Chapter 1
The Discovery of Heat Shock Response System and Major Groups of Heat Shock Proteins

Drastic changes in the genes expression pattern in response to heat stress were originally demonstrated in *Drosophila busckii* and *D. melanogaster* (Ritossa 1962, 1963). Initially, it was shown that in the both species a few new large puffs in the salivary gland chromosomes were formed immediately after heat shock treatment. Specifically, in *D. melanogaster* the puffs were observed at several chromosomal loci in all large autosomes (33B, 63B, 64B, 67B, 70A, 87A, 87B, 93D and 95C) (Ritossa 1963). These changes in chromosome morphology can be easily seen under a light microscope due to giant size of polythene chromosomes in the larval salivary glands of *Drosophila* (Fig. 1.1). Only one decade later the main groups of proteins corresponding to the individual heat-induced puffs were identified and called "heat shock proteins" (Hsps) (Ashburner and Bonnert 1979; Lewis et al. 1975; Lewis and Pelham 1985; Tissières et al. 1974).

After the discovery of heat shock proteins in *Drosophila* active studies began into the structure and functions of proteins of this class, which were found in practically all studied species: from *E. coli* to man (Schlesinger et al. 1982). It was demonstrated in numerous studies exploring various organisms that *Hsps* genes and in particular members of *Hsp70* family are exceptionally conservative like many house-keeping genes. For example, the comparison of human, *Drosophila* and *Escherichia coli* Hsp70 amino acid sequences showed that human HSP70 is 73 % identical to *Drosophila* and 47 % identical to orthologous *E. coli* Hsp70 (DnaK). Surprisingly, at the level of nucleotide sequences the human and *Drosophila* genes are 72 % identical while human and *E. coli* genes are 50 % identical, which is more highly conserved than expected given the degeneracy of the genetic code. The lack of accumulated silent nucleotide substitutions enables to speculate that there may be additional information in the nucleotide sequence of the *Hsp70* genes or the corresponding mRNAs that precludes certain level of divergence allowed in the silent codon positions (Hunt and Morimoto 1985).

Expression of the genes encoding some Hsps is maintained in most organisms under normal physiological conditions at a certain level or is altogether absent and is strongly induced in the presence of different stress factors. In addition to heat

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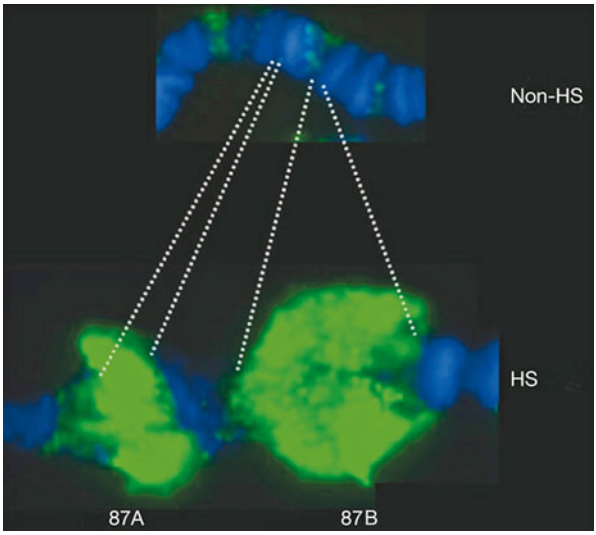

Fig. 1.1 A small segment of *D. melanogaster* fixed chromosome 3R before (*top*) and after (*bottom*) heat shock. Chromosomes are stained for DNA (Hoeschst dye; *blue*) and for RNA Polymerase II (fluorescent labeled antibodies; *green*). 87A and 87B-mark huge puffs containing *Hsp70* genes. *HS* heat shock (From Lis 2007 with permission)

shock, synthesis of HS proteins (Hsps) can be induced by a number of agents, including hypoxia, ultraviolet light, tissue damage, various chemicals including heavy metals, viruses, aging and other forms of stressful stimuli (Hunt and Morimoto 1985; Lindquist 1986; Lozovskaya and Evgen'ev 1984; Hightower 1991; Margulis and Guzhova 2000; Feder and Hofmann 1999). In this regard Hsps may be called "stress proteins". At present, Hsps are classified according to their molecular weights, amino acid sequences and functions and form several distinct groups (Guzhova and Margulis 2006; Hartl and Hayer-Hartl 2002; Lindquist 1986; Lozovskaya and Evgen'ev 1984; Sorensen et al. 2003).

