

REVIEW

Barcoding heat shock proteins to human diseases: looking beyond the heat shock response

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ABSTRACT

There are numerous human diseases that are associated with protein misfolding and the formation of toxic protein aggregates. Activating the heat shock response (HSR) – and thus generally restoring the disturbed protein homeostasis associated with such diseases – has often been suggested as a therapeutic strategy. However, most data on activating the HSR or its downstream targets in mouse models of diseases associated with aggregate formation have been rather disappointing. The human chaperonome consists of many more heat shock proteins (HSPs) that are not regulated by the HSR, however, and researchers are now focusing on these as potential therapeutic targets. In this Review, we summarize the existing literature on a set of aggregation diseases and propose that each of them can be characterized or ‘barcoded’ by a different set of HSPs that can rescue specific types of aggregation. Some of these ‘non-canonical’ HSPs have demonstrated effectiveness *in vivo*, in mouse models of protein-aggregation disease. Interestingly, several of these HSPs also cause diseases when mutated – so-called chaperonopathies – which are also discussed in this Review.

KEY WORDS: Chaperonopathies, Heat shock protein, Protein-aggregation diseases

Introduction

Many heat shock protein (HSP) family members are known to function as molecular chaperones, meaning that they stabilize and assist in the correct folding of nascent polypeptides (Ellis and Hartl, 1999). In addition to their role in *de novo* protein folding, HSPs are involved in various aspects of proteome maintenance, including macromolecular-complex assembly, protein transport and degradation, as well as aggregate dissociation and refolding of stress-denatured proteins. Under normal cellular conditions, HSP levels match the overall level of protein synthesis. Under conditions of stress, mature proteins unfold and exceed the capacity of chaperone systems to prevent aggregation. Such acute proteotoxic stress induces a regulated response resulting in increased expression of some HSPs, which helps to rebalance protein homeostasis.

The human genome encodes more than 100 different HSPs, which are grouped into seven different families: HSPH (Hsp110), HSPC (Hsp90), HSPA (Hsp70), DNAJ (Hsp40), HSPB [small Hsp (sHsp)],

the human chaperonins HSPD/E (HSP60/HSP10) and CCT (TRiC), plus several regulatory co-factors (Kampinga et al., 2009). In terms of their regulation, the HSP family members can also be categorized into three groups: (1) constitutively expressed, but not induced by stress; (2) constitutively expressed and induced upon stress; and (3) induced only upon stress (Morimoto, 2008). In addition to their differential regulation, the various HSPs also show a large degree of functional diversity with respect to client specificity and client processing (Kampinga and Craig, 2010). These functional differences could be very important when investigating their potential relevance for diseases in which cells are chronically exposed to proteins that are prone to form toxic protein aggregates. Examples of such diseases are polyglutamine (polyQ) diseases, Parkinson’s disease (PD), amyotrophic lateral sclerosis (ALS) and Alzheimer’s disease (AD). This Review discusses how these diseases can be labeled or ‘barcoded’ by specific sets of HSPs that can rescue their disease-specific aggregations.

The cellular functions of HSPs**HSPs and *de novo* protein folding**

The general organization of co-translational folding is highly conserved throughout evolution. Ribosome-binding chaperones (e.g. specialized Hsp70/HSPAs) first interact with the nascent polypeptide, followed by a second set of HSPs that do not have a direct affinity for the ribosome (the classical Hsp70/HSPA system). The Hsp70/HSPA family is the central component of the cellular network of molecular chaperones and folding catalysts (Fig. 1A). Hsp70/HSPA proteins are involved in a wide range of protein quality control (PQC) functions, including *de novo* protein folding, refolding of stress-denatured proteins, protein transport, membrane translocation and protein degradation. Hsp70/HSPAs never function alone; they require Hsp40/DNAJ proteins and nucleotide-exchange factors (NEFs) as partners. DNAJ proteins bind and deliver client proteins to the Hsp70/HSPA system, upon which the client protein and DNAJ function together to stimulate HSPA to hydrolyze ATP, leading to high substrate affinity of HSPA. Following ATP hydrolysis, NEFs such as BAG-1, HSPBP1 and HSPH bind HSPA and induce ADP-ATP exchange, leading to substrate release. DNAJs thus mainly confer client specificity to the Hsp70/HSPA machine, but can also affect the fate of HSPA clients, whereas NEFs seem to be mainly involved in client fate (Bukau et al., 2000; Kampinga and Craig, 2010; Young, 2014) (Fig. 1A). The DNAJ/HSPA system might also receive clients from small Hsp/HSPB proteins. HSPB chaperone activity does not need ATP. However, direct interaction with ATP-dependent chaperones such as HSPA promotes the release of the bound substrate and subsequent refolding (Boncoraglio et al., 2012; Garrido et al., 2012).

Proteins that cannot be completely folded by Hsp70/HSPA machines are transferred to, or handled independently by, the chaperonins or the Hsp90/HSPC system (Buchner, 1999; Yam et al., 2008) (Fig. 1A). Substrate transfer to Hsp90/HSPC protein is

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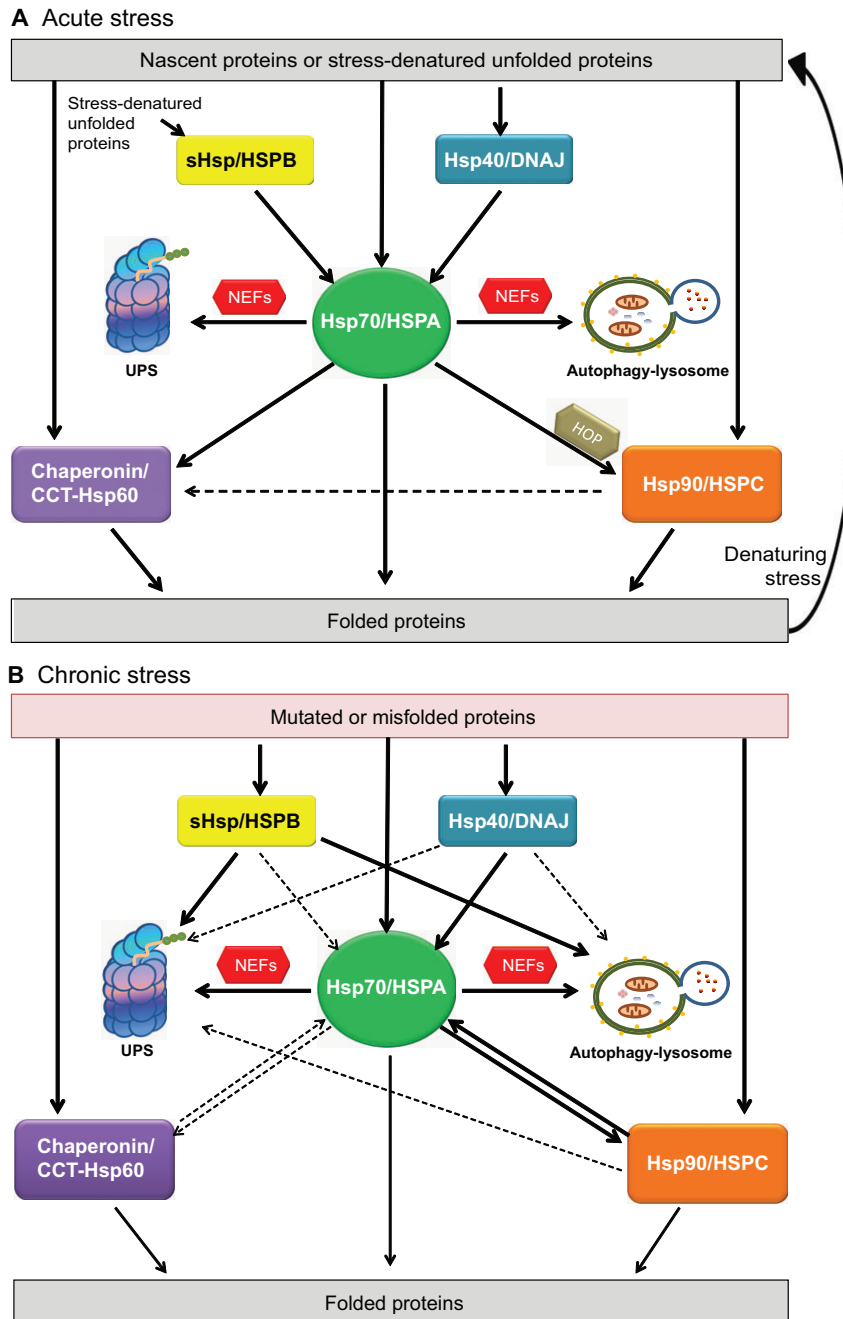


Fig. 1. Model of actions and interactions of the HSP network required for normal protein folding and refolding upon acute stress or during chronic stress. HSP families constitute a large group of chaperones that interact with non-native proteins, assisting their correct protein folding. HSPs are constitutively expressed, but their expression levels can increase under conditions of stress. They are mainly divided into groups: sHsp/HSPBs, Hsp70/HSPAs, Hsp90/HSPCs and members of the chaperonin (CCT-Hsp60) family (see main text for details). (A) During *de novo* protein folding and for the refolding of acute-stress-denatured unfolded proteins, the functional cooperation of different HSPs is primarily aimed at the structural stabilization of native proteins for (re)folding. However, in case of failure of protein folding, HSPs can also assist client degradation through the ubiquitin-proteasome system (UPS) or the autophagy-lysosome pathway. The central component of the chaperone network and folding catalysts is the Hsp70/HSPA family. Hsp40/DNAJs hydrolyze ATP (bound to Hsp70/HSPA) to ADP, increasing the affinity of its substrate-binding domain for unfolded proteins. Nucleotide-exchange factor (NEF) proteins remove ADP and substitute ATP, reducing Hsp70/HSPA's substrate-binding affinity, allowing release of the folded protein. Proteins that are unable to utilize Hsp70/HSPAs for complete folding are transferred to the chaperonin or the Hsp90/HSPC system. For transfer of substrates from Hsp70/HSPA to Hsp90/HSPC, HOP is required as a co-chaperone. Under acute stress conditions, HSPB oligomers dissociate into dimers to bind unfolded substrates, thereby avoiding irreversible aggregation of client proteins. This process allows ATP-dependent chaperones to assist in the substrates refolding when normal physiological conditions are restored. (B) In the presence of chronic stress, which triggers protein misfolding, re-folding attempts might be particularly unsuccessful. Under such conditions, the HSP network can assist in protein unfolding and disaggregation, and specific targeting of the misfolded or even aggregated proteins for degradation is usually required. Members of each HSP family are shown to interact with misfolded proteins and to reverse the formation of aggregates. However, whether different HSPs functionally cooperate with each other in order to modulate mutated protein toxicity is not yet clear. Solid lines indicate confirmed actions and interactions; hashed lines refer to those that are suggested but not fully proven.

mediated by the HSP-organizing protein (HOP), which uses multiple tetratricopeptide-repeat domains to form a bridge between HSPA and HSPC (Buchner, 1999; Young et al., 2001). The mechanism of handover from Hsp70 to chaperonins remains unclear in mammals; however, work in the prokaryotic system has begun to reveal some interesting possibilities. For example, it has recently been shown that the Hsp70 homolog DnaK binds the M domain of ClpB to recruit DnaK-bound substrates to the chaperonin (Seyffer et al., 2012).

HSPs and acute proteotoxic-stress conditions

Cells are constantly challenged by changes in their environment. Acute stress conditions such as heat shock cause many proteins to become unfolded. The accumulation of stress-denatured proteins increases the risk of aggregate formation. In addition to their role

in co-translational folding, the constitutively expressed HSP members might also assist in aggregate protection and refolding of stress-unfolded proteins (Fig. 1A). However, it has been shown in yeast that the stress-inducible cytosolic members of the families, which are strongly upregulated by the transcription factor heat shock factor-1 (HSF-1), become more important under such conditions (Albanèse et al., 2006). Next to this transcriptional response, HSPB proteins represent an even more rapid response to environmental stresses (Fig. 1A). Several HSPB members are rapidly and transiently phosphorylated, whereby their oligomeric state is dynamically altered and their protective activities are activated. These protective activities include prevention of cytoskeletal collapse and chaperoning of soluble proteins, which can enhance protein refolding or support client degradation (Garrido et al., 2012).

In parallel to the HSF-1-regulated heat shock response (HSR) in the cytosol, interconnected pathways in different cellular compartments also respond to acute cellular stress, including the unfolded protein response (UPR) in the endoplasmic reticulum and the mitochondria (Haynes and Ron, 2010; Morimoto, 2011; Walter and Ron, 2011). Each pathway not only induces the transcriptional upregulation of genes that enhance refolding capacity, but also the expression of HSP members that assist in degradation of unfolded proteins through the proteasome- and lysosome-mediated pathways, together protecting cells from stress (Parsell and Lindquist, 1993; Haynes and Ron, 2010; Morimoto, 2011; Walter and Ron, 2011).

HSPs and chronic stress conditions

Protein aggregation hallmarks a high number of chronic diseases (Balch et al., 2008) that can either be loss-of-function or toxic gain-of-function disorders. Loss-of-function diseases, including cystic fibrosis and Gaucher's disease, are typically caused by recessive mutations that lead to inefficient folding of the mutated proteins and their consequent degradation or dysfunction (Fan et al., 1999) (Fig. 1B). Of note, in recessive diseases, the HSF-1-regulated HSPs can promote some refolding of (metastable) mutant proteins, thereby displaying disease-rescuing potential (Yang et al., 2013). In addition, chaperone inhibition, resulting in less efficient recognition of the mutant peptides and therefore increasing their degradation, has been shown to be protective in such diseases (Chanoux and Rubenstein, 2012). Toxic gain-of-function diseases, on the other hand, usually manifest with the formation of intracellular and/or extracellular deposits of aggregated proteins, as will be further discussed below (Chiti and Dobson, 2006; Balch et al., 2008; Morimoto, 2008). These aggregates are often fundamentally different from those formed during acute stress because they initially are formed without being sensed by the (acute) stress responses in the cells. Moreover, unlike in response to acute stress, in which proteins are unfolded, proteins in chronic stress are intrinsically misfolded and can generally not be refolded; these misfolded proteins must be disposed of (Fig. 1B). This could imply that different HSPs might be crucial – or rate-limiting – to providing protection in chronic protein-aggregation diseases than for acute stress. Below, we will focus on toxic gain-of-function diseases and provide an overview of the literature on HSPs that could prevent aggregation or/and toxicity of the disease-associated proteins. Because we aim to identify HSPs that might be rate-limiting factors for aggregate prevention and thus targets for intervention in these diseases, we will mainly discuss effects of HSP overexpression and not include studies on the downregulation of HSPs. Interestingly, HSP downregulation is often associated with toxicity and lethality and can result in disease itself. Therefore, this Review will also provide an overview of aggregation diseases, known as chaperonopathies, which are caused by mutations in HSPs. In this way, we aim to recapitulate the role of HSPs in chronic aggregation diseases from two angles: the prevention of toxic gain-of-function diseases and their role in causing disease themselves.

