



Human Hsp90 cochaperones: perspectives on tissue-specific expression and identification of cochaperones with similar in vivo functions

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Abstract

The Hsp90 molecular chaperone is required for the function of hundreds of different cellular proteins. Hsp90 and a cohort of interacting proteins called cochaperones interact with clients in an ATP-dependent cycle. Cochaperone functions include targeting clients to Hsp90, regulating Hsp90 ATPase activity, and/or promoting Hsp90 conformational changes as it progresses through the cycle. Over the last 20 years, the list of cochaperones identified in human cells has grown from the initial six identified in complex with steroid hormone receptors and protein kinases to about fifty different cochaperones found in Hsp90-client complexes. These cochaperones may be placed into three groups based on shared Hsp90 interaction domains. Available evidence indicates that cochaperones vary in client specificity, abundance, and tissue distribution. Many of the cochaperones have critical roles in regulation of cancer and neurodegeneration. A more limited set of cochaperones have cellular functions that may be limited to tissues such as muscle and testis. It is likely that a small set of cochaperones are part of the core Hsp90 machinery required for the folding of a wide range of clients. The presence of more selective cochaperones may allow greater control of Hsp90 activities across different tissues or during development.

Keywords Molecular chaperone · Hsp90 · Cochaperone · Tetratricopeptide repeat · Aha1 · Cdc37

The Hsp90 folding cycle

The predominant model of Hsp90 and cochaperone interaction with client proteins is based on analysis of proteins that associate with steroid hormone receptors, such as the glucocorticoid receptor (GR). During GR folding and activation, Hsp90 progresses through a series of distinct complexes characterized by the presence of different cochaperones. This cycle was first established using cellular extracts and has since been confirmed using purified components. In a simplified model (Fig. 1a), the chaperones Hsp70 and Hsp40 interact

with the client first. Hop (human gene name STIP1) is able to bind simultaneously to both Hsp70 and Hsp90, facilitating transfer of client to Hsp90. Coordinated action of Aha1 (human gene name AHSA1) and Cyp40 (human gene name PPID) displace Hop, allowing formation of the closed nucleotide-bound state characterized by interaction with p23 (human gene name PTGES3). As the cycle progresses, Hsp90 undergoes dramatic structural changes, cycling from the open form dimerized at only the carboxyl-terminus to the closed form that additionally dimerizes the amino-terminal domains. Hsp90 ATPase activity is inhibited while bound to Hop and activated by Aha1. Details about cochaperone function and structure and functional interaction between Hsp90 and the GR are available (Kirschke et al. 2014; Lorenz et al. 2014; Prodromou 2012; Schopf et al. 2017).

The above model does not account for increasing evidence that different clients interact with different cochaperone proteins. The extent of overlap of the folding pathways for diverse clients is not known. As discussed below, almost 50 proteins have been identified in complex with Hsp90 clients. These proteins have been established as cochaperones based on shared characteristics with known cochaperones. These

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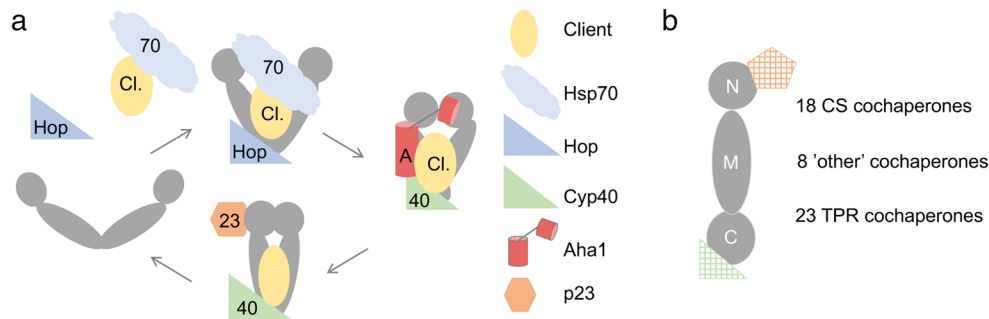


Fig. 1 **a** Simplified model of the Hsp90 folding pathway. The client protein (yellow, Cl.) bound to Hsp70 (light blue) is targeted to the open conformation of Hsp90 (dark gray) in a process facilitated by Hop (dark blue). Nucleotide binding promotes dimerization of the amino-termini of Hsp90 and displacement of Hop by Aha1 (red, A) and Cyp40 (green, 40).

