Chapter 6
Role of Heat Shock Proteins in Oxidative Stress and Stress Tolerance

Sumit Ghosh, Poulami Sarkar, Priyanka Basak, Sushweta Mahalanobish, and Parames C. Sil

Abstract Heat shock proteins (HSP) also referred to as stress proteins are a family of proteins produced by cells in response to exposure to stressful conditions like heat, cold, different kinds of environmental stress, such as infection, inflammation, exercise, exposure of the cell to toxins (ethanol, arsenic, trace metals, and UV light, among many others), starvation, hypoxia (oxygen deprivation), nitrogen deficiency (in plants), water deprivation and during wound healing or tissue remodeling. In this review, the authors have elucidated the role of heat shock proteins in stress tolerance both in eukaryotes and prokaryotes. Here, the role of heat shock proteins in survival during more extreme conditions and maintenance of normal cellular homeostasis have also been briefly discussed.

Keywords Heat shock element · Heat shock factor · Heat shock proteins · Oxidative stress · Stress tolerance

Abbreviations

ABA	Abscisic acid
AD	Alzheimer's disease
AHPND	Acute hepatopancreatic necrosis disease
ALS	Amyotrophic lateral sclerosis
aMCI	Amnestic mild cognitive impairment
AR	Amalaki Rasayana
Cd	Cadmium
Clp	Caseinolytic protease
COMT1	Caffeic acid O-methyltransferase1
Cpn	Chaperonin
DBMIB	2,5-dibromo-3-methyl-6-isopropyl-p-benzoquinone

S. Ghosh · P. Sarkar · P. Basak · S. Mahalanobish · P. C. Sil (✉)
Division of Molecular Medicine, Bose Institute, Kolkata, India
e-mail: parames@jcbose.ac.in

© Springer International Publishing AG, part of Springer Nature 2018

A. A. A. Asea, P. Kaur (eds.), *Heat Shock Proteins and Stress*,
Heat Shock Proteins 15, https://doi.org/10.1007/978-3-319-90725-3_6

ER	Endoplasmic reticulum
GolS	Galactinol synthase
GPx	Glutathione peroxidise
H_2O_2	Hydrogen peroxide
HD	Huntington's disease
HSC	Heat shock cognate
HSE	Heat shock elements
HSF	Heat shock factors
HSP	Heat shock proteins
HspA	Heat shock protein family A
HspB	Heat shock protein family B
MG	Methylglyoxal
miRNA	MicroRNA
MPK3	Mitogen-activated protein kinase
mRNA	Messenger RNA
NLHS	Non-lethal heat shock
NO	Nitric oxide
Nrf2	Nuclear factor (erythroid-derived 2)-like 2
PARK7	Parkinson disease protein 7
PD	Parkinson's disease
PEG	Polyethylene glycol
PSII	Photosystem II
RCS	Reactive carbonyl species
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
Se	Selenium
sHsp	Small heat shock proteins
SOD	Superoxide dismutase
T2DM	Type 2 diabetes mellitus
UPR	Unfolded protein response

6.1 Introduction

Since the dawn of cellular life, all living organism in this world is constantly challenged by ever changing variables of the environment. The ability of the organism to successfully adapt to its changing environment is critical to its survival and likely represents an integral driving force in evolution. To cope up with different conditions of stress, organisms have been found to exhibit selective upregulation in the expression of a group of proteins called the heat shock proteins (Hsp). Hsp constitutes a large family of proteins that are usually classified based on their molecular weight: Hsp10, Hsp40, Hsp60, Hsp70, Hsp90, etc. Hsp have been reported to be involved in antigen presentation as chaperones in course of transfer of antigenic peptides to the class I and class II molecules of the major histocompatibility

complexes (Arrigo 1994; Li et al. 2002). A link between heat shock proteins and oxidative stress has been established in a wide array of research (Sørensen 2010). Though the exact mechanisms are yet to be elucidated, it is suggested that oxidative stress can be a principal determinant of thermal tolerance (Abele et al. 2001; Pörtner 2001). The following chapter will inspect the role of heat shock proteins in oxidative stress and stress tolerance (especially thermal tolerance).

6.1.1 Heat Shock Proteins: An Overview

Heat shock proteins are ubiquitous proteins which render universal protective mechanisms from prokaryotes to eukaryotes to sustain cellular function and homeostasis (Table 6.1) (Lindquist and Craig 1988). These proteins were first discovered in *Drosophila* (Ritossa 1964) where it was found that increase in temperature of a few degrees above the physiological range induced the synthesis of these proteins from their salivary glands. The term "heat shock protein" is a misnomer. This family of proteins was originally named due to their expression after heat exposure. But now it is evident that Hsp synthesis is not only due to hyperthermia but also triggered by a wide range of environmental as well as metabolic stress conditions like heavy metal ions, ethanol, nicotine, anoxia, ischemia, glucose deprivation, surgical stress and viral agents (Feige et al. 2013; Santoro 2000). Consequently, the term

Table 6.1 Cellular location and function of mammalian heat shock proteins

HSP family	Molecular Size (kDa)	Cellular location	Proposed function
Ubiquitin	8	Cytosol/ nucleus	Facilitates targeting and removal of proteins denatured by stress
HSP10	10	Mitochondria	Cofactor for Hsp60
Small HSP	20 to 30	Cytosol/ nucleus	Some may be responsible for regulating the cellular cytoskeleton, and others regulate vascular tone and vesselwall remodeling
HSP56	56	Cytosol	Binds and stabilizes the steroid hormone receptor complex
HSP60	60	Mitochondria	Molecular chaperone
HSP70 family:			
HSP 72	72	Cytosol/ nucleus	Protein folding, cytoprotection (stress inducible)
HSP 73	73	Cytosol/ nucleus	Molecular chaperone (constitutively expressed)
HSP75(mHSP70)	75	Mitochondria	Molecular chaperone
HSP78(GRP78)	78	ER	Molecular chaperone, cytoprotection
HSP90	90	Cytosol/ER/ nucleus	Regulation of steroid hormone receptors, protein translocation
HSP110	110	Cytosol	Protein folding

