Chapter 21
Hsp90 Chaperone in Disease

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Abstract The molecular chaperone Hsp90 is at the heart of protein homeostasis control. A wide range of pathologies disturbs protein homeostasis, thus placing Hsp90 at the crossroads of many diseases. Here, we evaluate the impact of recent progress in understanding the molecular mechanism of Hsp90-client interactions and their role in disease. We discuss the role of Hsp90 for hormonal imbalances, cancer and neurodegenerative disorders. For each disease class we discuss implications of complexes in which Hsp90 binds to a paradigmatic client: the transcription factor Glucocorticoid Receptor, the kinase Cdk4 and the microtubule stabilizer Tau. The mechanistic insights allow us to elaborate on possible therapeutic intervention routes. Hsp90 is a druggable chaperone. Thus, understanding Hsp90 biology at molecular resolution offers an interesting approach to tackle protein-related diseases.

Keywords Kinases · Molecular chaperones · Neurodegeneration · Protein folding · Proteostasis · Steroid receptors

Abbreviations

Aha1	Activator of 90 kDa heat shock protein ATPase homolog 1
Cdk4	Cyclin-dependent kinase 4
CHIP	Carboxy terminus of Hsp70-interacting protein
FKBP51	51 kDa FK506-binding protein
GR	Glucocorticoid receptor
Grp94	94 kDa glucose-related protein

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Hop	Hsc70/Hsp90-organizing protein
HPA axis	Hypothalamic-pituitary-adrenal axis
Hsc70	Heat shock cognate 71 kDa protein
HSP	Heat shock protein family
Hsp40	Heat shock protein 40
Hsp70	Heat shock protein 70
Hsp90	Heat shock protein 90
Hsp90-C	Hsp90 C-terminal domain
Hsp90-M	Hsp90 middle domain
Hsp90-N	Hsp90 N-terminal domain
PPIase	Peptidyl-prolyl-cis/trans-isomerase
TPR	Tetratricopeptide repeat
Trap1	Tumor necrosis factor type 1 receptor-associated protein
XAP-2	HBV X-associated protein 2

21.1 Introduction

In the never-ending fight for adaptability, living systems and their constitutive molecules never settle, changing their internal properties to face environmental challenges (Weber 2010). A paradigmatic example of such fight is the response of a living system to temperature insults, requiring a massive, orchestrated reorganization of its internal components. This reorganization was described for the first time in fruit flies salivary glands subjected to heat shock, and aptly termed heat shock response (Ritossa 1962). Heat shock proteins orchestrate such response, navigating proteins in the turbulent waters of heat stress toward their mature folded forms, and they do so by establishing transient interactions with their assisted proteins, a mode of action that classifies them as molecular chaperones (Ellis 1987). Chaperones do not act solely in case of thermal stress. Indeed, they act in any physiological conditions or at any given environmental challenge affecting the internal protein homeostasis of living systems (Ellis 2013). At a molecular level, human diseases often create conditions challenging protein homeostasis inside cells, tissues or even entire organisms (van Oosten-Hawle and Morimoto 2014). Thus, molecular chaperones play a fundamental role in the onset and progression of any human disease (Klaips et al. 2018).

Chaperones act as a network of proteins, and a central node of this network is the molecular chaperone Hsp90 (Schopf et al. 2017; Taipale et al. 2010). This implies a major role of Hsp90 in human diseases, comprising hormone imbalances linked to metabolic stress (Patel et al. 2014), cancer (Butler et al. 2015; Jhaveri et al. 2014), neurodegenerative disorders such as Alzheimer, Huntington and Parkinson's diseases (Caron et al. 2018; Pratt et al. 2015), heart failure disorders (Ranek et al. 2018), diseases mediated by virus or parasites (Woodford et al. 2016), as in the case of Zika Virus (Pan et al. 2018) or Hepatitis B (Pei et al. 2017), and cystic fibrosis

(Ihrig and Obermann 2017). Understanding Hsp90 biology means understanding a node at crossroads of multiple diseases.

