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- 총 설 -

Family of Hsp70 Molecular Chaperones and Their Regulators

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Proteins are involved in promoting or controlling virtually every event on which our lives depend. Proteins are synthesized in cytosol and in the endoplasmic reticulum where their synthesis machinery are tightly controlled. However, not all of newly synthesized proteins are survived and conduct their essential functions to maintain cell's lives. It was reported that one-third of synthesized proteins are rapidly destroyed by proteasome under the most physiological conditions. Full-length translated proteins, which survived, must undergo proper folding and assemble process. Some proteins are spontaneously folded while others require molecular chaperones and folding enzymes to be properly folded. Molecular chaperones are ubiquitously present within the subcellular organelles and from bacteria to animals and plants. Among those members of Hsp70 family have been extensively studied and their regulators have been discovered in the last decade. Here, a brief overview is presented for functional mechanism of Hsp70 homologues and the roles of their regulators. Since biological function of Hsp70 family other than chaperonic function are expending the review would give basic understanding of partnership between Hsp70 family and their regulators.

Key words : Protein synthesis, molecular chaperones, Hsp70, BiP, cofactors

Molecular chaperones

Each of *Escherichia coli* growing at 37°C with a doubleing time of 40 min makes about 1000 polypeptide chains of average mass 40 kDa every second [22]. How the linear information contained in the amino acid sequence of the unfolded polypeptide gives rise to the unique three-dimensional structure of the native protein [23]. They must be properly folded to exert their functions. The folding of many proteins requires aid of a special group of proteins called molecular chaperones. Molecular chaperones were first identified in bacteria when *Escherichia coli* mutants that failed to allow bacteriophage lamda to replicate in them produced altered version of the chaperone machinery [1]. Bacteriophages in the mutant bacterial strain fail to assemble the viral proteins because altered molecular chaperones were defect in their functions. A group of molecular chaperones is dramatically increased in amount under the condition that the cells are briefly exposured to elevated temperature. Therefore, these are called the heat-shock proteins (Hsp) and familiar better to us. Under the elevated temperature condition misfolded proteins increase and the heat-shock proteins prevent misfolded protein to be aggregate and salvage them. Molecular chaperones are present ubiquitously in the subcellular compartments of the cell. We here discuss how a family of molecular chaperones, Hsp70 family, is working with their regulators in cytosol and the endoplasmic reticulum (ER).

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Cytosolic Hsp70 and its regulators

Highly conserved Hsp70 proteins are one of the well-known families of molecular chaperones and ubiquitously present in all organisms. Hsp70 proteins play essential roles in preventing misfolding of newly synthesized proteins and aggregation of misfolded proteins. They are also involved in the translocation into and the folding within organelles, assembly and disassembly of oligomeric protein structures, signal transduction, and cell cycle progression [20]. The family proteins consist of two distinct domains: a highly conserved N-terminal ATPase domain and a less conserved C-terminal polypeptide binding domain as shown in Fig. 1 [6]. The chaperone activity of Hsp70 proteins is controlled by the ATPase domain that undergoes a reaction cycle comprised of ATP binding, hydrolysis, and nucleotide exchange, which is tightly regulated by co-chaperones and cofactors. Bacterial Hsp70 homologue, DnaK, among the family has been extensively studied for its regulation and mammalian Hsp70 has extended more complex regulatory mechanism with discovery of its regulators

