Spotlight on Heat Shock Proteins

Proteasomes and Molecular Chaperones

Cellular Machinery Responsible for Folding and Destruction of Unfolded Proteins

Jun Imai[1,2]
Hideki Yashiroda[1]
Mikako Maruya[2,3]
Ichiro Yahara[2,3]
Keiji Tanaka[1,*]

[1]Department of Molecular Oncology; Tokyo Metropolitan Institute of Medical Science; Bunkyo-ku, Tokyo, Japan

[2]MBL Dendritic Cell Project; Keio Research Park 8N5; Department of Microbiology and Immunology; School of Medicine; Keio University; Tokyo, Japan

[3]CREST; Japan Science and Technology Corporation; Saitama, Japan

*Correspondence to: Keiji Tanaka; Department of Molecular Oncology; Tokyo Metropolitan Institute of Medical Science; Honkomagome 3-18-22; Bunkyo-ku, Tokyo 113-8613 Japan; Tel./Fax: +81.3.3823.2237; Email: tanakak@rinshoken.or.jp

Received 09/03/03; Accepted 09/03/03

Previously published online as a Cell Cycle E-publication at:
http://www.landesbioscience.com/journals/cc/tocnew26.php?volume=2&issue=6

KEY WORDS

molecular chaperone, proteasome, ubiquitin

ABSTRACT

Molecular chaperones recognize proteins of non-native structure, prevent them from irreversible intracellular aggregation, and then act with regulatory co-chaperones in the conversion of proteins to be properly folded and in a functional state. However, not every non-native protein is folded successfully. Those proteins that are not accurately folded/refolded are then directed to the ubiquitin-proteasome system (UPS) for destruction. Both chaperones and proteasomes act jointly together for selective removal of proteins with aberrant structure so as to keep protein homeostasis in cells. Though the precise nature of the cooperative linkage between chaperone and UPS pathways remains largely elusive so far, accumulating evidence from in vivo and in vitro studies shed some light on the molecular mechanisms that link proteasomes and molecular chaperones. This review focuses on how unfolded proteins are handled by these two machineries.

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INTRODUCTION

Considering on the intracellular environment, the concentration of proteins could rise leading to their aggregation as either partially folded or unfolded proteins. Over one third of the newly synthesized cellular proteins cannot fold correctly, even though they are normally synthesized without mutations of their genes or errors in the translation process. This phenomenon is provisionally called DRiPs (defective ribosomal products).[1] In addition, even when proteins are synthesized and folded correctly as functional proteins with a normal tertiary structure, they are often damaged by unfavorable environmental stresses such as heat shock, oxidization, and chemical modification.[2] The cells is equipped with two surveillance systems to manage these off-pathway reactions; the molecular chaperones and the ubiquitin-proteasome system (UPS), which serve to prevent accumulation of abnormal proteins formed through the protein biosynthetic pathway or postsynthesis damage.

Molecular chaperones play a role in maintaining protein homeostasis by regulating protein folding. They recognize nascent polypeptides and unstructured regions of proteins; e.g., exposed hydrophobic stretches of amino acids. Then cooperating with many co-chaperones that complement their functions, chaperones refold non-native proteins and prevent their irreversible aggregation with other proteins.[3-5] On the other hand, the UPS also participates in the regulation of protein homeostasis by selective destruction of misfolded/unassembled and impaired proteins generated in eukaryotic cells.[2] Namely, most of these unwanted proteins are covalently attached to ubiquitin, a highly conserved small protein consisting of 76 amino acids, in the form of a polyubiquitin chain functioning as a marker for proteolytic degradation by the 26S proteasome.[6,7]

It is also possible for molecular chaperones and proteasomes to act together in preventing aggregation and accumulation of abnormal proteins, thus maintaining protein homeostasis in cells; both of them are capable of recognizing common substrates under non-native states and are required for removal of aberrant cellular proteins to ensure protein homeostasis in cells. In this regard, the cellular apparatus monitoring the "normality" of proteins in the cell is usually referred to as "the protein quality control system".[8] This control system is highly flexible under constitutively changing environments, and thus the fate of unfolded proteins, i.e., either refolding or degradation, is largely dependent on environmental conditions. These facts indicate that regulation of intracellular balance of protein refolding and degradation is a critical issue for cells exposed to stressful environment, thus there is a special interest regarding the interplay between the chaperone system and the UPS pathway.

