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STRUCTURE AND FUNCTION
OF MOLECULAR CHAPERONE HSP90

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Introduction
Heat shock proteins (HSPs), an important group of molecular chaperones, belong to a protein family whose members can establish transitional complexes with virtually almost all proteins produced in living cells. They assist in a polypeptide chain folding and maintaining proper higher-order structures of client proteins. Using simple models it has been suggested (Anfinsen, 1973; Dobson and Karplus, 1999) that a manner in which protein molecule can fold depends on its amino acid sequence and that sequence itself is sufficient to set up an active protein. This idea has been based on a premise that for a given amino acid sequence there is only one highly preferred and energetically most suitable state of the macromolecule (Fitzkee et al., 2005; Vendruscolo et al., 2003). However, extrapolation of this view to other, often extremely complex proteins, seemed to be hardly likely. In addition, a very high concentration of proteins (up to 400g/L) inside the cell favouring intermolecular interactions does not result in non-productive aggregation under normal conditions (Ellis, 2001). Moreover, high protein concentrations at sites of their production do not lead to non-desired interactions among nascent polypeptide chains mediated by exposed hydrophobic residues and unstructured segments. To counteract these sort of effects the cells have been equipped with a web of molecular chaperones assisting in proper polypeptide folding and protein assembly. It has been shown (Dobson, 2003; Young et al., 2004) that the protein folding is strictly controlled from the very beginning by a chaperone binding to nascent polypeptides to stabilize their structure and/or prevent formation of premature protein assemblies with inappropriate intra- and intermolecular interactions. In general, chaperones represent a class of auxiliary proteins that could reversibly associate in a stoichiometric manner with nascent or near native proteins to assist in their correct folding without forming a part of the mature protein with which they interact (Rutherford, 2003; Young et al., 2004).

Heat shock proteins, discovered in the middle of twentieth century in ‘puffs’ of lampbrush chromosomes from heat-shocked fruit flies Drosophila melanogaster (Cossins, 1998), represent one of the most abundant cellular proteins. The term heat shock proteins is somehow misleading and refers only to one of the conditions under
which these proteins could be induced. In fact, the HSP synthesis is promoted by virtually all kind of stressors, including oxidative stress and free radical damage, exposure to heavy metals, spontaneous mutations or chronic degenerative diseases. Thus, they should be more correctly described as 'stress proteins' (Baga-tell and Whitesell, 2004; Cos-sins, 1998). The essential function of HSP proteins is to prevent inappropriate interactions within and between cellular proteins and/or to restore a native structure in the proteins damaged by stress, and if these measures fail, the HSPs may also facilitate degradation of misfolded proteins by ubiquitin-proteasome pathway (McClellan et al., 2005).

Roughly, three functional groups of heat shock proteins could be distinguished: (i) a subgroup, including members of Hsp70 family, which binds to nascent proteins on the ribosomes, (ii) a group represented by HSP90 family members whose main function is to facilitate final folding stage of the near-mature proteins, and (iii) a group of chaperones from Hsp104 family that can resolubilize aggregated polypeptides and recycle them through the chaperone network (Young et al., 2004). A division of HSP proteins into six families (HSP100, HSP90, HSP70, HSP60, HSP40 and small HSPs) is based on their molecular masses in kilodaltons and a sequence homology within family members (Muchowski and Wacker, 2005). Most of the HSP proteins is already abundant in normal unstressed cells but their level can increase in response to stressors. This property as well as a high evolutionary conservation of the Hsp genes that are present in virtually all prokaryotic and eukaryotic cells (Chen et al., 2006) shows that they are engaged in crucial and conservative cell functions.

The HSP90 chaperone family constitutes up to 1-2% of the total cytosolic proteins and their abundance may increase about twofold under stress conditions (Whitesell and Lindquist, 2005). Hsp90, a dimeric protein consisting of three domain (N-terminal ATP-binding domain, a middle region and a C-terminal domain involved in homodimerization) is featured by a capability of specific interaction at a late stage of folding with a set of cellular proteins engaged in regulatory or signalling pathways, such as transcription factors and protein kinases (Buchner, 1999). HSP90 is also involved in reactivation of inactivated or denatured proteins under environmental stress conditions (Nathan et al., 1997).

