Dancing with the Diva: Hsp90–Client Interactions

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Abstract

The molecular chaperone Hsp90 is involved in the folding, maturation, and degradation of a large number structurally and sequentially unrelated clients, often connected to serious diseases. Elucidating the principles of how Hsp90 recognizes this large variety of substrates is essential for comprehending the mechanism of this chaperone machinery, as well as it is a prerequisite for the design of client specific drugs targeting Hsp90. Here, we discuss the recent progress in understanding the substrate recognition principles of Hsp90 and its implications for the role of Hsp90 in the lifecycle of proteins. Hsp90 acts downstream of the chaperone Hsp70, which exposes its substrate to a short and highly hydrophobic cleft. The subsequently acting Hsp90 has an extended client-binding interface that enables a large number of low-affinity contacts. Structural studies show interaction modes of Hsp90 with the intrinsically disordered Alzheimer's disease-causing protein Tau, the kinase Cdk4 in a partially unfolded state and the folded ligand-binding domain of a steroid receptor. Comparing the features shared by these different proteins provides a picture of the substrate-binding principles of Hsp90.

Hsp90 binds a diverse spectrum of clients

Balanced protein folding, quality control, and degradation are prerequisites of life [1]. Errors in these processes lead to fatal diseases, including cancer, cystic fibrosis, and neurodegenerative disorders, such as Alzheimer's disease [2–6]. Therefore, cells have heavily invested in complex folding machineries that aid *de novo* synthesized or unfolded proteins to reach their adequate conformation, support domain and complex assembly, target damaged proteins to degradation, and disaggregate protein aggregates [7–12]. These folding machineries play an essential role in protecting cells from aggregation-prone, hydrophobic protein stretches, which seriously threaten the "well-being" of the cellular proteome [8,13,14].

The evolutionary most important chaperone classes are the ATP-driven machines Hsp70 and Hsp90 [15–18]. Hsp90 typically acts downstream of Hsp70 [19–22]. Many proteins require assistance from the Hsp70 chaperone machinery for the first steps on the folding path [23]. Hsp70 recognizes short, hydrophobic patches and shields them from aggregation by binding to them [24]. Next, partially folded, less hydrophobic intermediates may bind to Hsp90 [25,26]. Hsp90 regulates substrate intake from the Hsp70 system via ATP hydrolysis [23,27,28]. The ATP cycle regulates opening and closing of the Hsp90 dimer [29–31]. It is not clear, however, how the conformational changes control Hsp90–client interactions. Hsp90 fosters the folding, maturation and degradation of a large number of often structurally and sequentially very different client proteins [25,32–34]. The diversity of Hsp90 clients is astonishing, it includes many aggregation-prone and unstable regulatory proteins, such as kinases from every kinase family; transcription factors, including steroid hormone receptors; and surprisingly, disordered clients, such as Tau or

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α-synuclein [35] (https://www.picard.ch/downloads/Hsp90interactors.pdf). In the cellular context, many clients are targeted to Hsp90 by co-chaperones, such as Cdc37 in the case of kinases, Sgt1 for leucine-rich-repeat-containing proteins, and Hop for certain steroid receptors. The basis of Hsp90 substrate binding, however, is the chemical properties that drive the chaperone–client interaction itself. This had been enigmatic until recently [36–38].

Here, we provide an overview of current knowledge on the client-binding properties of Hsp90 with focus on the three available Hsp90–client structural models from the point of view of the clients as well as Hsp90 [26,39,40]. We examine several physical properties, including charges and hydrophobic content of binding interfaces of three Hsp90 clients (Tau, GR, and Cdk4) and Hsp90 to discuss important aspects of Hsp90–client interaction [26,39,40].

Hsp90 client binding

First, we will highlight the characteristics of the Hsp90 contact sites within the client, analyzing the structural models of Tau, GR-LBD, and Cdk4 in complex with Hsp90. Afterward, we will turn the tables and discuss common and divergent features of the substrate-binding interface as they are offered by Hsp90 in these three complexes. A detailed quantitative analysis and additional figures are provided in the supplement.

The Hsp90 binding site of a disordered client, Tau

First, we took a closer look at disordered Tau in complex with human Hsp90. At first glance, it may seem surprising that the intrinsically disordered, highly flexible, and soluble Tau protein is a *bona fide* client of Hsp90 [26,41]. Indeed, Hsp90 does not fold Tau. Instead, Hsp90 either supports association of Tau with microtubules or targets it for proteasomal degradation, in collaboration with the E3 ubiquitin–protein ligase CHIP [41–45]. The function of Tau is related to microtubule polymerization, stabilization, and intracellular organelle and vesicle trafficking [46–48]. Aggregation of Tau into fibrils, however, is an essential step in the development of Alzheimer's disease [49–51]. Intriguingly, the same segment of Tau, the repeat domain (Tau-RD; Q244–N368), is responsible for microtubule binding, Hsp90 interaction, and aggregation (Fig. 1a) [52,53]. Tau-RD consists of four pseudo-repeats, R1–R4, each of which comprises 31 or 32 residues (Q244–N368). The two C-terminal repeats R3 (V306–Q336) and R4 (V337–N368) are part of the fibrils found Alzheimer brain (V306–F378) [54].