THE PROTEASOME

The proteasome is a principal machinery that participates not only in the "regulated proteolysis" responsible for selective and rapid destruction of a diverse array of biologically important cellular proteins, but also in massive degradation of abnormal proteins generated in the cells.[9,10] It is a large multisubunit complex, consisting of a central catalytic 20S proteasome (alias CP, core particle), and two terminal regulatory subcomplexes, which are attached to both ends of the central portion in opposite orientations. The 20S proteasome is composed of two copies of 14 different subunits, seven distinct α type subunits and seven distinct β type subunits, arranged in a particle as four hetero-heptameric rings, $\alpha_{1\text{-}7}\beta_{1\text{-}7}\beta_{1\text{-}7}\alpha_{1\text{-}7}$, with C2 symmetry. Three β-type subunits of each inner ring have catalytically active threonine residues at their N-terminus (in which of β1, β2, and β5 corresponding to caspase-like, trypsin-like, and chymotrypsin-like activities, respectively), and these active sites face the interior of the cylinder and reside in a chamber formed by the centers of the abutting β rings.[11]

Interestingly, the center of the α-ring of the 20S proteasome is almost closed, preventing free penetration of proteins into the inner surface of the β-ring on which the proteolytically active sites are located. Substrates gain access to the active sites only after passing through a narrow opening corresponding to the center of the a rings and the amino-termini of the a subunits form an additional physical barrier for substrates to reach the active sites. To activate this latent 20S proteasome, three types of regulatory complexes; PA28, PA200, and PA700, are described to date. Although PA28 and PA700 play a prominent role in the quality control system, the role of recently identified PA200 appears to be rather restricted in DNA repair.[12]

PA700. PA700 (alias RP, regulatory particle or 19S complex), associates with either or both ends of the 20S proteasome in an ATP-dependent manner, producing the enzymatically active 26S proteasome with a molecular mass of ~2.5 Mda. The 26S proteasome is responsible for ATP-dependent degradation of a wide variety of cellular proteins tagged with a polyubiquitin chain that serves as a degradation signal and certain proteins in a manner independent on ubiquitylation.[9,10] PA700 is a 700-kDa protein complex composed of ~20 subunits with sizes of 25-110 kDa, which are organized into two distinguishable subcomplexes; the base and the lid.[10] The base is made up of six AAA-type ATPases ($Rpt_{1\text{-}6}$) and two large regulatory components; Rpn1 and Rpn2, while the lid contains multiple non-ATPase ($Rpn_{1\text{-}n}$) subunits. Most functions of multiple lid proteins are largely unknown, except for Rpn10, which functions as an acceptor for polyubiquitylated proteins, and Rpn11, a deubiquitylating enzyme involved in reutilization of ubiquitin. Furthermore, Rpn1, 2, and/or 10 also are responsible for interactions with various proteins with an ubiquitin-like domain.

Since the channel of the dilated 20S proteasome is cramped, only almost completely denatured proteins are permitted to access the catalytic sites within the chamber of the β-ring. Denaturation of the substrate primarily requires utilization of the energy liberated by ATP consumption. The base-complex, thought to bind ATP-dependently to the outer α-ring of the central 20S proteasome, seems to be involved in opening the gate of the α-ring for entry of the protein substrate. Finally, ATP energy is used for intra-molecular traffic of substrates so that they can penetrate the channel of the α- and β-rings of the 20S proteasome.[15]

It is worth emphasizing that the base complex has a putative unfoldase activity ensuring that the folded substrates are denatured before accessing the catalytic site. The base complex contains a site(s) that recognizes and interacts with unfolded proteins, represses their aggregation, and reactivates some of them, indicating that PA700 functions as a molecular chaperone, independent of the 20S proteasome. Indeed, the PA700 is demonstrated to retain the folding activity of partially denatured model proteins. However, it is unclear whether ATP hydrolysis is required for this process, because antagonizing results have been reported; one requiring ATP energy[16] and the other not.[17] In addition to facilitating proteasome-mediated proteolysis, PA700 itself shows several non-proteolytic roles, such as nucleotide excision repair,[18] stimulation of transcription elongation by RNA polymerase II,[19] and dissociation of the Cdc2-cyclin B complex.[20] Though the precise natures of the non-proteolytic processes are not yet clear, one reasonable hypothesis is that chaperone activity of this complex is responsible for these phenomena.

PA28. PA28 or the 11S regulator (REG) is another activator of the latent 20S proteasome, which enhanced only the peptidase activity in an ATP-independent manner.[21,22] However, it fails to enhance the hydrolysis of large protein substrates with native or denatured structures, even when they are polyubiquitylated, indicating that PA28 does not play a central role in the initial cleavage of protein substrates. Unlike PA700, association of PA28 with the 20S proteasome does not require energy.