**Structure and diversity of HSP90 family**

HSP90 has a strong tendency to form dimers, mostly homodimers. Each HSP90 monomer has a complex structure consisting of a negatively charged and variable in length middle region that is flanked by conservative N- and C-terminal domains (Prodromou and Pearl, 2003). Hsp90 promoters have a parallel linear arrangement so that N-terminal domains are at one end
of the dimer and the C-terminal domains at the other (Fig. 1). The protomers make a left-handed helical twist around the long axis of the dimer (Ali et al., 2006). A 25-kDa N-terminal domain is a binding site for both ATP and anticancer agents geldanamycin (GA) and radicicol. As revealed by X-ray crystallography, the N-terminus co-crystallized with GA contained nine α-helices (four of them of 3_10 type) and an antiparallel β-sheet of eight strands folded together into an α+β sandwich arranged in two layers. A hydrophobic pocket, about 15 Å deep and 10 Å in diameter, placed in the central part of N-terminal domain is the site for ATP and GA binding (Prodromou et al., 1997; Stebbins et al., 1997). ATP binding is followed by a conformational alteration in the domain (McLaughlin et al., 2004). Owing to an unconventional ATP-binding motif sometimes referred to as a Bergerat fold, the HSP90 belongs to GHKL superfamily (which includes DNA gyrase, HSP90, histidine kinases EnvZ and CheA and DNA-mismatch-repair MutL protein) (Dutta and Inouye, 2000). The N-domain is connected to a middle segment through a loop with an antiparallel β-strands separated by a charged linker.

The middle domain with a large three-layer αβα sandwich at its N-terminus connected to a smaller αβα domain at the C-terminus via an α3 helical coil is similar to that of dimeric GHKL proteins (Meyer et al., 2003; Pearl and Prodromou, 2006). A ten-residue amphipathic loop interacting with client proteins (Ali et al., 2006) projects from the inner face of the large αβα domain towards its counterpart in the other monomer. An extended 25-residue loop links the middle segment with the beginning of a curved α-helix at the start of the C-domain. A carboxy-terminal domain tail-to-tail dimerization is important for the HSP90 function as only dimers are fully active (Chadli et al., 2000). The dimer interface is formed by a pair of helices from each monomer packed together to create a four-helix bundle. At the very end of the C-terminus is located a conserved pentapeptide MEEVD implicated in binding TPR-domain co-chaperons (D'Andrea and Regan, 2003). Although the main ATP-binding domain resides in the N-terminus, there is evidence that the HSP90 C-terminus is harbouring a second site of ATP binding (Marcu et al., 2000). The C-terminal domain could bind novobiocin and cisplatin (Soti et al., 2002), and unexpectedly it possesses a weak but detectable affinity for ADP and GTP (Soti et al., 2002) that could be discernible only after a prior ATP binding to the N-terminal pocket. ATP-free HSP90 molecule assumes a bent conformation in which C-terminal domain is in a close contact with a charged region of the middle domain. Now, the only exposed motif available for ATP-binding resides in the aminoterminal domain. ATP binding to this site induces a conformational alteration which promotes binding of the lysine in the middle domain with the ATP γ-phosphate group.
liberating C-terminal ATP-binding motif (Soti et al., 2002). Despite low ATP hydrolysis rate (Scheibel et al., 1998), the C-terminus seems to be indispensable for HSP90 function in vivo (Panaretou et al., 1998).

Fig. 1. An outline of monomer structure of yeast Hsp90 with details of N-terminal, middle and C-terminal domains (Ali et al., 2006; Pearl and Prodromou, 2006).
Detailed molecular rearrangements during Hsp90 binding to its substrates and cochaperones have been clarified by a crystal structure determination in a complex with non-hydrolysable ATP analogue and the co-chaperone p23/Sba1 (Ali et al., 2006). The N-terminal β-strand (residues 1-9) of each monomer crosses over to make hydrogen bond to the edge of the main β-sheet in the N-terminal domain of the other monomer with concomitant movement of the first α-helix (residues 13-22) so that the lid segment (residues 94-125) swings nearly 180° to fold over the mouth of the nucleotide-binding pocket. This event exposes a hydrophobic region that forms an interface with which may interact a similar region of the adjacent monomer domain. Although the middle domains move closer to each other, they still stay separated. Each of the middle domains interact with the N-domain of the other monomer as well as with its own N-domain. Now, the 118-GXXGXG123- motif at the C-
terminal end of the lid is wrapped around the β- and γ-phosphates and distal parts of the lid interact with ribose ring of the bound ATP (Fig. 2). In the middle segment, a catalytic loop (residues 370-390) forming a short helix now unravels and extends down towards the opening of the nucleotide-binding pocket in the N-terminal domain. Activating cochaperone Aha1 promotes the mobility of this loop (Pearl and Prodromou, 2006).