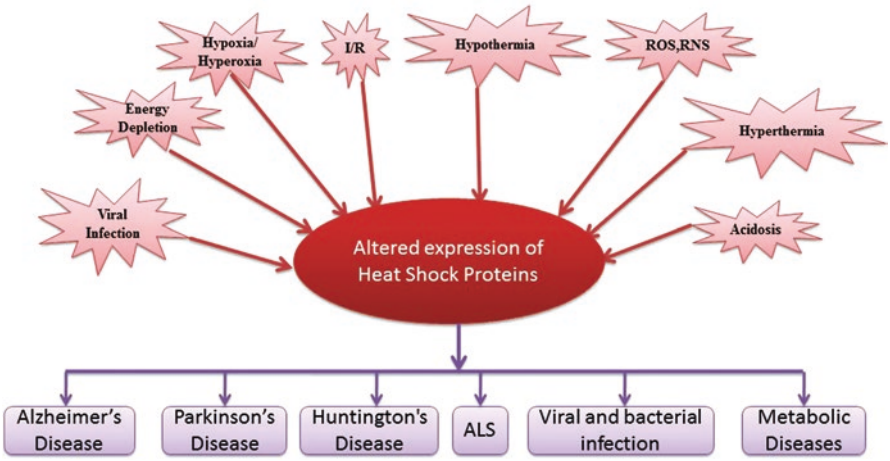

Fig. 6.1 Role of heat shock proteins in various conditions of stress

'stress protein' is preferably used (Whitley et al. 1999). Stress proteins belong to a multigene family and their nomenclature is given based on their molecular size (8-150 kDa). For example, Hsp 60, Hsp 70, Hsp 90 refers the family of heat shock proteins on the order of molecular size 60, 70 and 90 kDa respectively. Hsp are highly conserved and abundant in nearly all subcellular compartments. Many of these proteins show constitutive expression whereas expression level of others get increased under stressed condition (Fig. 6.1). In eukaryotic cells, heat shock factors (HSF) act as transcriptional activators for heat shock genes. There are different families of HSF that get activated under several stressed conditions. Among them, HSFs 1 and 3 function as stress responsive activators and show maximal heat shock responsiveness (Tanabe et al. 1998), whereas HSF 2 is activated during embryonic development and differentiation (Schuetz et al. 1991; Sistonen et al. 1992). HSF 4 seems to be preferentially expressed in the human heart, brain, skeletal muscle and pancreas (Nakai et al. 1997). HSF recognizes modular sequence elements referred to as HSE (a series of pentameric units arranged as inverted adjacent arrays of the sequence 5′-nGAAn-3′) located within the promoter region of heat shock gene (Amin et al. 1988; Perisic et al. 1989). In inactive stage, heat shock factors exist in monomeric form. But when activated, they trimerize into an active form that is capable of binding to the heat shock element (HSE) site of the stress protein gene and initiating transcription and translation of heat shock protein.

Stress proteins function as intracellular chaperones that permit the maturation and correct folding of most of the proteome. They play a crucial role in three dimensional folding of the newly translated polypeptide chain and assist to form proper protein conformation. In fact, they ensure that the newly synthesized polypeptide chain proceed correctly through successive folding and unfolding mechanism to achieve their functional conformation. They can recognize non-native conformation of the polypeptide and prevent their aggregation by binding to hydrophobic residues

that have been exposed during translocation or stress induced damage (Pirkkala and Sistonen 2001). Upon exposure of extreme stress condition, the damaged protein loses its ability to be successfully refolded. Hsp promote ubiquitin mediated proteasomal degradation of these abnormal, unstable proteins. Furthermore, they mediate protein translocation across organellar membranes. It has been found that synthesis of these stress proteins under non-lethal temperature appears to protect the organism from upcoming high temperature or other stress that would be otherwise lethal. In the case of exposure to heat, this phenomenon has been called 'thermotolerance'. Clinical evidences suggest that stress protein synthesis under hyperthermic condition may provide potential safeguard against cardiac ischemia, arterial injury, endotoxic shock, renal and hepatic ischemia, ethanol-induced gastric ulcerations and skeletal muscle ischemia-reperfusion (Morimoto and Santoro 1998; Suzuki et al. 1997). Stress proteins play a pivotal role in the maintenance of cellular homeostasis by regulating immunity, cell cycle progression and apoptosis during development and differentiation. HSP have a significant role on adaptive immunity. During the time of antigen presentation, these molecular chaperons (HSP) associate with a wide range of antigenic peptides and facilitate the delivery of antigenic peptides to the class I and class II molecules of the major histocompatibility complexes. In addition, extracellular HSP can stimulate professional antigen presenting cells (macrophages, dendritic cells) to onset immune response (Li et al. 2002). Members of Hsp family especially Hsp 27 and Hsp 70 function as potent antiapoptotic molecules. Upon exposure to oxidative stress, Hsp 27 inhibits cytochrome c release where inducible Hsp70 prevents apoptosis by interfering with the signaling cascades and by impairing the activation of effector caspases (Pirkkala and Sistonen 2001).

6.1.2 Role of Heat Shock Proteins in Oxidative Stress

Heat stress activates HSFs and also lead to accumulation of reactive oxygen species (ROS), thereby inducing oxidative damage. The HSFs bind to the HSE of the promoter region of HSF, Hsp, ROS scavenging genes and miRNA 398. miRNA 398 downregulates SOD scavengers, thereby leading to rapid accumulation of ROS. This activates Hsp which in turn, activates the ROS scavengers to avoid cellular damage (Fig. 6.2) (Driedonks et al. 2015). A range of physiological stimuli (oxidative stress, hypothermia, hyperthermia, ischemia-reperfusion, hypoxia, acidosis etc.) activate HSFs, which then get separated from HSP. On phosphorylation by protein kinases, HSFs form trimers in the cytosol. The trimer complexes then enter the nucleus and bind to the HSE in the promoter region of the corresponding Hsp gene. Hsp mRNA gets transcribed and leaves the nucleus for the cytosol. Hsp usually function as molecular chaperones and assist in the assembly and translocation of newly synthesized proteins within the cell along with the repair and refolding of damaged proteins (Kregel 2002). Constitutively expressed housekeeping molecular chaperones maintain cellular redox status and integrity of mitochondria (cytosolic Hsp), protect

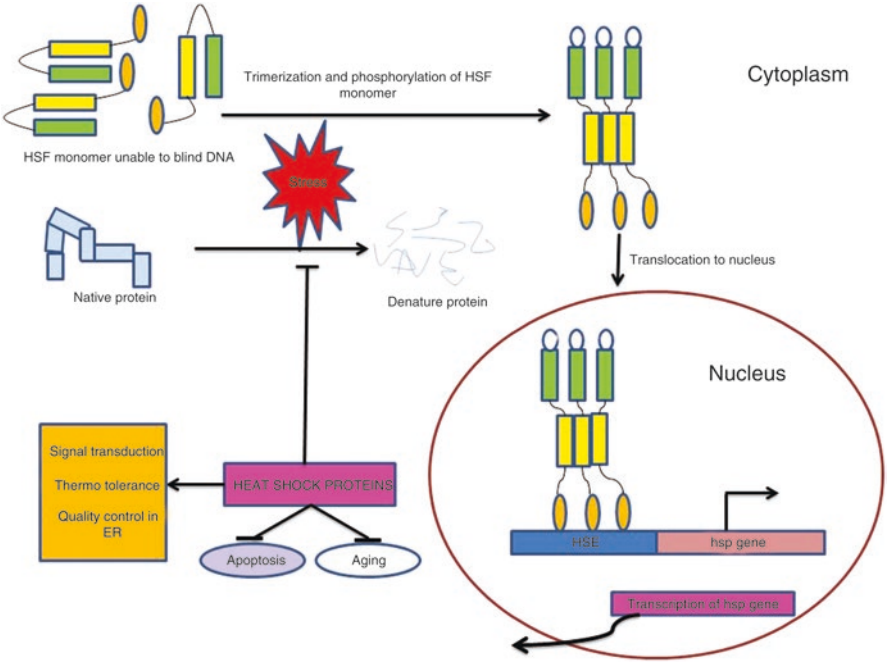

Fig. 6.2 Mechanism of action of heat sock proteins

and facilitate the assembly of respiratory complexes and facilitate their assembly (mitochondrial Hsp) (Kuzmin et al. 2004).