Basing on electrophoretic separation of labeled proteins it has been established that several fractions of proteins with various molecular masses are synthesized in the cells of different organisms after temperature elevation (Feder and Hofmann 1999; Parsell and Lindquist 1993). Moreover, basically the same distinct in size classes of Hsps are synthesized in highly diverged organisms from flies to humans (Lindquist 1986; Lindquist and Craig 1988). Hence, at the present time Hsps are routinely classified basing on their molecular masses into the following major groups: small heat shock proteins (sHsps) family which comprises proteins with molecular masses from 10 to 30 kD; Hsp40 family (40 kD); Hsp60 (or chaperonins) with molecular mass close to 60 kD; Hsp70 family (70 kD); Hsp90 family (83–90 kD); and, finally Hsp100/110 family with molecular masses of members exceeding or equal to 100 kD (Kampinga et al. 2009; Mayer 2010; Parsell et al. 1994). Each of the above mentioned families may include multiple members (homologues) with similar or slightly different functions which may significantly differ by molecular masses (up to 10 kD).

Besides classification based on molecular mass all Hsps may be divided basing on the expression pattern in two large classes, namely, inducible (Hsp) and constitutive or cognate proteins (Hsc). Inducible Hsps are usually synthesized at a very low level or are completely silent under normal temperature conditions. Thus, transcription of

Table 1.1 Classification of canonical eukaryotic heat shock proteins and their major functions

Family	Some of members	Localization	The most important functions in the cell
Small Hsps	Hsp22	Mitochondria	Protein aggregation preventing, microfilament remodeling
	Hsp23	Cytosol	
	Hsp26		
	Hsp27	Cytosol/nucleus	
Hsp40	DnaJA1	Cytosol	Co-chaperones of Hsp70, binding with protein substrates
	DnaJC1	ER	
	DnaJA3	Mitochondria	
Chaperonins	GroEL	Mitochondria	Direct protein folding
	GroES		
	CCT	Cytosol	Direct protein folding, cytoskeleton assembly
Hsp70	HSPA1A and HSPA1B	Cytosol	Direct protein folding, translocation of nascent proteins into organelles
	HSPA5 (GRP78 or BiP)	ER	
	HSPA9 (GRP75 or mortalin)	Mitochondria	
Hsp90	HSPC1	Cytosol	Modulation of activity of major regulatory proteins
	HSPC4 (GRP94)	ER	
	HSPC5 (TRAP1)	Mitochondria	
Hsp110	HSPH1	Cytosol	Nucleotide exchange factor for Hsp70, preventing protein aggregation
	HSPH4 (GRP170)	ER	

Localization of small Hsps is given for *Drosophila*, because correspondent data regarding cellular representation of certain human sHSPs is fragmentary. About heat shock protein functions see Chap. 2 for details

Hsp70 genes in *D. melanogaster* under physiological conditions can be detected by only highly sensitive RT-PCR technique, while temperature elevation leads to hundreds fold induction of Hsp70 synthesis within a few minutes after HS (Lakhotia and Prasanth 2002; Pardue et al. 1980). Cognate *Hsps* genes often representing products of reverse transcription of corresponding mRNA of heat-inducible genes exhibit 50–80 % homology with inducible members of the same family and may be either silent or play house-keeping functions in the cells under normal temperature conditions (Kampinga et al. 2009). Some of Hsp families got the name of molecular chaperones in accordance with their functions as companions in folding of other proteins (see Chap. 2 for details).

Each family may comprise several inducible and several constitutive members with different functions (see Table 1.1). Below we shall provide modern classification of Hsps families described in humans and *Drosophila melanogaster* as an example. Nomenclature of human HSPs is given basing on Kampinga et al. (2009).

Small heat shock proteins family (sHsps) are characterized by the presence of crystalline domain flanked with variable N- and/or C-terminal regions. Hsp27 and other proteins of this family are constitutively abundant and ubiquitously present in many organisms. In humans there are 11 genes encoding proteins of this family comprising *HSPB* group. Accordingly, these proteins are designated from HSPB1 to HSPB11.

HSPB1 or HSP27 is the best studied member of this family in humans as well as HSPB4 and HSPB5 that correspond to αA- and αB-crystallins respectively (Kampinga et al. 2009).

