophilins may weaken the association of TPR domain containing protein STIP1 with HSP90 complex (Li et al. 2011).

Preceded by: ATP binding to HSP90 triggers conformation change

Followed by: p23 (PTGES3) binds HSP90:ATP:FKBP5:nascent protein

Literature references

Erlejman, AG., Lagadari, M., Harris, DC., Cox, MB., Galigniana, MD. (2014). Molecular chaperone activity and biological regulatory actions of the TPR-domain immunophilins FKBP51 and FKBP52. *Curr. Protein Pept. Sci.*, 15, 205-15. ↗

Editions

2016-09-17	Reviewed	Rothfels, K.
2016-11-19	Authored	Shamovsky, V.
2017-02-22	Reviewed	Picard, D., Echeverria, PC.
2017-02-25	Edited	Shamovsky, V.

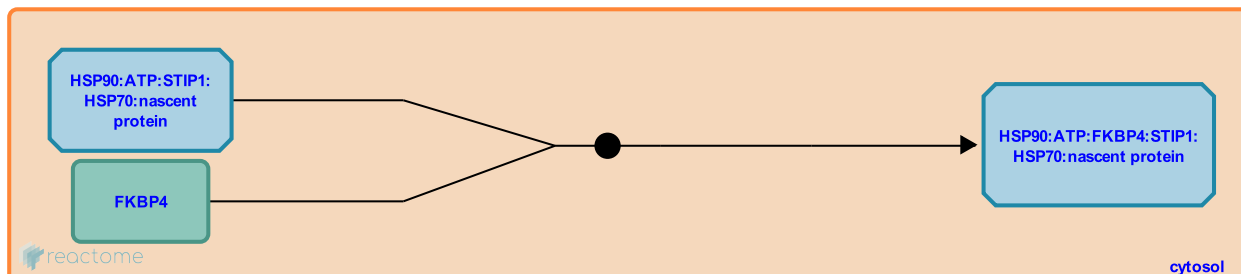
FKBP4 binds HSP90:ATP:STIP1:HSP70:nascent protein ↗

Location: [HSP90 chaperone cycle for steroid hormone receptors \(SHR\) in the presence of ligand](#)

Stable identifier: R-HSA-5618085

Type: binding

Compartments: cytosol



FKBP52 (also known as the large immunophilin FKBP4) is a co-chaperone containing tetratricopeptide repeat (TPR) domain, which binds the C-terminal sequence motif (MEEVD) of HSP90 (Wu B et al. 2004; Davies and Sanchez 2005). The stoichiometry of FKBP in receptor heterocomplexes was determined on the basis of the size of cross-linked complexes, a ratio of one molecule of receptor and two molecules of HSP90 to one molecule of FKBP52 was obtained for human PR , ER and mouse GR (Rexin M et al. 1992; Rehberger P et al. 1992; Segnitz B and Gehring U 1995). Mass spectrometry analysis showed that FKBP51 (FKBP5) and FKBP52 (FKBP4) form analogous complexes with GR:HSP90:STIP1:HSP70:ATP (Ebong IO et al. 2016). Binding of FKBP52 (FKBP4) and other immunophilins may weaken the association of TPR domain containing protein STIP1 with HSP90 complex (Li et al. 2011).

FKBP52 (FKBP4) is a member of the immunophilin (IMM) protein family of intracellular proteins that are able to bind immunosuppressant drugs, from which the term immunophilin derives (Pratt and Toft 1997; Kang et al. 2008). These proteins are also known as peptidyl-prolyl cis/trans isomerases (PPIases) for their ability to convert proline bonds from cis to trans form, a rate-limiting step in protein folding (Harding et al. 1989; Standaert et al. 1990; Galat 2003; Davies and Sanchez 2005). In addition to the PPIase and TPR domains, there are two additional domains - the nucleotide-binding domain (also called FKBD2 in FKBP proteins) where ATP binds and the calmodulin-binding domain, a poorly characterized domain able to interact with calmodulin.

Preceded by: [ATP binding to HSP90 triggers conformation change](#)

Followed by: [p23 \(PTGES3\) binds HSP90:ATP:FKBP4:nascent protein](#)

Literature references

Davies, TH., Sánchez, ER. (2005). FKBP52. *Int. J. Biochem. Cell Biol.*, 37, 42-7. ↗

Kang, CB., Hong, Y., Dhe-Paganon, S., Yoon, HS. (2008). FKBP family proteins: immunophilins with versatile biological functions. *Neurosignals*, 16, 318-25. ↗

Wu, B., Li, P., Liu, Y., Lou, Z., Ding, Y., Shu, C. et al. (2004). 3D structure of human FK506-binding protein 52: implications for the assembly of the glucocorticoid receptor/Hsp90/immunophilin heterocomplex. *Proc. Natl. Acad. Sci. U.S.A.*, 101, 8348-53. ↗

Editions

2016-09-17	Reviewed	Rothfels, K.
2016-11-19	Authored	Shamovsky, V.
2017-02-22	Reviewed	Picard, D., Echeverria, PC.
2017-02-25	Edited	Shamovsky, V.

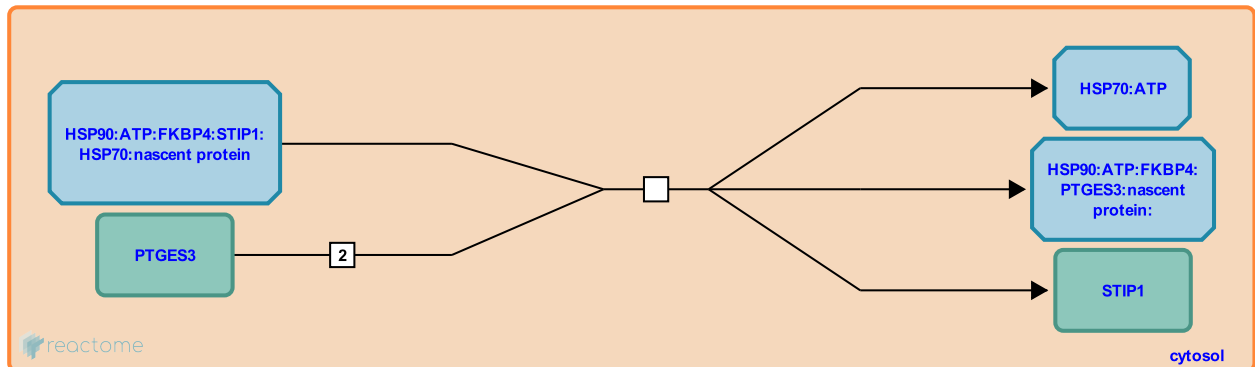
p23 (PTGES3) binds HSP90:ATP:FKBP4:nascent protein ↗

