Co-translational Involvement of the Chaperonin GroEL in the Folding of Newly Translated Polypeptides*

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A large fraction of the newly translated polypeptides emerging from the ribosome require certain proteins, the so-called molecular chaperones, to assist in their folding. In Escherichia coli, three major chaperone systems are considered to contribute to the folding of newly synthesized cytosolic polypeptides. Trigger factor (TF), a ribosome-tethered chaperone, and DnaK are known to exhibit overlapping co-translational roles, whereas the cage-shaped GroEL, with the aid of the co-chaperonin, GroES, and ATP, is believed to be implicated in folding only after the polypeptides are released from the ribosome. However, the recent finding that GroEL-GroES overproduction permits the growth of E. coli cells lacking both TF and DnaK raised questions regarding the separate roles of these chaperones. Here, we report the puromycin-sensitive association of GroEL-GroES with translating ribosomes in vitro. Further experiments in vitro, using a reconstituted cell-free translation system, clearly demonstrate that GroEL associates with the translation complex and accomplishes proper folding by encapsulating the newly translated polypeptides in the central cavity formed by GroES. Therefore, we propose that GroEL is a versatile chaperone, which participates in the folding pathway co-translationally and also achieves correct folding post-translationally.

Recent advances in the mechanistic understanding of chaperones have resulted in their classification into two major groups: “holder” and “folder” chaperones. The “holder” chaperones, such as trigger factor (TF) and DnaK, associate with nonnative proteins and thereby prevent their misfolding and irreversible aggregation (1, 2). The “folder” chaperones, such as GroEL-GroES, not only bind nonnative proteins but also complete their folding with the aid of GroES and ATP. It is generally thought that the holder chaperones act co-translationally, whereas the folder chaperones act post-translationally (2, 3). Although this classification is not absolute (e.g. DnaK also stabilizes the newly synthesized polypeptides post-translationally), post-translational involvement of the eubacterial GroEL-GroES has been suggested in recent years on the basis of several in vitro and ex vivo analyses (4–6).

The discovery of overlapping co-translational functions for TF and DnaK originated from the finding that their simultaneous deletion causes synthetic lethality (7, 8). However, recent genetic analyses confirmed that this lethality is abrogated either by growth at low temperature or by overproduction of GroEL-GroES (9, 10). The latter strongly suggests that GroEL substitutes for TF and DnaK by interacting co-translationally with newly translated peptides. A previous study demonstrated that a translating ribosome contains GroEL in addition to TF and DnaK (11), although another study reported that the translating ribosome does not bind to GroEL (12). These conflicting reports prompted us to reevaluate the interaction of GroEL with nascent polypeptides on ribosomes using different methodological approaches. Moreover, since a subset of proteins relies on GroEL for folding (6, 13–15), it remains to be determined how GroEL-dependent substrates rapidly recognize and associate with the chaperonin in the vast cytosol. It is especially unclear how this process is regulated under conditions of DnaK and TF double deletion, since these proteins play an important role in the co-translational folding pathway.

Although in principle in vivo approaches provide a better reflection of the actual working of chaperones in the cell, they present inherent difficulties in distinguishing different chaperone-assisted folding pathways co- or post-translationally (12, 16). Thus, a highly controllable translation-folding coupled system is urgently needed to determine the precise role of each chaperone in the co- and/or post-translational folding processes. To elucidate the involvement of individual chaperones during the translation process, an optimal solution would be the addition of chaperones to a “chaperone-free” translation system. However, complete removal of chaperones and other related factors from a cell-free system are intrinsically difficult because all conventional translation systems use cell extracts in some form (5, 17). To address this issue, instead of employing widely used cell lysates, here we utilize a well defined cell-free translation system, named PURE that only contains essential Escherichia coli factors responsible for protein synthesis (18, 19). The absence of all endogenous chaperones provides ideal conditions for identifying substrates that strictly require GroEL-GroES and for elucidating the individual steps of protein folding that are controlled by GroEL.

MATERIALS AND METHODS

Plasmids and Proteins—The genes encoding target proteins were subcloned from the genome of E. coli strain A19, into the pET20b vector, by using the Ndel and BamHI (or EcoRI) restriction sites. The plasmid pKY206, bearing the GroEL and GroES genes, was kindly provided by Dr. Koreaki Ito. Molecular chaperones (DnaK, DnaJ, GrpE, GroEL, GroES, and TF), their corresponding antibodies, and IgG-horseradish peroxidase conjugates were all sourced commercially or prepared as described previously (19). GroEL(D398A) was purified as described (20). The antiserum to E. coli ribosomal protein L18 was prepared against purified L18 protein.

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‡ The abbreviations used are: TF, trigger factor; TC, translation complex; RT, reverse transcription; RF, release factor.

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**Isolation of Translating Ribosomes from Growing Bacteria**—Cells in exponential growth were harvested and extracted according to the method of Flessel et al. (21, 22), with minor modifications. Mg(OAc)$_2$ was substituted for MgSO$_4$ to restore magnesium concentration. Also, the lysing medium for preparing cytoplasmic extracts was adjusted slightly and comprised the following: 0.2% sodium deoxycholate, 0.5% Brij 58, 100 µg/ml chloramphenicol, 20 unit/µl DNase I, 50 mM NH$_4$Cl, 10 mM Mg(OAc)$_2$, 10 mM Hepes-KOH (pH 7.6). After the crude lysate was centrifuged at 10,000 × g for 10 min, the supernatant was carefully decanted and analyzed by sucrose density gradient centrifugation.