HSPs and proteinopathies

There are numerous human diseases that are associated with the aggregation of a single dominant peptide or protein. Examples of such diseases, known as proteinopathies, include polyQ diseases, PD, ALS and AD. The monogenic forms of neurodegenerative proteinopathies are rare, and are generally histopathologically indistinguishable from their corresponding sporadic forms, making it likely that both forms share a final common pathway. Protein aggregates are either found inside neurons (e.g. tau tangles in AD)

or outside neurons, in the extracellular space [e.g. amyloid- β (A β) plaques in AD]. Aggregates are generated when proteins become destabilized, either by mutations changing their native state (e.g. SOD1 in ALS) or quantity (e.g. α -synuclein in PD), by the elongation of a certain domain [e.g. huntingtin (Htt) in Huntington's disease (HD)] or by domain truncations (e.g. TDP-43 in ALS). Aggregates range from extremely dense amyloidogenic aggregates with β -sheet cores (Htt, ataxin-3, A β) to more amorphous aggregates (α -synuclein, SOD1, TDP-43). Although it is still debated whether the small oligomers or the large inclusions are more toxic, the overall evidence from model systems strongly suggests that aggregate prevention generally results in disease amelioration. Therefore, this Review focuses on aggregate prevention by HSPs and will reveal that each of these proteinopathies is associated with a different pattern or 'barcode' of rescue depending either on the HSR or individual HSPs. The elucidation of these barcodes provides a platform for a rational design of disease-specific therapeutic strategies. For each disease, we have categorized evidence into four levels (Fig. 2): *in vitro* (lowest level), cell studies, non-mammalian model systems and mammals (highest level). Furthermore, evidence in Fig. 2 was graded according to the specific effects of each chaperone: prevention of aggregate formation (black), buffering of toxic effects caused by diseased protein (gray) and absence of protective effects (white).

Polyglutamine (polyQ) diseases

In polyQ diseases, the polyQ tract is elongated beyond a certain threshold. The transcribed polyQ peptide fragments are thought to be the initiators of amyloid fibrils and have a strong propensity to assemble into highly ordered polymers that are extremely rich in β -sheet structure, thereby creating sodium dodecyl sulfate (SDS)-insoluble aggregates (Wellington et al., 2000; Chiti and Dobson, 2009). PolyQ expansions in Htt, ataxins and the androgen receptor have been associated, respectively, with the dominant late-onset toxic gain-of-function diseases HD, spinocerebellar ataxias (SCA) and spinal bulbar muscular atrophy (SBMA). All these diseases are associated with severe motor problems and/or muscle atrophy (Chiti and Dobson, 2009; Banno et al., 2012; Seidel et al., 2012b). Both age of onset and protein-aggregation propensity are strongly associated with the length of the polyQ expansion, further suggesting that aggregate formation forms the basis of disease (Gusella and MacDonald, 2000; Wellington et al., 2000).

In cells and non-mammalian model organisms, activation of the acute HSR pathways has been shown to reduce the extent of polyQ aggregation. Overexpression of HSF-1 leads to fewer but larger polyQ aggregates in cells (Pierce et al., 2010). In agreement with this finding, chemical upregulation of the HSR in cells and non-mammalian animal organisms reduced a number of dysfunctions caused by polyQ overexpression (see Fig. 2 for associated references). Although overexpression of HSF-1 in muscle tissue of the R6/2 mouse model for HD increased lifespan, there were only small effects on aggregates (Fujimoto et al., 2005), implying that effects were compensatory and did not affect the underlying toxic gain of function. Chemical upregulation of the HSR by the use of Hsp90/HSPC inhibitors in the R6/2 mouse model leads to transient beneficial effects, which disappear during disease progression (Labbadia et al., 2011). Moreover, Hsp90/HSPC inhibition leads to accelerated degradation of soluble polyQ-Htt, which is apparently independent of HSR activation; however, this was most likely due to pleiotropic effects associated with the inhibition of Hsp90/HSPC instead (Baldo et al., 2012; Yam et al., 2008; Buchner, 1999).

Whereas injection of HSF-1 into an SBMA mouse model resulted in only small effects in neurons, Hsp90/HSPC inhibition by 17-AAG, geranylgeranylacetone (GGA) and geldanamycin (GA) not only substantially increased lifespan, but also diminished aggregates (Fig. 2). Hsp90s/HSPCs are required for the degradation, regulation, ligand-binding affinity and stabilization of the androgen receptor, as well as for its trafficking (Peterson and Blagg, 2009). The strong effects of Hsp90/HSPC inhibitors on SBMA – but not HD – suggest that HSF-1 activation and the resulting upregulation of the HSR is insufficient to modulate polyQ diseases in general. Protective effects of Hsp90/HSPC inhibitors, if found, are therefore most likely due to HSF-1-unrelated effects (Baldo et al., 2012).

Upregulation of individual members from HSF-1-regulated HSP families (e.g. HSPA1A, DNAJB1, HSPB1) was effective in preventing polyQ aggregation or the associated toxicity *in vitro* and in cellular models (Fig. 2). However, in comparative screens involving larger polyQ expansions, the HSR-regulated HSPs were usually rather ineffective compared with non-canonical HSPs (Vos et al., 2010; Hageman et al., 2011; Hageman et al., 2012). Some effects of Hsp70/HSPA overexpression on polyQ toxicity were reported in *Drosophila melanogaster* (Fig. 2). However, these effects were not associated with aggregate reduction, suggesting that the observed protection was due to compensatory effects downstream of aggregate formation; for instance, the loss of normal PQC functions owing to entrapment of key chaperones, such as DNAJB1 (Park et al., 2013). Yet, this loss of PQC is apparently not at the heart of disease in mammals, because restoration of PQC by HSP70 overexpression did not delay disease progression in the R6/2 HD mouse model (Hansson et al., 2003; Hay et al., 2004). The same is true for the canonical small HSP HSPB1. Although an earlier report suggested that HSPB1 overexpression led to a small delay of Htt toxicity in rats (Perrin et al., 2007), studies in a mouse model for HD (Zourlidou et al., 2007) as well as several studies in cells (Fig. 2) showed that HSPB1 is rather inefficient in delaying polyQ aggregation. Combining these results suggests that HSPB1 might have some compensatory effects that might initially slightly delay disease but, because HSPB1 seems not to affect aggregates directly, this is insufficient to substantially rescue the disease in mammals (Fig. 2).

In dedicated screens for members of the HSP families that might be better suppressors of polyQ aggregation, a number of very effective HSPs were identified, including DNAJB2, DNAJB6, DNAJB8, HSPB6, HSPB7, HSPB8 and HSPB9. Interestingly, most of these were not, or were only marginally, regulated by HSF-1 and were not effective in stimulating substrate refolding after acute stress (Vos et al., 2010; Hageman et al., 2011; Hageman et al., 2012; Kakkar et al., 2013). Instead, these HSPs were associated with degradation of clients through the proteasomal and autophagic degradation routes. Moreover, whereas DNAJB6, HSPB7 and HSPB8 delayed aggregation in *Drosophila*, DNAJB2 was the first HSP that demonstrated a protective effect on aggregate formation, functional end points and survival in mice (Labbadia et al., 2012). Interestingly, our preliminary data regarding transgenic overexpression of DNAJB6 indicate even larger protective effects in the R6/2 mice (our unpublished results). The effectiveness of these non-canonical HSPs in cells, non-mammalian model organisms and mice might be related to their ability to prevent initiation of aggregate formation or to assist aggregate clearance through autophagy, a finding that would be consistent with the important role that autophagy plays in proteinopathies (Vos et al., 2010; Boncoraglio et al., 2012; Rubinsztein et al., 2012; Gillis et al., 2013; Mansson et al., 2013).

In a nutshell, the HSR and individual HSF-1-regulated HSP members have marginal and mainly compensatory effects in polyQ diseases. In contrast, other members of the HSP families that can prevent aggregate initiation or dispose of aggregates might have potential as targets for therapy in polyQ diseases.

Parkinson's disease (PD)

About 5-10% of PD cases are monogenic and are caused by either loss-of-function or toxic gain-of-function mutations. The most commonly occurring PD-causing mutations are in the mitochondria-associated genes encoding Parkin (PARK2), PINK1 (PARK6) and DJ-1 (PARK7) (Lesage and Brice, 2009; Schapira and Tolosa, 2010; Martin et al., 2011; Klein and Westenberger, 2012). Mutations in these genes are recessively inherited and usually result in a loss-of-function effect, mainly impeding mitochondrial function and turnover. By contrast, a toxic gain-of-function phenotype resulting in PD is caused by rare dominantly inherited mutations and multiplications in the genes *SNCA* (PARK1, PARK4) and *LRRK2* (PARK8) (Lesage and Brice, 2009; Schapira and Tolosa, 2010; Klein and Westenberger, 2012). This Review will focus on these rare toxic gain-of-function mutations.

Mutations in or multiplications of *SNCA* lead to increased oligomerization of the gene product α -synuclein, which is an intrinsically disordered protein. This enhanced oligomerization increases the tendency of α -synuclein to form β -sheet structures and eventually fibrous amyloidogenic inclusions, called Lewy bodies and Lewy neurites (Lesage and Brice, 2009; Martin et al., 2011; Roostae et al., 2013). *LRRK2* is a kinase that is involved in the phosphorylation of α -synuclein. Mutations in *LRRK2* are thought to promote α -synuclein expression, aggregation and toxicity, thereby increasing the propensity of α -synuclein to self-aggregate (Schapira and Tolosa, 2010; Martin et al., 2011).

As in polyQ diseases, genetic or chemical activation of HSF-1 can temporarily compensate for *LRRK2* and α -synuclein toxicity in cells and *Drosophila* (Fig. 2).

Although individual HSPs such as DNAJA1, DNAJB2, HSPB2/HSPB3, HSPB6 and HSPB8 inhibited α -synuclein aggregation *in vitro*, none of them have proven to be effective in this action in cells thus far (Fig. 2). HSPB1 and HSPB5 were found to be effective in preventing α -synuclein aggregation *in vitro*, in cells and in *Drosophila*; however, there is currently no evidence of success in mouse models. Overexpression of HSPA1 was also shown to be able to inhibit α -synuclein aggregation *in vitro*, and decrease α -synuclein toxicity in cells and in *Drosophila*. Moreover, HSPA1 overexpression in mice did show some protective effects, although the data are still disputed (Klucken et al., 2004; Shimshek et al., 2010) (Fig. 2). As is the case for polyQ diseases, neither Hsp70/HSPA1 nor any other canonical HSP could prevent aggregate formation or reduce aggregate size and quantity.

These data taken together would suggest that compensation for loss of normal PQC by sequestration of HSPs into aggregates plays a more important role in PD than it does in polyQ diseases. In line with this notion, a study of α -synuclein in mice showed that transgenic overexpression of HSPA5 delayed disease onset without affecting cytosolic protein aggregation. Because HSPA5 is an ER-resident Hsp70/HSPA and is not expressed in the cytoplasm of the cell, its mode of action must be indirect. Instead of directly affecting aggregate formation, HSPA5 most likely compensates for downstream consequences of aggregation and thereby delays disease onset (Gorbatyuk et al., 2012).

To conclude, the biophysical nature and intracellular localization of α -synuclein aggregates are clearly different from aggregates in

polyQ diseases (Ciechanover and Brundin, 2003). Expression of (mutant) α -synuclein rapidly activates HSF-1, whereas polyQ expression either does not activate HSF-1 at all, or only transiently and very late in disease (Ciechanover and Brundin, 2003; Seidel et al., 2012a). The potential HSP suppressors of PD thus seem to differ from that of polyQ diseases, thereby resulting in a different HSP barcode of potential treatment targets (Fig. 2).

Amyotrophic lateral sclerosis (ALS)

About 5% of ALS cases are currently categorized as dominant monogenic ALS, the most commonly occurring mutations being in SOD1, TDP-43 and FUS (Andersen and Al-Chalabi, 2011; Al-Chalabi et al., 2012). Clinically, sporadic and monogenic ALS are virtually indistinguishable because SOD1- and TDP-43-positive inclusions are present in both forms of the disease, thereby implying a final common pathway (Turner et al., 2013). About 166 mutations in SOD1 have been associated with monogenic ALS. Although SOD1 mutations were initially thought to cause disease via a loss of wild-type SOD1 function, SOD1-knockout mice displayed no phenotype (Saccon et al., 2013). Instead, the overexpression of mutant SOD1 leads to disease, implying that the mutant gained a toxic function (Siddique and Deng, 1996; Andersen and Al-Chalabi, 2011). Mutations in SOD1 indeed structurally destabilize the protein, thereby increasing its aggregation propensity, which eventually results in amyloid-fibril formation (Luheshi and Dobson, 2009). Mutations in TDP-43, an RNA-processing protein that usually shuttles between the nucleus and cytoplasm of the cell, render the protein aggregation-prone, which leads to the formation of dense round or filamentous aggregates in the cytoplasm alongside stress granules (Luheshi and Dobson, 2009; Andersen and Al-Chalabi, 2011; Al-Chalabi et al., 2012). Mutations in FUS, another protein involved in RNA metabolism, also result in large globular and elongated cytoplasmic inclusions (Andersen and Al-Chalabi, 2011; Al-Chalabi et al., 2012). Nevertheless, FUS-related ALS is defined as an atypical form because TDP-43-positive aggregates are not part of the pathology; therefore, this Review will not discuss FUS-related ALS.

Treatment of *Drosophila* with the Hsp90/HSPC inhibitor 17-AAG reduced the characteristic ALS eye-degeneration phenotype in a TDP-43 model (Gregory et al., 2012). In addition, treatment of the SOD1-G93A mouse model with 17-AAG not only delayed age of symptom onset, but also increased lifespan (Kieran et al., 2004; Kiaei et al., 2005; Kalmar et al., 2008). However, these protective effects were not reproducible in the SOD1-G37R or the SOD1-G85R mouse model (Chiti and Dobson, 2009; Gifondorwa et al., 2012). These contradictory results indicate that protein aggregation and toxicity mechanisms might depend on the exact kind of mutation, and therefore result in a different barcode of HSPs for each SOD1 mutation.