Hsp90 binds in Tau to an extended surface, ranging over around 170 residues (approximately R210–E380) and including both Tau-RD and the fibril core [26]. The affinity is in low micromolar range, typical for chaperone–substrate interactions (4.8 μM). The extended binding interface renders the contribution of each individual residue to binding minimal. This is a marked difference to the short stretches that bind to Hsp70 and in which often a single leucine has a key role. Overall, the Hsp90 binding site in Tau is only of moderate hydrophobicity (1 large hydrophobic or aromatic residue per 4.4 residues) and exhibits a strong positive net charge (p*I* = 10.3). Within the extended binding region are six key binding stretches (Tau-90KBS), each of them five or six residues long, which NMR data suggest to be more prominently involved in interaction with Hsp90 [26]. They are more hydrophobic than the remainder of the Hsp90 binding site in Tau (see supplement for quantitative assessment; Supplementary Table 2).

The Hsp90 binding site of a folded client, GR-LBD

The ligand-binding domain (LBD) of the glucocorticoid receptor (GR) binds to Hsp90 as folding intermediate but also in its folded, native state [39]. Two clients could hardly be more different than Tau and the folded GR-LBD. GR is a multi-domain steroid hormone receptor that regulates development, metabolism, and immune responses [55,56]. In the absence of the hormone (e.g., cortisol), the LBD of GR (GR-LBD) is unstable and the protein resides in the cytosol exclusively in complex with chaperones [28,39,57]. Hsp90 is essential for GR function. It binds to GR-LBD with low micromolar affinity, similar to Tau, and maintains it in its semi-folded, hormone-receptive state [58–61]. Glucocorticoids stabilize GR-LBD but do not dissociate the complex [39,62]. Folded GR-LBD binds to Hsp90, and this complex reveals some interesting features for Hsp90–client interactions [39].

Structural analysis by NMR and SAXS of yeast Hsp90 in complex with GR-LBD reveals that the chaperone adopts a closed conformation (Fig. 1b) [39]. Two folded GR-LBD molecules can bind simultaneously to the Hsp90 dimer, and both have contacts with each Hsp90 protomer. One GR-LBD binds to the middle domain of one and the N-terminal domain of the other protomer, and *vice versa* [39]. However, throughout the functional maturation cycle, only one GR molecule binds to the Hsp90 dimer, also thanks to the action of co-chaperones [39].

The role of Hsp90 in guarding a semi-folded client, Cdk4

The recent cryo-EM model of Cdk4 in complex with Hsp90 and Cdc37 provided for the first time high-resolution structural information on a partially folded substrate of Hsp90 [40]. The semi-folded Cdk4 mainly binds to the middle domains of the Hsp90 dimer and it makes further contacts with the