Selenium (Se), a dietary trace element exhibits antioxidant properties. Recent experiments on chicken liver have shown that Hsp play an important role in the oxidative stress induced damage during Se deficiency. It has been reported that expression of Hsp 27, 40, 60, 70, and 90 increase with increment in oxidative stress during Se deficiency. Hsp have been found to exert protective effects during the generation of oxidative stress due to Se deficiency (Liu et al. 2015). Studies have shown that accumulation of ROS in yeast (*Saccharomyces cerevisiae)* is associated with the induction of a heat shock reporter gene over a range of heat shock temperatures (33-44°C). ROS-mediated signaling ensures cooperation between heat shock and antioxidant responses (Moraitis and Curran 2004).

Hsp 70 protects cells from oxidative damage. They bind to stress exposed hydrophobic residues of denatured proteins, thereby preventing them from aggregating and promoting refolding. In the thermophile anaerobe (*Thermatoga maritima*), Hsp 70 exhibits redox sensitive binding to concerned peptides in response to oxidative stress. It interacts with an E3 ubiquitin ligase to transfer proteins towards proteolysis (Lüders et al. 2000; Rajkumar et al. 2015).

Most neurons contain high levels of Hsc70 and low levels of Hsp70 (Cruz et al. 1991). In motor neurons, both forms of Hsp are present, but no increase in endogenous expression is observed during heat shock. Extracellular Hsp70 inhibits apop-

tosis. Johnson *et al*. (Johnson et al. 1990; Johnson et al. 1995) have shown that Hsc/Hsp70 improves resistance to nutrient-deprivation stress when bound to arterial smooth muscle cells after being added to the culture medium *in vitro*. Similar observations have been found in case of cultured monocytes (Guzhova et al. 1998). Tidwell *et al*. have shown that *in vivo* administration of a mixture of Hsc/Hsp70 inhibits motor and sensory neuronal degeneration after sciatic nerve axotomy (Tidwell et al. 2004; Yu et al. 2001). Oxidative stress is characteristic of different protein misfolding associated diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and Amyotrophic lateral sclerosis (ALS) (Andersen 2004; Rauchova et al. 2012; Yu et al. 2001). Oxidative stress disturbs calcium homeostasis, mitochondrial and cytoskeletal functions and can induce neuronal cell death. Thus, apoptosis have been reported in different neurodegenerative diseases (Friedlander 2003; Mattson 2000; Wyttenbach and Arrigo 2009). rhHsp70 protects motor neurons subjected to oxidative stress, common in neurodegenerative diseases such as AD, PD, ALS etc. (Robinson et al. 2005). The levels of different Hsp have been reported to increase in the brain of neurodegenerative disease patients (Brownell et al. 2012; Sun and MacRae 2005; Tóth et al. 2015; Wilhelmus et al. 2006). Several members of the HSPB family have been observed in the senile plaques and cerebral amyloid angiopathy of AD patients. HSPA1 have been found to colocalize with Aβ peptides and α-synuclein. HSPA8 has been found in intracellular inclusions in ALS (Muchowski and Wacker 2005). Overexpression of members of DNAJ protein family suppress the nuclear aggregation of mutant ataxin-1 and ataxin-3 thereby decreasing their toxicity in vitro model (Chai et al. 1999; Cummings et al. 2001). Overexpression of HSPA has been found to decrease polyglutamine induced neurodegeneration in *Drosophila* model of polyglutamine disease (Warrick et al. 1999).

ROS generation in the brain of AD patients lead to the increased expression of HSC 71, Hsp 27, HDJ 1 etc. (Najarzadegan et al. 2016). Poly(Q) mutation can generate ROS and is therefore prevented by Hsp 27 (Wyttenbach et al. 2002). HDJ-1 preserves mitochondrial function and proteasomal activity following oxidative injury (Ding and Keller 2001). Increased level of oxidation in AD brain is induced by HSC 71 (Castegna et al. 2002). Recent observations of the mechanism of induction of HSP and the decrease in the levels of Thioredoxin 1 in amnestic mild cognitive impairment (aMCI) brain suggest that alteration in the chaperone systems may contribute to the pathogenesis and progression of AD (Di Domenico et al. 2010).

Glial cells have been speculated to supply neighboring neurons with Hsp 70 by means of motor neurons during conditions of stress (Tytell et al. 1986). On the other hand, the HSPB protect cells from apoptosis and oxidative insult by binding to the cytoskeletal proteins (Tóth et al. 2015). HSPB decrease the level of ROS and regulate intracellular redox homeostasis, thereby protecting cytoskeleton, an important target for oxidative stress (Golenhofen et al. 2006; Mymrikov et al. 2011). HSPB 5/HSPB 2 deficiency affects cardiac function pointing towards their possible role in maintaining normal cardiac functions (Golenhofen et al. 2006; Morrison et al. 2004; Ray et al. 2001).

Ethanol consumption results in increased generation of ROS (Wu and Cederbaum 2003). The protective effects of HSP against ethanol induced toxicity have been reported in case of brain and hepatic cells (Russo et al. 2001). Vogt and coworkers (2001) have reported that metabolic stress caused by the high intensity activity, rather than stimulated hypoxia, is the primary cause of activation of Hsp 70. The accumulation of lactate and alterations of pH during intensive exercise act as the primary stimuli for Hsp expression (Mc Naughton et al. 2006). The heat shock protein 70–2 (*HSPA1B*) and 70-hom (*HSPA1L*) genes and their functional polymorphisms have been reported to play a role in the pathogenesis of type 2 diabetes mellitus (T2DM) (Umapathy et al. 2012). Toxic metals are associated with induction of oxidative stress. Accumulation of Cu^{2+} is associated with genetic disorders such as Wilson's and Menke's disease. Small Hsp (sHsp) such as Hsp27 and αB-crystallin bind to Cu^{2+} and inhibit Cu^{2+} mediated generation of ROS (Bakthisaran et al. 2015).

6.1.3 Role of Heat Shock Proteins in Stress Tolerance in Prokaryotes

Study of Sakthivel et al. have shown that HSPA and small heat shock proteins in general, play an important role in oxidative stress tolerance and help to stabilize membrane proteins like the photosystems and phycobilisomes in the cyanobacterium. In this study, both wild type and an *hspA* deleted strain from *Synechocystis* sp. PCC 6803 were being compared in the presence of methyl viologen or peroxide stress. The results showed that the cell growth, viability and pigment contents in thylakoid membranes were markedly reduced in the mutant even after enhancing the expression of other molecular chaperones. But *Synechococcus elongatus* strain ECT16–1, which constitutively expresses HSPA showed a much better cell growth and viability. The reduction of pigment contents was also arrested after 24 h in this strain (Sakthivel et al. 2009). It has been reported that *Salmonella typhimurium* gets adapted to oxidative stress when pre-treated with non-lethal dose of hydrogen peroxide by virtue of the induction of 30 proteins. Of these, 9 are constitutively overexpressed in hydrogen peroxide resistant *oxyR* mutants. Mutant *oxyR1* is resistant to oxidizing agents and overexpresses 3 Hsp (D 64a, E 89, F 52a). The *oxyR* regulatory network is a previously uncharacterized global regulatory network in enteric bacteria (Christman et al. 1985).