Regarding the effects of individual HSPs on SOD1 aggregation and toxicity, data in cell lines expressing mutant SOD1 suggest protective effects of HSPA1, DNAJB1, DNAJB2, HSPB1 and HSPB8 (Fig. 2). Furthermore, HSPB8 alleviated TDP-43 aggregation and toxicity in cells and HSPA1A reduced TDP43-associated eye degeneration in *Drosophila* (Estes et al., 2011). The intracranial injection of SOD1-G93A mice with HSPA1 was also protective, whereas long-term effects of HSPB1 overexpression in mice were absent, although this awaits further investigation (Gifondorwa et al., 2007; Krishnan et al., 2008; Sharp et al., 2008; Gifondorwa et al., 2012).

To conclude, except for the aforementioned Hsp90/HSPC inhibitors, none of the discussed HSPs resulted in long-term rescue or had direct effects on SOD1 aggregates (Fig. 2). Moreover, it is

not clear whether the effects of the Hsp90/HSPC inhibitors are due to the elevation of HSF-1-regulated HSPs, or whether they are due to the broad effects that these inhibitors exert on cell homeostasis. In summary, the barcode of HSPs that protect against ALS is still very limited.

Alzheimer's disease (AD)

The most commonly occurring form of AD is sporadic late-onset AD. In contrast, only about 1-2% of AD cases occur with early onset, and these are due to autosomal-dominant mutations in amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*) or presenilin 2 (*PSEN2*) (Guerreiro et al., 2012). Although intracellular tangles, consisting of hyperphosphorylated tau and extracellular A β plaques, are present in both sporadic and monogenic AD, it is unclear how toxicity in AD proceeds. It is disputed as to whether A β aggregation leads to cellular stress and results in tau hyperphosphorylation and aggregation (described as the amyloid cascade hypothesis), or whether tau hyperphosphorylation and aggregation precede A β accumulation (described as the tau axis hypothesis) (Götz et al., 2011). Here, we will provide an unbiased summary of the effects of HSPs on both A β - and tau-related aggregation.

A β peptides are the result of APP cleavage via one of two pathways: a non-amyloidogenic pathway that leads to the generation of the most common isoform, A β_{40} , or an amyloidogenic pathway that results in the generation of A β_{42} (Guerreiro et al., 2012). AD-related mutations in APP usually affect the ratio or properties of these different A β species (Guerreiro et al., 2012). Similarly, mutations in PSEN1 and PSEN2, which are rate-limiting components of the γ -secretase complex in the amyloidogenic pathway, result in increased generation of the more fibrillogenic A β_{42} (Götz et al., 2011; Guerreiro et al., 2012).

HSF-1 injection into an APP rat model increased neuronal health and reduced A β -plaque load (Jiang et al., 2013). Similarly, in another study, genetic overexpression of HSF-1 in APP mice diminished soluble A β levels (Pierce et al., 2013). In line with these findings, treatment of APP mice with the HSF-1 activator celastrol slightly decreased A β -plaque load (Paris et al., 2010).

In vitro, it was shown that HSPA1, HSPA5, HSPC1 and HSPA1/DNAJB1, as well as HSPB1, HSPB5, HSPB6 and HSPB8, slow down A β aggregation when upregulated individually (Fig. 2). Furthermore, when cells exposed to purified, extracellularly added A β were co-incubated with purified DNAJB1, HSPB1, HSPB5 or HSPB8, they were protected against A β toxicity (Wilhelmus et al., 2006; Carnini et al., 2012). However, considering that HSPs are intracellular proteins, whereas A β plaques are generally considered to be extracellular, the relevance of such findings could be debated. Interestingly, evidence stating that intracellular A β aggregation might precede extracellular plaque formation is accumulating, which increases the relevance of findings indicating that HSPs are able to prevent the initiation of aggregation in cells (Hu et al., 2009; Sakono and Zako, 2010). Although there is no cellular data available at present, these findings might explain why transgenic overexpression of HSPA1 and HSPB1 had protective effects in mouse models for A β (Hoshino et al., 2011; Tóth et al., 2013). However, it is questionable whether A β aggregation was directly affected by HSPA1 overexpression in transgenic mice, or whether the observed protective effects were due to more general compensatory effects of HSPA1 (Hoshino et al., 2011).

Another protein that has been associated with neuronal death in AD is tau. Tau is an unstructured and dynamic protein that is normally involved in stabilization of microtubules, but becomes hyperphosphorylated and detaches from microtubules under

conditions of stress. This detachment results in microtubular collapse and in the aggregation of tau into well-ordered and periodic protein deposits (Götz et al., 2011; Mandelkow and Mandelkow, 2012).

In cells, the HSF-1 activator HSF1A reduced tau aggregation by increasing proteasomal degradation of tau (Opattova et al., 2013). Likewise, Hsp90/HSPC-directed drugs, such as geldanamycin, enhanced clearance of tau from cells, thereby reducing its toxicity (Fig. 2). Moreover, the HSF-1 activator radicicol and the GA derivative 17-AAG alleviated tau toxicity in *Drosophila* larvae (Fig. 2).

Multiple HSPs alleviated tau toxicity in cells, including HSPA8, HSPA1, Hsp90s/HSPC, DNAJA1 and HSPB1 (Fig. 2). In addition, HSPB1 rescued behavioral defects in a mouse model for tauopathy (Abisambra et al., 2010). However, there have been no studies to investigate the role of the other HSPs in mammals to date.

To conclude, interpreting the data about the effects of HSPs on AD needs to be done with great caution for two main reasons. Firstly, it is not yet known whether AD is initiated by intracellular (tau or A β) or extracellular (A β) aggregates. Secondly, although extracellularly added or leaked HSPs might affect toxicity of A β plaques, it is still unclear how intracellular overexpression of HSPs can have direct effects on toxicity in AD. These factors currently limit elucidation of the barcode of HSPs for AD.

Different aggregation diseases have a different HSP barcode

Although all diseases discussed here are toxic gain-of-function aggregation diseases, the barcode of HSPs with protective potential clearly differs depending on the disease (Fig. 2). This variability strongly suggests that the neurodegenerative proteinopathies discussed in this Review are biochemically and biologically distinct. Because all proteinopathies presumably impede on overall protein homeostasis, simply rescuing the overall folding capacity by activation of the complete (acute) HSR (Fig. 1A), or expression of individual components thereof, might lead to some protective effects. However, these effects are generally small and transient, and do not actually affect aggregate formation of the specific diseased proteins themselves. Instead, the effects of the HSR might compensate for entrapment of chaperones and/or other components into aggregates (e.g. certain crucial transcription factors). The underlying toxicity of the aggregates themselves is likely to go beyond these effects on protein homeostasis and will furthermore directly impair other functions, such as axonal transport, organelle dynamics (physical obstruction or cytoskeletal collapse) and membrane integrity. Assuming that aggregation indeed is the reason for toxicity in all these diseases, each proteinopathy requires specific HSPs that either directly prevent aggregation or that recognize early aggregate intermediates and target these for degradation. These HSPs are likely to be found among the 'non-canonical HSPs', many of which have not yet been fully explored for each of these diseases.

Chaperonopathy: the case of 'sick' HSPs

So far, we have highlighted how HSPs might act as a first line of defense in preventing proteinopathies. Sometimes, however, HSPs themselves are mutated, leading to pathological conditions termed chaperonopathies (Macario and Conway de Macario, 2002; Macario et al., 2005; Macario and Conway de Macario, 2007). Although the term 'chaperonopathy' was initially used to include any condition associated with putative alteration in the expression, post-translational modification or localization of chaperones, this Review will only discuss those diseases in which genetically inherited mutations in the HSPs are the direct causative factor (Table 1).

Members of the HSPB, DNAJ and chaperonin families as well as some chaperone cofactors have been implicated in the genetic chaperonopathies described so far (Table 1). No genetic chaperonopathies are associated with the Hsp70/HSPA or Hsp90/HSPC family members, either because of functional redundancy within these families or because they are crucial to the central chaperone machinery such that mutations leading to functional defects are incompatible with life.

Clinically, genetic chaperonopathies can be categorized into neuropathies [hereditary spastic paraplegia, motor neuropathy, distal hereditary motor neuropathy (dHMN)], myopathies (dilated cardiomyopathy, leukodystrophy, desmin-related myopathy, mitochondrial myopathy, muscular dystrophy) or retina- and eye-lens-related diseases (congenital cataracts) (Macario et al., 2005). Although some chaperonopathies are recessive (and thus probably related to loss of function of the chaperone), most were found to be dominant, as is especially the case for the HSPBs (Table 1). We have labeled or 'barcoded' these HSP-associated chaperonopathies depending on the type of disease and mode of inheritance (Fig. 3).

Hsp60/HSPD- and TRiC/CCT-related chaperonopathies

A mutation in the Hsp60/HSPD chaperone system has been linked to an autosomal-dominant disease known as hereditary spastic paraplegia 13 (SPG13). The disease is characterized by spasticity of lower limbs due to massive degeneration of distal ends of long axons in the spinal cord. The mutation leads to reduced chaperonin activity, which has been attributed to haploid insufficiency due to incorporation of functionally deficient Hsp60/HSPD subunits (Bross et al., 2008; Hansen et al., 2002). Another chaperonopathy involving Hsp60/HSPD is the recessive mitCHAP-60 disease, associated with psychomotor developmental delay, in which mutations lead to entropic destabilization of the Hsp60/HSPD oligomer and cause its premature disassembly. This renders Hsp60/HSPD incapable of fulfilling its normal function, resulting in disease (Parnas et al., 2009).

The Hsp60/HSPD complex resides in mitochondria; however, a comparable eukaryotic chaperonin system known as TRiC (also known as CCT) is present in the cytosol and is mainly involved in tubulin and actin folding. Mutations in TRiC subunits might affect its complex formation and thereby its ability to bind and fold tubulin and actin. Because cytoskeletal integrity is crucial in axonal transport, this might explain why such mutants primarily affect functionality of long axons, thus leading to sensory neuropathies (Lee et al., 2003).

DNAJ-related chaperonopathies

There are four recessive chaperonopathies associated with members of the DNAJ family (Table 1). The first one involves a DNAJB2 splice mutation that causes dHMN, characterized by muscle weakness of the extremities as a consequence of progressive degeneration of motor neurons in the spinal cord (Blumen et al., 2012). DNAJB2 has several clients and possesses degradation-related functions (Chapple et al., 2004; Westhoff et al., 2005). The DNAJB2 mutant is unable to handle its natural clients, which therefore eventually aggregate and form intracellular inclusions (Blumen et al., 2012).

The second recessive disease caused by mutations in a member of the DNAJ family involves DNAJC29. Mutations in DNAJC29 lead to cerebellar ataxia with peripheral neuropathy, which is referred to as ARSACS. The disease is characterized by dysarthria, distal muscle wasting, foot deformities and truncal ataxia, including the absence of sensory evoked potentials in the lower

Table 1. Chaperonopathies

Family	Mutation	Inheritance	Disease	Chaperone-mediated rescue	References
Hsp60/HSPD					
SPG13	V72I in SPG13; chromosome 2q33.1; c.292G > A/p.V98I	Dominant	Hereditary spastic paraplegia	NV	Bross et al., 2008; Hansen et al., 2002
mitHSP60	D29G	Recessive	Hypomyelinating leukodystrophies (HMLs); MitCHAP-60 disease	NV	Magen et al., 2008
CCT/TRiC					
CCT γ /MKKS	20p12 in <i>MKKS</i> gene; H84Y, A242S	Recessive	McKusick-Kaufman syndrome (MKS)	NV	Stone et al., 2000
CCT/MKKS	<i>MKKS</i> locus BBS6, BBS10, BBS12	Recessive	Bardet- Biedel Syndrome (BBS)	NV	Stone et al., 2000; Katsanis et al., 2000; Slavotinek et al., 2000; Stoetzel et al., 2007
CCT delta/MKKS	C450Y in CCT delta	Recessive	Hereditary sensory neuropathy (HSN); Charcot-Marie-Tooth (CMT); hereditary motor and sensory neuropathy (HMSN)	NV	Lee et al., 2003
Hsp40/DNAJ					
DNAJB2 (HSJ1)	Splice mutation in <i>HSJ1</i> gene	Recessive	Distal hereditary motor neuropathy (dHMN)	NV	Blumen et al., 2012
DNAJB6	F93L, F89I, P96R	Dominant	Limb-girdle muscular dystrophy type 1D (LGMD1D)	NV	Sarparanta et al., 2012; Harms et al., 2012
DNAJC5	c.346_348 delCTC, c.344T>G; p.Leu116del, p.Leu115Arg	Dominant	Autosomal-dominant adult-onset neuronal ceroid lipofuscinosis (ANCL; also known as Kufs disease)	NV	Noskova et al., 2011; Velinov et al., 2012; Cadieux-Dion et al., 2013
DNAJC6	p.Q734X; c.801-2 A->G	Recessive	Juvenile Parkinsonism	NV	Edvardson et al., 2012; Koroğlu et al., 2013
DNAJC19	IVS3-1GRC; c.300delA	Recessive	Dilated cardiomyopathy with ataxia (DCMA)	NV	Davey et al., 2006; Ojala et al., 2012
DNAJC29	c.3484 G>T, p.E1162X; c.11,707C>T, p.R 3903X in <i>SACS</i> ; T3702A	Recessive	Spastic ataxia of Charlevoix-Saguenay (ARSACS)	NV	Bouchard et al., 1998; Engert et al., 2000; Bouhhal et al., 2011; Gregianin et al., 2013
Small Hsp/HSPB					
HspB1	P39L, G34R, E41K, G84R, L99M, R127W, S135F, R136W, R140G, K141Q, T151I, S156Y, T164A, T180I, P182L, R188W, 476_477delCT, p.Gln175X	Dominant; recessive (L99M)	Williams syndrome; Charcot-Marie-Tooth disease 2 (CMT2); distal hereditary motor neuropathy (dHMN)	HspB-mediated rescue for P182L mutation*	*(Carra et al., 2010); Boncoraglio et al., 2012; Datskevich et al., 2012
HspB3	R7S	Recessive	Motor neuropathy (MN)	NV	Kolb et al., 2010
HspB4	W9X, R12C, R21L, R49C, R54C, F71L, G98R, R116C	Dominant; recessive (W9X)	Autosomal-dominant congenital cataract (ADCC)	NV	Boncoraglio et al., 2012
HspB5	R11H, P20S, 450delA, R69C, D109H, D140N, A171T, R56W, c.343delT, R120G, Q151X, G154S, R157H, 464delCT	Dominant; recessive (R56W)	Congenital cataract; myofibrillar myopathy; dilated cardiomyopathy; desmin-related myopathy	HSPB1-, BAG3-, HSPB8-mediated rescue**	Boncoraglio et al., 2012; ** (Zhang et al., 2010; Hishiya et al., 2011; Raju and Abraham, 2013)
HspB8	K141E, K141N, K141T	Dominant	Distal hereditary motor neuropathy (dHMN); Charcot-Marie-Tooth disease 2 (CMT2)	NV	Irobi et al., 2004; Tang et al., 2005; Nakhro et al., 2013

NV, not verified.

limbs (Bouchard et al., 1998). Although the normal function of DNAJC29 is not well understood, roles in mitochondrial dynamics and in recruitment of HSPA for the mediation of ataxin-1 degradation have been suggested (Parfitt et al., 2009; Girard et al., 2012). In line with this, a recently identified ARSACS-causing mutation (T3702A) resides in the ubiquitin-binding domain of this

protein (Gregianin et al., 2013). However, mutations outside this domain can also lead to disease, so the loss-of-function mechanism remains unclear.