The closed conformation is further stabilized by p23 (orange, 23). **b** Additional co-chaperones that share a CS domain with p23, or a TPR domain with Hop or Cyp40 have also been found in Hsp90 complexes. Other co-chaperones do not contain either of those domains

include the ability to directly interact with Hsp90, the ability to modulate Hsp90 ATPase activity, the ability to prevent aggregation of other proteins, and/or the presence of conserved domains known to promote Hsp90 interaction. Another property is that overexpression or knockdown of co-chaperones alters resistance to Hsp90 inhibitors (Forafonov et al. 2008; Smith et al. 2009). It is important to note that some co-chaperones also have Hsp90-independent functions (Echtenkamp et al. 2011; Freeman and Yamamoto 2002; Sager et al. 2018).

The large number of co-chaperones is likely due to the diverse roles of Hsp90, which is both abundant and essential in eukaryotes (Borkovich et al. 1989). Hsp90 inhibition directly or indirectly impacts the function of 10–15% of all human proteins (Wu et al. 2012). Hsp90 interaction promotes client stability, provides a means of regulating client activity, and/or promotes assembly into multiprotein complexes. Some co-chaperones exhibit preferential binding to proteins with specific folds or domains. For example, Cdc37 binds directly to protein kinases, while Sgt1 binds clients with leucine-rich repeats (Taipale et al. 2014; Verba et al. 2016). A likely source of variation in Hsp90-client complexes is that many co-chaperones share a common Hsp90-interacting domain (Fig. 1b), allowing swapping of one co-chaperone for another. For instance, there are 18 proteins that share homology with p23, in what is now referred to as a cysteine and histidine-rich domain (CHORD) domain, or CS domain (Garcia-Ranea et al. 2002). An additional 23 co-chaperones, including Hop and Cyp40, are characterized by the presence of a tetratricopeptide repeat (TPR) domain (Schopf et al. 2017). Considering that an Hsp90 dimer has binding sites for two CS co-chaperones and two TPR co-chaperones, there is potential for vast variability in Hsp90 complexes. A further set of eight co-chaperones do not contain either of those domains. We summarize what is known about this collection of human co-chaperones, most of which have been diligently tracked and curated by Didier Picard over more than 20 years (<http://www.picard.ch/downloads/Hsp90facts.pdf>). We also examined differences

in co-chaperone expression level and tissue distribution, identifying cellular processes or tissues where groups of Hsp90 co-chaperones have been found to have shared functions.

P23-like co-chaperones that contain CS domains

The CS domain of p23 domain consists of a 7 strand antiparallel β -sandwich that is similar to crystallin (Ali et al. 2006). A total of 18 proteins that contain p23-like sequences have been identified. The structures of many of these proteins, or specifically the isolated CS domains, have been determined (Table S1 and (Garcia-Ranea et al. 2002)). Figure 2a shows a phylogenetic tree of the CS domains of the co-chaperones aligned with Clustal Omega (Madeira et al. 2019). Many of these proteins contain additional functional domains. Two families of proteins that are present in this group are the NudC (Nuclear distribution gene C) family and the PIH (protein interacting with Hsp90) family (Fu et al. 2016; Yamamoto et al. 2010). Two additional closely related proteins in this group are CHORDC1 and ITGB1BP2, also known as Morgana and Melusin (Ferretti et al. 2011).

