

Chapter 2

General Structural and Functional Features of Molecular Chaperones

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Introduction to Molecular Chaperones and Stress at a Cellular Level

Molecular chaperones are the guardians of protein homeostasis. Proteins require a particular three dimensional structure in order to fulfil their function, despite being synthesised as a linear string of amino acids joined by peptide bonds. These amino acids must subsequently fold to achieve the appropriate spatial arrangement of these residues in order to arrive at the final three dimensional structure of the protein. Sequence determines structure; the information required to adopt a native three-dimensional conformation is encoded in the primary amino acid sequence, although the number of possible theoretical conformations of even a small protein is tremendously large (Anfinsen 1973). Protein folding occurs spontaneously, often in a co-translational manner, whereby the N terminus of the protein begins to fold while the C terminal regions are still being translated. The folding process is driven largely by hydrophobic amino acids within the protein as they avoid the aqueous cellular environment. Once folded, certain proteins may also associate non-covalently with other proteins into higher order functional complexes. Proteins undergo this process in a crowded intracellular environment that should favour protein aggregation and misfolding (Ellis and Hartl 1999; Ellis 2001). Protein folding is assisted by a group of proteins known as molecular chaperones (Mayer 2010). Molecular chaperones are catalysts in the physiological folding process, which, through transient non-covalent associations with proteins, prevent aggregation and misfolding during de novo folding, as well as regulating subsequent stages of protein translocation and complex formation. The importance of molecular chaperones to protein folding is enhanced

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under non-physiological or stressful conditions. Cellular stress could include a wide range of stimuli, including heat, oxidation and chemicals. The main biological consequence of cellular stress is the loss of protein function due to stress induced protein unfolding and aggregation. This loss is potentially disastrous for any cell that cannot overcome it. Molecular chaperones prevent aggregation and promote refolding after stress and hence promote cell survival. This so-called stress response is ubiquitous and conserved across all organisms. Chaperone assisted protein folding in cells is largely controlled by a group of proteins known as heat shock proteins (HSP) (Bukau et al. 2006).

Classification of Heat Shock Proteins as Molecular Chaperones

Heat shock proteins are a group of proteins that form a significant share of the molecular chaperone protein class. These proteins are required for preserving the appropriate folding and conformation of other proteins in the cell and are consequently called molecular chaperones. As a result of the discovery of heat responsive genes by Ritossa (Ritossa 1962) after heat shock of *Drosophila* salivary glands, the products of these genes were isolated and subsequently called heat shock proteins (Tissieres et al. 1974). Under conditions of stress, heat shock proteins accumulate in the cell and control the potentially deleterious consequences associated with stress by preventing protein misfolding and actively refolding proteins; inhibiting protein aggregation or self-association; if proteins are irreversibly denatured, they are handed over to the proteasome for degradation (Hendrick and Hartl 1993; Becker and Craig 1994). Stressful circumstances induce the synthesis of over twenty heat shock proteins that enable cells to adapt to environmental and metabolic changes and to survive stress conditions (Arsene et al. 2000). However other than heat stress, these proteins are induced by many types of cellular stressors including hyperthermia, exposure to heavy metals, UV radiation, oxidative stress, nutrient deficiencies, dehydration, osmotic pressures and viral infections. As a consequence, heat shock proteins have been used to study the stress response of numerous organisms and their application as biomarkers continues to receive attention, particularly for marine organisms experiencing environmental stress (Clark and Peck 2009).

Heat shock proteins are evolutionarily conserved, abundant and ubiquitous proteins in all cells and play similar roles in organisms from bacteria to humans. They are amongst the most highly expressed and can account for 1–2 % of the total protein in unstressed cells, and this can increase up to 4–6 % after heat shock (Garrido et al. 2001). Heat shock proteins are localised to different compartments in the cell, and despite being highly conserved, carry out tasks specific to their environment. Not all heat shock proteins are expressed during cellular stress; under normal growth conditions, heat shock cognate (Hsc) proteins are constitutively expressed in the absence of stress and perform critical “housekeeping” functions to maintain cellular homeostasis (Ingolia and Craig 1982; Hartl and Hayer-Hartl 2002). The large and varied heat shock protein class is grouped into several subfamilies based on their