In *Drosophila melanogaster* the major proteins of this family (sHsps) are encoded by seven genes with various orientations in the genome located in the same locus 67B which forms large puff in salivary gland polytene chromosomes after HS (Ayme and Tissieres 1985). According to the modern view major protective functions after HS in flies are performed by the following four small heat shock proteins: Hsp22, Hsp23, Hsp26 and Hsp27. All these genes are strongly induced by HS, they are highly homologous and have different intracellulal localization. Thus, Hsp22 is found in mitochondrial matrix, Hsp23 and Hsp26 in cytosol and Hsp27 have predominantly intranuclear localization (Morrow et al. 2000; Marin and Tanguay 1996). Totally there are 12 ORFs in the genome of *D. melanogaster* that contain α-crystallin domain (Morrow et al. 2006).

Hsp40 family probably represents the most abundant family of Hsps described so far. The members of this family characteristically contain the so-called "J-domain" exhibiting homology with well-known *E. coli* DnaJ protein. J-domain containing proteins serve as co-factors (co-chaperones) of Hsp70 family members, by stimulation ATP-activity of the latter group of proteins (Hennessy et al. 2005). There are more than 50 genes encoding J-domain containing proteins in the human genome (Kampinga et al. 2009). These proteins are divided into three sub-groups basing on the degree of homology with DnaJ designated DNAJA, DNAJB and DNAJC. DNAJA subgroup includes four proteins (DNAJA1 – DNAJA4) with highly homologous J-domain located at the N-terminus of the molecule while C-terminus is variable. Subgroup DNAJB consists of 14 homologues and includes the most heat-inducible human DNAJ member, DNAJB1. Finally, human genome contains DNAJC subgroup also containing J-domain which, however, is not necessarily found at the N-terminal end of the molecule. Besides, computer search in various data bases exploring NCBI and InterPro provided at least eight hypothetical ORFs that may encode proteins with significant homology to DnaJ of *E. coli*. It is of note that in the course of computer analysis multiple pseudogenes apparently belonging to *hsp40* family were detected (Kampinga et al. 2009). In contrast to humans, the genome of *D. melanogaster* harbors only five members of *Hsp40* family, containing J-domain, however, this number may be increased after more thorough search is performed.

Chaperonins form another distinct class of stress proteins that are found in both prokaryotes and eukaryotes. This class is subdivided into two subfamilies. The first group is represented by Hsp60 and Hsp10 that are homologous to bacterial GroEL and and its cofactor GroES that help prokaryotes to survive sever stress (Lund 1995). In humans there are two single genes (*HSPD* and *HSPE*) belonging to this family, which correspond to bacterial *groEL* and *groES* and coding proteins located in mitochondria (Kampinga et al. 2009). The Berkley *Drosophila* Genome Project has revealed four *Hsp60* genes in *D. melanogaster*, which have been named *Hsp60A*, *Hsp60B*, *Hsp60C* and *Hsp60D* (Sarkar and Lakhotia 2005).

The second group of chaperonins designated CCT (chaperonins containing t-complex polypeptide 1) or TRiC (TCP1 Ring Complex) functions in archaea and in cytosol of different eukaryotic organisms. Thus, proteins belonging to this group were described in *Arabidopsis* and other plants (Hill and Hemmingsen 2001). In eukaryotes, proteins of this family form oligomers consisting of eight subunits encoded by different genes (Kampinga et al. 2009). Eukaryotic CCT/TRiC is a 16 subunits complex composed of two back-to-back stacked rings, each containing eight different subunits of approximately 60 kD (α, β, γ, δ, ε, ζ-1, η and θ). These subunits are 30 % homologous and exhibit 15–20 % similarity with GroEL suggesting that they have origin in common (Brackley and Grantham 2009).

The Hsp70 (DnaK in bacteria) family is the most thoroughly studied group of stress proteins in many organisms. This family is very diverse and includes many constitutive as well as stress-inducible proteins with multiple functions.