21.1.1 Hsp90: Chaperoning Disease-Relevant Proteins

Hsp90 binds to thousands of proteins, alternative named clients, with no particular common fold driving the binding (Taipale et al. 2014). Hsp90 preferentially binds to unstable proteins (Taipale et al. 2012), whose instability must be dictated by particular amino acidic patterns necessary to recognize the molecular chaperones. Such patterns emerge when we analyze structural models of Hsp90-client complexes resolved at atomic level: Hsp90 in complex with the transcription regulator glucocorticoid receptor (Kirschke et al. 2014), the kinase Cdk4 (Verba et al. 2016), the microtubule binding protein Tau (Karagöz et al. 2014) and the transport protein Transthyretin (Oroz et al. 2017). When looking at these protein complexes, common molecular recognition features arise (Karagöz and Rüdiger 2015; Radli and Rüdiger 2018). (i) Hsp90 binding surface is broad, from 50 to 170 amino acidic depending on the substrate. Hsp90 is a homodimer, each protomer is composed of three domains – the N, M and C-terminal domains – with Hsp90-N and Hsp90-M responsible for interactions with clients (Fig. 21.1). (ii) The established interactions are numerous, and the individual contributions are weak. (iii) The Hsp90 surface is heterogenous, characterized by scattered hydrophobics and charged residues. The first feature allows accommodating clients with different sizes, whereas the other two allow clients with different net charges and hydrophobic content to interact with

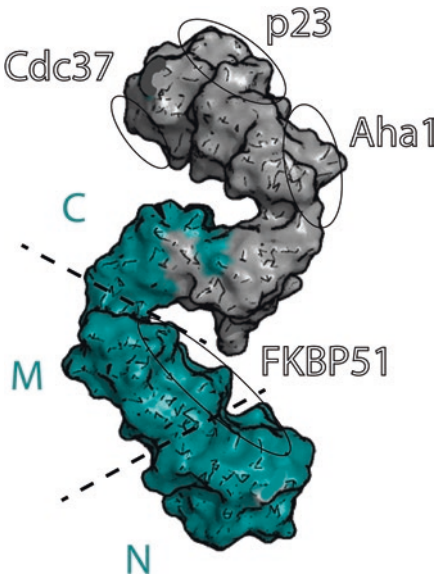

Fig. 21.1 Hsp90 structure and binding to co-chaperones. Hsp90 protomers (coloured in cyan and grey) interact via their C-terminal domains to form a homodimer. N, M and C indicate the three domains of the protomer. Circles represents docking surfaces of four representative co-chaperones, namely Cdc37, p23, Aha1 and FKBP51

Hsp90 surface. Taken together, these features explain on a structural level why Hsp90 clientele is so broad and heterogeneous.

The broad action of Hsp90 can be appreciated even further if we place this chaperon in the context of the living, dynamic environment of a cell. Hsp90 is essential in eukaryotes (Borkovich et al. 1989; Voss et al. 2000) and it is an abundant protein, accounting for ~1% of cellular protein content in non-stress conditions (Picard 2002). Hsp90 isoforms populate the major cellular compartments, with two isoforms resident in the cytoplasm (Hsp90α is the stress inducible form, while Hsp90β is the constitutive one and the main focus of this review (Schopf et al. 2017)), one in the endoplasmic reticulum (Grp94 (Melnick et al. 1992)) and one in the mitochondria (Trap1 (Felts et al. 2000)). Hsp90 centrality in the chaperones network and its broad clientele explain its involvement in otherwise unrelated diseases. Interaction of Hsp90 with disease-related clients is often regulated by co-chaperones. The co-chaperone network offers possibilities for subtle tackling of specific disease-relevant beneficiaries of Hsp90 action.

21.1.2 Hsp90 Co-chaperones: Dictating the fate of Disease-Relevant Clients

Hsp90 has a conserved role in folding of substrates in co-operation with Hsp70, a function spread throughout the evolutionary tree of life (Genest et al. 2011; Morán Luengo et al. 2018; Schumacher et al. 1996; Wegele et al. 2006). Next to this conserved role, Hsp90 acquired a regulatory role in the cytosol of eukaryotic cells, including humans (Morán Luengo et al. 2019). This means that human Hsp90 not only ensures that proteins reach their fold, but can further fine-tune their activity, for instance by delaying their interaction with a ligand (Schulke et al. 2010) or by determining their degradation (Kundrat and Regan 2010). This evolutionary acquired function is modulated by Hsp90 helpers, termed co-chaperones (Morán Luengo et al. 2019).

A recent, extensive study analyzing the folding of a family of steroid hormon receptors by Hsp90 and co-chaperones demonstrated that most of co-chaperones do not contribute to folding but rather slow down Hsp90 folding machinery (Radli and Rüdiger 2018; Sahasrabudhe et al. 2017). Co-chaperones most prominent role is to dictate the fate of clients. An elegant example is the competition of the co-chaperones CHIP and Hop for binding to the C-terminus of Hsp90. Both these co-chaperones can bind to the N-terminus of Hsp90 due to their tetratricopeptide repeat, or TPR domain (Scheufler et al. 2000; Zhang et al. 2005). Hop regulates Hsp90 interaction with the Hsp70 chaperone system (Kirschke et al. 2014; Morán Luengo et al. 2018) whilst CHIP promotes client degradation (Edkins 2015). Both co-chaperones compete for binding to the C-terminus of Hsp90, suggesting that the fate of an Hsp90 client depends on the co-chaperone winning the competition (Kundrat and Regan 2010).

