Acta Biologica Szegediensis
http://www.sci.u-szeged.hu/ABS

REVIEW

Heat shock proteins and their role in human diseases

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ABSTRACT Elevated expression of heat shock proteins (HSPs) has been demonstrated following various forms of stress, such as heat, heavy metal or ethanol treatment, hypoxia, ischemia, and they are also upregulated in several diseases and infections, as their most important function is to protect cells from the harmful effects of stress. As molecular chaperones they regulate the biosynthesis, folding/unfolding, transport and assembly of cellular proteins. Following cellular stress, they protect uncorrectly folded proteins against aggregation, facilitate the refolding of misfolded proteins. In addition, these proteins also can assist in the proteasomal degradation of peptides that cannot be refolded. They also have crucial role in membrane quality control by binding to lipid rafts maintaining the membrane stability during stress conditions. Moreover, HSPs can inhibit certain steps of the apoptotic pathway and they also can decrease the damaging effect of oxidative stress. These properties enable them to have protective effects in different pathological conditions. Here, we summarize our current view on the role of HSPs in human diseases like myocardial infarction, ischemic stroke, different neurodegenerative disorders, diabetes or cancer. **Acta Biol Szeged 59(Suppl.1):121-141 (2015)**

KEY WORDS

cancer
diabetes
ethanol toxicity
HSP families
ischemia/reperfusion
neurodegeneration

Heat shock proteins

Heat shock proteins (HSPs), also called stress proteins, are ubiquitously expressed, evolutionarily conserved chaperone proteins. The first observation of the heat shock response was the discovery of heat-induced chromosomal puffings on the *Drosophila buscii* salivary gland chromosomes (Ritossa 1962). Later it was observed that heat shock treatment led to the synthesis of new proteins that were similar in different tissues of *Drosophila melanogaster,* while the levels of other proteins were reduced (Tissieres et al. 1974). A number of specific proteins, called HSPs were later identified that are upregulated in different types of organisms in response to elevated temperature. It subsequently turned out that not only heat shock, but other stressors too can induce the expression of HSPs and they are therefore also called stress proteins. They can be induced by various forms of stress, such as heat, heavy metal or ethanol treatment, hypoxia, ischemia, and the genes of these proteins are also upregulated in several diseases and infections. HSPs are rapidly induced in response to cellular stress because their most important function is to protect cells from the harmful effects of stress. The synthesis of HSPs contributes to the development of a transient thermotolerance.

Submitted Jan 6, 2015; Accepted April 28, 2015
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A mild, sublethal heat-stress can induce the expression of HSPs and increase cell survival after a subsequent, normally lethal heat treatment. This phenomenon, called preconditioning, is observed in different cell types and tissues. Other stress factors such as hypoxia or ethanol treatment also can enhance HSP expression and transient stress resistance. Interestingly, thermotolerance is also induced when the initial heat-treatment drastically suppresses total protein synthesis (Li and Werb 1982). Under heat shock conditions overall protein synthesis is reduced, while HSP mRNA and protein synthesis is increased in the first few hours of hyperthermia (Hickey and Weber 1982). At high temperatures some steps of protein synthesis, such as RNA splicing, are inhibited. Compensating, HSP RNAs often do not contain introns (Csermely and Yahara 2002).

Most of the stress-induced proteins are molecular chaperones, that mediate the correct folding and assembly of other proteins, but they are not a component of the final structures (Ellis 1990). Recently, the term "proteostasis' is used to describe the function of chaperones controling protein synthesis, folding, trafficking, aggregation, disaggregation, and degradation (Powers et al. 2009). They also participate in antigen presentation by chaperoning and transferring antigenic peptides (Li et al. 2002). Some HSPs, especially members of the HSPC (HSP90) family, are also implicated in different signal transduction pathways (Csermely et al. 1998).

During stress conditions partially denatured, misfolded proteins accumulate and their exposed hydrophobic regions

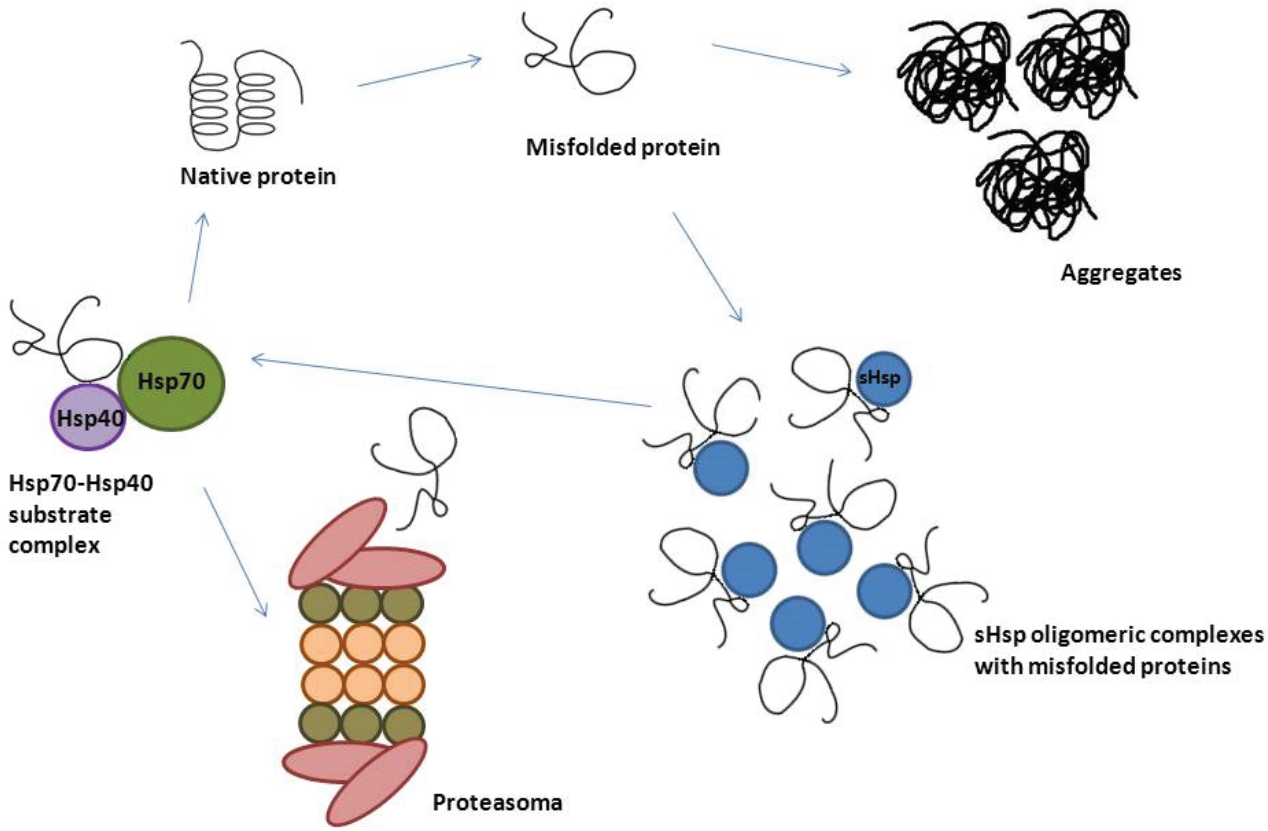

Figure 1. Chaperone functions of HSPs. During stress conditions, unfolded proteins accumulate and form large aggregates because of their exposed hydrophobic amino acids. However some HSPs, like HSPBs (sHSPs) can bind to unfolded proteins preventing their irreversible aggregation, maintaining them in a refolding competent state in an ATP-independent manner. Upon recovery after stress when the ATP level has been restored, the sequestered unfolded peptides can be transferred to ATP-dependent chaperone machineries, like the HSPA/DNAJ (HSP70/HSP40) complex, which are able to facilitate their refolding. On the other hand they also can assist in the proteasomal degradation of proteins that cannot be refolded.

dispose them to aggregate. HSPs help to prevent the change of the conformation of other proteins, and they protect uncorrectly folded proteins against aggregation. Upon recovery they facilitate the refolding of misfolded proteins, but they also can assist in the proteasomal degradation of peptides that cannot be refolded (Becker and Craig 1994) (Fig. 1). HSPs also have roles in membrane protection during stress conditions (Horvath et al. 2008). Moreover, they have anti-apoptotic functions, for example HSPA (HSP70) can block stress kinases (Gabai et al. 1998), while small HSPs (HSPBs) have caspase-inhibiting effects (Garrido et al. 1999).

