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HSP90AB1: helping the good and the bad

Michael Haase and Guido Fitze

Department of Pediatric Surgery, University Hospital Carl Gustav Carus, TU Dresden,
Fetscherstrasse 74, 01307 Dresden, Germany, Tel: ++49-351-458-13142, Fax: +
+49-351-458-5343

Abstract

HSP90AB1 (heat shock protein 90 kDA alpha, class B, member 1), also known as HSP90beta, is a member of the large family of HSPs which function as molecular chaperones. Chaperones, by binding to client proteins, support proper protein folding and maintain protein stability, especially after exposure to various kinds of cellular stress. Client proteins belong to various protein families including kinases, ubiquitin ligases and transcription factors. HSP90 proteins act as dimers and bind clients with the help of co-chaperones. The cochaperones influence many functions including client binding, ATPase activity or ATP binding of HSP90. HSPs are necessary for a large scale of cellular processes and therefore essential for cell survival. Since client proteins can be mutant proteins that would be degraded without the help of chaperones, HSPs also promote tumor formation and cancer cell proliferation. As such, they are also targets for new therapeutic approaches in cancer treatment. This review focuses on recent studies on HSP90AB1, if possible in comparison with its close homologue HSP90AA1.

Introduction

Heat shock proteins (HSP) are a large group of chaperones which are proteins that assist in protein folding, stabilize proteins and help to refold denatured proteins, processes that are dependent on hydrolysis of ATP (1). If proper folding is not possible, they also aid in protein degradation. The major groups of HSPs are shown in table 1. Chaperonins form a sub-class of HSPs and are characterized by a stacked double-ring structure forming barrels (Xu et al. 1997). Inside the barrel structures, they contain hydrophobic residues for client binding (Lindquist 1986). The prototypes of chaperonins are GroEL/GroES (large and small proteins of the GroE operon in *E. coli*, mutations of which affect the growth of lambda phage by interfering with assembly of its head protein E) in bacteria (Georgopoulos et al. 1973; Sternberg 1973b, a; Hendrix 1979; Yamamori & Yura 1980; Fayet et al. 1989) and Hsp60/Hsp10 proteins in eukaryotic cells (Johnson & Craig 1997).

Originally, HSPs were described as proteins that were up-regulated after elevated temperatures (Lindquist 1986). Meanwhile it is recognized that HSPs are involved in the

response to all kinds of stress reactions that disturb proper protein conformation such as reactions to chemicals like ethanol, arsenite, cadmium, zinc, copper, mercury, sulfhydryl reagents, calcium ionophores, steroid hormones, chelating agents, viruses and many more (Lindquist 1986). Of course, HSPs are strongly induced by DNA damage since this type of stress leads to mutations that often interfere with proper protein folding (Fornace et al. 1988). Since HSPs stabilize DNA binding proteins it is not surprising to detect genomic instability in HSP70 deficient mice (Hunt et al. 2004). Because also many undamaged proteins need assistance in folding, nearly all physiological processes require HSPs. Indeed, with the help of protein-protein interaction (PPI) studies, proteins could be identified as interaction partners that contribute to the following processes: transcription, mRNA splicing, translation, cell cycle control, DNA repair, apoptosis, intracellular transport, development, immune response, lipid and carbohydrate metabolism, cellular signaling, protein modification and many more (Gong et al. 2009; Tsaytler et al. 2009; Gano & Simon 2010; Echeverria et al. 2011; Hartson & Matts 2012; Taipale et al. 2014). HSPs are also involved in protein transport across membranes (e.g. of mitochondria or endoplasmic reticulum).

Several types of chaperones may act together, dependent on the type of protein or type of damage. One model suggests that client proteins (e.g. proteins in translation dependent on the stage of maturation) are first bound to Hsp70, then to chaperonins (Johnson & Craig 1997), then to more specialized proteins of the Hsp90 group (Hartl 1996; Johnson & Craig 1997). An alternative pathway, independent of HSP70 or HSP90, involves binding to CCT/ TriC (chaperonin containing T-complex polypeptide/ TCP-1 ring complex) proteins. This pathway is used by filamentous proteins like actin and tubulin (Johnson & Craig 1997) but also other types of proteins. There are also multichaperone complexes like HSP70/HSP90. Complex formation in this case is mediated by the adapter protein and co-chaperone Hop (HSP organizing protein) which binds to the peptide sequence EEVD at the C-terminus of both proteins (Chen & Smith 1998; Scheufler et al. 2000; Brinker et al. 2002). Often, the client proteins remain bound to a HSP, but they may be released once they are stable on their own. Co-chaperones mediate substrate specificity, regulate activity of client proteins or recruit chaperones to specific locations in order to perform special functions like their roles in clathrin uncoating, synaptic vesicle fusion, or regulating cytoskeleton functions (Young et al. 2003b).

There are a lot of excellent reviews on the family of HSP proteins in general (Hartl 1996; Wegele et al. 2004; Calderwood et al. 2006), but also on special subfamilies like HSP70 (Bukau & Horwich 1998) or HSP90 (Csermely et al. 1998; Pearl & Prodromou 2000; Taipale et al. 2010; Erleijman et al. 2014a), their role in signaling protein movement (Pratt et al. 2004) and on co-chaperones (Pratt et al. 2004; Davies & Sanchez 2005; Cioffi et al. 2011; Sivils et al. 2011; Storer et al. 2011).

This review is focused on HSP90AB1, primarily in humans. Because of overlapping functions and lack of discrimination in the past, the term HSP90 is used when it is not clear which member of the HSP90 protein family was studied.

Classification

Based on several suggestions (Chen et al. 2005; Chen et al. 2006a), lastly by Kampinga et al. (Kampinga et al. 2009), the human genome organization (HUGO) gene nomenclature committee (HGNC, <http://www.genenames.org/genefamilies/HSP>) recognizes 5 human families of HSPs (Table 1). At the moment, all these families encompass 97 genes.

With 5 genes listed, the HSP90/HSPC family is the smallest among all human HSPs. One of them is a pseudogene (HSP90AA3P), therefore four real HSP's of this family remain (Table 2) which have characteristic localizations in the cell. However, these localizations are only a general rule. Under certain circumstances, these proteins may be also found in other compartments of the cell and even extracellularly (Suzuki & Kulkarni 2010).

Cloning of HSP90AB1

Human HSP90AB1 (Rebbe et al. 1987) was cloned based on homology to HSP90AA1 which was the first HSP90 to be purified, as reported in 1982 (Welch & Feramisco 1982). Both proteins share 60 % overall homology and several regions of 50 amino acids (aa) or more share greater than 90 % homology (Rebbe et al. 1987). Mouse HSP90AB1 was cloned using the corresponding Drosophila cDNA as a hybridization probe (Moore et al. 1987; Hoffmann & Hovemann 1988). It codes for a protein containing 724 aa. The majority of the HSP90A proteins occur as homodimers (Minami et al. 1991). Human HSP90AB1 has 724 aa versus 732 aa in HSP90AA1. With the N-terminal methionins removed, which is usually the case, these numbers are 723 and 731 respectively (Lees-Miller & Anderson 1989b). In HSP90AB1, the amino acids ESEDK is removed between the phosphorylation sites (Lees-Miller & Anderson 1989b). In addition, the amino acids TQTQDQPM at the N-terminal end of HSP90AA1 are replaced by VHHG in HSP90AB1 (Lees-Miller & Anderson 1989b).

HSP90AB1 has the unique signature sequence LKID (residues 71–74) that is not present in other HSPs (Chen et al. 2006a).

Protein domains of HSP90

HSP90 is composed of five domains (Obermann et al. 1998; Chen et al. 2006a):

- N-terminal domain (NTD)
- Linker region/Charged domain 1 (CD1)
- middle domain (MD)
- charged domain 2 (CD2)
- C-terminal domain (CTD)

These main domains as well as their amino acid limits are shown in figure 1 for HSP90AB1 and the 732aa translation product of HSP90AA1. Chen et al. proposed further subdomains and shifts of domain borders based on sequence conservation or variability after analysis of a large number of HSP90 proteins of different species (Chen et al. 2006a).

The NTD contains the ATP-binding site which is essential for HSP function (Prodromou et al. 1997a; Stebbins et al. 1997; Obermann et al. 1998) and binds several co-chaperones (see below). The ATP binding site shares structural homology with other ATPases in the GHKL (gyrase, HSP90, histidine kinase and MutL) superfamily (Pearl & Prodromou 2006).

The CD1 influences binding of other proteins to the NTD (Scheibel et al. 1999). Deletion of the CD1 domain is lethal in yeast (Hainzl et al. 2009). In addition, the sensitivity for Aha1-mediated ATPase acceleration declines, binding of p23/PTGES3 is lost and the ability to facilitate client activation is reduced (Hainzl et al. 2009). This flexible domain facilitates intermolecular rearrangements on the milliseconds timescale between a state in which the NTD is docked to the middle domain and a state in which the N-domain is more flexible (Jahn et al. 2014). The MD is the main region for client binding, but also the co-chaperone Aha1/AHSA1 (see below) binds to this domain (Table 3).

The CD2 is only characterized by DNA analysis but not functionally defined (Chen et al. 2006a).