More generally, there are more than 40 Hsp90 co-chaperones (an updated list can be found at https://www.picard.ch/downloads) and the fate of many clients is dictated by a subgroup of them (Cox and Johnson 2018; Picard 2002). Co-chaperones compete fiercely for binding to Hsp90 (Harst et al. 2005), and competition is divided into two leagues: from one side, co-chaperones whose docking on Hsp90 surface is dictated by the interaction between their TPR domains and the EEVD motif at the C-terminus of Hsp90; from the other, co-chaperones whose docking is TPR-independent (Schopf et al. 2017). The winners of this competition are dictated by binding affinities, steric hindrances (in the case of co-chaperones sharing the same Hsp90 docking surface, Fig. 21.1), post-translational modifications and by the levels of co-chaperones, the latter constantly changing in response to environmental cues to readily modify the fate of hsp90 clients (Assimon et al. 2015; Schopf et al. 2017). This system can be hijacked in pathology, for instance in neurodegenerative disorders. Indeed, aging changes co-chaperones and chaperones abundance in human brain, exacerbating the onset of diseases (Blair et al. 2013; Brehme et al. 2014; Labbadia and Morimoto 2015).

Co-chaperones give thus regulational power to Hsp90: based on the cellular state, the availability of ligands, co-chaperones and degradation machinery, each client may be subjected to completely opposite outcomes, from proper folding to irreversible degradation. Co-chaperones add an extra level of regulation for cytoplasmic proteins dependent on Hsp90, and this is a crucial aspect to understand Hsp90 role in disease. We discuss in detail three Hsp90 clients, to extract the mechanistic role of Hsp90 and its co-chaperones in disease. Each client will serve as paradigm for a specific set of disorders, from disorders associated to hormonal imbalances (Glucocorticoid Receptor, (GR)) to cancer (Cdk4) and neurodegeneration (Tau).

21.1.3 Hsp90 and Hormonal Imbalances

21.1.3.1 The Hsp90-Client GR Controls Hormonal Response

Hsp90 interacts with hundreds of transcription factors (Taipale et al. 2012), and among them a well characterized client is the Steroid Hormon Receptor GR. GR is the end-product of hypothalamic-pituitary-adrenal (HPA) axis, a system-wide group of molecular feedback loops present in all human tissues and governing cellular responses to steroid hormones such as cortisol (Chrousos and Kino 2009). Being so ubiquitous, imbalances in the HPA axis are associated to many disorders of different nature. HPA (and GR) imbalances can cause for instance rare diseases such as Cushing syndrome and Addison disease, two metabolic disordered with either increased or depleted levels of the GR-ligand cortisol (Chrousos 2000) but can also be linked to complex pathophysiological effects such psychosocial stress (Wust et al. 2004). HPA imbalances are also associated to neurodegeneration (Du and Pang 2015), and cancer survivors can develop depression due to HPA imbalances

(Young and Singh 2018). Thus, HPA-axis and its end-product GR are valuable targets to treat a broad group of conditions.

21.1.3.2 The Hsp90 Machinery Dictates GR Folding and Activity

Hsp90 dictates GR folding and activity, hence controlling the whole HPA-axis end signaling. GR was one of the first identified Hsp90 clients (Sanchez et al. 1987), and its association to the ligand was shown to be dependent on the presence of the molecular chaperone (Picard et al. 1990). A cohort of chaperones and co-chaperones is involved in the balance of Hsp90-mediated GR activity. Hsp90 collaborates with the Hsp70 system to allow GR to interact with glucocorticoids and implement HPA signaling (Kirschke et al. 2014). The molecular chaperone Hsp70 and its co-chaperone Hsp40 recognize GR, keeping it partially unfolded and inactive. The co-chaperone Hop links Hsp70 and Hsp90 due to its three TPR domains, allowing the downstream interaction of GR with Hsp90. While Hsp70 keeps GR unfolded, Hsp90 releases the break and dictates binding to ligand, folding and consequent downstream activity (Morán Luengo et al. 2018).

