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Review

Neuropathy- and myopathy-associated mutations in human small heat shock proteins: Characteristics and evolutionary history of the mutation sites☆

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ABSTRACT

Mutations in four of the ten human small heat shock proteins (sHSP) are associated with various forms of motor neuropathies and myopathies. In HspB1, HspB3, and HspB8 all known mutations cause motor neuropathies, whereas in HspB5 they cause myopathies. Several features are common to the majority of these mutations: (i) they are missense mutations, (ii) most associated disease phenotypes exhibit a dominant inheritance pattern and late disease onset, (iii) in the primary protein sequences, the sites of most mutations are located in the conserved α-crystallin domain and the variable C-terminal extensions, and (iv) most human mutation sites are highly conserved among the vertebrate orthologs and have been historically exposed to significant purifying selection. In contrast, a minor fraction of these mutations deviate from these rules: they are (i) frame shifting, nonsense, or elongation mutations, (ii) associated with recessive or early onset disease phenotypes, (iii) positioned in the N-terminal domain of the proteins, and (iv) less conserved among the vertebrates and were historically not subject to a strong selective pressure. In several vertebrate sHSPs (including primate sHSPs), homologous sites differ from the human sequence and occasionally even encode the same amino acid residues that cause the disease in humans. Apparently, a number of these mutations sites are not crucial for the protein function in single species or entire taxa, and single species even seem to have adopted mechanisms that compensate for potentially adverse effects of 'mutant-like' sHSPs. The disease-associated dominant sHSP missense mutations have a number of cellular consequences that are consistent with gain-of-function mechanisms of genetic dominance: dominant-negative effects, the formation of cytotoxic amyloid protein oligomers and precipitates, disruption of cytoskeletal networks, and increased downstream enzymatic activities. Future therapeutic concepts should aim for reducing these adverse effects of mutant sHSPs in patients. Indeed, initial experimental results are encouraging.

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Abbreviations: EGCG, (−)-epigallocatechin-3-gallate; G6PD, glucose-6-phosphate dehydrogenaseGGAgeranylgeranylacetone; HDAC6, histone deacetylase 6; TMAO, trimethylamine oxide; TUDCA, tauroursodeoxycholic acid; sHSP, small heat shock protein.

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Contents

1. Introduction

The human genome encodes ten small heat shock proteins (sHSP), now systematically designated as HspB1 through HspB10 [1–3]. The defining feature of this protein superfamily is the presence of a characteristic stretch of ~85 amino acid residues, the so-called α-crystallin domain, regardless of whether the expression of these genes is regulated by heat or other stress factors [4,5]. The α-crystallin domain typically is flanked 5′ by a variable central region and a less conserved N-terminal domain, and 3′ by a variable C-terminal extension (Fig. 1) [1]. Proteins without the α-crystallin domain do not qualify for membership in this protein family, even if overall sequence similarity with sHSPs is detectable [6]. In evolution, sHSPs have been recruited for quite diverse functions resulting in their involvement in many cellular processes including light refraction, apoptosis and growth control (carcinogenesis), protection of tissues and organs from stress, oxidative homeostasis, regulation of the organization of the cytoskeleton, muscle contraction and relaxation, chaperoning, proteolysis, neuron development, and others [5,7–9]. In spite of this growing body of knowledge, the details of their cellular roles are not completely understood.

Since the first identification of a myopathy-associated missense mutation in HspB5 more than a decade ago [10], the number of reported mutations in sHSPs (HspB1, HspB3, HspB5, HspB8) that affect the functions of muscles or motor neurons has grown to more than 30 (Table 1). Even though the precise molecular and cellular consequences of the sHSP mutations are incompletely understood, they demonstrate the crucial roles of this group of proteins in both muscles and motor neurons. This effect was not entirely unexpected, as data accumulated in the preceding decades on the importance of sHSPs for the physiology of both muscular and neuronal tissues [11–13]. Among the disease-causing mutations, the majority are missense mutations associated with a dominant disease phenotype. In addition to the sHSP mutations with clearly associated diseases, sequence variants with unclear disease association have been found, representing mutations with low penetrance or rare polymorphisms. For example, a variant of HspB6 is suspected to be associated with the impaired ability of the heart to cope with pathological stress [14].

The evolutionary history of sHSPs seems to be different from that of other analyzed protein superfamilies in that the various domains and regions of the proteins have evolved independently [15]. sHSPs are found in all domains of life: archaea, bacteria, fungi, and other eukaryotes including metazoa and plants, suggesting their emergence early in evolution. All metazoan sHSPs seem to have evolved from the same single ancestral sequence [15]. In contrast, the shaping of the variable N- and C-terminal regions that border the α-crystallin domain on both sides took place many times in parallel throughout evolution, but independent of the evolution of the α-crystallin domain [15]. Whereas the reason for this peculiarity of sHSP evolution is unknown, this pattern may complicate the analysis of the evolutionary history of the mutation sites in human sHSPs (see Sections 2.3 and 3.1.3.5). Another specific feature of the evolution of the sHSPs is the absence of recombination events with domains that are common to other protein families, typically resulting in multidomain proteins. This pattern suggests that the functional specification of the sHSPs was achieved by the variation of the terminal sequences without the concomitant diversification of the α-crystallin domain [15,16]. In this light, it is remarkable that the known mutations in a given sHSP result in similar disease phenotypes, no matter which region of the molecule is affected by the mutation (Fig. 1 and Table 1).

In this study, we sought to identify common and disparate features of the myopathy- and neuropathy-associated sHSP mutations, and to elucidate the evolutionary history of the mutation sites. On this basis, conclusions are drawn for future therapeutic approaches to the associated disorders.

2. Methods

2.1. Identification of vertebrate sHSPs with similarity to human HspB1, HspB3, HspB5, HspB6, and HspB8

Gnathostomata (*Vertebrata*: *Gnathostomata*) sHSP-like sequences with significant similarity to human HspB1, HspB3, HspB5, HspB6,