Although these proteins share a common domain and are known or predicted to bind to the amino-terminus of Hsp90, they have different properties with regard to both Hsp90 interaction and client interaction. p23 binds the amino-terminus of Hsp90 while it is in the closed-ATP bound conformation (Ali et al. 2006), and it is able to weakly inhibit ATPase activity (McLaughlin et al. 2006). However, Sgt1 and CHORDC1 appear to bind different conformations of Hsp90 and have differing effects on ATPase activity (reviewed in (Shirasu 2009)). p23, NudC, NUDCD3 and CACYBP are co-chaperones able to protect other proteins from aggregating (Freeman et al. 1996; Fu et al. 2016; Goral et al. 2016; Zheng et al. 2011). A comparative analysis suggests that each of these co-chaperones may have unique client specificity. For

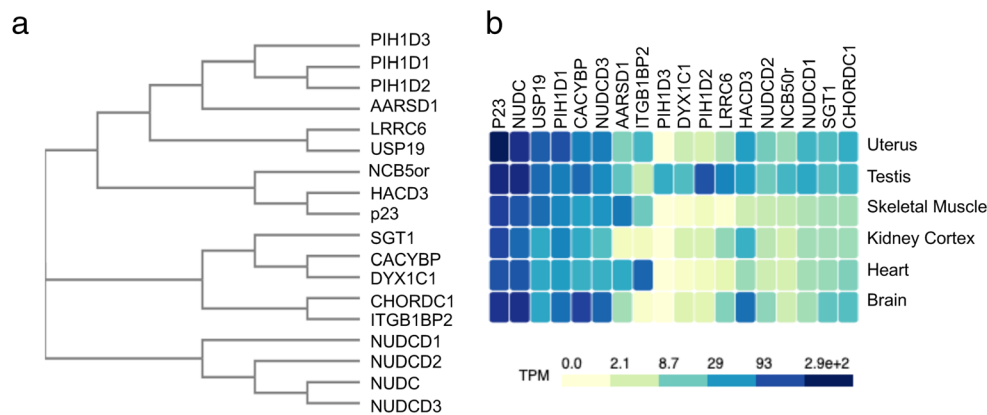


Fig. 2 **a** Phylogenetic tree showing homology of cochaperones with p23-like CS domains. The sequences corresponding to the CS domain of human cochaperones were aligned with Clustal Omega. The accession sequences for each cochaperone are listed in Table S1. **b** The Genotype-Tissue Expression (GTEx) database (gtexportal.org) was used to compare

example, Sgt1, NudC, NUDCD1, NUDCD2, and NUDCD3 exhibited preferential interaction with different types beta-propeller folds (Taipale et al. 2014).

Until recently, it has been difficult to compare the relative expression of the different cochaperones across a wide range of tissues. However, the Genotype-Tissue Expression (GTEx) project provides RNA sequence data for non-disease human tissue sites across multiple individuals (<https://www.gtexportal.org/home/>). We used that data to compare the overall transcript abundance of the cochaperones in a limited set of tissues. This approach allows us to examine how the composition of Hsp90 complexes may change in a tissue-specific manner. p23 was one of the first cochaperones identified, and it binds steroid hormone receptors, telomerase, certain chromatin remodelers, and other proteins (Echtenkamp et al. 2016). As shown in Fig. 2b, p23 is expressed abundantly and ubiquitously. Other cochaperones with CS domains are expressed at similar levels, suggesting they may function with a wide range of Hsp90 clients or interact with clients that are abundantly expressed. This includes NudC, USP19, PIH1D1, CACYBP, and NUDCD3. NudC has important roles in regulating dynein and actin organization during mitosis and cell migration, while the functions of NUDCD3 are largely unknown (Boitet et al. 2019; Zhu et al. 2010). PIH1D1 is part of a large R2TP complex involved in assembly of diverse protein complexes (Rivera-Calzada et al. 2017). USP19 is a deubiquitinase involved in a variety of functions (He et al. 2016). CACYBP is a multi-domain and multi-functional protein (reviewed in (Topolska-Wos et al. 2016)).

