The C-terminal Tails of HslU ATPase Act as a Molecular Switch for Activation of HslV Peptidase*

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The bacterial HslVU ATP-dependent protease is a homolog of the eukaryotic 26 S proteasome. HslU ATPase forms a hexameric ring, and HslV peptidase is a dodecamer consisting of two stacked hexameric rings. In HslVU complex, the HslU and HslV central pores are aligned, and the proteolytic active sites are sequestered in an internal chamber of HslV, with access to this chamber restricted to small axial pores. Here we show that the C-terminal tails of HslU play a critical role in the interaction with and activation of HslV peptidase. A synthetic tail peptide of 10 amino acids could replace HslU in supporting the HslV-mediated hydrolysis of unfolded polypeptide substrates such as α-casein, as well as of small peptides, suggesting that the HslU C terminus is involved in the opening of the HslV pore for substrate entry. Moreover, deletion of 7 amino acids from the C terminus prevented the ability of HslU to form an HslVU complex with HslV. In addition, deletion of the C-terminal 10 residues prevented the formation of an HslU hexamer, indicating that the C terminus is required for HslU oligomerization. These results suggest that the HslU C-terminal tails act as a molecular switch for the assembly of HslVU complex and the activation of HslV peptidase.

ATP-dependent proteolysis plays an essential role in controlling the levels of key regulatory proteins and in the elimination of abnormal polypeptides (1, 2). These tasks are carried out by architecturally related ATP-dependent proteases such as the 26 S proteasome in eukaryotes (3, 4) and the ClpAP, ClpXP, and HslVU (ClpQY) proteases in archa and eubacteria (5–7). The 26 S proteasome consists of the 20 S proteasome, which forms a proteolytic core, and the 19 S regulatory complex harboring multiple ATPase activities (8, 9). The barrel-shaped 20 S proteasome is composed of α- and β-type subunits. The α-type subunits, which are proteolytically inactive, form the outer ring, and the β-type subunits, which contain the active sites, form inner rings of the complex.

The bacterial HslVU protease is a homolog of the eukaryotic 26 S proteasome (10, 11). HslVU in Escherichia coli is the product of the hslVU operon, which encodes two heat shock proteins, the HslV peptidase and HslU ATPase (12). HslV forms a dodecamer of two back-to-back stacked hexameric rings (13). HslU forms a hexameric ring and binds to either one or both HslV ends (14, 15). The cod operon in Bacillus subtilis encodes the CodW and CodX proteins (in addition to CodV and CodY), both of which display more than 50% identity in their amino acid sequences with HslV and HslU in E. coli, respectively (16). Recently, we have demonstrated that CodW provides the peptidase activity, whereas CodX harbors the ATPase activity, both of which can function together as a new type of two-component ATP-dependent protease (17). Remarkably, CodW uses its N-terminal Ser hydroxyl group as the catalytic nucleophile, unlike HslV in E. coli and certain β-type proteosome subunits, which have N-terminal Thr as an active site residue (18, 19).

The HslU ATPase is a member of the Clp/Hsp100 family of molecular chaperones (20). Functions that have been attributed to this family member include facilitating the degradation of target proteins by cognate proteases (21–23) as well as disassembly of oligomeric protein complexes (22, 24). HslU supports the HslV-mediated degradation of SulA, an inhibitor protein of E. coli cell division, but by itself can also function in prevention of aggregation of the inhibitor protein (23, 25). Among these family members, ClpA and ClpX target ssrA-tagged polypeptides to the ClpP protease for degradation (21) but by themselves can also function in disassembly of oligomeric proteins, such as the plasmid P1 RepA replication initiator and the DNA-bound MuA transposase, respectively (22, 24). Moreover, recent studies using ssrA-tagged green fluorescent protein as a substrate have shown that ClpA and ClpX unfold green fluorescent protein in an ATP-dependent process and translocate it into the catalytic compartment of the ClpP protease (26, 27).