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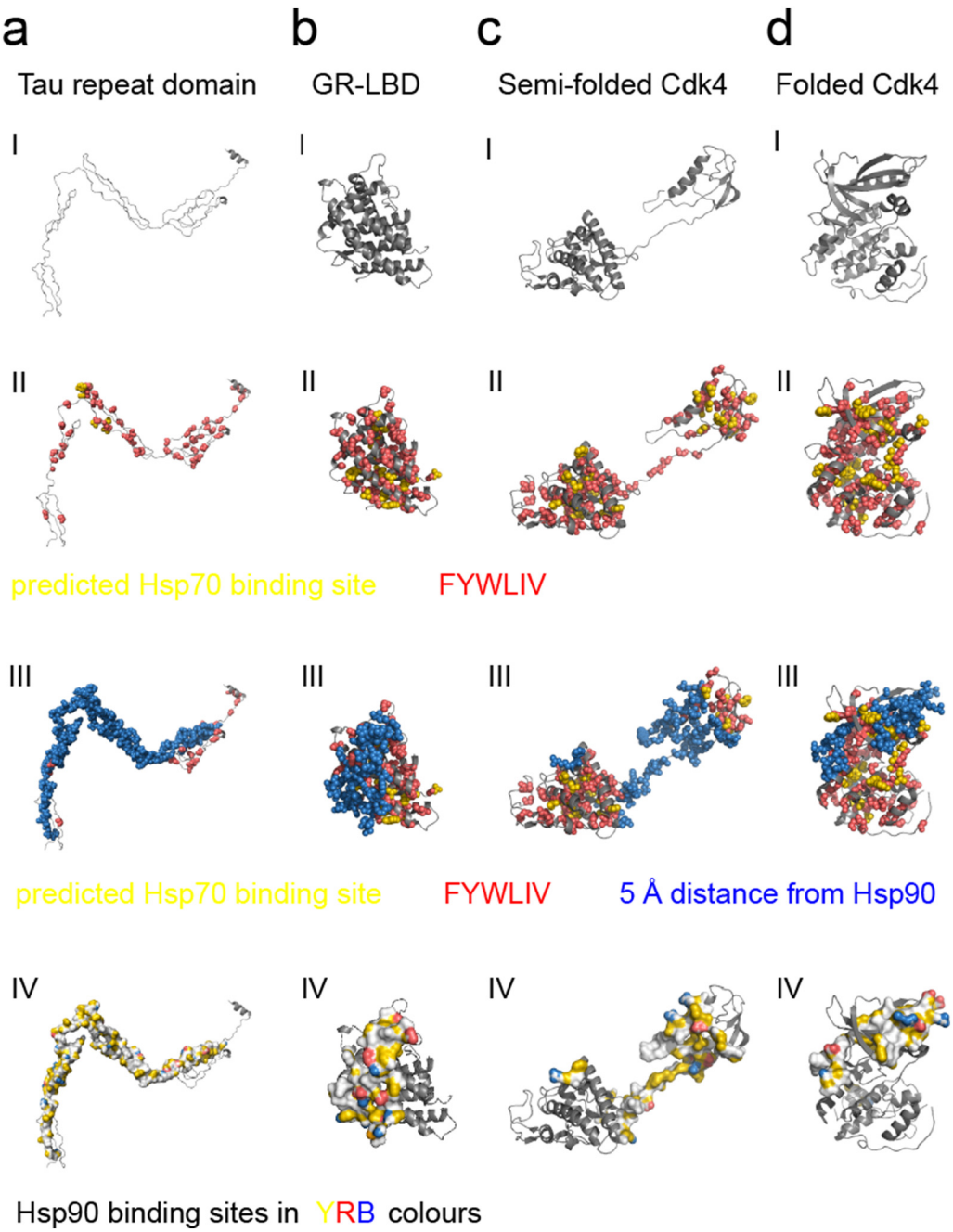

Fig. 1. Client proteins of Hsp90. (a) Tau. (I) Cartoon representation. (II) As in (I) with highlighted Hsp70 binding sites (side chains as yellow spheres) and other hydrophobic residues (main chain as red spheres). The Hsp70 sites were predicted using an algorithm [107] (III) As in (II) with the highlighted Hsp90 binding site (side chains as blue spheres, main chain as red or yellow spheres). (IV) Surface representation of the Hsp90 binding site of Tau with YRB coloring [hydrophobic content (yellow), positive (blue) and negative (red) charges, other (white)] [108]. (b) As in (a) with GR-LBD. (c) As in (a) with folded Cdk4 [68]. (d) As in (a) with semi-folded Cdk4 [40].

N- and C-terminal domains (Fig. 1c) [40]. The β-sheets β4 and β5 are unfolded and the thread proceeds through the narrow, hydrophobic channel formed by the closed protomers. This now allows intriguing comparisons with the Hsp90 complexes of intrinsically disordered Tau and natively folded GR-LBD.

The Hsp90–Cdk4–Cdc37 complex provides insights into Hsp90 action during kinase maturation [40]. Cdk4 needs to be in active state for the cell-

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cycle G1 phase progression (Fig. 1d) [63–67]. Effective regulation of the cell cycle requires stringent control of cyclin-dependent kinases, including Cdk4 [65,68,69]. Therefore, multiple steps need to be taken for Cdk4 activation: (1) proper folding, (2) binding of the regulator cyclin D, (3) association of ATP to the ATP binding loop, (4) positioning of the catalytic residue (active site) in the vicinity of the ATP molecule, and (5) phosphorylation of T172 [65,68,70–73]. Inhibitors, such as p16, may also hold back Cdk4 in its inactive state and can effectively control its activity [65,74,75]. Hsp90 plays an important role in the late folding process of Cdk4 [71]. Mapping of the interaction sites suggests that Hsp90 may also prevent the association of Cdk4 with cyclin D, because (i) the cyclin D binding site largely overlaps with the one of Hsp90 (Fig. 2a) and (ii) most of it is not accessible when the dimer is closed (Fig. 2b). Hsp90 may thus be directly involved in the regulation of the cell cycle.

Cdk4 is recruited to Hsp90 by Cdc37 [37,71,76,77]. Cdk4 has two Cdc37 binding sites, which are exposed in the semi-folded but partially buried in the folded Cdk4 structural model (Supplementary Fig. 1a). Therefore, Cdc37 is likely to capture Cdk4 in its semi-folded state, either on-pathway or after partial unfolding [78]. With the help of Cdc37, Hsp90 stabilizes Cdk4 in this semi-folded conformation, which renders the protein inactive, by maintaining a certain distance between the ATP binding loop and the active site (Supplementary Fig. 1b) [40].