<table>
<thead>
<tr>
<th>Protein</th>
<th>Species or cell compartment</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSP90α</td>
<td>Homo sapiens (major isoform)</td>
</tr>
<tr>
<td>HSP90β</td>
<td>Homo sapiens (minor isoform)</td>
</tr>
<tr>
<td>HSP90N</td>
<td>Homo sapiens</td>
</tr>
<tr>
<td>HSP86</td>
<td>Mus musculus</td>
</tr>
<tr>
<td>HSP84</td>
<td>Mus musculus</td>
</tr>
<tr>
<td>HSP83</td>
<td>Drosophila melanogaster</td>
</tr>
<tr>
<td>Hsc82</td>
<td>Saccharomyces cerevisiae</td>
</tr>
<tr>
<td>HSP82</td>
<td>Saccharomyces cerevisiae</td>
</tr>
<tr>
<td>HtpG</td>
<td>Escherichia coli</td>
</tr>
<tr>
<td>Grp94/gp96</td>
<td>Endoplasmic reticulum</td>
</tr>
<tr>
<td>TRAP1(HSP75)</td>
<td>Mitochondrial matrix</td>
</tr>
<tr>
<td>cpHSP82</td>
<td>Chloroplasts</td>
</tr>
</tbody>
</table>

Table 1. Members of HSP90 family.

HSP90 chaperons are members of a large protein family (Table 1) present in bacteria, yeast and multicellular organisms (Chen et al., 2006) with homologous proteins occurring not only in cytoplasm but also in endoplasmic reticulum, mitochondria and chloroplasts (Buchner, 1999; Csermely et al., 1998). There are two main cytoplasmatic HSP90 isoforms: an inducible HSP90α and constitutively expressed HSP90β.

The isoform HSP90α is usually less abundant, but its amount can increase under stress conditions. Slight differences in carboxy-terminal domain (Chen et al., 2005) are responsible for a weaker stability of ββ dimers, as compared to αα dimers. At low abundance, both isoforms can also exist as mono-mers, heterodimers αβ and oligo-mers. Although nucleotide sequen-ces of both forms are 76% identical and probably originated as a consequence of a gene duplication about 500 millions years ago, their amino acid sequences are less divergent, because differences are localised mostly in 5' and 3' untranslated regions, promoters and introns (however, most eukaryotic Hsp genes do not contain introns) (Csermely et al.,...
1998; Sreedhar et al., 2004). Recently, an additional isoform HSP90N was detected (Grammatikakis et al., 2002). This isoform is a 75 kDa protein with a shortened N-terminal domain consisting of 30 amino acids only and therefore deprived of ATPase function.

The other members of HSP90 family are Grp94, TRAP1 (HSP75) and cpHSP82 (Table 1 and Figure 3) (Sreedhar et al., 2004; Young et al., 2001). Chaperone Grp94 (glucose-regulated protein with molecular mass of 94 kDa), the most abundant protein of the endoplasmic reticulum (ER), is about 50% homologous to cytoplasmatic forms of HSP90, whereas TRAP1 (TNF receptor-associated protein 1), localised in mitochondrial matrix, is only 35% identical so that it exhibited less similarity to its eukaryotic counter-parts than to prokaryotic HSP90 homologue named HtpG). While the function of cytoplasmatic forms of HSP90 is quite broad, the organellar members of the family, restricted to higher eukaryotes, are more specialized (Picard, 2002).