6.1.4 Role of Heat Shock Proteins in Stress Tolerance in Plants

Heat stress induces protein denaturation which in turn, phosphorylates and activates Hsp 60, 70, 90, 100. Hsp 70 can be obtained from tomato rice etc., Hsp 90 from maize, wheat etc., Hsp 70 from Soyabean, Hsp 60 from barley, rye and sHsp from

millet, sorghum etc. 7Hsp 70, Hsp 60 (Chaperonin), Hsp 90, Hsp 100/Clp and small Hsp act as molecular chaperones and impart plant tolerance to various modes of stress. The various subfamilies (DnaK, Hsp 110) of Hsp 70 are distributed in the cytosol, chloroplast, mitochondria and endoplasmic reticulum. They are associated with the prevention of protein aggregation and assistance in refolding, translocation, transcriptional activation and signal transduction. The various subfamilies (Cpn 60 etc.) of Hsp 60 are distributed in the cytosol and mitochondria and assist in protein folding. The various subfamilies (AtHsp 90–1, 5, 6, 7) of Hsp 90 are found in the cytosol, chloroplast, mitochondria and endoplasmic reticulum. They facilitate genetic buffering and signal transduction. The various subfamilies (Clp B, Clp D etc.) of Hsp 100 are found in the cytosol, chloroplast and mitochondria and assist in protein unfolding. The various subfamilies (Hsp 17.6, 17.9 etc.) of sHsp are found in the cytosol, chloroplast, mitochondria and endoplasmic reticulum. They prevent protein aggregation and stabilize non-native proteins (Usman et al. 2014).

Hsp104, Hsp70, and Hsp40 are predominant during replication. On the other hand, Hsp90 is associated with transcriptional and post-transcriptional processes. Hsp70 and Hsp90, in combination, plays a major role in morphogenesis. Heat stress in fungi lead to increased expression of Hsp10, Hsp30, Hsp60, Hsp90, and Hsp104 proteins, while expression of Hsp12 increases in response to cold stress. Osmotic stress is controlled by small heat shock proteins and Hsp60. Expression of Hsp30, Hsp70, and Hsp90 increases in response to pH stress. Hsp104 is also associated with conditions of high pressure. Recent experimentations suggest that Hsp90 can be a potential antifungal target due to its role in morphogenesis (Tiwari et al. 2015).

In another study, the expression level of a small heat shock protein *EsHsp16.9,* isolated from Siberian wild rye (*Elymus sibiricus*) increases when exposed to stressors like heat, drought, arsenic, methyl viologen and H2O2 treatment. *In vitro* study, this protein has reduced thermal aggregation of malate dehydrogenase. When this *EsHsp16.9* is expressed in E. coli, it shows better cell growth under salt, arsenic, polyethylene glycol and heat (Lee et al. 2015). The yeast metallothionein gene CUP1 is transcriptionally activated during oxidative stress by means of a functional HSE and HSF. CUP1 imparts metal detoxification and protects against oxidative insult (Liu and Thiele 1996).

Heat stress is a primary factor of deterioration in summer creeping bentgrass (*Agrostis stolonifera*) (Heat Shock Proteins in Relation to Heat Stress Tolerance of Creeping Bentgrass at different nitrogen levels). Nitrogen medium helped the grass to better survive during long term heat stress. Fv/Fm, a correlation between chloroplast-sHsp production and PSII efficiency indicates that this chloroplast-sHsp plays a direct role in the protection of PSII (Heckathorn et al. 1998). 38It is also reported that heterologous expression of MsHsp 23in creeping bentgrass protects against thermal stress by chaperone activity, associated with the induction of ascorbate peroxidase.

Now-a-days, cross-stress tolerance possesses an important role in producing stress-resistant crops. Heat or cold priming-induced cross-tolerance is very common in plants. Multiple stress signaling pathways involving ROS, RNS, reactive carbonyl species (RCS), most particularly H_2O_2, nitric oxide (NO) and methylgly-

oxal (MG) provide resistance to abiotic stresses via modulating the expression of genes as well as modifying proteins post-translationally (Hossain et al. 2017). ROS influences the stress tolerance in the yeast. H_2O_2 promotes accumulation of Hsp 70 and Hsp 90 mRNA (Moraitis and Curran 2004). ROS, H_2O_2, and 2, 5-dibromo-3-methyl-6-isopropyl-p-benzoquinone (DBMIB), an endogenous H_2O_2 propagator induces HsfA3 transcription in seedlings leading to oxidative stress tolerance. The overexpression of several genes encoding galactinol synthase (GolS) increase galactinol levels (Song et al. 2016).

Studies in Arabidopsis (*Arabidopsis thaliana*) have shown that induction of HSFA4A enhances tolerance to salt and oxidative agents via altering transcription of a large set of genes. Its inactivation results in hypersensitivity to salt stress. hsfa4a mutants elevate H_2O_2 accumulation and lipid peroxidation (Pérez-Salamó et al. 2014). Chaperone production and improvement of stress resistance in arabidopsis can be elevated by overexpressing AtHSFA1b, AtHSFA2, AtHSFA3, AtHsfA4a and AtHSFA6a (Jacob et al. 2016) but this may lead to moderate to severe dwarfism (Yoshida et al. 2011). Alfalfa, (*Medicago sativa*) overexpressing Hsp gene (MsHSP70) is less sensitive to polyethylene glycol (PEG) than control group (Li et al. 2017). Arabidopsis Hsp 21 is a crucial component of thermomemory. It is a plastidial small heat shock protein that rapidly accumulates after heat stress (Sedaghatmehr et al. 2016). Lack of functional FtsH6, a plastid-localized metalloprotease promotes Hsp 21 accumulation during the later stages of thermomemory and increases thermomemory capacity.

In yeast (*Saccharomyces cerevisiae*) two-hybrid and bimolecular fluorescence complementation assays, homomeric interaction of HSFA4A is reduced by alanine replacement of three conserved cysteine residues. MPK3 and MPK6 phosphorylate HSFA4A in vitro on three distinct sites, among them serine-309 is the major phosphorylation site. They can form in vivo complexes with ZAT10/salt tolerance zinc finger and thus regulate plant defense responses (Mittler et al. 2006; Nguyen et al. 2012).

CsHSP17.2, a molecular chaperone present in the cytosol and the nucleus is essential for thermotolerance by maintaining maximum photochemical efficiency and protein synthesis, enhancing the scavenging ROS and inducing the expression of HS-responsive genes in tea plants (*Camellia sinensis*) (Wang et al. 2017). Its expression is significantly upregulated by heat stress. Transgenic E. coli and Pichia pastoris expressing CsHSP17.2 exhibit enhanced thermotolerance.

DcHsp17.7, another cytosolic Class I heat shock protein accumulates in carrot (*Daucus carota*) leaf tissue under oxidative and osmotic (PEG) stress conditions (Ahn and Song 2012). Heterologously expressed DcHsp17.7 enhanced E. coli cell viability under various abiotic stress conditions such as salinity (Song and Ahn 2011), heat (Kim and Ahn 2009), cold (Song and Ahn 2010), oxidation and osmotic stress. Transgenic carrot plants overexpressing DcHsp17.7 showed higher thermotolerance (Malik et al. 1999) and transgenic potato plants showed enhanced cellular membrane stability and tuberization under heat stress (Ahn et al. 2004).