sizes in kDa namely, small Hsps, Hsp40, Hsp60, Hsp70, Hsp90, and Hsp100. In 2009, new guidelines for the nomenclature of the human heat shock protein families were proposed, this had arisen as a result of increasing numbers of proteins and discrepancies in the existing nomenclature (Kampinga et al. 2009). In this classification, the human heat shock proteins have been renamed to the following: HSPH (former name HSP110), HSPC (HSP90), HSPA (HSP70), HSPD/E (HSP60/HSP10) and CCT (TRiC), DNAJ (HSP40), and HSPB (small HSP or sHSP) (Kampinga et al. 2009).

Heat shock proteins are integral components of the chaperone network in the cell and many of their functional cycles work in concert with a group of co-chaperones and cofactors that function as regulators (Hendrick and Hartl 1993, 1995). Molecular co-chaperones regulate the activity of selected chaperones and most can be classified according to the presence of particular domains: the bcl-2 associated athanogene (BAG) domain, the tetratricopeptide repeat (TPR) domain, or the DnaJ or J domain. Despite the fact that heat shock proteins differ in their size, structures and activity, they all bind non-native proteins (some bind native proteins as well); and some exert their functions co-translationally by interacting with nascent polypeptides, while others act post-translationally by providing an environment that enhances folding (Bhutani and Udgaonkar 2002). Most heat shock proteins are ATP-dependent and require ATP to control binding and dissociation of substrate polypeptides, while some use an ATP-independent mechanism.

The Hsp100 class of chaperones forms large hexameric structures and uses energy generated by the hydrolysis of ATP for protein remodelling (Bukau et al. 2006). The disaggregation activity of hexameric Hsp104 requires the collaboration of the Hsp70 system (Glover and Lindquist 1998). Hsp90 (HSPC) has more specialised roles in the cell. The ATP-dependent molecular chaperone Hsp90 is required for the activation and regulation of an ever growing list of client proteins involved in diverse biological processes, and unlike Hsp70 (HSPA), many of these client proteins are not in an extended conformation but are almost completely folded (Zuehlke and Johnson 2010). Many client proteins first interact with the Hsp70-Hsp40 chaperone system before being transferred to Hsp90 via the TPR-containing Hop (Hsp70-Hsp90 organising protein) (Wegele et al. 2004). The ATP-dependant chaperone activity of Hsp70 is based on the ability to bind short hydrophobic segments of proteins and this is regulated by Hsp40 (DNAJ), which functions as a co-chaperone of Hsp70 (Flynn et al. 1991; Gragerov and Gottesman 1994). The Hsp110 (HSPH) family, a subgroup of the Hsp70s, are essential nucleotide exchange factors for Hsp70 (Dragovic et al. 2006a). The highly diverse Hsp40 proteins provide specificity to the chaperone reaction by targeting substrates to Hsp70; the influence of this functional specificity of Hsp40 was the subject of a recent review by Kampinga and Craig (2010). In addition, Hsp40 proteins function as chaperones in their own right and are able to suppress protein aggregation in an ATP-independent manner (Lu and Cyr 1998).

Hsp60 (HSPD) proteins form large ring-shaped complexes composed of 14 subunits arranged in two stacked 7-membered rings, and ATP binding triggers conformational changes that result in the co-chaperone Hsp10 (HSPE) forming a lid over the structure (Braig et al. 1994). The folding of nascent polypeptides often

requires the cooperation of both the Hsp70 and Hsp60 families and these families are also responsible for most of the general folding events in the cell (Hartl et al. 1992; Fink 1999). The small heat shock proteins (HSPB) are the least conserved (Narberhaus 2002) and the least studied, due in part to the lack of a consistent model of oligomerization and substrate binding (Eyles and Gierasch 2010). The largely stress inducible small heat shock proteins function as ATP-independent chaperones to prevent protein aggregation and assist protein renaturation in cooperation with ATP-dependent chaperones (Jakob et al. 1993).