![Diagram of HSP90 variants](image)

Figure 3. Domain structure of various HSP90 variants: ATP, ATP-binding N-terminal domain (blue), charged region (yellow) with the rest of middle domain (purple) and C-terminal dimerization domain (dimer, red). Mitochondrial and endoplasmic reticulum signal sequences are indicated with 'M' and 'ER', respectively. Conserved C-terminal amino acid sequences are shown in a single letter code. The length of each protein is provided. Data are from (Buchner, 1999; Sreedhar et al., 2004; Wegele et al., 2004).
Table 2. A partial list of cochaperones and representatives of HSP90 client proteins (a full list is available at http://www.picard.ch/)

<table>
<thead>
<tr>
<th>Cochaperones:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aha1 and its homologue Hch1;</td>
</tr>
<tr>
<td>Cdc37/p50 and its homologue Harc</td>
</tr>
<tr>
<td>Hsj, human DnaJ homologue</td>
</tr>
<tr>
<td>HSP70 (Ssa1p);</td>
</tr>
<tr>
<td>HSP40 (Hdj1, Ydj1p);</td>
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<tr>
<td>Sba1/p23</td>
</tr>
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**Proteins with TPR motifs:** CHIP (an E3/E4-ubiquitin ligase required for proteasome-targeted destruction); Cns1 (cyclophilin seven supressor 1); Cyclophilin Cyp40 (Cpr6, Cpr7) and immunophilins FKBP51, FKBP52 (peptidyl-prolyl isomerases); HOP (p60, Sli1); PP5 phosphatase (Ser/Thr protein phosphatase).

**Client proteins:**

**Transcription factors:** Steroid hormone receptors: androgen, estrogen, glucocorticoid, mineralcorticoid and progesteron receptors; HSF-1; IRF2; p53; PPARα and β; STAT3;

**Kinases:** Akt/PTB; Aurora B; Bcr-Abl; casein kinase II; Cdk2; Cdk4; Cdk6; Cdc9; Chk1 (checkpoint kinase 1); ErbB2; Insulin receptor; JAK1; MEK; c-Mos; PKCλ; Polo; Raf-1, RET/PTC1; SRC-related; Wee1;

**Other:** calcineurin; calmodulin; CFTR; cytoskeletal proteins: actin, myosin, tubulin; DNA polimerase α; G protein (subunits α9, α12, βγ); HDAC6; Histones H1, H2A, H2B, H3 and H4; MRE11/Rad50/NBS1; MMP2 (matrix metalloproteinase 2); MTG8; Neuropeptide Y; Prolactin receptor; Proteasome; Smyd3; SV40 large T-antigen; α-Synuclein; Tau protein; Telomerase; Vimentin.

**HSP90 substrates**

Heat shock protein 90 is able to interact with an enormous number of highly specialized cellular substrate proteins called client proteins (Table 2) among which are steroid hormone receptors (SHR), tran-scription factors and plethora of kinases and other cellular proteins (Wegele et al., 2004). A formation of compact form of HSP90 dimer is directly controlled by ATP/ADP deposition and co-chaperone binding and most of interactions between HSP90 and substrates are localized on external interfaces formed during conformational arrangements (Ali et al., 2006; Shiu et al., 2006). Although HSP90 do not exhibit any specificity to a particular amino acid motif, it can recognize its client pro-teins in a specific manner.

HSP90 is an indispensable agent for activation of viral kinase p60^src that in its active state is attached to the plasma membrane and causes oncogenic proliferation of infected cells. Initially, kinase
p60\textsuperscript{v-src} is a soluble protein with a high affinity to HSP90. In this complex it is subjected to phosphorylation and myristylation and is finally transported in a direct proximity of plasma membrane where it is released (Buchner, 1999; Yahara, 1999). By contrast, its close homolog p60 \textsuperscript{c-src}, a constituent of regular cells, is far less dependent on HSP90 (Sangster et al., 2004).

Most of the HSP90 clients are transcription factors, housekeeping proteins or protein components of various signaling pathways controlling development and basic function of the living cells (Table 2). Little is known about a specificity of the HSP90 isoforms. The chaperone HSP90N can specifically interact with a Raf kinase and translocate it to a plasma membrane independently of c-Ras pathway (Grammatikakis et al., 2002). Although cytosolic HSP90 isoforms could also activate Raf kinases (van der Straten et al., 1997) it is believed (Grammatikakis et al., 2002) that most of their activity is owned to HSP90N.