Next to the conserved folding role, Hsp90 can delay GR activation by exploiting many co-chaperones. Most of co-chaperones do not contribute to general folding of substrates, instead they slow down Hsp90 folding machinery, with different clients having their own co-chaperones signature (Radli and Rüdiger 2018; Sahasrabudhe et al. 2017). Only the co-chaperones p23 exert a general role in folding of Hsp90 clients, slowing down the Hsp90 machinery to favor client late folding events (Sahasrabudhe et al. 2017). In the case of GR, the co-chaperones FKBP51 and XAP2 delay GR translocation in the nucleus and GR signaling (Laenger et al. 2009; Schulke et al. 2010). Thus, Hsp90 controls activity of GR, with co-chaperones delaying HPA-axis signaling in a client-specific manner.

21.1.3.3 Targeting Hsp90 to Treat Hormonal Imbalances

Can we use this molecular insight to use Hsp90 as a target to treat HPA-related disorders? Hsp90 is druggable and two Hsp90 inhibitors are currently in phase II clinical trials: the inhibitor AT13387 (Onalespib) tested to treat non-small cell lung cancers and lymphomas, and the inhibitor TAS-116 tested to treat advanced gastrointestinal stromal tumors (Miyata et al. 2013; Woodhead et al. 2010; Yuno et al. 2018). Chronical targeting of Hsp90 may be detrimental for humans, given the central role of this molecule in physiological processes too (Schopf et al. 2017; Taipale et al. 2010). To this end, more effective drugs targeting Hsp90 are being developed, for instance by targeting Hsp90 without eliciting a general stress response (Calamini et al. 2010; Neef et al. 2010). Another strategy to increase specificity and decrease off-side effects would be to target co-chaperones. An inhibitor targeting the

interface of Hsp90 in complex with the co-chaperone Aha1 has been recently developed, serving as proof of principle to rationally target co-chaperones instead of Hsp90 (Stiegler et al. 2017). The inhibitor developed alters Hsp90 activity stimulated by Aha1, without altering the intrinsic ATPase activity of Hsp90. Thus HPA-mediated hormonal imbalances can be potentially tackled by targeting the Hsp90 machinery.

GR is also druggable, with the drug Mifepristone used to treat Cushing disease (Johanssen and Allolio 2007) and to alleviate stress in mice (Lesuis et al. 2018). However, there are two good reasons to prefer the targeting of The Hsp90 machinery instead of GR itself. First, promising therapies developed for GR could be expanded to other steroid hormones receptors, all relying on the Hsp90 machinery (Sahasrabudhe et al. 2017). Second, co-chaperones could be targeted to enhance specificity, as different receptors are modulated by different sets of co-chaperones (Moffatt et al. 2008; Schulke et al. 2010). As a proof of principle, small molecules targeting FKBP51:GR:Hsp90 complex have been recently developed, with the aim of treating Post Thraumatic Stress Disorders caused by HPA imbalances (Sabbagh et al. 2018). To summarize, the Hsp90 machinery dictates GR activity, making the modulation of Hsp90-dependent GR assembly a valuable strategy to fight metabolic diseases and alleviate the effect of complex pathophysiological disorders (Fig. 21.2)**.**

21.1.4 Hsp90 and Cancer

21.1.4.1 Hsp90 Sustains Kinase-Mediated Cancer

Kinases deregulation is a common landmark of cancer, with many oncogenes coding for mutated versions of kinases (Joerger and Fersht 2007). Kinases bind to Hsp90, with the molecular chaperone preferring thermally unstable ones (Luo et al. 2017; Taipale et al. 2012). This thermodynamic preference is a crucial aspect for the development of tumors: mutated kinases are often more unstable compared to their evolutionary optimized wild-type counterparts, making them stronger Hsp90 clients. Cancerous cells become then 'addicted' to Hsp90, and indeed they are more sensitive to Hsp90 inhibition than non-cancerous cells (Isaacs et al. 2003; Whitesell et al. 1994; Whitesell and Lindquist 2005). Hsp90, together with other chaperones, sustains cancerous proliferation by reassembling into large complexes, collectively termed epichaperome (Rodina et al. 2016). Thus, Hsp90 is a key player in many forms of cancers, comprising multiple myeloma (Khong and Spencer 2011), breast cancer and lung cancer (Butler et al. 2015). In the specific case of the Hsp90-client Cdk4, deregulation of the kinase causes liposarcoma, where Cdk4 copies expand at genetic level (Barretina et al. 2010; Italiano et al. 2009), or familial melanoma, where Cdk4 is mutated to a constitutively active form (Zuo et al. 1996).