The CTD is the dimerization domain of HSP90. In addition, five C-terminal residues (Met-Glu-Glu-Val-Asp, MEEVD motif) make up a highly conserved tetratricopeptide repeat (TPR) domain binding site which mediates interaction with many co-chaperones (Bose et al. 1996; Owens-Grillo et al. 1996; Young et al. 1998).

Co-chaperones

As already mentioned, many HSP functions are influenced by co-chaperones. They have four major functions (Taipale et al. 2010):

- They coordinate the interplay between HSP90 and other chaperone systems, such as HSP70
- stimulate or inhibit ATPase activity of HSP90
- recruit specific classes of clients and other co-chaperones and
- have an enzymatic activity.

Some important co-chaperones are listed in table 3 and shortly characterized in the text below. The co-chaperone binding regions on HSP90 are depicted in figure 1.

The co-chaperone Cdc37 (cell division cycle 37) acts as an active scaffold molecule that allows binding of HSP90 with its C-terminal region and client proteins like kinases with its N-terminal domain. Cdc37 arrests the ATPase cycle of HSP90 by inserting an arginine side chain into the ATP binding pocket, thereby facilitating protein loading (Roe et al. 2004). The activation of several client protein kinases is regulated by chaperone-targeted dephosphorylation of Cdc37 (Vaughan et al. 2008).

Cdc37 interacts with Cdk4 (cyclin dependent kinase 4) and Cdk6, but not with Cdc2 (cell division cycle 2), Cdk2, Cdk3 or Cdk5 (Lamphere et al. 1997; Vaughan et al. 2006). The Cdc37/HSP90 complex stabilizes Cdk4 (Stepanova et al. 1996). In addition, Cdc37 facilitates complex formation between Cdk4 and Cyclin D1 in vitro (Lamphere et al. 1997).

Since p16 competes with Cdc37 for binding to Cdk4 it is likely that part of its inhibitory effect is the destabilization of Cdk4 by removal of Cdc37 (Lamphere et al. 1997). However, it has been found that Cdk9 (formerly called PITALRE due to its characteristic amino acid motif) interacts both with Hsp70 and with a HSP90/Cdc37 complex during Tat activation of HIV-1 transcription (O’Keeffe et al. 2000).

The p23/PTGES3 (prostaglandin E synthase 3) protein known as co-chaperone for HSP90 proteins is also a cytoplasmic terminal PGE2 (prostaglandin E2) synthase (cPGES). P23 binds to the N-terminal domain of HSP90 (Karagoz et al. 2011). P23 deficient mice display a phenotype characteristic of mice with GR (glucocorticoid receptor) deficiency, suggesting that its main function is that of the co-chaperone and not its role in prostaglandin synthesis (Lovgren et al. 2007). Expression of the co-chaperone p23 enhances estrogen receptor (ER)-mediated transcription of genes dependent on the presence of estrogen response elements (ERE) (Oxelmark et al. 2006). P23 also has an interesting role in RNA interference (RNAi). RNAi is a mechanism to control gene expression by regulating mRNA levels. The specificity of this mechanism is determined by small double-stranded RNA molecules, the siRNA (small interfering RNA molecules). The guide strand of this siRNA, which is complementary to a section of the target mRNA, is incorporated into the RNA-induced silencing complex (RISC). The catalytic component of the RISC is the endonuclease Argonaute (Ago) (Agrawal et al. 2003). It has been shown in vitro with plant proteins that HSP90 binds to Ago1 (Iki et al. 2010). RISC assembly is driven by the ATPase activity of HSP90 in a Hsc70 (heat shock cognate 70)/HSP90 complex (Iwasaki et al. 2010). The HSP90 co-chaperones p23 and FKBP52 interact with human Ago2 (hAgo2) and HSP90 before small RNA and RISC loading takes place (Pare et al. 2013). In addition, the co-chaperones Aha1 and Cdc37 are necessary for the mechanism of RNAi (Pare et al. 2013). HSP90 modifies Ago2 conformation in order to bind siRNA (Miyoshi et al. 2010).

SGT1 (Small glutamine-rich TPR-containing protein 1) interacts with both HSP90AA1 and HSP90AB1. Nuclear SGT1 is increased upon HSP90 inhibition with geldanamycin and is associated with apoptosis in HeLa cells (Yin et al. 2006).

AHA1 (activator of heat shock 90kDa protein ATPase homolog 1) interacts with both HSP90AB1 and HSP90AA1 (Echeverria et al. 2011). However, in a model of 293T cells, it has been shown that it preferentially interacts with (the middle domain of) HSP90AA1 (Synoradzki & Bieganowski 2015). It is involved in a broad range of cellular processes such as regulation of signal transduction, RNA metabolism, cell development, regulation of ubiquitin-protein ligase activity, glycolysis, induction of apoptosis and nucleo-cytoplasmic transport (Echeverria et al. 2011). AHA1 interacts with Importin-4 (IPO4) and karyopherin alpha 5 (Kpna5) whereas an interaction with exportin1 (Xpo1) could not be demonstrated by immunoprecipitation (Echeverria et al. 2011). AHA1 binds to HSP90 with its N-terminal domain, thereby stimulating ATP binding of HSP90 (Meyer et al. 2004). Silencing of p53 leads to elevated AHA1 levels. In addition, increased AHA1 levels, both by p53 silencing and by AHA1 overexpression, lead to increased HSP90 ATPase activity and enhanced cytochrome P450 levels both under basal conditions and after treatment with the carcinogen benzo[a]pyrene (Kochhar et al. 2014). Furthermore, after AHA1 and HSP90 activation, also Akt and GSK3beta are activated and Wnt target genes are expressed. Together with p53

rescue intervention, these experiments demonstrate a connection between the p53 and Wnt pathways (Okayama et al. 2014).

HOP (Hsp-organizing protein) mediates interaction between HSP70 and HSP90 proteins (Chen & Smith 1998). The TPR1 and TPR2A domains of Hop bind to the C-terminal (M)EEVD motifs of Hsp70 and HSP90 respectively (Scheufler et al. 2000). As explained below, this complex plays a role in stabilizing mutant p53 (King et al. 2001). Hop is also the first protein recruited to HSP90 in the chaperone cycle (see below).

CHIP/STUB1 (C-terminus of HSc70-interacting protein /STIP1 homology and U-box containing protein 1) is an E3 ubiquitin ligase that interacts and destabilizes fibroblast growth factor receptor 3 (FGFR3) (Laederich et al. 2011). FGFR3 stability is strongly dependent on HSP90 and Cdc37 (Laederich et al. 2011). Another client degraded by CHIP is PTK6 (protein tyrosine kinase 6), if not protected by HSP90 (Kang et al. 2012). PTK6 plays a role in tumor biology as described below. Mutations in KCNQ4 (potassium channel, voltage gated KQT-like subfamily Q, member 4) lead to a subtype of autosomal-dominant deafness. Mutant KCNQ4 is degraded by CHIP and protected by the HSP40-HSP70-HOP-HSP90(AB1 and AA1) pathway (Gao et al. 2013). Inducible HSP90AA1 and the constitutive HSP90AB1, had opposite effects on the cellular level of the KCNQ4 channel: HSP90AB1 over-expression partially restored KCNQ4 surface expression in cells mimicking heterozygous conditions in deafness patients (Gao et al. 2013). In TGF-beta signaling HSP70 and HSP90 differentially regulate complex formation of SMAD3 and CHIP. Increased levels of HSP70 and a decrease of HSP90 increased CHIP-mediated degradation of SMAD3 whereas the opposite changes in HSP levels stabilized SMAD3. HSP90AB1 is somewhat more effective in stabilizing SMAD3 than HSP90AA1. Consequently, HSP90AB1 overexpression leads to a higher activity of the TGFbeta pathway as measured with a luciferase reporter assay (Shang et al. 2014). In contrast, extracellular HSP90AB1 inhibits TGFbeta1 by binding to LAP (latency-associated peptide), thereby preventing the release of active TGFbeta1 from its complex with LAP and decreasing cell proliferation in a cell culture model with MG63 osteosarcoma cells (Suzuki & Kulkarni 2010).

FKBP (FK506 binding proteins) are members of the immunophilin family of proteins which are proteins that bind to immunosuppressants like FK506 or rapamycin. They encode proteins with peptidyl-prolyl cis-trans isomerase (PPIase) activity. FKBPL (FKBP-like) interacts with the HSP90-steroid hormone receptor complex (McKeen et al. 2008). Mutations of FKBPL are associated with azoospermia most likely due to a decrease in androgen receptor (AR) DNA binding caused by the destabilization of this protein (Sunnott et al. 2010).