The crystal structures of peptidase components such as ClpP and HslV reveal that the peptidases consist of two doughnut-shaped rings within which the proteolytic active sites are sequestered in an inner chamber, with access to this chamber restricted to small axial pores (13, 28). The diameters of these pores are so small that only a single strand of polypeptide can be threaded through (13, 29). Therefore, native protein substrates have to be unfolded by an associated ATPase and actively translocated into the cognate peptidase for degradation (30–32). This mechanism requires the specific docking of the ATPase with the peptidase. Recently, it has been demonstrated that a tripeptide, IGF, in E. coli ClpX is essential for ClpP recognition and that mutations in this IGF sequence disrupt ClpXP complex formation and prevent protease function (33).
On the other hand, HslU, which does not have the conserved IGF motif, does not bind ClpP but interacts with HslV. These findings imply that other motif in HslU ATPase may exist and mediate the interaction with and activation of HslV through different mechanisms.

To date, a number of crystal and solution structures of HslVU have been reported (34–37). We have recently characterized four distinct HslV conformational states (in complex with HslV) and determined the nucleotide-dependent conformational changes within them, especially including a conformational change of its C terminus (38). The highly conserved HslU C terminus is inserted at an HslV-HslV interface when ATP is bound; otherwise it is buried at the HslU-HslU interface (35, 38, 39). Therefore, we have suggested that the insertion of HslU C-terminal tails into pockets at the HslV-HslV interface in the ATP-bound state might cause the opening of the central pore of HslV peptidase for the access of unfolded polypeptide substrates into the proteolytic chamber. In the present studies, we provide biochemical evidence showing that the HslU C terminus is essential for its interaction with HslV and for activation of the peptidase. We demonstrate as well that the C-terminal tails of CodX ATPase are also involved in the activation of CodX peptidase.

EXPERIMENTAL PROCEDURES

Materials—All reagents for PCR, including Taq polymerase and restriction endonuclease, were purchased from Takara (Shiga, Japan). Peptide substrates were obtained from Bachem Feinchemikalien AG (Bubendorf, Switzerland). Synthetic peptides ADEDLBLRFL (HslU tail sequence), KNKDLSQFIL (CodX tail sequence), and SLDDARFKNE (scrambled tail sequence) were purchased from AnyGen (Kwangju, Korea). All other reagents were purchased from Sigma, unless otherwise indicated. HslV, HslU, CodW, CodX, and their mutant forms were purified as described previously (17, 40).

Mutagenesis—Site-directed mutagenesis was carried out using the QuikChange Site-Directed Mutagenesis Kit (Stratagene) with PGEM-T/HslVU as the templates. The PCR reactions were carried out using mutagenic primers, which were designed to replace the codons for Ser359, Asp437, or Ala434 by a stop codon (TAA) for generating the HslU deletion mutants lacking 5 (HslU/C5), 7 (HslU/C7), or 10 amino acid residues (HslU/C10) from its C terminus, respectively. The resulting plasmids were transformed into MC1000H carrying pGEM-T/H9004. Site-directed mutagenesis was also performed to prepare MOLMOL (57).

To determine whether the C-terminal tails of HslU indeed play an essential role in HslVU complex formation and thus in the activation of cognate peptidases (Fig. 2), implying the ubiquitous function of the C-terminal tail region of HslU family in the interaction with and thus in the activation of cognate peptidases.

RESULTS

Interaction of HslU C Terminus with HslV—The crystal and solution structures of HslVU complex (35, 38, 39) have revealed that the HslU C terminus interacts with the binding pocket of HslV. Notably, Leu443 (C-terminal carboxylate), Arg440, and Asp437 in the C-terminal tails of HslU ATPase are involved in a direct interaction with Lys28, Glu61, and Lys73 of HslV peptidase, respectively, by forming salt bridges (Fig. 1A). In addition, Leu138 and Ile442 in the C-terminal tails of HslU form a hydrophobic core with Val72, Val79, and Val107 of the adjacent HslV. Moreover, these amino acid residues in the C-terminal sequence of HslU are highly conserved in various microorganisms (Fig. 2), implying the ubiquitous function of the C-terminal tail region of HslU family in the interaction with and thus in the activation of cognate peptidases.