PA28 is composed of two subunits, named PA28α and PA28β, that share ~50% amino acid identity. These subunits assemble into a heteroheptameric ring with nearly equal stoichiometric amounts of PA28α and PA28β, which are mainly located in the cytoplasm of the cell.[23] PA28α and PA28β are upregulated by γ-interferon and other available evidence indicates that the heteropolymer of PA28 (α and β) is involved in the processing of intracellular antigens, generating MHC class I ligands.[24] Indeed, simultaneous disruption of both genes encoding PA28α/β suggests that PA28α/β is not a prerequisite for antigen presentation in general, but plays an essential role in the processing of certain antigens.[25] Interestingly, other studies reported the existence of the 'hybrid proteasome' that contains both PA28 and PA700,[26] in which PA28 and PA700 associate either end of the 20S proteasome.[27,28] γ-interferon induces the production of the hybrid proteasome in cells, indicating that it might play an important role in the efficient production of MHC class I ligands.[26]

Subsequent studies identified the third member of this family, named PA28γ, which forms a homopolymer predominantly present in the nucleus.[29] Analyses of mice deficient in the PA28γ gene revealed that PA28γ functions as a regulator of cell proliferation and body growth in mice.[30]

Of particular interest is that PA28 is considered as an effective component responsible for refolding of the thermally denatured firefly luciferase mediated by the Hsp90 and Hap70/40 chaperone team in reticulocyte lysate.[31] In fact, purified Hsc70, Hsp40 and PA28 were necessary and sufficient to fully reconstitute Hsp90-initiated refolding. PA28 may be the physical link between Hsp90-dependent capture of unfolded proteins and Hsc70- and ATP-dependent refolding process. Moreover, PA28 binding unfolded luciferase could combine with the 20S proteasome, suggesting that PA28 may serve as a coupling factor between protein folding and degradation. In other words, PA28 serves as a molecular carrier that transfers the heat-denatured protein from the Hsp90 captured state to the Hsp70/Hsp40-dependent refolding process, suggesting that PA28 is a multi-functional complex in the protein quality control system. Although no homolog of PA28 has been detected in lower eukaryotes such as fungi, other molecules, such as Cdc48 and Hsp104, might substitute PA28 in these organisms, though the counterpart of Hsp104 has not yet been identified in higher eukaryotes.

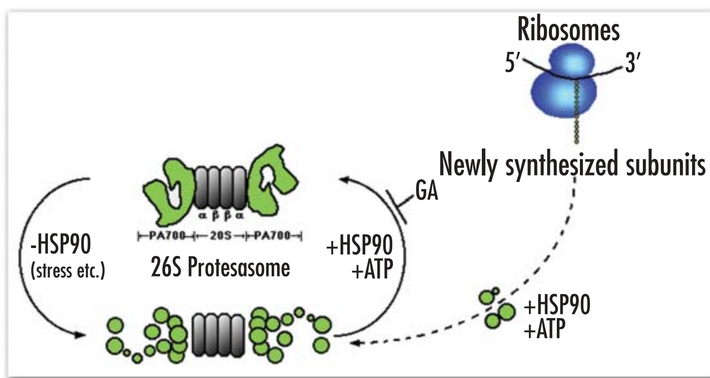

Figure 1. Model for the role of Hsp90 in the assembly and maintenance of the 26S proteasome. Dysfunction of Hsp90 causes rapid dissociation of regulatory PA700 complex of the 26S proteasome, without affecting the catalytic integrity of 20S proteasome. Dysfunction of Hsp90; e.g., loss of Hsp90, in the cell may occur under environmental stress, because Hsp90 is immensely required for refolding of unfolded cellular proteins. Hsp90 accelerates the 26S proteasome assembly in a manner requiring ATP energy, which can be prevented by geldanamycin (GA), an Hsp90 inhibitor. Hsp90 may be involved in the biogenesis of the 26S proteasome, although no evidence has been presented to date. See text for details.

MOLECULAR CHAPERONES

The molecular chaperones are a set of conserved protein families, divided into several functionally distinct classes of proteins that collaborate with a set of co-chaperones. Among them, Hsp70 and Hsp90 play general roles in protein quality control in eukaryotes. It is also worth noting that the molecular chaperones that interact with UPS, are rather limited to Hsp70 and Hsp90. This section will discuss the roles of Hsp70 and Hsp90 with a special reference to the proteasome.

Hsp70

20S Assembly. A member of the Hsp70 family protein, Hsc73 is essential for the final maturation steps of the 20S proteasome from the 16S precursor complex.[32] Removal of Hsc73 results in an immediate formation of aggregates of this precursor indicating that Hsc73 keeps the assembly of intermediate complex in a soluble and probably partially unfolded state to allow subunit processing and correct folding. Considering these notions, Hsc73 might regulate the amount of 20S complex under stressful conditions.

BAG-1 (BCL-2 Binding Athanogene-1). BAG-1, one of the co-chaperones of Hsp70, belongs to a family of proteins with an integral ubiquitin-like (UBL) domain capable of binding to Rpn10 or -Rpn1/2 of the 26S proteasome and acts as a coupling factor between Hsp70 and the 26S proteasome.[33] In addition, BAG-1 can stimulate the release of proteins captured by Hsp70 based on its nucleotide exchange activity through BAG domain.[34] It is possible that these chaperone-recruiting and chaperone-regulating activities can stimulate the transfer of Hsp70-captured substrates to the 26S proteasome and accelerate their degradation.

