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Review

Human small heat shock proteins: Protein interactomes of homo- and hetero-oligomeric complexes: An update

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ABSTRACT

Small heat shock proteins (sHsps) regulate a large number of fundamental cellular processes and are involved in many pathological diseases. They share complex oligomerization and phosphorylation properties allowing them to interact and modulate the activity of many client proteins. Here, the up-to date protein interactome of the ten human sHsps is presented as an illustration of their multiple cellular functions. In addition of forming homo-oligomers, some of these proteins interact whith each other and form hetero-oligomeric complexes that could bear new protein targets recognition abilities. Here, novel informations are presented on how the formation of HspB1/HspB5 complex can stimulate the activity of the oxidoresistance promoting enzyme glucose 6-phosphate dehydrogenase through its interaction with newly formed highly phosphorylated HspB1 homo-oligomers.
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1. Introduction

The ten polypeptides belonging to the human family of sHsps (HspB1 to HspB10) [1] (Fig. 1A) share a C-terminal alpha-crystallin domain [2–4], a N-terminal domain containing a hydrophobic WD/PF motif and optional phospho-serine sites [5]. The C-terminal domain bears a flexible tail and, excepted in the case of HspB6, the conservative tripeptide (I/V/L)-X-(I/V/L) motif [6–8]. HspB1 (Hsp27), HspB5 (αB-crystallin), HspB8 (Hsp22), HspB4 (αA-crystallin) and HspB6 (Hsp20) are ATP-independent chaperones [9–13]. HspB7 is a particular chaperone characterized by its aggregation suppressor property [14,15]. Only HspB1, HspB5 and HspB8 are stress inducible. Their expression induces cellular protection against different stress, particularly those that alter protein folding [4]. Through their dynamic ability to modulate their oligomerization, sHsps trap altered proteins and avoid their aggregation. Thereafter, they collaborate with the Hsp70–Hsp90 ATP-dependant refoldase machinery which refold or proteolyticaly eliminate stress-damaged polypeptides [9,11,16–25] A fundamental property is their ability to form reversible, polydispersed homo- or hetero-oligomers that can, depending on the sHsp, be regulated by phosphorylation [26–35]. In that respect, the dynamic plasticity of HspB1 phospho-oligomers can act as a sensor of the cellular environment [27,36,37]. Because of their constitutively expression in normal and pathological human tissues and the discovery of mutations in sHsp genes that are responsible of the development of neurodegenerative, myopathic and caratact diseases [10,38–43], the interest in sHsps has recently grown exponentially and they are nowdays considered as promising therapeutic targets [44–46]. sHsps are characterized by their incredible number of fundamental cellular roles [10,21,44,46–52]. In addition of being essential in signal transduction, transcription, and translation mechanisms, many reports have described their anti-apoptotic, anti-oxidant, tumorigenic and metastatic properties. They can also regulate proteolysis and cytoskeleton architecture integrity or attenuate aggregation or fibrillation of pathological proteins (i.e. mutant synuclein, parkin, Aβ-amyloid, polyQ-Huntingtin). They also could contribute to cardiac cell hypertrophy and survival hence, each sHsp appears to have its own specific functions. Their level is up-regulated in particular cellular events, such as changes in cell physiology (e.g., differentiation) [53], and in pathological conditions (neurodegeneration, myopathies, cardiomyopathies, cataracts, inflammatory diseases and cancers) [10,44,46,47,49]. It is now believed that the pleotropic functions of sHsps results of their interaction with many different proteins. We have proposed that the dynamic plasticity of sHsps phopho-oligomeric structure is probably the major parameter modulating the recognition of client proteins. At least in the case of HspB1, choosing the more appropriated client proteins in a define cellular situation is

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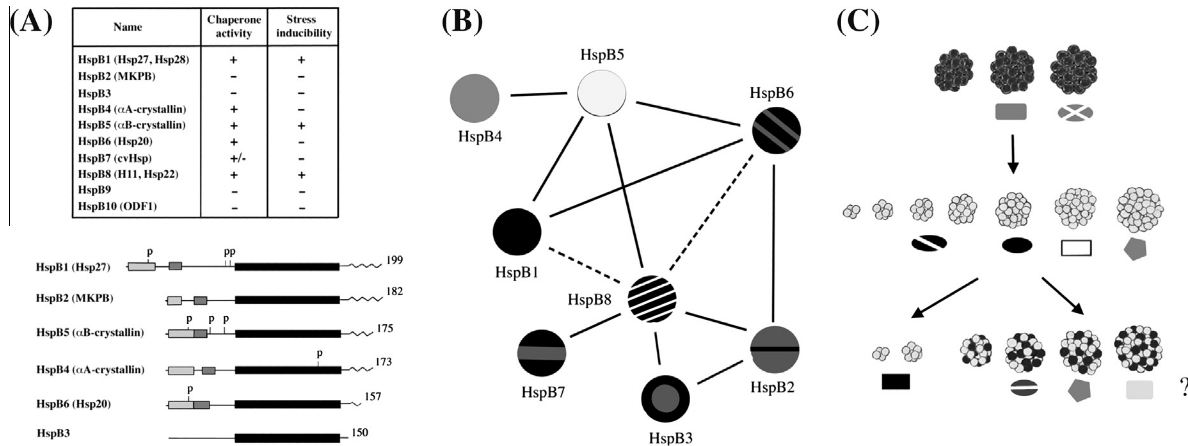