Activation of HslV Peptidase by HslU Tail Peptide—To determine whether the C-terminal tails of HslU indeed play an essential role in HslVU complex formation and thus in the activation of HslV peptidase, a peptide corresponding to the C-terminal 10 residues of HslU was synthesized and referred to as C10HslU. Site-directed mutagenesis was also performed to serially delete the amino acid residues in the C-terminal tail region of HslU (Fig. 3A). The mutant proteins (HslU/C5, HslU/C7, and HslU/C10) were purified to apparent homogeneity (Fig. 3C). Although we attempted to generate other HslU mutants with different C-terminal lengths (e.g. HslU/C1), they were recovered as insoluble precipitates (data not shown).

First, we examined whether C10HslU alone could support the...
hydrolysis of Cbz-Gly-Gly-Leu-AMC by HslV. As shown in Fig. 4A, the peptidase activity of HslV was dramatically stimulated by C10HslU. HslV (0.1 μg) in the presence of 20 μg of C10HslU hydrolyzed the peptide substrate at about one-half the rate seen with 0.4 μg of HslV. Moreover, the stimulatory effect of C10HslU was dependent on its concentration (Fig. 4B). On the other hand, a control peptide with scrambled sequence showed little or no effect (data not shown). These results indicate that C10HslU can replace HslU in the activation of the HslV-mediated peptidase hydrolysis, although its apparent affinity to HslV is much lower than that of HslU.

We then examined the effect of C10HslU on the degradation of protein substrates by HslV. α-Casein was incubated with HslV in the absence and presence of C10HslU for 2 h at 37 °C. After incubation, the samples were subjected to SDS-PAGE followed by staining with Coomassie Blue R-250. Each lane contained 3 g of protein.

FIG. 2. Amino acid sequences of the C-terminal tail region of HslU family members. The HslU tail sequence conservation is shown in gray scale from the most (dark) to least (white) conserved. At the top, the amino acid residues that may form salt bridges with those in cognate peptidases are marked by asterisks. The amino acids that may form hydrophobic cores are indicated by diamonds. The amino acid sequence data were obtained from the Swiss Protein, GenBank™, and EMBL databases.

Effects of HslU C-terminal Deletion Mutations-To define further the involvement of the C-terminal tails of HslU in the activation of HslV peptidase, we examined the effects of HslU deletion mutations in the tail region on the proteolytic activity of HslV. HslU/ΔC5 was capable of supporting the hydrolysis of Cbz-Gly-Gly-Leu-AMC by HslV ~40% as well as the wild-type HslU (Fig. 6A). In contrast, neither HslU/ΔC7 nor HslU/ΔC10 could support the peptidase activity of HslV. Similar to the peptidase hydrolysis, HslU/ΔC5 but not HslU/ΔC7 or HslU/ΔC10 could support the HslV-mediated degradation of protein substrates, including α-casein and MBP-SulA, about 40% as well as the wild-type HslU (data not shown). These results suggest that the shortening of C-terminal tail length (i.e. serial elimination of the amino acids that form salt bridges and hydrophobic interaction) reduces the affinity of HslU to the binding pocket of HslV, resulting in a gradual loss of its potential to activate the peptidase.
HslU alone hydrolyzes ATP, and its ATPase activity is enhanced severalfold upon interaction with HslV (40). To determine the effect of the deletion mutations in the C-terminal tail region of HslU on the ATPase activity, ATP hydrolysis was assayed in the absence and presence of HslV. Without HslV, HslU/C5 and HslU/C7 cleaved ATP nearly as well as the wild-type HslU (Fig. 6B), indicating that deletion of C-terminal tails up to seven amino acids does not influence on the ability of HslU in ATP binding and its hydrolysis. However, the ATPase activity of HslU/C10 was not stimulated at all by HslV.

Fig. 4. Effect of C10<sup>HslU</sup> on peptide hydrolysis by HslV. A, peptide hydrolysis was assayed by incubating 0.1 µg of HslV, 0.1 mM Cbz-Gly-Gly-Leu-AMC, and 1 mM ATP in the absence (C) and presence of 20 µg of C10<sup>HslU</sup> (•) or with 0.4 µg of HslU (△) for various periods of time at 37 °C. B, assays were also performed as described above except with incubation for 10 min with 0.1 µg of HslV and increasing amounts of C10<sup>HslU</sup>.

