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Review

Contribution of small heat shock proteins to muscle development and function

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ABSTRACT

Investigations undertaken over the past years have led scientists to introduce the concept of protein quality control (PQC) systems, which are responsible for polypeptide processing. The PQC system monitors proteostasis and involves activity of different chaperones such as small heat shock proteins (sHSPs). These proteins act during normal conditions as housekeeping proteins regulating cellular processes, and during stress conditions. They also mediate the removal of toxic misfolded polypeptides and thereby prevent development of pathogenic states. It is postulated that sHSPs are involved in muscle development. They could act via modulation of myogenesis or by maintenance of the structural integrity of signaling complexes. Moreover, mutations in genes coding for sHSPs lead to pathological states affecting muscular tissue functioning.

This review focuses on the question how sHSPs, still relatively poorly understood proteins, contribute to the development and function of three types of muscle tissue: skeletal, cardiac and smooth.

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1. Introduction

Organisms, to reduce their susceptibility to various environmental and cellular stresses, have developed so-called protein quality control (PQC) systems, in which all members of the small heat shock protein (sHSP) family take part. sHSPs are the first line of defense against misfolded polypeptides with a tendency to aggregation. Abnormalities in this defense mechanism caused, e.g. by mutations in genes encoding its components, may lead to disruption of protein folding, structure and function, and can result in diseases such as skeletal and cardiac myopathies and neurological disorders [for review see [1]].

sHSPs (HSPBs) [2] are described as molecular chaperones involved in the response to stress conditions such as heat or oxidative stress [3]. The activity of sHSPs does not require ATP, and unlike some other heat shock proteins they are unable to refold damaged proteins. Their main task is maintaining the soluble state of unfolded proteins and preventing their precipitation [3] (Fig. 1). Representatives of this family are known from all domains: Archaea [4], bacteria [5], and eukaryotes, including fungi [6], plants [7] and animals [8]. Most of the organisms have several different homologues of sHSPs: a few in bacteria and yeast [6], 10 in humans [9], 13 in zebrafish [10], and up to 15 in plants [11]. In higher eukaryotes the distribution of each sHSP is subcellular and/or tissue specific [12,13]. Mutations in sHSPs are connected with some severe pathologies such as desmin-related myopathy, distal hereditary motor neuropathy, Charcot–Marie–Tooth (CMT) disease, cataract and neurodegenerative diseases [14].

1.1. Structure and activity of sHSPs

The mass of a single sHSP molecule varies between 15 and 40 kDa. Each sHSP contains a highly conserved 80–100 amino acid α-crystalline domain (ACD), essential for its activity. There are a few atomic resolution structures obtained from whole molecules – the archeon *Methanococcus jannaschii* [4], wheat *Triticum aestivum* [7] and tape worm *Taenia saginata* [8] – and some from versions shortened on both ends containing an ACD core [15]. The ACD forms an immunoglobulin-like β sandwich fold composed of nine β strands. Two β sheets of the β sandwich are composed of respectively four (β2, β3, β8, β9) and three (β4, β5, β7) β strands. The core α-crystalline domain is flanked with longer N-terminal and shorter C-terminal regions, variable in length and amino acid composition [16]. Interactions between pockets formed in the α-crystalline

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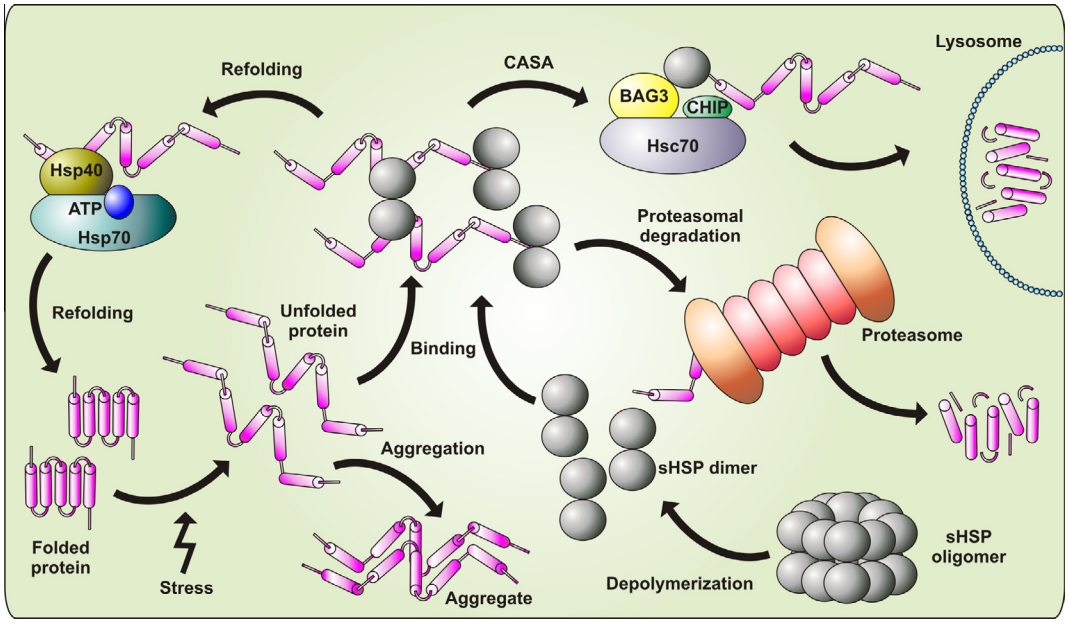

