Heat Shock Proteins 13
Series Editors: Alexzander A. A. Asea · Stuart K. Calderwood

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Regulation of Heat Shock Protein Responses

Springer

Heat Shock Proteins

Volume 13

Series editors

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Heat Shock Proteins: key mediators of Health and Disease. Heat shock proteins (HSP) are essential molecules conserved through cellular evolution required for cells to survive the stresses encountered in the environment and in the tissues of the developing and aging organism. These proteins play the essential roles in stress of preventing the initiation of programmed cell death and repairing damage to the proteome permitting resumption of normal metabolism. Loss of the HSP is lethal either in the short-term in cases of acute stress or in the long-term when exposure to stress is chronic. Cells appear to walk a fine line in terms of HSP expression. If expression falls below a certain level, cells become sensitive to oxidative damage that influences aging and protein aggregation disease. If HSP levels rise above the normal range, inflammatory and oncogenic changes occur. It is becoming clear that HSP are emerging as remarkably versatile mediators of health and disease. The aim of this series of volumes is to examine how HSP regulation and expression become altered in pathological states and how this may be remedied by pharmacological and other interventions.

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Preface

The heat shock response (HSR) is a key homeostatic mechanism that all cellular organisms utilize for resisting extracellular insult. The intracellular mediators of the HSR including the transcription factor heat shock factor 1 (HSF1) and the heat shock protein (HSP) have profoundly anti-inflammatory effects. HSF1 can be induced by the elevated temperatures encountered in inflamed tissues and in fever as well as by anti-inflammatory bioactive mediators.

The book *Regulation of Heat Shock Protein Responses* provides the most comprehensive review on contemporary knowledge on the regulation of HSP responses and its consequences to human diseases and disorders. Using an integrative approach to understanding the regulation of HSP responses, the contributors provide a synopsis of novel mechanisms by which HSP responses are regulated under normal physiological and pathophysiological conditions.

To enhance the ease of reading and comprehension, this book has been subdivided into various sections: Section I reviews current progress on the HSP and stress responses; Section II evaluates the chaperone function of HSP, including cellular proteostasis, disaggregation, protein folding, and calcium binding; Section III focuses the reader on the role of HSP in human diseases.

Key basic and clinical research laboratories from major universities and academic medical hospitals around the world contribute chapters that review present research activity and importantly project the field into the future. The book is a must read for researchers, postdoctoral fellows, and graduate students in the fields of Translational Medicine, Human Physiology, Biotechnology, Molecular Medicine, Infectious Diseases, and Pathology.

Toledo, OH, USA — Alexzander A. A. Asea
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Editors Biography

Prof. Dr. Alexzander A. A. Asea is a highly innovative and accomplished world-renowned clinical and basic research scientist and visionary executive leader who has exceptional experience spearheading clinical and basic science research, training, education, and commercialization initiatives within top-ranked academic biomedical institutes. Prof. Asea's initial findings studying the effects of Hsp72 on human monocytes led to the proposal of a novel paradigm that Hsp72, previously known to be as intracellular molecular chaperones, can be found in the extracellular milieu where it has regulatory effects on immunocompetent cells – a term now called chaperokine. Prof. Asea has authored over 255 scientific publications including peer-reviewed articles, reviews, books, book chapters, editorials, and news headliners in a wide range of biomedical-related disciplines. Prof. Asea is the series editor of the widely successful book series *Heat Shock Proteins* (Springer Nature Publications) and is an editorial board member of 13 other scientific peer-reviewed journals. Currently, Prof. Asea is at the University of Toledo College of Medicine and Life Sciences in Toledo, USA.