Cdk4 dissociates from the Hsp90–Cdc37 "prison" at the end of the G1 phase when the concentration of cyclin D significantly increases, the mechanism of which remains to be elucidated [63]. Potentially, this may be linked to dissociation of Cdc37 since the Hsp90–Cdk4 complex is unstable without the co-chaperone [71]. When free from chaperones and active, Cdk4 translocates to the nucleus where it phosphorylates retinoblastoma gene products (Rb) [63,79–81].

The folding mechanism of Cdk4 may be a general paradigm for kinase folding, including kinases that had been considered as Hsp90 independent [32,38]. Notably, part of the Cdc37 binding site of Cdk4 is rather conserved among all kinases, despite being in a loop, even when we compare kinases that stand far from each other evolutionarily (Supplementary

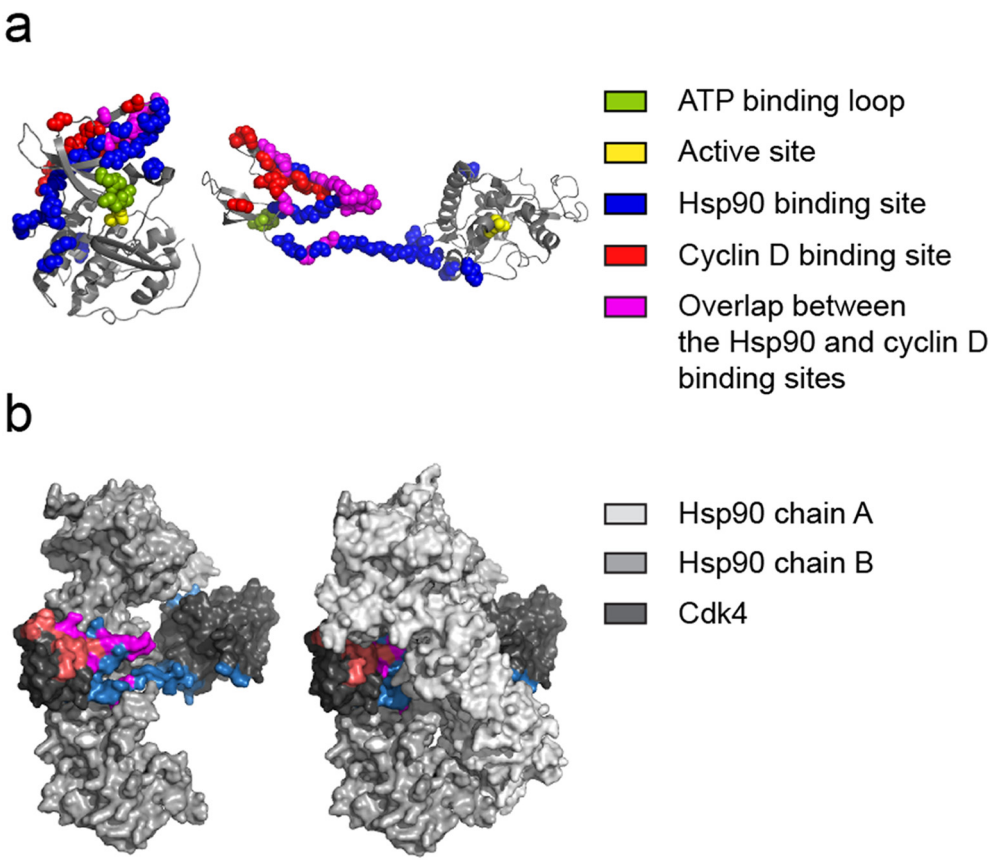

Fig. 2. Semi-folded CDK4 is inactive. (a) The Hsp90 binding site (side chains as blue spheres, main chain as red or yellow spheres) overlaps with the Cdk4-cyclin D interaction surface (side chains as red spheres). The overlap is depicted in magenta. (b) Part of the cyclin D binding site is buried when Cdk4 is bound to Hsp90. Hsp90 protomer with Cdk4 (left) and Hsp90 dimer with Cdk4 (right) in the same position.

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Fig. 1c and e). Thus, all these kinases can potentially bind to Cdc37 and be targeted to Hsp90 if this loop gets exposed. Notably, the two unfolding β-sheets of Cdk4, β4 and β5, are also conserved among kinases, regardless of their dependence on Hsp90 (Supplementary Fig. 1d and e) [68,82–84]. This suggests that any of these kinases could potentially be Hsp90–clients if their corresponding parts get exposed, but Hsp90 demands may be determined by folding path and protein stability [32,85,86].

