Small heat shock proteins: Structure and subcellular localization

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Heat-shock proteins (HSPs) are molecular chaperones participating primarily in protein folding preventing protein degradation and subsequent cellular distress.

heat-shock proteins autoimmunity heat-shock response

1. Introduction

Heat-shock proteins (HSPs) are molecular chaperones participating primarily in protein folding preventing protein degradation and subsequent cellular distress [1]. HSPs are regulated through heat-shock factor 1(HSF-1) [2]. In the steady state HSF-1 is bound to HSP90 or HSP70 [3][4]. Upon stressful signals HSF-1 dissociates from HSPs and translocates into the nucleus where it stimulates HSP expression [1]. HSPs can be exposed to the immune system through tissue necrosis and the resultant cellular debris, via organized release of exosomes/endosomes, or through their presence on the cellular membrane [5][6][7]. Their evolutionary conservation can elicit interspecies immune recognition [8]. The resulting immune response can be either immunoregulatory or immunostimulatory [9] [10]. Furthermore specific HSP domains as well as certain HSP isoforms and their client proteins induce a differential autoimmune response.

2. Structure and Subcellular Localization of the Small HSP Family

The small HSP (sHSP) gene family has 11 family members [11], which are located in the nucleus, cytoplasm, extracellular space, and the cytoskeleton where they can modulate its structure [12][13][14]

Small HSPs have a central alpha crystallin domain (ACD) bounded by N-terminal and C-terminal domains (**Figure 1**a) [15][16][17]. The ACD entails many antiparallel β-sheets which form its final β-sandwich conformation [15]. The N-terminal domain contains serine residues which can be phosphorylated by intracellular kinases. For example, MAPK-activated protein kinase 5 (MK5) can interact with HSP27 in vivo and influence F-actin-dependent cytoskeletal organization [18]. Binding of denatured proteins (client proteins) to sHSPs is characterized by diversity in terms of their docking sites. The N-terminal domain as well as the ACD can serve as client protein-binding sites [15][19].

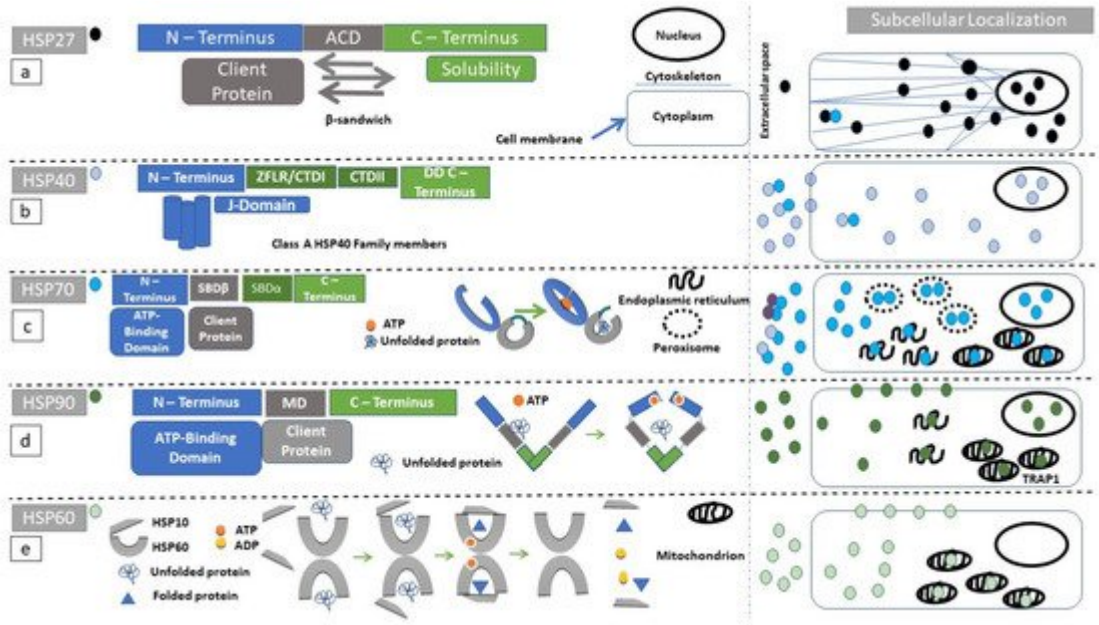

Figure 1. Structure and function of heat shock proteins (HSPs): Diagrammatic representation of the domain structure and subcellular localization of HSPs under discussion. Of note is the fact that heat-shock proteins can form complexes with other molecular chaperones. These chaperone complexes may exert a different action than the uncomplexed HSPs. (**a**) HSP27 (black circle) secondary structure, consists of an N-terminal (blue rectangle) substrate-binding region, followed by an alpha crystallin domain (ACD, gray rectangle) ending in the C-terminus (green rectangle). ACD has a β-sandwich conformation. Client proteins dock to ACD. The C-terminus is highly variable among protein members and facilitates HSP27 oligomerization. (**b**) Class A HSP40 (blue circle) protein family secondary structure consists of an N-terminal (blue rectangle) substrate-binding region, followed by a zinc finger-like region (ZFLR), C-terminal domains I and II (CTDI and II, green rectangles in c-terminal region), and ending in a dimerization domain (DD). The J-domain localizes within N-terminal region. Class B preserves the N-terminal localization of the J-domain but the C-terminus can acquire a more diverse structure. In class C, the J-domain can be localized anywhere within the amino-acid sequence. (**c**) HSP70 (turquoise circle) secondary structure consists of an N-terminal domain (blue rectangle), followed by a substrate-binding domain (SBDβ, gray rectangle), a substrate-binding domain α-helical (SBDα, gray rectangle), and ending in the C-terminus (green rectangle). The reaction cycle involves ATP docking within N-terminal domain since ATP hydrolysis powers the structural opening of the substrate cleft within the SBDβ (gray arc). (**d**) The HSP90 (dark green circle) secondary structure consists of an N-terminus (blue rectangle), followed by a middle domain (MD, gray rectangle), ending in a c-terminus (green rectangle). HSP90 homodimerizes with the use of its c-terminal region. Unfolded proteins are docking in the MD. ATP hydrolysis is required for substrate processing. (**e**) The HSP60 (light green circle) reaction cycle. Unfolded substrates enter the HSP60 processing cleft. HSP10 acts as a lid, and ATP-hydrolysis is necessary for substrate folding.

Each one of the sHSPs plays a pivotal role in stabilizing denatured native proteins. They lack, however, the ability to refold destabilized proteins [20], thus sHSP interaction with larger HSPs such as HSP40 or HSP70 is necessary [15]. Larger HSPs, in contrast with sHSPs, have an ATPase function which provides the energy needed to refold the client protein [21]. Normally sHSP molecules are in a polymeric/oligomeric state equilibrium. The presence of

noxious stimuli favors their oligomerization. N- and C-termini confer to sHSPs solubility facilitating their oligomerization (**Figure 1**a) [15][22]. sHSP oligomers can be engaged within protein aggregates in order to facilitate protein folding [23][24].

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