Certain heat shock proteins are essential for the maintenance of viability, eukaryotic cytoplasmic Hsp90 is essential for viability under all growth conditions (Borkovich et al. 1989). This observation has led to the emergence of Hsp90 as an anti-cancer drug target, including breast cancer (Beliakoff and Whitesell 2004). In addition to their critical role in cellular homeostasis, heat shock proteins have been implicated in the induction and propagation of human disease. New roles of heat shock proteins in human physiology and disease are rapidly emerging. This has led to the concept of chaperonopathy to indicate a pathologic condition resulting from defective chaperones (Brodsky and Chiosis 2006; Macario and Conway de Macario 2007a, b). In addition, the use of heat shock proteins as therapeutic tools and potential cancer vaccines are also being investigated (Lee et al. 2006). Heat shock proteins also play important roles in immunity and protection as well as pathogenesis of infectious diseases as both the host and pathogen increase heat shock protein production (Zugel and Kaufmann 1999). Heat shock proteins also exert their function outside of the cell and form the extracellular heat shock protein complement; these proteins reach the extracellular space via a variety of mechanisms including cell lysis and participate in processes such as cell signalling and immunity (Calderwood et al. 2007; Tsan and Gao 2009). Several extracellular heat shock proteins play a role in the migration of cancer cells and thus this population of proteins also needs to be considered in the fight against cancer (Schmitt et al. 2007; Sims et al. 2011).

Foldases: Molecular Chaperones Involved in Protein Folding

The Hsp60/Chaperonin Family of Molecular Chaperones

The Hsp60 (HSPD) family is well characterised and highly conserved. Members of the Hsp60 protein family, also referred to as chaperonins, are represented by GroEL in prokaryotes, and mitochondrial Hsp60, plastid Rubisco subunit binding protein, archaea group II chaperonins and TRiC/CCT in eukaryotes (Hartl et al. 1992). Chaperonins assist in the folding of nascent and misfolded proteins in an ATP-dependent manner (Houry et al. 1999) but their mechanism of action is different to that of Hsp70. It is estimated that under normal growth conditions, 10–15 % of all cytoplasmic proteins rely on GroEL in order to fold correctly, and this increases to 30 % under conditions of stress (Ewalt et al. 1997). Many of the cytoplasmic proteins that interact with GroEL have been identified (Houry et al. 1999) and GroEL acts

downstream of the *Escherichia coli* (*E. coli*) molecular chaperones, DnaK (prokaryotic Hsp70) and trigger factor, in the folding of 10 % of cytosolic proteins (Ewalt et al. 1997; Houry et al. 1999). In a proteomic study of *E. coli* proteins, 85 proteins were dependent on GroEL for folding and 13 of these are essential proteins (Kerner et al. 2005). GroEL is essential for viability at all temperatures in *E. coli* (Fayet et al. 1989) and *S. cerevisiae* is non-viable in the absence of CCT subunits (Stoldt et al. 1996). The TCP-1 (CCT) complex, found in the cytosol of all eukaryotic cells, is essential for enabling the cytoskeletal proteins actin and tubulin to fold and assemble into their native states (Sternlicht et al. 1993). While CCT is not upregulated during heat shock (Horwich et al. 2007), GroEL and mitochondrial Hsp60 are heat inducible. Hsp60 members also play critical roles in cell signalling, immunity as well as anti-apoptotic roles (reviewed by Calderwood et al. 2007; Chandra et al. 2007). Members of this family exhibit molecular masses of approximately 60 kDa, but are usually part of large oligomeric structures (Fig. 2.1a).

Chaperonins are further subdivided into two classes: group I and group II. Group I chaperonins are found in eubacteria and in eukaryotic mitochondria and require the cooperation of cochaperonins, GroES is the cochaperonin of GroEL, whilst the Rubisco binding protein and mitochondrial Hsp60 require chloroplast and mitochondrial cpn 10 respectively. These chaperonins form large homo-oligomeric protein complexes consisting of two stacked heptameric rings (Fig. 2.1), while the cochaperonins form a single ring that forms a lid-like structure on top of the chaperonin. Group II chaperonins, found in the archaeobacteria and the eukaryotic cytosol, form heterooligomeric structures and do not require a cochaperonin as they have a built-in lid (Leroux and Hartl 2000; Saibil 2000; Frydman 2001; Feldman et al. 2003; Horwich et al. 2006; Bigotti and Clarke 2008).