FKBPL influences the cytoskeleton through a PPIase domain that interacts with the dynamin motor protein dynamin (McKeen et al. 2008). In addition, FKBPL binds to CD44 and inhibits cell migration, as shown in endothelial cells and breast cancer cells (Yakkundi et al. 2013). A high level of FKBPL and the FKBPL-interacting protein RBCK1 (RanBP-type and C3HC4-type zinc finger-containing protein 1) correlates with increased patient survival in breast cancer (Donley et al. 2014), suggesting decreased migration and consequential

inhibition of metastasis as an underlying mechanism. The role of FKBP52 in RNAi has been mentioned above (Pare et al. 2013). Like FKBPL, FKBP52 interacts with steroid hormone receptors. It does not only stabilize them, but is also necessary for their nuclear translocation (Storer et al. 2011). The interaction between FKBP52 (FKBP4) and HSP90 is regulated by phosphorylation of FKBP52 by casein kinase II (CKII) (Miyata et al. 1997). GR and mineralocorticoid receptor (MR) hormone binding activity and their activity upon gene transcription is higher in association with FKBP52 compared to PP5, whereas FKBP51 has an inhibitory effect (Davies et al. 2005; Gallo et al. 2007). As already mentioned for FKBPL, loss of FKBP52 in mice also leads to azoospermia (Storer et al. 2011). FKBP52 influences microtubule dynamics by isomerization of the microtubule binding protein Tau to its cis configuration, which enhances its dephosphorylation by PP5 (protein phosphatase 5) (Cioffi et al. 2011). Ret51 (a variant of the Ret transmembrane tyrosine kinase) activation by both glial cell line-derived neurotrophic factor (GDNF) and nerve growth factor (NGF) triggers the formation of RET51/FKBP52 complex (Fusco et al. 2010). Mutations in Ret51 and FKBP52 that disrupt this complex have been found in rare cases of parkinson's disease (PD) (Fusco et al. 2010).

Overexpression of FKBP52 increases aggregation of alpha-synuclein, commonly observed in patients with PD (Gerard et al. 2010). However, FKBP52 seems to play an opposite role in Alzheimers disease (AD). Overexpression of FKBP52 in *Drosophila* suppressed the toxicity of amyloid beta, a protein which forms aggregates in AD (Sanokawa-Akakura et al. 2010). During early neural differentiation, FKBP52 enhances and FKBP51 inhibits neurite outgrowth (Quinta et al. 2010). Whereas in undifferentiated cells, FKBP52, HSP90 and p23 are located in the perinuclear region, they are rapidly dispersed in the cytoplasm upon induction of differentiation (Quinta & Galigniana 2012). Neuronal damage induces redistribution of these three proteins to the perinuclear region. During adipocyte differentiation, FKBP51 rapidly increases whereas FKBP52 decreases. In addition, FKBP51 translocates from the mitochondria to the nucleus, a process which is dependent on PKA (protein kinase A) (Toneatto et al. 2013). Also in other cell types, like 3T3 fibroblasts, FKBP51 has been found in the mitochondria, which is also true for GR, but this subcellular localization and the trafficking of both proteins is independent from each other (Gallo et al. 2011). FKBP51 protects cells from oxidative stress and translocates to the nucleus upon exposure to oxidative stress (Gallo et al. 2011). FKBP38 (not mentioned in the table) has an anti-apoptotic function by anchoring the pro-apoptotic proteins Bcl-2 and Bcl-x(L) to mitochondria (Shirane & Nakayama 2003).

Cyp40 (cyclophilin 40), also an immunophilin, is involved in steroid hormone receptor assembly. It prefers HSP90 over HSP70 binding (Carrello et al. 2004). Cyp40 binds to the DNA repair protein Ku70 and to Rack1 (receptor of activated protein kinase C 1) (Park et al. 2011). Rack1 promotes stabilization of HIF-1alpha (hypoxia inducible factor 1 alpha) in prostate cancer cells (Yu et al. 2014). However, RACK1 can also down-regulate HIF-1alpha after cobalt chloride treatment of MCF-7 breast cancer cells (Park et al. 2011).

PP5 (protein phosphatase 5, also abbreviated PPP5C) is a serine/threonine protein phosphatase that functions in signaling pathways that control cellular responses to stress, steroid hormones and DNA damage (Chinkers 2001; Yang et al. 2005; Hinds & Sanchez

2008). PP5 phosphatase activity is auto-inhibited in a state unbound to HSP90 or fatty acids by a special conformation of the TPR domain and a C-terminal subdomain. Binding to HSP90 or fatty acids (e.g. arachidonic acid) to the TPR domain activates phosphatase activity (Yang et al. 2005). PP5 is up-regulated in breast cancer, as shown by immunohistochemical staining of a tissue microarray (TMA) (Golden et al. 2008).

The translocation machinery (or “translocase”) of the outer mitochondrial membrane (TOM) is a multiprotein complex containing, among other proteins, TOM20 and TOM70 (named after their approximate molecular weight). Tom70 preferentially binds pre-proteins with internal targeting sequences (Brix et al. 1997). TOM70 binds to a multichaperone complex including HSP70 and HSP90 via specialized TPR domains in which three TPR domains are organized into a superhelical structure (Scheufler et al. 2000; Young et al. 2003a). Proteins are translocated through the import pore to the TIM (translocase of the inner mitochondrial membrane) machinery in an ATP-dependent manner (Young et al. 2003a). Pre-proteins with N-terminal pre-sequences are translocated with the help of Tom20, a process which is less dependent on chaperones (Brix et al. 1997).

TPR2 binds to Rad9 (Xiang et al. 2001), which is part of the Rad1-Hus1-Rad9 complex that is important for DNA-damage induced cell-cycle checkpoint activation (Parrilla-Castellar et al. 2004). The J-domain (DNAJ homology domain) of TPR2 regulates TPR2-Rad9 interaction (Xiang et al. 2001) and thereby potentially the stability of the checkpoint complex.

Deletion of CPR7 (7th cyclophilin homolog, interacting with the yeast global transcriptional regulator Rpd3) caused severe growth defects when combined with mutations that decrease the amount of Hsp90 or Hop. Cpr7 null mutations caused defects in GR and pp60/v-src kinase activity (Duina et al. 1996b). In addition, Cpr7 deletion resulted in a significant impairment of cell division (Duina et al. 1996a). Both Cpr6 and Cpr7 interact with the ribosome and may be involved in the regulation of protein synthesis (Tenge et al. 2015).

The HSP90 homodimer can bind several co-chaperones at once, even different co-chaperones that bind to the TPR domain. For example, a HSP90(2)-FKBP52(1)-p23(2)-HOP(2)-complex could be demonstrated by immunoprecipitation, chromatographic methods and dynamic light scattering (Hildenbrand et al. 2011).

The chaperone cycle

After binding of the client protein to the HSP90 homodimer (open configuration), ATP binds to the NTD and induces transition of the complex to a closed ATP bound form. During proper folding, the conformation closes further and the NTDs dimerize transiently, coupled to ATP hydrolysis (Prodromou et al. 2000). Finally, the configuration opens up, the folded client protein is released and ADP dissociates (figure 2).

For proper functioning of this simplified chaperone cycle, several co-chaperones are necessary. The interaction with co-chaperones occurs in a ordered, sequential manner (Li et al. 2011). The first co-chaperone entering the cycle is the HSP90 ATPase inhibitor Hop (Chen & Smith 1998), that binds to the Hsp90 homodimer. Together with Hop or after that,

Hsc70 binds. After that, a PPIase, such as Fkbp51, Fkbp52 or Fkbp37 binds to the opposite side of the HSP90 dimer. HSP90 converts to a closed conformation after binding of ATP and binding of p23 (Johnson et al. 1994; Johnson & Toft 1995; Freeman et al. 2000; McLaughlin et al. 2006; Forafonov et al. 2008), releasing Hop and HSC70 from the complex, leaving space for another PPIase molecule. After ATP hydrolysis, all remaining co-chaperones are released from the HSP90 dimer which converts to an open conformation. This allows the start of another HSP90 cycle (Li et al. 2011). In a cell-free system with progesterone receptor (PR) as a client protein it could be shown that such an assembly/disassembly cycle has a $t_{1/2}$ of about 5 min (Smith 1993).

Mechanism of HSP90 induction

In general, heat shock generates a higher induction of HSP90AA1 compared to HSPAB1 (Ullrich et al. 1989). The first level of regulation is during gene transcription. HSF1 (heat shock factor 1), which binds to HSE (heat shock elements), is thought to be the major transcription factor for HSPs (Ciocca et al. 2013). However, the basal level of HSP90AB1 transcripts does not depend on HSF1 since HSF1 knockout leads to no transcript reduction in a model of oocytes (Metchat et al. 2009). In contrast, HSP90AA1 transcripts are reduced by ~50 % in HSF1 knockout oocytes (Metchat et al. 2009). The functional importance of the two HSE in the HSP90AA1 promoter has been demonstrated with reporter constructs in Jurkat cells (Zhang et al. 1999). The HSP90AB1 promoter contains a TATA box and a CAAT box. In addition, there is an Sp1 binding site and typical as well as some atypical HSEs are located up- and downstream the transcription initiation site (Rebbe et al. 1989). The two typical HSEs in the first intron are functionally important for inducibility of HSP90AB1 by heat shock (Shen et al. 1997). Binding of KLF4 (Krüppel-Like-Factor 4) to the promoters of HSP90AB1 and HSP90AA1 leads to a higher expression of these HSPs (Liu et al. 2010). During induction of HSP90AB1 after heat shock, Stat1 phosphorylation is indispensable. The dominant kinases for phosphorylation of Stat1 (Y701 and S727) are Jak2 and PKCepsilon (Cheng et al. 2010). However, the activation of these kinases requires the association with an HSP90 protein, leading to a positive auto-regulatory loop. For full activation, Brg1 (brm (Brahma)/SWI2-related gene), an ATPase subunit of the SWI/SNF chromatin remodeling complex, is recruited to the transcription factor complex (Cheng et al. 2010). The mTORC1 (mTOR complex 1) regulates mRNA translation of HSP90AB1 as detected in a high-resolution transcriptome-scale ribosome profiling analysis. It has been found that a TOP (5' terminal oligopyrimidine) motif in HSP90AB1 is necessary for this translational regulation, although the mechanism is not known (Thoreen et al. 2012). As a general negative feedback mechanism, the HSP90 complex represses HSF1 activation, thereby inhibiting an over-activation of the HSF1 response (Zou et al. 1998).