The most extensively studied members of the HSPs are the heat-inducible ones (like HSPB1 (HSP27) and HSPA1 (HSP70)), but it emerged, that most HSP families contain several members, among others constitutively expressed proteins, e.g. HSPA8 (HSC70). The increasing number of HSPs led to inconsistencies in their nomenclature. Originally, most of the HSPs were grouped by molecular weight, but Kampinga and co-workers (2009) proposed a new guideline to the nomenclature of human HSP families. Accordingly, human HSPs are classified into the following groups: HSPH (HSP110), HSPC (HSP90), HSPA (HSP70), DNAJ (HSP40), HSPB (small HSP) and the chaperonin families HSPD/E (HSP60/HSP10) and CCT (TRiC) (Table 1).

HSPB (Small heat shock protein) family

The small heat shock proteins (sHSPs/HSPBs), with molecular weights in the range 16-40 kDa, are characterized by a conserved C-terminal domain of 100 amino acids, referred to as the α-crystallin domain (de Jong 1998). Mammalian HSPB family consists of at least 10 members. The heat inducible HSP16.2 was proposed as the 11th member of the human HSPB family, as it has a low molecular weight and chaperone-like activity, however the presence of the α-crystallin domain is not documented, therefore the classification of this protein

Table 1. The heat shock protein families based on Kampinga et al. 2009

Family	Number of members in human	Best studied members	Most important functions
HSPB (sHSP)	11	HSPB1 (HSP27), HSPB5 (αB-crystallin), HSPB4 (αA-crystallin)	Stabilizing unfolded proteins in ATP independent manner (holdase function)
HSPA (HSP70)	13	HSPA1 (HSP70), HSPA8 (Hsc70), HSPA9 (GRP75), HSPA5 (GRP78)	Folding of new proteins, refolding of damaged proteins, protein transport across membranes
DNAJ (HSP40)	~50		Regulation the activity of other chaperones (for example promoting HSPA ATP-ase activity)
HSPC (HSP90)	5	HSPC1 (HSP90), HSPC4 (GRP94)	Stabilizing protein aggregates, folding signalling molecules
HSPH (HSP110)	4		Stabilizing unfolded proteins; promoting nucleotide exchange of HSPA

is controversial (Kappe et al. 2010). HSPBs usually form homo- or heterooligomeric complexes up to ~700 kDa and can undergo post-translational modifications, often involving the phosphorylation of serine residues. The best-studied members of this family are HSPB1 (HSP27), HSPB4 (αA-crystallin) and HSPB5 (αB-crystallin). Although HSPBs are highly conserved they do vary a little in molecular weight in different species (e.g. the equivalent of the 27-kDa HSPB1 in human is a 25-kDa isoform in the mouse). Both HSPB1 and HSPB5 are constitutively expressed in a variety of tissues; however their expression is up-regulated under stress conditions and in several diseases. HSPB4 found mainly in the eye lens (Horwitz et al. 1999). Crystallins are the major structural proteins in the lens and have an important role in maintaining the transparency (Kumar et al. 2007). Some members, like HSPB5, HSPB1, HSPB2 (MKBP), are expressed highly in cardiac and skeletal muscles (Golenhofen et al. 2004; Kampinga et al. 2009). The HSPBs can protect cells from apoptosis and oxidative stress and can also bind to the cytoskeleton and membranes, stabilize them and protect them against stress (Sun and MacRae 2005). However, their most characteristic function is that they can bind to unfolded, partially denatured, damaged proteins and, thus, preventing their irreversible aggregation, maintaining them in a refolding competent state (Nakamoto and Vígh 2007). As the ATP level of the cells can decrease seriously during stress conditions, these HSPBs act in an ATP independent manner. Upon recovery after stress when the ATP level has been restored, the sequestered damaged proteins can be transferred to ATP-dependent chaperone machineries, like the HSPA/DNAJ (HSP70/HSP40) complex, which can facilitate the refolding or the degradation of these proteins (Garrido et al. 2003; Kappe et al. 2003; Sun and MacRae 2005) (Fig. 1).

HSPA (HSP70) family

The human HSP70 family has 13 members with similar structural and functional properties. HSPA1A (HSP70-1) and HSPA1B (HSP70-2) only differ in two amino acids, and probably they are completely interchangeable proteins usually referred as HSPA1 (HSP70) (reviewed in Kampinga et al. 2009). HSPA6 (HSP70B') gene has 77% sequence similarity to the HSPA1 gene, and similarly to HSPA1, it is also a heat inducible protein, although expressed only at higher temperature (Leung et al. 1990). HSPA8 (HSC70) is constitutively expressed in different cell types, and under unstressed conditions it has important roles in the folding of newly synthesized proteins and in the facilitation of protein transport across intracellular membranes. There are also compartment specific members of the HSPA family: HSPA9 (GRP75) is found in the mitochondria (Kampinga et al. 2009) while HSPA5 (GRP78), the glucose-regulated endoplasmatic-reticulum (ER) protein, is a central regulator of ER stress (Lee 2005).

During stress conditions one of the most important role of HSPA proteins is the refolding of the denatured proteins. HSPA proteins contain two functional units: the N-terminal regulatory ATPase domain, and the C-terminal substrate-binding domain that binds hydrophobic regions of polypeptides (Gragerov et al. 1994; Zhu et al. 1996). Hydrophobic amino acids are exposed in unfolded polypeptides, and binding of HSPA can prevent the aggregation of these proteins. In the absence of ATP (ADP bound state), HSPA strongly binds protein substrate, but if ATP binds to the N-terminal region, the HSPA-peptide complex dissociates (Gragerov et al. 1994). Repeated binding and release of the protein

substrate is necessary for its refolding; this cyclic process proceeds until hydrophobic regions are no longer exposed in the polypeptide. HSPA proteins usually have very low basal ATPase activity, and ATP binding and hydrolysis are regulated by co-chaperons. For example DNAJ (HSP40) promote ATP hydrolysis and substrate binding, while nucleotide exchange factors, like BAG-1 or the members of HSPH (HSP110) family catalyze the release of ADP and the binding of ATP (Qiu et al. 2006; Dragovic et al. 2006). Another co-chaperon, CHIP (C-terminus of heat-shock cognate 70 stress protein-interacting protein) binds to HSPA reducing its ATPase and chaperone activity (Ballinger et al. 1999). CHIP has E3 ubiquitin ligase activity, and selectively ubiquitylates misfolded proteins in cooperation with HSPA (or HSPC (HSP90)) promoting their proteasomal degradation (Murata et al. 2001).

Under heat shock conditions a portion of HSPA proteins migrates to the nucleus, while upon recovery it returns to the cytosol (Welch and Feramisco 1984; Zeng et al. 2004). It is proposed that HSPA translocates to the nucleus to facilitate DNA repair and protect cells against single-strand DNA brakes (Kotoglou et al. 2009).

DNAJ (HSP40) family

This is the largest human HSP family containing at least 50 members, categorized into three subgroups (DNAJA, DNAJB and DNAJC; Kampinga et al. 2009). DNAJ (HSP40) proteins are characterized by a conserved, usually N-terminal J-domain, through which they bind to HSPA proteins. They are important in protein folding, refolding and translocation as they are responsible for the stimulation of HSPA ATPase activity (Qiu et al. 2006; Kampinga et al. 2009). DNAJ proteins can bind substrate peptides and transfer them to HSPA, while the J-domain promotes ATP hydrolysis. Certain members of DNAJ family also regulate the activity of other HSPs, like HSPC proteins. They can be found in different cell compartments, such as cytosol, nucleus, ER, mitochondria, endosomes and ribosomes. Some of them show tissue specific expression (reviewed in Qiu et al. 2006).

