Review

The diversity of the DnaJ/Hsp40 family, the crucial partners for Hsp70 chaperones

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Abstract. DnaJ/Hsp40 (heat shock protein 40) proteins have been preserved throughout evolution and are important for protein translation, folding, unfolding, translocation, and degradation, primarily by stimulating the ATPase activity of chaperone proteins, Hsp70s. Because the ATP hydrolysis is essential for the activity of Hsp70s, DnaJ/Hsp40 proteins actually determine the activity of Hsp70s by stabilizing their interaction with substrate proteins. DnaJ/Hsp40 proteins all contain the J domain through which they bind to Hsp70s and can be categorized into three groups, depending on the presence of other domains. Six DnaJ homologs have been identified in Escherichia coli and 22 in Saccharomyces cerevisiae. Genome-wide analysis has revealed 41 DnaJ/Hsp40 family members (or putative members) in humans. While 34 contain the typical J domains, 7 bear partially conserved J-like domains, but are still suggested to function as DnaJ/Hsp40 proteins. DnaJA2b, DnaJB1b, DnaJC2, DnaJC20, and DnaJC21 are named for the first time in this review; all other human DnaJ proteins were dubbed according to their gene names, e.g. DnaJA1 is the human protein named after its gene DNAJA1. This review highlights the progress in studying the domains in DnaJ/Hsp40 proteins, introduces the mechanisms by which they interact with Hsp70s, and stresses their functional diversity.

Keywords. DnaJ, Hsp40, Hsp70, chaperone, heat shock.

Introduction

Molecular chaperones are involved in protein translation, folding, unfolding, translocation, and degradation. Heat shock protein 70s (Hsp70s) are key components of the cellular chaperone network. The expression of the Hsp70 family is either inducible by various stresses or constitutive. Some Hsp70s are differentially regulated at various stages of development. For example, Hsp70-2 and Hsc70t have been shown to play special roles in spermatogenesis [1, 2]. Hsp70s bind selectively to unfolded hydrophobic regions of substrate polypeptides, and their activity is controlled by the cycle of ATP binding, hydrolysis, and nucleotide exchange [3]. ATP hydrolysis converts Hsp70s from an open state with high association and dissociation rates for substrates to a closed state with low exchange rates [4]. This cycle is regulated by co-chaperones, such as members of the DnaJ family (also referred to as heat shock protein 40s, Hsp40s), which stimulate the ATP hydrolysis [5, 6]. Because the ATP hydrolysis is essential for the activity of Hsp70s, DnaJ/Hsp40 proteins actually determine the activity of Hsp70s by stabilizing their interaction with substrates. Numerous reports have demonstrated that Hsp70s and DnaJ/Hsp40s are implicated in various human diseases, such as neurodegenerative disorders [7–9]. DnaJ was first known to stimulate the ATPase activity of DnaK, the bacterial Hsp70 homolog, and to help replicate...
λ phage DNA in host cells [10, 11]. A large number of DnaJ homologs have been identified in both prokaryotes and eukaryotes. Six DnaJ homologs have been found in *Escherichia coli*, and 22 in *Saccharomyces cerevisiae* [12]. In mammals, more than 20 DnaJ homologs with diverse activities have been reported, but the exact numbers of such proteins in mammalian genomes remain unknown. Some of them may also regulate the activity of other chaperones, such as Hsp90. For example, the recycling of incompletely folded polypeptides from Hsp90 onto an Hsp70 protein might be regulated by the mammalian DnaJ protein TPR2/TTC2/DJC7 [13]. Certain DnaJ proteins bind directly to unfolded protein substrates through their zinc fingers and C-terminal domains. *E. coli* DnaJ, the yeast cytosolic DnaJ protein Ydj1, and the yeast mitochondrial DnaJ protein Mdj1 can all bind to the substrates by themselves [14–16].

**Structure and organization of domains in the DnaJ/Hsp40 family**

All the members of the DnaJ/Hsp40 family contain the J domain through which they bind to their partner Hsp70s [17, 18]. With few exceptions, this domain is usually present at the N-terminal region of the proteins. The J domain is a 70-amino acid sequence consisting of four helices and a loop region between helices II and III that contains a highly conserved tripeptide of histidine, proline, and aspartic acid (the HPD motif) [19] (Fig. 1).

In addition to the J domain, many DnaJ/Hsp40 proteins contain other conserved regions, which are critical to their functions [20]. Based on the difference in these regions, DnaJ proteins can be categorized into three groups [21] (Fig. 2). Type I proteins are similar to *E. coli* DnaJ with the J domain, the Gly/Phe-rich region, and the cysteine repeats. Type II proteins possess the J domain and the Gly/Phe-rich region, but lack the cysteine repeats. Type III proteins do not have any of these conserved regions other than the J domain. Although type I and II proteins are different in their conserved regions, it seems that both types function similarly and bind to non-native substrates [22]. In contrast, the type III proteins may not bind to non-native polypeptides and thus should not function as molecular chaperones on their own.

Aside from the above conserved domains or regions, some DnaJ family members contain additional domains, which may determine the functional diversity of DnaJ proteins [23, 24]. For example, the mammalian DnaJ protein ERdj5/JPD1 promotes the formation of appropriate disulfide bonds of endoplasmic reticulum (ER) proteins, because of the presence of both the protein disulfide isomerase-like domain and the J domain; the latter sequesters the ER-associated Hsp70, BiP [25, 26]. Recently, a C-terminal region in DnaJ proteins was found to be essential for their dimerization and chaperone activity [27, 28].

**Genome-wide analysis and classification of DnaJ/Hsp40 family members**

DnaJ/Hsp40 proteins in an organism are present in much larger numbers than Hsp70 proteins. Six DnaJ homologs have been found in *E. coli*. In higher organisms, there are more such proteins. For example, there are at least 10 DnaJ-related proteins in *Plasmodium falciparum*. As indicated in a recent review [12], the genome of *S. cerevisiae* has 22 proteins that bear well-conserved J domains. Many mammalian DnaJ-like proteins have been reported, but the exact numbers are still unknown. In the database of the Human Genome Resource, 140 human protein entries are annotated as DnaJ-related. But many of them represent repeated entries (under different names) of the same genes, and some do not contain any DnaJ domains.