Posttranslational modifications

The tyrosine (Y) phosphorylation of Hsp90AA1 and Hsp90AB1 induced by LPS in endothelial cells is mediated by pp60src (Barabutis et al. 2013). Mass spectrometry identified Y309 as a major site of Y phosphorylation on Hsp90AA1 (and Y300 on Hsp90AB1) (Barabutis et al. 2013). Phosphorylation of Ser225 and Ser254 (counted after removal of the first methionine) of HSP90AB1 inhibited binding of AHR (arylhydrocarbon

receptor) (Ogiso et al. 2004). The phosphorylation of HSP90 is inhibited by 17-allyl-amino-demethoxy-geldanamycin (17-AAG) (Barabutis et al. 2013). DNA-activated protein kinase (DNA-PK), a protein that is important for DNA repair, phosphorylates two threonine residues in HSP90AA1. Since HSP90AB1 lacks these threonine residues, no DNA-PK dependent phosphorylation occurs in HSP90AB1 (Lees-Miller & Anderson 1989a).

Methylated HSP90AB1 increases the proliferation of cancer cells (Hamamoto et al. 2014). Methylation of lysines 531 and 574 of HSP90AB1 occurs by SMYD2 (SET/MYND domain containing 2) histone H3 lysine (K) 36-specific methyltransferase (KMT) (Donlin et al. 2012; Hamamoto et al. 2014). Methylated HSP90AB1 is associated with increased proliferation of cancer cells (Hamamoto et al. 2014). Acetylation seems to inhibit HSP90 function (Yang et al. 2013) as shown in a model of Gaucher disease. This is a lysosomal storage disorder caused by mutations in the enzyme glucocerebrosidase (GCase), leading to a misfolded enzyme. HSP90AB1 is essential for the degradation of misfolded GCase by guiding it to a valosin-containing protein (VCP)-associated proteasomal degradation pathway (Dai & Li 2001; Zhong et al. 2004; Yang et al. 2013). Inhibition of HDAC (histone deacetylases) keeps HSP90 in an acetylated state and inhibits GCase degradation, thereby alleviating the disease phenotype (Yang et al. 2013). Conversely, HSP90 also influences HDAC levels. Hsp90 interacts with HDAC6 and is a key effector of HDAC6 levels (New et al. 2013). Nitric oxide (NO) induces S-nitrosylation of HSP90AB1 at its C-terminus and thereby reduces its activity (Retzlaff et al. 2009). Obviously, also citrullination occurs on HSP90 proteins since autoantibodies against citrullinated HSP90AA1 and HSP90AB1 are detected in patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD), but not in patients with RA without ILD, MCTD (mixed connective tissue disease) and IPF (interstitial pulmonary fibrosis) (Harlow et al. 2013).

Inhibition of HSP90

Derivatives of geldanamycin, like 17-dimethylaminoethylamino-17-demethoxy-geldanamycin (17-DMAG) or 17-AAG bind to the ATP pocket in the NTD of HSP90 (Grenert et al. 1997; Prodromou et al. 1997b; Stebbins et al. 1997; Roe et al. 1999). The HSP90 inhibitor radicicol, a macrocyclic antifungal antibiotic, also binds to the ATP binding pocket of HSP90 (Schulte et al. 1998; Roe et al. 1999). Celastrol, a triterpenoid compound that inhibits HSP90AB1 activity, alters the three-dimensional structure of the co-chaperone p23 resulting in a more selective destabilization of steroid receptors (Chadli et al. 2010) or acts by disrupting the HSP90-Cdc37 complex (Zhang et al. 2009). Celastrol also inhibits the production of matrix metalloproteinases (MMPs), inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) from chondrocytes derived from patients with osteoarthritis (Ding et al. 2013). This effect may be mediated by direct interaction of HSP90AB1 with these proteins or by its interaction with NF-kappaB (nuclear factor kappaB) (Ding et al. 2013). The natural product drug BTMNP_D004 inhibits, dependent on cell type, HSP90AB1 and/or HSP90AA1 and a number of proliferation-associated signaling proteins (Samadi et al. 2009). A kind of non-specific HSP inhibition is exerted by free radicals formed during oxidative stress. They can lead to a cleavage of HSP90AB1 at two positions near the N-terminus of the protein, which occurs through a Fenton-Reaction (Beck et al. 2012).

Inductors of HSP90(AB1)

As already described, there is a great number of stress types that are able to induce HSP protein levels. In this paragraph, some studies are summarized that show a specific induction of HSP90AB1. Infection is a basic type of stress and therefore a common reason for HSP induction. Increased HSP90AB1 has been detected after influenza infection in infected cells (Wahl et al. 2010). Bacterial challenge in the abalone *Haliotis tuberculata* leads to an up-regulation of HSP90AB1 (Travers et al. 2010). LPS treatment or challenge with src-adenovirus lead to an increased phosphorylation of HSP90AB1 (Y300) in endothelial cells (Barabutis et al. 2013).

Necrosis causes an inflammatory reaction in order to clean up the damaged region. Extracellular HSP90AB1 can elicit such a response independently from IL-8 and MCP-1 in cultured retinal pigment epithelial (RPE) cells. A cell-impermeable geldanamycin derivative can inhibit the production of inflammatory cytokines in this model (Qin et al. 2011). *H. pylori* induces the translocation of HSP90AB1 from the cytosol to the membrane causing interaction of HSP90AB1 and Rac1, which leads to the activation of NADPH oxidase and production of ROS in gastric epithelial cells (Cha et al. 2010).

Heat shock or increased expression of HSP90AB1 restore reduced infectivity of HIV with incompletely processed capsid-spacer protein 1 (CA-SP1) (Joshi & Stoddart 2011; Joshi et al. 2013). Increased thermotolerance of hepatoma cells (Reuber H35 cells) in late G1/early S-phase as compared to G0 phase correlated with enhanced basal synthesis of HSP65, HSP68 and HSP90AB1 as well as with increased phosphorylation of non-histone chromosomal proteins (van Dongen et al. 1986). Not only heat stress but also cold stress can induce HSPs. HSP90AB1 is up-regulated during hibernation in the hearts of ground squirrels and protects them from ischemia-reperfusion injury and apoptosis (Grabek et al. 2011).

Benzo[a]pyrene (B[a]P), a cancer promoting agent, induces HSP90AB1 mRNA (Sadeu & Foster 2013). Chronic opioid treatment leads to increased HSP90AB1 transcript and protein levels. This contributed to an enhanced responsiveness of adenylate cyclase to forskolin treatment. Thus, HSP90AB1 contributes to opioid induced adenylate cyclase sensitization (Koshimizu et al. 2010). Overexpression of TRIM14 (T-cell receptor interacting molecule 14) leads to increased levels of HSP90AB1 (Nenasheva et al. 2014). Trim14 increases mesodermal differentiation and inhibits ectodermal differentiation of mouse ES cells (Novosadova et al. 2009).

Also normal developmental processes as shown in *Drosophila* can induce HSP (Lindquist 1986). Induction of HSP90AB1 occurs during adipogenesis in a cell culture model (Fromm-Dornieden et al. 2012).

HSP90AB1 and protein transport

As already briefly mentioned, HSP90AB1 is necessary for the shuttle of client proteins between cytoplasm and nucleus (Galigniana et al. 2010a; Galigniana 2012). The interaction of steroid hormone receptors with Hsp90 is required for their translocation to the nucleus

(Czar et al. 1997). In addition to Hsp90 homodimers, transport protein complexes consist of Hsp70, Hop, Hsp40, p23 and PP5 (Chen et al. 1996; Silverstein et al. 1997; Pratt et al. 1999; Murphy et al. 2001). The protein complexes are transported along microtubular tracks with the help of the motor protein dynein (Harrell et al. 2004; Pratt et al. 2004), as shown for the tumor suppressor protein p53 (Galigniana et al. 2004). Directionality is mediated by recognition sequences in the client proteins and/or by interaction with additional proteins. For example, immunophilins target the complexes in the nuclear direction (Pratt et al. 1999), as shown for FKBP52 (Czar et al. 1995). For this transport, a nuclear localization sequence (NLS) is necessary. However, it has been shown, that in addition to the classical NLS (NS1), also other recognition sequences contribute to the guiding of proteins in the direction of the nucleus (Piwien Pilipuk et al. 2007). For transport in the opposite direction (nucleus-to-membrane transport) it has been suggested that the transport is mediated by interaction of the transport complex with Cdc37 instead of FKBP52 (Pratt et al. 1999).