Several crystal structures of GroEL are available (Braig et al. 1994), including GroEL complexed with ATP (Boisvert et al. 1996), GroEL bound to GroES and ADP (Xu et al. 1997) and a GroEL-peptide complex (Chen and Sigler 1999). Each chaperonin monomer has three domains, an apical domain contains the substrate and co-chaperone binding sites, an equatorial domain contains an ATP binding site and the intermediate domain which acts as a hinge inducing conformational changes upon ATP binding (Braig et al. 1994; Ranson et al. 1998). The chaperonin monomers are arranged in two rings stacked back to back of 7 subunits each, forming a cyclinder-shaped structure essential for its folding activity, which provides a central cavity for binding unfolded proteins by hydrophobic interactions (Fig. 2.1; Braig et al. 1994). The functional cycle requires the binding of chaperonin 10 which forms a lid-like structure on top of the cyclinder when ATP is bound which causes the cavity to expand to allow for protein folding (Chandrasekhar et al. 1986; Saibil 1996). The transition between the open conformation, that is receptive to protein binding, and the closed state, in which the protein is isolated, is induced by ATP binding and hydrolysis (Horovitz and Willison 2005). In the absence of ATP, the substrate binding surface is in a hydrophobic state and has a high affinity of protein substrates; when ATP is bound, GroES binds to GroEL inducing a conformational change in the apical domain that causes the substrate binding surface to become more hydrophilic displacing the substrate (Bukau and Horwich 1998; Ranson et al. 1998). Negative cooperativity