Name	Chaperone activity	Stress inducibility
HspB1 (Hsp27, Hsp28)	+	+
HspB2 (MKPB)	–	–
HspB3	–	–
HspB4 (αA-crystallin)	+	–
HspB5 (αB-crystallin)	+	+
HspB6 (Hsp20)	+	-
HspB7 (cvHsp)	+/-	-
HspB8 (H11, Hsp22)	+	+
HspB9	–	–
HspB10 (ODF1)	–	–

Fig. 1. Human sHsps. (A) Name, chaperone function and stress inducibility of the ten members of the human small heat shock family of proteins. The organization of the domains of some sHsps is also presented. Black box: alpha crystallin domain; light gray box: conserved N-terminal WD/EPF domain; dark gray box: conserved domain; ΛΛΛΛΛ: conserved IXI/V motif and flexible C-terminal domain; P: phosphorylated serine residues. Amino acids number is indicated. (B) Schematic representation of the interactions between sHsps when they are expressed in the same cells. The interactions depend on the tissue, the physiology of the cells and the phosphorylation of sHsps. Dotted lines: interations that have been reported in some but not all publications. (C) Interaction between sHsps results in the formation of complex chimeric oligomeric structures. Interactions can be complete or not leaving a fraction of non-interacting sHsps as homo-oligomers. The interaction with putative client proteins is indicated. It is not known if the hetero-oligomers interact with same client proteins as the parental sHsps. The example presented concerns HspB5 (black) and HspB1 (gray) expressed at similar levels in HeLa cells (see Fig. 2).

probably linked to its ability to drastically rearrange its phospho-oligomeric structure [36,45,46,52,54]. Here, the proteins that have been reported to interact with the different human small Hsps are classified depending on their functions in the cell. Emphasis is then given towards the hetero-oligomers that can form when several sHsps are expressed in the same cells and their putative proprieties to recognize new protein targets. In that respect, a novel observation is presented concerning the indirect stimulation of the activity of the oxidoresistance promoting enzyme glucose 6-phosphate dehydrogenase (G6PD) by the formation of HspB1/HspB5 hetero-oligomer complex.

2. sHsps pleotropic activities result of their ability to interact with many protein clients

Protein interactomes are useful tool that can help in the understanding of protein functions, particularly chaperones which have apparent pleotropic activities resulting of their interactions with a large number of crucial regulator polypeptides. The best example is Hsp90, which has been described for quite a while to interact with an incredible number of proteins [55]. Hence, collecting data from the scientific literature is the only way to build a comprehensive interactome since individual experimental approaches are too limited. Here, the aim was to list the proteins that are already known to interact with the different sHsps. As seen in Table 1, the interacting proteins are classified in function of their role in cells and in function of the number of interations that have been discovered. However, it should be kept in mind that the listed interactions are probably specific for only some cells and in particular physiological conditions. HspB1 and HspB5 are the most represented sHsps since they have been studied for longer time periods than the other recently discovered sHsps. HspB9 and HspB4 interact with only one protein partner, TCTEL1 and HspB5 respectively, and no interaction has yet been discovered concerning Hsp10. Of interest, the largest number of proteins that interact with sHsps are linked to cell adhesion, tissue integrity, epithelial to mesenchimal transition and cytoskeleton. This particular subgroup is represented by HspB1, HspB2, HspB3, HspB5, HspB6, HspB8 and HspB9. Hence, it can already be concluded that a major activity of sHsps is to modulate human cell architecture confirming the important role of these proteins in metastatic and myopathic diseases. Inhibition of protein aggregation or fibrillation responsive of neurodegenerative, cataract and myopathic diseases is ranked second and involves HspB1, HspB2, HspB3, HspB5, HspB7 and HspB8. Next, we found the interactions dealing with transduction pathways and cell activation. Receptors, protein kinases and phosphatases as well as signaling molecules are targets of sHsps, particularly HspB1, HspB2, HspB5, HspB6 and HspB8. This leads to the conclusion that sHsps are deeply involved in the regulation of signal transduction pathways. Negative modulation of apoptotic processes is also an important phenomenon that has crucial consequences, particularly in cancer pathologies where sHsps are often over-expressed. In that respect, HspB1, HspB5 and HspB8 are key modulators of apoptosis. In contrast, only one autophagy example is known which relates to HspB8 and HspB6 in a complex with Bag3. Then, several reports show that sHsps modulate transcription and translation machineries. The interactions mediated by HspB1, HspB5 and HspB8 promote stabilization or degradation of transcription factors, pre-mRNAs processing as well as modulation of translation initiation. Down-stream to translation and/or protein refolding, sHsps (HspB1 and HspB5) also regulate protein degradation through interaction with crucial regulators such as ubiquitin, HDM2, FBX4 or Smad/Smurf2. In contrast, protein transport is less represented than protein degradation. Enzymes are also targets of sHsps and some examples are known where the interactions stimulate their activities. In that regard, one can cite the effect of phosphorylated HspB1 towards G6PD (see Fig. 2) [56]. sHsps also interact with each other and with protein inhibitors of their activity (e.g., p66Shc or PASS1). In the lens cells, HspB5 can chaperone other crystalline polypeptides such as βB2 and γC.

