

Heat Shock Proteins 14

Series Editors: Alexzander A. A. Asea · Stuart K. Calderwood

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Editors

HSP70 in Human Diseases and Disorders

 Springer

Heat Shock Proteins

Volume 14

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 seventy kilo Dalton heat shock protein (HSP70) family is amongst the most studied HSP. The HSP70 family consists of several proteins, including the heat shock cognate 70 (Hsc70 also named Hsp73), which are constitutively expressed whilst others, like the heat shock protein 70 (Hsp70 also named Hsp72), are inducible. It has been proposed that Hsp70 would be requested to amplify the chaperone function carried out under normal conditions by the cognate Hsc70. These proteins are synthesised in response to a variety of stressors including hyperthermia, ischemia, infarct, lesions and seizures or following less drastic metabolic changes as those produced by physical exercise or psychological stress.

The book *HSP70 in Human Diseases and Disorders* provides the most comprehensive review on contemporary knowledge on the role of HSP70 in human diseases and disorders. Using an integrative approach to understanding HSP70 structure, function and immunobiology, the contributors provide a synopsis of novel mechanisms by which HSP70 is involved in the regulation of human diseases and disorders.

To enhance the ease of reading and comprehension, this book has been subdivided into various parts, including Part I, reviews current progress on the role of HSP70 in neuro-oncological disorders; Part II, evaluates the role of HSP70 in circulatory disorders including cardiovascular diseases and kidney disease and Part III, focuses the reader on the role of HSP70 as a novel therapeutic target.

Key basic science 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 medical students and residents, clinical and basic science researchers, postdoctoral fellows and graduate students in the fields of Medicine, Physiology, Pharmacology, Biotechnology, Molecular Medicine and Pathology.

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Editors Biography

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.

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
Hsp70 in Neuro-oncological Disorders

Heat Shock Protein 70 and Molecular Confession During Neurodegeneration



Komal Panchal, Ajay Kumar, and Anand K. Tiwari

Abstract Molecular chaperones are the group of proteins that participate in the maintenance of cellular homeostasis by regulating several cellular events and protein homeostasis (proteostasis). It has been shown that failure of protein quality control system, formation of protein aggregates and their ectopic accumulation in the neuronal cells is the common pathological hallmark of most of the neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington disease (HD), Amyotrophic Lateral Sclerosis (ALS), prion disease and various forms of spinocerebellar ataxia (SCA) etc. Heat shock protein 70 (Hsp70), an evolutionary conserved protein family has been shown to be a key regulator in several neurodegenerative diseases. Hsp70 shows its strong expression in stress condition and is associated with protein folding, refolding of misfolded protein, transport of proteins to different cellular compartments, cell death and cell cycle regulation etc. Several recent studies have suggested that Hsp70 can be a key molecule to address the major pathologies associated with neurodegenerative diseases. This chapter briefly summarizes the Hsp70 and its possible role during neurodegenerative diseases.

Keywords Heat Shock Protein 70 (Hsp70) · Neurodegenerative diseases
Alzheimer's disease (AD) · Parkinson's disease (PD)

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Abbreviations

17-AAG	17-allylamino-17-demethoxygeldanamycin
17-DMAG	17-(dimethylaminoethylamino)-17- demethoxygeldanamycin
α -Syn	α -synuclein
γ PKC	Protein kinase C γ
A β ₄₂	Amyloid Beta 42
AC	Azure C
AD	Alzheimer's disease
ADP	Adenosine diphosphate
AIF	Apoptosis inducing factor
ALS	Amyotrophic Lateral Sclerosis
Apaf-1	Apoptotic protease activation factor 1
APP	Amyloid precursor protein
AR	Androgen receptor
Ask1	Apoptosis signal-regulating kinase
ATPase	Adenosine tri phosphatease
Bag-1	Bcl-2-associated athanogene-1
Bap	Benzo(a)pyrene
BiP	Binding immunoglobulin protein
CHIP	Carboxy-terminus of HSC70-interacting protein
CMA	Chaperone mediated autophagy
CNS	Central nervous system
DA	Dopaminergic
<i>E. coli</i>	<i>Escherichia coli</i>
ER	Endoplasmic reticulum
FMRP	Fragile X mental retardation protein
GBA	Glucocerebrosidase
GFP	Green fluorescent protein
GGA	Geranylgeranyl acetone
Grp75	Glucose-regulated protein
HD	Huntington disease
HOP	HSP70 and HSP90 organizing protein
HSC	Heat shock cognate
HSF1	Heat shock transcription factor-1
HSP	Heat shock proteins
Hsp70	Heat shock protein 70
IDE	Insulin degrading enzyme
JNK	c-Jun N-terminal kinase
LBs	Lewy bodies
LRRK2	Leucine-rich repeat kinase 2
MAPK	Mitogen-activated protein kinases
MB	Methylene blue
MY	Myricetin