CHIP (Carboxyl-Terminus of Hsc70 Interacting Protein). CHIP, originally identified as a co-chaperone of Hsp70,[35] can associate with Hsp70 and Hsp90 through the amino-terminal TPR domain and adjacent charged domain.[36,37] Since CHIP attenuates stimulation of ATPase activity of Hsc70 by Hsp40, addition of CHIP diminishes the refolding activity of the Hsc70-Hsp40 complex for denatured substrates.[35] CHIP also uniquely carries a U-box domain on its carboxyl-terminal region among many TPR-containing proteins. The U-box domain has a tertiary structure that resembles the RING-finger domain of ubiquitin-protein ligase (E3), which covalently attaches ubiquitin to target proteins, designating them for destruction by the proteasome.[38] As anticipated from its tertiary structure, CHIP executes E3 ubiquitin ligase activity upon specific substrates; CHIP ubiquitylates substrates of Hsp70 and Hsp90 and stimulates their degradation by the proteasome.[35,36,39] Consequently, CHIP appears to be chaperone-dependent E3 that ubiquitylates Hsp90-captured unfolded proteins.[40] Thus, CHIP is an ideal molecule acting as a protein quality-control E3 that selectively leads abnormal proteins recognized by molecular chaperones to degradation by the proteasome. It should be emphasized that CHIP is the first molecule that realizes the expected situation where an unfolded protein is handled by the UPS pathway as well as molecular chaperones.

Since both BAG-1 and CHIP are molecules that integrate molecular chaperones and UPS, cooperation of these two cofactors appears to reflect the fate of chaperone-captured proteins. CHIP converts Hsp70/Hsp90 chaperones into substrate recognition factors of a functional ubiquitin ligase complex, whereas BAG-1 supports binding of the Hsp70 complex to the proteasome and triggers the release of ubiquitylated substrates from Hsc/Hsp70 for their transfer to the proteasome. Since BAG-1 and CHIP bind to different domains of Hsp70, these two co-chaperones are able to associate simultaneously with Hsp70. CHIP also regulates the association of BAG-1 with proteasome by K 11-linked polyubiquitylation of BAG-1.[41] The formation of the ternary chaperone-cofactor complex might accelerate the degradation of chaperone-captured unfolded proteins by the UPS pathway.[42-45]

Hsp90

The molecular chaperone Hsp90 is one of the most abundant proteins in eukaryotic cells, comprising 1–2% of total cellular proteins even in conditions of non-stress. Hsp90 is an evolutionarily conserved protein and contributes to a wide variety of fundamentally common and species-specific processes in cells.[46] For example, it is essential for maintenance of functional integrity of various fragile proteins, such as steroid hormone receptors and many of protein kinases.[47] It is also notable that Hsp90 functions as a protein-folding machinery collaborating with other chaperone molecules, such as Hsp70 and Hsp40, and co-chaperones containing p23 and Hop.[48,49] Indeed, Hsp90 can bind non-native proteins through N- and C-terminal domains for re-folding.[50]

In addition, Hsp90 appears to be closely linked to the protein degradation in the cell. Hsp90 also shows direct interaction with the proteasome and might possess regulatory roles, other than determination of the fate of unfolded proteins that cooperate with co-chaperones, PA28 and CHIP.[31,40] Initially, Hsp90 was considered to inhibit the 20S proteasome[51,52] and also to protect it from oxidative stress.[53] Proteomics analysis of proteasome-interacting proteins revealed physical interactions between Hsp70 and Hsp90 with the 26S proteasome.[54] Evidence for a functional interplay between Hsp90 and PA28 also indicates that Hsp90 appears to compensate the loss of PA28 function in MHC class I antigen processing, suggesting that Hsp90 and PA28 operate either redundantly or specifically for generation of MHC class I ligands.[55] However, the biological relevance of these interactions is not clear at this stage.

We have recently shown that Hsp90 participates in the ATP-dependent assembly of the 26S proteasome, as depicted in the model shown in Figure 1.[56] These findings may provide new mechanistic insight into the cooperative interactions between the molecular chaperone and proteolysis systems. In the same study, we found that in vivo and in vitro inactivation of Hsp90 caused