The interaction of sHsps with specific polypeptides can have several consequences. Inhibition of proteolytic degradation is often observed [54], as for example AR, Her2, Stat-2, Stat-3, HDAC-6, Procaspase-3, Snail, and HDM2 which are stabilized by HspB1. These "clients" have a biochemical behavior close to that of some Hsp90 interacting partners [57]. The interaction with sHsps can also promote enhanced degradation or modulation of enzymatic activities.

Table 1
Major polypeptides interacting with human sHsps.

Interacting proteins	sHsps	Functional modulation	Refs.
Cytoskeleton, cell adhesion, tissue integrity, epithelial to mesenchymal transition			
F-actin	HspB1	Protection integrity, inhibition formation of F-actin stress fibers	[15,86,87]
	HspB5	Protection integrity	[88–91]
	HspB6	Inhibits formation F-actin stress fibers	[15]
	HspB7	Inhibits formation F-actin stress fibers	[15]
	HspB8	Inhibition Rho GTPase	[15]
	HspB2	nk	[92]
	HspB3	nk	[92]
Tubulin	HspB1	Chaperoning	[93]
	HspB5	Chaperoning	[94,95]
MAPs	HspB5	Inhibition microtubules aggregation	[96]
Vimentin	HspB1	Chaperoning	[97]
	HspB5	Chaperoning	[97–99]
Desmin	HspB5	Chaperoning	[91]
Peripherin	HspB5	Chaperoning	[98,99]
Neurofilaments	HspB1	Protection integrity	[100]
GFAP	HspB1	Inhibits IF interaction	[97]
p66Shc	HspB1	Cytoskeleton disruption	[101]
β-Catenin	HspB1	Cell adhesion	[102]
	HspB5	Cell adhesion	[103]
Cadherin-16	HspB5	Cadherin-16-cytoskeleton connection	[104]
Snail	HspB1	Promotes MET	[105]
DSTN	HspB8	Destrin, actin depolymerization	[106]
Filensin	HspB5	Chaperoning	[107]
Phakinin	HspB5	Chaperoning	[107]
GRIFIN	HspB5	nk	[108]
GFAP	HspB5	Stabilization/degradation GFAP	[91,97,109]
Neurofilaments	HspB5	Protection integrity	[100]
Keratins	HspB1	Keratin networks dissassembly	[110]
TCTEL1	HspB9	Role in spermatogenesis?	[111]
Protein aggregation, fibrillation, neurodegeneration			
α-Synuclein	HspB1	Inhibition of fibrillation	[112,113]
	HspB5	Inhibition of fibrillation	[59,112]
	HspB8	Inhibition of fibrillation	[112]
	HspB3/B2	Inhibition of fibrillation	[112]
Aβ-amyloid	HspB1	Inhibition of aggregation	[114]
	HspB5	Inhibition of fibrillation	[59,115]
PolyQ proteins	HspB1	Inhibition of aggregation	[116]
	HspB5	Inhibition of aggregation	[116]
	HspB8	Inhibition of aggregation	[117]
	HspB7	Inhibition of aggregation	[14]
SOD1	HspB1	Inhibition of aggregation	[118]
	HspB8	Inhibition of aggregation	[74]
Parkin	HspB1	Inhibition of aggregation	[113]
p150 Dynactin	HspB1	Inhibition of aggregation	[119]
NF-M	HspB1	Inhibition of aggregation	[119]
Phosphorylated Tau	HspB1	Facilates P-Tau degradation	[120]
Tubulin	HspB5	Inhibition of aggregation	[94,95]
Desmin	HspB5	Inhibition of aggregation	[91]
Vimentin	HspB5	Inhibition of aggregation	[97–99]
Serpin	HspB5	Inhibition of aggregation	[121]
SOD1	HspB5	Inhibition of aggregation	[118]
PrPc	HspB5	Inhibition of aggregation	[122]
κ-Casein	HspB5	Inhibition of aggregation	[116]
Apolipoprotein-CII	HspB5	Inhibition of aggregation	[123]
TDP-43	HspB8	Inhibition of aggregation	[74]
β2-Microglobulin	HspB5	Inhibition of fibrillation	[59]
Transthyretin	HspB5	Inhibition of fibrillation	[59]
Titin, Myotilin, ZASP, Filamin C	HspB5	Inhibition of aggregation	[124]
Transduction pathways, cell activation			
Membrane signaling proteins			
CD10	HspB1	nk	[125]
β2-Microglobulin	HspB5	Inhibition of fibrillation	[59]
TLR4	HspB8	TLR4 ligand, dentritic cells activation	[126]
Growth factors, Receptors, transduction pathway factors			
NGF-beta	HspB5	Chaperone NGF-beta	[103]
Her2	HspB1	Her2 stabilization	[127]
ERβ	HspB1	Estrogen signaling	[128]
FGF-2	HspB5	Chaperone FGF-2	[103]
VEGF	HspB5	Chaperone VEGF	[103,129]
AR	HspB1	AR stabilization	[130]
14-3-3zeta	HspB6	Modulation signaling pathways	[131]

(continued on next page)

Table 1 (*continued*)