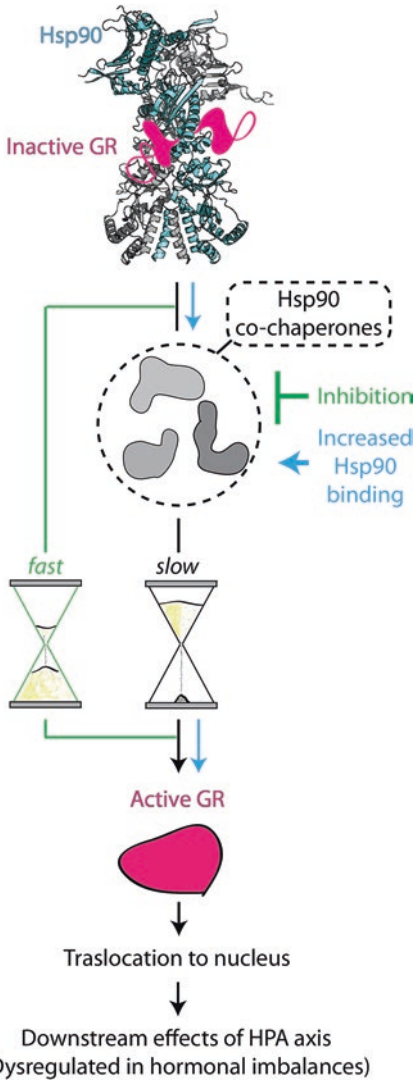

Fig. 21.2 Hsp90 controls hormone imbalances. Hsp90 homodimer is represented in blue and cyan, GR in violet. Hsp90 receives GR from the Hsp70 system (not shown) and is responsible for its downstream folding and activation. Active GR recognizes steroids and translocates to the nucleus to implement hormone-dependent signaling of the hypothalamic-pituitary-adrenal (HPA) axis. Hsp90 co-chaperones slow Hsp90 activity, delaying GR activation and signaling. Therapeutic intervention may either target co-chaperones to shortcut their inhibitory action and increase GR signaling (marked in green), or stabilize Hsp90 in complex with co-chaperones, to further delay GR signaling (marked in blue). Therapeutic intervention varies in accordance to the disease-dependent hypo- or hyper-activation of the HPA axis

21.1.4.2 Kinases Rely on the Hsp90 System for Folding and Activity

Hsp90 binding to kinases is assisted by the co-chaperones Cdc37. Together, they bind the highly conserved kinase domain, which is necessary and sufficient for a kinase to bind to the chaperon complex (Xu et al. 2001). A recent structure of the Hsp90:Cdk4:Cdc37 complex shows Hsp90 and Cdc37 stabilization of a folding client at near-atomic level (Verba et al. 2016). This structure shows how Cdc37 mimics structural features of the mature kinase, whilst Cdk4 is kept in a metastable

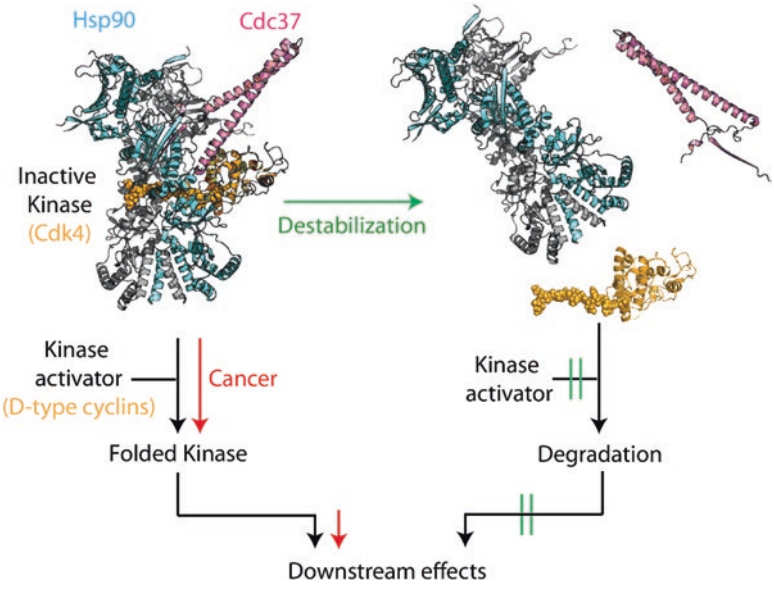

Fig. 21.3 Hsp90 stabilizes kinases promoting cancer. Hsp90 (homodimers in cyan and grey), in cooperation with Cdc37 (pink), folds a wide range of kinases, in this case Cdk4 (orange). Hsp90 and Cdc37 stabilize a partially folded kinase structure, with β-strands 4 and 5 of the kinase unravelled (atoms represented as spheres). Partially folded kinases can then react with downstream activators (e.g. enzymes modifying the kinase post translationally, such as D-type cyclins in the case of Cdk4) and in turn exert their downstream functions. Many kinases are hyper-activated in cancer and sustain growth and activity of tumor cells (extra red arrows). Therapeutic intervention (marked in green) may disrupt the Hsp90:Cdc37:kinase complex to favor kinase degradation by the proteasome system and inhibit its interaction with kinase activator and consequent downstream effects