HSPH (HSP110) family

The human HSPH (HSP110) family consists of three cytosolic and one ER specific members. They are highly homologous to HSPA proteins, but they have a longer linker region between the N-terminal ATPase domain and the C-terminal peptide-binding domain (Kampinga et al. 2009). Like HSPBs they act as 'holdases', they recognize and bind denatured proteins maintaining them in a refolding-competent state (Oh et al. 1997). A yeast HSP110 family member has been described as a cochaperone for HSP90 (Liu et al. 1999). HSPH family members also cooperate with HSPA in protein folding, as they function as nucleotid exchange factors, removing ADP after ATP hydrolysis. Interestingly the ATPase domain and the peptide binding domain both necessary for the nucleotide exchange function of HSPH (Dragovic et al. 2006).

HSPC (HSP90) family

A genome-wide study revealed six functional genes encoding HSP90 proteins, however HSP90N was found to be a chimeric gene (Chen et al. 2005), therefore, later Kampinga and co-workers (2009) defined five members of the family, HSPC1-5. HSPH members are the most abundant proteins in cells, producing 1-2% of total cellular proteins (Csermely et al. 1998). They can be found in different cell copmpartment such as cytosol, endoplasmatic reticulum (ER) and the mitochondria. Most studied members of this group are the cytoplasmic isoforms and the ER specific HSPC4 (Grp94). In the cytosol there are two isoforms of the protein, the inducible HSPC1 (HSP90AA1) and the constitutive HSPC3 (HSP90AB1). The N-terminal of HSPC and the highly charged central region are responsible for the binding of different target proteins. A binding site for ATP/ADP also can be found in the N-terminal region, while the C-terminal domain contains a dimerization site (reviewed in Csermely et al. 1998). The main function of HSPC proteins is to suppress the aggregation of unfolded proteins. They also can disaggregate loose protein aggregates, and enhance the refolding of partially denatured proteins, as they maintain them in a refolding competent state for HSPA members (Myata and Yahara 1992; Freeman and Morimoto 1996; reviewed in Csermely et al. 1998). HSPC has a crucial role in cellular signalling, as it participates in the folding of steroid hormone receptors, protein kinases and other signalling components.

Transcriptional regulation of heat shock proteins

The stress induced expression of HSPs is mediated by special transcription factors, called heat shock factors (HSFs). Under stress conditions these regulators activate the heat shock genes by binding to the heat shock elements (HSEs) that are located in the promoter region of the HSP

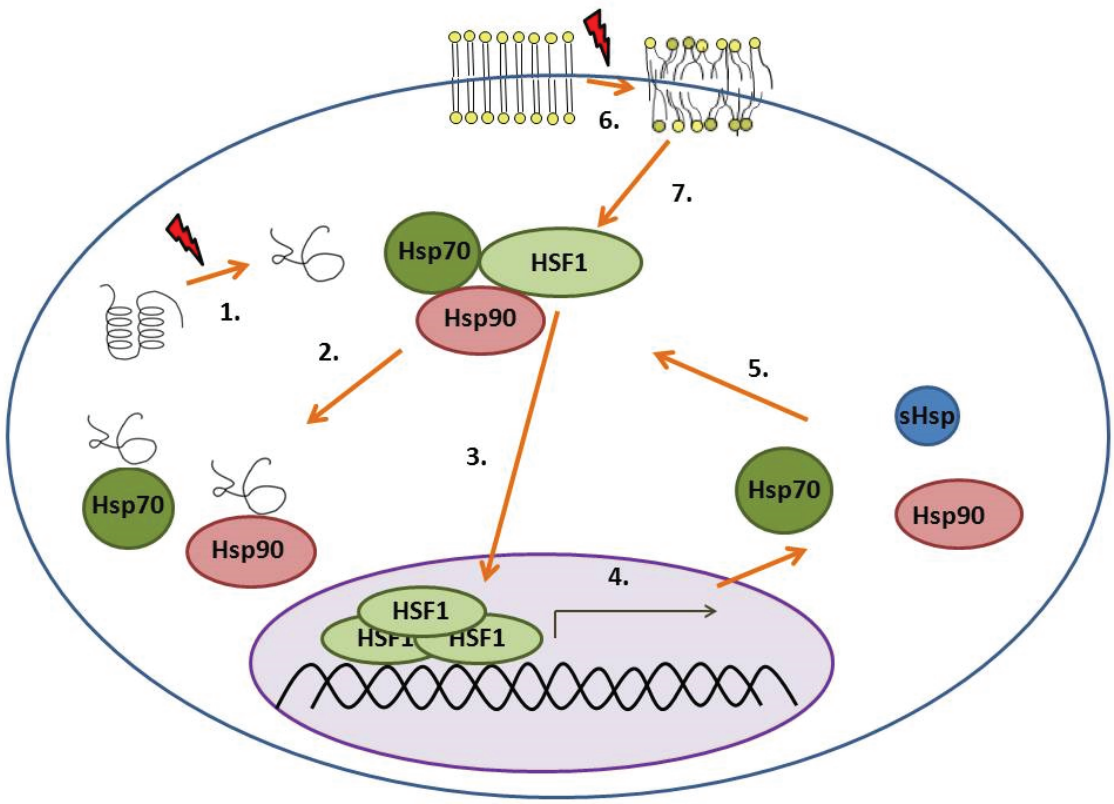

Figure 2. Transcriptional regulation of heat shock proteins. The inactive, monomeric form of HSF is sequestered in the cytoplasm of unstressed cells by binding to different HSPs, such as HSPC (HSP90), HSPA (HSP70) or DNAJ (HSP40). During stress conditions, the amount of partially denatured proteins increases (1), which can bind to HSPs, thereby liberating the HSFs (2). The released HSFs undergo trimerization, phosphorylation and translocate to the nucleus (3), where they bind to the HSE of the promoters of heat shock induced genes and activate them (4). The newly synthesized HSPs than associate with HSF, thereby negatively regulate their own expression via an autoregulatory loop (5). On the other hand there is an alternative, membrane-associated "thermosensor" that can initiate heat shock gene activation. During heat stress, the membrane fluidity rapidly increases (6), which can activate stress sensing and signaling pathways leading to the elevated expression of HSPs, and this transcription activation is also mediated by HSF1 (7).

genes. The genom of invertebrates such as *Saccharomyces* or *Drosophila*, encodes only one HSF, whereas higher eukaryotes express different types of HSFs (Morimoto et al. 1992; Morimoto 1998). In vertebrates, at least four members of the HSF family can be detected. The earliest-discovered and most widely studied HSF is HSF1, which is functionally analogous to yeast and *Drosophila* HSF as it plays a major role in the heat shock response (Morimoto 1998), while other members of the family are mainly involved in normal development, cell differentiation and life span regulation. HSF1 is expressed in most tissues and cell types, it is activated in response to different cellular stressors, such as heat shock, oxidative stress, heavy metal and ethanol treatment, and it regulates the expression of HSPs. HSF2 operates mostly during differentiation and development, but it has also been shown to interact with HSF1 during the stress response (He et al. 2003; Akerfelt et al. 2010; Björk and Sistonen 2010). Interestingly, HSF2 is activated by specific inhibitors of the ubiquitin-dependent protein degradation machinery, and it induces the same set of HSPs as HSF1 during heat stress (Mathew et al. 1998). HSF3 originally was detected only in avians, where it is activated by different stressors like HSF1, but only upon more severe stress conditions (Tanabe et al. 1997). Later HSF3 was also identified in mouse, where it is translocated to the nucleus during heat shock and activates stress-induced genes other than classical heat shock genes (Fujimoto et al. 2010). The expression of HSF4 is restricted to only a few tissues (Björk and Sistonen 2010) and plays a role in the modulation of the constitutive expression of heat shock genes (Tanabe et al. 1999). HSFs are varied in size, but all of them contain an N-terminal DNA-binding domain, a hydrophobic oligomerization domain, and a C-termial transactivation domain (Morimoto 1998).

