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Review

The potential role of small heat shock proteins in mitochondria

Liuwang Zeng [a], Jieqiong Tan [b], Wei Lu [a], Tonglin Lu [a], Zhiping Hu [a,*]

[a] Department of Neurology, Second Xiangya Hospital, Central South University, Changsha, Hunan, 410011, China
[b] National Key Laboratory of Medical Genetics, Central South University, Changsha, Hunan, 410078, China

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ABSTRACT

Mitochondria play a central role in cellular metabolism, calcium homeostasis, redox signaling and cell fates. Mitochondrial homeostasis is tightly regulated, and mitochondrial dysfunction is frequently associated with severe human pathologies. Small heat shock proteins are molecular chaperones that play major roles in development, stress responses, and diseases, and have been envisioned as targets for therapy. The mechanisms that lie behind the cytoprotection of small heat shock proteins are related to the regulation of mitochondrial functions. This review recapitulates the current knowledge of the expression of various small heat shock proteins in mitochondria and discusses their implication in the role of mitochondria and their regulation. Based on their involvement in mitochondrial normal physiology and pathology, a better understanding of their roles and regulation will pave the way for innovative approaches for the successful treatment of a range of stress-related syndromes whose etiology is based upon dysfunction of mitochondria.

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* Corresponding author. Tel.: +86 13637401459.
E-mail address: xyneurology@gmail.com (Z. Hu).

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1. Introduction

Mitochondria are highly dynamic organelles present in all eukaryotic organisms. Mitochondrial physiological functions include energy production, reactive oxygen species (ROS) production and detoxification, fatty acid oxidation, iron–sulfur cluster biogenesis, stress sensing, Ca^{2+} signaling, cross-talk with other organelles, biogenesis, fusion/fission events, and orchestration of some cell death modalities. Mitochondrial homeostasis is a complex and tightly regulated process, and failure to maintain mitochondrial homeostasis is frequently associated with severe human pathologies [1,2]. Therefore, mitochondria are of an increasing interest in pharmaceutical and medical research and the mitochondrial organelle is a potential therapeutic target [3].

Small heat shock proteins (sHsps) are molecular chaperones ubiquitously distributed in numerous species, from bacteria to humans. By far, ten proteins have been assigned to the superfamily of mammalian small heat shock proteins: Hsp27 (HspB1, Hsp25), myotonic dystrophy protein kinase-binding protein (MKBP) (HspB2), HspB3, alphaA-crystallin (HspB4), alphaB-crystallin (HspB5), Hsp20 (p20, HspB6), cardiovascular heat shock protein (cvHsp) (HspB7), Hsp22 (HspB8), HspB9 and HspB10 (Table 1). These proteins have molecular mass in the range of 17.0–28.4 kDa. A conserved C-terminal "alpha-crystallin" domain organized in a beta-sheet sandwich and oligomeric structure are common features of sHsps. All small heat shock proteins play important "housekeeping" roles and regulate many vital processes and they are considered as attractive cytoprotective agents [4].

Small heat shock proteins are detected in mitochondria and they can protect NADH:ubiquinone oxidoreductase and NADH dehydrogenase activity (i.e., complex I) in submitochondrial vesicles during heat and oxidative stress [5]. Moreover, NaCl stress damages mitochondrial Complex I via oxidative stress, while mitochondrial Complex I is protected by antioxidants and sHsps, suggesting that sHsps may protect Complex I as antioxidants [6]. Here, we review the current state of knowledge about the role of sHsps in mitochondria, with a specific focus on the cytoprotective mechanisms of sHsps that can affect mitochondrial homeostasis under normal and stress-related conditions.

2. Hsp27 and mitochondria

2.1. Hsp27 and mitochondrial autophagy

Autophagy is a dynamic process for degradation of cytosolic components such as dysfunctional organelles and proteins and a means for generating metabolic substrates during periods of starvation. Mitochondrial autophagy ("mitophagy") is a selective form of autophagy, which is important in maintaining mitochondrial homeostasis. As a cytoskeleton regulator, Hsp27 is critical for dynamic intracellular trafficking during autophagy and mitophagy. Loss of Hsp27 results in a phenotypically similar deficiency in mitophagy typified by mitochondrial fragmentation with decreased aerobic respiration and adenosine triphosphate (ATP) production [7].