Common properties of Hsp90 binding sites in the various substrates

Together, the comparison of the Hsp90 binding sites of Tau, GR-LBD, and Cdk4 reveal some features that may be general trademarks for Hsp90 clients (Fig. 1, Supplementary Fig. 2, Supplementary Table 2) [26,39,40]. Although the three clients are very different, a common pattern emerges.

Surface area

Compared to the relatively short stretches involved in Hsp70 binding (core regions of no more than five residues), Hsp90 binding sites are extended (50–170 amino acids) (Fig. 1a–d, Supplementary Table 2) [24,26,39,40]. This is consistent with the concept that Hsp90 binds its clients via a large number of low-energy contacts allowing for dynamic, transient interactions [26]. In the middle domain of Hsp90, the binding sites of Tau and GR-LBD overlap to a large extent. Tau, however, is the much more extended molecule and also covers a significant part on the surface of the N-terminal domain of Hsp90.

Hydrophobicity and charge

Overall, the interaction interfaces are less hydrophobic and more charged than Hsp70 binding sites, consistent with fact that Hsp90 acts downstream of Hsp70 on the folding path (Fig. 1a–d, Supplementary Fig. 2c–d, Supplementary Table 2) [19,21,22,26,28]. The Hsp90 binding sites contain a higher fraction of positively charged residues compared to the full-length protein, and as a result, the binding interfaces of Tau and Cdk4 have a net positive charge. The Hsp90 binding site of GR-LBD, however, is overall negatively charged as the negatively charged residues outnumber the increase in basic residues (Supplementary Fig. 2a–c, Supplementary Table 2) [39]. It is interesting that all clients minimize potentially adverse charge interactions in their Hsp90 interaction sites. Coulomb interactions influence protein–protein interactions over large distances. Thus, prevention of potential repulsion could be an important principal to empower chaperoning of a diverse substrate pool.

Hsp70–Hsp90 connection

The Hsp70 and Hsp90 binding sites barely overlap in GR-LBD and Cdk4 (Fig. 1a–d) [39,40]. Hsp70 binds to very hydrophobic, aggregation-prone short stretches that typically form the hydrophobic core of proteins (Fig. 1a–d) [24]. The observation that Hsp90 avoids these sites in folded proteins indicates that it preferentially binds to late folding intermediates where these sites are already buried (Fig. 1a–d) [26]. Tau only has two Hsp70 sites, consistent with its inability to fold (Fig. 1a) [87]. Both Hsp70 binding sites remain exposed and are (a small) part of the extended Hsp90 binding region [26,88].

The substrate interaction sites of Hsp90

After so far analyzing the Hsp90 binding sites in the various clients, we now turn sides and look at the client-binding patches on the surface of the Hsp90 structure. The client-binding patches of three very different clients seem surprisingly similar to each other regarding charges and hydrophobicity, especially when we compare them to the variable co-chaperone binding sites (Fig. 3a–d, Supplementary Fig. 3a–e, Supplementary Fig. 4a–d, Supplementary Tables 3–4) [26,39,40,89–91]. The binding patches of the three clients together form a consecutive, extended binding surface involving mostly the N-terminal and middle domains (Fig. 3a–d, Supplementary Fig. 4a–d). Notably, the analysis of a complex of destabilized transthyretin with Hsp90 revealed a similar binding site to Tau, further confirming the concept of the long consecutive binding site [92]. We can learn some general lessons for protein–protein interactions of Hsp90.

Surface area

The Hsp90 client-binding interface is a consecutive, extended surface covering part of the surface of the N-terminal and middle domains. The different client sites overlap partially, and the use of different patches of the client-binding sites may reflect both their shape and chemical properties (Fig. 3a–d, Supplementary Fig. 4a–d) [26,39,40]. The extended nature suggests that Hsp90 forms many low-energy contacts with its clients [26,39,40]. The structural models show Hsp90 homologs binding to Tau in open and to GR-LBD and Cdk4 in its closed conformation [26,39,40]. The available surface areas considerably differ when Hsp90 is an open or a closed conformation as a substantial part of the Hsp90 surface gets buried upon N-terminal dimerization. Each client-binding surface covers a spread-out area on the surface of Hsp90 but with varying sizes (82 amino acids for Tau, 66 or 70 for GR-LBD, and 65 for Cdk4 binding are within 5 Å of the client). Tau binds to the open human Hsp90 both in the