Genetic engineering develops crop plants possessing enhanced stress tolerance (Bhatnagar-Mathur et al. 2008). During abiotic stress, methylglyoxal accumulates to toxic levels in affected cells. In stress affected cells it is routinely detoxified through the action of DJ1/PARK7/Hsp31 proteins via targeting mitochondria and inducing expression of key stress-related genes. Hsp31 confers dual biotic and abiotic stress tolerance in*Nicotiana tabacum* as well as stress tolerance against diverse biotic stress inducers such as viruses, bacteria and fungi in tobacco plants (Melvin et al. 2017). 39On the other hand, the Hsp 90 and isocitrate lyase genes of *Nicotiana tobacum* plants have been reported to be associated with the development and reproduction of a root knot nematode *Meloidogyne incognita*.

HSFA6b plays a pivotal role in the response to ABA and in thermotolerance (Huang et al. 2016). ABA-responsive element-binding protein1 activates the HSFA6B promoter, as a result increased HSFA6B directly binds to the promoter of dehydration-responsive element-binding protein2A and enhances its expression. Under salt stress conditions, ER-sHsp transgenic plants have more vigorous roots, maintain a higher relative water content, absorb less sodium, accumulate more osmolytes, and sustain less damage to the photosystem, compared to wild-type non-transgenic plants. This study proves that UPR signaling pathway affects plant abiotic tolerance (Fu et al. 2016).

The tomato (*Lycopersicon esculentum*) chloroplast small heat shock protein (sHsp), Hsp 21 is induced by thermal stress in leaves and in developing fruits in course of transition of chloroplasts to chromoplasts. Hsp 21 protects PSII from temperature dependent oxidative stress. Analysis of leaf phenotype, chlorophyll content, and photosynthetic efficiency reveals that silencing of heat-shock factor A1a (HsfA1a) gene decreases melatonin levels and cadmium (Cd) tolerance, whereas its overexpression enhances the expression of the melatonin biosynthetic gene caffeic acid O-methyltransferase1 (COMT1) and melatonin accumulation leading to Cd tolerance in tomato plants (Cai et al. 2017; Neta-Sharir et al. 2005).

6.1.5 Role of Heat Shock Proteins in Stress Tolerance in Animals

A study by Dwivedi and Lakhotia have shown that Amalaki Rasayana (AR), an ayurvedic herbal formulation, improves tolerance in *Drosophila melanogaster* against crowding, thermal (Dwivedi et al. 2012; Wang et al. 2004) or oxidative stress. The expression of Hsp 27 which is important in stress tolerance like starvation, oxidative stress and in life span determination (Hao et al. 2007; Pandey et al. 2016; Shi et al. 2011; Wang et al. 2004) is elevated in both AR-fed wild type control and AR-treated heat shocked larvae (Dwivedi and Lakhotia 2016).

Antarctic sea urchin (*Sterechinus neumayeri)* are reported to be capable of overexpressing stress proteins (Hsp 90, Hsc 70, Hyou 1etc.) as a result of thermal stress (González et al. 2016).

It is reported that Hsp 70 family of proteins are essential for the cellular survival from heat stress and other types of physiological challenges in fish. Although programs of gene therapy have made impressive advances in recent years, the over expression of Hsp70 has proven to be problematic. Thus, its therapeutic role needs further investigation (Basu et al. 2002).

However, it has been shown that oxidative stress mediates upregulation of Hsp 90α in the hepatocytes of *Mugil cephalus* living in a polluted estuary. The stress resistance imparted by Hsp 90α involves proteins such as apoptosis signal-regulating kinase 1 (ASK 1), c-Jun NH2-terminal protein kinase 1/2, signal transducers and activators of transcription (STAT), extracellular signal-regulated kinase 1/2 (ERK 1/2), protein kinase B, nuclear factor-kappa B (NF kB), Ets-like protein 1, and B cell lymphoma-2 (Padmini and Rani 2011).

According to one study, both acute and chronic non-lethal heat shock (NLHS) treatment enhances the survival rate of shrimps *Peneaus vannamei* against acute hepatopancreatic necrosis disease (AHPND) caused by *Vibrio parahaemolyticus* than non-treated shrimps (Junprung et al. 2017). The authors have shown that the expression levels of heat shock proteins like LvHSP70, LvHSP90 and immune-related genes like LvproPO and LvCrustin are upregulated in chronic NLHS treated shrimps. But in shrimps with LvHSP70 and LvHSP90 gene knockdown, tolerance against chronic NLHS was absent, suggesting a vital role of heat shock proteins like Hsp70 and Hsp90 in bacterial defence in shrimp. Not only that, knockdown of Hsp 70 also influences the heat and bacterial infection tolerance in *Artemia franciscana* nauplii (Iryani et al. 2017). Fishes of hot spring run-off areas (*Puntius sophore*) have shown high expression level of Hsp 90 and Hsp 47 to tolerate heat shock (Mahanty et al. 2017).

Nrf2 (Nuclear factor (erythroid-derived 2)-like 2) helps in stress tolerance. A study by Mohanty et al. have shown that dietary curcumin supplementation in *Puntius sophore* enhances the expression levels of Nrf-2, SOD, catalase, gpx, Hsp 60, Hsp 70, Hsp 90 and Hsp 110 in gill and liver compared to control group. The result suggests that curcumin supplemented group exerts better stress tolerance via Nrf2 induced upregulation of various antioxidative enzymes and heat shock proteins (Mahanty et al. 2017). According to another study, in thermal tolerance, the expression mode of Hsp 70 is much more crucial than Hsp 70 itself. When *P. olivaceus* and the hybrids (*P.olivaceus* ♀ × *P. dentatus* ♂) are subjected to both acute and chronic heat stress, the hybrids shows better thermotolerence via increased temperature thresholds, shorter durations, stronger magnitudes and increased delays of Hsp 70expression (Liu et al. 2017).

Kurino et al. have shown in their study that *Caenorhabditis elegans* exertsmore longevity and thermotolerance when treated with isoamyl alcohol and acetic acid as odor stimuli. In presence of isomethyl alcohol, the expression levels of SOD 3 and Hsp 12.6 are increased and heat stress tolerance is mediated through DAF-16 activation whereas acetic acid odor stimulus increases the expression level of Hsp 16.2 and the stress tolerance is mediated through HSF-1 activation (Kurino et al. 2017).

6.2 Conclusions

Owing to their evolutionary significance, heat shock proteins have been extensively studied. Their link with oxidative stress has been reported in a wide range of studies. However, their detailed molecular mechanisms are yet to be investigated. Oxidative stress has also been reported to be a principal component of thermal tolerance. This chapter has ventured into the ocean of information put forward by a wide range of research articles related to the role of heat shock proteins in oxidative stress. The related studies have imparted valuable knowledge of the interplay of heat shock proteins and oxidative insult in a wide range of diseases like Alzheimer's, Parkinson, diabetes etc. The various mechanisms of stress tolerance associated with heat shock proteins have also been provided with respect to prokaryotes, plants and animals.

Acknowledgements The authors thank Bose Institute, Kolkata for providing the facility needed to gather information in relation to this chapter.