dissociation of the 26S proteasomes into their constituents. Conversely, these dissociated constituents reassembled in Hsp90-dependent fashion both in vivo and in vitro. These processes were ATP-dependent and were suppressed by geldanamycin, an Hsp90 inhibitor. These results strongly suggest that the ATPase activity of Hsp90 is essential to the assembly and maintenance of the 26S proteasome and that Hsp90 plays some regulatory roles on the UPS pathway through assembly and disassembly of the 26S proteasome (Fig. 1). At this point of view, the complete dissociation of the 26S proteasome after severe heat shock might be worth mentioning. Our data showed that during 4-hour after incubation at 50°C, the activities and the amount of the 26S proteasome were repressed during this period and were partially suppressed by overexpression of Hsp90. Such suppression is rational, considering that the 26S proteasome presumably requires heat-shock protein, Hsp90, for its biogenesis. Hsp90s are also required for heat-damaged proteins and might be busy after thermal insults. The disappearance of the 26S proteasome is also reasonable because while cells must acquire vital proteins without protein synthesis, they have to refold heat-denatured proteins, which usually might be degraded by the 26S proteasome. In this regard, the regulation of the 26S proteasome by Hsp90 is important for cell viability under severe stress conditions, which might form part of a fundamental survival mechanism. Considering this regulatory role of Hsp90, impairment of the UPS pathway caused by protein aggregation[57] might be partially brought about by the collapse of this regulation; the protein aggregates deprived of Hsp90 in cells.

PERSPECTIVES

Although recent studies have revealed that multiple steps of interactions between molecular chaperones and the UPS pathway enable cells to survive stressful environments, our understanding of these interactions is not fully satisfactory. In the endoplasmic reticulum (ER) quality control system, the fate of unfolded proteins is regulated by two transcriptional programs to induce ER chaperones[58] and ER-associated degradation (ERAD)-components,[59] depending on the quality and/or quantity of unfolded proteins accumulated in ER. Since the degradation of unfolded proteins in both ER and cytosol is responsible for the cytosolic UPS pathway, more highly organized mutual interaction between cytosolic molecular chaperones and UPS might be required to give versatility to cells; cells have to change the proportions of unfolded proteins to be refolded or to be degraded in response to environmental conditions. Further identifications should be made to define these interactions and their physiological significance.

One of the unanswered fundamentally critical issues in the protein quality control system is how unfolded proteins are designated to either refolding or degradation in the cell. How does the cellular machinery know the degree of protein impairment? Is there a pathway for severely unfolded proteins incapable of refolding by the chaperone team to be processed through the UPS pathway for their degradation? Even though molecular chaperones and UPS are principal players that work jointly in this pathway, the possibility that as-yet-unidentified molecule(s) handles refolding and destruction of unfolded proteins cannot be excluded. Whether the cell can indeed manage such a balance awaits future study.

In this review, we focused on the Hsp70 and Hsp90 as chaperone molecules responsible for the quality control system, but we should keep in mind that ubiquitin is also a member of the heat shock family proteins. During the last decade, it has become evident that cells have at least two or more polyubiquitin genes encoding multiple ubiquitins in a tandem fashion,[6] and expression of the polyubiquitin gene is up-regulated in response to various stresses. This elegant way devised evolutionarily to produce ubiquitin efficiently means that large amounts of ubiquitin are required for cell survival under environmental stressful conditions. In fact, two polyubiquitin genes are not necessary in normally proliferative budding yeast, but they become essential under stress conditions. Thus, it is worth emphasizing that not only the refolding machine but also the degrading machinery is also stress-inducible. Intriguingly, inhibition of the UPS pathway induces heat shock-response,[60-62] and increased ubiquitin-mediated proteolysis can replace the essential requirement for the heat shock protein induction.[63] Moreover, molecular chaperones, such as Hsp70 and Hsp90, are responsible for the maintenance of functional states of the UPS pathway, particularly the 26S proteasome as mentioned above.[56] These observations uncover a strong functional link between UPS and molecular chaperones.

Various diseases are caused by failure of proper protein folding. Accumulation of protein aggregates, which are cytotoxic, is tightly linked to neurodegenerative diseases,[2] and the instability caused by misfolding is associated with cystic fibrosis, maple syrup urine disease, cancer,[64] myotonic dystrophy,[65] immunodeficiency,[66] and type 2 diabetes.[67] These facts indicate that regulation of intracellular balance between refolding and degradation is a critical issue for cells. We speculate that not only mutations of each protein, but also the deficiency of the chaperone or the UPS system may cause protein misfolding or aggregation. It is noteworthy to point out that proteasome inhibitors increase the frequency of ubiquitin-positive intracellular inclusions that carry the genes of many neurodegenerative disorders.[68,69] Therefore, one could assume that a critical aspect of various neuronal degenerative diseases is failure of protein quality control mediated by molecular chaperones and/or UPS. There is a great interest in the interaction between some putative protein folding diseases and the chaperone system or the UPS pathway. Further studies are required to clarify this issue molecularly.