Fig. 5. Effect of C10<sup>HslU</sup> on protein degradation by HslV. α-Casein (A) or MBP-SulA (B) was incubated with HslV (0.5 µg) in the absence and presence of C10<sup>HslU</sup> (20 µg) or with HslU (2 µg) for 2 h at 37 °C. After incubation, the samples were subjected to SDS-PAGE as described under “Experimental Procedures.” The arrowhead indicates the degradation product from MBP-SulA. The bands corresponding to α-casein and MBP-SulA were scanned using a densitometer, and their intensities were expressed as 100%; the other bands were expressed relative to the values shown at the bottom of the gels.

Fig. 6. Effects of deletion mutations in the C-terminal tail region of HslU on peptide hydrolysis by HslV and on its ATPase activity. A, peptide hydrolysis was assayed by incubating 0.1 µg of HslV, 0.1 mM Cbz-Gly-Gly-Leu-AMC, 1 mM ATP, and increasing amounts of the wild-type HslU (•), HslU/C5 (○), HslU/C7 (△), or HslU/C10 (□) for 10 min at 37 °C. B, ATP hydrolysis was assayed by incubating 1 mM ATP and 1 µg of the wild-type HslU or its mutant forms in the absence (gray bars) and presence of 1 µg of HslV (black bars). After incubation for 1 h at 37 °C, the phosphates released were then determined as described under “Experimental Procedures.”
In addition, the extent of HslV-activated ATPase activity of HslU/C5 was reduced to about one-half of that seen with the wild-type HslU. These results suggest that HslU/C5 but not HslU/C7 is capable of interaction with HslV, albeit with a lower affinity than the wild-type HslU. In contrast, little or no ATPase activity was observed with HslU/C10 whether or not HslV was present, suggesting that HslU/C10 is unable to bind ATP or to form a hexameric complex, which is essential for ATP hydrolysis.

To confirm whether the C-terminal tails of HslU are indeed essential for its interaction with HslV, cross-linking analysis was performed by incubating each of the C-terminal deletion mutants with glutaraldehyde in the absence and presence of HslV. Fig. 7A shows that HslU/C5 and HslU/C7 but not HslU/C10 could oligomerize into a hexameric form in the absence of HslV. However, HslU/C7 could not form a HslVU complex, unlike the wild-type HslU and HslU/C5 (Fig. 7B). In addition, the extent of HslVU complex formation by HslU/C5 was significantly lower than that by the wild-type HslU. On the other hand, HslU/C10, which is unable to oligomerize into a hexamer, could not form a HslVU complex with HslV. These results indicate that the C-terminal tails of HslU play a key role not only in its oligomerization but also in HslVU complex formation with HslV.

**Activation of CodW Peptidase by CodX C-terminal Tails**—
Recently, we have shown that CodWX in *B. subtilis*, which is a homolog of HslVU in *E. coli*, is a new type of ATP-dependent protease, harboring the Ser active site for proteolysis at the N terminus of CodW (17). Because the structure of CodWX has not been determined yet, modeling on the binding pocket of CodW peptidase for the C terminus of CodX ATPase was performed on the basis of the structure of HslVU complex. In this modeling (Fig. 1B), CodX has Gln464 at the position corresponding to Arg440 of HslU, which forms a salt bridge with Glu67 in HslV (see Fig. 1A). Therefore, the Gln residue in the C-terminal tails of CodX is unlikely to form a salt bridge with Glu67 in CodW, which corresponds to Glu61 in HslV. Moreover, CodW has Lys78 at the position corresponding to Val72 in HslV, which forms a hydrophobic core with Leu438 and Ile442 in the C-terminal tails of HslU (Leu662 and Ile666 in CodX) as well as with Val76 and Val81 in the same HslV polypeptide (Val82 and Val818 in CodW). Thus, the hydrophobic interaction around the C-terminal tail region of CodX in CodWX complex would not be as strong as that in HslVU. This modeling implies that CodWX would be a weaker protease than HslVU. To test this possibility, we compared the activity of CodWX with that of HslVU by incubation of the same amounts of the enzymes for the same period with Cbz-Gly-Gly-Leu-AMC or α-casein. CodWX was found to degrade both substrates only about 3-4% as well as HslVU (data not shown).