Location: HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of ligand

Stable identifier: R-HSA-5618110

Type: transition

Compartments: cytosol



Immunophilin p23 (also known as PTGES3) binds selectively to the ATP-bound state of HSP90. p23 stabilizes the closed state of HSP90, which weakens the binding of STIP1(HOP) and promotes its exit from the complex (McLaughlin H et al. 2006; Karagöz GE et al. 2011). When p23 is added to the client-transfer complex in the absence of the immunophilin or with FKBP51 (FKBP5), two copies of p23 are incorporated with concomitant loss of HSP70 and HOP (Ebong I et al. 2016). By contrast no stable complex with two p23 subunits is observed in the presence of FKBP52 (FKBP4); expulsion of HSP70, HOP and p23 occur with a low population of a complex incorporating only one p23 subunit (Ebong I et al. 2016).

Preceded by: FKBP4 binds HSP90:ATP:STIP1:HSP70:nascent protein

Followed by: NR3C1 ligands bind NR3C1 (in the HSP90 chaperone complex), P4 bind PGR (in the HSP90 chaperone complex), NR3C2 ligands bind NR3C2 (in the HSP90 chaperone complex)

Literature references

McLaughlin, SH., Sobott, F., Yao, ZP., Zhang, W., Nielsen, PR., Grossmann, JG. et al. (2006). The co-chaperone p23 arrests the Hsp90 ATPase cycle to trap client proteins. *J. Mol. Biol.*, 356, 746-58. ↗

Karagöz, GE., Duarte, AM., Ippel, H., Uetrecht, C., Sinnige, T., van Rosmalen, M. et al. (2011). N-terminal domain of human Hsp90 triggers binding to the cochaperone p23. *Proc. Natl. Acad. Sci. U.S.A.*, 108, 580-5. ↗

Editions

2016-09-17	Reviewed	Rothfels, K.
2016-11-19	Authored	Shamovsky, V.
2017-02-22	Reviewed	Picard, D., Echeverria, PC.
2017-02-25	Edited	Shamovsky, V.

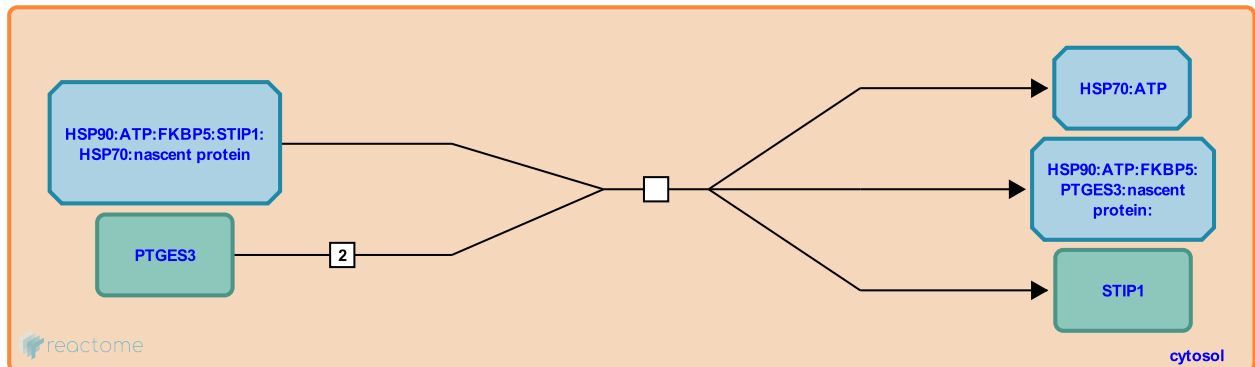
p23 (PTGES3) binds HSP90:ATP:FKBP5:nascent protein ↗

Location: HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of ligand

Stable identifier: R-HSA-5618098

Type: transition

Compartments: cytosol



Immunophilin p23 (also known as PTGES3) binds selectively to the ATP-bound state of HSP90. p23 stabilizes the closed state of HSP90, which weakens the binding of STIP1(HOP) and promotes its exit from the complex (McLaughlin H et al. 2006; Karagöz GE et al. 2011). When FKBP51 (FKBP5) is present, a stable intermediate FKBP51:GR:HSP90:p23 is formed by expulsion of HSP70 and STIP1(HOP) (Ebong I et al. 2016).

Preceded by: FKBP5 binds HSP90:ATP:STIP1:HSP70:nascent protein

Followed by: FKBP4 replaces FKBP5 within HSP90:ATP:FKBP5:unfolded protein

Literature references

McLaughlin, SH., Sobott, F., Yao, ZP., Zhang, W., Nielsen, PR., Grossmann, JG. et al. (2006). The co-chaperone p23 arrests the Hsp90 ATPase cycle to trap client proteins. *J. Mol. Biol.*, 356, 746-58. ↗

Karagöz, GE., Duarte, AM., Ippel, H., Uetrecht, C., Sinnige, T., van Rosmalen, M. et al. (2011). N-terminal domain of human Hsp90 triggers binding to the cochaperone p23. *Proc. Natl. Acad. Sci. U.S.A.*, 108, 580-5. ↗

Editions

2016-09-17	Reviewed	Rothfels, K.
2016-11-19	Authored	Shamovsky, V.
2017-02-22	Reviewed	Picard, D., Echeverria, PC.
2017-02-25	Edited	Shamovsky, V.