References

1. Princiotta MF, Finzi D, Qian SB, Gibbs J, Schuchmann S, Buttgereit F, Bennink JR, Yewdell JW. Quantitating protein synthesis, degradation, and endogenous antigen processing. Immunity 2003; 18:343-54.
2. Sherman MY, Goldberg AL. Cellular defenses against unfolded proteins: a cell biologist thinks about neurodegenerative diseases. Neuron 2001; 29:15-32.
3. Frydman J. Folding of newly translated proteins in vivo: the role of molecular chaperones. Annu Rev Biochem 2001; 70:603-47.
4. Bukau B, Horwich AL. The Hsp70 and Hsp60 chaperone machines. Cell 1998; 92:351- 66.
5. Morimoto RI. Regulation of the heat shock transcriptional response: cross talk between a family of heat shock factors, molecular chaperones, and negative regulators. Genes Dev 1998; 12:3788-96.
6. Hershko A, Ciechanover A, Varshavsk A. The ubiquitin system, Nat Med 2000; 6:1073-81.
7. Pickart CM, Mechanisms underlying ubiquitination, Annu Rev Biochem. 2001; 70:503-33.
8. Wickner S, Maurizi MR, Gottesma S. Posttranslational quality control: folding, refolding, and degrading proteins. Science 1999; 286:1888-93.
9. Coux O, Tanaka K, Goldberg AL. Structure and functions of the 20S and 26S proteasomes, Annu Rev Biochem 1996; 65:801-47.
10. Baumeister W, Walz J, Zuhl F, Seemuller E. The proteasome: paradigm of a self-compartmentalizing protease. Cell 1998; 92:367-80.
11. Bochtler M, Ditzel L, Groll M, Hartmann C, Huber H, The proteasome, Annu Rev Biophys Biomol Struct 1999; 28:295-317.
12. Ustrell V, Hoffman L, Pratt G, Rechsteiner M. PA200 a nuclear proteasome activator involved in DNA repair. EMBO J 2002; 21 3516-25.
13. DeMartino GN, Slaughter CA. The proteasome, a novel protease regulated by multiple mechanisms. J Biol Chem 1999; 274:22123-6.
14. Glickman MH, Ciechanover A. The ubiquitin-proteasome proteolytic pathway: destruction for the sake of construction, Physiol Rev 2002; 82:373-428.