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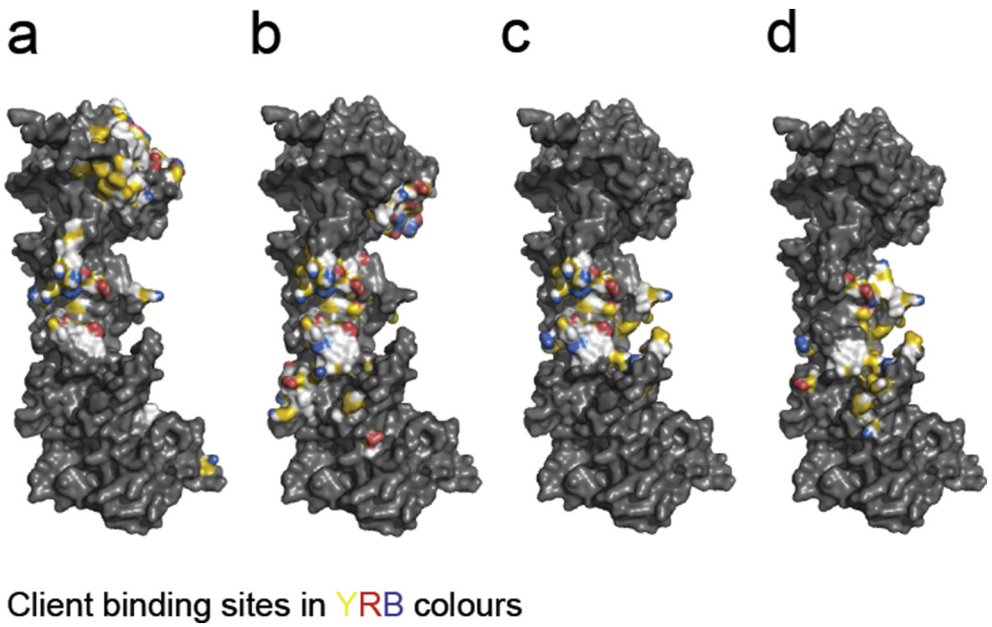

Fig. 3. Client-binding sites of Hsp90. The binding sites are visualized using YRB coloring [hydrophobic content (yellow), positive (blue) and negative (red) charges, other (white)] [108]. (a) The Tau binding site of Hsp90. (b) GR-LBD binding site of Hsp90. (c) Cdk4 binding site of chain A of the Hsp90 dimer. (d) Cdk4 binding site of chain B of the Hsp90 dimer.

presence and the absence of nucleotide, resulting in an extended binding area [26]. When binding in its closed conformation, the number of contacts per Hsp90 protomer is lower. However, this is compensated by the possibility to bind to both Hsp90 protomers, such as in case of GR-LBD, which interacts with yeast Hsp90 in its ATP state [39] A closed conformation further allows to increase the intimacy of the interaction, as it is seen for the Hsp90-Cdk4-Cdc37 complex [40].

Hydrophobicity

The hydrophobic content of the patches that bind to the clients Tau and GR-LBD is similar to that of entire Hsp90. The hydrophobic residues scatter throughout the client-binding sites (Fig. 3a–d, Supplementary Figs. 4a–d and 5d, Supplementary Table 4) [26,39]. In contrast, the Cdk4 binding patch of Hsp90, particularly for chain B, is significantly more hydrophobic (Fig. 3d; Supplementary Figs. 4d, 5d, and 6; Supplementary Tables 1, and 4) [40]. This may represent a specific entry point early in the client maturation cycle. The patches covered by Cdk4 chain A, GR-LBD, and Tau may represent the later stages (Fig. 3a–b, Supplementary Figs. 4a–b and 6) [26,39]. These polar interfaces may be crucial for chaperoning function as they may encourage the client to expose its charged and polar residues, too.

Fig. 4. The unified Hsp90–client cycle. (a) The newly synthetized polypeptide chain exposes a large number of hydrophobic residues (Hsp70 sites: yellow dots, other hydrophobic residues: red dots). Some of these quickly form a hydrophobic core, while other short, strongly hydrophobic stretches stay accessible for the Hsp70 (70, dark green)–Hsp40 (J, light green) machinery (left). Certain exposed sequences are recognized by Cdc37 (37, cyan), the kinase-targeting co-chaperone of Hsp90 co-chaperone (right). (b) The Hsp70–hsp40 complex targets the client to Hsp90 (90, dark blue, supported by the adaptor protein, Hop (pink). ATP hydrolysis by Hsp90 is necessary for passing on the substrate; therefore, Hsp90 dimerizes via its N-terminal domains. After ATP hydrolysis, Hsp70, Hsp40, ATP, and Pi dissociate (left). Hsp90 binds to the kinase client with the help of Cdc37. This step is probably also accompanied by the hydrolysis of an ATP molecule by the closed Hsp90 dimer. Contrary to Hsp70 and Hsp40, Cdc37 remains part of the complex, ADP and Pi dissociate (right). (c) The partially folded client stays in contact with the Hsp90–Hop complex, to which other co-chaperones may bind. The ATP hydrolysis step may be repeated (without the re-binding of Hsp70 and Hsp40) (left). The closed Hsp90 dimer may open up to release the partially folded client. The opening–closing coupled to ATP hydrolysis may be repeated several times (right). (d) Hop dissociates. The ligand (orange) binds to the fully folded client and stabilizes it. p23 (23, brown) reinforces the closed conformation. (e) The ligand-bound client may stay in contact with Hsp90 (left). The ligand stabilizes the fully folded client. Some kinases stay in contact with Hsp90 after folding (right). Subsequently, the active ligand dissociates from Hsp90 and enters a new folding cycle [28,38,109].