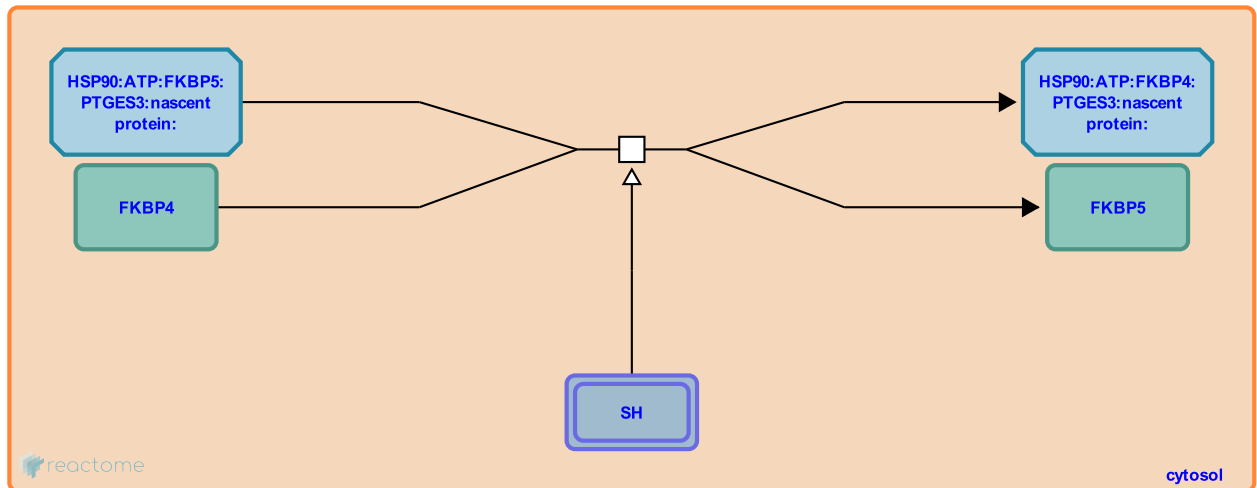
FKBP4 replaces FKBP5 within HSP90:ATP:FKBP5:unfolded protein ↗

Location: HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of ligand

Stable identifier: R-HSA-5618073

Type: transition

Compartments: cytosol



Mass spectrometry analysis showed that FKBP51 (FKBP5) and FKBP52 (FKBP4) form analogous complexes with GR:HSP90:STIP1:HSP70:ATP (Ebong IO et al. 2016). Without hormone, FKBP51 is the major immunophilin in GR:HSP90 complexes, whereas after hormone treatment, FKBP52 rapidly replaces FKBP51 (Davies et al., 2002).

Preceded by: p23 (PTGES3) binds HSP90:ATP:FKBP5: nascent protein

Followed by: NR3C1 ligands bind NR3C1 (in the HSP90 chaperone complex), P4 bind PGR (in the HSP90 chaperone complex), NR3C2 ligands bind NR3C2 (in the HSP90 chaperone complex)

Literature references

Ebong, IO., Beilsten-Edmands, V., Patel, NA., Morgner, N., Robinson, CV. (2016). The interchange of immunophilins leads to parallel pathways and different intermediates in the assembly of Hsp90 glucocorticoid receptor complexes. *Cell Discov*, 2, 16002. ↗

Davies, TH., Ning, YM., Sánchez, ER. (2002). A new first step in activation of steroid receptors: hormone-induced switching of FKBP51 and FKBP52 immunophilins. *J. Biol. Chem.*, 277, 4597-600. ↗

Editions

2016-09-17	Reviewed	Rothfels, K.
2016-11-19	Authored	Shamovsky, V.
2017-02-22	Reviewed	Picard, D., Echeverria, PC.
2017-02-25	Edited	Shamovsky, V.

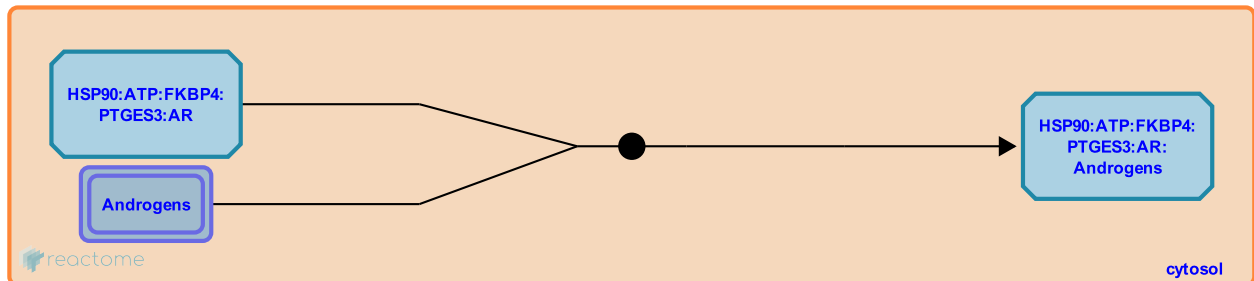
Androgens binds AR (in the HSP90 chaperone complex) ↗

Location: [HSP90 chaperone cycle for steroid hormone receptors \(SHR\) in the presence of ligand](#)

Stable identifier: R-HSA-9705925

Type: binding

Compartments: cytosol



Steroid hormones receptors (SHRs) are intracellular transcription factors that can be activated by binding specific ligands (steroid hormones (SH)) to the ligand-binding domain (LBD) (Ray DW et al. 1999; Pike AC et al. 1999; Bledsoe RK et al. 2002; Li Y et al. 2005; Kumar R and McEwan IJ 2012; Kumar R et al. 2011; Williams SP & Sigler PB 1998; Tanenbaum DM et al. 1998; Lusher SJ et al. 2012). LBD (E-region) resides in the C-terminal half of the receptor and in addition to ligand binding function contains a transcriptional activation function (AF2), sequences for dimerization, heat shock protein association, intermolecular silencing and intramolecular repression (Kumar R and McEwan IJ 2012). The binding of hormone acts as an allosteric switch to regulate SHR-DNA and SHR-protein interactions, including interdomain interactions and/or dimerization (Kumar R and McEwan IJ 2012).