Taken together, HSP90s are unique among other heat shock proteins most of which, including the best examined HSP70, associate with their clients already during their synthesis or when they recognize hydrophobic residues on the surface of damaged proteins. In contrast to other HSPs, the clients of HSP90 are highly specific near-native metastable proteins (Wegele et al., 2004). Usually, the interaction of HSP90 with its client proteins is involved in their translocation, activation or/and stabilization (Young et al., 2003). Unfortunately, we do not know what determines the affinity of HSP90 to each protein and as noted above no specific sequence motifs have been identified so far.

**HSP90 co-chaperones**

In addition to its clients, HSP90 interacts with a special group of proteins including other chaperones which can form multiprotein complexes. These proteins are referred to as co-chaperons (Table 2). A make-up of these complexes is diverse and directly determines the kind of interacting clients. Most of the co-chaperons harbour TPR (tetra-trico-peptide repeat) domains, 34-amino-acid degenerate repeat sequences, with help of which the proteins interacts with each other (D’Andrea and Regan, 2003; Young et al., 2004). TPR domains have a high affinity to carboxy-terminal pentapeptide MEEVD of the HSP90 (Fig. 3). A similar motif EEVD can be found at HSP70 C-terminus (Wegele et al., 2004). This highly conserved sequence contributes in a significant way to the affinity of HSP90 to its TPR – containing co-chaperones (Pearl and Prodromou, 2006).

The best studied example of the cooperation between HSP90 and other co-chaperones is activation of steroid hormone receptors (SHRs) (Grad and Picard, 2007; Pratt and Toft, 2003). In the absence of ligand the steroid hormone receptors are bound into complexes containing HSP90. The HSP90
chaperone allows the receptor to achieve a structural conformation that is competent for ligand binding, nuclear translocation and consequently, gene regulation (Kovacs et al., 2005a). The chaperone multiprotein complex is changing in a cyclic manner so that the successive auxiliary proteins (mainly co-chaperones) associate and dissociate in due time from the complex after fulfilling their function. In addition, the whole process is depended on and regulated by ATP (Fig. 4). The minimal complex indispensable for SHR activation encompasses HSP40, HSP70, HOP (Hsp organizing protein), HSP90 and p23/Sba1 protein (Kosano et al., 1998). Initially, just after completion its translation, the steroid hormone receptor binds to HSP40 and HSP70 (Fig. 4a). Then it is donated to the HSP90 through interaction with HOP protein (Wegele et al., 2004) that is almost entirely composed of TPR domains and serves as a linker between HSP70 and HSP90 connecting them by their carboxy-terminal domains (Odunuga et al., 2004). This transfer takes place only if ADP is bound to HSP90. The exchange of ADP to ATP inside N-terminal pocket induces dissociation of HSP70 and its co-chaperones from the complex that now is free to associate with protein p23/Sba1, which binds to the N-terminal side of HSP90 dimer and prevents ATP hydrolysis (Ali et al., 2006; McLaughlin et al., 2002), and immunophilin, which generally substitutes for HOP (Fig. 4). Until recently, the function of immunophilins FKBP51 (FK-506-binding protein 51) and FKBP52 with peptidyl-prolyl cis-trans isomerase activity (Davies and Sanchez, 2005) that can catalyze the conversion of prolyl–peptide bonds from trans- to cis-proline, often a rate-limiting step in protein folding, was little known. The name for FKBP5s derives from their ability to bind immunosuppressive drug FK-506 (Davies and Sanchez, 2005). Recently, it has been reported (Pratt et al., 2004) that they are responsible for transportation of HSP90-SHR-ligand complexes along the microtubule fibers. In this way a translocation of hormones (Davies and Sanchez, 2005; Pratt et al., 2004), p53 protein (Galigniana et al., 2004) and probably other HSP90 substrate proteins within cytoplasm is fast and tightly controlled. ATP hydrolysis inside HSP90 nucleotide-binding pocket leads to the dissociation of the complex, and liganded steroid hormone receptors dimerize and are translocated to the nucleus (Fig. 4d). Subsequently, SHR-hor-mone complexes bind to particular DNA sequences in the promoters of hormone-responsive genes to control their transcription. Remarkably, the movement of SHRs inside the nucleus is also HSP90- and ATP-dependent (Elbi et al., 2004). Details of the translocation of liganded SHRs are still unclear (Grad and Picard, 2007) and likely depend on HSP90-HSP70 complexes that could be transmitted through the nuclear envelope pores as a whole to deliver the signal to the nuclear interior in a direct vicinity of the chromatin (Pratt et al., 2004). But
on the other hand an opposite scenario in which steroid hormone receptors could shuttle between separate HSP90 molecular complexes on both sides of the nuclear envelope is also possible (Elbi et al., 2004).