The remaining proteins in this group exhibit lower overall expression or strong tissue-specific expression patterns. Sgt1 is required for the function of nucleotide-binding domain and leucine-rich repeat-containing proteins (NLR) proteins that are required for innate immunity. Sgt1 also has roles in kinetochore complex formation, activation of the leucine-rich

mRNA expression data for each of the cochaperones across a range of human tissues. Brain = frontal cortex, heart = atrial appendage. The hatched polygons show the mean transcripts per million (TPM) of the mRNA encoding the indicated cochaperone in the tissue shown. Darker colors represent higher expression levels

repeat adenylyl cyclase Cyr1, and formation of the SCF ubiquitin-ligase complex (reviewed in (Shirasu 2009)). CHORDC1 has important roles in regulating genomic stability by regulating the centrosome cycle (Ferretti et al. 2010). NUDCD2 was recently shown to play a role in modulating sister chromatin cohesion during mitosis (Yang et al. 2019), and NUDCD1 is involved in dynein signaling (He et al. 2018).

The expression of some of these cochaperones is tissue-specific. LRR6, PIH1D2, PIH1D3, and DYX1C1 are highly expressed in the testis (Dong et al. 2014), while Aarsd1 and ITGB1BP2 are highly expressed in muscle tissues (Echeverria et al. 2016; Tarone and Brancaccio 2015). Two additional family members in this group have varied expression and poorly understood functions. HACD3 has a role in viral replication and was shown to share some functions with p23 (Taguwa et al. 2008). The reason it may be highly expressed in the brain is unknown, but it may be related to its interaction with Rac, a member of the Ras superfamily (Courilleau et al. 2000). NCB5or (NADH-cytochrome b₅ oxidoreductase) is implicated in diabetes and neurological diseases, but the role of Hsp90 in these functions is unclear (Benson et al. 2019).

TPR-containing cochaperones

The tetratricopeptide repeat (TPR) is a degenerate 34 amino acid sequence (D'Andrea and Regan 2003; Scheufler et al. 2000). Figure 3a shows a phylogenetic tree of the TPR domains of the cochaperones aligned with Clustal Omega. TPR-containing cochaperones vary in the number of TPR repeats in a tandem array, and some cochaperones, such as Hop, contain more than one TPR domain. Thus, alternate alignments are possible. The structure of the TPR domains of many of these cochaperones has been determined (Table S2). Most of the 23