Mutations in DNAJC19 have been identified to cause an autosomal-recessive cardiomyopathy (Davey et al., 2006; Ojala et al., 2012). DNAJC19 normally plays a crucial role in mitochondrial

Family	Members	Neuropathy				Myopathy				Retina-related disease	
		h-SP	dHMN	MN	CMT2	DCM	MFM	LD	MD	CC	DT
Hsp90/HSPC											
Hsp70/HSPA											
Hsp60/HSPD	SPG13										
	mitHsp60										
CCT/Tric	gamma										
	CCT/Tric										
	delta										
Hsp40/DNAJ	DNAJB2										
	DNAJB6										
	DNAJC5										
	DNAJC19										
	DNAJC29										
Small Hsp/HSPB	HSPB1										
	HSPB3										
	HSPB4										
	HSPB5										
	HSPB8										

Fig. 3. Overview of chaperonopathies caused by mutations in HSPs. Mutations that lead to either recessive (white boxes) or dominant (black boxes) chaperonopathies have been described for six 'families' of HSP. Each chaperonopathy is categorized as a neuropathy, myopathy or retina-related disease (cataracts). The mutations in HSPs involved in both recessive and dominant diseases have been shaded gray. h-SP, hereditary-spastic paraplegia; dHMN, distal hereditary motor neuropathy; MN, motor neuropathy; CMT2, Charcot-Marie-Tooth disease 2; DCM, dilated cardiomyopathy; MFM, myofibrillar myopathy; LD, leukodystrophy; MD, muscular dystrophy; CC, congenital cataract; DT, dystrophy.

import (Mokranjac et al., 2003), implying that mitochondrial defects underlie the disease.

More recently, mutations in DNAJC6 were found to be associated with juvenile-onset Parkinsonism (Edvardson et al., 2012; Köroğlu et al., 2013). DNAJC6 (also known as auxilin) is a neuron-specific protein that assists Hsc70/HSPA8 in mediating clathrin-coated-vesicle disassembly and thus plays a role in synaptic-vesicle recycling (Ungewickell et al., 1995; Xing et al., 2010). Mutations in DNAJC6 are predicted to lead to a truncated version of the protein, which fails to support Hsc70/HSPA8 in its normal function.

In addition to these recessive diseases, two DNAJ-related chaperonopathies are dominantly inherited (Table 1) and could cause disease either through haploinsufficiency, by dominant-negative effects or via a toxic gain of function. Mutations in DNAJB6, all of which map to a glycine-phenylalanine-rich region, are associated with limb-girdle muscular dystrophy type 1D (LGMD1D). The molecular mechanism underlying the disease has been suggested to involve loss of function resulting in protein accumulations and autophagic pathology in muscle fibers (Harms et al., 2012; Sarparanta et al., 2012). This reduced chaperone function might be due to haploinsufficiency but, because DNAJB6 is present in cells as polydispersed complexes, mutants might also exert dominant-negative effects on the wild-type protein.

Mutations in DNAJC5 cause an autosomal-dominant neurodegenerative disease, named Kufs disease or adult-onset neuronal ceroid lipofuscinosis. Clinical symptoms include dementia, ataxia and speech impairments that worsen over time. Normally, DNAJC5 is found in synaptic vesicles, where it is involved in polymerization of dynamin (Zhang et al., 2012). Dysfunction of DNAJC5 owing to mutations at a crucial lysine position leads to its reduced palmitoylation and hence abnormal sorting and localization of DNAJC5, which colocalized ER and Golgi markers (Nosková et al., 2011). This leads to decreased levels of DNAJC5 in the brain of diseased individuals, meaning that the disease is most likely caused by haploinsufficiency.

HSPB-related chaperonopathies

Mutations in several members of the HSPB family, irrespective of the member involved, are found in highly conserved amino acid residues or in the α -crystallin domain, which is a characteristic feature of this family of HSPs (Boncoraglio et al., 2012). The α -crystallin domain is required for intra/intermolecular interactions and the stabilization of homo- and hetero-oligomer formations of the HSPB members. Because HSPBs are highly expressed in muscles and have a role in cytoskeleton stability (Tessier et al., 2003; Kampinga and Garrido, 2012), mutations usually affect cellular axonal transport (neurological and sensory disorders) and contractile functions (muscular disorders).

The presence of many of the dominant HSPB mutants in protein aggregates implies that they might have acquired a toxic gain of function similar to the proteins in proteinopathies (Fig. 2). There is indeed biochemical evidence that some mutants, such as the P182L mutant of HSPB1 (Ackerley et al., 2006), R49C and R116C of HSPB4 (Andley et al., 2002; Mackay et al., 2003), and R120G, Q151X and 464delCt of HSPB5 (Bova et al., 1999; Perng et al., 2004; Hayes et al., 2008) are intrinsically unstable and might thus cause disease by forming aggregates (toxic gain of function). However, it must be noted that the presence of HSPBs in aggregates could also be due to a loss of function, reflecting their failed attempt to handle a client with which they subsequently co-aggregate.

Evidence for haploinsufficiency, at least for HSPB1 mutations, is suggested by findings implying that reduced levels of HSPB1 lead to damage in sensory and motor neurons that can be rescued by ectopic expression of HSPB1 (Lewis et al., 1999; Boncoraglio et al., 2012). Partial evidence for haploinsufficiency has also been provided for HSPB8 mutants, which have lost the HSPB8 chaperone-like activity to deal with aggregation-prone polyQ proteins, resulting in Charcot-Marie-Tooth disease (Carra et al., 2008).

Moreover, considering that HSPBs are known to form oligomers with other members of the same family, it is possible that HSPB

mutants could affect the function of other HSPBs via dominant-negative effects. For example, HSPB8 mutants have an abnormally high affinity for endogenous HSPB1, thus potentially impairing HSPB1 or HSPB1-HSPB8 complex function (Irobi et al., 2004). Similarly, certain HSPB1 mutants affect endogenous HSPB8, leading to loss of HSPB8-HSPB1 complex formation (Fontaine et al., 2006). Furthermore, abnormal interaction of the R116C-HSPB4 mutant with HSPB5 and HSPB1 has been reported (Fu and Liang, 2002; Fu and Liang, 2003).

Therefore, not only a toxic gain of function (aggregation) might be responsible for HSPB-related chaperonopathies, but also a loss of function, which could either be direct, due to the mutation, or indirect, due to sequestration of wild-type HSPBs by the mutated HSPB forms. In addition, alteration of HSPB oligomerization properties and interactions with other HSPB members and/or haploinsufficiency might play a role in HSPB-related chaperonopathies.

Chaperone intervention to rescue chaperonopathies

Different HSPs have a role in anti-aggregation of various proteinopathies (Fig. 2). However, whether other HSPs might be able to rescue chaperonopathies has been scarcely studied. A few reports suggest that this could indeed be possible. Firstly, aggregation caused by some HSPB5 mutants is prevented by overexpression of wild-type HSPB1 (Zhang et al., 2010; Raju and Abraham, 2013), BAG3 (Hishiya et al., 2011) and wild-type HSPB8 (Chávez Zobel et al., 2003). Secondly, aggregation associated with the expression of the P182L-HSPB1 mutant in cell models was significantly reduced by the overexpression of wild-type HSPB8 (Carra et al., 2010). Whether such rescues are due to prevention of the formation of toxic aggregates containing mutant HSPB or whether they reflect compensation of loss of HSPB functions remains to be elucidated.

Conclusions and future perspectives

The existence of different ‘barcodes’ for the rescue of specific aggregation diseases suggests that, although loss of protein homeostasis with aging might contribute to disease initiation (e.g. by HSF-1 abrogation, restoring general protein homeostasis or components thereof), boosting HSF-1 activity is usually insufficient for long-term protection in most dominantly inherited proteinopathies. Chronic expression of these aggregation-prone proteins in fact often does not trigger activation of the HSR until late in disease. By then, aggregates might have already sequestered chaperones and thereby disturbed normal protein homeostasis, resulting in cell death. In earlier stages of disease, protein aggregates could already affect neuronal and muscular cell function (even without causing cell death) by altering functions such as axonal transport, organelle dynamics and plasma-membrane-receptor function, without directly impairing protein homeostasis. It has been shown in several mouse models for HD that reversible functional impairments precede neuronal cell loss (Yamamoto et al., 2000). However, in cellular and simple animal models, such functional defects could be missed, and cell-death-related effects (including disturbances in protein homeostasis) might prevail, which would explain the observed rescue by the activation of the HSR or by the overexpression of its individual components. However, these HSR-related effects usually do not coincide with aggregate prevention and therefore do not lead to significant long-term effects in mammalian animal models.

The human genome encodes many HSP members that are not regulated by the acute HSR. Although not yet studied intensively,

our review clearly shows that some of these ‘non-canonical’ members can specifically rescue aggregation caused by the distinct proteinopathies, some of which have now also been demonstrated to be effective in mouse models. Interestingly, several of these non-canonical HSPs also cause chaperonopathies if mutated (DNAJB2, DNAJB6, HSPB8). This not only indicates that these HSPs have essential PQC functions, but also suggests that their effects on proteinopathies might not be an artifact of their overexpression, but rather reflect an augmentation of their natural function.

A potential worry in all HSP-overexpression or -boosting studies is that it leads to network adaptations (which would annihilate long-term effectiveness) or to multiple side effects, including enhancement of carcinogenesis, as was demonstrated for the manipulation of HSF-1 activity (Mendillo et al., 2012). Although network adaptations are to be expected upon manipulation of the driving forces of chaperone machinery (e.g. Hsp90/HSPC or Hsp70/HSPA), such effects might be less likely for those components that only steer the specificity of these machines (e.g. HSPBs or DNAJs). Although we found no evidence for effects of DNAJB6 on the chaperone network (our unpublished results), it remains important to further investigate whether long-term overexpression of DNAJB6 or other proteinopathy-rescuing HSPs might have side effects.

Finally, only limited comparative data on the potential rescue of the non-HSR-regulated HSPs and the various proteinopathies or chaperonopathies are available. There still might be many currently unknown suppressors of specific diseases to be uncovered, which would further barcode these diseases. This would not only help to pinpoint therapeutic targets for intervention, but would also help with understanding differences and similarities between the toxic mechanisms underlying the various proteinopathies.

This article is part of a review series on protein-folding diseases. See related articles at <http://dmm.biologists.org/site/protein-folding-disease.xhtml>.

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Competing interests

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References

- Abisambra, J. F., Blair, L. J., Hill, S. E., Jones, J. R., Kraft, C., Rogers, J., Koren, J., 3rd, Jinwal, U. K., Lawson, L., Johnson, A. G. et al. (2010). Phosphorylation dynamics regulate Hsp27-mediated rescue of neuronal plasticity deficits in tau transgenic mice. *J. Neurosci.* **30**, 15374-15382.
- Abisambra, J. F., Jinwal, U. K., Suntharalingam, A., Arulselvam, K., Brady, S., Cockman, M., Jin, Y., Zhang, B. and Dickey, C. A. (2012). DnaJA1 antagonizes constitutive Hsp70-mediated stabilization of tau. *J. Mol. Biol.* **421**, 653-661.
- Ackerley, S., James, P. A., Kalli, A., French, S., Davies, K. E. and Talbot, K. (2006). A mutation in the small heat-shock protein HSPB1 leading to distal hereditary motor neuropathy disrupts neurofilament assembly and the axonal transport of specific cellular cargoes. *Hum. Mol. Genet.* **15**, 347-354.
- Adachi, H., Katsuno, M., Minamiyama, M., Sang, C., Pagoulatos, G., Angelidis, C., Kusakabe, M., Yoshiki, A., Kobayashi, Y., Doyu, M. et al. (2003). Heat shock protein 70 chaperone overexpression ameliorates phenotypes of the spinal and bulbar muscular atrophy transgenic mouse model by reducing nuclear-localized mutant androgen receptor protein. *J. Neurosci.* **23**, 2203-2211.
- Agrawal, N., Pallos, J., Slepko, N., Apostol, B. L., Bodai, L., Chang, L. W., Chiang, A. S., Thompson, L. M. and Marsh, J. L. (2005). Identification of combinatorial drug regimens for treatment of Huntington's disease using *Drosophila*. *Proc. Natl. Acad. Sci. USA* **102**, 3777-3781.
- Al-Chalabi, A., Jones, A., Troakes, C., King, A., Al-Sarraj, S. and van den Berg, L. H. (2012). The genetics and neuropathology of amyotrophic lateral sclerosis. *Acta Neuropathol.* **124**, 339-352.