Fig. 4. HSP90-dependent cycle of steroid hormone receptor (SHR) activation. 
a) Establishing HSP70-SHR complex; b) transmission of SHR onto HSP90 dimer with the help of HSP70 and HOP; c) association of p23/Sba1 rearranges HSP90 conformation.

Now, if the chaperone binds geldanamycin, which mimics ADP binding, proteins p23 and HOP dissociate. CHIP, an E3 ubiquitin ligase, is attached to the complex and SHR receptor is being degraded through the proteasome-mediated pathway. On the other hand, if HSP90 binds ATP, the HSP70 and its co-chaperones dissociate giving the place for immunophilins (FKBP51, which is substituted following ligand binding by FKBP52); d) HSP90-immunophillin-p23 complex activates SHR, which can now bind a steroid
hormone. After that the complex binds to dynamitin and dynein, the microtubule-associated proteins, and is moving along cytoskeleton structures towards nucleus. Liganded SHRs dimerize and interact with promoter sequences of target genes. For simplicity, the HDAC6 influence has been omitted. See text for details.

As mentioned above, the ATPase function of HSP90 is crucial for determining its full activity. If ADP/ATP binding pocket is occupied by inhibitory agents mimicking nucleotide structure (radicicol, gelda-namycin and their relatives), the client protein cannot dissociate from the chaperone complex and will bind CHIP, an E3 ubiquitin ligase, which stimulates proteasomal degradation of the client protein (Fig. 4c) (Chiossi et al., 2004; Cyr et al., 2002; Neckers and Neckers, 2005).

A large set of HSP clients are protein kinases (Table 2). The interaction between Hsp90 and kinases is facilitated by Cdc37 chaperone (Caplan et al., 2007). The Cdc37 binds both to a catalytic domain of the kinase and to the N-terminal domain of HSP90. Cdc37 dimers localized between N-termini and the charged region of middle domains of HSP90 prevent ATP hydrolysis, as p23/Sba1 does (Roe et al., 2004; Zhang et al., 2004). Additionally, HSP90-Cdc37-kinase complexes include other specific proteins like HOP, Aha1 and protein phosphatase PP5 (Pearl, 2005).

Both HSP90 structure and ATPase activity are influenced by co-chaperone binding. Initially, ATP hydrolysis rate is almost undetectable but increases up to 200-fold after binding of glucocorticoid recap-tor (Pratt et al., 2004). The co-chaperons HOP, p23/Sba1, Aha1 and others act as HSP90 suppressors or activators that regulate a shift in its structure or/and ATPase activity (Pearl and Prodromou, 2006).

Recent investigations indicate that a reversible acetylation of HSP90 is a key factor in controlling its function. Yu and co-workers (Yu et al., 2002) established that HSP90 is one of many substrates for histone deacetylase HDAC6. Inactivation of HDACs using specific inhibitors (Bali et al., 2005), RNA interference (Murphy et al., 2005) or mutational analysis (Scroggins et al., 2007) leads to hyperacetylation of HSP90, including a conserved K294 in the middle domain (Scroggins et al., 2007), and rapid disassembly of the multiprotein complexes (Murphy et al., 2005) or even proteosomal degradation of clients such as Raf-1, AKT, Bcl-Abl and p53 proteins (Bali et al., 2005; Yu et al., 2002). Hypera-cetylated HSP90 forms only short-lived complexes incapable of effective and stable SHR ligand binding, nuclear translocation and gene activation (Murphy et al., 2005); (Kovacs et al., 2005b). Acetylated HSP90-SHR complex has a low affinity to ATP and p23/Sba1 co-chaperone what prevents further remodeling and SHR receptor activation (Murphy et
al., 2005). HDAC6 is a unique histone deacetylase because of its cytoplasmatic localisation where it associates with microtubules to deacetylate α-tubulin (Boyault et al., 2007). Presumably, HDAC6 keeps a low level of HSP90 acetylation during the translocation of the complex along microtubules (Fig. 4d). Although an enzyme acetylating HSP90 protein has not been revealed yet (Scroggins et al., 2007), it should be localised in the vicinity or inside the nucleus. HSP90 appears to become transiently acetylated upon receptor activation after ligand stimulation (Kovacs et al., 2005a). HSP90 acetylation might allow the conversion of SHR-HSP90 from a stable complex into a dynamic one by dissociating p23/Sba1 from the HSP90 complex, thereby enabling SHR to enter the nucleus for transcriptional activation. As acetylated HSP90 exhibits reduced binding toward SHR and p23/Sba1, the subsequent deacetylation by HDAC6 would then allow HSP90 to restore the productive chaperone complex (Kovacs et al., 2005a). Therefore, HSP90 acetylation may represent a regulatory signal triggering a discharge of the SHR-HSP90 complexes. After SHR release, the deacetylase HDAC6 may sneak again to the complex to restore a low level of HSP90 acetylation.

