Minireview

The heat shock protein 70 family: Highly homologous proteins with overlapping and distinct functions

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Abstract **The human heat shock protein 70 (Hsp70) family contains at least eight homologous chaperone proteins. Endoplasmatic reticulum and mitochondria have their specific Hsp70 proteins, whereas the remaining six family members reside mainly in the cytosol and nucleus. The requirement for multiple highly homologous although different Hsp70 proteins is still far from clear, but their individual and tissue-specific expression suggests that they are assigned distinct biological tasks. This concept is supported by the fact that mice knockout for different Hsp70 genes display remarkably discrete phenotypes. Moreover, emerging data suggest that individual Hsp70 proteins can bring about non-overlapping and chaperone-independent functions essential for growth and survival of cancer cells. This review summarizes our present knowledge of the individual members of human Hsp70 family and elaborate on the functional differences between the cytosolic/nuclear representatives.**
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Keywords: Cancer; Cell death; Evolution; Gene expression; Heat shock proteins; Thermotolerance

1. Introduction

The discovery of heat inducible chromosome puffs in the salivary glands of *Drosophila* larvae in 1962 by Ritossa and the subsequent identification of the puff-encoded genes and proteins initiated a rapidly expanding research field on heat shock response [1–3]. Several independent groups noted that a mild, non-lethal heat shock protected cells of various origins against cell death induced by a subsequent severe heat shock as well as other lethal stimuli [4–8]. Soon it became clear that the enhanced cell survival was intimately linked to the induction and accumulation of heat-inducible proteins and especially to that of a 70 kD protein that was designated heat shock protein 70 (Hsp70) [9–12]. In 1984 Hugh Pelham suggested that the ability of Hsp70 to enhance the recovery of stressed cells

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Abbreviations: CBF, CCAAT-box binding factor; ER, endoplasmatic reticulum; Hsc70, heat shock cognate 70; HSE, heat shock element; HSF, heat shock factor; Hsp70, heat shock protein 70; MHC, major histocompatibility complex; siRNA, small interfering RNA; TNF, tumor necrosis factor

was mediated by its ability to catalyze the reassembly of damaged ribosomal proteins [13]. Subsequent research revealed that such a chaperoning function, indeed, was characteristic for Hsp70 proteins and that it was essential for the Hsp70-mediated protection against stresses that cause protein denaturation as well as for many of the newly discovered house-keeping roles of constitutively expressed Hsp70 proteins in non-stressed cells (reviewed in [14–18]). The house-keeping functions of Hsp70 chaperones include transport of proteins between cellular compartments, degradation of unstable and misfolded proteins, prevention and dissolution of protein complexes, folding and refolding of proteins, uncoating of clathrin-coated vesicles, and control of regulatory proteins.

2. Heat shock protein 70 family is structurally and functionally conserved in evolution

Hsp70 is, by far, the most conserved protein in evolution [14,19,20]. It is found in all organisms from archaebacteria and plants to humans, and the prokaryotic Hsp70 protein DnaK shares approximately 50% amino acid identity with eukaryotic Hsp70 proteins. Accordingly, Hsp70 is a highly appreciated phylogenetic nominator in the field of molecular evolution. It has been used to disclose a monophyletic relationship among the entire metazoan kingdom and a specific bootstrap-confident (91%) phylogenetic relationship between animals and fungi [19,21,22]. The conservation of Hsp70 sequence is also reflected by conserved functional properties across the species. For example, *Drosophila* Hsp70 expressed in mammalian cells efficiently protects them against heat stress [13], and rodent Hsp70 can be functionally complimented by human Hsp70 to grant cellular protection against various stresses both in vitro [23–25], and in transgenic animals [26–28].

Interestingly, all eukaryotes have more than one gene encoding Hsp70 proteins. For example, the fungus *Blastocladiella emersonii* has 10 putative family members with high homology to the Hsp70s in yeast *Saccharomyces cerevisiae* [29]. The yeast contains eight Hsp70 homologues, of which six are localized to the cytosol (Ssa1, Ssa2, Ssa3, Ssa4, Ssb1, and Ssb2) and two are compartment-specific Ssc1 residing in mitochondria and Ssd1/Kar2 in endoplasmatic reticulum (ER) [30]. Genetic studies have revealed that the four Ssa proteins can compensate for each other, whereas their simultaneous deletion is lethal [31]. Interestingly, the cytosolic Ssb proteins cannot substitute for the survival function of Ssa proteins suggesting that cytosolic Hsp70

family members have both overlapping and diverse functions in yeast [22]. Emerging data indicate that akin to yeast, human Hsp70 family members have both redundant and specific functions that are summarized and discussed in more detail below.