Yeast HSF binds constitutively to DNA and is phosphorylated following heat treatment, thereby increasing its

transcriptional activity (Jakobsen and Pelham 1988). In higher eukaryotes the inactive, monomeric form of HSF is sequestered by different HSPs, such as HSPC, HSPA or DNAJ, in the cytoplasm of unstressed cells. During stress conditions, the amount of partially denatured proteins gradually increases, and these proteins upon binding to HSPs, liberate HSFs. The released HSFs undergo trimerization, phosphorylation and translocate to the nucleus, where they bind to the HSE of the promoters of heat shock induced genes and activate them. This activation is rapid, the DNA-binding form of HSF can be detected within minutes following heat treatment (Morimoto et al. 1992; Morimoto 2002; Sőti et al. 2005). The activation of heat shock genes leads to the increased expression of HSPs, which than associate with HSF. In this way HSPs negatively regulate the expression of heat shock genes via an autoregulatory loop (Morimoto et al. 1992) (Fig. 2).

Several studies show that different stress factors can lead to HSP induction without protein denaturation, suggesting that there is an alternative, membrane-associated "thermosensor" that can initiate heat shock gene activation (Vígh et al. 1998; Horváth et al. 2012; Balogh et al. 2013). According to the "membrane sensor" hypotheses the physical properties and microdomain organization of the membrane might have a crutial role in heat shock response activation. During heat stress, the membrane fluidity rapidly increases, leading to the elevated expression of HSPs (Vígh et al. 1998; Balogh et al. 2013) (Fig. 2). Increasing the fluidity of membranes with membrane fluidizers like benzyl alcohol or heptanol leads to the activation of different HSPs without measurable protein denaturation, and this transcription activation is mediated by HSF1 (Nagy et al. 2007; Balogh et al. 2005). Like heat shock, benzyl alcohol treatment resulted in the reorganization of cholesterol-rich membrane microdomains, which can activate stress sensing and signaling pathways (Vígh et al. 2007a, 2007b).

Role of HSPs during stress conditions

There are several properties of HSPs that enables them to have protective effects in different pathological conditions. As molecular chaperones they have central role in cellular protein quality control. Certain HSPs such as HSPBs or HSPH family members can bind partially denatured proteins in an ATP-independent manner, preventing their irreversible aggregation with each other or with different cell components, like cellular membranes. HSPBs are unable to restore misfolded proteins, but they can transfer them to ATP-dependent chaperones, like HSPA1, that promote their refolding. In addition HSPA1, in cooperation with its co-chaperons, also can facilitate the proteasomal degradation of damaged proteins. Thus, the heat shock protein network and the protein degradation systems are together responsible for the maintaining of the normal protein homeostasis which is essential to proper cellular function. However, protein quality control is weakening during aging and in different neurodegenerative diseases, which eventually leads to the accumulation of misfolded proteins (Sőti and Csermely 2002).

HSPs also have a crucial role in membrane quality control. Increasing evidence suggests that a pool of HSPs binds to lipid membranes, especially to lipid rafts, increasing their physical order, maintaining the membrane stability and restoring membrane functionality under stress conditions. Beside their membrane protein-protecting activity, HSPs can bind to membrane lipids directly, stabilizing the lipid phase of the membranes. It seems that the membrane association of HSPs can antagonize the membrane perturbing effects of stress conditions, therefore HSPs may play a role in cellular stress management (reviewed in Nakamoto and Vígh 2007 and Horváth et al. 2008). On the other hand several disorders like neurodegenerative diseases, diabetes or cancer are associated with altered membrane lipid composition, which can be related to suboptimal HSP expression. Therefore, altering membrane properties and normalizing HSP expression by "membrane lipid therapy" pharmaceuticals may provide potential treatment of certain diseases (Crul et al. 2013).

Increased oxidative stress was observed during aging and different human diseases, like neurodegenerative disorders, stroke, atherosclerosis or myocardial infarction. Several studies suggest that HSPs have protective effects against oxidative stress. For instance, HSPBs can decrease the level of reactive oxygen species (ROS) and regulate intracellular redox homeostasis, thereby protect cytoskeleton, which is a sensitive target for oxidative stress. Furthermore as molecular chaperons they prevent aggregation and promote proteasomal degradation of the oxidized proteins (Arrigo et al. 2005; Mymrikov et al. 2011).

Apoptotic and necrotic cell death both have been reported in different pathological conditions (Takayama et al. 2003). In the intrinsic pathway of apoptosis, changes in the inner mitochondrial membrane resulted in the release of pro-apoptotic proteins, like cytochrome c, into the cytosol. Cytochrome c then binds to Apaf-1 and procaspase-9 forming the so called apoptosome, leading to the activation of caspase-9, which in turn activates caspase-3 and initiates the apoptotic protease cascade (Elmore 2007). Interestingly, certain HSPs can inhibit different stages of this process (Latchman 2001). For example overexpression of HSPB1 can protect cells against different apoptotic stimuli by binding to cytochrome c and inhibiting apoptosome formation, and this antiapoptotic effect seems to depend on the oligomeric status of HSPB1 (Mehlen et al. 1996; Garrido et al. 1999; Bruey et al. 2000, reviewed for example in Latchman 2001; Takayama et al. 2003). HSPC can also prevent the formation of the apoptosome, by forming a cytosolic complex with Apaf-1 (Pandey et al. 2000). HSPA

can inhibit the recruitment of procaspase-9 to the apoptosome complex (Beere et al. 2000), but it also can inhibit apoptosis later in the cell death signaling pathway, downstream of caspase activation (Jaattela et al. 1998).

Ischemia/reperfusion injury

Ischemia/reperfusion injury is characteristic for myocardial infarction or ischemic stroke. During ischemia, the oxygen and nutrient supply of cells is inhibited, while certain toxic metabolites can accumulate in the tissues. Due to oxygen deprivation, ATP production rapidly decreases, which is compensated with anaerobic glycolysis, but later this is suppressed by intracellular acidosis. The calcium homeostasis of the cells is also affected and results in calcium accumulation. These events finally lead to abnormal ROS production, mitochondrial dysfunctions, and loss of membrane integrity. Restoration of blood supply can results in additional ROS generation and calcium overload causing further damage to tissues, referred to as reperfusion injury (reviewed in Nishizawa and Nagata 2000).

Several reports showed the increased expression of different HSPs in the heart after ischemia/reperfusion injury. Repeated ischemia/reperfusion episodes increased the level of HSPB1, HSPA and HSPC mRNA in isolated rat hearts (Das et al. 1993). Like heat shock, ischemia/reperfusion injury activates HSF1. The activation of HSF can be detected in minutes during global ischemia in heart, but then it is rapidly attenuated. However, the post-ischemic reperfusion induced a more significant activation of HSF. It was also showed, that the expression rate of HSPs differs between heat shock and ischemia/reperfusion injury. A greater expression of HSPA was found in heat shock compared to ischemia/reperfusion injury, while the level of HSPC mRNA was significantly higher in post-ischemic reperfusion than in heat shock (Nishizawa et al. 1996). Certain members of the HSPB family, like HSPB5 or HSPB2 show a constitutive high level expression in muscle tissues, and have important myofibrillar stabilizing functions during stress conditions. HSPB5 is associated with the desmin filaments of the Z-lines in cardiomyocites, and its binding affinity to actin and desmin increases during stress conditions (Longoni et al. 1990; Bennardini et al. 1992). In response to ischemic treatment, HSPB5 rapidly translocates from the cytosol to the Z-lines of the myofibrils (Chiesi et al. 1990; Golenhofen et al. 1998). This redistribution was also observed in the case of other small heat shock proteins, like HSPB1, HSPB2, HSPB7 and HSPB8 (Golenhofen et al. 2004).