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Charge

All client-binding patches have a close to neutral net charge, despite being highly charged (Supplementary Table 4). The sites for folded GR-LBD and semi-folded Cdk4 are enriched in positive and unchanged in negative residues, whereas the binding site of the disordered client is enriched in positively but depleted in negatively charged residues (Supplementary Fig. 5a–c) [26,39,40]. This may be crucial for Hsp90 to interact with clients independent of the total charge of the client, despite the high negative net charge of Hsp90 itself. While Hsp90 has a high negative net charge, the Hsp90 client-binding surface

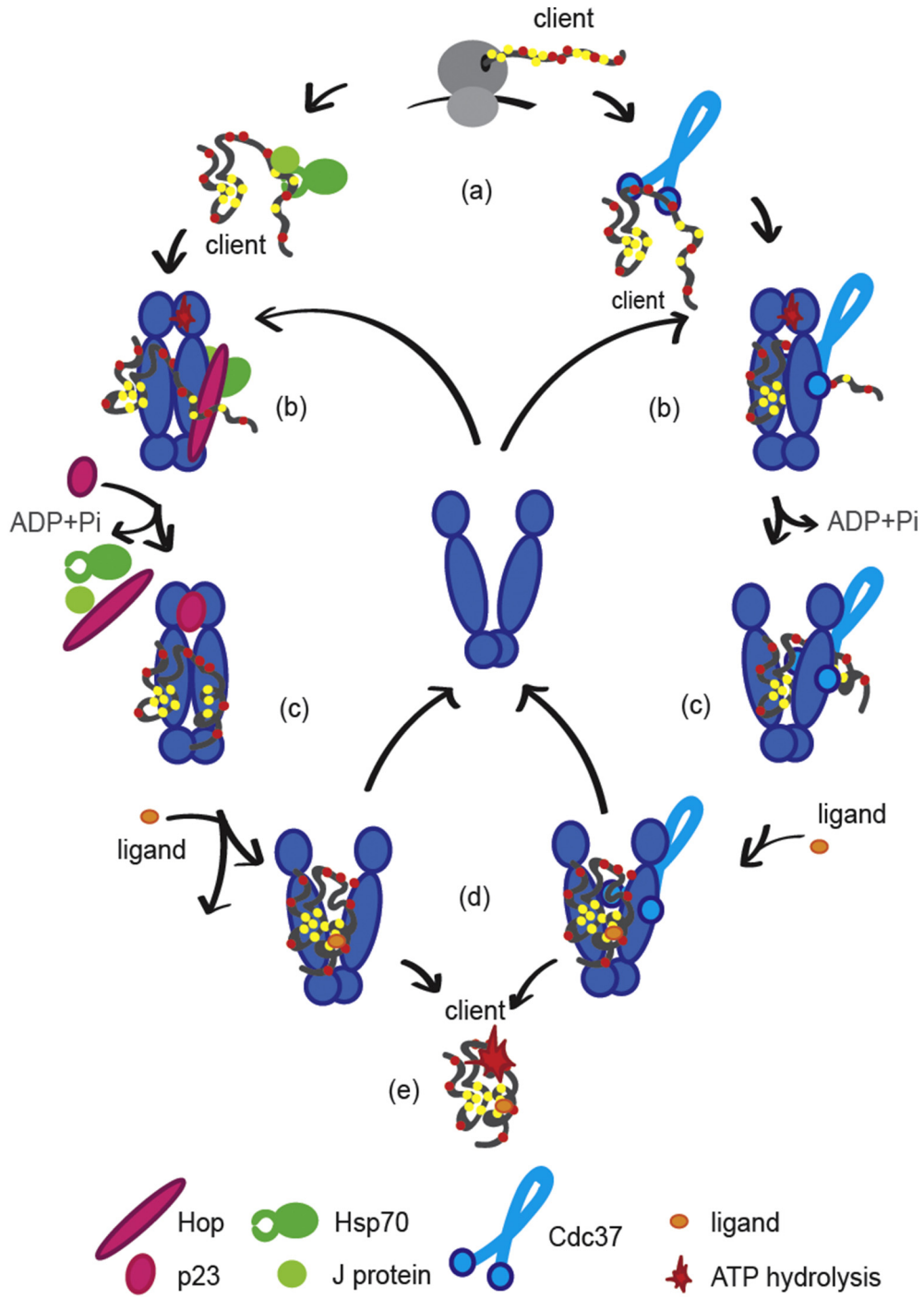

Fig. 4 *(legend on previous page)*

is reduced in charge and is close to a neutral net charge, achieved by the presence of a large number of both positively and negatively charged residues (Supplementary Fig. 5a–c, Supplementary Table 4) [26,39,40]. This may be crucial for the role of Hsp90 in guarding late folding intermediates as this may favor burial of hydrophobic residues.