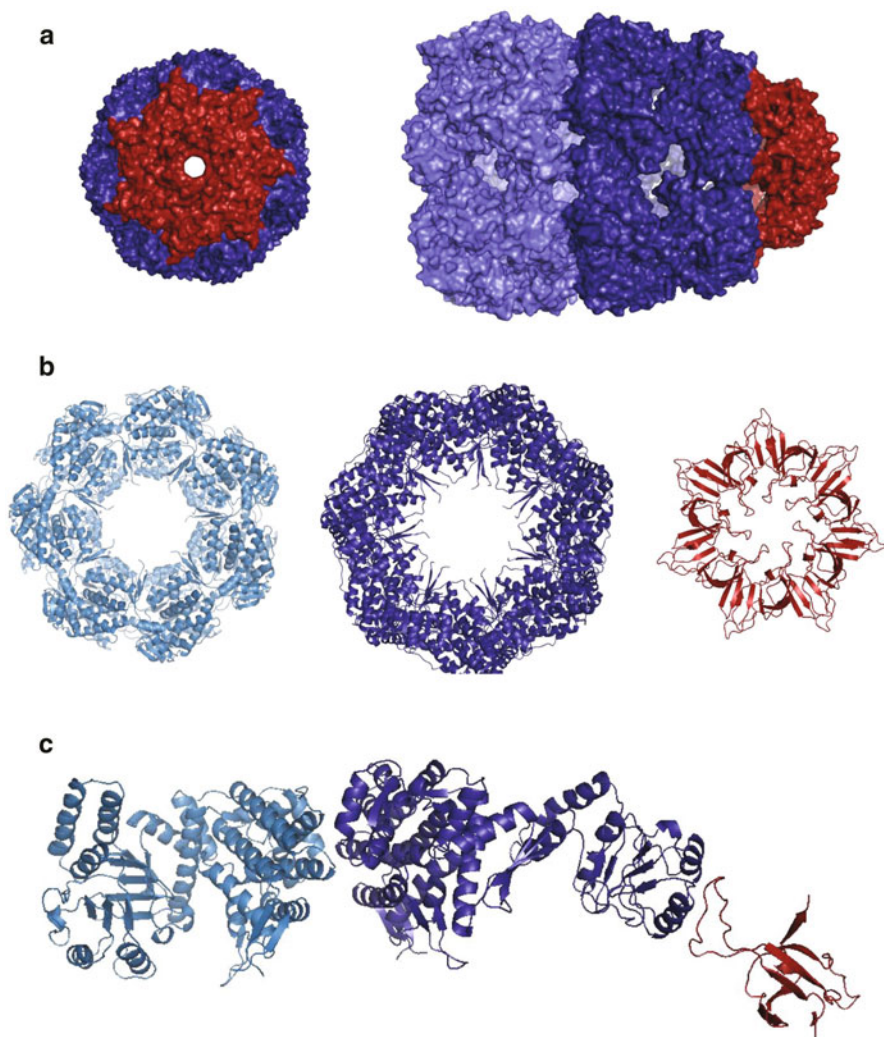


Fig. 2.1 Structural features of the GroEL/GroES chaperone complex. **a** The GroEL/GroES complex comprises of two heptameric rings of GroEL (*light blue* and *dark blue*) stacked back-to-back with the attached GroES 'lid' (*red*) to form a barrel-shaped complex, showing the top and the side views of the complex. **b** Ribbon diagram of the top view of each *cis* (*dark blue*) and *trans* (*light blue*) ring consisting of seven GroEL subunits each and the seven GroES subunits capping the *cis* ring. Each ring surrounds an open cavity to receive unfolded proteins. **c** Ribbon diagram of the side view of each GroEL subunit present in the *trans* (*dark blue*) and *cis* (*light blue*) rings and the GroES unit (*red*). The images were generated using PyMol (DeLano Scientific) from coordinates in PDB: 1AON

is displayed between the two GroEL rings, when ATP is bound in the *trans* ring, it results in the release of ADP and GroES from the polypeptide-containing *cis* ring

(Rye et al. 1997). It has been proposed that protein folding by GroEL is either passive with the closed interior providing an environment for proteins to fold themselves, or active whereby the energy landscape on the surface of the interior is altered (Brinker et al. 2001; Chakraborty et al. 2010). These two models of action have been reviewed by Bhutani and Udgaonkar (2002) and the use of NMR to observe substrate binding to GroEL was first described by Horst and colleagues (Horst et al. 2005).

There are considerable differences between the folding mechanisms of GroEL (group I) and CCT (group II). The assembly of the proteins is different, CCT has a more complex binding interface for substrate capture and CCT does not carry out general folding but rather folds a subset of proteins (Dobrzynski et al. 1996; Klumpp et al. 1997). The mechanism for group II chaperonins has not been fully resolved and remains debatable, greater insight into the differences between the mechanisms of action of group I and the more complicated group II chaperonins was revealed by the work of Yébenes and colleagues (Yebeenes et al. 2011).

The Hsp90 Family of Molecular Chaperones

In eukaryotic cells, the cytoplasmic Hsp90 species are one of the most abundant molecular chaperones, comprising 1–2 % of total cytosolic protein (Csermely et al. 1998). Hsp90 isoforms are also found in the mitochondria (Hsp75/TRAP-1/HSPC5) and the endoplasmic reticulum (Grp94/Gp96/HSPC4). The prokaryotic Hsp90 is termed HtpG in *E. coli*, although it does not display any obvious chaperone activity and knock-out studies have determined it to be dispensable for cell growth. Cytosolic Hsp90 has two isoforms, the α and β isoforms, which are also detected in the nucleus. Hsp90 α (HSPC2) and Hsp90 β (HSPC3) display 85 % sequence identity and are encoded for by separate genes. Hsp90 α expression is defined as more inducible than that of Hsp90 β (Terasawa et al. 2005). Hsp90 β is essential; knockout of this gene is lethal (Voss et al. 2000), while knockout of Hsp90 α surprisingly resulted in relatively few effects, most notably an effect on spermatogenesis (Grad et al. 2010). Hsp90 can exist as both intracellular and extracellular forms, which have defined functions. The fifth isoform, Hsp90N (HSPC1), is a truncated version of Hsp90 α and is thought to be predominantly extracellular or membrane associated (Grammatikakis et al. 2002). Whether this is a true Hsp90 isoform is controversial, with some researchers believing it to be a distinct gene while others propose that it was an artefact of the cell line in which it was identified (Zurawska et al. 2008). Hsp90 is also subject to post-translational modification, including s-nitrosylation, phosphorylation and acetylation, which may influence its chaperone function and cellular localization (Csermely et al. 1998; Aoyagi and Archer 2005; Martinez-Ruiz et al. 2005; Duval et al. 2007; Rao et al. 2008; Yang et al. 2008).