NBD	Nucleotide binding domain
ND	Neurodegenerative diseases
NEF	Nucleotide exchange factor
NF- κ B	Nuclear factor-kappaB
NFT	Neurofibrillary tangles
PD	Parkinson's disease
PDB	Protein data bank
PQC	Protein quality control
PTEN	Phosphatase and tensin homolog
rhHSP70	Recombinant human Hsp70
ROS	Reactive oxygen species
SBD	Substrate binding domain
SBMA	Spinal & Bulbar Muscular Atrophy
SCA	Spinocerebellar ataxia
SOD	Superoxide dismutase
Ubl	Ubiquitin-like protein
UCHL-1	Ubiquitin c-terminal hydrolase-1
UPS	Ubiquitin proteasome system
TGF- β 1	Transforming growth factor beta 1
TLR4	Toll-like receptor-4
UMN	Upper motor neurons
LMN	Upper motor neurons
NMJ	Neuromuscular junction
FUS	Fused-in-sarcoma
TDP43	TAR DNA binding protein

Introduction

The Heat Shock Proteins (HSP) are a group of proteins categorized under the molecular chaperones family, plays an important role during different cellular events such as protein folding, protein trafficking, autoimmunity and protection from environmental stress etc. (Jaattela and Wissing 1992; Ross and Poirier 2004). The optimum level of HSP in the cell maintains the protein homeostasis, hence represents the “Protein Quality Control” (PQC) system of the cell in different cellular conditions (Sheikh et al. 2013; Meijering et al. 2014; Kakkar et al. 2016; Gidalevitz et al. 2011; Van Drie 2011; Verghese et al. 2012). HSP have been categorized on the basis of their molecular mass such as Hsp100, 90, 70, 60, 40, 27 & 26 etc. Heat shock protein 70 (Hsp70) is one of the most conserved ubiquitously expressed protein, present in the organism from archaeobacteria to human (Gupta and Singh 1994; Lindquist and Craig 1988; Hunt and Morimoto 1985). This protein was discovered by Ritossa in 1960 in the fruit fly “*Drosophila*”. He examined chromosomal puff in the flies that indicates the transcriptional active region of chromatin, named as “heat shock

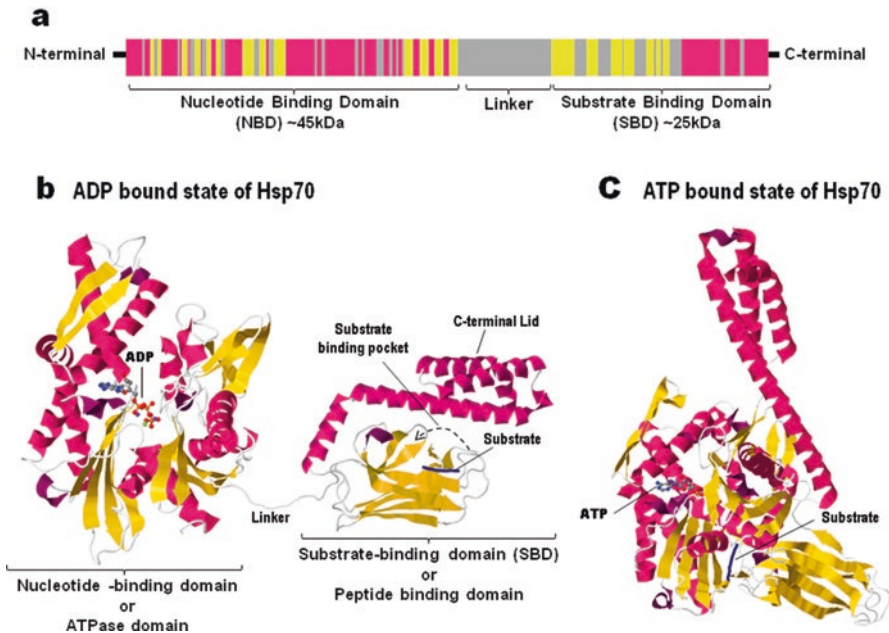


Fig. 1 Hsp70 domain architecture. (a) Schematic representation of human Hsp70 domain structure. The N & C terminal domains along with ~45 kDa Nucleotide Binding Domain (NBD), a short Linker and a ~25 kDa Substrate Binding Domain (SBD). (b) Three dimensional model of HSP70 showing ADP bound conformational state; that represents the nucleotide-binding domain (Protein Data Bank (PDB) Code: 3HSC) (Flaherty et al. 1990) and substrate binding domain (PDB Code: 1DKZ) (Zhu et al. 1996), are joint together by a flexible linker, the substrate (blue) is locked in substrate binding pocket by lid of substrate binding domain. (c) The ATP bound conformational state of HSP70 (PDB Code: 4B9Q) (Kityk et al. 2012) showed the docking of the lid and substrate binding domain showing the folding event of substrate

response” and the protein formed by heat shock was named as “Heat-shock proteins” (HSP) (Ritossa 1964; Lindquist and Craig 1988).