SHs are synthesized from cholesterol in the adrenal cortex (glucocorticoids, mineralocorticoids, and adrenal androgens), the testes (testicular androgens, estrogen), and the ovary and placenta (estrogen and progesterone or progestins) (Payne AH & Hales DB 2004; Hu J et al. 2010;). SHs reach their target cells via the blood, where they are bound to specific carrier proteins (Grishkovskaya I et al. 2000; Hammond GL 2016). SHs detach from the carrier proteins and because of their lipophilic nature readily diffuse through the plasma membrane of cells (Oren I et al. 2004). Within the target cells SHs bind to steroid hormone receptors (SHRs) which are present in a heterocomplex with heat shock protein HSP90 and co-chaperones (e.g., immunophilins p23) (Echeverria PC & Picard D 2010). The ATP-bound form of HSP90 and chaperone-mediated conformational changes are required to keep SHRs in a ligand binding-competent state (McLaughlin SH et al. 2002; Pratt WB et al. 2008; Krukenberg KA et al. 2011). Here, the androgens testosterone (TEST), dihydrotestosterone (DHTTEST), androst-4-en-3,17-dione (ANDST) and 6-dehydrotestosterone bind the androgen receptor (AR), within the HSP90 chaperone complex.

Followed by: [HSP90:ATP:p23:FKBP52:SHR:SH translocates to the nucleus](#)

Literature references

Kumar, R., McEwan, IJ. (2012). Allosteric modulators of steroid hormone receptors: structural dynamics and gene regulation. *Endocr. Rev.*, 33, 271-99. ↗

Echeverria, PC., Picard, D. (2010). Molecular chaperones, essential partners of steroid hormone receptors for activity and mobility. *Biochim. Biophys. Acta*, 1803, 641-9. ↗

Editions

2016-09-17	Reviewed	Rothfels, K.
2016-11-19	Authored	Shamovsky, V.
2017-02-22	Reviewed	Picard, D., Echeverria, PC.
2020-11-03	Edited	Jassal, B.

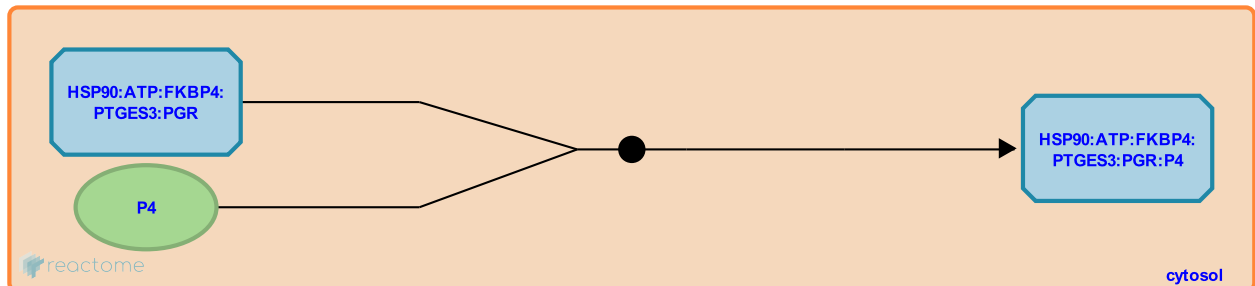
P4 bind PGR (in the HSP90 chaperone complex) ↗

Location: HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of ligand

Stable identifier: R-HSA-9725885

Type: binding

Compartments: cytosol



Steroid hormones receptors (SHRs) are intracellular transcription factors that can be activated by binding specific ligands (i.e., steroid hormones (SH)) to the ligand-binding domain (LBD) (Ray DW et AL. 1999; Pike AC et al. 1999; Bledsoe RK et al. 2002; Li Y et al. 2005; Kumar R and McEwan IJ 2012; Kumar R et al. 2011; Williams SP & Sigler PB 1998; Tanenbaum DM et al. 1998; Lusher SJ et al. 2012). LBD (E-region) resides in the C-terminal half of the receptor and in addition to ligand binding function contains a transcriptional activation function (AF2), sequences for dimerization, heat shock protein association, intermolecular silencing and intramolecular repression (Kumar R and McEwan IJ 2012). The binding of hormone acts as an allosteric switch to regulate SHR-DNA and SHR-protein interactions, including inter-domain interactions and/or dimerization (Kumar R and McEwan IJ 2012).

SHs are synthesized from cholesterol in the adrenal cortex (glucocorticoids, mineralocorticoids, and adrenal androgens), the testes (testicular androgens, estrogen), and the ovary and placenta (estrogen and progesterone or progestins) (Payne AH & Hales DB 2004; Hu J et al. 2010;). SHs reach their target cells via the blood, where they are bound to specific carrier proteins (Grishkovskaya I et al. 2000; Hammond GL 2016). SHs detach from the carrier proteins and because of their lipophilic nature readily diffuse through the plasma membrane of cells (Oren I et al. 2004). Within the target cells SHs bind to steroid hormone receptors (SHRs) which are present in a heterocomplex with heat shock protein HSP90 and co-chaperones (e.g., immunophilins p23) (Echeverria PC & Picard D 2010). The ATP-bound form of HSP90 and chaperone-mediated conformational changes are required to keep SHRs in a ligand binding-competent state (McLaughlin SH et al. 2002; Pratt WB et al. 2008; Krukenberg KA et al. 2011).

Preceded by: FKBP4 replaces FKBP5 within HSP90:ATP:FKBP5:unfolded protein, p23 (PTGES3) binds HSP90:ATP:FKBP4:nascent protein

Followed by: HSP90:ATP:p23:FKBP52:SHR:SH translocates to the nucleus

Literature references

- Kumar, R., McEwan, IJ. (2012). Allosteric modulators of steroid hormone receptors: structural dynamics and gene regulation. *Endocr. Rev.*, 33, 271-99. ↗
- Echeverria, PC., Picard, D. (2010). Molecular chaperones, essential partners of steroid hormone receptors for activity and mobility. *Biochim. Biophys. Acta*, 1803, 641-9. ↗

Editions

2016-09-17	Reviewed	Rothfels, K.
2017-02-22	Reviewed	Picard, D., Echeverria, PC.
2021-04-01	Authored, Edited	Jassal, B.