In humans there are 13 genes encoding the proteins of this family named HSPA with different numbers. After temperature elevation maximal induction has been demonstrated for *HSPA1A*, *HSPA1B* and *HSPA6* genes and correspondent proteins move into nuclei after HS and bind chromatin. On the other hand, HSPA1L and HSPA2 are tissue-specific proteins and are intensively synthesized in testis and a few other tissues. HSPA5 also named GRP78 or BiP (Immunoglobulin heavy chain Binding Protein) is localized in the endoplasmic reticulum and is necessary for correct folding of proteins entering endoplasmic reticulum including immunoglobulins. *HSPA7* was considered to be a pseudogene for a long time but basing on the recent data probably it is a functional gene sharing high homology with *HSPA6* (Kampinga et al. 2009). HSPA8, previously named HSC70 or HSP73, represents the major house-keeping protein highly abundant in human cells. This protein is localized in cytosol and actively participates in cotranslational folding of various proteins and their transport through membranes into different cellular compartments. HSPA9 is a mitochondrial protein previously named "mortalin" (or mtHSP70/GRP75). There are two highly homologous isoforms of mortalin (mot-1 and mot-2) in mouse (Kaul et al. 2007). HSPA13 is localized in microsomes and may be yet another compartment-specific HSPA member with house-keeping functions. HSP12A, HSP12B and HSP14 represent more evolutionary diverse forms of HSP70 family in human with not yet defined functions (Kampinga et al. 2009). *HSPA1A*, *HSPA1B* and *HSPA1L* genes form a cluster in human genome and in the genomes of other mammals while other family genes are scattered in the genome (Brocchieri et al. 2008; Kampinga et al. 2009).

D. melanogaster genome contains 5–6 copies of highly homologous copies preserved by gene-conversion and responsible for the synthesis of inducible Hsp70 after HS (Bettencourt and Feder 2001; Maside et al. 2002). These copies are found in two clusters localized at 87A and 87B loci of polytene chromosomes. Heat-inducible *Hsp68* gene located at 95D locus also belongs to Hsp70 family and has slightly different functions after stress (Holmgren et al. 1979; Kellett and McKechnie 2005). Besides, the inducible members in *D. melanogaster* there are seven genes belonging to the same family but encoding constitutive proteins (Hsc70)

that are expressed under normal temperature conditions namely, *Hsc70-1*, *Hsc70-2*, *Hsc70-3*, *Hsc70-4*, *Hsc70-5*, *Hsc70-6* и *Hsc70Cb*. The functions of most of these cognate proteins are known, thus, *Hsc70-1* and *Hsc70-4* genes encode proteins located in cytosol that are 82 % homologous and have similar molecular mass (70 kD). *Hsc70-3* encodes the protein with molecular mass equal to 72 kD localized in endoplasmic reticulum, while *Hsc70-5* encodes 74 kD protein which contains signal sequence for transport to mitochondria. This particular protein shares 64 % homology with yeast mitochondrial Hsp70, and exhibits only 50 % similarity with the rest *Drosophila* Hsc70 members. Generally speaking, different members of *Hsp70* family genes often exhibit higher homology with orthologs from other unrelated organisms than with other endogenous members of the same family (Rubin et al. 1993). This feature suggests early amplification of different sub-families of *Hsp70* family in the course of species divergent evolution.

Likewise, baker's yeast *Saccharomyces cerevisiae* genome contains eight individual genes belonging to the *Hsp70* superfamily that are divided into a few different groups according with their evolutionary relations and intracellular localization. Thus, the Ssa proteins group consists of four members, designated "Ssa1 – Ssa4", with cytosolic localization. The Ssb group has two members, Ssb1 and Ssb2, which are also located in the cytosol. Both *S. cerevisiae* mitochondria and endoplasmic reticulum contain single Hsp70 member, Ssc1 and Kar2, respectively (Boorstein et al. 1994).

Another group of Hsps (Hsp110) with molecular mass varying from 100 to 170 kD, and exhibits significant homology with Hsp70 and probably diverged from it at the early stages of evolution of higher eukaryotes (Lee-Yoon et al. 1995). Proteins belonging to this family are found in different organisms (Kampinga et al. 2009). In humans there are four genes belonging to this family named *HSPH1 – HSPH4*. The proteins encoded by the *HSPH1 – 3* members of the family are found in cytosol, while HSPH4 (GRP170) is localized in endoplasmic reticulum (Kampinga et al. 2009).

In *D. melanogaster* two genes, *Hsp70Cb* and *CG2918*, were preliminarily described as belonging to this group but they are not yet thoroughly characterized at the present time (Easton et al. 2000). However, accordingly to their amino acid sequence one may conclude that Hsp70Cb is a homolog of the human cytosolic protein HSPH1, while CG2918 has a strong homology with HSPH4 (GRP170).