Dr. Punit Kaur is an expert in onco-proteogenomics, with extensive training and experience in quantitative mass spectrometry imaging, protein chemistry, and biomarker discovery. Dr. Kaur's main research focus is on the use of heat-induced nanotechnology in combination with radiotherapy and chemotherapy in the cancer stem cell therapy. Dr. Kaur has published more than 40 scientific articles, book chapters, and reviews, and currently serves as editorial board member for the *European Journal of Cancer Prevention* and the *Journal of Proteomics and Bioinformatics*. Dr. Kaur is an editor of five books in the highly successful *Heat Shock Proteins* book series by Springer Nature Publishers. Currently, Dr. Kaur is a Visiting Scientist Professor at the University of Texas MD Anderson Cancer Center in Houston, USA.

Part I
HSP and Stress Responses

Chapter 1
Regulation of Mammalian HSP70 Expression and Stress Response

Kamalakshi Deka and Sougata Saha

Abstract Abnormal environmental and physiological conditions can damage protein structures creating a toxic state in the cell due to loss of protein function and homeostasis. In many disease conditions the effect is so profound that interaction of structurally damaged proteins and aggregates with cellular macromolecules leads to cell and tissue damage as observed in protein misfolding related neurodegenerative disorders like Alzheimer's, Parkinson's and others. Thus structurally damaged proteins bring an organizational and functional challenge for the cells and tissue which need to be resolved very quickly and efficiently to prevent cell and tissue damage. One of the ways cell senses and mounts protective response to proteotoxic stress is by heat shock response (HSR) which constitutes high expression of chaperone proteins also called heat shock proteins (HSP) to tackle sudden increased demand for chaperones in a cell. HSR induces HSP70, one of the major chaperones, which protect cells from proteotoxic stress by prevention of misfolding and aggregation of polypeptides. Thus, a rapid and potent stress response depends on quick supply of large amount of HSP70 proteins. This extraordinary demand of HSP70 proteins is satisfied by an efficient gene expression programme which regulates HSP70 expression at every step from chromatin modification during transcriptional activation to stability of translated protein molecules. Stress dependent regulation of mammalian HSP70 expression is focus of this chapter and regulation at each of these steps will be discussed in detail.

Keywords Heat shock proteins · HSF1 · HSP70 · Regulation of HSP70 expression · Stress response

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Abbreviations

AD	Activation domain
AMP	Adenosine monophosphate
AMPKα	AMP-activated protein kinase α
ARE	AU rich element
ATE1	Arginyl transferase 1
ATF1	Activating transcription factor 1
Atxn	Attexin
BAG2	BCL2 associated athanogene 2
CBP	CCAAT binding proteins
CCDC127	Coiled-coil domain-containing protein 127
CCT	Cytosolic chaperonin containing *t*-complex
CHBF	Constitutive HSE binding factor
CHIP	Carboxy terminus of Hsp70-binding protein
COX	Cyclooxygenase
CPSF	Cleavage and polyadenylation specificity factor
CREB	cAMP response element binding protein
CRM1	Chromosomal maintenance 1
CSF-1	Colony stimulating factor 1
CstF	Cleavage stimulatory factor
CTD	C-terminal domain
CTF	CCAAT box transcription factor
DBD	DNA binding domain
eEF1A1	Eukaryotic elongation factor 1A1
eIF4F	Eukaryotic translation initiation factor 4
ELAV	Embryonic lethal abnormal vision
ER	Endoplasmic reticulum
ERK	Extracellular signal–regulated kinase
GSK-3β	Glycogen synthase kinase 3 β
HBP	HSF1 binding protein
HLE	Human limbo-corneal epithelial
HR	Heptapeptide repeats
HS	Heat shock/ heat stress
HSE	Heat shock element
HSF	Heat shock factor
HSP	Heat shock protein
HSPBP	Heat shock protein binding protein
HSR	Heat shock response
HuR	Human antigen R
INFγ	Interferon γ
IRES	Internal ribosome entry site
JAK	Janus tyrosine kinase
JNK	c-Jun N-terminal kinase

LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase
MEF	Mouse embryonic fibroblast
miRNA	micro RNA
MRPL18	Mitochondrial ribosomal protein L 18
NAD	Nicotinamide adenine dinucleotide
NF	Nuclear transcription factor
NF-IL6	Nuclear factor Interleukin 6
Nmi	N-myc and Stat interactor
OLA1	Obg-like ATPase 1
PGC-1α	Peroxisome proliferator-activated receptor γ coactivator 1-alpha
PIC	Pre transcription initiation complex
PKCα	Protein kinase C α
PKR	RNA-dependent protein kinase
PN	Proteostasis network
PP2A	Protein phosphatase 2A
SIRT	Sirtuin
SKI1	Snf1-related kinase interacting protein
SNRPE	Small nuclear ribonucleoprotein polypeptide E
SSBP1	Single strand DNA binding protein
STAT	Signal transducer and activator of transcription
StIP1	Stress induced phosphoprotein 1
SUMO	Small ubiquitin-like modifier
SWI/SNF	SWItch/sucrose non-fermentable
TNFα	Tumor necrosis factor α
TRiC	TCP-1 Ring *Complex*
UTR	Untranslated region

1.1 Introduction

During our evolution, environment acts as an important selecting pressure and thus every organism lives in a habitat which has a specific environment. Such adjustment to a particular environment is achieved by establishing a homeostasis in its internal physiological components such as transcriptome, proteome, metabolome and intercellular signaling in case of metazoans. Thus, changes in the environment beyond a tolerable level or changes in the internal physiological balance put living systems under stress. To sense such changes and overcome the stressful conditions several protective pathways exist, commonly termed cellular stress response, which is aimed to reestablish homeostasis among cellular components. One such cellular stress response module is heat shock response (HSR) which is induced during many stressful conditions like temperature stress, oxidative stress, heavy metal stress and many disease conditions which causes imbalance in protein homeostasis (proteostasis) (Morimoto 2011). Thus HSR mainly comprises of induction of molecular

chaperones which help to reestablish proteostasis and recover the cells from the stress induced damage by modulating protein folding, activity and stability. One of the key chaperones in HSR and the focus of this book is heat shock protein 70 (HSP70). HSR and HSP70 are highly conserved across the evolutionary history from bacteria to mammals with some variations. In this chapter we will focus on regulatory mechanisms which govern the induction and expression of cytosolic HSP70 during stress in mammals.

The HSP70 is a family of molecular chaperones with molecular weight ranging from 66–78 kDa. HSP70 is highly conserved largest family of HSP comprising of as many as 7 genes in mouse and 13 genes in human (Hunt and Morimoto 1985; Radons 2016). HSP70 family members are monomeric proteins with diverse localizations like cytosol, nucleus, ER, mitochondria, exosomes in tissue fluids, and extracellular space in mammals (Asea et al. 2008; Asea et al. 2000; Lindquist and Craig 1988; Radons 2016; Welch and Feramisco 1984). For example in human while, HSPA1A, HSPA1B and HSPA8 (Hsc70) are predominantly cytosolic protein, HSPA5 (Grp78) and HSPA9 (Grp75/mortalin) is localized in ER and mitochondria respectively. In addition these HSP are known to translocate in different subcellular or extracellular locations at different physiological conditions. Another important regulation which differentiates HSP70 family members is ability to be induced in stress and diseases. The induction of HSP70 gene expression under same stress condition varies between tissue and cell types. For example, neuronal cells show very poor induction of HSP70 during proteotoxic stresses and thus higher susceptibility to protein aggregation disorders as seen in many neurodegenerative diseases like Alzheimer's, Parkinson's and others (Turturici et al. 2011). Many of the HSP70 family members like HSPA8, 5 and 9 are constitutively expressed and perform housekeeping function in proteostasis network (PN). While constitutively expressed HSPA8 accumulates in cytosol and nucleus and acts as a major component in PN by preventing protein aggregation and promoting protein folding, ER specific HSPA5 helps in transport and folding of nascent polypeptides inside ER. Mitochondria specific constitutive HSPA9 helps in transport of protein across mitochondrial membrane. On the other hand HSP70 family members HSPA1A (HSP70–1) and HSPA1B (HSP70–2) acts as a sensor of proteotoxic stress and show a very quick induction during temperature and other types of stresses to counteract the proteostasis imbalance by helping in protein folding, stabilization and degradation if the damage is unrepairable. In recent time, HSP70 is also implicated in coupling proteostasis to mRNA metabolism (ribostasis) (Walters and Parker 2015) which help in minimizing gene expression other than the stress response pathways. Three other HSP70 family member in human, HSPA6, HSPA7 and HSPA14 are also inducible genes, with HSPA7 considered as a pseudogene by many (Brocchieri et al. 2008; Parsian et al. 2000; Radons 2016). To deal with extreme proteotoxic condition caused by environmental and physiological stress, the regulation of HSP70 induction and expression also has to be fast and robust. HSP70 gene expression during stress represent one of the unique example where a strong induction in gene transcription is coupled with posttranscriptional, translational and posttranslational regulation to ensure a robust protein output in a critical condition when gen-