Although HSP90 function seems to be inseparably associated with a large number of chaperones and other proteins, it turned out that HSP90 can go without cochaperones and retain its chaperone activity outside the cell as well. In some cases HSP90 is expressed extracellularly where it interacts with MMP2 (matrix metalloproteinase 2), an enzyme involved in spreading and invasion of tumour cell (Eustace et al., 2004). Most interestingly, only HSP90α isoform, but not HSP90β, take part in this process. This is a direct evidence for functional diversification among HSP90 variants (Eustace et al., 2004).

**HSP90 function**

A basic HSP90 function, shared by all heat shock proteins, is a protection ("chaperoning") against a loss of activity by other proteins under stress conditions. Under unfavourable circumstances, the proteins tend to unfold and/or aggregate. Heat shock proteins including HSP90 target conformationally altered polypeptides to restore their proper native structure. A cursory glance at the list of HSP90 client proteins (Table 2) shows that a majority of substrate proteins is engaged in multiple signaling pathways (Rutherford et al., 2007b; Soti et al., 2005; Zhao and Houry, 2007), chromatin transactions and transcriptional regulation (Wong and Houry, 2006; Zhao and Houry, 2005), cell cycle regulation (Burrows et al., 2004) and malignant growth (Beliakoff and White, 2004; Neckers, 2007). These bizarre activities could reflect a need for both quick and accurate response to external and internal stimuli. This can be achieved only through extremely precise
transduction of individual information signals through a cellular signalling network needed for cell cycle progression and regulation, and successful completion of development. The interactions of kinases, nuclear receptors and transcription factors with HSP90 enable achieving a proper and precise folding and maturation as well as movement of signal molecules to their destination within the cell (Richter and Buchner, 2001). Additionally, in last years the heat shock proteins, including HSP90, were implicated in immune responses as well (Gullo and Teoh, 2004; Nardai et al., 2006).

Although HSP90 chaperone is only one of many HSP proteins, it is an indispensable cellular protein given its ubiquitous occurrence, high evolutionary conservation and a type and number of HSP90 client proteins. In fact, detrimental effects of the lack of HSP90 was experimentally confirmed in yeast S. cerevisiae (Borkovich et al., 1989), nematode Caenorhabditis elegans (Birnby et al., 2000) and fruitfly D. melanogaster (van der Straten et al., 1997) deprived of Hsp90 genes. In mice, homozygous individuals with only one mutated gene coding HSP90β isoform, in the presence of normal HSP90α counterpart, did not develop placental labyrinth and died at early embryonic stages (Voss et al., 2000).

HSP90 through interactions with specific set of proteins can act as a genetic capacitor during exposure to stressful conditions in Drosophila (Carey et al., 2006; Debat et al., 2006; Milton et al., 2006; Rutherford and Lindquist, 1998), Arabido-psis thaliana (Queitsch et al., 2002; Sangster et al., 2007; Sangster et al., 2004; Sangster and Queitsch, 2005) and fish Danio rerio (Yeyati et al., 2007). There is a growing body of fossil records suggesting that organisms could have evolved in a rapid and step-wise manner, as opposite to a well established Darwinian model of gradual changes (Cossins, 1998). Genetic capacitors moderate expression of heritable variation and provide a mechanism for rapid evolution (Rutherford et al., 2007a; Rutherford, 2003) through stress-sensitive storage and release of genetic variation to facilitate adaptive evolution in unpredictable environments.

Literature:


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