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PROTEIN SEQUENCE MOTIFS

# A module of the DnaJ heat shock proteins found in malaria parasites

The DnaJ heat shock protein of *Escherichia coli* plays an essential role in the chaperone function of the hsp70-like DnaK protein[1]. DnaJ stimulates the ATPase activity of DnaK[2] and also directly interacts with specific substrates of the DnaK chaperone machinery[1,3]. Several proteins of *Saccharomyces cerevisiae* possess extensive sequence homologies to DnaJ[4–7] and a human homologue has also been identified[8]. Sequence alignments suggest four areas of homology[5,6]: a low homology region generally found at the carboxy-terminal end, a glycine-rich region, a domain containing four CXXCXGXG motifs and a more highly conserved region often found near the amino terminus. The yeast protein Sec63 contains only the region of highest homology and this is located away from the amino terminus, between two of its three putative membrane-spanning segments[4] (Fig. 1a). Thus, the DnaJ family shows typical features of mosaic proteins[9] which contain different building units (modules) with separate functions.

A database search with sequence consensus patterns[10] of the most conserved (amino-terminal) domain of DnaJ revealed a surprising similarity to the ring-infected erythrocyte surface antigen (RESA)[11] of the malaria parasite *Plasmodium falciparum*. The sequence identity to DnaJ is as high as 39% over a length of 70 residues (Fig. 1b), only slightly below that of Sec63 (42%), higher than that of the human DnaJ-like protein (37%), and clearly above the threshold for structural homology of globular proteins[12]. RESA contains two glutamate-rich regions, one next to the homologous segment and the other one at the carboxyl terminus (Fig. 1a). An equivalent acidic region is also found in Sec63 (Fig. 1a) confirming the modular architecture of both proteins.

RESA is an important non-polymorphic malaria antigen[13] that has been shown to confer some degree of protective immunity on monkeys[14]. A fragment of RESA that includes the DnaJ region of homology was shown to be effective in providing partial immunity[14]. RESA is synthesized prior to *P. falciparum* merozoite differentiation and later becomes associated with the red-cell membrane skeleton of newly invaded erythrocytes where it binds to spectrin[15]. Membrane association in turn is one of the common features known for most DnaJ-like proteins[1,4–8]. The homology to *E. coli* DnaJ suggests that RESA also may participate in a molecular complex similar to the DnaJ–DnaK–GrpE chaperone system[1] with the motif participating in protein–protein interactions.

As more members are added to the DnaJ family, the number of possible key residues of the motif involved in these interactions can be confined. In addition to several positions in which only aromatic or hydrophobic amino acids seem to be accepted (Fig. 1b) there is one conserved aspartate as well as an invariant tripeptide HPD (YPY in the malaria parasite).

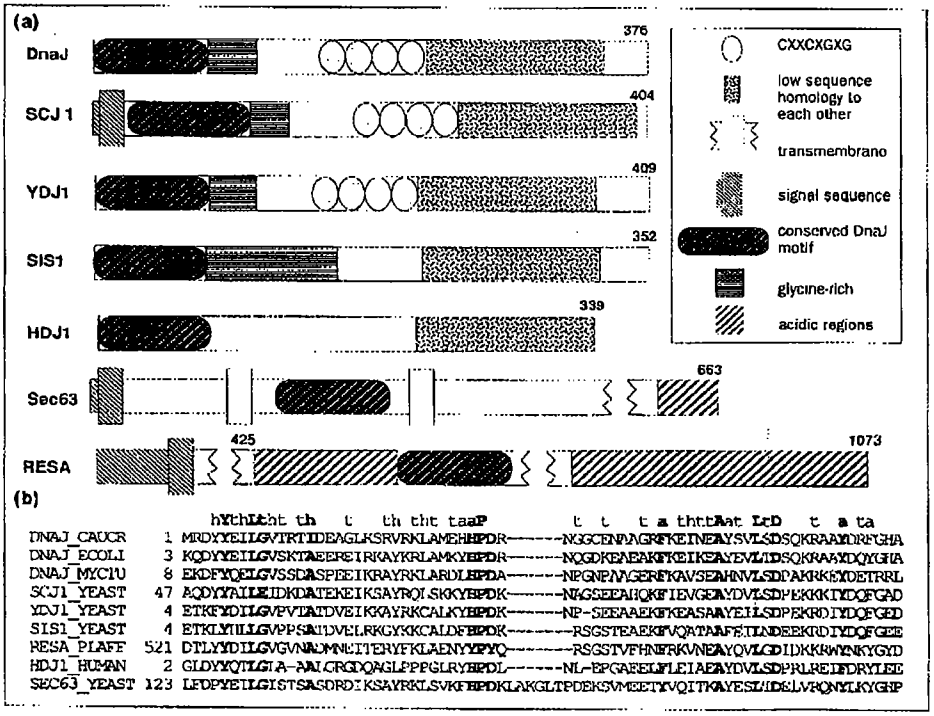


**Figure 1**

**(a)** Modular architecture of DnaJ-like proteins. Both the glycine-rich and the acidic regions differ in detail between the proteins, but nevertheless suggest similar functions. SCJ1 and Sec63 are involved in protein sorting[4,7], YDJ1 participates in chromosome segregation[5] and SIS1 is required for nuclear migration during mitosis[6]. The occurrence of the highly conserved motif in all these proteins suggests a common function for this domain. **(b)** Multiple alignment of the proteins sharing the conserved motif. Residues that are conserved in all except one sequence are shown in bold type. The top consensus line indicates conserved features (capitals, conserved amino acids; lower cases, conserved properties such as h, hydrophobic; a, aromatic; t, turn-like or polar).

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