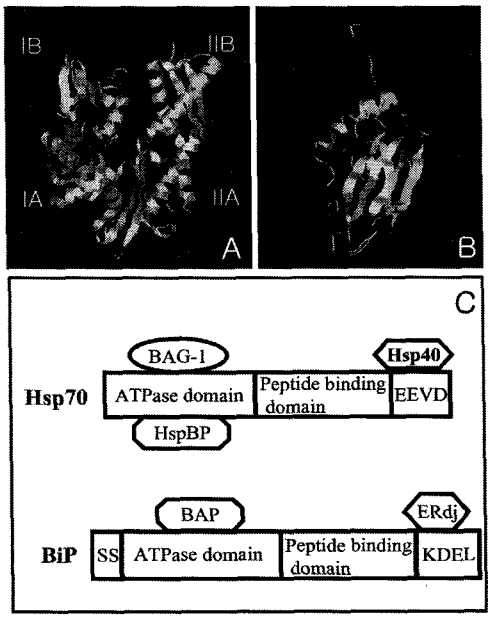

Fig. 1. Structure of Hsc70. The ATPase domain and subdomains are indicated (A). The substrate domain (B). A schematic model of interaction between Hsp70 and its regulators (C). EEVD: Four amino acids of the C-terminus of Hsp70, SS: Signal sequence targeting to the endoplasmic reticulum, KDEL: Four amino acids of the C-terminus of BiP.

in the last decade.

The ATPase domain of Hsp70 is able to bind both ATP and ADP. The ATP-bound Hsp70 has a low affinity for substrates but high substrates association and dissociation rate constants. Although Hsp70 has its intrinsic ATPase ability the ATP hydrolysis is stimulated by **Hsp40** (DnaJ for DnaK) which belongs to the J-domain protein family (see below). Consequently, the bound ATP is hydrolyzed to ADP, which leads to the transition from the low affinity to high affinity state, and a substrate protein is then trapped in the ADP-bound Hsp70 resulting in a complex of the ADP-bound Hsp70-substrate-Hsp40. To release the bound substrate ADP must be exchanged with ATP. ADP dissociation is accelerated by nucleotide exchange factors such as HspBP for Hsp70 and grpE for DnaK. ATP then reloaded to Hsp70, which transits a low affinity for substrates and release of substrates. In this way Hsp70 undergoes cycles of ATP to ADP hydrolysis as well as binding to and releasing from an unfolded substrate (Fig. 2).

The J-domain protein family (JDP) including Hsp40 and DnaJ comprise a large family of multi-domain protein that are characterized by a highly conserved stretch of 70 amino acids containing the hallmark tripeptide HPD motif (His-

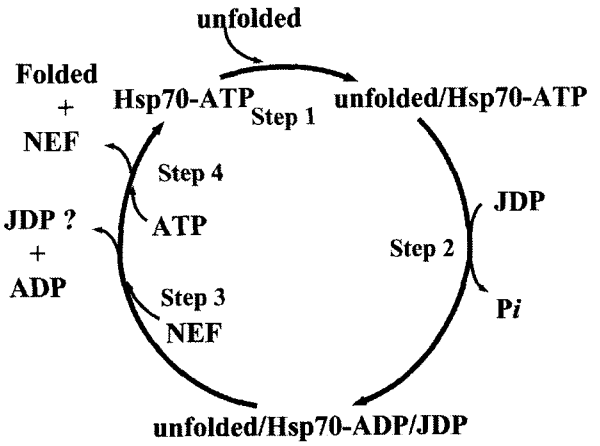

Fig. 2. A Diagram of Hsp70 Cycle. Molecular function of Hsp70 is dependent on ATP hydrolysis, which is orchestrated with its regulators. Unfolded: unfolded protein, Folded: folded protein, JDP: J-domain protein, NEF: Nucleotide exchange factor.

Pro-Asp) referred to as the J-domain [17]. A flexible Gly/Phe-rich domain links the J-domain to a cystein-rich Zn^{2+}-binding domain. Distal to the Cys-rich domain is a poorly conserved region that accounts for nearly half of the JDP molecule. Presently, more than 100 JDP family members have been identified, which can be found in all species and organelles. They can be divided into three subgroups based on the degree of domain homology with DnaJ and possess all four domains (Fig 3). The type I JDPs share significant homology to all four domains of DnaJ. The type II JDPs have an N-terminal J-domain and the Gly/Phe-rich linker but lack the Zn^{2+}-binding domain. The type III JDPs possess only the J-domain, which can occur anywhere in the protein.