Based on these findings, we intended to generate an artificial CodWX protease with improved activity by replacing Gln464 of CodX by Arg and Lys78 of CodW by Val, thus allowing the substituted amino acids to form a salt bridge and hydrophobic interaction, respectively. The mutant proteins, referred to as CodX/Q464R and CodW/K78V, were purified to apparent homogeneity as described (see Fig. 3C) (17). Table I shows that the peptidase activity of CodWX increased by about 1.5- and 4.7-fold upon substitution of Gln464 of CodX by Arg and Lys78 of CodW by Val, respectively. Furthermore, when CodW/K78V and CodX/Q464R were incubated together, the peptidase activity was increased further to about 7.5-fold. Under similar assay conditions, the ATPase activity was not significantly changed upon the mutations. These results strongly suggest that the activation mechanism involving the C-terminal tail of ATPase is also functional in CodWX complex.

Whereas HslV itself is a weak peptidase, CodW cannot cleave Cbz-Gly-Gly-Leu-AMC without CodX. Moreover, the ATPase activity of CodX is essential for activation of CodW peptidase, whereas ATP binding, but not its hydrolysis by HslU, is required for degradation of peptides by HslV (48).

**Effects of mutations in putative interacting regions in CodW and CodX on peptide and ATP hydrolysis**

Hydrolysis of Cbz-Gly-Gly-Leu-AMC was assayed by incubation of 0.1 μg of CodW or CodWX/K78V with 0.4 μg of CodX or CodX/Q464R in the indicated combination for 10 min at 37 °C. For ATP hydrolysis, assays were performed as described above but by incubation for 1 h at 37 °C using 1 μg of each protein. The activities seen with the mixtures of the wild-type CodW and CodX proteins were expressed as 100%, and the others were expressed relative to the value.

**TABLE I**

| Proteins                         | Relative activity against Cbz-Gly-Gly-Leu-AMC | ATPase % |
|----------------------------------|-----------------------------------------------|----------|
| CodW plus CodX                   | 100                                           | 100      |
| CodW plus CodX/Q464R             | 122                                           | 105      |
| CodWX/K78V plus CodX             | 472                                           | 121      |
| CodWX/K78V plus CodX/Q464R       | 750                                           | 148      |

**Activation of HslV by C-terminal Tail of HslU**

![Image](http://www.jbc.org/Downloadedfrom/fig7a.png)

**Fig. 7. Effects of deletion mutations in the C-terminal tail region of HslU on its oligomerization and complex formation with HslV.** Cross-linking analysis was performed by incubation of 4 μg of the wild-type HslU (lane a), HslU/C5 (lane b), HslU/C7 (lane c), or HslU/C10 (lane d) with 1 mM ATP and 0.4% glutaraldehyde in the absence (A) and presence of 4 μg of HslV (B). After incubation for 20 min at 37 °C, the samples were subjected to SDS-PAGE followed by silver staining.

**TABLE I**

| Proteins                         | Relative activity against Cbz-Gly-Gly-Leu-AMC | ATPase % |
|----------------------------------|-----------------------------------------------|----------|
| CodW plus CodX                   | 100                                           | 100      |
| CodW plus CodX/Q464R             | 122                                           | 105      |
| CodWX/K78V plus CodX             | 472                                           | 121      |
| CodWX/K78V plus CodX/Q464R       | 750                                           | 148      |
DISCUSSION

Recent structural studies on HslVU complex as well as on uncomplexed HslU have shown that in the dADP-bound state the C-terminal tail of HslU, which forms a short loop and helix, is buried inside a hydrophobic pocket at the HslU-HslU interface (35, 38, 39). When ATP is bound, it distends and9 binds at an HslV-HslV interface. This conformational change, which is likely to cycle upon ATP hydrolysis, reflects the role of the HslU C-terminal tails as a molecular switch for binding and functional interaction with HslV.