Interacting proteins	sHsps	Functional modulation	Refs.
Protein kinases, phosphatases			
IKKβ	HspB5	Stimulation kinase activity	[132]
DAXX	HspB1	Inhibition activity	[133]
IKK	HspB1	Activation via TRAF6 ubiquitination	[134]
DMPK	HspB2	Activation DMPK	[135]
PKCδ	HspB1	Inhibition of HspB1 activity	[136]
RhoA, PKCα	HspB1	Muscle contraction	[137]
Akt, P38, MK2	HspB1	Akt activation	[138]
Phk	HspB1	nk	[139]
p90Rsk	HspB1	HspB1 phosphorylation	[140]
PTEN	HspB1	Increased PTEN level	[141]
PRKD1	HspB1	nk	[142]
PPM1A	HspB1	nk	[143]
Apoptotic and autophagic factors			
Caspase-3	HspB1	Pro-caspase-3 stabilization	[54,144]
	HspB5	Negative regulation of activity	[145]
Cytochrome c	HspB1	Inhibition binding to APAF	[146]
Bax	HspB5	Inhibition translocation mitochondria	[145,147]
Bcl-xs	HspB5	Inhibition translocation mitochondria	[147]
P53	HspB5	Inhibition translocation mitochondria	[148]
DAXX	HspB1	Inhibition Fas apoptosis	[133]
PEA-15	HspB1	Inhibition Fas apoptosis	[149]
GranzymeA	HspB1	GranzymeA stimulation	[150]
CIAPIN1	HspB8	nk	[106]
Bag-3	HspB8	Co-chaperone	[11,75]
	HspB6	Co-chaperone	[75]
Transcription/translation, gene expression			
Transcription factors			
Stat-2	HspB1	Stat-2 stabilization	[54]
Stat-3	HspB1	Stat-3 stabilization	[151]
HSF-1	HspB1	HSF sumoylation	[152]
GATA-1	HspB1	GATA-1 degradation	[153]
Snail	HspB1	Snail stabilization	[105]
P53	HspB5	Inhibition P53 translocation	[148]
Activators of transcription factors			
IKKβ	HspB5	Activation of NF-κB	[132]
Spliceosome assembly, pre-mRNA processing			
SAM68	HspB8	Inhibition SAM68 activity	[154]
Ddx20	HspB8	Ribonucleoprotein processing	[40]
EFTUD2	HspB1	nk	[62]
Translation initiation factors			
eIF4G	HspB1	Inhibition translation during HS	[155]
eIF4E	HspB1	Tumor cell survival	[156]
mRNA half-life			
AUF1	HspB1	AUF1 degradation	[157,158]
Ribosomes			
p90Rsk	HspB1	HspB1 phosphorylation	[140]
Regulators of protein degradation			
Smad/Smurf2	HspB1	HspB1 ubiquitination/degradation	[159]
p27kip1	HspB1	p27kip1 ubiquitination/degradation	[21]
Ubiquitin	HspB1	Protein degradation	[160]
HDM2	HspB1	HDM2 stabilization	[161]
FBX4	HspB5	Cyclin D1 ubiquitination/degradation	[162]
C8/α7 Proteasome	HspB5	Proteasome assembly/degradation of HspB5 interacting proteins	[18]
Protein ubiquitinated by sHsps-E3 complexes			
TRAF6	HspB1	TRAF6 ubiquitination	[134]
Cyclin D1	HspB5	Ubiquitination by HspB5-FBX4	[162]
HspB1	HspB1	Ubiquitination by HspB1-Smurf2	[159]
p27kip1	HspB1	p27kip1 ubiquitination/degradation	[21]
Protein sumoylation			
Ubc9	HspB1	Sumoylation by Ubc9-HspB1:	
		HSF-1: modulation of activity	[152]
		F508del CFTR: degradation	[163]
Protein transport			
XPORT	HspB1	Transport of TRP and Rh1	[164]
Neurofilaments	HspB5	Chaperone	[100]
MAPs	HspB5	Inhibition microtubules aggregation	[96]
SMN	HspB5	SNR nuclear import and assembly	[165]
Enzymes			
Factor XIII	HspB1	Platelet FXIII regulation	[166]
Catalase	HspB1	Protection against inactivation	[167]
Insulin	HspB5	nk	[103]
SOD-1	HspB1	Protection against inactivation	[168]

Table 1 (*continued*)

Interacting proteins	sHsps	Functional modulation	Refs.
G6PD	HspB1	Stimulation of activity by P-HspB1	[56]
HDAC6	HspB1	Inhibition HDAC6 degradation	[54]
Golgi			
GM130	HspB5	Golgi vesicles	[169]
Cell cycle			
Cyclin D1	HspB5	Ubiquitination by HspB5- FBX4	[162]
Senescence			
HDM2	HspB1	Inhibition of P53 induced senescence through HDM2 stabilization	[161]
Viruses			
Hepatitis C	HspB1	Interaction with NS5A	[170]
Lens crystallin proteins			
HspB4	HspB5	Chaperoning	[29,34]
HspB5	HspB4	Chaperoning	[34]
	HspB1	Chaperoning	[34]
Beta B2-crystallin	HspB5	Chaperoning	[171]
Gamma C-crystallin	HspB5	Chaperoning	[171]
Chimeric sHsps complexes and sHsps regulators			
HspB1	HspB5	HspB1 chaperoning	[30]
	HspB6	NK	[35]
	HspB8	NK	[172]
HspB5	HspB1	HspB5 chaperoning	[30,173]
HspB8	HspB5	nk	[31,35]
HspB6	HspB8	nk	[31]
HspB3	HspB8	nk	[31]
	HspB2	Role in myogenic differentiation	[174]
HspB7 (cvHsp)	HspB8	nk	[172]
HspB2 (MKBP)	HspB8	nk	[172]
HspB4	HspB5	HspB4 chaperoning	[29,32–34,173]
HspB6 (Hsp20)	HspB5	nk	[35]
Hic-5 (ARA55)	HspB1	Negative regulator of HspB1	[175]
p66Shc	HspB1	Negative regulator of HspB1	[101]
PASS1	HspB1	Negative regulator of HspB1	[176]
Bag-3	HspB8	Co-chaperone of HspB8	[11,75]