The role of JDP in association with Hsp70 is stimulation

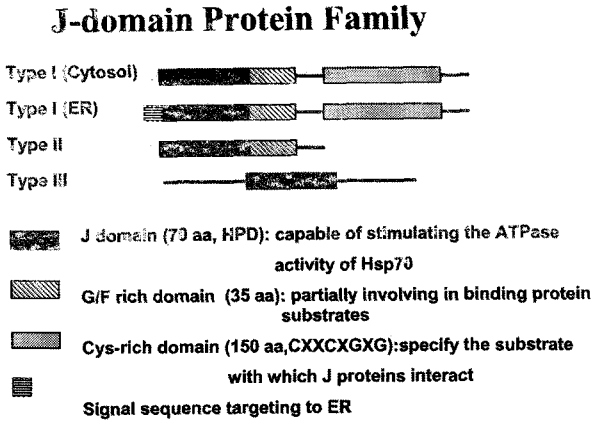

Fig. 3. The J-domain Protein Family. Three different types of the J-domain proteins are illustrated. ER: Endoplasmic reticulum, aa: amino acid.

of the ATP hydrolysis by Hsp70 proteins. But JDP is not able to release ADP from Hsp70, resulting lock Hsp70 on an unfolded substrate. The HPD motif of the J-domain is required and is essential for association with Hsp70 and ATP hydrolysis based on the mutation studies.

Nucleotide Exchange Factors

GrpE is a 22 kDa protein and binds to the ADP-bound and nucleotide-free states of DnaK. It promotes nucleotide exchange of ADP to ATP, consequently recharging DnaK with ATP and releasing an unfolded substrate from DnaK [19,27]. GrpE is the first found nucleotide exchange factor for the Hsp70 family proteins. Association of GrpE with DnaK induces opening up the nucleotide-binding cleft and ADP is released. Furthermore, GrpE stabilizes the open conformation of the nucleotide-binding pocket, which facilitates rapid binding of ATP to the nucleotide-free state of DnaK. Prokaryote Hsp70 homologue, DnaK, is regulated mainly by DnaJ and GrpE for its molecular chaperone function. However, in contrast to DnaK, Hsp70 has many additional regulatory factors and two of nucleotide exchange factors, BAG-1 and HspBP1, are involved in the Hsp70 cycle. Interestingly, BAG-1 and HspBP1 do not share amino acid sequence homology each other nor with GrpE.

BAG-1 (RAP46) was identified by independent two groups as the second cofactor for Hsp70 that interacts with the ATPase domain of Hsp70 but originally with no direct association of Hsp70. BAG-1 was screened out as a Bcl-2-binding protein [28] and a glucocorticoid receptor protein [34]. Two years later, interesting observations on the function of BAG-1 was published. Hohfeld and Jentsch [12] demonstrated that BAG-1 is interacting with the ATPase domain of Hsc70 and has GrpE-like function as it is increasing the ATPase activity of Hsc70 by stimulating exchange of bound ADP with ATP. Two other groups reported that BAG-1 is inhibiting refolding of denatured proteins by Hsc70 *in vitro* while interacting with the ATPase domain of Hsc/Hsp70 [29,30]. A follow up data showed that BAG-1 functions as a negative cofactor uncoupling ATP hydrolysis from substrate release, which brought up controversy on the function of BAG-1 as a cofactor for Hsc70 [4]. Cocrystal structural study of a BAG-1/Hsc70 revealed that BAG-1 binds to subdomain IB and IIB of the ATPase domain by electrostatic interactions, inducing a conformational switch in the ATPase domain that is incompatible with nucleotide binding [26]. The same switch is observed in the bacterial DnaK upon binding of GrpE, which causes release of both ADP and ATP. In contrast to GrpE, BAG-1 does not stimulate dissociation of ATP because structural differences in the ATPase subdomain between prokaryotic DnaK and eukaryotic Hsc70 subfamilies [7].