Client matching

When binding to Hsp90, most of the highly hydrophobic segments predicted to bind to Hsp70 are buried (Fig. 1a–d). This can be seen for both Cdk4 and GR-LBD (Fig. 1b–d, Supplementary Fig. 7) [39,40]. Also, the binding site in the repeat domain of Tau is characterized by a moderate content in hydrophobics (Fig. 1a, Supplementary Fig. 2d) [26]. As most of the proteins have parts with hydrophobic content within this range, it is possible that Hsp90—at least transiently—may also bind to many proteins that are currently not considered Hsp90 clients.

Co-chaperone interaction

In comparison with clients, the binding sites of co-chaperones are more variable regarding both charges and hydrophobic content (Supplementary Fig. 3, Supplementary Table 3) [26,39,40,89–91]. This indicates that these interfaces are tailored for a specific interactor, while the client interaction patches need to be able to interact with a structurally and chemically diverse population. They are also more condensed than the client-binding sites, indicating that Hsp90 forms fewer contacts with higher energy with co-chaperones in comparison with clients (Supplementary Fig. 3a–e, Supplementary Table 3) [26,39,40,89–91,93]. The hydrophobic content often forms a center around which charges scatter (Supplementary Fig. 3a–e) [40,90,91].

The N-terminal and middle domains of human but not bacterial Hsp90 are connected by a long disordered linker, which had been suggested to participate in substrate binding [94–96]. However, the mechanistic implications of this linker for substrate binding are poorly understood, as it is not visible in the structural models.

Hsp90 chaperoning

The current progress on Hsp90 client recognition and the knowledge assembled over the years on Hsp90-chaperoned folding paths, in particular of kinases and steroid receptors, leads to a unified scheme for the folding mechanism of Hsp90 clients (Fig. 4).

Step a

During early folding, some of the most hydrophobic patches of proteins need to bury and the hydrophobic core is formed, still leaving a number of scattered hydrophobic residues exposed (Fig. 1a–d). Hsp70 aids GR (and perhaps also Cdk4) interfere with this process by scavenging hydrophobic stretches that are exposed at this stage, potentially recovering dead end folding intermediates [22,28].

Step b

Next, the folding intermediate is targeted to Hsp90 by the Hsp70–Hsp40–Hop complex where Hop bridges the two chaperones, significantly facilitating client transfer [28,97–100]. ATP hydrolysis by Hsp90 may be only required for the transfer from the Hsp70 to the Hsp90 system [28,101]. In the case of kinases, this targeting is accomplished by Cdc37, in other cases potentially by other targeting factors [102]. After binding to Hsp90, most Hsp70 binding stretches are buried in the core of the folding intermediate, leading to a semi-folded state (Figs. 1d and 2b).

Step c

The client binds to Hsp90 and the complex is stabilized by an ATPase inhibitor co-chaperone, such as p23 for GR-LBD and Cdc37 for Cdk4 [28,40,103,104].

Step d

The client remains in this semi-folded state, protected by Hsp90 and co-chaperone until it binds its substrate/stabilizing factor/inhibitor (e.g., hormone in the case of GR and cyclin D for Cdk4) and may be released [40,57].

Step e

The client proceeds to the native, active state, which typically does not need further chaperone support. Some clients, however, may even remain bound to Hsp90 after co-factor binding. For example, GR translocates to the nucleus with the help of Hsp90 and co-chaperones where it activates its target genes [105,106]. Possibly also kinases bind to Hsp90 after folding, as mature kinases may depend on Cdc37–Hsp90 post-folding under certain conditions [38]. Together with cyclin D, Cdk4 also migrates to the nucleus to activate its target proteins [63,79,80].

The Hsp90 chaperone is a versatile molecular machine that interacts with a remarkably variable clientele. The progress in molecular understanding of the substrate interaction interfaces shows surprisingly similar properties in the recognition of in particular disordered Tau and folded GR-LBD, but also part of the kinase Cdk4. Notably, the binding site for semi-folded Cdk4 contains a specific

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hydrophobic stretch that does not come into action for binding Tau and GR-LBD. It is tempting to speculate that this stretch represents a first contact mode for folding intermediates, while the substrates move in later stages to the extended and less hydrophobic surface as seen in the case of Tau and GR-LBD. The partial overlap of the binding sites of both proteins and the similarity of the interaction chemistry explain how the Hsp90 chaperone machine is able to interact with a large range of structurally entirely different clients.

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Appendix A. Supplementary data

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Abbreviations used:
LBD, ligand-binding domain; GR, glucocorticoid receptor.

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