nk: not known; MAPs: Microtubule-associated proteins; GFAP: Glial fibrillary acidic protein; F508del CFT: deletion F508 of CFT that is responsible for most cystic fibrosis pathologies; CD10: 100 kDa transmembrane metallo-endopeptidase; DSTN: Destrin or actin depolymerizing factor or ADF; ZASP: Z-band alternatively spliced PDZ motif containing protein; GRIFIN: galectin-related interfiber protein; VEGF: vascular endothelial growth factor; FGF-2: Fibroblast growth factor 2; NGF-beta: Nerve growth factor beta; PrPc: bovine prion protein; Her2: Human Epidermal Growth Factor Receptor-2; HDAC6: histone deacetylase 6; SMN: survival motor neuron protein; NSC: nuclear speckle components; p90rsk: Snail: zinc finger protein that binds and inhibits E-cadherin promoter to induce epithelial mezanchymal transformation; p90 ribosomal S6 kinase; IF: intermediate filaments; GATA-1: globin transcription factor 1; HSF-1: heat shock factor 1; GFAP: glial fibrillary acidic protein; DAXX: death domain-associated protein 6; STAT2 and 3: signal transducer and activator of transcription 2 and 3; Fbx4: Fbox only protein 4; eIF4E, eukaryotic translation initiation factor 4E; eIF4G: eukaryotic translation initiation factor 4G; Smad-Smurf2: Smad ubiquitination regulatory factor 2; Factor XIII: transglutaminase, platelet Factor XIII; PhK: rabbit skeletal muscle phosphorylase kinase; XPORT: exit protein of TRP and Rh1; TRP: transient receptor potential channels; Rh1: rhodopsin; MK2: MAPK-activated protein kinase-2; P38: MAP Kinase; TRAF6: tumor necrosis factor receptor-associated factor 6; AR: androgen receptor; ER beta: estrogen receptor beta. PKCα: protein kinase Cα; PKCδ: protein kinase C δ. Akt: also known as protein kinase B (PKB); p27kip1: cyclin-dependent kinase inhibitor p27kip1; PEA-15: astrocytic phosphoprotein PEA-15; PTEN: phosphatase and TENsin homolog; HDM2: human double minute2; Bax: Bcl-2-associated X protein; Bag3: Bcl-2-associated athanogene 3; Ubc6: ubiquitin conjugating enzyme E2 6; SOD1: Copper-Zinc superoxide dismutase; SOD2: Manganese superoxide dismutase; Hic-5 (ARA55): androgen receptor associated protein 55; NF-κB: nuclear factor kappaB; G6PD: glucose 6-phosphate dehydrogenase; p66Shc: 66 kDa isoform of ShcA (Src homology 2 domain containing transforming protein 2); CIAPIN1: Anamorsin, a cytokine-induced inhibitor of apoptosis; eIF2: eukaryotic initiation factor 2; TDP-43: major disease protein in ubiquitin-positive, tau-, and alpha-synuclein-negative frontotemporal dementia; SC35: Splicing factor SC35; PASS1: protein associated with small stress proteins 1; SRp38: splicing regulator p38, SR proteins constitute a family of pre-mRNA splicing factors; NF-M: Neurofilament middle chain subunit; a protein kinase of the MLK family. TAK1: TGF-β activated kinase 1; Ddx20: DEAD box protein Ddx20 (gemin3, DP103); SOD-1: Cu/Zn-superoxide dismutase; SAM68: c-Src kinase during mitosis; SOD-1: Cu/Zn-superoxide dismutase; TCTEL1: dynein subunit; EFTUD2: U5-116KD, Snu114, Snrp116, elongation factor Tu GTP-binding domain-containing protein 2; PRKD1: Serine/threonine-protein kinase D1; Smurf2: E3 ubiquitin protein ligase 2; PPM1A: protein phosphatase 1A (formerly 2C), magnesium-dependent, alpha isoform.

Little information is available concerning the protein domains and/or the structural organization of sHsps that interact with specific proteins [58]. This complex problem can be illustrated by the fact that, in HeLa cells, pro-caspase-3, HDAC6 and STAT2 interact with different phospho-oligomeric structures of HspB1 [54,58]. It was also reported that different domains of HspB5 are effective, at least in vitro, to recognize specific target proteins [59].