3. The human Hsp70 family

The human Hsp70 family comprises at least eight unique gene products that differ from each other by amino acid sequence, expression level and sub-cellular localization (Table 1) [32]. The localization of Hsp70-5 (also known as Bip or Grp78) and Hsp70-9 (mtHsp70 or Grp75) is confined to the lumen of the ER and the mitochondrial matrix, respectively, whereas the remaining six Hsp70 proteins reside mainly in the cytosol and nucleus suggesting that they either display specificity for their client proteins or serve chaperone-independent particular functions. Common to all known Hsp70 species, also the human Hsp70 proteins display highly conserved amino acid sequences and domain structures consisting of: (i) a conserved ATPase domain; (ii) a middle region with protease sensitive sites; (iii) a peptide binding domain; and (iv) a G/P-rich C-terminal region containing an EEVD-motif enabling the proteins to bind co-chaperones and other Hsps (Fig. 1) (reviewed in [16,17,32]). Furthermore, the members localized to specific cellular compartments have a localization signal in their N-terminus and Hsp70-5 has a C-terminal retention signal sequence that inhibits its exit from the ER [33]. The conserved domain structure consolidates the chaperone function of the Hsp70 proteins and enables them to bind and release extended stretches of hydrophobic amino acids, exposed by incorrectly folded globular proteins in an ATP-dependent manner (reviewed in [16,17]). The C-termini contain the least conserved sequences that may explain the non-redundant functions of Hsp70 family members (see below).

3.1. Hsp70-1a and Hsp70-1b

A large part of the data published on human Hsp70 family deals with the major stress-inducible members of the family, Hsp70-1a and 1b (collectively called Hsp70-1). Hsp70-1a and -1b are encoded by closely linked, stress-inducible and intron-less genes, *HSPA1A* and *HSPA1B*, that reside in the major histocompability class (MHC) III cluster between the complement- and tumor necrosis factor (TNF) locus on the short arm of chromosome 6 [34,35]. According to the published sequences, Hsp70-1a (NM_005345) and Hsp70-1b (NM_005346) share all but two (E110D, N499S) of their 641 amino acids being more than 99% identical (Table 1 and Fig. 1). During various stress conditions, both Hsp70-1 genes are activated by binding of a stress-inducible transcription factor, heat shock factor 1 (HSF1), to heat shock elements (HSE) found in multiple copies in the upstream regulatory regions of the genes (reviewed in [35,36]). During normal conditions, Hsp70-1 proteins are expressed in a cell type and cell cycle dependent manner accumulating in G_1- and S-phase [37,38]. Accordingly, Hsp70 promoters also contain several binding sites for basal transcription factors such as TATA factors, CCAAT-box-binding transcription factor and SP1 [39]. The basal expression of *HSPA1A* and *HSPA1B* mRNAs differ slightly in most tissues, with somewhat higher expression of *HSPA1A* in most tissues and cell types (Fig. 2).

Table 1
The human Hsp70 family

Protein	Alternative names	Homology to Hsp70-1a (%)	Locus	Accession	Localization	Affymetrix annotation	Cellular localization	Stress-induced	Ref.
Hsp70-1a	Hsp70, Hsp72, Hsp70-1	100	HSPA1A	NM_005345	6p21.3	200799_at	Cytosol, Nucleus, Lysosomes	Yes	[34]
Hsp70-1b	Hsp70, Hsp72, Hsp70-1	99	HSPA1B	NM_005346	6p21.3	202581_at	Cytosol, Nucleus, Lysosomes	Yes	[34]
Hsp70-1t	Hsp70-hom	91	HSPA1L	NM_005527	6p21.3	210189_at	Cytosol, Nucleus	No	[75]
Hsp70-2	Hsp70-3, HspA2	84	HSPA2	NM_021979	14q24.1	211538_s_at	Cytosol, Nucleus	No	[76]
Hsp70-5	Bib, Grp78	64	HSPA5	NM_005347	9q33-q34.1	211936_at	ER	No	[83]
Hsp70-6	Hsp70B'	85	HSPA6	NM_002155	1cen-qter	213418_at	Cytosol, Nucleus	Yes	[88]
Hsc70	Hsp70-8, Hsp73	86	HSPA8	NM_006597[a]	11q23.3-q25	210338_s_at	Cytosol, Nucleus	No	[91]
Hsp70-9	Grp75, mtHsp75, Mortalin	52	HSPA9	NM_004134	5q31.1	200690_at	Mitochondria	No	[95,96]