15. Ogura T, Tanaka K. Dissecting various ATP-dependent steps in proteasomal degradation, Mol Cell 2003; 11:3-5.
16. Braun BC, Glickman M, Kraft R, Dahlmann B, Kloetzel PM, Finley D, Schmidt M. The base of the proteasome regulatory particle exhibits chaperone-like activity. Nat Cell Biol 1999; 1:221-6.
17. Strickland E, Hakala K, Thomas PJ, DeMartino GN. Recognition of misfolding proteins by PA700, the regulatory subcomplex of the 26 S proteasome. J Biol Chem 2000; 275:5565-72.
18. Gillette TG, Huang W, Russell SJ, Reed SH, Johnston SA, Friedberg EC. The 19S complex of the proteasome regulates nucleotide excision repair in yeast. Genes Dev 2001; 15:1528-39.
19. Ferdous A, Gonzalez F, Sun L, Kodadek T, Johnston SA. The 19S regulatory particle of the proteasome is required for efficient transcription elongation by RNA polymerase II. Mol. Cell 2001; 7:981-91.
20. Nishiyama A, Tachibana K, Igarashi Y, Yasuda H, Tanahashi N, Tanaka K, Ohsumi K, Kishimoto T. A nonproteolytic function of the proteasome is required for the dissociation of Cdc2 and cyclin B at the end of M phase. Genes Dev. 2000; 14:2344-57.
21. Ma CP, Willy PJ, Slaughter CA, DeMartino GN. PA28, an activator of the 20S proteasome, is inactivated by proteolytic modification at its carboxyl terminus. J Biol Chem 1993; 268:22514-9.
22. Dubiel W, Pratt G, Ferrell K. Rechsteiner M. Purification of an 11 S regulator of the multicatalytic protease. J Biol Chem 1992; 267:22369-77.
23. Rechsteiner M, Realini C, Ustrell V. The proteasome activator 11 S REG (PA28) and class I antigen presentation. Biochem J 2000; 345:1-15.
24. Tanaka K, and Kasahara M, The MHC class I ligand generating system: Roles of immunoproteasomes and INF-γ inducible PA28. Immunol Rev 1998; 163:161-76.
25. Murata S, Udono H, Tanahashi N, Hamada N, Adachi K, Yamano T, Yui K, Kobayashi N, Kasahara M, Tanaka K, Chiba T. Immunoproteasome assembly and antigen processing in mice lacking both PA28α and PA28β. EMBO J 2001; 20: 5898-5907.
26. Tanahashi N, Murakami Y, Minami Y, Shimbara N, Hendil KB, Tanaka K. Hybrid proteasomes: Induction by interferon-γ and contribution to the ATP-dependent proteolysis. J Biol Chem 2000; 275:14336-45.
27. Kopp F, Dahlmann B, Kuehn L. Reconstitution of hybrid proteasomes from purified PA700-20 S complexes and PA28alphabeta activator: ultrastructure and peptidase activities. J Mol Biol 2001; 313:465-71.
28. Cascio P, Call M, Petre BM, Walz T, Goldberg AL. Properties of the hybrid form of the 26S proteasome containing both 19S and PA28 complexes. EMBO J 2002; 21:2636-45.
29. Tanahashi N, Yokota K, Ahn JY, Chung CH, Fujiwara T, Takahashi E, DeMartino GN, Slaughter CA, Toyonaga T, Yamamura K, Shimbara N, Tanaka K. Molecular properties of the proteasome activator PA28 family proteins and gamma-interferon regulation. Genes Cells 1997; 2:195-211.
30. Murata S, Kawahara K, Tohma S, Yamamoto K, Kasahara M, Nabeshima Y, Tanaka K, Chiba T. Growth retardation in mice lacking the proteasome activator PA28. J Biol Chem 1999; 274:38211-5.
31. Minami Y, Kawasaki H, Minami M, Tanahashi N, Tanaka K, Yahara I. A critical role of the proteasome activator PA28 in the Hsp-90-dependent protein folding. J Biol Chem 2000; 275:9055-61.
32. Kloetzel PM. Antigen processing by the proteasome. Nat Rev Mol Cell Biol 2001; 2:179-87.
33. Luders J, Demand J, Hohfeld J. The ubiquitin-related BAG-1 provides a link between the molecular chaperones Hsc70/Hsp70 and the proteasome. J Biol Chem 2000; 275:4613-7.
34. Gassler CS, Wiederkehr T, Brehmer D, Bukau B, Mayer M. Bagaccelerates nucleotide release for human Hsc70 and Hsp70 and can act concentration-dependent as positive and negative cofactor. J Biol Chem 2001; 276:32538-44.
35. Ballinger CA, Connell P, Wu Y, Hu Z, Thompson LJ, Yin LY, Patterson C. Identification of CHIP, a novel tetratricopeptide repeat-containing protein that interacts with heat shock proteins and negatively regulates chaperone functions. Mol Cell Biol 1999; 19:4535-45.
36. Connell P, Ballinger CA, Jiang J, Wu Y, Thompson LJ, Hohfeld J, Patterson C. The co-chaperone CHIP regulates protein triage decisions mediated by heat-shock proteins. Nat Cell Biol 2001; 3:93-6.
37. Meacham GC, Patterson C, Zhang W, Younger JM, Cyr DM. The Hsc70 co-chaperone CHIP targets immature CFTR for proteasomal degradation. Nat Cell Biol 2001; 3:100-5.
38. Aravind L and Koonin EV. The U box is a modified RING finger—a common domain in ubiquitination. Curr Biol 2000; 10:R132-4.
39. Jiang J, Ballinger CA, Wu Y, Dai Q, Cyr DM, Hohfeld J, Patterson C. CHIP is a U-box-dependent E3 ubiquitin ligase: identification of Hsc70 as a target for ubiquitylation. J Biol Chem 2001; 276:42938-44.
40. Murata S, Minami Y, Minami M, Chiba T, Tanaka K. CHIP is a chaperone-dependent E3 ligase that ubiquitylates unfolded protein. EMBO Rep 2001; 2:1133-8.
41. Alberti S, Demand J, Esser C, Emmerich N, Schild H, Hohfeld J. Ubiquitylation of BAG-1 suggests a novel regulatory mechanism during the sorting of chaperone substrates to the proteasome. J Biol Chem 2002; 277:45920-7.