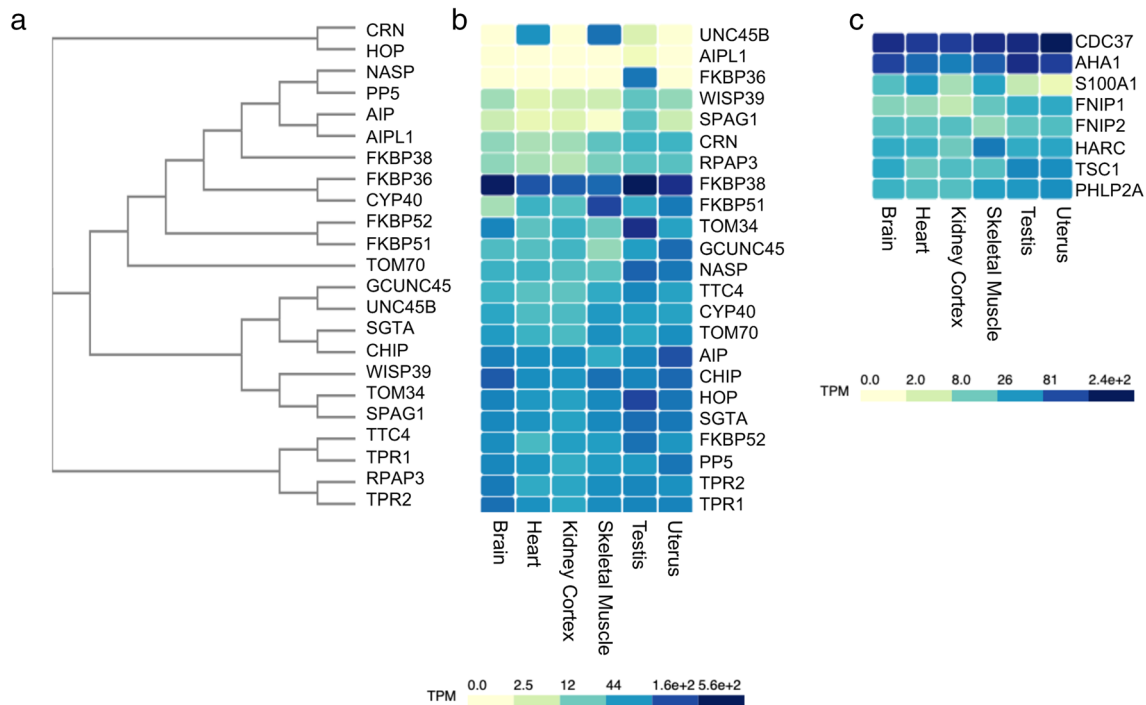


Fig. 3 **a** Phylogenetic tree showing homology of cochaperones containing TPR domains. The sequences corresponding to the TPR domains of human cochaperones were aligned with Clustal Omega. The accession sequences for each cochaperone are listed in Table S2. **b**, **c** The Genotype-Tissue Expression (GTEx) database (gtexportal.org) was

used to compare mRNA expression data for each of the cochaperones across a range of human tissues. Brain = frontal cortex, heart = atrial appendage. The hatched polygons show the mean transcripts per million (TPM) of the mRNA encoding the indicated cochaperone in the tissue shown. Darker colors represent higher expression levels

TPR cochaperones are known or predicted to function primarily by binding to the EEVD sequence at the carboxy-terminus of Hsp90, but some may also bind the conserved sequence in cytosolic Hsp70. A discussion of the determinants of the specificity of TPR cochaperones may be found elsewhere (Assimon et al. 2015). TPR cochaperones may bind different conformations of Hsp90: Hop is known to preferentially interact with the nucleotide-free form of Hsp90, while others, such as FKBP51, FKBP52, and Cyp40, preferentially interact with the ATP-bound form of Hsp90 (Johnson et al. 1994; Richter et al. 2003). TPR cochaperones also have varied effects on the Hsp90 ATPase activity (Blundell et al. 2017; Prodromou et al. 1999; Schopf et al. 2017). Each monomer of Hsp90 can bind one TPR protein at a time, and competition for TPR binding sites on Hsp90 appears to shape chaperone activity (Assimon et al. 2015).

The TPR cochaperones are diverse, and many of them have domains that confer additional functions, such as peptidyl-prolyl isomerase, protein phosphatase, or ubiquitin ligase activity (Golden et al. 2008; Guy et al. 2015; Zhang et al. 2005). In some cases, client activity is known to vary depending on the identity of the bound cochaperone. For instance, activity of the GR is positively affected by FKBP52 interaction, but not by FKBP51 interaction, and changes in the relative levels of cochaperones may be a method to regulate client activity or degradation (Connell et al. 2001; Erlejan et al. 2014;

Reynolds et al. 1999). The range of functions of many of these cochaperones is not known, but it is likely that they have differing specificity for clients and/or distinct effects on client activity (Guy et al. 2015; Taipale et al. 2014).

Data obtained from the GTEx project (<https://www.gtexportal.org/home/>) shows variation in the expression levels and tissue distribution of human TPR cochaperones (Fig. 3b). Surprisingly, the one that is expressed at the highest level across a range of tissue is FKBP38, a membrane-anchored protein distributed predominantly in mitochondria (Blundell et al. 2017; Shirane and Nakayama 2003). Many of the other TPR cochaperones are expressed at similar levels across a range of tissues. This includes most of the proteins identified in complex with steroid hormone receptors: Hop, PP5, FKBP52, Cyp40, GCUNC45, SGTA, CHIP, and TPR2 (Chadli et al. 2006; Connell et al. 2001; Moffatt et al. 2008; Paul et al. 2014; Pratt and Toft 1997). Other cochaperones without a clear tissue specificity that are expressed at varying levels include TPR1, which is involved in Ras signaling (Kwan et al. 2012); aryl hydrocarbon receptor interacting protein (AIP) (Morgan et al. 2012); TOM70, part of the mitochondrial outer membrane complex essential for protein import into mitochondria (Young et al. 2003); TTC4, which interacts with the licensing factor Cdc6 (Crevel et al. 2008); NASP, a linker histone-binding protein (Alekshev et al. 2005); RPAP3, which, like PIH1D1, is part of the large R2TP complex (Rivera-Calzada et al. 2017); CRN (Hatakeyama et al. 2004); and WISP39, which

plays a role in cell migration and regulation of the cell cycle (Howell et al. 2015; Jascur et al. 2005).