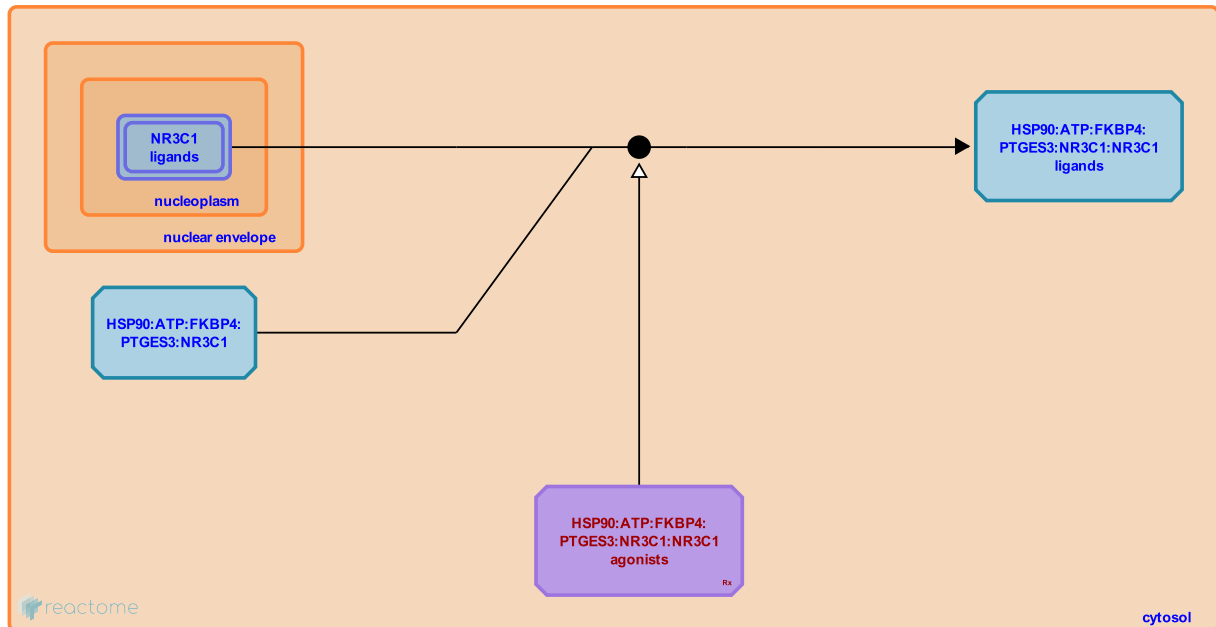
NR3C1 ligands bind NR3C1 (in the HSP90 chaperone complex) ↗

Location: HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of ligand

Stable identifier: R-HSA-9690534

Type: binding

Compartments: cytosol



Steroid hormones receptors (SHRs) are intracellular transcription factors that can be activated by binding specific ligands (i.e., steroid hormones (SH)) to the ligand-binding domain (LBD) (Ray DW et al. 1999; Pike AC et al. 1999; Bledsoe RK et al. 2002; Li Y et al. 2005; Kumar R and McEwan IJ 2012; Kumar R et al. 2011; Williams SP & Sigler PB 1998; Tanenbaum DM et al. 1998; Lusher SJ et al. 2012). LBD (E-region) resides in the C-terminal half of the receptor and in addition to ligand binding function contains a transcriptional activation function (AF2), sequences for dimerization, heat shock protein association, intermolecular silencing and intramolecular repression (Kumar R and McEwan IJ 2012). The binding of hormone acts as an allosteric switch to regulate SHR-DNA and SHR-protein interactions, including inter-domain interactions and/or dimerization (Kumar R and McEwan IJ 2012).

SHs are synthesized from cholesterol in the adrenal cortex (glucocorticoids, mineralocorticoids, and adrenal androgens), the testes (testicular androgens, estrogen), and the ovary and placenta (estrogen and progesterone or progestins) (Payne AH & Hales DB 2004; Hu J et al. 2010;). SHs reach their target cells via the blood, where they are bound to specific carrier proteins (Grishkovskaya I et al. 2000; Hammond GL 2016). SHs detach from the carrier proteins and because of their lipophilic nature readily diffuse through the plasma membrane of cells (Oren I et al. 2004). Within the target cells SHs bind to steroid hormone receptors (SHRs) which are present in a heterocomplex with heat shock protein HSP90 and co-chaperones (e.g., immunophilins p23) (Echeverria PC & Picard D 2010). The ATP-bound form of HSP90 and chaperone-mediated conformational changes are required to keep SHRs in a ligand binding-competent state (McLaughlin SH et al. 2002; Pratt WB et al. 2008; Krukenberg KA et al. 2011).

Preceded by: FKBP4 replaces FKBP5 within HSP90:ATP:FKBP5:unfolded protein, p23 (PTGES3) binds HSP90:ATP:FKBP4:nascent protein

Followed by: HSP90:ATP:p23:FKBP52:SHR:SH translocates to the nucleus

Literature references

Kumar, R., McEwan, IJ. (2012). Allosteric modulators of steroid hormone receptors: structural dynamics and gene regulation. *Endocr. Rev.*, 33, 271-99. [↗](#)

Echeverria, PC., Picard, D. (2010). Molecular chaperones, essential partners of steroid hormone receptors for activity and mobility. *Biochim. Biophys. Acta*, 1803, 641-9. [↗](#)

Editions

2016-09-17	Reviewed	Rothfels, K.
2016-11-19	Authored	Shamovsky, V.
2017-02-22	Reviewed	Picard, D., Echeverria, PC.