42. Demand J, Alberti S, Patterson C, Hohfeld J. Cooperation of a ubiquitin domain protein and an E3 ubiquitin ligase during chaperone/proteasome coupling. Curr Biol 2001; 11:1569-77.
43. Hohfeld J, Cyr DM, Patterson C. From the cradle to the grave: molecular chaperones that may choose between folding and degradation. EMBO Rep 2001; 2:885-90.
44. Cyr DM, Hohfeld J, Patterson C. Protein quality control: U-box-containing E3 ubiquitin ligases join the fold. Trends Biochem Sci 2002; 27:368-75.
45. Wiederkehr T, Bukau B, Buchberger A. Protein turnover: a CHIP programmed for proteolysis. Curr Biol 2002; 12:R26-8.
46. Young JC, Moarefi I, and Hartl FU. Hsp90: a specialized but essential protein-folding tool. J Cell Biol 2001; 154:267-73.
47. Richter K, Buchner J. Hsp90: chaperoning signal transduction. J Cell Physiol 2001; 188:281-90.
48. Buchner J. Hsp90 & Co. - a holding for folding. Trends Biochem Sci. 1999; 24: 136-141.
49. Young JC, Moarefi I, and Hartl FU, Hsp90: a specialized but essential protein-folding tool. J Cell Biol 2001; 154:267-73.
50. Minami Y, Minami M. Hsc70/Hsp40 chaperone system mediates the Hsp90-dependent refolding of firefly luciferase. Genes Cells 1999; 4:721-9.
51. Tsubuki S, Saito Y, Kawashima S. Purification and characterization of an endogenous inhibitor specific to the Z-Leu-Leu-Leu-MCA degrading activity in proteasome and its identification as heat-shock protein 90. FEBS Lett 1994; 344:229-33.
52. Wagner BJ, Margolis JW. Age-dependent association of isolated bovine lens multicatalytic proteinase complex (proteasome) with heat-shock protein 90, an endogenous inhibitor. Arch Biochem Biophys 1995; 323:455-462.
53. Conconi M, Petropoulos I, Emod I, Turlin E, Biville F, Friguet B. Protection from oxidative inactivation of the 20S proteasome by heat-shock protein 90. Biochem J 1998; 333:407-15.
54. Verma R, Chen S, Feldman R, Schieltz D, Yates J, Dohmen J, Deshaies RJ. Proteasomal proteomics: identification of nucleotide-sensitive proteasome-interacting proteins by mass spectrometric analysis of affinity-purified proteasomes. Mol Biol Cell 2000; 11:3425-39.
55. Yamano T, Murata S, Shimbara N, Tanaka N, Chiba T, Tanaka K, Yui K, Udono H. Two distinct pathways mediated by PA28 and hsp90 in major histocompatibility complex class I antigen processing. J Exp Med 2002; 196:185-96.
56. Imai J, Maruya M, Yashiroda H, Yahara I, Tanaka K. The molecular chaperone Hsp90 plays a role in the assembly and maintenance of the 26S proteasome. EMBO J 2003; 22:3557-67.
57. Bence NF, Sampat RM, Kopito RR. Impairment of the ubiquitin-proteasome system by protein aggregation. Science 2001; 292:1552-5.
58. Yoshida H, Matsui T, Hosokawa N, Kaufman RJ, Nagata K, Mori K. A time-dependent phase shift in the mammalian unfolded protein response. Dev Cell 2003; 4:265-71.
59. Yoshida Y. A novel role for N-glycans in the ERAD system, J Biochem. (2003) in press.
60. Bush KT, Goldberg AL, Nigam SK. Proteasome inhibition leads to a heat-shock response, induction of endoplasmic reticulum chaperones, and thermotolerance. J Biol Chem 1997; 272:9086-92.
61. Lee DH, Goldberg AL, Proteasome inhibitors cause induction of heat shock proteins and trehalose, which together confer thermotolerance in Saccharomyces cerevisiae. Mol Cell Biol 1998; 18:30-8.
62. Tanahashi-Hori T, Tanahashi N, Tanaka K, Chiba T. Conditional knockdown of proteasomes results in cell-cycle arrest and enhanced expression of molecular chaperones Hsp70 and Hsp40 in chicken DT40 cells. J Biol Chem 2003; 278:16237-43.
63. Friant S, Meier KD, Riezman H, Increased ubiquitin-dependent degradation can replace the essential requirement for heat shock protein induction. EMBO J 2003; 22:3783-91.
64. Thomas PJ, Qu BH, Pedersen PL. Defective protein folding as a basis of human disease. Trends Biochem Sci 1995; 20:456-9.
65. Sugiyama Y, Suzuki A, Kishikawa M, Akutsu R, Hirose T, Waye MM, Tsui SK, Yoshida S, Ohno S. Muscle develops a specific form of small heat shock protein complex composed of MKBP/HSPB2 and HSPB3 during myogenic differentiation. J Biol Chem 2000; 275:1095-104.
66. Matsuda S, Suzuki-Fujimoto T, Minowa A, Ueno H, Katamura K, Koyasu S. Temperature-sensitive ZAP70 mutants degrading through a proteasome-independent pathway. Restoration of a kinase domain mutant by Cdc37. J Biol Chem 1999; 274:34515-8.
67. Oyadomari S, Koizumi A, Takeda K, Gotoh T, Akira S, Araki E, Mori M. Targeted disruption of the Chop gene delays endoplasmic reticulum stress-mediated diabetes. J Clin Invest 2002; 109:525-32.
68. Mayer RJ, Landon M, Lowe J. Ubiquitin and the molecular pathology of human disease. In "Ubiquitin and the Biology of the Cell" (ed by Peters J-M, Harris JR, Finley D) 1998; 147-189, Plenum Press, New York.
69. Floyd JA, Hamilton BA. Intracellular inclusions and the ubiquitin-proteasome pathway: digestion of a red herring? Neuron 1999; 24:765-66.