condition. Cdc37 splits the kinases lobes at the N- and C-termini, and 'opens' the kinase by complete unfolding of the β-strands 4 and 5 (Verba et al. 2016) (Fig. 21.3). Cdc37 opening of the kinases is necessary for consequent binding of Hsp90, as shown for Fibroblast Growth Factor Receptor 3, a kinase involved in bladder cancer (Bunney et al. 2018; McConkey and Choi 2018). Stabilizing a Cdk4 folding intermediate may favor its transition between active or inactive states and accessibility to post translational modifications (Miyashita et al. 2003; Verba and Agard 2017). Indeed, Hsp90:Cdc37 binds to Cdk4, and the complex dissociates upon phosphorylation of the kinase by D-type cyclins (Stepanova et al. 1996). This highlights the evolutionary acquired function of Hsp90 as a fine-tuner of the biological activity of proteins. In the case of kinases, this function may have evolved to add an extra system to further control their activity, as kinase de-regulation is dangerously linked to cancer.

21.1.4.3 Destabilizing Hsp90:Kinase Complexes to Treat Cancer

Targeting the Hsp90:Cdc37:Cdk4 complex may prove an interesting strategy to treat Cdk4-dependent cancers. For instance, in the case of increased copies of Cdk4 causing liposarcoma, destabilization of the complex would be a valuable strategy to reduce the amount of available Cdk4, exposing Cd4 to the degradation system. As a proof of principle, targeting of the Hsp90:Cdc37:kinase complex with Whitaferin has shown promising results in the case of the kinase LRRK2, a protein linked to neurodegeneration (Narayan et al. 2015). In this case, targeting the complex reduced kinase activity, increased kinase clearance and alleviated neuronal death (Fig. 21.3). This strategy can be extended to other kinases dependent on Hsp90 and Cdc37 (Li et al. 2018; Zhang et al. 2008), potentially to the whole human kinome, as kinase dependency on Hsp90:Cdc37 is thought to be a continuum of affinities, with no clear cut between binders and non-binders (Verba and Agard 2017). Targeting the chaperone complex instead of the kinase itself may facilitate translation of therapies among different cancers caused by different Hsp90 clients.

Hsp90 targeting to treat cancer is a strategy currently under investigation: a part from the previously mentioned phase II clinical trials to treat non-small cell lung cancers lymphomas and gastrointestinal stromal tumors, there are 13 ongoing phase I clinical trials to treat chronic lymphocytic leukemia, neuroendocrine tumours, refractory hematological malignancies, solid tumors, unresectable BRAF mutated stage III/IV melanoma, advanced squamous cell carcinoma of the head and neck, advanced triple negative breast cancer, non-Hodgkin's lymphoma and myeloma (Yuno et al. 2018). Kinase deregulation is involved also in neurodegeneration, as we saw in the case of LRRK2, but plays an outstanding role in proliferation of certain viruses and parasites, capable of hijacking host Hsp90 to stabilize their own kinases (Woodford et al. 2016). This is true for instance in the case of Rous Sarcome Virus, whose transforming protein was one of the first Hsp90 clients discovered (Brugge and Darrow 1982). Thus, mastering the Hsp90:Cdc37 action on kinases may prove useful to treat a broad spectrum of diseases.

21.1.5 Hsp90 and Neurodegeneration

21.1.5.1 Protein Aggregation, Hallmark of Neurodegeneration

Hsp90 interaction with a client may also dictate its end by initiating degradation via the ubiquitin-proteasome system (Kundrat and Regan 2010). When clearance fails to be performant, proteins start to aggregate in cells. Protein aggregation is a common hallmark of many diseases, playing an outstanding role in neurodegeneration (Hartl 2017; Stoecklin and Bukau 2013). Protein aggregates may establish abnormal, toxic interactions in the cell and impair the whole protein homeostasis network (Gidalevitz et al. 2006; Hipp et al. 2014). Moreover, aggregates cannot be degraded anymore by the ubiquitin-proteasome system, further exacerbating their

accumulation and their toxic effects (Bence et al. 2001). The aggregation of the Hsp90-client Tau is linked to Alzheimer's disease and other Tauopathies, comprising progressive supranuclear palsy, Pick's disease and chronic traumatic encephalopathy (Goedert et al. 2017; Lee et al. 2001; Wang and Mandelkow 2016). Hsp90 is responsible for Tau clearance, and Tau accumulation is linked to neurodegeneration, drawing a connection between the chaperone machinery and dementia.