eral transcription translation machinery is halted (Morimoto 2011). In this chapter each of these aspects of HSP70 induction and expression will be discussed in detail.

1.2 Inducible HSP70 Genes in Mammals

Mouse inducible HSP70 genes HSP70.1 (HSPA1A) and HSP70.3 (HSPA1B) encode almost identical protein of 68 kDa. HSPA1A and HSPA1B ORF differs in only six single nucleotides encoding proteins that only differ by two amino acids and are thought to be functionally interchangeable proteins (Daugaard et al. 2007). However two genes show certain sequence differences in promoter region and 3'UTR which do play a role in transcriptional and post transcriptional regulation of both the transcripts during stress. These two genes located ~8 kb apart within the MHC class III locus in chromosome 6 in mouse genome (Milner and Campbell 1990). Two major inducible HSP70 proteins in human, HSPA1A and HSPA1B, are also highly identical proteins differing only by two amino acids and map to same locus in human chromosomes 6 (Harrison et al. 1987). The other stress inducible gene HSPA6 is highly homologous to HSPA1A (Leung et al. 1992) and located in human chromosome 1. Nearby resides another stress inducible gene, HSPA7, which is homologous to HSPA6 but the ORF is half in size compared to other HSP70s and thought to be a pseudo gene. However HSPA7 promoter shows stress specific regulation and can be induced by nutritional stress, but not by oxidative stress or change in pH (Siddiqui et al. 2008). A dendritic cell specific inducible HSP70 gene is HSPA14 (located in human chromosome 10) which produces little smaller protein compared to other HSP70s and play important role in immune cell regulation, cell transformation and metastasis (Wan et al. 2004; Wu et al. 2011; Yang et al. 2015).

1.3 HSP70 Promoter Organization and Activation

The promoter region of HSPA1A and HSPA1B genes are highly conserved in mammals. The key regulatory element which makes these promoters unique is the presence of conserved sequences known as the heat shock elements (HSEs) which binds the heat shock factor 1 (HSF1) complex upon heat stress causing Transcriptional activation of HSP70 promoters. HSEs are located upstream of the basal promoter elements, TATA box, and human promoter has two of such elements. HSEs are made up of conserved sequence: 5'NAGAANNTTCNNGAANN- 3′, where N is any nucleotide (Amin et al. 1988). Several other key transcription factor binding sites are also present in HSP70 promoter. These include NF-Y (nuclear transcription factor Y), NF-κB (nuclear factor kappa B), CREB (cAMP response element binding protein), CCAAT, sp1 and STAT3 Table 1.1.

Basal transcription form mammalian HSP70 promoters are mediated by Sp1, CCAAT binding proteins (CBP) and CCAAT box transcription factor (CTF)