References

Abele D, Tesch C, Wencke P, Pörtner HO (2001) How does oxidative stress relate to thermal tolerance in the Antarctic bivalve Yoldia eightsi? Antarct Sci 13:111–118

Ahn Y-J, Song N-H (2012) A cytosolic heat shock protein expressed in carrot (Daucus carota L.) enhances cell viability under oxidative and osmotic stress conditions. Hortscience 47:143–148

Ahn Y-J, Claussen K, Zimmerman JL (2004) Genotypic differences in the heat-shock response and thermotolerance in four potato cultivars. Plant Sci 166:901–911

Amin J, Ananthan J, Voellmy R (1988) Key features of heat shock regulatory elements. Mol Cell Biol 8:3761–3769

Andersen JK (2004) Oxidative stress in neurodegeneration: cause or consequence? Nat Med 10

Arrigo A-P (1994) Expression and function of the low-molecular-weight heat shock proteins. The biology of heat shock proteins and molecular chaperones, 335–373

Bakthisaran R, Tangirala R, Rao CM (2015) Small heat shock proteins: role in cellular functions and pathology. Biochim Biophys Acta Proteins Proteomics 1854:291–319

Basu N, Todgham A, Ackerman P, Bibeau M, Nakano K, Schulte P, Iwama GK (2002) Heat shock protein genes and their functional significance in fish. Gene 295:173–183

Bhatnagar-Mathur P, Vadez V, Sharma KK (2008) Transgenic approaches for abiotic stress tolerance in plants: retrospect and prospects. Plant Cell Rep 27:411–424

Brownell SE, Becker RA, Steinman L (2012) The protective and therapeutic function of small heat shock proteins in neurological diseases. Front Immunol 3:74

Cai SY, Zhang Y, Xu YP, Qi ZY, Li MQ, Ahammed GJ, Xia XJ, Shi K, Zhou YH, Reiter RJ (2017) HsfA1a upregulates melatonin biosynthesis to confer cadmium tolerance in tomato plants. J Pineal Res 62

Castegna A, Aksenov M, Thongboonkerd V, Klein JB, Pierce WM, Booze R, Markesbery WR, Butterfield DA (2002) Proteomic identification of oxidatively modified proteins in Alzheimer's disease brain. Part II: dihydropyrimidinase-related protein 2, α-enolase and heat shock cognate 71. J Neurochem 82:1524–1532

Chai Y, Koppenhafer SL, Bonini NM, Paulson HL (1999) Analysis of the role of heat shock protein (Hsp) molecular chaperones in polyglutamine disease. J Neurosci 19:10338–10347

Christman MF, Morgan RW, Jacobson FS, Ames BN (1985) Positive control of a regulon for defenses against oxidative stress and some heat-shock proteins in salmonella typhimurium. Cell 41:753–762

Cruz T, Kandel R, Brown I (1991) Interleukin 1 induces the expression of a heat-shock gene in chondrocytes. Biochem J 277:327–330

Cummings CJ, Sun Y, Opal P, Antalffy B, Mestril R, Orr HT, Dillmann WH, Zoghbi HY (2001) Over-expression of inducible HSP70 chaperone suppresses neuropathology and improves motor function in SCA1 mice. Hum Mol Genet 10:1511–1518

Di Domenico F, Sultana R, Tiu GF, Scheff NN, Perluigi M, Cini C, Butterfield DA (2010) Protein levels of heat shock proteins 27, 32, 60, 70, 90 and thioredoxin-1 in amnestic mild cognitive impairment: an investigation on the role of cellular stress response in the progression of Alzheimer disease. Brain Res 1333:72–81

Ding Q, Keller JN (2001) Proteasome inhibition in oxidative stress neurotoxicity: implications for heat shock proteins. J Neurochem 77:1010–1017

Driedonks N, Xu J, Peters JL, Park S, Rieu I (2015) Multi-level interactions between heat shock factors, heat shock proteins, and the redox system regulate acclimation to heat. Front Plant Sci 6

Dwivedi V, Lakhotia SC (2016) Ayurvedic Amalaki Rasayana promotes improved stress tolerance and thus has anti-aging effects in Drosophila melanogaster. J Biosci 41:697–711

Dwivedi V, Anandan E, Mony RS, Muraleedharan T, Valiathan M, Mutsuddi M, Lakhotia SC (2012) In vivo effects of traditional Ayurvedic formulations in Drosophila melanogaster model relate with therapeutic applications. PLoS One 7:e37113

Feige, U., Morimoto, R.I., Polla, B. (2013) Stress-inducible cellular responses. *Birkhäuser*

Friedlander RM (2003) Apoptosis and caspases in neurodegenerative diseases. N Engl J Med 348:1365–1375

Fu C, Liu X, Yang W, Zhao C, Liu J (2016) Enhanced salt tolerance in tomato plants constitutively expressing heat-shock protein in the endoplasmic reticulum. Genet Mol Res 15

Golenhofen N, Redel A, Wawrousek E, Drenckhahn D (2006) Ischemia-induced increase of stiffness of αB-crystallin/HSPB2-deficient myocardium. Pflugers Arch 451:518–525

González K, Gaitán-Espitia J, Font A, Cárdenas CA, González-Aravena M (2016) Expression pattern of heat shock proteins during acute thermal stress in the Antarctic Sea urchin, Sterechinus neumayeri. Rev Chil Hist Nat 89:2

Guzhova IV, Arnholdt AC, Darieva ZA, Kinev AV, Lasunskaia EB, Nilsson K, Bozhkov VM, Voronin AP, Margulis BA (1998) Effects of exogenous stress protein 70 on the functional properties of human promonocytes through binding to cell surface and internationalization. Cell Stress Chaperones 3:67

Hao X, Zhang S, Timakov B, Zhang P (2007) The Hsp27 gene is not required for drosophila development but its activity is associated with starvation resistance. Cell Stress Chaperones 12:364–372

Heckathorn SA, Downs CA, Sharkey TD, Coleman JS (1998) The small, methionine-rich chloroplast heat-shock protein protects photosystem II electron transport during heat stress. Plant Physiol 116:439–444

Hossain MA, Li Z-G, Hoque TS, Burritt DJ, Fujita M, Munné-Bosch S (2017) Heat or cold priming-induced cross-tolerance to abiotic stresses in plants: key regulators and possible mechanisms. *Protoplasma*:1–14

Huang Y-C, Niu C-Y, Yang C-R, Jinn T-L (2016) The heat stress factor HSFA6b connects ABA signaling and ABA-mediated heat responses. Plant Physiol 172:1182–1199

Iryani MTM, MacRae TH, Panchakshari S, Tan J, Bossier P, Wahid MEA, Sung YY (2017) Knockdown of heat shock protein 70 (Hsp70) by RNAi reduces the tolerance of Artemia franciscana nauplii to heat and bacterial infection. J Exp Mar Biol Ecol 487:106–112

Jacob P, Hirt H, Bendahmane A (2016) The heat shock protein/chaperone network and multiple stress resistance. Plant Biotechnol J

Johnson AD, Berberian PA, Bond MG (1990) Effect of heat shock proteins on survival of isolated aortic cells from normal and atherosclerotic cynomolgus macaques. Atherosclerosis 84:111–119

Johnson AD, Berberian PA, Tytell M, Bond MG (1995) Differential distribution of 70-kD heat shock protein in atherosclerosis. Arterioscler Thromb Vasc Biol 15:27–36

Junprung W, Supungul P, Tassanakajon A (2017) HSP70 and HSP90 are involved in shrimp Penaeus vannamei tolerance to AHPND-causing strain of Vibrio parahaemolyticus after non-lethal heat shock. Fish Shellfish Immunol 60:237–246