Several studies have shown that induction of HSPs with mild stress stimuli has protective effect against a subsequent more severe stress in the heart. First, Currie et al. demonstrated that there is an association between heat shock response and enhanced post-ischemic recovery. In this study, rats were heat shock treated, then 24 hours later hearts were isolated and contractility was examined during and after global ischemia on a Langerdorff perfusion apparatus. Contractility during ischemia was not affected by the prior heat treatment, but upon recovery, heat-shocked heart had significantly improved recovery in contractile force and rate of contraction. After 30 minutes of reperfusion they found reduced ultrastructural injury of mithocondria, and increased expression of HSPA in the heat-shocked hearts (Currie et al. 1988). Later, this protective effect of heat shock treatment was also demonstrated in intact animals (reviewed in Latchmann 2001). Heat shock pretreatment significantly reduced the infarct size after a left coronary artery occlusion, correlating with a marked increase of HSPA expression (Donelly et al. 1992). Later, it was demonstrated that not only heat shock but a sublethal ischemic pretreatment also can reduce the infarct volume following coronary artery ligation in rabbits. In this study heat and ischemic pretreatments resulted in a similar level of HSPA expression, while HSPD1 (HSP60) was induced moderately only by ischemia (Marber et al. 1993). Moreover, it was shown, that the amount of induced HSPA is directly correlated with the degree of infarct size reduction (Hutter et al. 1994). These results suggest that the induction of HSPs is responsible for the protective effects of the different stress pretreatments, which was further confirmed by studies, in which individual HSPs were overexpressed (reviewed in Latchmann 2001). Overexpression of HSPA protects primary rat cardiac myocytes and coronary endothelial cells against ischemia (Cumming et al. 1996; Suzuki et al. 1998). However, rather interestingly, overexpression of HSPD1 or HSPC had no such a protective effect against ischemic stress (Cumming et al. 1996). Later, overexpression of HSPBs, HSPB1 and HSPB5 was also proved to be protective against hypoxic stress in rat cardiomyocyte cultures, and shown that decreasing the level of endogenous HSPB5 resulted in increased damage after ischemia (Martin et al. 1997; Brar et al. 1999). HSPB5/HSPB2 deficiency affects cardiac function, as isolated hearts and papillary muscles of HSPB5/HSPB2 double knock-out mice showed contractile dysfunction, reduced recovery and increased cell death after ischemia reperfusion (Morrison et al. 2004; Golenhofen et al. 2006), while elevated expression of HSPB5 can preserve postischemic contractile function and decrease the level of oxidative stress and myocardial apoptosis (Ray et al. 2001). Transgenic overexpression of HSPB1 protected the heart from an ischemia-reperfusion injury by decreasing the effects of oxidative stress in mice (Hollander et al. 2004). High level, constitutive expression of the inducible HSPA in the myocardium of transgenic mice led to the protection of hearts against ischemia/reperfusion injury (Plumier et al. 1995; Marber et al. 1995; Radford et al. 1996; reviewed in Latchmann 2001). Pharmacological induction of HSPs by a hidroxylamine derivative, Bimoclomol, also had

cytoprotective effects in a murine model of ischemia (Vígh et al. 1997). Moreover, increasing the expression level of HSPA by exercise training reduced the degree of myocardial lipid peroxidation following short-term ischemia-reperfusion (Demirel et al. 1998).

The protective effect of ischemic preconditioning was also demonstrated in the brain of a rodent model of bilateral cerebral ischemia. Repetitive, short periods of ischemia before a 5 min bilateral occlusion of carotids resulted in a decreased neuronal cell death in the CA1 region of hippocampus (Kitagawa et al. 1991). After transient middle cerebral artery occlusion, HSPA was expressed in neurons, microglia and endothelial cells, but not in astrocytes, in the penumbral area around the focal ischemic center. Expression level of HSPA positively correlated with the duration of ischemia (Li et al. 1992). Constitutive transgenic overexpression of HSPA can reduce the neuronal damage following cerebral ischemia in mice (Plumier et al. 1997). This result was confirmed also in rats using viral overexpression of HSPA (Yenari et al. 1998). Injecting the HSP inducer geldanamycin into cerebral ventricles 24 h before ischemia successfully reduced infarct size, brain edema and the number of apoptotic cells, and improved behavioral outcomes, while protein levels of HSPA in neurons and HSPB1 in glial cells were increased (Lu et al. 2002). Later, it was also shown that HSPA has an anti-inflammatory role in cerebral ischemia. In the ischemic brain of HSPA overexpressing transgenic mice the number of activated microglia/macrophages was reduced, and the microglia-induced astrocyte death was prevented while several pro-inflammatory genes were downregulated (Zheng et al. 2008). Small heat shock proteins also have beneficial properties during ischemic stroke. HSPB5 deficiency leads to increased infarct size after middle cerebral artery occlusion, while recombinant HSPB5 treatment can reduce the lesion size in HSPB5 knock-out and wild type mice as well (Arac et al. 2011).

Cytotoxic effects of ethanol

Ethanol has several cell type-independent cytotoxic effects, thus alcohol consumption impairs almost all tissues in the human organism (reviewed in Baker and Kremer 1999; Tóth et al. 2014). Ethanol can increase the fluidity of the plasma membrane, membranes of endoplasmic reticulum, mitochondria and liposomes (Goldstein 1986). Alterations in the physical structure of membranes as well as the direct interaction with ethanol can influence the functions of membrane-associated proteins such as receptors, ion channels and enzymes, and can therefore alter cellular processes, like membrane transport, enzymatic reactions and signaling pathways (Fadda and Rossetti 1998; Escriba et al. 2008).

Ethanol administration resulted in an increased generation of ROS and decreased activity of the protective antioxidant system, leading to the oxidative damage of different cell components, like cellular membranes, DNA or the cytoskeleton (Wu and Cederbaum 2003). For example lipid peroxidation can alter the structure and function of membranes and different membrane proteins (Mason et al. 1997; Vígh et al. 2005; Escriba et al. 2008), while the oxidative stress induced protein denaturation leads to protein aggregation and the loss of enzymatic activity. Therefore oxidative stress plays central roles in the pathogenesis of alcoholic liver disease (Wu and Cederbaum 2003) but increased free radical production and lipid peroxidation also have been demonstrated in extrahepatic tissues such as the heart and brain (reviewed in Nordmann et al. 1990).

Similarly, ethanol can induce apoptosis in different tissues, such as the liver and the brain. Even a single day of binge ethanol treatment can induce apoptotic cell death in the liver (Zhou et al. 2001). Neurons are extremely sensitive to the cytotoxic effect of ethanol in the developing mammalian brain during the synaptogenesis, which occurs prenatally in human and after birth in rodents. The acute ethanol treatment of 7-day-old rats led to extensive neuronal apoptosis in different brain regions (Ikonomidou et al. 2000).

Like heat shock and other stress factors, ethanol administration activates HSFs and induces the expression of HSPs in the liver, brain and inflammatory cells. *In vitro* ethanol treatment promotes the translocation of HSF1 from cytoplasm to the nucleus in cultured cortical neuronal cells (Pignataro et al. 2007), as well as in macrophages and monocytes (Mandrekar 2008), increasing its DNA-binding activity, and inducing the expression of different HSPs, such as HSPB1, DNAJ or HSPA. Both acute and chronic ethanol consumptions resulted in elevated level of HSPA in the hippocampus, cerebellum, cortex, striatum and liver of rats (Calabrese et al. 1996; Calabrese et al. 1998). In the different brain regions, the amount of HSPA protein correlated negatively with the level of lipid peroxidation. Maternal ethanol consumption also leads to increased expression of HSPA in different brain regions of rat pups (Holownia et al. 1995).

It has been demonstrated, that a mild ethanol administration, similar to heat shock or ischemia, can induce preconditioning, probably due to the elevated expression of HSPs. For example, ethanol pretreatment resulted in enhanced resistance against subsequent heat shock and H_2O_2 exposure in cell cultures (Su et al. 1998) or against cerebral ischemia/reperfusion injury in gerbils (Wang et al. 2007).

Several studies have demonstrated that pharmacological inductions of HSPs had protective effects against ethanol induced toxicity, especially in ethanol induced gastric lesions. Pretreatment of gastric mucosal cell cultures with an anti-ulcer drug, geranylgeranylacetone (GGA) that have been

demonstrated to induce the expression of HSPA, can prevent ethanol induced apoptotic cell death in a dose-dependent manner (Mizushima et al. 1999). Pretreatment with ginseng, which can increase HSPB1 and HSPA expression, prevented the ethanol-induced gastric lesions and apoptotic cell death in the rat gastric mucosa *in vivo* (Yeo et al. 2008). Other plant extracts were also proved to be effective in the prevention of ethanol induced gastric ulcer, while upregulating HSPA. Moreover, omeprazole, a gastroprotective drug used as control in these studies, also induced HSPA protein expression (Golbabapour et al. 2013; Sidahmed et al. 2013).