Similar to the CS-CHORD cochaperones, some TPR cochaperones exhibit tissue-specific expression. Levels of FKBP51, FKBP36, SPAG1, and TOM34 were highest in the testis (Jarczowski et al. 2009; Lin et al. 2001; Trcka et al. 2014). In contrast, levels of the Unc45B, a myosin-specific cochaperone (Srikakulam et al. 2008), were highest in muscle cells. Finally, although not highly expressed in any of the tissues shown, AIPL1 has critical roles in the retina (Hidalgo-de-Quintana et al. 2008).

Other cochaperones

The remaining cochaperones do not contain either CS or TPR domains, and most of them interact with the middle domain of Hsp90. Structural information of some of the cochaperones in this category is available (Table S3). A comparison of the mRNA levels in the GTEx project shows that one of the most highly expressed is Cdc37 (Fig. 3c). Cdc37 and Hsp90 are required for the folding and stabilization of approximately 60% of protein kinases (Taipale et al. 2012). The structure of Cdc37 in complex with both Hsp90 and a protein kinase shows extensive contacts between the three proteins (Verba et al. 2016). Hrc, which is homologous to Cdc37 but appears to have different specificity, was expressed at the highest levels in skeletal muscle (Scholz et al. 2001; Taipale et al. 2014).

Another highly expressed cochaperone in this group is Aha1, which stimulates ATP hydrolysis by promoting a conformational change that allows a catalytic loop of the middle domain to associate with the amino-terminus (reviewed in (LaPointe et al. 2020)). Aha1 plays a critical role in the quality control process that leads to degradation of the mutant cystic fibrosis transmembrane conductance regulator (CFTR) (Wang et al. 2006), and other interactors have been identified (Sun et al. 2015). The remaining cochaperones are expressed at varied and lower levels. FNIP1 and FNIP2 are homologous cochaperones that compete with Aha1 for binding to Hsp90. TSC1 similarly regulates Hsp90 complexes by blocking Aha1 interaction (Woodford et al. 2016; Woodford et al. 2017). S100A1, which binds calcium (Okada et al. 2004), was expressed at highest levels in muscle tissues. PhLP2a, which interacts with an angiogenic VEGF receptor and functions in apoptosis (Krzemien-Ojak et al. 2017; Srinivasan et al. 2013), showed relatively high and ubiquitous expression levels.

Cochaperone functions in cancer, neurodegeneration, and dynein assembly

Hsp90 is overexpressed in cancer cells and the role of Hsp90 in cancer has been the subject of recent reviews (Calderwood and

Gong 2016; Vartholomaïou et al. 2016). Many of the cochaperones are also overexpressed in cancer cells or have been shown to have other roles in tumorigenesis (Buchanan et al. 2007; Calderwood 2013; Chen et al. 2009; Crevel et al. 2008; De Leon et al. 2011; Dunn et al. 2015; Ferretti et al. 2010; Golden et al. 2008; Han et al. 2018; McDowell et al. 2009; Muller et al. 2019; Pearl 2005; Pei et al. 2009; Srinivasan et al. 2013; Woodford et al. 2016; Woodford et al. 2017). The role of Hsp90 cochaperones in neurodegenerative disease has also been the subject of recent reviews, including one that summarizes findings in which cochaperones that are upregulated in cancer are downregulated in neurodegenerative disease (Calderwood and Murshid 2017). Specific cochaperones implicated in neurodegeneration are p23, Sgt1, CACYBP, CHORDC1, USP19, FKBP51, FKBP52, CYP40, Hop, PP5, CHIP, Cdc37, PhLP2a, and Aha1. Changes in the expression of some of the cochaperones during aging have also been noted (Bohush et al. 2019; Brehme et al. 2014; Herold et al. 2016; Lackie et al. 2017; Shelton et al. 2017).