Kim H, Ahn Y-J (2009) Expression of a gene encoding the carrot HSP17. 7 in Escherichia coli enhances cell viability and protein solubility under heat stress. Hortscience 44:866–869

Kregel KC (2002) Invited review: heat shock proteins: modifying factors in physiological stress responses and acquired thermotolerance. J Appl Physiol 92:2177–2186

Kurino C, Furuhashi T, Sudoh K, Sakamoto K (2017) Isoamyl alcohol odor promotes longevity and stress tolerance via DAF-16 in Caenorhabditis elegans. Biochem Biophys Res Commun 485:395–399

Kuzmin EV, Karpova OV, Elthon TE, Newton KJ (2004) Mitochondrial respiratory deficiencies signal up-regulation of genes for heat shock proteins. J Biol Chem 279:20672–20677

Lee S-H, Lee K-W, Lee D-G, Son D, Park SJ, Kim K-Y, Park HS, Cha J-Y (2015) Identification and functional characterization of Siberian wild rye (Elymus sibiricus L.) small heat shock protein 16.9 gene (EsHsp16. 9) conferring diverse stress tolerance in prokaryotic cells. Biotechnol Lett 37:881–890

Li Z, Menoret A, Srivastava P (2002) Roles of heat-shock proteins in antigen presentation and cross-presentation. Curr Opin Immunol 14:45–51

Li Z, Long R, Zhang T, Wang Z, Zhang F, Yang Q, Kang J, Sun Y (2017) Molecular cloning and functional analysis of the drought tolerance gene MsHSP70 from alfalfa (Medicago sativa L.). J Plant Res 130:387–396

Lindquist S, Craig E (1988) The heat-shock proteins. Annu Rev Genet 22:631–677

Liu X-d, Thiele DJ (1996) Oxidative stress induced heat shock factor phosphorylation and HSF-dependent activation of yeast metallothionein gene transcription. Genes Dev 10:592–603

Liu C, Fu J, Xu F, Wang X, Li S (2015) The role of heat shock proteins in oxidative stress damage induced by se deficiency in chicken livers. Biometals 28:163–173

Liu Y, Ma D, Zhao C, Xiao Z, Xu S, Xiao Y, Wang Y, Liu Q, Li J (2017) The expression pattern of hsp70 plays a critical role in thermal tolerance of marine demersal fish: multilevel responses of Paralichthys olivaceus and its hybrids (P. Olivaceus♀× P. Dentatus♂) to chronic and acute heat stress. Mar Environ Res 129:386–395

Lüders J, Demand J, Höhfeld J (2000) The ubiquitin-related BAG-1 provides a link between the molecular chaperones Hsc70/Hsp70 and the proteasome. J Biol Chem 275:4613–4617

Mahanty A, Purohit GK, Yadav RP, Mohanty S, Mohanty BP (2017) hsp90 and hsp47 appear to play an important role in minnow Puntiussophore for surviving in the hot spring run-off aquatic ecosystem. Fish Physiol Biochem 43:89–102

Malik MK, Slovin JP, Hwang CH, Zimmerman JL (1999) Modified expression of a carrot small heat shock protein gene, Hsp17. 7, results in increased or decreased thermotolerance. Plant J 20:89–99

Mattson MP (2000) Apoptosis in neurodegenerative disorders. Nat Rev Mol Cell Biol 1:120

Mc Naughton L, Lovell R, Madden L (2006) Heat shock proteins in exercise: a review. J Exerc Sci Physiother 2:13

Melvin P, Bankapalli K, D'Silva P, Shivaprasad P (2017) Methylglyoxal detoxification by a DJ-1 family protein provides dual abiotic and biotic stress tolerance in transgenic plants. Plant Mol Biol:1–17

Mittler R, Kim Y, Song L, Coutu J, Coutu A, Ciftci-Yilmaz S, Lee H, Stevenson B, Zhu J-K (2006) Gain-and loss-of-function mutations in Zat10 enhance the tolerance of plants to abiotic stress. FEBS Lett 580:6537–6542

Moraitis C, Curran BP (2004) Reactive oxygen species may influence the heat shock response and stress tolerance in the yeast Saccharomyces cerevisiae. Yeast 21:313–323
Morimoto RI, Santoro MG (1998) Stress–inducible responses and heat shock proteins: new pharmacologic targets for cytoprotection. Nat Biotechnol 16:833–838
Morrison LE, Whittaker RJ, Klepper RE, Wawrousek EF, Glembotski CC (2004) Roles for αB-crystallin and HSPB2 in protecting the myocardium from ischemia-reperfusion-induced damage in a KO mouse model. Am J Phys Heart Circ Phys 286:H847–H855
Muchowski PJ, Wacker JL (2005) Modulation of neurodegeneration by molecular chaperones. Nat Rev Neurosci 6:11
Mymrikov EV, Seit-Nebi AS, Gusev NB (2011) Large potentials of small heat shock proteins. Physiol Rev 91:1123–1159
Najarzadegan M, Ataei E, Akbarzadeh F (2016) The role of heat shock proteins in Alzheimer disease: a systematic review. J Syndr 3:6
Nakai A, Tanabe M, Kawazoe Y, Inazawa J, Morimoto RI, Nagata K (1997) HSF4, a new member of the human heat shock factor family which lacks properties of a transcriptional activator. Mol Cell Biol 17:469–481
Neta-Sharir I, Isaacson T, Lurie S, Weiss D (2005) Dual role for tomato heat shock protein 21: protecting photosystem II from oxidative stress and promoting color changes during fruit maturation. Plant Cell 17:1829–1838
Nguyen XC, Hoang MHT, Kim HS, Lee K, Liu X-M, Kim SH, Bahk S, Park HC, Chung WS (2012) Phosphorylation of the transcriptional regulator MYB44 by mitogen activated protein kinase regulates Arabidopsis seed germination. Biochem Biophys Res Commun 423:703–708
Padmini E, Rani MU (2011) Heat-shock protein 90 alpha (HSP90α) modulates signaling pathways towards tolerance of oxidative stress and enhanced survival of hepatocytes of Mugil cephalus. Cell Stress Chaperones 16:411–425
Pandey A, Saini S, Khatoon R, Sharma D, Narayan G, Chowdhuri DK (2016) Overexpression of hsp27 rescued neuronal cell death and reduction in life-and health-span in drosophila melanogaster against prolonged exposure to dichlorvos. Mol Neurobiol 53:3179–3193
Pérez-Salamó I, Papdi C, Rigó G, Zsigmond L, Vilela B, Lumbreras V, Nagy I, Horváth B, Domoki M, Darula Z (2014) The heat shock factor A4A confers salt tolerance and is regulated by oxidative stress and the mitogen-activated protein kinases MPK3 and MPK6. Plant Physiol 165:319–334
Perisic O, Xiao H, Lis JT (1989) Stable binding of drosophila heat shock factor to head-to-head and tail-to-tail repeats of a conserved 5 bp recognition unit. Cell 59:797–806
Pirkkala L, Sistonen L (2001) Heat shock proteins (HSPs): structure, function and genetics. *eLS*
Pörtner H (2001) Climate change and temperature-dependent biogeography: oxygen limitation of thermal tolerance in animals. Naturwissenschaften 88:137–146
Rajkumar U, Vinoth A, Rajaravindra K, Shanmugham M, Rao S (2015) Effect of in ovo inoculation of vitamin E on expression of Hsp-70 m RNA and juvenile growth in coloured broiler chicken. Indian J Poult Sci 50:104–108
Rauchova H, Vokurkova M, Koudelova J (2012) Hypoxia-induced lipid peroxidation in the brain during postnatal ontogenesis. Physiol Res 61:S89
Ray PS, Martin JL, Swanson EA, Otani H, Dillmann WH, Das DK (2001) Transgene overexpression of αB crystallin confers simultaneous protection against cardiomyocyte apoptosis and necrosis during myocardial ischemia and reperfusion. FASEB J 15:393–402
Ritossa F (1964) Experimental activation of specific loci in polytene chromosomes of drosophila. Exp Cell Res 35:601–607
Robinson MB, Tidwell JL, Gould T, Taylor AR, Newbern JM, Graves J, Tytell M, Milligan CE (2005) Extracellular heat shock protein 70: a critical component for motoneuron survival. J Neurosci 25:9735–9745
Russo A, Palumbo M, Scifo C, Cardile V, Barcellona M, Renis M (2001) Ethanol-induced oxidative stress in rat astrocytes: role of HSP70. Cell Biol Toxicol 17:153–168