In addition to the major proteins listed in Table 1, new protein targets are nowdays detected using automated yeast two-hybrid interaction systems and immunological means. Another example, which was not included in Table 1, concerns the 70 proteins (acute phase proteins, coagulation factors and proteins of the complement) which appear to interact with plasma HspB5 [60]. Hence, sHsps may have far more interacting proteins then those described here [61,62].

3. The ability of some sHsps to interact with each other results in the formation of hetero-oligomers bearing new biochemical properties

A fascinating property of sHsps concerns their ability to form hetero-oligomeric structures in vivo and in vitro. The phenomenon was first described in the developing lens cells. During lens differentiation, αB-crystallin (HspB5) is synthesized earlier than αA-crystallin (HspB4), however, because these two proteins are differentially expressed, in differentiated lens fiber cells αA and αB form a unique large hetero-oligomer oligomer (αA to αB ratio: 3 to 1) denoted as α-crystallin [63–65]. Hence, the particular association of HspB5 and HspB4 in lens fiber cells results in the formation of the α-crystallin molecule essential for the lens refractive and light focusing properties. Of interest, this property is not

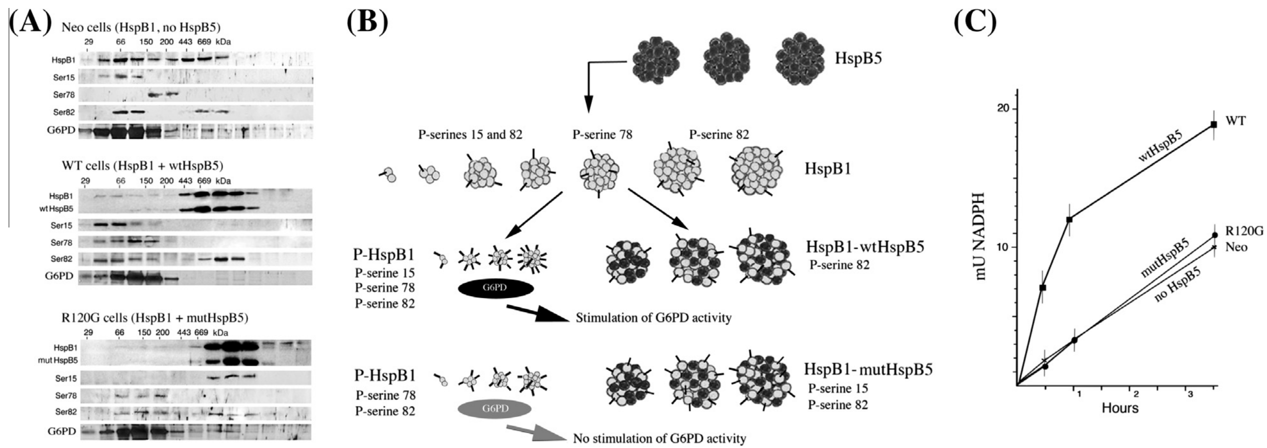

Fig. 2. HspB1/HspB5 interaction indirectly modulates G6PD activity. (A) Analysis of the chimeric complex formed by HspB1 and HspB5 in HeLa cells. HeLa cells, which express a high load of endogenous HspB1 (5 ng/μg of total cellular proteins) but no HspB5, have been genetically modified [68] to express rather similar levels (6 ng/μg of total cellular proteins) of either wild type (denoted WT cells) or mutant (R120G) HspB5 (denoted R120G cells). Control clone is denoted Neo (no HspB5). Cells were lysed and the 10000×*g* soluble fractions were applied to Sepharose CL-6B gel filtration columns to analyze the native size of HspB5, HspB1 and its phosphorylated isoforms and G6PD. The presence of these proteins was detected in immunoblots of the collected fractions probed with the corresponding antibodies. Autoradiographs of ECL-revealed immunoblots are presented. 29, 66, 150, 200, 443, 669 kDa are gel filtration markers. B) Shematic illustration of the phenomenon presented in A. As previously described [36], Neo cells contain three size sub-populations of HspB1, each of them being characterized by a different set of phosphorylated serines. Phosphoserine 15 is present only in the oligomers of less than 150 kDa together with a fraction of the total HspB1 content of phosphoserine 82. Phosphoserine 78 is the only phosphoserine present in the medium sized oligomers (150–400 kDa). In contrast, the large oligomers contained the remaining content of phosphoserine 82. The particular oligomeric pattern of HspB1 was no more observed in WT cells since most of this protein interacted with HspB5 (400–800 kDa). In R120G cells, the hetero-complex had a higher native size (up to about 900 kDa) compared to that formed with wild-type HspB5. Of interest, in WT cells, the low level of HspB1 (<10%) not trapped in the HspB1/HspB5 complex and recovered as small homo-oligomers showed a 6-fold increased phosphorylation (at the level of the three phosphoserine sites) compared to HspB1 in control cells. In R120G cells, the small oligomers of HspB1 only displayed phosphorylation at the level of serines 78 and 82, since phosphorylated serine 15 was recovered in the HspB1/mutantHspB5 complex. In the three types of cells, G6PD was recovered in the fractions smaller than 200 kDa where highly phosphorylated HspB1 (P-HspB1) accumulates. G6PD is known to increase its activity when it interacts with highly phosphorylated HspB1 small oligomers [56]. In WT cells, interaction of G6PD with the highly phosphorylated HspB1 small oligomers was confirmed as well as its stimulated activity (see Fig. 2C). (C) Analysis of G6PD activity in Neo, WT and R120G cells. G6PD activity was measured in cell extracts through its ability to produce NADPH (mU/ml) in function of time using the Glucose-6-phosphate dehydrogenase assay kit of Biovision Inc. (Mountain View, CA). Standart deviations are presented, $n = 3$. Note the stimulated activity of G6PD in WT cells (up to almost 4-fold) that was not observed in cells devoid of HspB5 or expressing HspB5 R120G mutant.