Meanwhile, high-mobility group box 1 (HMGB1), an evolutionarily conserved chromatin-associated protein which maintains nuclear homeostasis, is also a critical regulator of mitochondrial function and morphology. Hsp27 is the downstream mediator of this effect. Disruption of the Hsp27 gene in embryonic fibroblasts with wild-type HMGB1 recapitulates the mitochondrial fragmentation, deficits in mitochondrial respiration, and adenosine triphosphate (ATP) synthesis observed with targeted deletion of HMGB1. Forced expression of Hsp27 reverses this phenotype in HMGB1 knockout cells. Mitochondrial effects mediated by HMGB1 regulation of Hsp27 expression serve as a defense against mitochondrial abnormality, enabling clearance and autophagy in the setting of cellular stress [8].

2.2. Hsp27 and mitochondria in apoptosis

Ubiquitously expressed Hsp27 is involved in the control of protein folding and directly or indirectly participates in the regulation of apoptosis, protects the cell against oxidative stress, and is involved in the regulation of the cytoskeleton [4,9]. Hsp27 inhibits mitochondrial injury and apoptosis in both normal and cancer cells (Fig. 1). Hsp27 antagonizes Bax-mediated mitochondrial injury and apoptosis by promoting Akt activation via a PI3-kinase-dependent mechanism [10].

Hsp27 interferes specifically with the mitochondrial pathway of caspase-dependent cell death. Hsp27 protects against apoptosis through its interaction with cytosolic cytochrome c. Hsp27 also interferes, in a manner dependent on level of expression, with the release of cytochrome c from mitochondria. A decreased level of endogenous Hsp27 reduced the delay required for cytochrome c release and procaspase 3 activation [11]. Meanwhile, Hsp27 inhibits cytochrome-c-mediated activation of caspases in the cytosol. Hsp27 binds to cytochrome c released from the mitochondria to the cytosol and prevents cytochrome-c-mediated interaction of Apaf-1 with procaspase-9 [12]. Moreover, mitochondrial cytochrome c release in response to pro-apoptotic signals leads to the formation of a cytochrome c/Apaf-1/procaspase-9 complex (the apoptosome) and resultant activation of caspase-9 and caspase-3. Hsp27 inhibits cytochrome c-mediated caspase activation by sequestering both pro-caspase-3 and cytochrome c, and thus prevent the correct formation/function of the apoptosome complex [13].

As suggested above, Hsp27 inhibits apoptotic pathways triggered by a variety of stimuli in mammalian cells. Hsp27 inhibits etoposide-induced apoptosis by preventing cytochrome c and dATP-triggered activity of caspase-9, downstream of cytochrome c release [14].

Table 1
Some properties of the ten members of mammalian small heat shock proteins.

Name	Alternative names	Chromosome location	Number of amino acid residues	Molecular weight (kDa)	Tissue distribution	Associated diseases
HspB1	Hsp25(mouse), Hsp27, Hsp28	7q11.23	205	22–23	Ubiquitous	Neuropathy, cancer, ischemia/reperfusion
HspB2	MKBP, myotonic dystrophy protein kinase binding protein	11q22–q23	182	20	Cardiac and skeletal muscle	Myopathy, ischemia/reperfusion
HspB3	HspL27	5q11.2	150	17	Cardiac and skeletal muscle	Motor neuropathy
HspB4	αA-crystallin/CRYAA	21q22.3	173	20	Eye lens	Cataract
HspB5	αB-crystallin/CRYAB	11q22.3–q23.1	175	20	Ubiquitous	Neuropathy, myopathy, ischemia/reperfusion, cancer, cataract
HspB6	Hsp20, p20	19q13.12	157	17	Ubiquitous	Neuropathy, ischemia/reperfusion
HspB7	cvHsp, cardiovascular heat shock protein	1p36.23–p34.3	170	18–19	Cardiac and skeletal muscle	
HspB8	Hsp22, H11 protein kinase, product of E2IG1 gene	12q24–23	196	21–22	Ubiquitous	Neuropathy, cancer, ischemia
HspB9	None	17q21.2	159	17–18	Testis	Cancer
HspB10	ODF1, outer dense fiber proteins	8q22.3	250	28–29	Testis	

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