Nuclear transport of GR occurs after hormone binding and exchange of FKBP51 for FKBP52, generating a GR-HSP90-FKBP52-dynein complex that travels to the nucleus (Davies et al. 2002). FKBP52 facilitates hormone binding (Riggs et al. 2003). Interaction with dynein is mediated by the PPI domain of immunophilins (Galigniana et al. 2002) via the dynamin component of the dynactin complex (Galigniana et al. 2004). The requirement of dynein for steroid receptor movement along microtubules has been demonstrated in a cell-free system (Harrell et al. 2004). At the nuclear pore, the complex interacts with importin-beta and the nucleopore glycoprotein Nup62 and passes undissociated (Echeverria et al. 2009). Dissociation occurs within the nucleus, releasing GR for binding to DNA. A similar mechanism applies for the MR (Galigniana et al. 2010b), and in general also for plant cells (Harrell et al. 2002). With the MR model it has been shown that the whole undissociated complex is detectable in the nucleus for several minutes after translocation (Galigniana et al. 2010b; Grossmann et al. 2012). One other protein that can be associated with the nuclear translocation complex is RAC3 (receptor-associated co-activator 3), a protein that exerts an anti-apoptotic activity by activating NF-kappaB, AKT and p38 MAPK and by inhibition of caspase 9, AIF (apoptosis-inducing factor) and ERK2 (extracellular signal regulated kinase 3/MAPK6) (Colo et al. 2008; Alvarado et al. 2014).

HSP90 and protein degradation

A few examples of HSP90-associated protein degradation have been described. Apo(lipo)proteinB (apoB) is essential for the assembly and secretion of lipoproteins. In a cell-free system it has been shown that apoB degradation is dependent on HSP90 (Gusarova et al. 2001). The degradation of misfolded proteins can be mediated by HSP90. The VHL (von-Hippel-Lindau) tumor suppressor protein possesses ubiquitin ligase activity and is involved in the degradation of hypoxia inducible factor (HIF) (Maxwell et al. 1999). Folding of VHL and degradation of mutated VHL is dependent on HSP70 whereas the chaperonin TriC is necessary for its folding but not for the degradation (McClellan et al. 2005). In contrast, HSP90 is not responsible for VHL folding or maintenance of misfolded protein solubility but for its degradation (McClellan et al. 2005). The role of HSP90AB1 in degradation of misfolded GCase in Gaucher disease has been described above and its role in cystic fibrosis is described in the following paragraph.

Diseases aggravated by HSP90AB1 or its co-chaperones

Cystic fibrosis (CF, mucoviscidosis) is a genetic disorder with increased viscosity of various secretions leading to damage in the affected organs, most importantly lung and pancreas. The genetic basis is a mutation in the cAMP-regulated chloride ion channel CFTR (cystic fibrosis transmembrane conductance regulator), in most cases a deletion of Phe508. This causes a maturation defect of the protein, leaving the nucleotide binding domain 2 (NBD2) permanently in a protease-sensitive state (Riordan 2005) which leads to increased processing in the ERAD (endoplasmic reticulum associated degradation) pathway. Linked by Hop, CFTR binds to both an Hsc-Hsp40/70 complex and also to Hsp90. Whether proteins are properly folded for export from ER by ERAF (ER-associated folding) machinery or degraded by ERAD seems to be dynamically controlled by co-chaperones. Deletion of AHA1 leads to stabilization of mutated CFTR, a finding that may lead to a potential therapy for CF (Wang et al. 2006).

Diseases alleviated by HSP90AB1

Bronchopulmonary dysplasia (BPD), a disease caused by prolonged high oxygen delivery to immature lungs involves cellular damage by oxygen free radicals. Thioredoxin-1 (Trx) is a radical scavenger stabilized by HSP90ab1 and HSP90AB2. Consequently HSP90 proteins prevent hyperoxic cell death (Floen et al. 2014).

Genetic variations

Genetic variations in HSPAB1 have been described that are likely to have an influence on stress-induced mortality, GR level, and GRE (glucocorticoid-response element) binding activity in C57BL/6 mice compared to BALB/c mice (Shen et al. 2010). Some SNPs in HSP90AB1 in laying hens are associated with longer life and higher productivity (Sun et al. 2013), but a very limited number of SNPs in human HSP90AB1 are likely to have a functional consequence (Urban et al. 2012). SNPs in HSP90AB1 in Thai native cattle are associated with increased heat tolerance (Charoensook et al. 2012). A study on a turkish population found significantly more polymorphisms in HSP90AA1, HSP90AB1 and HSP90B1 in patients with non-small cell lung cancer (NSCLC) (Coskunpinar et al. 2014).

Role in molecular evolution

Mutations can cause defects in protein folding. Their stability can often only be maintained by binding to HSPs. In addition, molecular evolution by gene duplication and subsequent progressive mutation is only conceivable with the help of a strong and versatile chaperone machinery (Rutherford & Lindquist 1998; Yahara 1999; Jarosz & Lindquist 2010; Jarosz et al. 2010).

HSP90AB1 client proteins

Large scale protein-protein interaction studies revealed many new client proteins (Tsaytler et al. 2009; Taipale et al. 2014). Although the spectrum of interaction partners can be well described, they cannot be easily predicted based on protein structures. Therefore, it remains largely enigmatic why some proteins are clients of HSPs and others not. However, interaction of HSP90 chaperone and its Cdc37 co-chaperone with kinases depends on the

thermal stability of the kinase domain (Taipale et al. 2012) which can be exploited for high-throughput in-vivo screens for kinase inhibitors (Lambert et al. 2013; Taipale et al. 2013). In addition to the well-known interaction with steroid hormone receptors (Catelli et al. 1985; Mendel & Orti 1988; Rexin et al. 1991), HSP90 interacts with 7 % of transcription factors, 30 % of ubiquitin ligases and 60 % of kinases. A study of the MAPK interactome revealed the interaction of HSP90AB1 with a large number of MAPK, and its functional relevance in examples such as MAPK6 and p38MAPK/MAPK14 has been demonstrated (Bandyopadhyay et al. 2010).

PTK6 (protein tyrosine kinase 6) is a client protein of HSP90 as described below in the cancer paragraph (Kang et al. 2012). ERK5 (extracellular regulated kinase 5) is retained in the cytoplasm by binding to a HSP90AB1-Cdc37 complex. Activated ERK5 dissociates from HSP90AB1-Cdc37 and can subsequently be transported to the nucleus (Erazo et al. 2013). Nanog is an important transcription factor in ES (embryonic stem) cells. TRIM8, a member of the tripartite motif (TRIM) family, binds to HSP90AB1 and inhibits translocation of SMAD3 into the nucleus thereby reducing the transcription of Nanog in ES cells (Okumura et al. 2011). A novel ADP-dependent HSP90 interaction with the cysteine- and histidine-rich domain (CHORD)-containing protein CHORDC1 (Gano & Simon 2010), a protein associated with inclusion conjunctivitis.

The serine/threonine kinase Wee1 is necessary G2/M checkpoint in yeast and is a client of HSP90AB1. USP50 (ubiquitin-specific protease 50), a deubiquitinating enzyme (DUB), prevents Wee1 degradation, thereby repressing entry into mitosis following activation of the G2/M DNA damage checkpoint (Aressy et al. 2010). Conversely, HSP90AB1 interacts with cell cycle regulator Cdc25A, which promotes cell cycle progression (Giessrigl et al. 2012). HSP90 stabilizes tau protein which forms precipitates in Alzheimer disease and other tauopathies (Karagoz et al. 2014). FKBP51 recruits HSP90 to tau and helps to stabilize tau and to maintain hyperphosphorylated Tau levels, a status that perpetuates Alzheimer's disease (Jinwal et al. 2010). Thus, a possible therapeutic approach for tauopathies is the inhibition of HSPs. In a mouse model, it has been demonstrated that inhibition of HSP90 promotes Tau degradation (Dickey et al. 2007). One possible mediator is the co-chaperone CHIP, a tau ubiquitin ligase. It has also been shown that the inhibition of another co-chaperone, Cdc37, leads to tau degradation (Jinwal et al. 2011). This is also true for other co-chaperones like p23, PP5, FKBP51 and S100A1 (Jinwal et al. 2013). All these might be valuable therapeutic targets. Methylene blue (MB) is a small molecule that leads to tau degradation. Treatment with MB leads to dissociation of HSP70 from tau and increased association of HSP90 with tau (Thompson et al. 2012). In this model, HSP90 is important in tau clearance from cells, as shown by siRNA mediated HSP90 knockdown.

The transcription factor NF-kappaB is involved in cell cycle control, cellular differentiation, and inflammation. It is activated by degradation of its inhibitor IkappaB (inhibitor of NF-kappaB), mainly IkappaBalpha. This ubiquitin-dependent degradation is initiated by phosphorylation of an IKK (IkappaB kinase or IKBK) complex that usually consists of three subunits, IKK alpha, beta and gamma (Karin & Lin 2002; Senftleben & Karin 2002). HSP90 is required for IKK biosynthesis and function (Broemer et al. 2004). A heterocomplex of Cdc37 and HSP90 is required for TNFalpha dependent activation of IKK (and NF-kappaB)

(Chen et al. 2002; Hinz et al. 2007). In contrast, HSP70 binds to TRAF6 (TNF receptor associated factor 6), thereby inhibiting LPS (lipopolysaccharide)-triggered NF-kappaB activation (Chen et al. 2006b). Immunophilins have opposite effects on NF-kappaB. Whereas FKBP52 enhances NF-kappaB activity, FKBP51 plays an inhibitory role (Erlejan et al. 2014b).