21.1.5.2 Hsp90 Regulates Tau Turnover and Aggregation

The Hsp90:Tau complex reveals that Hsp90-N and Hsp90-M domains bind to Tau aggregation-prone regions (Karagöz et al. 2014). This interaction may inhibit Tau aggregation itself: recent data show that chaperones have different propensities to inhibit Tau aggregation, however Hsp90 activity was not tested (Mok et al. 2018). Aside from this potential buffering role, the Hsp90 machinery plays an established role in degrading Tau by bridging it to the ubiquitin-proteasome system. Many co-chaperones, with or without TPR domains, regulate Tau degradation rates (Shelton et al. 2017b). As for GR, CHIP can compete with Hop for the binding to Hsp90, dictating in this case whether Tau is degraded or linked to the Hsp70 system and kept soluble (Dickey et al. 2007; Jinwal et al. 2013; Karagöz et al. 2014; Thompson et al. 2012). FKBP51, another TPR co-chaperone, delays Tau degradation by the ubiquitin-proteasome system and favors Tau aggregation (Jinwal et al. 2010). A recent structure of Hsp90 in complex with Tau and FKBP51 shows that the co-chaperone proline isomerization domain is placed in close proximity to Tau proline-rich region, possibly favoring abnormal isomerization linked to neurodegeneration (Oroz et al. 2018) (Fig. 21.4). Aha1, a non-TPR co-chaperone, also increases Tau aggregation rates, and interestingly both Aha1 and FKBP51 levels increase in brains affected by Alzheimer's Disease (Brehme et al. 2014; Shelton et al. 2017a). As for GR and kinases, the Hsp90 machinery is a major modulator of Tau biology, and in contrast to GR and kinases Hsp90 does not influence ligand binding but rather degradation rates.

Targeting Hsp90 to Alleviate Neurodegeneration

The importance of the Hsp90 system in Tau biology and the lack of effective drugs to treat neurodegeneration make Hsp90-mediated Tau clearance an interesting approach to treat Alzheimer and other Tauopathies (Blair et al. 2014). The ratio is that reducing Tau levels may be a valuable approach to alleviate dementia, as shown in genetics studies in mice and by exploiting anti-sense nucleotides and short interference RNAs to lower Tau protein levels (DeVos and Miller 2013; Roberson et al. 2007; Wolfe 2014) (Fig. 21.4). The advantage of small chemicals over nucleotide-based therapies lies in their general ability to cross blood brain barrier more easily, a crucial factor for the designing of drugs for the central nervous system (Patel and Patel 2017). In this light, a recent study showed that chronically treating a cohort of