Hsp90, when associated with client protein and co-chaperones, is considered activated and described as highly “complexed”. Under these conditions, Hsp90 displays an enhanced sensitivity to and binding of anti-Hsp90 drugs compared to free or un-complexed Hsp90 (Kamal et al. 2003). This fact and the direct link between Hsp90 and the signalling pathways in mammalian cells have made it a recent focus for

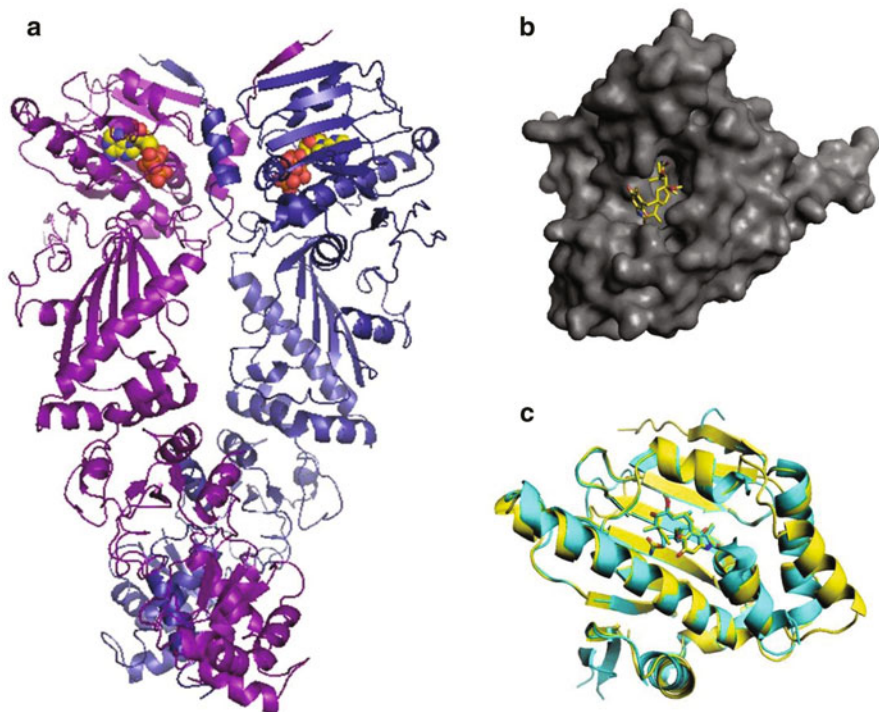


Fig. 2.2 Structural features of the Hsp90 chaperone. **a** Structure of the Hsp90 dimer in the closed conformation (PDB ID: 2CGE). ATP bound to the N terminal domains of the dimer is shown in *red* spheres. The two subunits making up the dimer are shown in *purple* and *blue*. **b** Structure of the ATPase domain of Hsp90 showing the binding of geldanamycin (sticks) to the ATP binding site. **c** Alignment of the ATPase domains of Hsp90 (*cyan*; PDB ID: 1YET) and Grp94 (*yellow*; PDB ID: 2EXL) with geldanamycin bound. Images were generated using Pymol (DeLano Scientific)

the design of targeted inhibitors. The natural antibiotic geldanamycin is a specific inhibitor of Hsp90 ATPase activity and its synthetic derivatives (such as 17-AAG) are leading the current focus in Hsp90 inhibitors (Chiosis et al. 2006). Due to the structural similarity, many compounds that bind to the ATPase domain of cytosolic Hsp90, including geldanamycin, will also bind to Grp94 and TRAP1 (Fig. 2.2; Lawson et al. 1998; Immormino et al. 2009).