Fig. 1. Involvement of sHSPs in maintenance of cellular protein homeostasis. The main task of sHSPs is maintaining the soluble state of unfolded proteins and preventing their precipitation and formation of potentially toxic aggregates. They are part of the multicomponent machinery responsible for monitoring all steps of the protein life cycle which comprises *inter alia* synthesis, folding, aggregation, refolding and degradation. sHSPs participate, together with the Hsp70/Hsp40 machinery, in restoration of native conformation of unfolded or partially folded polypeptides, or in their proteasomal degradation when the repair of damage is impossible. Due to interactions with different partners some sHSPs direct proteins to alternative degradation pathways such as CASA (chaperone-assisted selective autophagy). See main text for a detailed description.

domain and terminal extensions play a role in the further assembly of sHSP and in the formation of clusters [17,18].

In the inactive state most sHSPs form large oligomers, assembled from both homo- and heterodimers [19]. Monomers within a dimer are connected in an antiparallel manner, by reciprocal fitting of a β6 strand into the neighboring protein molecule or by interactions between elongated β6/β7 strands [18]. The C-terminal region is rather involved in dimer formation, whereas the N-terminal region is found to stabilize highly organized oligomers [16,17]. The C-terminal end contains a conservative I/V/L-X-I/V/L sequence which is reported to fit inside the β4/β8 groove [20] and is responsible for the intrinsically disordered state of this part of the protein. Since forms of sHSPs truncated on the C-termini are connected with cataract, the accessibility of the β4/β8 groove affected by a flexible C-terminus may be significant in regulation of chaperone activity [18,21]. Dissociation of both monomers and dimers from the oligomers is required for sHSP activity, and is regulated by phosphorylation of multiple sites in the N-termini [22,23]. Additionally, the dimeric state enables creation of a hydrophobic groove between monomers, essential for binding unfolded peptides [24]. Distortions and charge shifts present in many mutated forms of sHSPs slightly alter the interfaces inside the dimer and cause closure of the groove [24].

The most prominent activity of sHSPs is binding proteins and protecting them from aggregation. Antiaggregation properties of sHSPs may inhibit aggregation of many pathogenic proteins which cause various neurodegenerative diseases, such as Parkinson's disease (PD), Alzheimer's disease (AD), dementia with Lewy bodies or Huntington's disease (HD). Formation of filaments by both wild-type and mutated (PD) forms of alpha-synuclein can be stopped in the presence of sHSPs, especially HSPB8 [25]. There are also reports suggesting that some sHSPs enhance dissolving of senile plaques present in AD [26,27] and suppress aggregation of polyglutamate proteins by interacting with their Josephin domain, which is responsible for the initial steps of aggregation of polyQ proteins [28]. It is suggested that some of these effects can be caused by promoting autophagy and/or an inflammatory response after detection of misfolded proteins by sHSPs [29–31].

sHSPs are able to bind most unfolded proteins in a non-specific manner, preventing their aggregation; however, there are also more regular partners and a pin array assay indicated specific binding sites for different proteins. HSPB5 (a.k.a αB-crystallin) has, aside from chaperone sites, the ability to bind intermediate filaments (desmin, GFAP), actin microfilaments and some growth factors [32–34]. Also HSPB8 is noted to interact with partner protein Bag3 [35], which connects sHSP with Hsc70, directing proteins to refolding, and to autophagy or proteasomal degradation [29,30,36,37].

1.2. Interaction of sHSPs with cytoskeletal elements and other binding partners

Many representatives of the sHSP family – HSPB1 (a.k.a HSP27), HSPB4, HSPB5 and HSPB6 – have been studied in the context of their cytoskeleton interactions. Their interactions with the cytoskeleton and abilities to affect its structure and dynamics are mainly described at the level of microfilaments and intermediate filaments (IFs) [34,38–41]. Different sHSPs were noted to colocalize with various IFs such as keratin 18, GFAP or desmin [34]. All mentioned sHSPs stabilize and modulate monomer assembly/disassembly of the filaments. The character of this activity is closely connected with the phosphorylated/unphosphorylated state of sHSPs. For example, unphosphorylated HSPB1, in its large oligomeric state, is able to bind up to 30 actin monomers, whereas its phosphorylation leads to disintegration of the large complex [42]. Since HSPB5 can inhibit both aggregation and assembly of desmin, mutations in its crystalline domain that increase affinity toward IF cause aberrant desmin aggregation [43,44]. A similar mechanism can also lead to formation of vimentin aggregates in cataract originating from HSPB5 mutation [45]. Additionally, CMT disease phenotype caused by HSPB1 (S135F) mutation also corresponds to abnormal microtubule stabilization due to higher affinity of the

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