beared by the parental molecules. The interaction of HspB1 with HspB5 is the second example of hetero-oligomers that has been reported [66]. This complex dissociates in response to heat shock or oxidative stress suggesting that HspB1/HspB5 hetero-oligomers are probably unable to play an efficient protective role in stress conditions and/or may bear different functions that the parental chaperones. Hence, it has been proposed that if several sHsps are expressed in the same cell, they can form a variety of multiple combinatorial chimeric oligomeric complexes that could bear new protein target recognition abilities and/or modulate those of the parental molecules [31]. The recognition ability of the different sHsps is indeed a very complex phenomenon that may depend on the type of cell considered and its physiology. Moreover, recent observations revealed that not all sHsps have the same efficiency to interact with each other (see Fig. 1B). For example, HspB4 appears to interact only with HspB5 while HspB1 interacts with HspB5, HspB6 and HspB8. HspB2 interacts with HspB3, HspB8 and HspB6 and HspB3 interacts only with HspB8 and HspB2. HspB6 is rather efficient since it can interact with HspB5, HspB1, HspB8 and HspB2. HspB7 has been described to interact only with HspB8 and no interaction have yet been reported concerning HspB9 and HspB10. It should nevertheless be mentioned that the interaction of HspB8 with either HspB1 or HspB6 has been reported in some, but not in all publications, hence it remains questionable. This point is also illustrated by the in vitro formation of any heterodimers with participation of HspB8 which is more difficult to produce compared to those formed between HspB1/HspB5, HspB1/HspB6 and HspB5/HspB6 [35]. Another parameter to take into account is the structural organization of the parental sHsps that could modulate their interaction with other sHsps (Fig. 1C). It is well known, at least in the case of HspB1, that this parameter is highly dependent on cell physiology [36].

Formation of hetero-oligomers between sHsps mutually affects the structure of both partners [67]. This could stimulate the chaperone activity of the parental sHsps, as demontrated for HspB1 once it interacts with HspB5 [34,68–70]. On the other hand, dominant negative effects can dramatically spread between interacting sHsps through the formation of hetero-oligomers with a mutated sHsp partner [70,71]. In addition, mutant HspBs can have an increased ability to interact with other small Hsps. For example, some mutants of HspB8 have an increased efficiency to interact with HspB5 and HspB1 but not with HspB6, hence each mutant can have a characteristic pattern of abnormal interaction properties [72]. These interactions can also result in the formation of cytoplasmic protein aggregates linked to pathological diseases.

What about a putative interaction between three sHsps? In that respect, an interesting study reported that the hetero-oligomers formed by HspB2/HspB3 cannot interact with HspB6, HspB1 or HspB5, whereas the homomeric form of HspB2, thus not in complex with HspB3, could associate efficiently with HspB6. Hence, despite the high level of sequence homology within the sHps, the biochemical properties of the HspB2/HspB3 complex appears different from that of HspB2 homo-oligomers [73]. Other studies revealed that the size of the hetero-oligomers formed by HspB1/HspB6 and HspB5/HspB6 is different from the size of the corresponding homo-oligomers. Similar observations were made concerning HspB1 and HspB5 [69]. Other studies concluded that HspB6 and HspB1 mutually affect the structure of each other and formation of hetero-oligomeric complexes may influence diverse cellular processes [67]. Another crucial factor to take into account is phosphorylation (see below Fig. 2). Hence, hetero-oligomers appear to structurally differ from the parental sHsps and could have their own cellular functions.

4. Do sHsp hetero-oligomers bind to the same proteins as parental sHsps or interact with novel protein partners?

Based on the fact that the multiple combinatorial hetero-oligomeric oligomeric complexes are probably structurally different from the parental sHsps, they may confer surfaces able to interact with novel protein targets (Fig. 1 C). However, it cannot be excluded that some parental-specific clients could still be able to interact. Nowdays, we cannot answer these questions since clear-cut reports describing the interaction of sHsp hetero-oligomers with specific protein targets have not been reported yet. In that regard, one example concerns the autophagic removal of misfolded proteins which appears to occur through a large multi-heteromeric complex made of HspB8, HspB6, Bag3, Hsc70 and the E3 ligase CHIP [74,75]. The co-chaperone Bag3, which plays a central role by targetting sHsps substrate proteins for degradation, can interact with either HspB8 or HspB6 homo-oligomers [75,76]. Of interest, the interaction between HspB6 and Bag3 requires the same regions of Bag3 that are involved in the HspB8-Bag3 association [75]. However, it is not known whether the large multiheteromeric complex mentioned above also contains HspB8/HspB6 hetero-oligomers. At least one mutant of Bag3 is associated with the development of severe dominant childhood muscular dystrophy, suggesting crucial physiological roles for Bag3-HspB complexes [75].