The composition of Hsp90 complexes varies between the testis and muscle

The expression levels of many of the cochaperones are different upon comparison of the muscle and testis (Table 1). Tissue-specific cochaperone expression may allow greater control of more widely expressed clients, such as GR (Connell et al. 2001; Reynolds et al. 1999; Riggs et al. 2004). For example, Aarsd1 is a muscle-specific cochaperone that interacts with Hsp90 during muscle differentiation (Echeverria et al. 2016). Aarsd1 displaces p23, resulting in reduced GR activity. Further analysis of how interacting cochaperones alter client activity may provide new insights in to how altered cochaperone levels during differentiation, aging, or disease impacts activity of a wide range of Hsp90 clients. Hsp90 is very abundant, and there are two isoforms of human Hsp90, Hsp90 alpha (encoded by HSP90AA1), and Hsp90 beta (encoded by HSP90AB1). The relative levels of the two isoforms also vary between the testis and muscle. Hsp90 beta is more predominant in muscle, while Hsp90 alpha is expressed at high levels in the testis. Some of the cochaperones, such as GCUNC45 and Aarsd1, preferentially interact with one isoform or the other, contributing to the specificity of their effects (Chadli et al. 2008; Echeverria et al. 2016).

Hsp90-specific functions in the muscle

Some Hsp90 cochaperones are likely required to assist client proteins unique to those tissues. As shown in Table 1, the levels of the mRNAs encoding FKBP51, S100A1, ITGB1BP2, Unc45B, Aarsd1, and Hrc are elevated in the skeletal muscle, and most are also elevated in the heart tissue. These cochaperones have known muscle-specific functions.

Table 1 Differential expression of Human Hsp90 isoforms and cochaperones in the muscle and testis

Cochaperone	Skeletal muscle Mean TPM	Testis Mean TPM	Function
FKBP51	176.7	28.8	Promotes myogenesis
S100A1	21.7	2.8	Localizes to Z-discs and sarcoplasmic reticulum
ITGB1BP2	7.7	2.4	Integrin binding protein
UNC45B	83.7	2.2	Myosin chaperone
AARSD1	38.4	9.1	Muscle wasting and GR activity
HARC	40.5	18.0	Mutations linked to heart failure
NASP	15.4	106.4	testis- and sperm-specific histone-binding protein
TOM34	12.6	293.0	
PIH1D2	0.6	66.0	Dynein assembly
FKBP36	0	76.7	
HACD3	2.2	21.1	
NUDCD1	3.7	18.2	Dynein assembly
NCB5or	2.7	12.9	
LRRC6	0.1	32.1	Dynein assembly
DYX1C1	0.2	11.0	Dynein assembly
SPAG1	0.3	16.5	Dynein assembly
PIH1D3	0	16.2	Dynein assembly
HSP90AA1	239.4	902.0	Hsp90 alpha
HSP90AB1	929.3	541.8	Hsp90 beta

TPM, transcripts per million (gtexportal.org)

ITGB1BP2 binds integrin as part of costameres that regulate the interaction between the cytoskeleton and the extracellular matrix and has been shown to have cardioprotective effects (reviewed in (Tarone and Brancaccio 2015)). Unc45B assists the folding myosin (Srikakulam et al. 2008), and S100A1 is a regulator of muscle contractility (Most et al. 2001). FKBP51 has roles in myoblast differentiation and regulating muscle mass (Ruiz-Estevez et al. 2018; Shimoide et al. 2016). A recent study suggests that mutations in the gene encoding Harc may be associated with heart failure (Huang et al. 2018). Cochaperones that are more widely expressed, such as Sgt1, USP19, FNIP1, and Cdc37, also have established roles in the heart or muscle function (Coyne et al. 2018; Kapustian et al. 2013; Ota et al. 2010; Reyes et al. 2015). Hsp90 cooperates with Aha1, Aarsd1, Hop, and Cdc37 during myoglobin maturation (Ghosh et al. 2019). FKBP38, Aha1, Hop, and Hsp90 are involved in the folding of the CLC-1 chloride channel in the skeletal muscle (Peng et al. 2016). These results suggest that muscle tissues may be an excellent model system to study how variations in Hsp90 complexes affect client function.