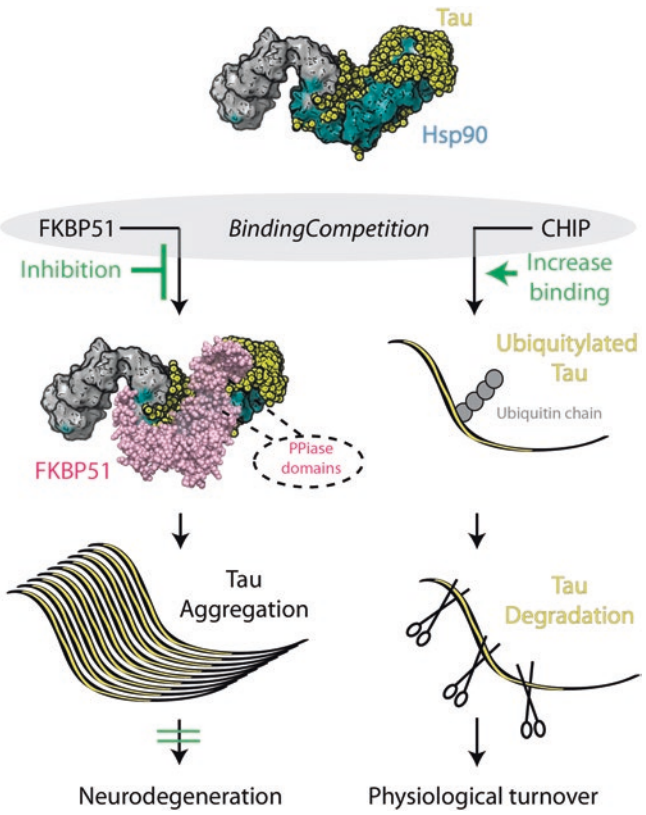

Fig. 21.4 Hsp90 control of protein aggregation in neurodegeneration. Hsp90 (homodimers in cyan and grey), in cooperation CHIP, promotes Tau physiological turnover by the proteasome (right branch of scheme). FKBP51 competes with CHIP for binding to Hsp90:Tau, reducing the amount of degraded Tau, increasing Tau soluble pool and possibly isomerizing Tau prolines via its PPIase domain (peptidyl-prolyl-cis/trans-isomerase domain), favoring overall Tau aggregation. Chaperone-based therapeutics (marked in green) shall either boost Tau turnover or disfavor interactions between Hsp90 and FKBP51 to tip the balance against protein aggregation and consequent neurodegeneration

patients with an inhibitor of FKBPs decreased the incidence of Alzheimer (Taglialatela et al. 2015), thus paving the way to possible treatments focused on the Hsp90 machinery. Other strategies to tackle neurodegeneration via the chaperon system could be also exploited. Recent studies show that the co-chaperone Cyp40 and the chaperone Hsc70 can disaggregate Tau and α-synuclein fibrils (Baker et al. 2017; Ferrari et al. 2018; Gao et al. 2015). These studies collectively imply that the chaperone machinery can be tackled from different angles to treat protein aggregation and neurodegeneration.

Hsp90 binds to other aggregation-prone proteins, such as huntingtin, α-synuclein and transthyretin, whose aggregation processes are linked respectively to Chorea Huntington, Parkinson's disease and transthyretin amyloidosis (Inda et al. 2016;

Oroz et al. 2017; Pratt et al. 2015). Thus, most of the neurodegenerative disorders rely on the Hsp90 system (Lackie et al. 2017), and this can have implications for the design of medical treatments too, as therapies targeting the Hsp90 system developed for one protein could be translated to other neurodegenerative disorders. Of note, protein aggregation can also cause certain forms of cancer, as shown for the signaling protein Axin (Anvarian et al. 2016). Thus, chaperone-based treatments against protein aggregates may cross the borders of neurodegenerative disorders and treat other types of diseases. The Hsp90 core machinery is a master regulator of protein activity and it is a versatile target to treat disease.

21.2 Conclusions

The current challenge is to bridge the molecular information obtained about Hsp90 to the pathology at the system level, with the ultimate goal of developing effective treatments. Hsp90 is a ubiquitous protein, and three crucial aspects of its machinery can allow us to treat specific sets of diseases: (i) There are more than 40 co-chaperones, allowing for targeting of unique interaction surfaces established within clients and chaperone system. (ii) As different co-chaperones add different flavors of regulational power to Hsp90, we can pinpoint one or more co-chaperones that will contribute more to a certain disease, increasing specificity. (iii) Pathological statuses are often 'addicted' to Hsp90 buffering role at the cellular level, thus pathological cells are often more vulnerable than physiological ones, allowing the latter to have higher fitness upon Hsp90 treatments. We can envision that a complete understanding of Hsp90 fine tuning of clients – in terms of co-chaperones, folding outcome and downstream effects – will allow us to target an even wider range of disease. Thus, the current challenge is to master combinatoriality of the Hsp90 machinery, *i.e.* to understand the output effect on a client given the thousands of possible Hsp90:co-chaperones different complexes that can assemble in a cell. The knowledge we accumulated for the main co-chaperones, such as Cdc37, p23, CHIP, Hop, must embrace also less studied co-chaperones. The combinations of effective complexes need to take into account sub-cellular compartmentalization, stress-inducible isoforms, availability of co-chaperones and post translational modifications, all influencing the assembly of the Hsp90 machinery when dealing with a specific client (Cox and Johnson 2018; Mayer and Le Breton 2015; Mollapour et al. 2014). Hsp90 buffering of protein folds is reflected not only on physiology and pathology at the system level, but on a broader scale when whole populations are considered. Indeed, Hsp90 is known to hide cryptic variations of proteins within a population, allowing these variations to reveal in time of stress, to boost adaptability (Rutherford and Lindquist 1998). The same principles applies to diseases: in the case of Fanconi anemia, Hsp90 buffers a group of protein mutants linked to mild phenotypes, which worsen upon Hsp90 inhibition (Karras et al. 2017). These findings imply that within the same disease some patients may react better to Hsp90 treatments than others. This is an important consideration when placed in the

context of precision medicine, namely the designing of treatments based on the personal network of interactions and disease-variants of each patient. True mastering of Hsp90 biology will be a powerful weapon relevant for fatal diseases.

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