HspBP1 was identified by a yeast two-hybrid screening with the ATPase domain of Hsp70 [24]. HspBP1 inhibits the ATPase activity and chaperonic function of Hsp70 and the inhibitory effect is due to possibly rebinding of ATP. Yeast homologue of HspBP1, Fes1p, was identified in *Saccharomyces cerevisiae* and the data from Fes1p were consistent with the previous results of HspBP1 although HspBP1/Fes1p exerted nucleotide exchange function [15,16].

Endoplasmic Reticulum-localized Hsp70 Homologue, BiP, and its Regulators

In eukaryotic organisms, BiP (Immunoglobulin-heavy chain **Bi**nding **P**rotein or Grp78) localized in the endoplasmic reticulum (ER) is another homologue of the Hsp70 family. Like other Hsp70, BiP plays essential roles in protein folding and assembly in ER. Proteins destined to membranes and to be excreted are synthesized in the cytosol on ER associated ribosomes. A hydrophobic signal sequence present on the nascent polypeptide chain directs it to the translocon [13]. Approximately 70 amino acids are required before the N-terminus can enter the ER lumen [9]. It appears that the growing polypeptide chain remains unfolded during its transit through the ribosome and translocon [18]. The polypeptide inside the ER begins folding co-translationally and subunit assembly of some proteins can occur before the individual chains are completely translated [3]. This is aided by BiP along with other molecular chaperones and chaperonic enzymes residing in the ER. It is thus reasonable to speculate that the ATPase activity of BiP should be regulated in a way similar to that of other members of the Hsp70 family. Since cofactors for cytosolic Hsp70 have been discovered investigation to identify cofactor(s) for BiP was strongly demanded. Not only BiP's similarity to Hsp70 there was an early observation that can indicate possibility of regulatory system for the ATPase activity of BiP. Purified recombinant BiP from bacteria was associated with ADP rather than ATP although affinity for ATP is 1.5 times greater than one for ADP [32], which is not due to limited level of the bacterial

nucleotide exchanger, GrpE. This suggests that ADP bound on BiP is not exchanged to ATP by biochemical affinity preference in the bacterial cell, thus a nucleotide exchange factor for BiP is required.

The first clue for a nuclear exchange factor for BiP came out from the study of translocation of secretory proteins in the yeast, *Yarrowia lipolytica*. A genetic screening was emplyed to identify partners of the signal recognition particles in cotranslational translocation using the *scr2* mutant strain which is thermosensitive [5]. The identified *SLS1* gene was responsible for a temperature-sensitive growth and secretory protein synthesis, and its gene product, Sls1p, was localized in ER. Subsequently a homologue of Sls1p, ScSls1p, was identified in *Saccharomyces cerevisiae*, which is also known as Per100p [30] and Sil1p [31]. Further studies showed that **Sls1p** interacts better with the ADP-bound ATPase domain of Kar2p, the *S. cervisiae* homologue of BiP, and enhances ATP hydrolysis by Kar2p in the presence of the luminal J domain of Sec63p, a yeast membrane homologue of DnaJ, suggesting that Sls1p acts as a nucleotide exchange factor for Kar2p [16,31].

Mammalian nucleotide exchange factor for BiP was independently discovered by our group [8]. We used a yeast two-hybrid screen to identify potential mammalian regulators of the ATPase activity of BiP using the ATPase domain of a BiP mutant, BiPT229G [10,33]. **BAP** (**B**iP-**A**ssociated **P**rotein) was identified by screening a human liver cDNA library and shared low sequence homology with both Sls1p and HspBP1. BAP is a glycoprotein localized in ER and expressed ubiquitously but higher level in tissues, such as liver, that secretory pathway is well-developed. In contrast to Sls1p whose expression level is increased by ER stress, total protein of BAP appears to be reduced. The binding of BAP to BiP *in vivo* is significantly different between wild type and mutant BiPs whose conformation is ADP-bound state. Also, yeast cells carrying wild type BiP and BAP failed to grow on a selective medium whereas yeast cells carrying mutant BiP (T229G) and BAP is able to do so, which is consistent with mammalian in vivo system. These data showed that BAP binds better or more stably to ADP-bound state of BiP, which is a critical characteristic to be a nuclear exchange factor for BiP. BAP stimulated the ATPase activity of BiP cooperating with the J domain of ERdj4 and promoted nucleotide exchange from BiP. The identified nucleotide exchange factors and their partner Hsp70s are summarized in Table 1.