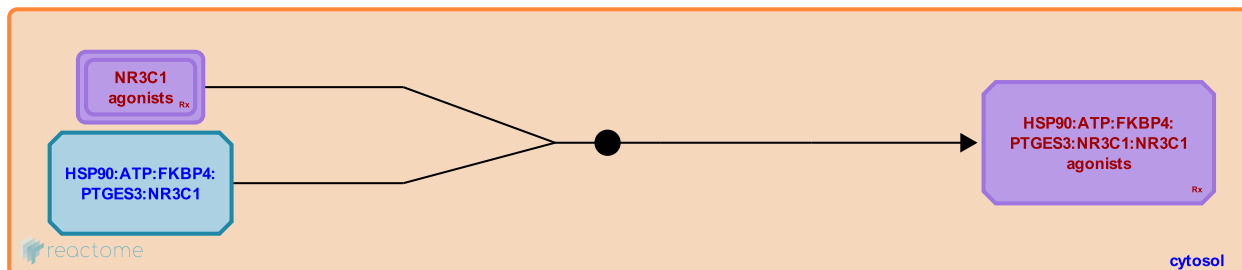
NR3C1 binds NR3C1 agonists ↗

Location: HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of ligand

Stable identifier: R-HSA-9678925

Type: binding

Compartments: cytosol



Corticosteroids bind to the glucocorticoid receptor NR3C1 (Rupprecht et al. 1993, Lind et al. 2000), inhibiting pro-inflammatory NF-Kappa B and other inflammatory transcription factors, and promoting anti-inflammatory genes like interleukin-10. The short term effects of corticosteroids are decreased vasodilation and permeability of capillaries, as well as decreased leukocyte migration to sites of inflammation. From the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial in June 2020, dexamethasone was recommended for use in COVID-19 patients with severe respiratory symptoms. In the trial, dexamethasone reduced deaths by approximately one third in patients requiring ventilation and by one fifth in those requiring oxygen.

Literature references

Rupprecht, R., Reul, JM., van Steensel, B., Spengler, D., Söder, M., Berning, B. et al. (1993). Pharmacological and functional characterization of human mineralocorticoid and glucocorticoid receptor ligands. *Eur. J. Pharmacol.*, 247, 145-54. ↗

Lind, U., Greenidge, P., Gillner, M., Koehler, KF., Wright, A., Carlstedt-Duke, J. (2000). Functional probing of the human glucocorticoid receptor steroid-interacting surface by site-directed mutagenesis. Gln-642 plays an important role in steroid recognition and binding. *J. Biol. Chem.*, 275, 19041-9. ↗

Editions

2020-03-23	Authored, Edited	Jassal, B.
2020-05-14	Reviewed	Shoichet, BK.

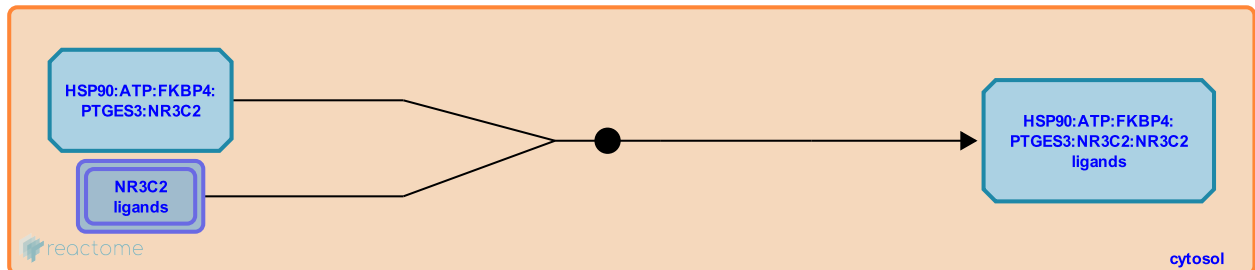
NR3C2 ligands bind NR3C2 (in the HSP90 chaperone complex) ↗

Location: HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of ligand

Stable identifier: R-HSA-5618099

Type: binding

Compartments: cytosol



Steroid hormones receptors (SHRs) are intracellular transcription factors that can be activated by binding specific ligands (i.e., steroid hormones (SH)) to the ligand-binding domain (LBD) (Ray DW et al. 1999; Pike AC et al. 1999; Bledsoe RK et al. 2002; Li Y et al. 2005; Kumar R and McEwan IJ 2012; Kumar R et al. 2011; Williams SP & Sigler PB 1998; Tanenbaum DM et al. 1998; Lusher SJ et al. 2012). LBD (E-region) resides in the C-terminal half of the receptor and in addition to ligand binding function contains a transcriptional activation function (AF2), sequences for dimerization, heat shock protein association, intermolecular silencing and intramolecular repression (Kumar R and McEwan IJ 2012). The binding of hormone acts as an allosteric switch to regulate SHR-DNA and SHR-protein interactions, including inter-domain interactions and/or dimerization (Kumar R and McEwan IJ 2012).

SHs are synthesized from cholesterol in the adrenal cortex (glucocorticoids, mineralocorticoids, and adrenal androgens), the testes (testicular androgens, estrogen), and the ovary and placenta (estrogen and progestogen or progestins) (Payne AH & Hales DB 2004; Hu J et al. 2010;). SHs reach their target cells via the blood, where they are bound to specific carrier proteins (Grishkovskaya I et al. 2000; Hammond GL 2016). SHs detach from the carrier proteins and because of their lipophilic nature readily diffuse through the plasma membrane of cells (Oren I et al. 2004). Within the target cells SHs bind to steroid hormone receptors (SHRs) which are present in a heterocomplex with heat shock protein HSP90 and co-chaperones (e.g., immunophilins p23) (Echeverria PC & Picard D 2010). The ATP-bound form of HSP90 and chaperone-mediated conformational changes are required to keep SHRs in a ligand binding-competent state (McLaughlin SH et al. 2002; Pratt WB et al. 2008; Krukenberg KA et al. 2011).

Preceded by: FKBP4 replaces FKBP5 within HSP90:ATP:FKBP5:unfolded protein, p23 (PTGES3) binds HSP90:ATP:FKBP4:nascent protein

Followed by: HSP90:ATP:p23:FKBP52:SHR:SH translocates to the nucleus

Literature references

- Kumar, R., McEwan, IJ. (2012). Allosteric modulators of steroid hormone receptors: structural dynamics and gene regulation. *Endocr. Rev.*, 33, 271-99. ↗
- Echeverria, PC., Picard, D. (2010). Molecular chaperones, essential partners of steroid hormone receptors for activity and mobility. *Biochim. Biophys. Acta*, 1803, 641-9. ↗

Editions

2016-09-17	Reviewed	Rothfels, K.
2016-11-19	Authored	Shamovsky, V.
2017-02-22	Reviewed	Picard, D., Echeverria, PC.
2017-02-25	Edited	Shamovsky, V.