The protective effects of HSPs against ethanol induced toxicity were also showed in brain and hepatic cells. In primary astrocyte cultures ethanol treatment led to oxidative stress and a significant increase in the level of HSPA. However, blocking HSPA using antisense oligonucleotides resulted in an additional significant decrease in cell viability, and increase in ROS formation, lipidperoxidation and apoptotic DNA fragmentation, suggesting that HSPA has beneficial effect against ethanol induced cell damage (Russo et al. 2001). Indeed, increasing HSPA expression by GGA treatment can suppress ethanol induced apoptosis in primary cultures of rat hepatocytes (Ikeyama et al. 2001). Curcumin pretreatment, that can activate HSP expression, also reduced the level of ethanol induced oxidative stress, lipid peroxidation and toxicity in liver slice culture (Naik et al. 2004).

In our lab we investigated the neuroprotective effects of HSPB1 against acute and chronic ethanol administrations in HSPB1-overexpressing transgenic mice. After a single intraperitoneal ethanol injection, the ethanol treated wild-type mice exhibited ataxia and incoordination, whereas the overexpression of HSPB1 protein significantly reduced these harmful effects. HSPB1 overexpression also resulted in a significantly lower number of degenerating neurons in different brain regions of ethanol treated mice compared to wild type littermates after long term ethanol consumption (Tóth et al. 2010).

Aging and neurodegenerative disorders

In the aging cells several post-translational protein modifications occur, such as deamidation, methionine oxidation or protein glycation. These age-related modifications lead to conformational changes that can influence protein function and facilitate protein aggregation. As a compensatory mechanism, the levels of several HSPs are constitutively increased during aging; however their inducibility and chaperone activity are impaired (reviewed by Sőti and Csermely 2002). Moreover, HSPs are sequestered within the protein aggregates which may reduce their availability. Aging is accompanied by a decrease in the activity of the protein degradation systems, and as aggregated proteins can not be degraded properly, ubiquitinated proteins and components of the ubiquitin-proteasome system are also enriched in protein aggregates (Perry et al. 1987; Choi et al. 2004; Ross and Pickart 2004; Wyttenbach and Arrigo 2009). The weakening of the capacity of the chaperone and protein degradation system in aged organisms finally can lead to massive protein aggregation and the development of neurodegenerative diseases termed protein-misfolding disorders (Sőti and Csermely 2002). These neurodegenerative diseases are characterized by the accumulation of different aggregation-prone proteins that show some similarities, for example they are highly insoluble and can fold into β-sheet-rich structures (Haass and Selkoe 2007).

Alzheimer's disease (AD) is one of the most common neurodegenerative diseases which is characterized by progressive memory loss, formation of senile plaques and neurofibrillary tangles, induction of oxidative stress and neuronal cell death. The major component of senile plaques, the Aβ protein, probably has a central role in the disease pathology. This 4 kDa polypeptide is generated from the intramembrane amyloid precursor protein (APP) by the proteolytic cleavage of β- and γ-secretases. According to the amyloid cascade hypothesis the enhanced production or reduced clearance of the peptide leads to the relative increase in $A\beta_{42}$ level, which enhances oligomer formation (Haass and Selkoe 2007). The intracellular, soluble Aβ oligomers can interact with different cell components such as cytoplasmic proteins and lipid membranes, leading to the induction of apoptosis or several other detrimental changes in the cell for example in synaptic structure and plasticity. Therefore, the intracellular Aβ hypothesis emphasizes the primary role of intracellular Aβ in initiating the disease (Penke et al. 2012). In parallel, $A\beta_{42}$ polymerizes into insoluble fibrils resulting in the formation of extracellular amyloid plaques that do not appear to be as neurotoxic as the soluble oligomers, however they can initiate a chronic inflammation in the brain (Khandelwal 2011).

Aβ peptides can interact with membrane lipids, proteoglycans and proteins (reviewed in Verdier et al. 2004), thereby influencing the condition of the plasma membrane and membranes of subcellular organelles, however the exact effect of Aβ on the membrane fluidity might depend on the membrane composition, such as the cholesterol content (Yip et al. 2001). Because amyloidogenic APP processing and Aβ fibrillogenesis are membrane attached events, changed membrane fluidity can affect these processes as well (Peters et al. 2009). According to the amyloid channel hypothesis, at neurotoxic concentration Aβ can form cation selective ion channels in cell membranes resulting in abnormal neuronal ion (especially Ca^{2+}) homeostasis (Arispe et al. 1993; reviewed by Shirwany et al. 2007). Moreover, not only Aβ, but other neurotoxic proteins also have been demonstrated

to exert pore-like activities, such as polyglutamine proteins (Monoi et al. 2000) or α-synuclein protofibrils (Rochet et al. 2004).

During aging, the level of reactive oxygen species is increasing, while the ability of cells to respond to oxidative damage is decreasing, leading to enhanced level of oxidative protein alterations which can result in a greater degree of protein misfolding and impaired degradation (reviewed by Andersen 2004). On the other hand, the overexpression of aggregation-prone proteins like Aβ, α-synuclein, mutant huntingtin or SOD1 might themselves can increase the level of ROS (Behl et al. 1994; Hsu et al. 2000; Wyttenbach et al. 2002; Lee et al. 2001). Therefore, oxidative stress is characteristic of the different protein misfolding diseases, lipid peroxidation and protein oxidation have been reported in the brain of patients with AD, PD or HD and in the spinal cord of patients with ALS (reviewed by Andersen 2004 and Reed 2011).

Oxidative stress, disturbed calcium homeostasis, mitochondrial and cytoskeletal dysfunctions all can induce neuronal cell death, therefore apoptosis have been reported in different neurodegenerative diseases (for reviews, see Mattson 2000; Friedlander 2003; Wyttenbach and Arrigo 2009). Toxic Aβ peptide or α-synuclein can directly induce apoptosis in cultured neurons and transgenic mice (Loo et al. 1993; LaFerla et al. 1995; Forloni et al. 1996; El-Agnaf et al. 1998).

The levels of different HSPs are increased in the brain of neurodegenerative disease patients (for reviews see Sun and MacRae 2005; Wilhelmus et al. 2007; Brownell 2012). Moreover different HSPs have been found to be associated with the abnormal protein aggregates. For example several members of the HSPB family were observed in senile plaques and cerebral amyloid angiopathy, the pathological lesions of AD (Wilhelmus et al. 2006), and α-synuclein containing Lewy bodies. HSPA1 also colocalized with Aβ peptides and α-synuclein, while HSPA8 was found in intracellular inclusions in ALS (reviewed in Muchowski and Wacker 2005). Members of the DNAJ and HSPA families have been demonstrated to interact with huntingtin in a polyglutamine length-dependent manner (Jana et al. 2000). A DNAJ family member was found to be localized to ataxin-1 inclusions in the brain of spinocerebellar ataxia (SCA1) patient and SCA1 transgenic mice (Cummings et al. 1998).

Several studies suggest that the elevated level of HSPs has protective function in these neurodegenerative diseases. Overexpression of members of DNAJ protein family can suppress the nuclear aggregation of mutant ataxin-1 and ataxin-3 decreasing their toxicity in cell culture model (Cummings et al. 1998; Chai et al. 1999). HSPA overexpression decreased polyglutamine induced neurodegeneration in a *Drosophila* model of polyglutamine disease (Warrick et al. 1999) and in SCA1 transgenic mice (Cummings et al. 2001, reviewed in Turturici et al. 2011). HSPB1 has been shown to decrease polyglutamine toxicity without suppressing protein aggregation by protecting cells against oxidative stress (Wyttenbach et al. 2002). Overexpression of HSPB1 has a potent preventive anti-apoptotic effect against the damaging effects of α-synuclein (Zourlidou et al. 2004). HSPA expression can reduce α-synuclein aggregation *in vitro* and *in vivo*, and can decrease α-synuclein induced toxicity in cell culture and *Drosophila* model of PD (Klucken et al. 2004; Auluck et al. 2001; reviewed in Turturici et al. 2011). In SOD1/HSPB1 double transgenic mice Sharp et al. (2008) demonstrated a delayed decline in motor strength and an improved survival of the spinal motor neurons. Increased expression of HSPA reduced the aggregation and toxicity of mutant SOD1 and prolonged cell survival in primary motor neurons (Bruening et al. 1999). However, elevated expression of multiple HSPs resulted in enhanced protection against mutant SOD-1 compared to HSPB1 or HSPA expressed alone (Batulan et al. 2006). Transgenic overexpression of HSPA can reduce Aβ plaque formation, neuronal loss and cognitive deficits in a mouse model of AD (Hoshino et al. 2011). HSPB1, HSPB5 and HSPB6 are able to bind to Aβ inhibiting its fibril formation, therefore decreasing its toxicity in cultured cerebrovascular cells (Wilhelmus et al. 2006b).