[a] A 54 kDa Hsc70 splice variant (NM_153201) has been reported, but its functional significance remains unclear [94].
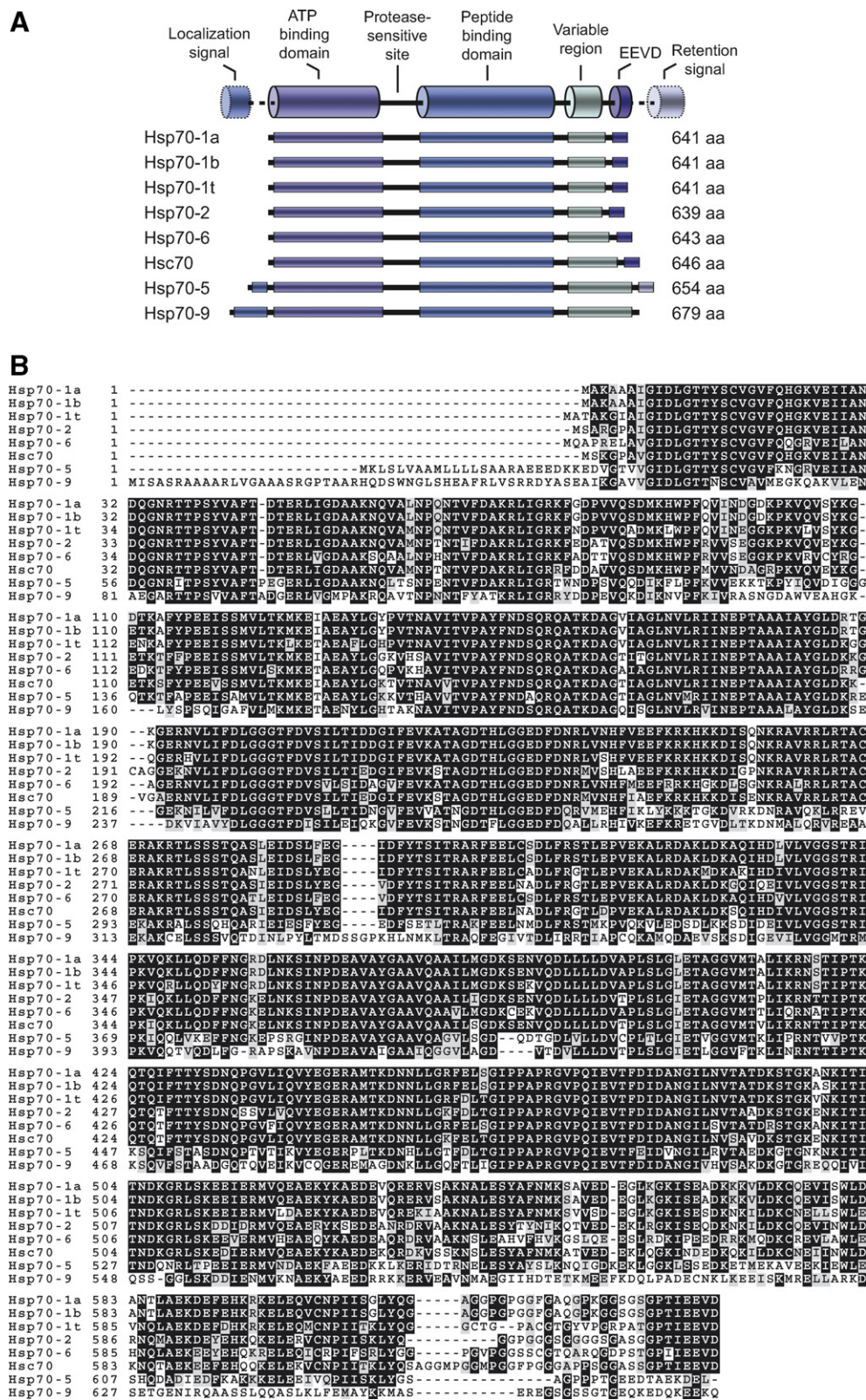
Fig. 1. The human Hsp70 family. (A) Cartoon showing a linear representation of the human Hsp70 family in respect to known domains. (B) A complete protein alignment of the human Hsp70 family generated in Boxshade 3.21 from the sequences NM_005345 (Hsp70-1a), NM_005346 (Hsp70-1b), NM_005527 (Hsp70-1t), NM_021979 (Hsp70-2), NM_002155 (Hsp70-6), NM_006597 (Hsc70), NM_005347 (Hsp70-5) and NM_004134 (Hsp70-9). Black squares indicate complete homology; gray squares indicate changes in functionally conserved amino acids. White squares indicate functionally non-conserved amino acid disagreement.