The Hsp70 is ~66–78 kDa proteins possess three functional domains N-terminal ATPase domain (~45 kDa), Substrate binding domain (~25 kDa) and C-terminal domain (Fig. 1) (Hartl 1996; Hendrick and Hartl 1993) ATP hydrolysis in the N-terminal domain is linked to a conformational change in the client binding domain (Vogel et al. 2006). In humans, 13 members of Hsp70 i.e. HSPA1A, HSPA1B, HSPA1L, HSPA2, HSPA3, HSPA4, HSPA5, HSPA5BP1, HSPA6, HSPA7, HSPA8, HSPA9B and HSPA10 are present (Brocchieri et al. 2008). Human Hsp70 is 72% homologues to *Drosophila* (Fruit fly) Hsp70 and 47% to *E.coli* dnaK (Jaattela and Wissing 1992; Hunt and Morimoto 1985; Daugaard et al. 2007). *Drosophila* HSP70 family contains two heat inducible (HSP68 and HSP70) and six constitutively expressed members (HSC1–HSC6) (Kumar and Tiwari 2017) (Shopland and Lis 1996); (Rubin et al. 1993). The HSC4 protein (Hsc4p) is the most abundantly produced cytoplasmic Hsc70 members and the HSC3 protein

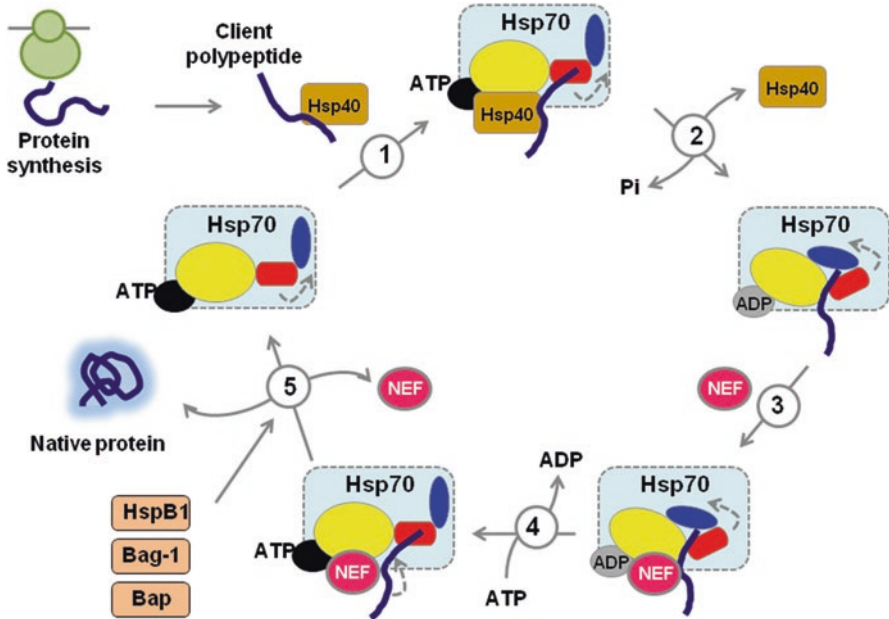


Fig. 2 The chaperone cycle of Hsp70: (1) The co chaperone of Hsp70, the Hsp40, first recognized and bind to the client polypeptide or newly synthesized polypeptide chain, later it interact and stimulates the ATPase domain of Hsp70. (2) The Hsp70 interact with unfolded client polypeptide chain by its substrate-binding domain (SBD) in an ATP-bound state, in this state Hsp40 stimulate the ATP hydrolysis ($ATP = ADP + Pi$) hence dissociate itself from Hsp70 machine, this makes a more tight interaction between Hsp70 and client protein. (3) A crucial co-factor, nucleotide exchange factor (NEF) bind with Hsp70 + client protein complex and (4) promotes the replacement of ADP to ATP. (5) The other co-factors: HspB1, Bag-1 and Bap enter into the cycle and folded client polypeptide and NEF are separate from the Hsp70 molecule, representing the completion of one chaperone cycle

(Hsc3p) is the sole endoplasmic reticulum (ER) resident Hsc70 family member. Hsc3p and Hsc4p are homologous to the mammalian ER resident protein BiP and the cytoplasmic clathrin uncoating ATPase protein respectively (Elefant and Palter 1999). The Hsp70 possess housekeeping function and are associated with variety of cellular processes in normal condition such as it binds with an unfolded protein substrate, maintain it in an extended conformation and stabilized its exposed hydrophobic regions, involved in protein folding through its chaperonin cycle (Fig. 2), refolding, degradation of misfolded proteins, protein trafficking, possess anti-apoptotic activity by inhibiting the translocation of Bax into mitochondria, release of cytochrome c from mitochondria, formation of apoptosome and inhibit activation of initiator caspases, eye development in *Drosophila* (Kumar and Tiwari 2017) etc. (Hartl 1996; Arya et al. 2007; Gething and Sambrook 1992). Under stress condition activation of Hsp70 reduces cellular stress, oxidative stress, promotes cell survival and refolding of the misfolded proteins (Fig. 3 and 4).