We have investigated the effect of HSPB1 on cognitive, memory and synaptic functions, Aβ accumulation, and neurodegeneration in a mouse model of AD. We found that learning abilities were impaired in AD model mice but this was rescued by HSPB1 overexpression (Tóth et al. 2013). Synaptic abnormalities, like increased excitability and impaired long-term potentiation, were normalized in HSPB1 overexpressing AD model mice as well. Using anti-amyloid antibody, we counted significantly less amyloid plaques in the cortical and hippocampal brain regions of AD/HSPB1 animals compared to AD model mice. These results suggest that overexpression of HSPB1 protein might ameliorate certain symptoms of AD (Tóth et al. 2013).

Different HSP inducers also have been shown to be effective in moderating of the symptoms of certain neurodegenerative diseases. Treatment of a mouse model of polyglutamine disease with GGA can prevent pathogenic protein aggregation and alleviate the related phenotype (Katsuno et al. 2005). *Drosophila* models of HD and spinocerebellar ataxia treated with a geldanamycin derivative showed reduced polyglutamine-induced neurodegeneration and lethality (Fujikake et al. 2008). Treatment with a HSP coinducer, Arimoclomol can improve hind limb muscle function and motoneuron survival, leading to an increase in lifespan in a mouse model of ALS (Kieran et al. 2004).

These studies suggested that elevated expression of HSPs exert a protective function in these neurodegenerative diseases. However, it should be noted that not all type of HSPs appeared to be effective in all of the diseases. Rather,

each of the disorders can be characterized by a different set of HSPs that ameliorate the symptoms (reviewed by Kakkar et al. 2014).

Obesity and diabetes

Obesity, metabolic syndrome and diabetes share certain similarities with aging, as they represent a chronic stress state, where disturbed protein homeostasis can be found with a concomitant decline in the stress response. Metabolic disturbances can lead to the loss of stability and function of different cellular proteins as their post-translational modifications accumulate during the disease (reviewed in Dancsó et al. 2010). The level of sugars and their derivatives are elevated in different tissues of diabetic patients, which favors the non-enzymatic glycation of proteins. Glycation of α-crystallins of the eye lens resulted in significant conformational changes and decreased chaperone activity, finally leading to the development of diabetes related cataract (Kumar et al. 2007). Chronic high level of glucose can cause oxidative stress and endoplasmic reticulum stress especially in insulin expressing pancreatic β-cells, leading to protein misfolding, aggregation and apoptotic cell death. Indeed, large aggregates of ubiquitinated proteins can be found in certain tissues, like pancreas, liver or the hippocampus, isolated from the obese Zucker diabetic fatty rat. This rat strain is a validated model of diabetes, which exhibit obesity and the related diabetic phenotype due to a mutation in the leptin receptor. The clearance of the hyperglycemia induced protein aggregates is seems to be mediated mainly by autophagy rather than proteasomal degradation (Kaniuk et al. 2007). The accumulation of misfolded proteins normally imply the activation of HSPs. Elevated levels of HSF1, HSPA and HSPC family members were found in the pancreatic tissues of type 2 diabetes mellitus (t2DM) monkeys and pancreas of human patients express high level of the ER chaperon HSPA5 (Kavanagh et al. 2009, Laybutt et al. 2007). The increased level of chaperon proteins probably represents a compensatory mechanism for the altered protein homeostasis (Dancsó et al. 2010). In contrast, hepatic cells of diabetic monkey have 50% lower level of HSF1, HSPA and HSPC compared to control (Kavanagh et al. 2009). Similarly, the level of HSPs and their inducibility are low in the liver, the skeletal and cardiac muscle of hyperglycemic rodents (Atalay et al. 2004; Ooie et al. 2005), and reduced expression of HSPA was also found in the skeletal muscle of insulin resistant and diabetic patients, where the level of HSPA correlates with the rate of insulin-stimulated glucose uptake and glucose tolerance (Kurucz et al. 2002; Chung et al. 2008). High-fat diet induced insulin resistance also resulted in a reduced HSPA expression in the arteries of rats (Karpe and Tikoo, 2014). The finding that the level of HSPs and their response to stress stimuli are decreased in insulin responsive tissues in diabetes suggests that the loss of cellular stress response is a central event in the pathogenesis of the disease (Hooper et al. 2014).

Indeed, exercise training, which induces HSP expression, can improve the whole-body insulin sensitivity and glucose tolerance, and have anti-inflammatory effects in obese and diabetic patients (reviewed in Hooper et al. 2014). Moreover, mimicking the physiological effects of exercise by warming skeletal muscle is also effective. Treating t2DM patients with daily hot tub submersion for 3 weeks led to improved fasting glucose, a trend toward weight loss, and the relief of neuropathic symptoms (Hooper 1999). The phenomenon was also confirmed in several animal models (reviewed in Hooper et al. 2014). Whole body hyperthermia induced by far infrared light therapy, improved obesity related insulin resistance in diabetic mice (Kokura et al. 2007). Increasing body temperature can induce the expression of certain HSPs, like HSPA, HSPB1, and mitochondrial HSPD1 in the skeletal muscle, liver and adipose tissue, resulting in improved glucose tolerance, insulin-stimulated glucose transport, and increased insulin signaling in high-fat-diet rats (Gupte et al. 2009). Later, it was showed that, at least in part, the elevated level of HSPA is responsible for the protective effect, as not only heat treatment, but transgenic overexpression of HSPA in the skeletal muscle also can prevent high-fat-diet induced hyperglycemia, hyperinsulinemia, glucose intolerance and insulin resistance in mice (Chung et al. 2008; Henstridge et al. 2014). HSPA transgenic mice seem to be resistant to the high-fat-diet induced obesity, which is probably related to an elevated whole body energy utilization and increased number of mitochondria (Henstridge et al. 2014). Pharmacological induction of HSPs is also effective. Diabetes can be induced in rodents with a single injection of a pancreatic β-cell toxin, streptozoicin. A Bimoclomol derivative, BRX-220, was able to improve insulin sensitivity and diabetes-related deficits in muscle motor and sensory nerve functions in streptozoicin-treated rats (Kürthy et al. 2002). Treatment with another hydroximic acid derivative, BGP15 can reduce fasting levels of glucose and insulin in leptin-deficient obese mice, and this protection was associated with the blocking of inflammation (Chung et al. 2008). BGP15 increased insulin sensitivity and the number of mitochondria in the skeletal muscle of a rat model of diabetes (Henstridge et al. 2014). BGP-15 was also successfully applied in human patients. BGP-15 administration has significantly improved insulin sensitivity in insulin-resistant, non-diabetic human patients, while adverse drug effects were not observed (Literáti-Nagy et al. 2009). It is known from the literature that treatment of different psychiatric diseases, such as schizophrenia or bipolar disorder, with atypical antipsychotic drugs, like olanzapine, leads to metabolic side effects, obesity and insulin resistance. However, BGP15 can also prevent the olanzapine induced insulin

resistance (Literáti-Nagy et al. 2010, 2012). Impaired wound healing is a common symptom of diabetic patients. Expression of HSPA, HSPD1 and HSPB1 is rapidly induced during wound healing in different animal models, suggesting that is has a role in this process (reviewed in Atalay et al. 2009). Indeed, treatment with Bimoclomol containing cream can improve wound healing on the skin of streptozoicin treated diabetic rats (Vígh et al. 1997). Treatment with a HSPC inhibitor, that can upregulate HSPA, ameliorated diabetic peripheral neuropathy in a mouse model of diabetes, and this was correlated with improved sensory neuron mitochondrial bioenergetics. As the drug was ineffective in HSPA knockout mice, the authors suggested, that modulating HSPA is necessary for its function (Ma et al. 2014).