Stress-induced Hsp70-1 functions as a chaperone enabling the cell to cope with harmful aggregations of denatured proteins during and following the stress (reviewed in [15,16]). Accordingly, its ectopic expression confers protection against stresses that induce protein damage, e.g. heat, ischemia and oxidative stress both in cultured cells [23,40–47], and in transgenic mice [26–28,48]. Supporting the major role for Hsp70-1 in protection against external stresses, mice deficient of the equivalent murine proteins, Hsp70.1 or Hsp70.3, are viable and fertile, but Hsp70.1 deficient mice display increased sensitivity to pancreatitis, UV light (epidermis), osmotic stress (renal medulla) and ischemia (brain), and reduced capacity to acquire resistance to TNF-induced liver toxicity and inflammatory shock after preconditioning with heat [49–53] (Table 2). Furthermore, cells lacking either Hsp70.1 or Hsp70.3 display increased sensitivity to heat [54]. Remarkably, mice deficient for both stress-inducible Hsp70 proteins are also viable and fertile, but they are sensitized to sepsis, have reduced capacity to develop tolerance to cardiac ischemia, and their cells display genomic instability and increased sensitivity to radiation [55–57]. These data underline additive and synergistic effects of the two stress-inducible Hsp70 proteins and the evolutionary significance of multiple Hsp70 genes.

In the case of the heat stress, it has been demonstrated that the chaperone function of the Hsp70-1 is required for its cytoprotective effect, and Hsp70-1 has been suggested to inhibit the accumulation of protein aggregates and thereby to remove the stimulus that triggers cell death [58,59]. Also, Hsp70-1 protects mitotic cells against division abnormalities due to heat-induced centrosome damage [60]. However, Hsp70-1 also protects mice against pancreatitis and TNF [50,53], and enhances the survival of cultured cells exposed to various stimuli not known to induce protein denaturation or aggregation, e.g. activation of death receptors of TNF receptor family [25,61], glucose starvation [62], ceramide [61], doxorubicin [63], ultraviolet light [64], microtubule disturbing drugs [47] and cancer-associated cellular changes [65–67]. Emerging data suggest that the protective effect against many of the above-mentioned stimuli is mediated by Hsp70-1 located on the luminal side of the lysosomal membrane [68–72]. In this location, Hsp70 stabilizes the lysosomal membrane and inhibits the release of lysosomal hydrolases into the cytosol, where they can initiate apoptosis-like programmed cell death [68,73,74]. Supporting this notion, increased amount of lysosomal cathepsin activity is found in extra-lysosomal localization in the pancreas of Hsp70.1 deficient mice [53].

3.2. Hsp70-1t

The gene encoding Hsp70-1t (*HSPA1L*) is intronless and located in the same MHC class III region as *HSPA1A* and *HSPA1B*[35,75]. The protein is 91% identical to Hsp70-1a (Table 1), the major variation being in the C-terminal end (Fig. 1). The *HSPA1L* gene contains no HSE in its promoter region and it is constitutively expressed at high levels in testis and at very low levels in other tissues (Fig. 2). The function and transcriptional regulation of Hsp70-1t are currently unknown.