- Albanèse, V., Yam, A. Y., Baughman, J., Parnot, C. and Frydman, J. (2006). Systems analyses reveal two chaperone networks with distinct functions in eukaryotic cells. *Cell* **124**, 75-88.
- Almeida, M. B., do Nascimento, J. L. M., Herculano, A. M. and Crespo-López, M. E. (2011). Molecular chaperones: toward new therapeutic tools. *Biomed. Pharmacother.* **65**, 239-243.
- Andersen, P. M. and Al-Chalabi, A. (2011). Clinical genetics of amyotrophic lateral sclerosis: what do we really know? *Nat. Rev. Neurol.* **7**, 603-615.
- Andley, U. P., Patel, H. C. and Xi, J. H. (2002). The R116C mutation in α -crystallin diminishes its protective ability against stress-induced lens epithelial cell apoptosis. *J. Biol. Chem.* **277**, 10178-10186.
- Ansar, S., Burlison, J. A., Hadden, M. K., Yu, X. M., Desino, K. E., Bean, J., Neckers, L., Audus, K. L., Michaelis, M. L. and Blagg, B. S. J. (2007). A non-toxic Hsp90 inhibitor protects neurons from A β -induced toxicity. *Bioorg. Med. Chem. Lett.* **17**, 1984-1990.
- Aridon, P., Geraci, F., Turturici, G., D'Amelio, M., Savettieri, G. and Sconzo, G. (2011). Protective role of heat shock proteins in Parkinson's disease. *Neurodegener. Dis.* **8**, 155-168.
- Auluck, P. K. and Bonini, N. M. (2002). Pharmacological prevention of Parkinson disease in Drosophila. *Nat. Med.* **8**, 1185-1186.
- Auluck, P. K., Chan, H. Y. E., Trojanowski, J. Q., Lee, V. M.-Y. and Bonini, N. M. (2002). First demonstration of Hsp70's neuroprotective effect in a drosophila model of Parkinson's disease. *Drosophila. Nat. Med.* **8**, 1185-1186.
- Auluck, P. K., Meulener, M. C. and Bonini, N. M. (2005). Protein synthesis, post-translation modification, and degradation: Mechanisms of suppression of α -synuclein neurotoxicity by Geldanamycin in Drosophila. *J. Biol. Chem.* **280**, 2873-2878.
- Balch, W. E., Morimoto, R. I., Dillin, A. and Kelly, J. W. (2008). Adapting proteostasis for disease intervention. *Science* **319**, 916-919.
- Baldo, B., Weiss, A., Parker, C. N., Bibel, M., Paganetti, P. and Kaupmann, K. (2012). A screen for enhancers of clearance identifies huntingtin as a heat shock protein 90 (Hsp90) client protein. *J. Biol. Chem.* **287**, 1406-1414.
- Banno, H., Katsuno, M., Suzuki, K., Tanaka, F. and Sobue, G. (2012). Pathogenesis and molecular targeted therapy of spinal and bulbar muscular atrophy (SBMA). *Cell Tissue Res.* **349**, 313-320.
- Batulan, Z., Taylor, D. M., Aarons, R. J., Minotti, S., Doroudchi, M. M., Nalbantoglu, J. and Durham, H. D. (2006). Induction of multiple heat shock proteins and neuroprotection in a primary culture model of familial amyotrophic lateral sclerosis. *Neurobiol. Dis.* **24**, 213-225.
- Bauer, P. O., Goswami, A., Wong, H. K., Okuno, M., Kurosawa, M., Yamada, M., Miyazaki, H., Matsumoto, G., Kino, Y., Nagai, Y. et al. (2010). Harnessing chaperone-mediated autophagy for the selective degradation of mutant huntingtin protein. *Nat. Biotechnol.* **28**, 256-263.
- Behrends, C., Langer, C. A., Boteva, R., Böttcher, U. M., Stemp, M. J., Schaffar, G., Rao, B. V., Giese, A., Kretschmar, H., Siegers, K. et al. (2006). Chaperonin TRiC promotes the assembly of polyQ expansion proteins into nontoxic oligomers. *Mol. Cell* **23**, 887-897.
- Blumen, S. C., Astord, S., Robin, V., Vignaud, L., Toumi, N., Cieslik, A., Achiron, A., Carasso, R. L., Gurevich, M., Braverman, I. et al. (2012). A rare recessive distal hereditary motor neuropathy with HSP70 chaperone mutation. *Ann. Neurol.* **71**, 509-519.
- Boillée, S., Vande Velde, C. and Cleveland, D. W. (2006). ALS: a disease of motor neurons and their nonneuronal neighbors. *Neuron* **52**, 39-59.
- Boncoraglio, A., Minoia, M. and Carra, S. (2012). The family of mammalian small heat shock proteins (HSPBs): implications in protein deposit diseases and motor neuropathies. *Int. J. Biochem. Cell Biol.* **44**, 1657-1669.
- Bouchard, J. P., Richter, A., Mathieu, J., Brunet, D., Hudson, T. J., Morgan, K. and Melançon, S. B. (1998). Autosomal recessive spastic ataxia of Charlevoix-Saguenay. *Neuromuscul. Disord.* **8**, 474-479.
- Bouhail, Y., Amouri, R., El Euch-Fayeche, G. and Hentati, F. (2011). Autosomal recessive spastic ataxia of Charlevoix-Saguenay: an overview. *Parkinsonism Relat. Disord.* **17**, 418-422.
- Bova, M. P., Yaron, O., Huang, Q., Ding, L., Haley, D. A., Stewart, P. L. and Horwitz, J. (1999). Mutation R120G in alphaB-crystallin, which is linked to a desmin-related myopathy, results in an irregular structure and defective chaperone-like function. *Proc. Natl. Acad. Sci. USA* **96**, 6137-6142.
- Bross, P., Naundrup, S., Hansen, J., Nielsen, M. N., Christensen, J. H., Kruhøffer, M., Palmfeldt, J., Corydon, T. J., Gregersen, N., Ang, D. et al. (2008). The Hsp60-(p.V98I) mutation associated with hereditary spastic paraplegia SPG13 compromises chaperonin function both in vitro and in vivo. *J. Biol. Chem.* **283**, 15694-15700.
- Bruinsma, I. B., Bruggink, K. A., Kinast, K., Versleijen, A. A., Segers-Nolten, I. M., Subramanian, V., Kuiperij, H. B., Boelens, W., de Waal, R. M. and Verbeek, M. M. (2011). Inhibition of α -synuclein aggregation by small heat shock proteins. *Proteins* **79**, 2956-2967.
- Buchner, J. (1999). Hsp90 and Co. - a holding for folding. *Trends Biochem. Sci.* **24**, 136-141.
- Bukau, B., Deuerling, E., Pfund, C. and Craig, E. A. (2000). Getting newly synthesized proteins into shape. *Cell* **101**, 119-122.
- Cadioux-Dion, M., Andermann, E., Lachance-Touchette, P., Ansoorge, O., Meloche, C., Barnabé, A., Kuzniecky, R. I., Andermann, F., Faught, E., Leonberg, S. et al. (2013). Recurrent mutations in DNAJC5 cause autosomal dominant Kufs disease. *Clin. Genet.* **83**, 571-575.
- Carnini, A., Scott, L. O., Ahrendt, E., Proft, J., Winkfein, R. J., Kim, S. W., Colicos, M. A. and Braun, J. E. A. (2012). Cell line specific modulation of extracellular α 42 by Hsp40. *PLoS ONE* **7**, e37755.
- Carra, S. and Landry, J. (2006). Small heat shock proteins in neurodegenerative diseases. In *Heat Shock Proteins in Biology and Medicine*, (ed. J. Radons and G. Multhoff), pp. 331-351. Kerala, India: Research Signpost.
- Carra, S., Seguin, S. J., Lambert, H. and Landry, J. (2008). HspB8 chaperone activity toward poly(Q)-containing proteins depends on its association with Bag3, a stimulator of macroautophagy. *J. Biol. Chem.* **283**, 1437-1444.
- Carra, S., Boncoraglio, A., Kanon, B., Brunsting, J. F., Minoia, M., Rana, A., Vos, M. J., Seidel, K., Sibon, O. C. M. and Kampinga, H. H. (2010). Identification of the Drosophila ortholog of HSPB8: implication of HSPB8 loss of function in protein folding diseases. *J. Biol. Chem.* **285**, 37811-37822.
- Chai, Y., Koppenhafer, S. L., Bonini, N. M. and Paulson, H. L. (1999). Analysis of the role of heat shock protein (Hsp) molecular chaperones in polyglutamine disease. *J. Neurosci.* **19**, 10338-10347.
- Chan, H. Y. E., Warrick, J. M., Gray-Board, G. L., Paulson, H. L. and Bonini, N. M. (2000). Mechanisms of chaperone suppression of polyglutamine disease: selectivity, synergy and modulation of protein solubility in Drosophila. *Hum. Mol. Genet.* **9**, 2811-2820.
- Chan, H. Y. E., Warrick, J. M., Andriola, I., Merry, D. and Bonini, N. M. (2002). Genetic modulation of polyglutamine toxicity by protein conjugation pathways in Drosophila. *Hum. Mol. Genet.* **11**, 2895-2904.
- Chanoux, R. A. and Rubenstein, R. C. (2012). Molecular chaperones as targets to circumvent the CFTR defect in cystic fibrosis. *Front Pharmacol.* **3**, 137.
- Chapple, J. P., van der Spuy, J., Poopalasundaram, S. and Cheetham, M. E. (2004). Neuronal DnaJ proteins HSP11a and HSP11b: a role in linking the Hsp70 chaperone machine to the ubiquitin-proteasome system? *Biochem. Soc. Trans.* **32**, 640-642.
- Chávez Zobel, A. T. C., Loranger, A., Marceau, N., Thériault, J. R., Lambert, H. and Landry, J. (2003). Distinct chaperone mechanisms can delay the formation of aggregates by the myopathy-causing R120G alphaB-crystallin mutant. *Hum. Mol. Genet.* **12**, 1609-1620.
- Chiti, F. and Dobson, C. M. (2006). Protein misfolding, functional amyloid, and human disease. *Annu. Rev. Biochem.* **75**, 333-366.
- Chiti, F. and Dobson, C. M. (2009). Amyloid formation by globular proteins under native conditions. *Nat. Chem. Biol.* **5**, 15-22.
- Ciechanover, A. and Brundin, P. (2003). The ubiquitin proteasome system: Sometimes the chicken, sometimes the egg. *Neuron* **40**, 427-446.
- Cummings, C. J., Sun, Y., Opal, P., Antalfy, B., Mestri, R., Orr, H. T., Dillmann, W. H. and Zoghbi, H. Y. (2001). Over-expression of inducible HSP70 chaperone suppresses neuropathology and improves motor function in SCA1 mice. *Hum. Mol. Genet.* **10**, 1511-1518.
- Danzer, K. M., Ruf, W. P., Putcha, P., Joyner, D., Hashimoto, T., Glabe, C., Hyman, B. T. and McLeary, P. J. (2011). Heat-shock protein 70 modulates toxic extracellular α -synuclein oligomers and rescues trans-synaptic toxicity. *FASEB J.* **25**, 326-336.
- Datskevich, P. N., Nefedova, V. V., Sudnitsyna, M. V. and Gusev, N. B. (2012). Mutations of small heat shock proteins and human congenital diseases. *Biochemistry* **77**, 1500-1514.
- Davey, K. M., Parboosingh, J. S., McLeod, D. R., Chan, A., Casey, R., Ferreira, P., Snyder, F. F., Bridge, P. J. and Bernier, F. P. (2006). Mutation of DNAJC19, a human homologue of yeast inner mitochondrial membrane co-chaperones, causes DCMA syndrome, a novel autosomal recessive Barth syndrome-like condition. *J. Med. Genet.* **43**, 385-393.
- Dickey, C. A., Dunmore, J., Lu, B., Wang, J. W., Lee, W. C., Kamal, A., Burrows, F., Eckman, C., Hutton, M. and Petrucelli, L. (2006). HSP induction mediates selective clearance of tau phosphorylated at proline-directed Ser/Thr sites but not KXGS (MARK) sites. *FASEB J.* **20**, 753-755.
- Dou, F., Netzer, W. J., Tanemura, K., Li, F., Hartl, F. U., Takashima, A., Gouras, G. K., Greengard, P. and Xu, H. (2003). Chaperones increase association of tau protein with microtubules. *Proc. Natl. Acad. Sci. USA* **100**, 721-726.
- Edvardsson, S., Cinnamon, Y., Ta-Shma, A., Shaag, A., Yim, Y. I., Zenvirt, S., Jalas, C., Lesage, S., Brice, A., Taraboulos, A. et al. (2012). A deleterious mutation in DNAJC6 encoding the neuronal-specific clathrin-uncoating co-chaperone auxilin, is associated with juvenile parkinsonism. *PLoS ONE* **7**, e36458.
- Ellis, R. J. and Hartl, F. U. (1999). Principles of protein folding in the cellular environment. *Curr. Opin. Struct. Biol.* **9**, 102-110.
- Engert, J. C., Bérubé, P., Mercier, J., Doré, C., Lepage, P., Ge, B., Bouchard, J. P., Mathieu, J., Melançon, S. B., Schalling, M. et al. (2000). ARSACS, a spastic ataxia common in northeastern Québec, is caused by mutations in a new gene encoding an 11.5-kb ORF. *Nat. Genet.* **24**, 120-125.
- Estes, P. S., Boehringer, A., Zwick, R., Tang, J. E., Grigsby, B. and Zarnescu, D. C. (2011). Wild-type and A315T mutant TDP-43 exert differential neurotoxicity in a Drosophila model of ALS. *Hum. Mol. Genet.* **20**, 2308-2321.
- Evans, C. G., Wisén, S. and Gestwicki, J. E. (2006). Heat shock proteins 70 and 90 inhibit early stages of amyloid β -(1-42) aggregation in vitro. *J. Biol. Chem.* **281**, 33182-33191.
- Fan, J. Q., Ishii, S., Asano, N. and Suzuki, Y. (1999). Accelerated transport and maturation of lysosomal alpha-galactosidase A in Fabry lymphoblasts by an enzyme inhibitor. *Nat. Med.* **5**, 112-115.
- Fliss, A. E., Rao, J., Melville, M. W., Cheetham, M. E. and Caplan, A. J. (1999). Domain requirements of DnaJ-like (Hsp40) molecular chaperones in the activation of a steroid hormone receptor. *J. Biol. Chem.* **274**, 34045-34052.
- Fontaine, J.-M., Sun, X., Hoppe, A. D., Simon, S., Vicart, P., Welsh, M. J. and Benndorf, R. (2006). Abnormal small heat shock protein interactions involving neuropathy-associated HSP22 (HSPB8) mutants. *FASEB J.* **20**, 2168-2170.
- Fu, L. and Liang, J. J. (2002). Detection of protein-protein interactions among lens crystallins in a mammalian two-hybrid system assay. *J. Biol. Chem.* **277**, 4255-4260.