These studies suggest that restoration of heat shock response and the level of HSPs in insulin responsive tissues may be an effective therapeutic strategy for improving insulin sensitivity and reducing the complications of diabetes.

Cancer

The microenvironment of a tumor is rather stressful, because they have poor blood supply resulted in inadequate glucose, oxygen and pH level. The various forms of chemotherapies and other cancer treatments, such as radiotherapy can also induce stress response, therefore the expression level of different HSPs is elevated in several types of cancers, and HSP overexpression usually leads to a poor prognosis in survival and response to therapy. However, it is rather difficult to conclude a general role of HSPs in tumor progression, as there are a number of different cancers and a tumor tissue usually consists of mixed clones (reviewed for example in Sőti and Csermely 1998). Elevated level of HSPC2 was found in breast cancer cells, which may play a role in cell proliferation (Yano et al. 1996). HSPB1 expression is correlated with bad prognosis for example in gastric, liver, prostate cancer, and osteosarcomas (reviewed in Ciocca and Calderwood 2005) and also in pancreatic cancer patients (Baylot et al. 2011). Malignant ovarian tumors have been showed to express higher level of HSPB1 compared to benign tumors (Langdon et al. 1995). HSPB1 is upregulated in a highly metastatic variant of a human breast cancer cell line (Li et al. 2006). On the other hand, it has been demonstrated that overexpression of HSPB1 can decrease the osteolytic bone metastases of breast cancer cells (Lemieux et al. 1999), and high level of the same chaperone has been associated with good prognosis in endometrial adenocarcinomas, oesophageal cancer, and in malignant fibrous histiocytomas. High HSPA expression is correlated with poor prognosis in breast cancer, endometrial cancer, uterine cervical cancer, and transitional cell carcinoma of the bladder. In contrast, elevated expression of HSPA has been associated with good prognosis in oesophageal cancer, pancreatic cancer, renal cancer, and melanoma (reviewed in detail by Ciocca and Calderwood 2005). They suggest that the role of certain HSPs in the disease prognosis may depend on the unique molecular context of each cancer type.

Elevated expression of HSPs has also been proposed to be predictive of poor response to different anticancer therapies (reviewed in Ciocca and Calderwood 2005; Vidyasagar et al. 2012). In breast cancer patients treated with combination chemotherapies, the high nuclear expression of HSPA was correlated with drug resistance, and the increased level of HSPB1 was associated with a shorter disease-free survival (Vargas-Roig et al 1998). Elevated expression of HSPB1 has been also showed to be associated with increased resistance to chemotherapy in the case of ovarian cancer (Langdon et al. 1995) and leukemia (Kasimir-Bauer et al. 1998). High level of HSPA predicted lower response of breast cancers to radiation and hyperthermia (Liu et al. 1996). On the other hand, in lung cancer cells only a weak correlation was found between HSPA expression and drug resistance (Volm and Rittgen 2000), while HSPA expressing osteosarcomas responded better to neoadjuvant chemotherapy compared to HSPA negative tumors (Trieb et al. 1998, reviewed by Ciocca and Calderwood 2005).

HSPs overexpression can lead to resistance to cancer therapies by several ways like preventing apoptotic cell death of the tumor cells, refolding denatured proteins damaged by cytotoxic drugs, and improving DNA repair (Ciocca and Calderwood 2005). In breast cancer, the epidermal growth factor receptor (EGFR)-related tyrosine kinase Her2 is an important therapeutic target. Herceptin treatment can decrease the level of Her2 in different human breast cancer cell lines, probably through the degradation of Her2 protein. However, the response rates to Herceptin monotherapy are low, and in most cases resistance develops within 1 year. It has been demonstrated that HSPB1 is upregulated in a Herceptin resistant human breast cancer cell line. Moreover, using co-immunoprecipitation study, HSPB1 has been shown to bind to Her2, suggesting that HSPB1 is responsible for Herceptin resistance, probably by binding to Her2 and stabilizing it. Indeed, suppression of HSPB1 by siRNA transfection resulted in increased susceptibility to Herceptin (Kang et al. 2008). In another study it was shown that HSPB1 overexpression can inhibit doxorubicin-induced apoptosis in human breast cancer cells (Hansen et al. 1999). Cancer stem cells, that exhibit increased resistance to different cytotoxic agents, also showed increased level of HSPB1 and decreased apoptotic response to chemotherapeutic treatment (Hsu et al. 2011). Therefore, inhibition or downregulation of HSPs seems to be a possible treatment additional to traditional chemotherapy. In a mouse model of lung cancer it has been demonstrated, that quercetin, an inhibitor of HSPB1, combined with traditional chemotherapeutics, was more effective in inhibition of tumor

progression than the traditional chemotherapeutics alone (Hsu et al. 2011). OGX-427 is a modified antisense oligonucleotide complementary to HSPB1 that inhibits HSPB1 expression and enhances drug efficacy in cancer models. OGX-427 can significantly reduce tumor volume and enhance the apoptotic effect of gemcitabine treatment in a mouse model of pancreatic cancer. Phase II clinical trials using OGX-427 are in progress in the United States and Canada for different type of cancers such as breast, ovarian, bladder, prostate and lung cancer (Baylot et al. 2011). Interestingly, certain viruses are oncolytics. Remarkably, viruses like Newcastle Disease Virus kills cancer cells in humans and animal cancer models, yet are not toxic to non-malignant tissues. Indeed, the oncolytic viruses appear to selectively knock out tumor HSPs, promoting cancer cell death while improving host survival in most malignant of cancers like pancreatic cancer and malignant melanoma (Hooper et al. 2012).

On the other hand HSPs can also participate in the elimination of tumor cells. Certain HSPs like HSPA and HSPC family members were found to be expressed on the surface of different cancer cells as tumor-specific antigens. Interestingly, HSPs are expressed on the surface of tumor cells, similarly to virally or bacterially infected cells, but not on the surface of normal cells (Multhoff and Hightower 1996). These surface expressions of HSPs results in the sensitization of tumor cells against the immune system through the enhanced recognition by the natural killer cells (reviewed by Csermely and Yahara 2002; Sreedhar and Csermely 2004). The protein structure of the surface expressed HSPs isolated from different tumors were similar, however their immunogenicity were different. Srivastava first proposed that not HSPs themselves, rather the tumor specific peptides, carried by the chaperones, are responsible for the immunogenicity. It was also suggested, that HSPs help to present these peptides to the MHC-I complex, inducing a cytotoxic T-cell response (Srivastava et al. 1994, reviewed in Csermely and Yahara 2002; Sreedhar and Csermely 2004). This facilitates to induce an anti-tumor immune response by vaccination with HSP-peptide complexes. Immunization with autologous cancer-derived HSP preparations resulted in a reduced growth rate of the primary tumor, a decreased metastatic potential, and increased life span in mice (Tamura et al. 1997). HSP-peptide complex prepared from resected colorectal liver metastasis significantly increased T-cell response against colon cancer, and the occurrence of immune response resulted in a better tumor-free survival in human patients (Mazzaferro et al. 2003).

Conclusion

HSPs are classified into five families that consist of proteins with different structure and more or less different functions. Functionally, they are similar in their role in proteostasis. They assist in the folding of the newly synthesized proteins as well as in the facilitation of protein degradation, thereby they have important roles in maintaining the protein homeostasis during normal cellular functions. Under stress conditions, the increased level of unfolded proteins and the increased membrane fluidity can activate the stress signalling pathway finally leading to an elevated expression of the HSPs. In turn, HSPs protect the different cell components against stress, as they can prevent protein aggregation, maintain the membrane stability, inhibit certain steps of the apoptotic pathway, and decrease oxidative stress. Therefore it is not surprising, that the levels of HSPs can be increased in different diseases protecting tissues. While in other diseases, HSPs are under expressed, resulting in tissues vulnerable to stress and injury. Modulation of HSPs can open vast therapeutic opportunities to treat previously untreatable diseases.

Acknowledgment

This work was supported by grant from National Innovation Office (TÁMOP-4.1.1.C-13/1/KONV-2014-0001).

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