HSPs interact with the cytoskeleton, on one side leading to modification and stabilization of cytoskeletal structures and on the other side using the cytoskeleton for transport purposes (Quinta et al. 2011). HSP90 binds to actin and crosslinks actin filaments (Koyasu et al. 1986). HSP90 also binds to N-WASP (neuronal Wiskott-Aldrich Syndrome Protein, now called WASPL, WASP-like), a protein which activates the Arp2/3 (actin related/released protein 2/3) complex. The Arp2/3 complexes serve as nucleation sites for actin polymerization. HSP90 bundles branched actin filaments and promotes the formation of unbranched actin structures (Park et al. 2007). HSP90 increases N-WASP phosphorylation by v-Src, thereby enhancing actin polymerization (Park et al. 2005). In addition, HSP90 protects N-WASP from proteasomal degradation (Park et al. 2005). Upon HSP90 inhibition, association of HSP90 with G-actin (globular actin) is increased, associated with decreased actin polymerization and concomitantly decreased cell motility and invasion (Taiyab & Rao Ch 2011). HSP90 also binds to several other actin-binding proteins like calponin (Ma et al. 2000) and LIMK (LIM kinase) (Li et al. 2006). LIMK contains a LIM domain, named after the three proteins LIN-11, ISL1 and MEC-3 that contain this domain. HSP90 activates LIMK by promoting its homodimerization (Li et al. 2006). LIMK phosphorylates and thereby activates cofilin, a protein that promotes disassembly of actin filaments. Thus, HSP90 is able to promote antagonizing functions with regard to actin polymerization. ILK (integrin linked kinase) is located at the interface between actin filaments and cell membrane. ILK is stabilized by HSP90 and HSP90 inhibition leads to decreased cell migration (Radovanac et al. 2013). Both HSP90AA1 and HSP90AB1 bind to microtubules, dependent on the level of tubulin acetylation (Giustiniani et al. 2009). This tubulin acetylation also influences binding and activity of the HSP90 client proteins Akt and p53 (Giustiniani et al. 2009). HSP90 protects tubulin, the major component of microtubules, from thermal injury (Weis et al. 2010). Some effects of HSP90 on the cytoskeleton may be mediated by other proteins like the lysine demethylase Kdm3a. Mutant Kdm3a mice display male infertility and their cells show an altered fractionation of actin and tubulin (Kasioulis et al. 2014).

Diseases with down-regulated HSP90

Hsp90ab1, expressed in oligodendrocyte precursor cells, has been shown to be down-regulated in a rat model of acute spinal cord injury (ASCI) (Zhou et al. 2014). HIV virus causes a progressive decline in CD4+ T-cells. This involves an aging-like phenotype with decline of telomerase activity. This is, at least partly, caused by a reduction of HSP90AB1 which is mediated by the HIV-protein Tat (Comandini et al. 2013). In a rat model of radiation-induced fibrosing alveolitis, it has been shown that HSP90AB1 was progressively down-regulated in radiation-damaged lung cells other than mast cells (Haase et al. 2014).

Diseases with up-regulated HSP90

HSP90 is increased in systemic sclerosis (SSc) of the skin. Inhibition of Hsp90 by 17-DMAG inhibited canonical TGF-beta signaling and completely prevented the stimulatory effects of TGF-beta on collagen synthesis and myofibroblast differentiation (Tomcik et al. 2014). Thus, HSP is pro-fibrotic in this model. Conversely, HSP90 inhibitors repress TGFbeta1 signaling (Noh et al. 2012) by a mechanism dependent on Smurf2-mediated degradation of TGFbetaRII. This lead to a decreased expression of alpha-smooth muscle actin, fibronectin, and collagen I and a decrease of renal fibrosis in an animal model (Noh et al. 2012).

Miscellaneous roles of HSP90 in diseases

Huntington's disease, an autosomal dominant disease, is caused by increased amounts of repetitive trinucleotide repeats (CAG) in the vicinity of promoters which leads to precipitation of polyglutamin protein. This leads to massive loss of interneurons in the caudate nucleus, especially affecting GABA- and cholinergic neurons. The trinucleotide expansion comprises up to 100 repeats whereas 11–35 repeats are normal. Inhibition of cytoplasmic HSP90 supports clearance of Huntingtin protein and is a promising approach for the treatment of Huntington's disease (Ernst et al. 2014).

In trauma patients, a higher HSP90ab1 promoter activity (–144AA genotype) was associated with low expression of the inflammatory cytokine TNFalpha (tumor necrosis factor alpha) and with lower organ dysfunction scores (Zhao et al. 2013). High levels of HSP90ab1 resulted in lower hypoxia-induced apoptosis in a model of intestinal epithelial cells (IEC) (Zhang et al. 2013).

DNA damage recognition/DNA repair/Free radicals

The tumor suppressor protein p53 is normally degraded after binding to the E3 ubiquitin ligase MDM2 (mouse double minute 2 homolog). Mutant p53 is commonly overexpressed in cancer cells. HSP90AB1 binds to mutant p53 in cancer cells and stabilizes it (Sepehrnia et al. 1996). P53 binds with its DNA binding domain to the middle and CTD of HSP90AB1 (Muller et al. 2004). It has been demonstrated that the complex is only stable in the presence of HSC70, HSP40, HOP and ATP (King et al. 2001). Degradation of wild type p53, which is initiated by MDM2, is inhibited by the co-chaperone TPR2 that binds p53 and thereby blocks complex formation with MDM2 (Kubo et al. 2013). In the latter complex, no HSP90 has been described (Kubo et al. 2013). After exposure to ionizing radiation, inhibition of HSP90 by a geldanamycin analogue inhibits p53 activation and subsequent apoptosis in human peripheral blood mononuclear cells (Fukumoto & Kiang 2011). In a cell-free system, HSP90AA1 has been shown to stabilize wild-type p53 and to maintain binding of p53 to the p21 promoter sequence (Walerych et al. 2004).

The stability of DNA-PKcs is dependent on the activity of HSP90, since inhibition of the HSP90 with radicicol decreased the expression of DNA-PKcs in HeLa cells (Falsone et al. 2005). HSP90(AA1 and AB1) specifically binds to REV1 (reversionless 1), a Y-family polymerase that causes lack of UV-induced reversion of the arg4–17 ochre allele in yeast

and plays a central role in mutagenic translesion DNA synthesis (TLS) (Lawrence & Christensen 1976; Ohmori et al. 2001; Pozo et al. 2011). HSP90 inhibition disrupts the interaction between REV1 and monoubiquitinated PCNA (proliferating cell nuclear antigen), a molecule that recruits REV1 to damaged DNA sites. Thus, HSP90 inhibition suppresses TLS-mediated mutagenesis (Pozo et al. 2011). HSP90AB1 inhibition decreased IL-1 β induced NO (nitric oxide) production in chondrocytes (Calamia et al. 2011).

Cancer

HSPs are frequently up-regulated in cancer. One way of promoting cancer cell survival and proliferation is by stabilizing proteins with activating mutations, and other cancer promoting proteins that would otherwise be degraded. A systematic analysis of the expression of HSP90AA1 and HSP90AB1 proteins, their co-chaperones (Aha1, Cdc37, p23, Tpr2) and the Hsp90 dependent transcription factor HSF1 in 17 cancer types suggested that the overexpression is tumor-specific and obviously random. However, the study demonstrated that in more than half of the tumor tissues at least one of the factors mentioned is overexpressed (McDowell et al. 2009). In salivary gland tumors, the expression of HSP90AA1 and HSP90AB1 correlated with malignancy, proliferation, neural invasion and metastasis (Wang et al. 2013). HSP90AB1 is also up-regulated in lung cancer cells and this up-regulation correlates with pathological grade, lymphatic invasion and poor survival (Biaoxue et al. 2012). In lung cancer cell lines, it has been shown that resistance to ionizing radiation is partially caused by stabilization of a HSP90-HIF1 α (hypoxia inducible factor 1 α) complex and that inhibition of HSP90 increased radiosensitivity of the tumor cells (Kim et al. 2009). HSP90AB1 is overexpressed in GISTs (gastrointestinal stromal tumors) (Tsumuraya et al. 2010), tumors that originate from gastrointestinal pacemaker cells (Cajal cells). In melanoma tumor cells it was shown that Bcl-2 protein stabilizes HIF-1 (hypoxia-Inducible Factor 1), a critical mediator of the cellular response to hypoxia. Increased HIF-1 leads to increased tumor angiogenesis, metastasis, therapeutic resistance and poor prognosis. The stabilization of HIF-1 is due to the formation of a ternary complex between HIF-1, Bcl-2 and HSP90AB1 (Trisciuglio et al. 2010). The proliferation of Multiple Myeloma (MM) cells is critically dependent upon a number of protein kinases. One of them is GRK6 (G-protein coupled receptor protein kinase 6) which is required for STAT3 phosphorylation and subsequent activation of MCL1 (myeloid cell leukemia 1) protein (Tiedemann et al. 2010). GRK6 expression is regulated by HSP90AA1 and HSP90AB1 (Tiedemann et al. 2010). Tumor cell growth to a visible size is critically dependent on angiogenesis. HSP90AB1 interacts with and stabilizes the mRNA of the VEGF-A-induced pro-angiogenic protein BAZF (BCL-6 associated zinc finger protein) and thus may positively regulate angiogenesis (Miwa et al. 2013). A fibronectin (FN) matrix is important for cell migration and invasion, processes that are features of cancer cells (Lowrie et al. 2004; Lobert et al. 2010). HSP90AB1 stabilizes extracellular FN in a study with the breast cancer cell line Hs578T (Hunter et al. 2014). Reduction of HSP90AB1 leads to a reduction in extracellular fibronectin (Hunter et al. 2014). The tumor suppressor kinases of the hippo pathway, LATS1 (large tumor suppressor kinase 1) and LATS2, are clients of HSP90AB1. In this case, inhibition of HSP90AB1 leads to a disruption of the LATS tumor suppressor pathway, i.e. to a promotion of cancer growth (Huntoon et al. 2010). In a cell culture model with the hepatocellular carcinoma cell line HepG2 it was shown that HSP90AB1 expression

was up-regulated by Hepatitis B virus encoded X protein (HBx) (Li et al. 2009). The oncogenes c-Myc and MYCN determine malignancy in neuroblastomas. Inhibition of HSP90 leads to inhibition of neuroblastoma cell proliferation and to accumulation of p53 (Regan et al. 2011).