Many of the observations mentioned here are deduced from in vitro analysis. However, *in vivo,* the interaction between sHsps appears far more complex, since intracellular factors (e.g., kinases/phosphatases) could play crucial roles. Moreover, it is also possible that only a fraction of the sHsps present in cells interact with each other. This point is illustrated by our analysis of HspB1/HspB5 interaction in genetically modified human cancerous HeLa cells. We have observed that, even if the molecular ratio between endogenous HspB1 and exogenous HspB5 was slightly in favor of HspB5, a fraction of HspB1 (about 10%) was not associated with the hetero-oligomeric complex formed by HspB1/HspB5 while all HspB5 oligomeric complexes contained HspB1 (Fig. 1C and 2A). In cells devoid of HspB5 expression, HspB1 homo-oligomers have a surprizing size-dependent phosphorylation pattern that allowed us to define three size sub-populations each of them being characterized by a different set of phosphorylated serines [36,58,70]. As seen in Fig. 2A, phosphoserine 15 is present only in the oligomers of less than 150 kDa together with about 60% of the total HspB1 content of phosphoserine 82. These small oligomers are devoid of phosphorylated serine 78 which is present only in the medium sized oligomers (150–400 kDa) while the large oligomers contained the remaining HspB1 content of phosphoserine 82 (40%). This particular in vivo phospho-oligomeric pattern of HspB1 was lost in the presence of HspB5, since most of this protein was in large HspB1/HspB5 hetero-oligomers. Of interest, the low level of small sized HspB1 homo-oligomers not interacting with HspB5 showed a 6-fold increased phosphorylation (at the level of the three phosphoserine sites of HspB1) compared to parental small HspB1 homo-oligomers. Why these small HspB1 homo-oligomers are differently phosphorylated than the corresponding small sized oligomers of HspB1 present in cells devoid of HspB5? One possibility could be that phosphoserine 78 is necessary for the formation of intermediate sized oligomers, a phenomenon abolished by the interaction with HspB5. The phenomenon could also result of an enhanced recognition of these particular homo-oligomers by HspB1 kinases. In comparison, the HspB1/HspB5 hetero-oligomers, which in spite of containing about 90% of HspB1, are weakly phosphorylated at only one HspB1 site (phosphoserine 82). Consequently, the formation of HspB1/HspB5 complex indirectly generates the formation of a new-type of highly phosphorylated small HspB1 homo-oligomers. Of interest, highly phosphorylated HspB1 has been reported to interact with a particular protein target: the first enzyme of the pentose phosphate pathway, glucose 6-phosphate dehydrogenase (G6PD) [56] whose activity was previously reported to be modulated by HspB1 level of expression [77,78]. This enzyme represents the major reducing power in the cell throught its ability to transform $NADP^+$ in NADPH + H^+ leading to the reduction of oxidized glutathione [79]. This induces the detoxification of reactive oxygen species and promote resistance to oxidative stress [80], a phenomenon already described to be linked to HspB1 and HspB5 expression [77,81–83]. The interaction of G6PD with the highly phosphorylated homo-oligomers of HspB1 resulted in a drastic stimulation of its activity (Fig. 2C) and triggered oxidoresistance. In cells expressing the myopathy and cataract inducing R120G mutant of HspB5 instead of the wild type form, a similar formation of HspB1 small homo-oligomers was observed (Fig. 2 AB). However, their phosphorylation was only at the level of two serine sites since HspB1 phosphorylated at serine 15 was now located inside the HspB1–HspB5 mutant complex. This altered phosphorylation of HspB1 homo-oligomers did not correlate with an increased activity of G6PD (Fig. 2C) and oxidoresistance [70]. Hence, this example illustrates the high level of complexity associated to the in vivo formation of small Hsp hetero-oligomers.

5. Conclusions

sHsps, also called the "forgotten chaperones" [84], are now recognized to have fundamental roles in physio-pathological processes and human diseases. By reading the scientific literature related to sHsps functions one can be surprized by the incredible numbers of crucial, but most of the time unrelated, cellular effects induced by either up- or down–regulating their constitutive expression. We have proposed that these activities could result of their ability to recognize, interact and modulate the activity of many different proteins [45,46,52,58]. Indeed, the number of proteins that are discovered to interact with sHsps is growing exponentially. The aim of this report was therefore to up-date the list of proteins that interact with the ten members of the family of human small sHsps. Unfortunately, only little information is yet available concerning the multiple combinatorial chimeric hetero-oligomeric complexes that can form in cells expressing several sHsps and about the proteins that could interact with them. These structures, which seem to have lost some of the properties associated to sHsp homo-oligomers, probably bear new protein targets recognition abilities. Moreover, the formation of hetero-oligomers can modulate the interactome of parental molecules. In that regard, it is shown here that the formation of HspB1/HspB5 complex generates some highly phosphorylated HspB1 homo-oligomers that can interact with G6PD and stimulate its activity, a phenomenon resulting in enhanced cellular oxidoresistance. Hence, it can be concluded that more studies are needed before comprehensive sHsp interactomes could be build and used to search for therapeutic drugs that modulate the interaction of these Hsps with pathological protein targets. Based on the considerations described here, it can easily been concluded that alteration of sHsps vast interactome by broad approches could have deleterious side effects to patients, as it has already been observed in the case of Hsp90 [85].

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