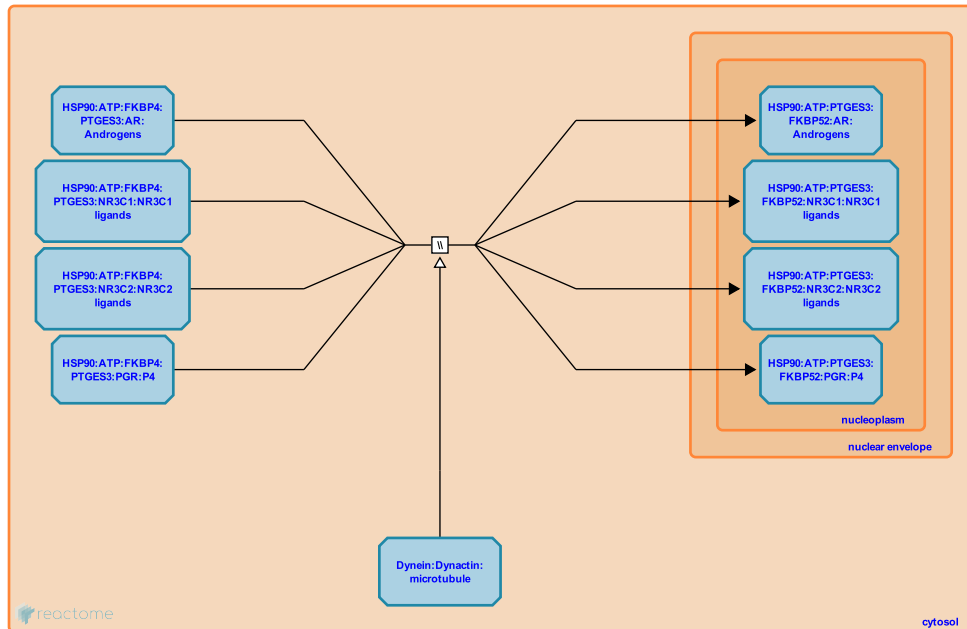
HSP90:ATP:p23:FKBP52:SHR:SH translocates to the nucleus ↗

Location: HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of ligand

Stable identifier: R-HSA-5618080

Type: omitted

Compartments: cytosol, nuclear envelope, nucleoplasm



Steroid hormone receptors (SHRs) are shuttling proteins, which continuously undergo nuclear import and export. Although the various SHRs have different resting localizations in cells, rapid and almost complete nuclear translocation following ligand addition is a common behavior observed for almost all SHRs (except the already nuclear estrogen receptors). The Reactome event shows microtubule-associated nuclear translocation through the recruitment of the large immunophilin FKBP52 (FKBP4) to the SHR:HSP90 complex (Galigniana et al. 2002; Wochnik et al. 2005; Davies and Sanchez 2005; Galigniana MD et al. 2010). FKBP52 links glucocorticoid receptor (GR):HSP90 and mineralocorticoid receptor (MR):HSP90 complexes to dynein/dynactin motors favoring transport of the cytoplasmic SHR to the nucleus (Wochnik et al. 2005; Gallo L et al. 2007). Moreover, the cytoplasmic-nuclear movement of GR was blocked in fibroblasts co-expressing dynamitin, which dissociates dynein from its cargoes (Harrell et al. 2004). FKBP52 directly binds to the motor protein dynein through the peptidyl-prolyl isomerase (PPIase) domain (Wochnik et al. 2005). Interestingly, the PPIase domain of another immunophilin FKBP51 (FKBP5) is unable to interact with dynein. Without hormone, FKBP51 is the major immunophilin in GR:HSP90 complexes, whereas after hormone treatment, FKBP52 rapidly replaces FKBP51 such that these complexes are now able to translocate to the nucleus with an accelerated rate (Davies et al. 2002). In addition, replacement of FKBP52 by FKBP51 favored the cytoplasmic localization of MR (Galigniana MD et al. 2010). On the other hand, GR was apparently able to translocate to the nucleus with the same rate even if the microtubule network was completely disrupted suggesting that the subcellular localization of SHRs can be controlled by several coexisting mechanisms (Czar et al. 1995). Indeed, in yeast and mammalian cells liganded and unliganded SHRs can bind several importins to be translocated into the nucleus (Freedman & Yamamoto 2004; Picard & Yamamoto 1987). In addition, importin beta and the integral nuclear pore glycoprotein NUP62 interact with HSP90, HSP70, p23, and the TPR domain proteins FKBP52 and PP5. NUP62 and GR are able to interact in a more efficient manner when chaperoned by the HSP90-based heterocomplex (Echeverria et al. 2009). GR cross-linked to the HSP90 heterocomplex is able to translocate to the nucleus in digitonin-permeabilized cells treated with steroid, suggesting that GR

could pass through the pore in its untransformed state (Echeverria et al. 2009).

Preceded by: [NR3C2 ligands bind NR3C2 \(in the HSP90 chaperone complex\)](#), [NR3C1 ligands bind NR3C1 \(in the HSP90 chaperone complex\)](#), [Androgens binds AR \(in the HSP90 chaperone complex\)](#), [P4 bind PGR \(in the HSP90 chaperone complex\)](#)

Followed by: [ATP hydrolysis by HSP90](#)

Literature references

Galigniana, MD., Erlejman, AG., Monte, M., Gomez-Sanchez, C., Piwien-Pilipuk, G. (2010). The hsp90-FKBP52 complex links the mineralocorticoid receptor to motor proteins and persists bound to the receptor in early nuclear events. *Mol. Cell. Biol.*, 30, 1285-98. [↗](#)

Wochnik, GM., Rüegg, J., Abel, GA., Schmidt, U., Holsboer, F., Rein, T. (2005). FK506-binding proteins 51 and 52 differentially regulate dynein interaction and nuclear translocation of the glucocorticoid receptor in mammalian cells. *J. Biol. Chem.*, 280, 4609-16. [↗](#)

Editions

2016-09-17	Reviewed	Rothfels, K.
2016-11-19	Authored	Shamovsky, V.
2017-02-22	Reviewed	Picard, D., Echeverria, PC.
2017-02-25	Edited	Shamovsky, V.