3.3. Hsp70-2

The *HSPA2* gene product, Hsp70-2, is constitutively expressed at low levels in most tissues, but in high levels in testis
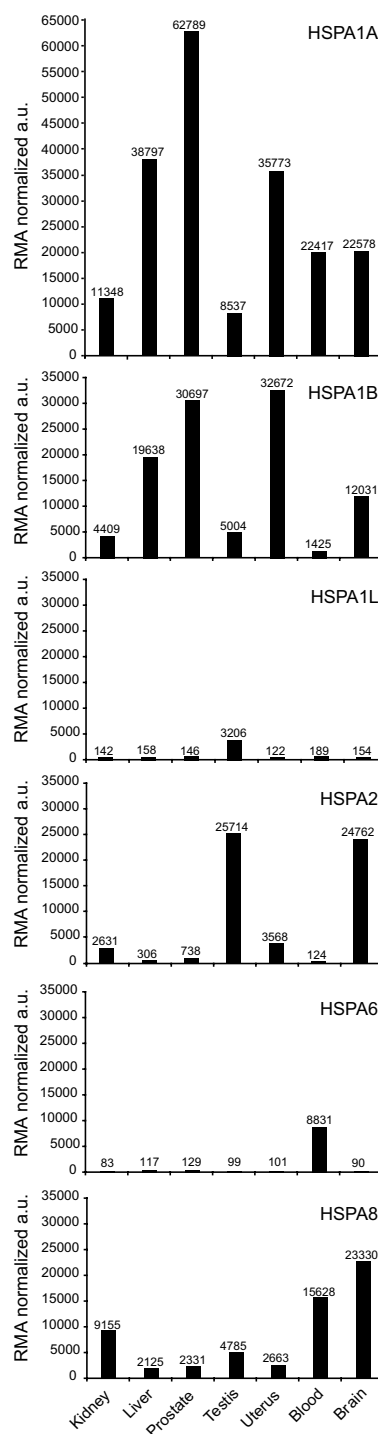

Fig. 2. Expression of nuclear and cytosolic members of the human Hsp70 family in various tissues. The Robust Multi-Array (RMA)-normalized GNF1h data (a.u.) of seven selected normal human tissues (Kidney, Liver, Prostate, Testis, Uterus, Blood and Brain) are extracted from The Genomics Institute of the Novartis Research Foundation Gene Expression Database SymAtlas (outlined in [86]) and presented according to the Affymetrix U133A Hsp70 annotations listed in Table 1. All normalized data sets and information about tissue sample origin are available online at http://symatlas.gnf.org and at the Gene Expression Omnibus (www.ncbi.nih.gov/geo).

and brain (Fig. 2) [76,77]. The gene is located on chromosome 14 and the protein shows 84% homology to Hsp70-1a (Table 1

Table 2
Phenotypes of Hsp70 knockout mice

Protein	Gene locus	Chromosomal localization	Analogous Human gene	Phenotype	Ref.
Hsp70.1	*Hspa1a*	17 B1	*HSPA1A*	Viable and fertile. Susceptible to UV, osmotic stress, ischemia, TNF, pancratitis and heat	[49–53]
Hsp70.3	*Hspa1b*	17 B1	*HSPA1B*	Viable and fertile. Susceptible to Heat	[54]
Hsp70.1 + Hsp70.3	*Hspa1a + Hspa1b*	17 B1	*HSPA1A + HSPA1B*	Viable and fertile. Susceptible to radiation and sepsis. Increased genomic instability	[55–57]
Hsp70.2	*Hspa2*	17 B1	*HSPA2*	Viable and female fertility. Meiotic defects in male germ cells	[78–80]
Hsc70	*Hspa8*	9 A5.1	*HSPA8*	Not applicable. Knockout cells are non-viable	[92]
Bip, GRP78	*Hspa5*	2 B	*HSPA5*	Lethal at embryonic day 3.5	[87]

and Fig. 1). Its expression is frequently reduced in men with abnormal spermatogenesis [77], and male *HSPA2* knockout mice are sterile due to massive germ cell apoptosis (Table 2) [78]. In the mouse spermatocytes, Hsp70-2 has been assigned specific roles as an essential chaperone for cyclinB/cdc2 complex during meiotic cell division [79,80], and for transition protein-1 and -2, that are DNA-packaging proteins involved in the post-meiotic genome reorganization process [81]. Furthermore, Hsp70-2 is required for the growth and survival of various human cancer cells [67,82] (see chapter 5.3).

