ATP hydrolysis by HSP90

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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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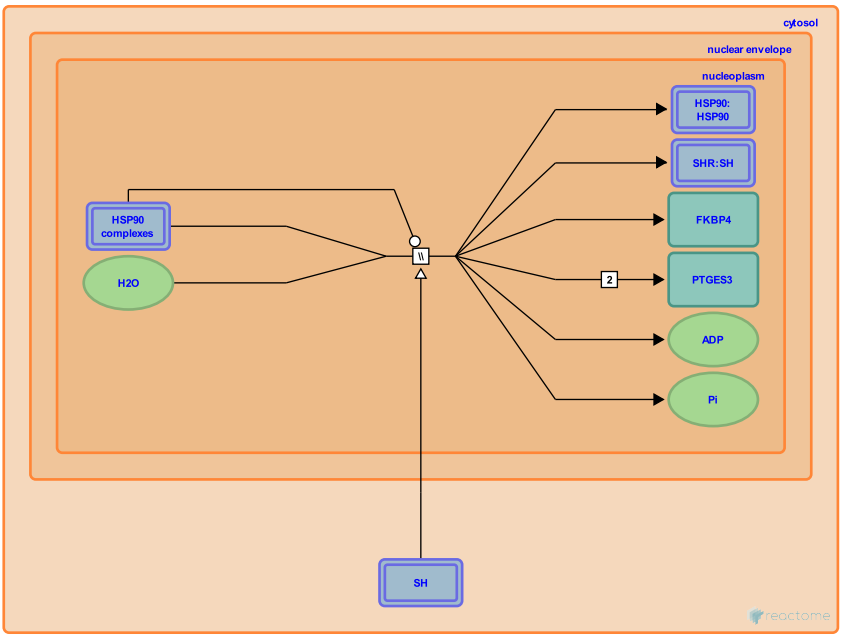
Type: omitted

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 studied 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.

Literature references

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Editions

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