Lines of biochemical evidence provided in the present study indicate that the C-terminal tails of HslU ATPase acts as a molecular switch for the assembly of HslVU complex and for the activation of HslV peptidase. First, a synthetic peptide corresponding to the C-terminal 10 residues of HslU, C10HslU, could activate the peptidase activity of HslV. Moreover, C10HslU could also support the hydrolysis of unfolded protein substrates such as α-casein nearly as well as HslU. These results clearly suggest that the binding of C10HslU to the HslV-HslV interface leads to opening of the HslV pore for the entry of unfolded polypeptides as well as small peptides into its proteolytic chamber. These results also suggest that ATP hydrolysis is not essential for opening of the HslV pore and that the catalytic activation reflects a simple opening of the pore. However, C10HslU was unable to support the degradation of SulA, indicating that ATP hydrolysis is required for unfolding of native folded proteins by HslU prior to their access to the HslV pore.

Second, a mutant form of HslU, HslU/ΔC7 lacking the C-terminal seven amino acids, could not form a HslVU complex with HslV, indicating that the tail region provides a critical motif for interaction with HslV. In the C-terminal tail region of HslU, the last seven amino acids are highly conserved among the HslU family members in various microorganisms (see Fig. 2). Moreover, most of these residues are involved in the formation of salt bridges and a hydrophobic core with the adjacent amino acids in HslV (35, 39). Noteworthy is the finding that HslU/ΔC10 lacking the C-terminal 10 amino acids is unable to form a hexamer, unlike HslU/ΔC7 or the wild-type HslU. Structural analysis of HslVU complex has shown that Glu436 in HslU forms a salt bridge with Lys314 in adjacent HslU subunit (39), implying that the Glu residue may play a critical role in oligomerization of HslU although we cannot exclude the possibility that two adjacent amino acids (i.e. Ala314 and Asp435) in HslV are also involved in the oligomer phase. Thus, the C-terminal tails of HslU appear to play an essential role in the assembly of HslVU complex with HslV as well as the oligomerization of itself.

Finally, a catalytically improved CodWX protease could be engineered by introduction of a salt bridge and hydrophobic interaction between the C-terminal region of CodX ATPase and the binding pocket of CodW peptidase, which were not present in the authentic CodWX complex, unlike HslVU, due to the difference in the sequences of the binding region. Moreover, a synthetic peptide corresponding to the C-terminal 10 residues of CodX, C10CodX, could activate the peptidase activity of CodW, which by itself is inactive, although the extent of the activation by C10CodX was far lower than that by CodX. These results further support the idea that the activation mechanism involves the interaction of the C-terminal tail of HslU with the binding pocket of HslV.

In certain structures of HslVU complex, HslV is in contact with HslU through the intermediate (I) domain, and the pores of HslV and HslU are not aligned with each other (34). However, this structure appears not feasible, because the activation of HslV requires its binding with the C-terminal tail region of HslU located opposite the I domain and because the deletion of seven amino acids from the C terminus prevents the formation of HslVU complex. Thus, the HslVU structure, in which HslV is contacted by HslU through the N and C domains, appears relevant.

Crystallographic and biochemical analyses have recently demonstrated that the eukaryotic 20 S proteasome is a gated protease and that opening of the gate can be achieved by binding of PA26 and 19 S regulatory complex (49–51). PA26 (also called 11 S regulator, REG, and PA28) is a heptamer that stimulates the peptidase activities of the 20 S proteasome (52–55). In the latent state of the 20 S proteasome, substrate entry into the inner proteolytic chamber is blocked by the gate formed by the N-terminal tails of certain α-subunits that reside in the outer ring (49, 56). Groll et al. (49) have shown that deletion of the tails opens the gate for substrate entry and that exogenously added N-terminal tail peptide masks the gate, thus preventing proteolysis. Whitby et al. (50) have revealed that the binding affinity provided by insertion of the PA26 C-terminal tails into pockets of 20 S proteasome in the complex structure is used to open the gate. In analogy, the insertion of HslU C-terminal tails into the HslV-HslV interface in the ATP-bound state causes the HslU and HslV rings to twist around their mutual 6-fold axis, opening the HslV pore in a “twist-and-open” mechanism (38). Fig. 8 shows a schematic model for the opening of the HslV pore upon interaction of a HslU tail peptide with HslV. Thus, it is interesting that both bacterial and eukaryotic proteasomes share a similar activation mechanism using the C-terminal tails of their regulatory components.

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