3.4. Hsp70-5, Bip

The gene *HSPA5* is located on chromosome 9 and encodes a constitutively expressed compartment-specific protein, Hsp70-5 (Table 1). Hsp70-5 (also known as Bip or Grp78) is located in the ER, where it facilitates the transport of newly synthesized proteins into the ER lumen and their subsequent folding [83–85]. Hsp70-5 contains a presumed N-terminal ER localization signal that guides its localization into the ER. In its far C-terminal end, it has a highly conserved "KDEL" ER retention signal that is common for soluble ER-localized proteins (Fig. 1) [33]. According to the SymAtlas gene expression resource [86], Hsp70-5 is found in all cell types but is highly expressed in secreting cells like thyroid and pancreatic islets. The *Hspa5* knockout mouse embryos die at embryonic day 3.5 (Table 2), and therefore Hsp70-5 is to be regarded as an essential housekeeping gene [87].

3.5. Hsp70-6

Hsp70-6 is a strictly stress-inducible member of the Hsp70 family encoded by the gene *HSPA6* located on chromosome 1 [88]. The Hsp70-6 protein is 85% homologous to Hsp70-1a (Table 1 and Fig. 1) and it is induced only after severe stress insults [89]. Although 15% different from the two other stress-induced Hsp70 proteins (Hsp70-1a and -1b), it is likely that Hsp70-6 functions in a similar way as a component of the general stress-response. According to the SymAtlas gene expression resource [86], Hsp70-6 is expressed at moderate levels in blood, especially in dendritic cells, monocytes and natural killer cells, but is close to absent in other blood cells as well as other tissues (Fig. 2). Hsp70-6 knock-out mice have not been reported and it is presently not known whether Hsp70-6 has some specific functions in blood cells. Chromosome 1 contains also a pseudogene, *HSPA7*, which is transcribed in response to stress. This transcript does, however, not encode a functional Hsp70 protein due to a nucleotide insertion at codon 340 that creates a frame-shift and a subsequent stop-codon at position 368 [89,90].

3.6. Hsp70-8, Hsc70

The gene, *HSPA8*, is located on chromosome 11 and it is expressed constitutively in most tissues (Table 1 and Fig. 2) [91]. The *HSPA8* gene encodes the cognate Hsp70 family member, Hsc70 (Hsp70-8), which is 86% identical to Hsp70-1a (Fig. 1). Hsc70 has been reported to be involved in a multitude of the housekeeping chaperoning functions including folding of nascent polypeptides, protein translocation across membranes, chaperone-mediated autophagy, prevention of protein aggregation under stress conditions, and disassembly of clathrin-coated vesicles (reviewed in [14,17]). Thus, Hsc70 is considered as an essential housekeeping gene and it has been reported that Hsc70 knockout mouse cannot be created due to the essential role of Hsc70 for cell survival (Table 2) [92]. Accordingly, RNA interference-based knock-down of Hsc70 results in massive cell death in various cell types [67]. Recently, Hsc70 has been assigned an interesting role in the cytokine-mediated post-transcriptional regulation of the pro-apoptotic Bcl-2 family-member Bim in human blood cells [93]. Hsc70 binds to AU-rich elements in the 3′-untranslated region of the Bim mRNA and stabilizes the messenger in a co-chaperone-dependent manner. This demonstrates that the chaperone activity of Hsc70 proteins is not limited to protein–protein interactions. It should be noted that a shorter 54 kDa Hsc70 splice variant that uses an alternate in-frame splice site in the 3′ coding region has been reported, but its functional significance remains unclear [94].

3.7. Hsp70-9

The *HSPA9* gene is localized to chromosome 5 and is not induced in response to stress. The Hsp70-9 protein (mtHsp70) is 52% identical to stress-induced Hsp70-1a (Table 1) and 65% homologous to the yeast mitochondrial Hsp70, SSC1 protein [95–97], which demonstrates higher sequence conservation between trans-species mitochondrial Hsp70s than among the Hsp70 family of a single species. A specific 42 amino acid targeting signal delivers Hsp70-9 to mitochondrial lumen, where it interacts with incoming proteins and assists them in correct folding after the trans-membrane transport [97,98]. The Ssc1 deletion is lethal in yeast [99] and to our knowledge no Hsp70-9 knockout has never been established in the mouse.