- Fu, L. and Liang, J. J. (2003). Alteration of protein-protein interactions of congenital cataract crystallin mutants. *Invest. Ophthalmol. Vis. Sci.* **44**, 1155-1159.
- Fujikake, N., Nagai, Y., Popiel, H. A., Okamoto, Y., Yamaguchi, M. and Toda, T. (2008). Heat shock transcription factor 1-activating compounds suppress polyglutamine-induced neurodegeneration through induction of multiple molecular chaperones. *J. Biol. Chem.* **283**, 26188-26197.
- Fujimoto, M., Takaki, E., Hayashi, T., Kitauro, Y., Tanaka, Y., Inouye, S. and Nakai, A. (2005). Active HSF1 significantly suppresses polyglutamine aggregate formation in cellular and mouse models. *J. Biol. Chem.* **280**, 34908-34916.
- Garrido, C., Paul, C., Seignuric, R. and Kampinga, H. H. (2012). The small heat shock proteins family: the long forgotten chaperones. *Int. J. Biochem. Cell Biol.* **44**, 1588-1592.
- Gifondorwa, D. J., Robinson, M. B., Hayes, C. D., Taylor, A. R., Prevette, D. M., Oppenheim, R. W., Caress, J. and Milligan, C. (2007). Exogenous delivery of HSP70 increases lifespan in a mouse model of ALS. *Neurobiol. Dis.* **27**, 13173-13180.
- Gifondorwa, D. J., Jimenez-Moreno, R., Hayes, C. D., Rouhani, H., Robinson, M. B., Strupe, J. L., Caress, J. and Milligan, C. (2012). Administration of recombinant heat shock protein 70 delays peripheral muscle denervation in the SOD1 G93A mouse model of ALS. *Neuro. Res. Int.* **2012**, 170426.
- Gillis, J., Schipper-Krom, S., Juenemann, K., Gruber, A., Coolen, S., van den Nieuwendijk, R., van Veen, H., Overkleef, H., Goedhart, J., Kampinga, H. H. et al. (2013). The DNAJB6 and DNAJB8 protein chaperones prevent intracellular aggregation of polyglutamine peptides. *J. Biol. Chem.* **288**, 17225-17237.
- Girard, M., Larivière, R., Parfitt, D. A., Deane, E. C., Gaudet, R., Nossova, N., Blondeau, F., Prenosil, G., Vermeulen, E. G. M., Duchon, M. R. et al. (2012). Mitochondrial dysfunction and Purkinje cell loss in autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS). *Proc. Natl. Acad. Sci. USA* **109**, 1661-1666.
- Gorbatyuk, M. S., Shabashvili, A., Chen, W., Meyers, C., Sullivan, L. F., Salganik, M., Lin, J. H., Lewin, A. S., Muzyczka, N. and Gorbatyuk, O. S. (2012). Glucose regulated protein 78 diminishes α -synuclein neurotoxicity in a rat model of Parkinson disease. *Mol. Ther.* **20**, 1327-1337.
- Götz, J., Eckert, A., Matamales, M., Ittner, L. M. and Liu, X. (2011). Modes of A β toxicity in Alzheimer's disease. *Cell. Mol. Life Sci.* **68**, 3359-3375.
- Gregianin, E., Vazza, G., Scaramel, E., Boaretto, F., Vettori, A., Leonardi, E., Tosatto, S. C., Manara, R., Pegoraro, E. and Mostacciolo, M. L. (2013). A novel SACS mutation results in non-ataxic spastic paraplegia and peripheral neuropathy. *Eur. J. Neurol.* **20**, 1486-1491.
- Gregory, J. M., Barros, T. P., Meehan, S., Dobson, C. M. and Luheshi, L. M. (2012). The aggregation and neurotoxicity of TDP-43 and its ALS-associated 25 kDa fragment are differentially affected by molecular chaperones in *Drosophila*. *PLoS ONE* **7**, e31899.
- Guerreiro, R. J., Gustafson, D. R. and Hardy, J. (2012). The genetic architecture of Alzheimer's disease: beyond APP, PSENs and APOE. *Neurobiol. Aging* **33**, 437-456.
- Gunawardena, S., Her, L.-S., Bruschi, R. G., Laymon, R. A., Niesman, I. R., Gordesky-Gold, B., Sintasath, L., Bonini, N. M. and Goldstein, L. S. B. (2003). Disruption of axonal transport by loss of huntingtin or expression of pathogenic polyQ proteins in *Drosophila*. *Neuron* **40**, 25-40.
- Gusella, J. F. and MacDonald, M. E. (2000). Molecular genetics: unmasking polyglutamine triggers in neurodegenerative disease. *Nat. Rev. Neurosci.* **1**, 109-115.
- Hageman, J., Rujano, M. A., van Waarde, M. A., Kakkar, V., Dirks, R. P., Govorukhina, N., Oosterveld-Hut, H. M., Lubsen, N. H. and Kampinga, H. H. (2010). A DNAJB chaperone subfamily with HDAC-dependent activities suppresses toxic protein aggregation. *Mol. Cell* **37**, 355-369.
- Hageman, J., van Waarde, M. A. W. H., Zyllicz, A., Walerych, D. and Kampinga, H. H. (2011). The diverse members of the mammalian HSP70 machine show distinct chaperone-like activities. *Biochem. J.* **435**, 127-142.
- Hageman, J., Rujano, M. A., van Waarde, M. A., Kakkar, V., Dirks, R. P., Govorukhina, N., Oosterveld-Hut, H. M., Lubsen, N. H. and Kampinga, H. H. (2012). A DNAJB chaperone subfamily with HDAC-dependent activities suppresses toxic protein aggregation. *Mol. Cell* **37**, 355-369.
- Hansen, J. J., Dürr, A., Courneau-Rebeix, I., Georgopoulos, C., Ang, D., Nielsen, M. N., Davoine, C. S., Brice, A., Fontaine, B., Gregersen, N. et al. (2002). Hereditary spastic paraplegia SPG13 is associated with a mutation in the gene encoding the mitochondrial chaperonin Hsp60. *Am. J. Hum. Genet.* **70**, 1328-1332.
- Hansson, O., Nylandsted, J., Castilho, R. F., Leist, M., Jäättelä, M. and Brundin, P. (2003). Overexpression of heat shock protein 70 in R6/2 Huntington's disease mice has only modest effects on disease progression. *Brain Res.* **970**, 47-57.
- Harms, M. B., Somerville, R. B., Allred, P., Bell, S., Ma, D., Cooper, P., Lopate, G., Pestronk, A., Weihl, C. C. and Baloh, R. H. (2012). Exome sequencing reveals DNAJB6 mutations in dominantly-inherited myopathy. *Ann. Neurol.* **71**, 407-416.
- Hay, D. G., Sathasivam, K., Tobaben, S., Stahl, B., Marber, M., Mestrlil, R., Mahal, A., Smith, D. L., Woodman, B. and Bates, G. P. (2004). Progressive decrease in chaperone protein levels in a mouse model of Huntington's disease and induction of stress proteins as a therapeutic approach. *Hum. Mol. Genet.* **13**, 1389-1405.
- Hayes, V. H., Devlin, G. and Quinlan, R. A. (2008). Truncation of alphaB-crystallin by the myopathy-causing Q151X mutation significantly destabilizes the protein leading to aggregate formation in transfected cells. *J. Biol. Chem.* **283**, 10500-10512.
- Haynes, C. M. and Ron, D. (2010). The mitochondrial UPR - protecting organelle protein homeostasis. *J. Cell Sci.* **123**, 3849-3855.
- Herbst, M. and Wanker, E. E. (2007). Small molecule inducers of heat-shock response reduce polyQ-mediated huntingtin aggregation. A possible therapeutic strategy. *Neurodegener. Dis.* **4**, 254-260.
- Hishiyama, A., Salman, M. N., Carra, S., Kampinga, H. H. and Takayama, S. (2011). BAG3 directly interacts with mutated alphaB-crystallin to suppress its aggregation and toxicity. *PLoS ONE* **6**, e16828.
- Hoshino, T., Murao, N., Namba, T., Takehara, M., Adachi, H., Katsuno, M., Sobue, G., Matsushima, T., Suzuki, T. and Mizushima, T. (2011). Suppression of Alzheimer's disease-related phenotypes by expression of heat shock protein 70 in mice. *J. Neurosci.* **31**, 5225-5234.
- Howarth, J. L., Kelly, S., Keasey, M. P., Glover, C. P. J., Lee, Y. B., Mitrophanous, K., Chapple, J. P., Gallo, J. M., Cheetham, M. E. and Uney, J. B. (2007). Hsp40 molecules that target to the ubiquitin-proteasome system decrease inclusion formation in models of polyglutamine disease. *Mol. Ther.* **15**, 1100-1105.
- Hu, X., Crick, S. L., Bu, G., Frieden, C., Pappu, R. V. and Lee, J.-M. (2009). Amyloid seeds formed by cellular uptake, concentration, and aggregation of the amyloid- β peptide. *Proc. Natl. Acad. Sci. USA* **106**, 20324-20329.
- Irobi, J., Van Impe, K., Seeman, P., Jordanova, A., Dierick, I., Verpoorten, N., Michalik, A., De Vriendt, E., Jacobs, A., Van Gerwen, V. et al. (2004). Hot-spot residue in small heat-shock protein 22 causes distal motor neuropathy. *Nat. Genet.* **36**, 597-601.
- Jana, N. R., Tanaka, M., Wang, G. and Nukina, N. (2000). Polyglutamine length-dependent interaction of Hsp40 and Hsp70 family chaperones with truncated N-terminal huntingtin: their role in suppression of aggregation and cellular toxicity. *Hum. Mol. Genet.* **9**, 2009-2018.
- Jiang, Y., Lv, H., Liao, M., Xu, X., Huang, S., Tan, H., Peng, T., Zhang, Y. and Li, H. (2012). GRP78 counteracts cell death and protein aggregation caused by mutant huntingtin proteins. *Neurosci. Lett.* **516**, 182-187.
- Jiang, Y.-Q., Wang, X.-L., Cao, X. H., Ye, Z. Y., Li, L. and Cai, W.-Q. (2013). Increased heat shock transcription factor 1 in the cerebellum reverses the deficiency of Purkinje cells in Alzheimer's disease. *Brain Res.* **1519**, 105-111.
- Jinwal, U. K., Abisambra, J. F., Zhang, J., Dharja, S., O'Leary, J. C., Patel, T., Braswell, K., Jani, T., Gestwicki, J. E. and Dickey, C. A. (2012). Cdc37/Hsp90 protein complex disruption triggers an autophagic clearance cascade for TDP-43 protein. *J. Biol. Chem.* **287**, 24814-24820.
- Kakkar, V., Prins, L. C. and Kampinga, H. H. (2013). DNAJ proteins and protein aggregation diseases. *Curr. Top. Med. Chem.* **12**, 2479-2490.
- Kalmar, B., Novoselov, S., Gray, A., Cheetham, M. E., Margulis, B. and Greensmith, L. (2008). Late stage treatment with arimoclomol delays disease progression and prevents protein aggregation in the SOD1 mouse model of ALS. *J. Neurochem.* **107**, 339-350.
- Kampinga, H. H. and Craig, E. A. (2010). The HSP70 chaperone machinery: J proteins as drivers of functional specificity. *Nat. Rev. Mol. Cell Biol.* **11**, 579-592.
- Kampinga, H. H. and Garrido, C. (2012). HSPBs: small proteins with big implications in human disease. *Int. J. Biochem. Cell Biol.* **44**, 1706-1710.
- Kampinga, H. H., Hageman, J., Vos, M. J., Kubota, H., Tanguay, R. M., Bruford, E. A., Cheetham, M. E., Chen, B. and Hightower, L. E. (2009). Guidelines for the nomenclature of the human heat shock proteins. *Cell Stress Chaperones* **14**, 105-111.
- Katsanis, N., Beales, P. L., Woods, M. O., Lewis, R. A., Green, J. S., Parfrey, P. S., Ansley, S. J., Davidson, W. S. and Lupski, J. R. (2000). Mutations in MKKS cause obesity, retinal dystrophy and renal malformations associated with Bardet-Biedl syndrome. *Nat. Genet.* **26**, 67-70.
- Katsuno, M., Sang, C., Adachi, H., Minamiyama, M., Waza, M., Tanaka, F., Doyu, M. and Sobue, G. (2005). Pharmacological induction of heat-shock proteins alleviates polyglutamine-mediated motor neuron disease. *Proc. Natl. Acad. Sci. USA* **102**, 16801-16806.
- Kiaei, M., Kipiani, K., Petri, S., Chen, J., Calingasan, N. Y. and Beal, M. F. (2005). Celastrol blocks neuronal cell death and extends life in transgenic mouse model of amyotrophic lateral sclerosis. *Neurodegener. Dis.* **2**, 246-254.
- Kieran, D., Kalmar, B., Dick, J. R. T., Riddoch-Contreras, J., Burnstock, G. and Greensmith, L. (2004). Treatment with arimoclomol, a coinducer of heat shock proteins, delays disease progression in ALS mice. *Nat. Med.* **10**, 402-405.
- Klein, C. and Westerberger, A. (2012). Genetics of Parkinson's disease. *Cold Spring Harb. Perspect. Med.* **2**, a008888.
- Klucen, J., Shin, Y., Masliah, E., Hyman, B. T. and McLean, P. J. (2004). Hsp70 reduces α -synuclein aggregation and toxicity. *J. Biol. Chem.* **279**, 25497-25502.
- Kolb, S. J., Snyder, P. J., Poi, E. J., Renard, E. A., Bartlett, A., Gu, S., Sutton, S., Arnold, W. D., Freimer, M. L., Lawson, V. H. et al. (2010). Mutant small heat shock protein B3 causes motor neuropathy: utility of a candidate gene approach. *Neurology* **74**, 502-506.
- Kondo, N., Katsuno, M., Adachi, H., Minamiyama, M., Doi, H., Matsumoto, S., Miyazaki, Y., Iida, M., Tohna, G., Nakatsuji, H. et al. (2013). Heat shock factor-1 influences pathological lesion distribution of polyglutamine-induced neurodegeneration. *Nat. Commun.* **4**, 1405.
- Köröglu, Ç., Baysal, L., Cetinkaya, M., Karasoy, H. and Tolun, A. (2013). DNAJC6 is responsible for juvenile parkinsonism with phenotypic variability. *Parkinsonism Relat. Disord.* **19**, 320-324.
- Koyama, S., Arawaka, S., Chang-Hong, R., Wada, M., Kawanami, T., Kurita, K., Kato, M., Nagai, M., Aoki, M., Itoyama, Y. et al. (2006). Alteration of familial ALS-linked mutant SOD1 solubility with disease progression: its modulation by the proteasome and Hsp70. *Biochem. Biophys. Res. Commun.* **343**, 719-730.
- Krishnan, J., Vannuvel, K., Andries, M., Waelkens, E., Robberecht, W. and Van Den Bosch, L. (2008). Over-expression of Hsp27 does not influence disease in the mutant SOD1(G93A) mouse model of amyotrophic lateral sclerosis. *J. Neurochem.* **106**, 2170-2183.
- Labbadia, J., Cunliffe, H., Weiss, A., Katsyuba, E., Sathasivam, K., Seredenina, T., Woodman, B., Moussaoui, S., Frentzel, S., Luthi-Carter, R. et al. (2011). Altered