Up-regulation of HSP90 is one reason for increased telomerase activity in tumors, as shown in a model of prostate cancer (Akalın et al. 2001). HSP70, p23 and HSP90 are associated with hTERT (human telomerase reverse transcriptase subunit), but upon recruitment of hTR (human telomerase RNA template), HSP70 dissociates from this complex (Forsythe et al. 2001). Overexpression of hTERT together with HSP90 in pheochromocytomas has been shown to be associated with more aggressive tumors (Boltze et al. 2003). In transformed natural killer (NK) cells it has been shown that, after IL-2 stimulation, hTERT forms a complex with HSP90, Akt, mTOR (mammalian target of rapamycin) and p70S6 kinase (70 kDa ribosomal subunit S6 kinase) (Kawauchi et al. 2005). In contrast, disruption of HSP90 function by geldanamycin leads to proteasome-mediated degradation of hTERT. In this model, the RING finger gene MKRN1 (makorin ring finger protein 1) is the E3 ligase that mediated ubiquitination of hTERT (Kim et al. 2005). In addition to the mechanisms described above, HSP90 can interact with the hTERT promoter and thereby increase promoter activity. This interaction is independent of the transcription factors Sp1 and c-Myc, that also bind to this promoter (Kim et al. 2008).

Caspase-induced cleavage of the co-chaperone p23 leads to a truncated p23 molecule, Δ p23. Overexpression of a truncated p23 corresponding to Δ p23 leads to a decrease in hTERT levels and to down-regulation of telomerase activity (Woo et al. 2009).

Protein tyrosine kinase 6 (PTK6, also known as breast tumor kinase, BRK) is expressed in most breast cancer tissues and cell lines as well as in other tumors. In normal breast epithelial cells, it is expressed but obviously not active (Peng et al. 2014). In breast cancer cells, PTK6 is activated by Y342 phosphorylation and recruited to the cell membrane (Peng et al. 2014). HSP90 stabilizes PTK6 and may therefore be a therapeutic target for cancers with overexpression of PTK6 (Kang et al. 2012). High mRNA expression driven by chromosome coding region amplifications of HSP90AB1 correlated with poor prognosis in Her2-negative/ER-positive breast cancer (Cheng et al. 2012).

Treatment of AML (acute myeloid leukemia) patients with the HDACi (histone deacetylase inhibitor) valproic acid (VPA) increases survival in more than 20 % of patients with advanced disease due to increased apoptosis of AML cells. HSP90AB1 is among the genes up-regulated in response to VPA and might be a resistance mechanism. Indeed, the rate of apoptosis in AML cells could be increased by parallel administration of geldanamycin (Forthun et al. 2012).

The consumption of cruciferous vegetables is associated with a lower incidence of cancer. They contain isothiocyanates, membrane-permeable electrophilic compounds that form adducts with thiols. One major target of such a thiocarbamoylation is Cys-521 of HSP90AB1. This thiocarbamoylation leads to a dissociation of HSF-1 (heat shock factor 1) from HSP90AB1 and translocation of active HSP-1 to the nucleus, provoking a heat shock

response (Shibata et al. 2011). However, the mechanistic link between thiocarbamylation and suppression of cancer cell growth remains to be established.

Sometimes, mutations in the HSP90 gene might cause drug resistance. Selection of inhibitor-resistant mutants in yeast yielded resistant cell lines. For example, a HSP90AB1 I123T mutation was sufficient to confer inhibitor resistance and a corresponding HSP90AA1 I128T mutation yielded cell lines resistant to inhibitors of the Hsp90 ATPase (Zurawska et al. 2010).

Since tumor growth is supported by HSP proteins, inhibition of HSP is an obvious strategy for tumor treatment. Inhibition of HSP90 (with small-molecule NXD30001) suppressed proliferation of NF2 (neurofibromatosis type 2 gene)-deficient cells (Tanaka et al. 2013). Cancers with mutated KRAS cannot be treated with EGFR inhibitors, but they require the serine/threonine kinase STK33 for their viability and proliferation. Since STK33 is a target for the HSP90/CDC37 complex, HSP inhibitors might be a new treatment option for those tumors (Azoitei et al. 2012). Multiple ongoing clinical trials test the utility of HSP inhibition in a great variety of tumors (Den & Lu 2012; Jhaveri et al. 2012; Hong et al. 2013; Ramalingam et al. 2015).

Miscellaneous functions

In a study of 55 women with primary ovarian failure and 65 women with infertility, about 30 % had anti-ovarian antibodies (AOA) (Pires et al. 2007). None of the 60 control women had AOA. Using chromatography and mass spectrometry, the predominant antigen could be identified as HSP90AB1 (Pires & Khole 2009).

Concluding remarks

Since HSP90AB1 is involved in stabilization and transport of all types of proteins, it belongs to the proteins with most universal impact on biological functions. Because it is an ubiquitous protein, its importance for these various processes is often not enough estimated. Its overexpression in cancers together with its stabilizing function of proteins that promote essential functions of tumor cells make HSP inhibition a promising strategy for tumor treatment. Many clinical trials are under way. In addition, modulation of chaperone or co-chaperone activity might benefit inflammatory diseases, like rheumatoid arthritis, diseases caused by protein misfolding, like cystic fibrosis, or caused by increased protein aggregation like Alzheimer's disease.

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Abbreviation

17-DMAG 17-dimethylaminoethylamino-17-demethoxy-geldanamycin

AD	Alzheimers disease
Ago	argonaute protein
AHA	activator of heat shock 90kDa protein ATPase homolog
AHR	arylhydrocarbon receptor
AIF	apoptosis-inducing factor
AOA	anti-ovarian antibodies
AR	androgen receptor
Arp2/3	actin related/released protein 2/3
ASCI	acute spinal cord injury
B[a]P	Benzo[a]pyrene
BAZF	BCL-6 associated zinc finger protein
Bcl	B-cell lymphoma protein (influences apoptosis)
BPD	bronchopulmonary dysplasia
Brg1	brm (Brahma)/SWI2-related gene
BTk	breast tumor kinase
CA-SP	capsid-spacer protein
CCT	chaperonin containing T-complex polypeptide
CD	charged domain
Cdc37	cell division cycle 37
CDK	cyclin dependent kinase
CF	cystic fibrosis
CHIP	C-terminus of HSc70-interacting protein (same as STUB1)
CHORD	cysteine- and histidine-rich domain
CHORDC1	cysteine- and histidine-rich domain containing protein 1
CKII	casein kinase II
cPGES	cytoplasmic terminal prostaglandin E2 synthase
CPR7	7 th cyclophilin homolog, interacting with the yeast global transcriptional regulator Rpd3
CTD	C-terminal domain

Cyp-40	cyclophilin 40
DNA-PK	DNA damage-activated protein kinase
DUB	deubiquitinating enzyme
EGFR	epidermal growth factor receptor
ER	estrogen receptor
ERAD	endoplasmic reticulum associated degradation
ERAF	ER-associated folding
ERE	estrogen response elements
ERK	extracellular signal regulated kinase
ES cells	embryonic stem cells
FGFR	fibroblast growth factor receptor
FKBP	FK506-binding protein
G-actin	globular actin
GCase	glucocerebrosidase
GDNF	glial cell line-derived neurotrophic factor
GIST	gastrointestinal stromal tumor
GRE	glucocorticoid-response element
GRK	G-protein coupled receptor protein kinase
GroEL	large protein of the GroE operon in E. coli, mutations of which affect the growth of lambda phage by interfering with assembly of its head protein E
GroES	small protein of the GroE operon in E. coli, mutations of which affect the growth of lambda phage by interfering with assembly of its head protein E
HBx	Hepatitis B virus encoded X protein
HDAC	histone deacetylase
HDACi	histone deacetylase inhibitor (HDI)
HDI	histone deacetylase inhibitor
HGNC	human genome organization gene nomenclature committee
HIF	hypoxia inducible factor
HOP	HSP organizing protein
HSE	heat shock element