Structurally Hsp90 functions as a dimer, with each monomer consisting of three highly conserved functional domains that define its function, namely an N-terminal domain (25 kDa), a middle (M) domain (35 kDa) and a C-terminal domain (12 kDa) (Fig. 2.2; Nemoto and Sato 1998). The N-terminal and M-domain are connected by a charged linker region, which varies in length and amino acid composition according to the species or isoform (and is not present in the prokaryotic Hsp90). The Hsp90 ATPase domain has a Bergerat fold formed from an α/β sandwich structure made up of an anti-parallel, eight strand β sheet with nine helix bundles (Stebbins et al. 1997; Fig. 2.2). This domain contains the primary binding site for ATP/ADP (Prodromou

et al. 1997), as determined by crystallization studies on both yeast and human Hsp90. This ATP/ADP binding site is the same as that bound by the natural Hsp90 inhibitor, geldanamycin (Grenert et al. 1997). However, while the primary binding site for ATP is contained in the N-terminal domain, in isolation, this domain lacks any detectable ATP hydrolysis activity. The ATPase activity of Hsp90 is therefore dependent on the presence of both the N-terminal domain and M-domain (which contains a binding site for the γ -phosphate of ATP), resulting in its classification as a “split” ATPase (similar to GHKL proteins) (Terasawa et al. 2005). The low basal ATPase activity of Hsp90 (kcat of $1.7 \times 10^{-3} \text{ s}^{-1}$) is stimulated by co-chaperones (McLaughlin et al. 2002). Therefore, when acting alone Hsp90 has very little ATPase activity (Obermann et al. 1998). In eukaryotic cells, the N-terminal domain of Hsp90 is linked to the M domain by a flexible, charged linker region (Terasawa et al. 2005; Hainzl et al. 2009). The M domain of Hsp90 is primarily involved in client protein binding (Meyer et al. 2003; Hawle et al. 2006). The M domain also coordinates the γ -phosphate of ATP during ATP hydrolysis. The co-chaperone Aha1 stimulates the Hsp90 ATPase activity by interacting with the M and N domains of the chaperone (Meyer et al. 2003; Soti et al. 2003).

The C terminus of Hsp90 contains the dimerisation domain and a putative C-terminal binding site for nucleotides. This cryptic site is less specific than the N-terminal site, with a preference for binding UTP and GTP, and is only exposed when the N-terminal ATP binding site is occupied (Soti et al. 2003). Novobiocin was the first C-terminal inhibitor identified (Marcu et al. 2000a). The binding site for novobiocin partially overlaps the dimerisation domain (amino acids 538–728) (Marcu and Neckers 2003). At the extreme C-terminus is the MEEVD motif which is the primary binding site for the TPR containing co-chaperones, such as Hop (Hsp70/Hsp90 organising protein) (Brinker et al. 2002). Novobiocin competes with ATP for binding to this region and can disrupt the binding of co-chaperones that associate with this region (Callebaut et al. 1994; Marcu et al. 2000a; Scheuffler et al. 2000; Garnier et al. 2002; Odunuga et al. 2003; Terasawa et al. 2005; Zhang et al. 2005; Pearl et al. 2008; Wandinger et al. 2008).

Hsp90 mediates the folding of a range of client proteins, which are involved in signal transduction pathways that control the fundamental cellular processes, such as growth. Over 300 different Hsp90 client proteins have been described. Hsp90 maintains its client proteins in an inactive, but easily inducible state (Whitesell and Lindquist 2005). As these intermediate states are often inherently unstable and labile in the absence of substrate, the role of the Hsp90 multi-chaperone complex is to enhance client protein stability, such as the stabilization of protein kinases and the maintenance of steroid receptor integrity in the absence of steroid ligand (Buchner 1999). Although there are differences in the structure and co-chaperone associations between the cytosolic and organelle Hsp90, the general mechanism of the ATPase cycle is conserved between the different isoforms. Phylogenetic analysis suggested that cytosolic and organelle Hsp90 (Grp94 and TRAP1) developed from a common ancestor (Emelyanov 2002; Chen et al. 2005).