Hsp90 represents another important family of heat shock proteins that are usually constitutively active but may be strongly induced by stressful stimuli (Kampinga et al. 2009). Hsp90 family is distinct from other molecular chaperones in that most proteins of this family display chaperoning functions predominantly for multiple unstable signal transducers to keep them poised for activation and thus represent important components of cellular networks under normal temperature conditions and after stress. In humans this family is represented by five members, named HSPC1 – 5 with different localization. *HSPC1*, *HSPC2* and *HSPC3* encode cytosolic proteins while HSPC4 (previously designated GRP94) is endoplasmic protein, and HSPC5 (old designations TRAP1, HSP90L) is localized in mitochondria (Kampinga et al. 2009). Genome of *D. melanogaster* contains a single gene (*Hsp83*)

which encodes cytosolic protein with molecular weight 83 kD; there are also genes belonging to this family encoding endoplasmic and mitochondrial proteins (Felts et al. 2000; Sorger and Pelham 1987). Correspondent bacterial protein with molecular weight 90 kD is designated HtpG (Chen et al. 2006).

Several of the above mentioned Hsps may be separated into a distinct group of the so-called glucose regulated proteins (GRP) because the proteins of this family were first discovered when the polypeptides synthesized in cells deprived of glucose were studied in details. This group includes certain members of Hsp70, Hsp90 and Hsp110 families designated as GRP78, GRP94 and GRP170 or HSPA5, HSPC4 and HSPH4, respectively, using modern nomenclature (Kampinga et al. 2009). These proteins are localized in endoplasmic reticulum (ER) while function of GRP75 (HSPA9) is restricted to mitochondria. All these glucose-regulated proteins share the same type of regulation named unfolded protein response (UPR) triggered by ER proteins misfolding. Thus, expression of all GRP is induced by the disturbances of normal proteins folding in endoplasmic reticulum which may be induced by heat shock, heavy metals, inhibitors of N-glycosylation and several other factors (Chen and Brandizzi 2013).

Another special chaperones belong to "AAA+" family (ATPases associated with a wide variety of cellular activities). In yeast and bacteria these chaperones have molecular weight near 100 kD and take part in protein aggregates resolubilization and proteolysis (Parsell et al. 1994). In eukaryotes this family includes many highly diverse proteins taking part in refolding and degradation of proteins often exploring ubiquitin-dependent pathway (Ciechanover and Stanhill 2014; Mayer 2010).

It is of note, that not all proteins induced by HS and other forms of stress are chaperones *per se*. There are multiple proteins such as collagenase, heme oxygenase, many regulatory proteins (e.g. eIF2α) and many others that are induced by stress and participate in many cellular events in a chaperone independent manner. In this respect ubiquitin represents the most illustrative example of "non-standard" heat-induced proteins. Thus, it has been demonstrated that temperature elevation (HS) leads to five to six fold increase in ubiquitin mRNA increase because large quantities of ubiquitin is require to utilize high cellular proteins damaged by HS. Importantly, promoter regions of all heat-induced genes usually contain heat shock elements (HSEs) necessary for binding of heat shock factor (HSF1) which induces *in cis* heat shock genes (Fornace et al. 1989).

In parallel with the induction of *Hsp* genes transcription and rapid accumulation of correspondent proteins, HS and other stimuli strongly induces transcription of certain genes that produce non-coding RNAs as functional end product. Thus, the *hsr*-ω gene of *D. melanogaster* is developmentally active in many tissues and is one of the most strongly induced genes following temperature elevation. The 10 kbs nucleus limited transcripts of this gene are associated with different hnRNAs and participate in the formation of the nucleoplasmic omega speckles. It was suggested that the omega speckles play important role in regulation of nuclear trafficking and availability of hnRNPs and other RNA binding proteins in the cell (Lakhotia 2012). Moreover, recently, various elegant experiments of Lakhotia's group implicated *hsr*-ω transcripts in apoptosis (Mallik and Lakhotia 2011).

1.1 Conclusions

After the discovery of heat shock genes in *Drosophila* a great number of papers appeared describing similar batteries of genes in various organisms from yeast to humans. Amazingly, genomes of all organisms studied contain virtually the same classes of *Hsp* genes exhibiting high similarity even between phylogenetically very distant organisms suggesting early appearance of heat shock genes in eukaryotes which apparently predated their divergence and specialization.

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