Hsp90-specific functions in the testis

A subset of cochaperones has recently been linked to the preassembly of dynein arms or regulation of dynein functions (reviewed in (Fabczak and Osinka 2019)), and dynein plays

an important role in spermatogenesis (Wen et al. 2018). This includes PIH1D1, PIH1D2, PIH1D3, RPAP3, SPAG1, DYX1C1, LRRC6, and NUDCD1. Although transcription of genes encoding NASP, TOM34, HACD3, and NCB5or is elevated in testis, details on their functions are scarce. However, loss of FKBP36 results in chromosome mispairing during meiosis and mutations are suspected to cause azoospermia (Crackower et al. 2003; Zhang et al. 2007). FKBP52 is required for androgen receptor signaling (Cheung-Flynn et al. 2005), and Hsp90 and cochaperones are required for the function of testis-specific serine/threonine kinases essential for male fertility (Jha et al. 2013). Altered function of a pathway that includes TSC1 has also been shown to cause disruption of spermatogenesis (Tanwar et al. 2012). In addition, the Hsp90 alpha isoform is highly expressed in the testis, and loss of Hsp90 alpha causes infertility in mice (Grad et al. 2010). Part of this effect of Hsp90 alpha may be due to its role in fetal PIWI-interacting RNAs (piRNA) in male germ cells (Ichiyanagi et al. 2014). These results demonstrate that the Hsp90 machinery plays a critical role in male fertility.

Concluding remarks

Hsp90 is a complicated molecular chaperone machine that directly or indirectly impacts the function of 10–15% of all proteins in humans (Wu et al. 2012). Cochaperones have a

wide variety of functions, such as modulating Hsp90 ATPase activity or conformational changes and targeting clients to Hsp90. The benefit of such a wide variety of cochaperones is largely unknown. The most likely explanation is that the large cohort of cochaperones enables Hsp90 to interact with hundreds of diverse proteins that do not share any sequence or structural similarity. A few studies have undertaken the daunting task of matching up client-cochaperone pairs (Echeverria et al. 2011; Taipale et al. 2014). However, in most cases, the individual roles of cochaperones in client folding remain unknown. The number and types of Hsp90 cochaperones varies from species to species, suggesting a correlation between client diversity and the range of available cochaperones (Johnson and Brown 2009). Analysis of yeast cochaperones suggests that a few cochaperones are required for core Hsp90 functions, while others have more specialized functions (Biebl et al. 2020; Sahasrabudhe et al. 2017).

Despite the discovery of an unexpectedly large cohort of cochaperones, the current model of the Hsp90 folding cycle is very similar to the model that was first established over 20 years ago. Early in the cycle, clients are transferred to Hsp90 from Hsp70 in a process mediated by cochaperones. Nucleotide binding and hydrolysis results in additional changes in the types of bound cochaperones and/or Hsp90 conformation. The expanded list of cochaperones increases the likelihood that different clients bind different cochaperones throughout the cycle. Further analysis Hsp90 and cochaperone complexes with diverse clients will help identify the core features of the human Hsp90 folding machine. In contrast, a better understanding of cochaperones that have selective client interactions will provide new insights into how cochaperones contribute to client folding and broaden the scope of Hsp90 functions. This may lead to novel approaches to selectively inhibiting a subset of Hsp90 clients without disrupting essential functions. Another area of research is understanding how post-translational modifications of Hsp90 provide directionality to the folding process by promoting progression to the next cochaperone complex in the folding pathway (Mollapour and Neckers 2012; Sager et al. 2019). More studies are also needed to understand how changes in the composition of Hsp90-complexes due to aging, development, or disease affect client function.

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Authors' contributions MED helped gather data and assisted with manuscript preparation. JLJ conceived the idea for the publication and wrote the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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