TRAP1 (TNF receptor associated protein) is the mitochondrial Hsp90 isoform. Localized predominantly in the mitochondrial matrix, TRAP1 exists as at least six different isoforms. TRAP1 contains an N terminal mitochondrial targeting sequence and the mature TRAP1 protein contains 645 amino acids and has the Bergerat fold

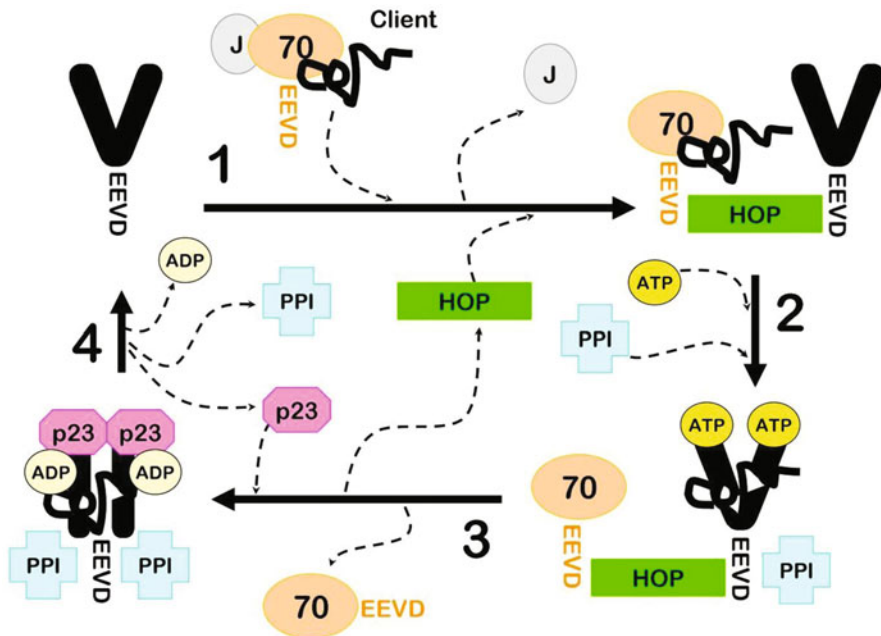


Fig. 2.3 Chaperone mediated folding by Hsp90 and co-chaperones. 1 Inactive Hsp90 is constitutively dimerised at the C terminus but the N termini are not associated. The Hsp70-Hsp40 complex captures client proteins and delivers it to the Hsp90 chaperone via the co-chaperone Hop. 2 Hop binds simultaneously to the C termini of Hsp70 and Hsp90 using its TPR domains and acts as a scaffold for the transfer of the client protein from Hsp70 to Hsp90. The client protein associates with the middle domain of Hsp90. Other co-chaperones including peptidyl-prolyl cis-trans isomerases (PPIase) associate with Hsp90 at this stage to form the asymmetric complex. 3 Hsp70 and Hop dissociate from the complex and are replaced by p23 to generate the closed late complex. 4 The N terminus dimerises and ATP is hydrolysed and the client protein is released

ATPase domain characteristic of Hsp90 isoforms (Felts et al. 2000; Leskovar et al. 2008). TRAP1 ATPase activity is substantially enhanced in response to heat shock and TRAP1 has a higher affinity for ATP than Hsp90 (Leskovar et al. 2008). Similar to cytosolic Hsp90, TRAP1 exists as a dimer and is similarly inhibited by ansamycin antibiotics like geldanamycin that bind to the ATPase domain (Neckers et al. 2007). TRAP1 however lacks the C terminal EEVD motif found in cytosolic Hsp90 and therefore does not associate with the same co-chaperones as Hsp90 α or Hsp90 β (Altieri et al. 2012).

The N terminus of Grp94 contains the ER signal peptide while at the C terminus, the MEEVD peptide is replaced with the KDEL motif that is required for retention in the ER (Argon and Simen 1999). Grp94 share structural similarity with Hsp90 beyond these differences. The ATPase domain and functionally important residues are conserved, as is the C terminal regions. Grp94 is a dimer like cytosolic Hsp90 and geldanamycin and similar compounds will also bind to the ATPase domain of Grp94 (Dollins et al. 2006, Frey et al. 2007). The molecular chaperone activity of Hsp90 is regulated by conformational changes which are dependent on two factors (Fig. 2.3). The first is the intrinsic ATPase activity of Hsp90 (Panaretou et al. 1998),

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