- chromatin architecture underlies progressive impairment of the heat shock response in mouse models of Huntington disease. *J. Clin. Invest.* **121**, 3306-3319.
- Labbadia, J., Novoselov, S. S., Bett, J. S., Weiss, A., Paganetti, P., Bates, G. P. and Cheetham, M. E.** (2012). Suppression of protein aggregation by chaperone modification of high molecular weight complexes. *Brain* **135**, 1180-1196.
- Lee, M. J., Stephenson, D. A., Groves, M. J., Sweeney, M. G., Davis, M. B., An, S.-F., Houlden, H., Salih, M. A. M., Timmerman, V., de Jonghe, P. et al.** (2003). Hereditary sensory neuropathy is caused by a mutation in the delta subunit of the cytosolic chaperonin-containing t-complex peptide-1 (Cct4) gene. *Hum. Mol. Genet.* **12**, 1917-1925.
- Lesage, S. and Brice, A.** (2009). Parkinson's disease: from monogenic forms to genetic susceptibility factors. *Hum. Mol. Genet.* **18** R1, R48-R59.
- Lewis, S. E., Mannion, R. J., White, F. A., Coggeshall, R. E., Beggs, S., Costigan, M., Martin, J. L., Dillmann, W. H. and Woolf, C. J.** (1999). A role for HSP27 in sensory neuron survival. *J. Neurosci.* **19**, 8945-8953.
- Liangliang, X., Yonghui, H., Shunmei, E., Shoufang, G., Wei, Z. and Jiangying, Z.** (2010). Dominant-positive HSF1 decreases α -synuclein level and α -synuclein-induced toxicity. *Mol. Biol. Rep.* **37**, 1875-1881.
- Luheshi, L. M. and Dobson, C. M.** (2009). Bridging the gap: from protein misfolding to protein misfolding diseases. *FEBS Lett.* **583**, 2581-2586.
- Macario, A. J. L. and Conway de Macario, E.** (2002). Sick chaperones and ageing: a perspective. *Ageing Res. Rev.* **1**, 295-311.
- Macario, A. J. L. and Conway de Macario, E.** (2007). Chaperonopathies and chaperonotherapy. *FEBS Lett.* **581**, 3681-3688.
- Macario, A. J. L., Grippo, T. M. and Conway de Macario, E.** (2005). Genetic disorders involving molecular-chaperone genes: a perspective. *Genet. Med.* **7**, 3-12.
- Mackay, D. S., Andley, U. P. and Shiels, A.** (2003). Cell death triggered by a novel mutation in the alphaA-crystallin gene underlies autosomal dominant cataract linked to chromosome 21q. *Eur. J. Hum. Genet.* **11**, 784-793.
- Magen, D., Georgopoulos, C., Bross, P., Ang, D., Segev, Y., Goldsher, D., Nemirovski, A., Shahar, E., Ravid, S., Luder, A. et al.** (2008). Mitochondrial hsp60 chaperonopathy causes an autosomal-recessive neurodegenerative disorder linked to brain hypomyelination and leukodystrophy. *Am. J. Hum. Genet.* **83**, 30-42.
- Malik, B., Nirmalanathan, N., Gray, A. L., La Spada, A. R., Hanna, M. G. and Greensmith, L.** (2013). Co-induction of the heat shock response ameliorates disease progression in a mouse model of human spinal and bulbar muscular atrophy: implications for therapy. *Brain* **136**, 926-943.
- Mandelkow, E.-M. and Mandelkow, E.** (2012). Biochemistry and cell biology of tau protein in neurofibrillary degeneration. *Cold Spring Harb. Perspect. Med.* **2**, a006247.
- Mansson, C., Kakkar, V., Monsellier, E., Sourigues, Y., Härmak, J., Kampinga, H. H., Melki, R. and Emanuelsson, C.** (2013). DNAJB6 is a peptide-binding chaperone which can suppress amyloid fibrillation of polyglutamine peptides at substoichiometric molar ratios. *Cell Stress Chaperones* **19**, 227-239. PubMed
- Martin, I., Dawson, V. L. and Dawson, T. M.** (2011). Recent advances in the genetics of Parkinson's disease. *Annu. Rev. Genomics Hum. Genet.* **12**, 301-325.
- McLear, J. A., Lebrecht, D., Messer, A. and Wolfgang, W. J.** (2003). Combinational approach of intrabody with enhanced Hsp70 expression addresses multiple pathologies in a fly model of Huntington's disease. *FASEB J.* **22**, 2003-2011.
- Mendillo, M. L., Santagata, S., Koeva, M., Bell, G. W., Hu, R., Tamimi, R. M., Fraenkel, E., Ince, T. A., Whitesell, L. and Lindquist, S.** (2012). HSF1 drives a transcriptional program distinct from heat shock to support highly malignant human cancers. *Cell* **150**, 549-562.
- Miyata, Y., Koren, J., Illi, Kiray, J., Dickey, C. A. and Gestwicki, J.** (2011). Molecular chaperones and regulation of tau quality control: strategies for drug discovery in tauopathies. *Future Med. Chem.* **3**, 1523-1537.
- Mokranjac, D., Sichting, M., Neupert, W. and Hell, K.** (2003). Tim14, a novel key component of the import motor of the TIM23 protein translocase of mitochondria. *EMBO J.* **22**, 4945-4956.
- Morimoto, R. I.** (2008). Proteotoxic stress and inducible chaperone networks in neurodegenerative disease and aging. *Genes Dev.* **22**, 1427-1438.
- Morimoto, R. I.** (2011). The heat shock response: systems biology of proteotoxic stress in aging and disease. *Cold Spring Harb. Symp. Quant. Biol.* **76**, 91-99.
- Mymrikov, E. V., Seit-Nebi, A. S. and Gusev, N. B.** (2011). Large potentials of small heat shock proteins. *Physiol. Rev.* **91**, 1123-1159.
- Nakhro, K., Park, J. M., Kim, Y. J., Yoon, B. R., Yoo, J. H., Koo, H., Choi, B. O. and Chung, K. W.** (2013). A novel Lys141Thr mutation in small heat shock protein 22 (HSPB8) gene in Charcot-Marie-Tooth disease type 2L. *Neuromuscul. Disord.* **23**, 656-663.
- Neef, D. W., Turski, M. L. and Thiele, D. J.** (2010). Modulation of heat shock transcription factor 1 as a therapeutic target for small molecule intervention in neurodegenerative disease. *PLoS Biol.* **8**, e1000291.
- Neef, D. W., Jaeger, A. M. and Thiele, D. J.** (2011). Heat shock transcription factor 1 as a therapeutic target in neurodegenerative diseases. *Nat. Rev. Drug Discov.* **10**, 930-944.
- Nosková, L., Stránecký, V., Hartmannová, H., Přistoupilová, A., Barešová, V., Ivánek, R., Hůlková, H., Jahnová, H., van der Zee, J., Staropoli, J. F. et al.** (2011). Mutations in DNAJC5, encoding cysteine-string protein alpha, cause autosomal-dominant adult-onset neuronal ceroid lipofuscinosis. *Am. J. Hum. Genet.* **89**, 241-252.
- Ojala, T., Polinati, P., Manninen, T., Hiippala, A., Rajantie, J., Karikoski, R., Suomalainen, A. and Tyni, T.** (2012). New mutation of mitochondrial DNAJC19 causing dilated and noncompaction cardiomyopathy, anemia, ataxia, and male genital anomalies. *Pediatr. Res.* **72**, 432-437.
- Opatova, A., Filipcik, P., Cente, M. and Novak, M.** (2013). Intracellular degradation of misfolded tau protein induced by geldanamycin is associated with activation of proteasome. *J. Alzheimers Dis.* **33**, 339-348.
- Outeiro, T. F., Klucken, J., Strathearn, K. E., Liu, F., Nguyen, P., Rochet, J. C., Hyman, B. T. and McLean, P. J.** (2006). Small heat shock proteins protect against α -synuclein-induced toxicity and aggregation. *Biochem. Biophys. Res. Commun.* **351**, 631-638.
- Parfitt, D. A., Michael, G. J., Vermeulen, E. G. M., Prodromou, N. V., Webb, T. R., Gallo, J.-M., Cheetham, M. E., Nicoll, W. S., Blatch, G. L. and Chapple, J. P.** (2009). The ataxia protein saccin is a functional co-chaperone that protects against polyglutamine-expanded ataxin-1. *Hum. Mol. Genet.* **18**, 1556-1565.
- Paris, D., Ganey, N. J., Laporte, V., Patel, N. S., Beaulieu-Abdelahad, D., Bachmeier, C., March, A., Ait-Ghezala, G. and Mullan, M. J.** (2010). Reduction of β -amyloid pathology by celastrol in a transgenic mouse model of Alzheimer's disease. *J. Neuroinflammation* **7**, 17.
- Park, S. H., Kukushkin, Y., Gupta, R., Chen, T., Konagai, A., Hipp, M. S., Hayer-Hartl, M. and Hartl, F. U.** (2013). PolyQ proteins interfere with nuclear degradation of cytosolic proteins by sequestering the Sis1p chaperone. *Cell* **154**, 134-145.
- Parnas, A., Nadler, M., Nisemblat, S., Horovitz, A., Mandel, H. and Azem, A.** (2009). The MitChAP-60 disease is due to entropic destabilization of the human mitochondrial Hsp60 oligomer. *J. Biol. Chem.* **284**, 28198-28203.
- Parsell, D. A. and Lindquist, S.** (1993). The function of heat-shock proteins in stress tolerance: degradation and reactivation of damaged proteins. *Annu. Rev. Genet.* **27**, 437-496.
- Pemberton, S., Madiona, K., Pieri, L., Kabani, M., Bousset, L. and Melki, R.** (2011). Hsc70 protein interaction with soluble and fibrillar α -synuclein. *J. Biol. Chem.* **286**, 34690-34699.
- Perng, M. D., Wen, S. F., van den IJssel, P., Prescott, A. R. and Quinlan, R. A.** (2004). Desmin aggregate formation by R120G alphaB-crystallin is caused by altered filament interactions and is dependent upon network status in cells. *Mol. Biol. Cell* **15**, 2335-2346.
- Perrin, V., Régulier, E., Abbas-Terki, T., Hassig, R., Brouillet, E., Aebischer, P., Luthi-Carter, R. and Déglon, N.** (2007). Neuroprotection by Hsp104 and Hsp27 in lentiviral-based rat models of Huntington's disease. *Mol. Ther.* **15**, 903-911.
- Peterson, L. B. and Blagg, B. S. J.** (2009). To fold or not to fold: modulation and consequences of Hsp90 inhibition. *Future Med. Chem.* **1**, 267-283.
- Petrucelli, L., Dickson, D., Kehoe, K., Taylor, J., Snyder, H., Grover, A., De Lucia, M., McGowan, E., Lewis, J., Prihar, G. et al.** (2004). CHIP and Hsp70 regulate tau ubiquitination, degradation and aggregation. *Hum. Mol. Genet.* **13**, 703-714.
- Pierce, A., Wei, R., Halade, D., Yoo, S.-E., Ran, Q. and Richardson, A.** (2010). A Novel mouse model of enhanced proteostasis: Full-length human heat shock factor 1 transgenic mice. *Biochem. Biophys. Res. Commun.* **402**, 59-65.
- Pierce, A., Podlaskaya, N., Halloran, J. J., Hussong, S. A., Lin, P. Y., Burbank, R., Hart, M. J. and Galvan, V.** (2013). Over-expression of heat shock factor 1 phenocopies the effect of chronic inhibition of TOR by rapamycin and is sufficient to ameliorate Alzheimer's-like deficits in mice modeling the disease. *J. Neurochem.* **124**, 880-893.
- Raju, I. and Abraham, E. C.** (2013). Mutants of human α B-crystallin cause enhanced protein aggregation and apoptosis in mammalian cells: influence of co-expression of HspB1. *Biochem. Biophys. Res. Commun.* **430**, 107-112.
- Redeker, V., Pemberton, S., Bienvenu, W., Bousset, L. and Melki, R.** (2012). Identification of protein interfaces between α -synuclein, the principal component of Lewy bodies in Parkinson disease, and the molecular chaperones human Hsc70 and the yeast Ssa1p. *J. Biol. Chem.* **287**, 32630-32639.
- Riedel, M., Goldbaum, O., Schwarz, L., Schmitt, S. and Richter-Landsberg, G.** (2010). 17-AAG induces cytoplasmic α -synuclein aggregate clearance by induction of autophagy. *PLoS ONE* **5**, e8753.
- Rimoldi, M., Servadio, A. and Zimmarino, V.** (2001). Analysis of heat shock transcription factor for suppression of polyglutamine toxicity. *Brain Res. Bull.* **56**, 353-362.
- Roostaei, A., Beaudoin, S., Staskevicius, A. and Roucou, X.** (2013). Aggregation and neurotoxicity of recombinant α -synuclein aggregates initiated by dimerization. *Mol. Neurodegener.* **8**, 5.
- Rubinsztein, D. C., Codogno, P. and Levine, B.** (2012). Autophagy modulation as a potential therapeutic target for diverse diseases. *Nat. Rev. Drug Discov.* **11**, 709-730.
- Saccon, R. A., Bunton-Stasyshyn, R. K., Fisher, E. M. C. and Fratta, P.** (2013). Is SOD1 loss of function involved in amyotrophic lateral sclerosis? *Brain* **136**, 2342-2358.
- Sakono, M. and Zako, T.** (2010). Amyloid oligomers: formation and toxicity of Abeta oligomers. *FEBS J.* **277**, 1348-1358.
- Sarparanta, J., Jonson, P. H., Golzio, C., Sandell, S., Luque, H., Screen, M., McDonald, K., Stajich, J. M., Mahjneh, I., Vihola, A. et al.** (2012). Mutations affecting the cytoplasmic functions of the co-chaperone DNAJB6 cause limb-girdle muscular dystrophy. *Nat. Genet.* **44**, 450-455, S1-S2.
- Schapira, A. H. V. and Tolosa, E.** (2010). Molecular and clinical prodrome of Parkinson's disease: implications for treatment. *Nat. Rev. Nephrol.* **6**, 309-317.
- Seidel, K., Meister, M., Dugbartey, G. J., Zijlstra, M. P., Vinet, J., Brunt, E. R., van Leeuwen, F. W., Rüb, U., Kampinga, H. H. and den Dunnen, W. F. A.** (2012a). Cellular protein quality control and the evolution of aggregates in spinocerebellar ataxia type 3 (SCA3). *Neuropathol. Appl. Neurobiol.* **38**, 548-558.
- Seidel, K., Siswanto, S., Brunt, E. R. P., den Dunnen, W., Korf, H.-W. and Rüb, U.** (2012b). Brain pathology of spinocerebellar ataxias. *Acta Neuropathol.* **124**, 1-21.
- Seyffer, F., Kummer, E., Oguchi, Y., Winkler, J., Kumar, M., Zahn, R., Sourjik, V., Bukau, B. and Mogk, A.** (2012). Hsp70 proteins bind Hsp100 regulatory M domains to activate AAA+ disaggregase at aggregate surfaces. *Nat. Struct. Mol. Biol.* **19**, 1347-1355.
- Sharp, P. S., Akbar, M. T., Bouri, S., Senda, A., Joshi, K., Chen, H. J., Latchman, D. S., Wells, D. J. and de Belleruche, J.** (2008). Protective effects of heat shock