Sakthivel K, Watanabe T, Nakamoto H (2009) A small heat-shock protein confers stress tolerance and stabilizes thylakoid membrane proteins in cyanobacteria under oxidative stress. Arch Microbiol 191:319–328

Santoro MG (2000) Heat shock factors and the control of the stress response. Biochem Pharmacol 59:55–63

Schuetz TJ, Gallo GJ, Sheldon L, Tempst P, Kingston RE (1991) Isolation of a cDNA for HSF2: evidence for two heat shock factor genes in humans. Proc Natl Acad Sci 88:6911–6915

Sedaghatmehr M, Mueller-Roeber B, Balazadeh S (2016) The plastid metalloprotease FtsH6 and small heat shock protein HSP21 jointly regulate thermomemory in Arabidopsis. Nat Commun 7:12439

Shi Y, Nishida K, Di Giammartino DC, Manley JL (2011) Heat shock-induced SRSF10 dephosphorylation displays thermotolerance mediated by Hsp27. Mol Cell Biol 31:458–465

Sistonen L, Sarge K, Phillips B, Abravaya K, Morimoto R (1992) Activation of heat shock factor 2 during hemin-induced differentiation of human erythroleukemia cells. Mol Cell Biol 12:4104–4111

Song N-H, Ahn Y-J (2010) DcHsp17. 7, a small heat shock protein from carrot, is upregulated under cold stress and enhances cold tolerance by functioning as a molecular chaperone. Hortscience 45:469–474

Song N-H, Ahn Y-J (2011) DcHsp17. 7, a small heat shock protein in carrot, is tissue-specifically expressed under salt stress and confers tolerance to salinity. New Biotechnol 28:698–704

Song C, Chung WS, Lim CO (2016) Overexpression of heat shock factor gene HsfA3 increases Galactinol levels and oxidative stress tolerance in Arabidopsis. Mol Cells 39:477

Sørensen JG (2010) Application of heat shock protein expression for detecting natural adaptation and exposure to stress in natural populations. Curr Zool 56:703–713

Sun Y, MacRae TH (2005) The small heat shock proteins and their role in human disease. FEBS J 272:2613–2627

Suzuki K, Sawa Y, Kaneda Y, Ichikawa H, Shirakura R, Matsuda H (1997) In vivo gene transfection with heat shock protein 70 enhances myocardial tolerance to ischemia-reperfusion injury in rat. J Clin Investig 99:1645

Tanabe M, Kawazoe Y, Takeda S, Morimoto RI, Nagata K, Nakai A (1998) Disruption of the HSF3 gene results in the severe reduction of heat shock gene expression and loss of thermotolerance. EMBO J 17:1750–1758

Tidwell JL, Houenou LJ, Tytell M (2004) Administration of Hsp70 in vivo inhibits motor and sensory neuron degeneration. Cell Stress Chaperones 9:88–98

Tiwari S, Thakur R, Shankar J (2015) Role of heat-shock proteins in cellular function and in the biology of fungi. Biotechnol Res Int 2015:1

Tóth ME, Gombos I, Sántha M (2015) Heat shock proteins and their role in human diseases. Acta Biol Szeged 59:121–141

Tytell M, Greenberg S, Lasek R (1986) Heat shock-like protein is transferred from glia to axon. Brain Res 363:161–164

Umapathy D, Krishnamoorthy E, Muthukumaran P, Rajaram R, Padmalayam I, Viswanathan V (2012) Association of A1538G and C2437T single nucleotide polymorphisms in heat shock protein 70 genes with type 2 diabetes. Lab Med 43:250–255

Usman MG, Rafii M, Ismail M, Malek M, Latif MA, Oladosu Y (2014) Heat shock proteins: functions and response against heat stress in plants. Int J Sci Technol Res 3:204–218

Wang H-D, Kazemi-Esfarjani P, Benzer S (2004) Multiple-stress analysis for isolation of drosophila longevity genes. Proc Natl Acad Sci U S A 101:12610–12615

Wang M, Zou Z, Li Q, Sun K, Chen X, Li X (2017) The CsHSP17. 2 molecular chaperone is essential for thermotolerance in Camellia sinensis. Sci Rep 7:1237

Warrick JM, Chan HE, Gray-Board GL, Chai Y, Paulson HL, Bonini NM (1999) Suppression of polyglutamine-mediated neurodegeneration in drosophila by the molecular chaperone HSP70. Nat Genet 23:425–428

Whitley D, Goldberg SP, Jordan WD (1999) Heat shock proteins: a review of the molecular chaperones. J Vasc Surg 29:748–751

Wilhelmus M, Otte-Höller I, Wesseling P, De Waal R, Boelens W, Verbeek M (2006) Specific association of small heat shock proteins with the pathological hallmarks of Alzheimer's disease brains. Neuropathol Appl Neurobiol 32:119–130

Wu D, Cederbaum AI (2003) Alcohol, oxidative stress, and free radical damage. Alcohol Res Health 27:277–284

Wyttenbach A, Arrigo AP (2009) The role of heat shock proteins during neurodegeneration in Alzheimer's, Parkinson's and Huntington's disease. In: Heat shock proteins in neural cells, pp 81–99

Wyttenbach A, Sauvageot O, Carmichael J, Diaz-Latoud C, Arrigo A-P, Rubinsztein DC (2002) Heat shock protein 27 prevents cellular polyglutamine toxicity and suppresses the increase of reactive oxygen species caused by huntingtin. Hum Mol Genet 11:1137–1151

Yoshida T, Ohama N, Nakajima J, Kidokoro S, Mizoi J, Nakashima K, Maruyama K, Kim J-M, Seki M, Todaka D (2011) Arabidopsis HsfA1 transcription factors function as the main positive regulators in heat shock-responsive gene expression. Mol Gen Genomics 286:321–332

Yu Q, Kent CR, Tytell M (2001) Retinal uptake of intravitreally injected Hsc/Hsp70 and its effect on susceptibility to light damage. Mol Vis 7:48–56