HSF1	heat shock factor 1
HSP	heat shock protein
HSP90AB1	heat shock protein 90 kDA alpha, class B, member 1 (also known as HSP90beta)
hTERT	human telomerase reverse transcriptase subunit
hTR	human telomerase RNA template
HUGO	human genome organization
IEC	intestinal epithelial cells
IkappaB	inhibitor of NF-kappaB
IKBK	IkappaB kinase
IKK	IkappaB kinase
ILK	integrin linked kinase
IPF	interstitial pulmonary fibrosis
IPO4	Importin-4
J-domain	DNAJ homology domain
KCNQ4	potassium channel, voltage gated KQT-like subfamily Q, member 4
KLF4	Krüppel-Like-Factor 4
KMT	histone H3 lysine (K) 36-specific methyltransferase
Kpna5	karyopherin alpha 5
LAP	latency-associated peptide
LIMK	LIM kinase
MAPK	mitogen activated protein kinase
MB	methylene blue
MCL1	myeloid cell leukemia protein 1
MCTD	mixed connective tissue disease
MD	middle domain
MDM2	mouse double minute 2 homolog
MEEVD	Met-Glu-Glu-Val-Asp motif
MKRN1	makorin ring finger protein 1

MMP	matrix metalloproteinases
mTOR	mammalian target of rapamycin
MTORC1	mammalian TOR complex 1
NF2	neurofibromatosis type 2
NF-kappaB	nuclear factor kappaB
NGF	nerve growth factor
NLS	nuclear localization sequence
NO	nitric oxide
NSCLC	non-small cell lung cancer
NTD	N-terminal domain
N-WASP	neuronal Wiskott-Aldrich Syndrome Protein, now called WASPL
p23	protein with ~23 kDa (same as PTGES3)
p70S6	70 kDa ribosomal subunit S6 kinase kinase
PD	Parkinson's disease
PGE2	prostaglandin E2
PKA	protein kinase A
PP5	protein phosphatase 5, also abbreviated PPP5C
PP1ase	peptidyl-prolyl cis-trans isomerase
PR	progesterone receptor
PTGES3	prostaglandin E synthase 3 (same as p23
PTK	protein tyrosine kinase
PTK6	protein tyrosine kinase6 (also called BTK)
RAC	receptor-associated co-activator
Rack	receptor of activated protein kinase C
RA-ILD	rheumatoid arthritis-associated interstitial lung disease
RBCK1	RanBP-type and C3HC4-type zinc finger-containing protein 1
REV-1	reversionless 1
RISC	RNA-induced silencing complex
RNAi	RNA interference

RPE	retinal pigment epithelium
SGT	small glutamine-rich TPR-containing protein
siRNA	small interfering RNA
SSc	systemic sclerosis
STUB1	STIP1 homology and U-box containing protein 1 (same as CHIP)
TIM	translocation machinery (translocase) of the inner mitochondrial membrane
TLS	translesion DNA synthesis
TMA	tissue microarray
TNFalpha	tumor necrosis factor alpha
TOM	translocation machinery (translocase) of the outer mitochondrial membrane
TOP	5' terminal oligopyrimidine
TPR	tetratricopeptide repeat
TriC	TCP-1 ring complex protein
TRIM	T-cell receptor interacting molecule
Trx	thioredoxin-1
VPA	valproic acid
WASPL	Wiskott-Aldrich Syndrome Protein-like

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Highlights

This is a review on HSP90AB1 (heat shock protein 90 kDA alpha, class B, member 1), also known as HSP90beta.

HSP90AB1 binds to all kinds of proteins including steroid hormone receptors, transcription factors, ubiquitin ligases and kinases.

HSP90AB1 is a chaperone that stabilizes proteins in a properly folded structure, but is also involved in protein transport and protein degradation.

Inhibition of HSP90AB1 function is a promising therapeutic approach for a variety of diseases including cancer, inflammatory diseases and inherited diseases.

Figure 1.

Domain structure of human HSP90AA1 (732aa translation product, Ensembl transcript ID ENST00000216281) and HSP90AB1 (ENSEMBL transcript ID ENST00000371554).

Amino acid borders of the main domains are given above each molecule. Co-chaperones that bind to the respective regions are depicted below. NTD, N-terminal domain; CTD, C-terminal domain; MD, middle domain.

Figure 2.

Simplified chaperone cycle. ATP and ADP bound states during protein folding as well as open configuration of HSP90 homodimer are shown. NTD, N-terminal domain; CTD, C-terminal domain; MD, middle domain.

Table 1

Chaperone families according to HNGC (Human Genome Organization Gene Nomenclature Committee, <http://www.genenames.org/genefamilies/HSP>) proposed by Kampinga et al. (Kampinga et al. 2009) and representative members of each family.

Chaperone family: short name	Representative members	References
HSP70	HSPA1A (Hsp70–1), HSPA8 (HSC70/71, heat shock cognate 70/71 kDa)	(Liu et al. 2012; Stricher et al. 2013)
DNAJ (HSP40)	DNAJB1 (Hsp40), HSCB (Hsc20)	(Ohtsuka & Hata 2000; Fan et al. 2003; Cyr & Ramos 2015)
HSPB (small heat shock proteins)	HSPB1 (Hsp27)	(Garrido et al. 2003; Acunzo et al. 2012)
HSPC (HSP90)	HSP90AA1 (Hsp90alpha), HSP90AB1 (HSP90beta)	(Pearl & Prodromou 2000; Taipale et al. 2010)
chaperonins	HSPD1 (GroEL, Hsp60), HSPE1 (GroES, Hsp10), TriC	(Horwich et al. 2006; Krishna et al. 2007)

Table 2

HSP90/HSPC family according to HNGC (HUGO gene nomenclature committee, <http://www.genenames.org/genefamilies/HSP>) proposed by Kampinga et al. (Kampinga et al. 2009).

Abbreviation	Full name	Other common names: abbreviations	Other common names: full names	Localization
HSP90AA1	heat shock protein 90 kDa alpha, class A, member 1	HSP90alpha, HSP86	heat shock protein 90 kDa alpha, heat shock protein 86 kDa	cytoplasm
HSP90AB1	heat shock protein 90 kDa alpha, class B, member 1	HSP90beta, Hsp84	heat shock protein 90 kDa beta, heat shock protein 84 kDa	cytoplasm
HSP90B1	heat shock protein 90 kDa beta, member 1	Grp94/96	glucose-regulated protein 94/96 kDa	endoplasmic reticulum
Trap1	TNF receptor-associated protein 1	HSP90L	heat shock protein 90 like	mitochondria

Table 3

Important co-chaperones, modified after Taipale et al. (Taipale et al. 2010). CS, CHORD and Sglt1 domain; CT, C-terminal; CTD, C-terminal domain; MD, middle domain; MEEVD, motif named after its amino acids; NTD, N-terminal domain; TPR, tetratricopeptide domain; +, acceleration; -, inhibition; 0, no influence.

Abbreviation	Full Name/other names/gene name	Binding domain in HSP90	Binding domain in co-chaperone	ATPase activity	References
Cdc37	cell division cycle 37	NTD	CTD	-	(Stepanova et al. 1996; Lamphere et al. 1997)
p23	Protein with ~23 kDa; PTGES3, prostaglandin E synthase 3; cPGES (cytoplasmic PGES)	NTD	CS	-	(Oxelmark et al. 2006; Lovgren et al. 2007; Karagoz et al. 2011)
SGT1	Small glutamine-rich TPR-containing protein 1	NTD	CS		(Yin et al. 2006)
AHA1	AHSA1, activator of heat shock 90kDa protein ATPase homolog 1	MD	NTD	+	(Wang et al. 2006; Echeverria et al. 2011)
HOP	Hsp-organizing protein; Sti1/STIP1, stress induced phosphoprotein 1	CTD MEEVD	TPR	-	(Young et al. 1998; Carrello et al. 1999; Scheufler et al. 2000; King et al. 2001; Brinker et al. 2002; Millson et al. 2008)
CHIP	C-terminus of HSC70-interacting protein; STUB1, STIP1 homology and U-box containing protein 1	CTD MEEVD	TPR		(Ballinger et al. 1999; Shang et al. 2014)
FKBP1	FK506 binding protein-like; WISp39, WAF1/CIP1 stabilizing protein 39 kDa	CTD MEEVD	TPR		(McKeen et al. 2008; Sunnotel et al. 2010; Valentine et al. 2011; Yakkundi et al. 2013; Donley et al. 2014)
FKBP2	FKBP52/54 (FK506-binding protein, 52/54 kDa; FKBP4, F506 binding protein 4)	CTD MEEVD	TPR		(Miyata et al. 1997; Carrello et al. 1999; Pirkel & Buchner 2001; Scammell et al. 2003; Davies & Sanchez 2005; Cioffi et al. 2011; Storer et al. 2011)
FKBP5	FK506 binding protein 51 kDa; FKBP5, FK506 binding protein 5	CTD MEEVD	TPR		(Pirkel & Buchner 2001; Hubler et al. 2003; Cioffi et al. 2011; Storer et al. 2011)
CYP40	cyclophilin 40	CTD MEEVD	TPR	0	(Duina et al. 1996a; Pirkel & Buchner 2001; Carrello et al. 2004; Mok et al. 2006; Park et al. 2011)
PP5	protein phosphatase 5	CTD MEEVD	TPR		(Silverstein et al. 1997; Hahn 2005; Hinds & Sanchez 2008)
TOM70	translocase of outer membrane 70 kDa	CTD MEEVD	TPR		(Young et al. 2003a)
TPR2	tetratricopeptide repeat containing protein 2	CTD MEEVD	TPR		(Xiang et al. 2001; Kubo et al. 2013)
Cpr6 and Cpr7	6 th and 7 th cyclophilin homolog, interacting with the yeast global transcriptional regulator Rpd3	CTD MEEVD	TPR	+	(Duina et al. 1996a; Tenge et al. 2015)