- protein 27 in a model of ALS occur in the early stages of disease progression. *Neurobiol. Dis.* **30**, 42-55.
- Shimshek, D. R., Mueller, M., Wiessner, C., Schweizer, T. and van der Putten, P. H.** (2010). The HSP70 molecular chaperone is not beneficial in a mouse model of alpha-synucleinopathy. *PLoS ONE* **5**, e10014.
- Siddiqui, T. and Deng, H. X.** (1996). Genetics of amyotrophic lateral sclerosis. *Hum. Mol. Genet.* **5**, 1465-1470.
- Sinadinos, C., Quraishe, S., Sealey, M., Samson, P. B., Mudher, A. and Wyttenbach, A.** (2013). Low endogenous and chemical induced heat shock protein induction in a ON3Rtau-expressing Drosophila larval model of Alzheimer's disease. *J. Alzheimers Dis.* **33**, 1117-1133.
- Sittler, A., Lurz, R., Lueder, G., Priller, J., Lehrach, H., Hayer-Hartl, M. K., Hartl, F. U. and Wanker, E. E.** (2001). Geldanamycin activates a heat shock response and inhibits huntingtin aggregation in a cell culture model of Huntington's disease. *Hum. Mol. Genet.* **10**, 1307-1315.
- Slavotinek, A. M., Stone, E. M., Mykytyn, K., Heckenlively, J. R., Green, J. S., Heon, E., Musarella, M. A., Parfrey, P. S., Sheffield, V. C. and Biesecker, L. G.** (2000). Mutations in MKKS cause Bardet-Biedl syndrome. *Nat. Genet.* **26**, 15-16.
- Song, Y., Nagy, M., Ni, W., Tyagi, N. K., Fenton, W. A., López-Giráldez, F., Overton, J. D., Horwich, A. L. and Brady, S. T.** (2013). Molecular chaperone Hsp110 rescues a vesicle transport defect produced by an ALS-associated mutant SOD1 protein in squid axoplasm. *Proc. Natl. Acad. Sci. USA* **110**, 5428-5433.
- Sontag, E. M., Joachimiak, L. A., Tan, Z., Tomlinson, A., Housman, D. E., Glabe, C. G., Potkin, S. G., Frydman, J. and Thompson, L. M.** (2013). Exogenous delivery of chaperonin subunit fragment ApiCCT1 modulates mutant Huntingtin cellular phenotypes. *Proc. Natl. Acad. Sci. USA* **110**, 3077-3082.
- Stenoien, D. L., Cummings, C. J., Adams, H. P., Mancini, M. G., Patel, K., DeMartino, G. N., Marcelli, M., Weigel, N. L. and Mancini, M. A.** (1999). Polyglutamine-expanded androgen receptors form aggregates that sequester heat shock proteins, proteasome components and SRC-1, and are suppressed by the HDJ-2 chaperone. *Hum. Mol. Genet.* **8**, 731-741.
- Stoetzel, C., Muller, J., Laurier, V., Davis, E. E., Zaghoul, N. A., Vicaire, S., Jacquelin, C., Plewniak, F., Leitch, C. C., Sarda, P. et al.** (2007). Identification of a novel BBS gene (BBS12) highlights the major role of a vertebrate-specific branch of chaperonin-related proteins in Bardet-Biedl syndrome. *Am. J. Hum. Genet.* **80**, 1-11.
- Stone, D. L., Slavotinek, A., Bouffard, G. G., Banerjee-Basu, S., Baxeavanis, A. D., Barr, M. and Biesecker, L. G.** (2000). Mutation of a gene encoding a putative chaperonin causes McKusick-Kaufman syndrome. *Nat. Genet.* **25**, 79-82.
- Stope, M. B., Schubert, T., Staar, D., Rönna, C., Streittböcker, A., Kroeger, N., Kubisch, C., Zimmermann, U., Walther, R. and Burchardt, M.** (2012). Effect of the heat shock protein HSP27 on androgen receptor expression and function in prostate cancer cells. *World J. Urol.* **30**, 327-331.
- Tam, S., Geller, R., Spiess, C. and Frydman, J.** (2006). The chaperonin TRiC controls polyglutamine aggregation and toxicity through subunit-specific interactions. *Nat. Cell Biol.* **8**, 1155-1162.
- Tam, S., Spiess, C., Auyeung, W., Joachimiak, L., Chen, B., Poirier, M. A. and Frydman, J.** (2009). The chaperonin TRiC blocks a huntingtin sequence element that promotes the conformational switch to aggregation. *Nat. Struct. & Mol. Biol.* **16**, 1279-1285.
- Tang, B. S., Zhao, G. H., Luo, W., Xia, K., Cai, F., Pan, Q., Zhang, R. X., Zhang, F. F., Liu, X. M., Chen, B. et al.** (2005). Small heat-shock protein 22 mutated in autosomal dominant Charcot-Marie-Tooth disease type 2L. *Hum. Genet.* **116**, 222-224.
- Tessier, D. J., Komalavilas, P., Panitch, A., Joshi, L. and Brophy, C. M.** (2003). The small heat shock protein (HSP) 20 is dynamically associated with the actin cross-linking protein actinin. *J. Surg. Res.* **111**, 152-157.
- Thomas, M., Harrell, J. M., Morishima, Y., Peng, H. M., Pratt, W. B. and Lieberman, A. P.** (2006). Pharmacologic and genetic inhibition of hsp90-dependent trafficking reduces aggregation and promotes degradation of the expanded glutamine androgen receptor without stress protein induction. *Hum. Mol. Genet.* **15**, 1876-1883.
- Tiffany-Castiglioni, E. and Qian, Y.** (2012). ER chaperone-metal interactions: links to protein folding disorders. *Neurotoxicology* **33**, 545-557.
- Tóth, M. E., Szegedi, V., Varga, E., Juhász, G., Horváth, J., Borbély, E., Csibrányi, B., Alföldi, R., Lénárt, N., Penke, B. et al.** (2013). Overexpression of Hsp27 ameliorates symptoms of Alzheimer's disease in APP/PS1 mice. *Cell Stress Chaperones* **18**, 759-771.
- Tue, N. T., Shimaji, K., Tanaka, N. and Yamaguchi, M.** (2012). Effect of α B-crystallin on protein aggregation in Drosophila. *J. Biomed. Biotechnol.* **2012**, 252049.
- Turner, M. R., Hardiman, O., Benatar, M., Brooks, B. R., Chio, A., de Carvalho, M., Ince, P. G., Lin, C., Miller, R. G., Mitsumoto, H. et al.** (2013). Controversies and priorities in amyotrophic lateral sclerosis. *Lancet Neurol.* **12**, 310-322.
- Ungewickell, E., Ungewickell, H., Holstein, S. E., Lindner, R., Prasad, K., Barouch, W., Martin, B., Greene, L. E. and Eisenberg, E.** (1995). Role of auxilin in uncoating clathrin-coated vesicles. *Nature* **378**, 632-635.
- van der Putten, H. and Lotz, G. P.** (2013). Opportunities and challenges for molecular chaperone modulation to treat protein-conformational brain diseases. *Neurotherapeutics* **10**, 416-428.
- Veereshwarayya, V., Kumar, P., Rosen, K. M., Mestrlil, R. and Querfurth, H. W.** (2006). Differential effects of mitochondrial heat shock protein 60 and related molecular chaperones to prevent intracellular β -amyloid-induced inhibition of complex IV and limit apoptosis. *J. Biol. Chem.* **281**, 29468-29478.
- Velinov, M., Dolzhanskaya, N., Gonzalez, M., Powell, E., Konidari, I., Hulme, W., Staropoli, J. F., Xin, W., Wen, G. Y., Barone, R. et al.** (2012). Mutations in the gene DNAJC5 cause autosomal dominant Kufs disease in a proportion of cases: study of the Parry family and 8 other families. *PLoS ONE* **7**, e29729.
- Vos, M. J., Zijlstra, M. P., Kanon, B., van Waarde-Verhagen, M. A., Brunt, E. R., Oosterveld-Hut, H. M., Carra, S., Sibon, O. C. and Kampinga, H. H.** (2010). HSPB7 is the most potent polyQ aggregation suppressor within the HSPB family of molecular chaperones. *Hum. Mol. Genet.* **19**, 4677-4693.
- Wacker, J. L., Zareie, M. H., Fong, H., Sarikaya, M. and Muchowski, P. J.** (2004). Hsp70 and Hsp40 attenuate formation of spherical and annular polyglutamine oligomers by partitioning monomer. *Nat. Struct. Mol. Biol.* **11**, 1215-1222.
- Walter, P. and Ron, D.** (2011). The unfolded protein response: from stress pathway to homeostatic regulation. *Science* **334**, 1081-1086.
- Wang, L., Xie, C., Greggio, E., Parisiadou, L., Shim, H., Sun, L., Chandran, J., Lin, X., Lai, C., Yang, W. J. et al.** (2008). The chaperone activity of heat shock protein 90 is critical for maintaining the stability of leucine-rich repeat kinase 2. *J. Neurosci.* **28**, 3384-3391.
- Waza, M., Adachi, H., Katsuno, M., Minamiyama, M., Sang, C., Tanaka, F., Inukai, A., Doyu, M. and Sobue, G.** (2005). 17-AAG, an Hsp90 inhibitor, ameliorates polyglutamine-mediated motor neuron degeneration. *Nat. Med.* **11**, 1088-1095.
- Waza, M., Adachi, H., Katsuno, M., Minamiyama, M., Tanaka, F. and Sobue, G.** (2006). Alleviating neurodegeneration by an anticancer agent: an Hsp90 inhibitor (17-AAG). *Ann. N. Y. Acad. Sci.* **1086**, 21-34.
- Wellington, C. L., Leavitt, B. R. and Hayden, M. R.** (2000). Huntington disease: new insights on the role of huntingtin cleavage. *J. Neural Transm. Suppl.* **58**, 1-17.
- Westhoff, B., Chapple, J. P., van der Spuy, J., Höfheld, J. and Cheetham, M. E.** (2005). HSP70 is a neuronal shuttling factor for the sorting of chaperone clients to the proteasome. *Curr. Biol.* **15**, 1058-1064.
- Wilhelmus, M. M. M., Boelens, W. C., Otte-Höller, I., Kamps, B., de Waal, R. M. and Verbeek, M. M.** (2006). Small heat shock proteins inhibit amyloid-beta protein aggregation and cerebrovascular amyloid-beta protein toxicity. *Brain Res.* **1089**, 67-78.
- Wilhelmus, M. M. M., de Waal, R. M. W. and Verbeek, M. M.** (2007). Heat shock proteins and amateur chaperones in amyloid-beta accumulation and clearance in Alzheimer's disease. *Mol. Neurobiol.* **35**, 203-216.
- Xing, Y., Böcking, T., Wolf, M., Grigorieff, N., Kirchhausen, T. and Harrison, S. C.** (2010). Structure of clathrin coat with bound Hsc70 and auxilin: mechanism of Hsc70-facilitated disassembly. *EMBO J.* **29**, 655-665.
- Yam, A. Y., Xia, Y., Lin, H. T., Burlingame, A., Gerstein, M. and Frydman, J.** (2008). Defining the TRiC/CCT interactome links chaperonin function to stabilization of newly made proteins with complex topologies. *Nat. Struct. Mol. Biol.* **15**, 1255-1262.
- Yamamoto, A., Lucas, J. J. and Hen, R.** (2000). Reversal of neuropathology and motor dysfunction in a conditional model of Huntington's disease. *Cell* **101**, 57-66.
- Yang, C., Rahimpour, S., Lu, J., Pacak, K., Ikejiri, B., Brady, R. O. and Zhuang, Z.** (2013). Histone deacetylase inhibitors increase glucocerebrosidase activity in Gaucher disease by modulation of molecular chaperones. *Proc. Natl. Acad. Sci. USA* **110**, 966-971.
- Yerbury, J. J., Gower, D., Vanags, L., Roberts, K., Lee, J. A. and Ecroyd, H.** (2013). The small heat shock proteins α B-crystallin and Hsp27 suppress SOD1 aggregation in vitro. *Cell Stress Chaperones* **18**, 251-257.
- Young, J. C.** (2014). The role of the cytosolic HSP70 chaperone system in diseases caused by misfolding and aberrant trafficking of ion channels. *Dis. Model. Mech.* **7**, 319-329.
- Young, J. C., Moarefi, I. and Hartl, F. U.** (2001). Hsp90: a specialized but essential protein-folding tool. *J. Cell Biol.* **154**, 267-274.
- Zhang, H., Rajasekaran, N. S., Orosz, A., Xiao, X., Rechsteiner, M. and Benjamin, I. J.** (2010). Selective degradation of aggregate-prone CryAB mutants by HSPB1 is mediated by ubiquitin-proteasome pathways. *J. Mol. Cell. Cardiol.* **49**, 918-930.
- Zhang, Y. Q., Henderson, M. X., Colangelo, C. M., Ginsberg, S. D., Bruce, C., Wu, T. and Chandra, S. S.** (2012). Identification of CSP α clients reveals a role in dynamin 1 regulation. *Neuron* **74**, 136-150.
- Zourlidou, A., Gidalevitz, T., Kristiansen, M., Landles, C., Woodman, B., Wells, D. J., Latchman, D. S., de Bellerocche, J., Tabrizi, S. J., Morimoto, R. I. et al.** (2007). Hsp27 overexpression in the R6/2 mouse model of Huntington's disease: chronic neurodegeneration does not induce Hsp27 activation. *Hum. Mol. Genet.* **16**, 1078-1090.