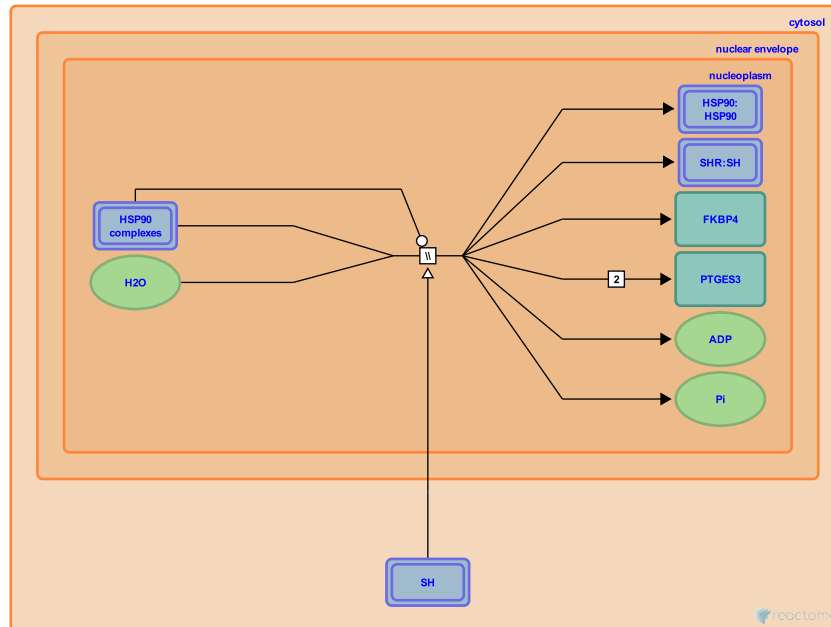
ATP hydrolysis by HSP90 ↗

Location: HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of ligand

Stable identifier: R-HSA-5618093

Type: omitted

Compartments: nucleoplasm



The chaperoning function of HSP90 is coupled to its ATPase activity. Our current understanding of the ATPase mechanism of Hsp90 is based largely on structural and functional studies for the *Saccharomyces cerevisiae* Hsp90 complexes (Meyer P et al. 2003, 2004; Ali MM et al. 2006; Prodromou C et al. 2000; Prodromou C 2012). The ATPase cycle of human HSP90 is less well understood, however several studies suggest that the underlying enzymatic mechanisms and a set of conformational changes that accompany the ATPase cycle are highly similar in both species (Richter K et al. 2008; Vaughan CK et al. 2009). Once ATP is bound it helps to stabilize the closed ATP lid state, in which the gamma-phosphate of ATP provides a hydrogen bonding that promotes a stable association of the ATP lid with N-terminal domain (NTD) (Ali MM et al. 2006; Prodromou C et al. 2000; Chadli A et al. 2000). The association of ATP with NTD then stimulates structural changes in NTD and in the middle domain that are likely to involve movements of the ATP lid segment within each N-terminal domain that locates over the bound ATP. The movement of the lids exposes surface residues that are subsequently involved in transient dimerization of the N-terminal domains of HSP90 (Ali MM et al. 2006; Prodromou C et al. 2000; Chadli A et al. 2000). Furthermore, the intrachain associations of NTD with the middle domain leads to the active conformation of the catalytic loop of HSP90, which commits the ATP for hydrolysis (Meyer P et al. 2003). The subsequent conformational changes upon ATP binding are regulated by co-chaperone activities. For example, 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). In addition, client protein binding to HSP90 was found to increase ATPase activity of HSP90 up to 200-fold (McLaughlin SH et al. 2002).

After hydrolysis of ATP the ligand-bound steroid hormone receptor (SHR) is released from HSP90 complex. The Reactome module describes ATPase activity of HSP90 in the nucleus, however it is not entirely clear whether cytosolic hormone-bound SHR translocates through the nuclear pores before or after ATP-dependent dissociation from the HSP90 complex.

Preceded by: [HSP90:ATP:p23:FKBP52:SHR:SH translocates to the nucleus](#)

Literature references

Li, J., Sun, L., Xu, C., Yu, F., Zhou, H., Zhao, Y. et al. (2012). Structure insights into mechanisms of ATP hydrolysis and the activation of human heat-shock protein 90. *Acta Biochim. Biophys. Sin. (Shanghai)*, 44, 300-6. [↗](#)

Editions

2016-09-17	Reviewed	Rothfels, K.
2016-11-19	Authored	Shamovsky, V.
2017-02-22	Reviewed	Picard, D., Echeverria, PC.
2017-02-25	Edited	Shamovsky, V.

Table of Contents

Introduction	1
☰ HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of ligand	2
↳ HSP70 binds to HSP40:nascent protein	4
↳ ATP hydrolysis by HSP70	5
↳ STIP1(HOP) binds HSP90 and HSP70:HSP40:nascent protein	7
↳ ATP binding to HSP90 triggers conformation change	9
↳ FKBP5 binds HSP90:ATP:STIP1:HSP70:nascent protein	11
↳ FKBP4 binds HSP90:ATP:STIP1:HSP70:nascent protein	12
↳ p23 (PTGES3) binds HSP90:ATP:FKBP4:nascent protein	14
↳ p23 (PTGES3) binds HSP90:ATP:FKBP5:nascent protein	15
↳ FKBP4 replaces FKBP5 within HSP90:ATP:FKBP5:unfolded protein	16
↳ Androgens binds AR (in the HSP90 chaperone complex)	17
↳ P4 bind PGR (in the HSP90 chaperone complex)	19
↳ NR3C1 ligands bind NR3C1 (in the HSP90 chaperone complex)	21
↳ NR3C1 binds NR3C1 agonists	23
↳ NR3C2 ligands bind NR3C2 (in the HSP90 chaperone complex)	24
☰ HSP90:ATP:p23:FKBP52:SHR:SH translocates to the nucleus	26
☰ ATP hydrolysis by HSP90	28
Table of Contents	30