Table 1. Distribution of Hsp70 families and their nucleotide exchange factors

Organism	Organelle	Hsp70 Family	Nucleotide Exchange Factor
Prokaryotes		DnaK	GrpE
Eukaryotes	Cytosol	Hsc70 (Ssa1p)	BAG-1, HspBP1 (Fes1p)
	ER	BiP (Kar2p)	BAP (Sls1p)

Yeast homologues are in each parentheses.

Summary

Cofactors suggest that evolutionary conserved Hsp70 family proteins would be regulated upon distinct physiological events by their proper partner. Although precise roles of cytosolic nucleotide exchange factors, BAG-1 and HspBP1, have not yet been elucidated *in vivo*, they would not interact simultaneously with Hsp70 for a particular single role of Hsp70 as Fes1p, a yeast homologue of HspBP1, is possibly involved in protein translation. Also, homologous nucleotide exchange factors in cytosol and ER, HspBP1 and BAP, shows opposite effect *in vitro* on the ATPase activity of their partner chaperones. Recently, loss-of-function mutation in BAP was reported to cause an autosomal recessive disorder, Marinesco-Sjogren syndrome in human [2,25,36]. Diseases by cofactor dysfunction indicate the importance of roles of cofactors on chaperone functions. We now understand better regulatory mechanisms of the Hsp70 family than before. However, it may be the time to reconsider investigation on multiple functions of conserved Hsp70 family proteins with their diverse cofactors, yet-to-be identified cofactors, and importance of cofactor functions *in vivo*.

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초록 : Hsp70 분자 샤페론과 조절인자

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생명체 내에서 일어나는 거의 모든 반응은 단백질이 촉진하거나 수행한다. 단백질은 세포질과 소포체에서 합성될 때 엄격하게 조절된다. 그러나, 새로이 합성된 모든 단백질이 살아남아서 생명을 유지시키는 기능에 관여하게 되지는 않는다. 가장 알맞은 생리학적 *in vitro* 실험 조건에서 새로이 합성된 단백질의 약 3분의 1 정도는 합성되자마자 proteasome에 의해 빠르게 분해된다고 보고되었다. 또한, 단백질은 합성이 성공적으로 이루어진 이후에는 3차원 구조를 갖기 위해 접힘(folding)이 이루어져야 하고, subunit들은 assembly 과정을 거쳐야 비로소 성숙된 단백질로서 기능을 하게 된다. 어떤 단백질군은 자연적으로 접힘이 일어나는 반면 어떤 단백질군은 분자 샤페론(molecular chaperones)과 folding enzymes의 도움을 받아야만 접힘이 일어난다. 분자 샤페론은 세포 전역에 분포하고 있으며, 세균에서부터 고등 동식물에 이르기까지 모든 생명체에 존재한다. 이들 중 Hsp70군은 많이 연구된 분자 샤페론으로서 지난 10여년 동안 조절인자들이 새로이 발견되어 작용 mechanism이 보다 자세히 밝혀졌다. 본 총설에서 Hsp70군과 그 조절인자들에 대한 전반적인 서술을 하였으며, 이들의 기능이 분자 샤페론 기능 외에 생체 내에서 중요한 기능들이 새롭게 밝혀지고 있어 이들의 작용 mechanism을 조명함으로 이해를 돕고자 한다.