4. Why do we have six cytosolic/nuclear Hsp70 proteins?

4.1. Hsp70 deficient mice

The function of the two compartment-specific Hsp70 family members (Hsp70-5 and Hsp70-9) is to facilitate chaperone-

dependent transport and correct folding of proteins targeted for the ER and mitochondria, respectably. Conversely, the individual functions and the reasons for needing six Hsp70 family members in the cytosol and nucleus have proven hard to deduce. A part of the explanation may lie in the fact that only three of the proteins are stress-inducible proteins, namely Hsp70-1a, Hsp70-1b and Hsp70-6, whereas the other three (Hsc70, Hsp701t and Hsp70-2) are not. The logic implication would be that the first group would have their primary function during stress, and the other three would be required for basal housekeeping functions. This interpretation is largely supported by results from the mouse knock-out models. It is evident that mice deficient for the murine homologues of human Hsp70-1a and –1b (Hsp70.1 and Hsp70.3) are more susceptible to stress but develop normally in unstressed conditions [49–52,55–57]. On the other hand, mice lacking the Hsp70-2 homologue (Hsp70.2) have a developmental defect in spermatogenesis [78], and Hsc70 appears to be absolutely essential for cell viability [92,100]. The transgenic models thus support the idea that some of the cytosolic Hsp70 family members (Hsp70-1a and Hsp70-1b) deal with the cellular stress response while others are involved in tissue-specific and housekeeping biological tasks.

4.2. Hsp70 mRNA expression patterns in human tissues

Another indication of functional differences among the cytosolic members of the human Hsp70 family arises from gene expression data that reveals a potential tissue-selective need for specific cytosolic family members (Fig. 2). For instance, the expression patterns of *HSPA1A* (Hsp70-1a) and *HSPA1B* (Hsp70-1b) are close to identical in the different types of tissue except for blood where the expression of *HSPA1B* (Hsp70-1b) is dramatically lower than *HSPA1A* (Hsp70-1a). *HSPA1L* (Hsp70-1t) is exclusively expressed in testis that expresses relatively low levels of both *HSPA1A* (Hsp70-1a) and *HSPA1B* (Hsp70-1b). Besides its high expression in testis, *HSPA2* (Hsp70-2) is also highly expressed in the nervous system, indicating a special role for Hsp70-2 in these tissues. And *HSPA6* (Hsp70-6) is close to undetectable in most tissues during normal unstressed conditions except for certain blood cells where it is expressed in substantial levels. Although circumstantial, the unrelated expression patterns of the individual genes make it plausible that the Hsp70 family members have tissue selective functions. Furthermore, multiple Hsp70 genes make it possible to regulate the total level of Hsp70 differently in different tissues for example during the development.

4.3. Hsp70 family in cancer

A long line of experimental evidence positions Hsp70-1 as a cancer relevant survival protein. It is abundantly expressed in malignant tumors of various origins (reviewed in [15,101]), and its expression correlates with increased cell proliferation, poor differentiation, lymph node metastases and poor therapeutic outcome in human breast cancer [102–105]. The role of Hsp70 in tumourigenesis is further supported by data showing that its high expression is required for the survival of tumor cells of various origins in vitro as well as for the growth of human tumour xenografts in immunodeficient mice [65,66]. Furthermore, it enhances the tumourigenic potential of rodent cells in syngenic animals [106–109]. Recent data indicate that also Hsp70-2 is upregulated in a subset of primary and meta-

static breast cancers and that it has growth and survival promoting effects in cancer cells [67,82]. Knowledge on the expression of other Hsp70 proteins in cancer tissue is as yet limited. However, all cytosolic Hsp70 mRNAs are expressed at detectable levels in various immortalized and transformed human cell lines that have provided the first human model system for testing whether the cytosolic Hsp70 proteins have overlapping or distinct functions [67]. A study based on a panel of small interfering RNAs (siRNAs) specifically targeting the individual family members clearly demonstrates that whereas Hsc70 is required for the survival of both non-transformed and transformed cells, Hsp70-1 and Hsp70-2 have non-overlapping and specific functions related to cancer cell growth and survival. Cancer cells depleted of Hsp70-1 and Hsp70-2 displayed strikingly different morphologies (detached and round vs. flat senescent-like), cell cycle distributions (G2/M vs. G1 arrest) and gene expression profiles [67]. In conclusion this means that, although different Hsp70 proteins may serve many overlapping chaperone functions and in some cases can substitute for each other, some of them perform specific functions that are not necessarily related to protein stress.

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