**Enzyme Activity**—Adenosylmethionine synthetase activity was assayed using a standard protocol (24). The cell-free translation reaction was stopped by the addition of puromycin (19). The translation mixture was subsequently added to the assay mixture, containing 100 mM Tris-HCl (pH 8.3), 100 mM KCl, 20 mM MgCl$_2$, 10 mM ATP, and 1.2 mM L-$^3$-labeled adenosylmethionine (55 mCi/mmol; ARC), and a real time filter assay was performed using Whatman P81 phosphocellulose paper. The amount of the catalytic product, adenosyl[$^14$C]methionine, bound to the filter was determined by immersing it in scintillation mixture (22) and reading in a liquid scintillation counter (ALOKA). The ratio of the maximal rate of [$^14$C]-labeled adenosylmethionine synthesis to the soluble amount of the cell-free translated product was calculated as the relative biological activity of the enzyme.

**Precipitation and Western blot Analysis**—Samples collected from the sucrose density gradient centrifugation were precipitated with trichloroacetic acid, followed by alternate washing with diethyl ether (for dehydration) and acetone. The final precipitates were dissolved and subjected to SDS-PAGE. Western blotting was performed to detect the presence of the chaperones and the ribosome protein L18 using appropriate antibodies, as described previously (19).

**Preparation of Translation Complexes**—Single round translation was quenched by the addition of an equal volume of chilled translation buffer. The resultant mixture was immediately loaded onto a cold, 11-ml linear sucrose gradient (10–50%) in standard buffer (20 mM Hepes-KOH, pH 7.6, 6 mM Mg(OAc)$_2$, 30 mM NH$_4$Cl, 1 mM spermidine, 8 mM magnesium acetate, 0.5 mM mercaptoethanol), followed by ultracentrifugation in a rotor SW41Ti (35,000 rpm, 4 h). Upon layering of the mixture by sucrose density gradient centrifugation, it was portioned using a piston gradient fractionator (Towa), and the fraction was monitored at 254 nm in a continuously recording spectrophotometer (AKTA; Amersham Biosciences). The fractionated samples were automatically collected in a 96-well UV plate (Corning) with a fraction collector (Gibson).

**Immunoprecipitation of Translating mRNAs and RT-PCR**—Commercially available magnet beads containing covalently bound sheet antibodies to mouse anti-GroEL monoclonal antibody at 4 °C and subsequently blocked with 0.5% bovine serum albumin in Tris-buffered saline to reduce nonspecific binding in subsequent specific isolation steps. The single round translation reaction mixture was fractionated (Qiagen) with a pair of universal primers containing the T7 promoter sequence at the 5’-end or the T7 terminator sequence at the 3’-end.

**RESULTS**

**GroEL and GroES Are Associated with Nascent Polypeptides in Vivo**—Initially, we examined whether the ribosome undergoing translation is associated with GroEL in growing E. coli cells. Ribosomes were isolated from cytoplasmic extracts prepared from the cells in the exponential growth phase using a sucrose density gradient centrifugation protocol, and the components in the various fractions were analyzed by Western blotting (Fig. 1). The protein content of each loaded ribosome fraction was normalized to the level of ribosomal protein L18, which is present in the 50 S, 70 S, and polysome fractions but absent in the 30 S fraction. The polysomal ribosome fraction contained all three major chaperone systems: TF, DnaK, and GroEL-GroES. Their ribosomal binding may occur via the nascent polypeptide, since the addition of a translation inhibitor, puromycin, which releases translating polypeptides from the ribosome, abolished the interaction between the ribosome and these chaperones. This puromycin-sensitive association of GroEL with the ribosome suggests that GroEL plays a co-translational role in the folding of nascent polypeptides, similar to the known “holder” chaperones (TF and DnaK). However, this interpretation has a potential pitfall. Despite the observed puromycin sensitivity, we could not completely rule out the possibility that it was nascent GroEL polypeptides, rather than GroEL attached to the nascent polypeptide, that we detected by Western blotting, since growing E. coli is known to constitutively translate chaperones (e.g. ~1% of total protein is GroEL). Thus, to confirm that GroEL associates with the ribosome through nascent polypeptides, we employed an in vitro translation system (the PURE system), which is reconstituted with minimal translation components and exogenous chaperones.

**GroEL-GroES Is Essential for Functional Folding of MetK**—In focusing on the role of GroEL in translation, we developed the rationale that the folding of target polypeptides in the translation process is strictly GroEL-dependent, such that these are defined as stringent substrates. According to previous reports (6, 15, 25–27), 16 E. coli proteins were subcloned from the genome and translated in the PURE system, and their solubilities were tested in the presence or absence of chaperones (Table I). When the influence of major chaperone...
Chaperonin-dependent Protein Folding

Table I
Chaperone dependency of target proteins

| Genes | Proteins | Molecular mass | Chaperone-free | Chaperone dependency (solubility) |
|-------|----------|----------------|----------------|----------------------------------|
|       |          | kDa            | Productivity | Solubility | DnaK/J-GriPK | GroEL/ES | Both systems |
| eno   | 2-Phosphoglycerate dehydratase (enolase) | 47 | +++ " | +/− | − | +/− |
| godA  | Glutamate decarboxylase | 53 | + | + | + | + |
| galD  | Galactitol-1-phosphate 5-dehydrogenase | 38 | +/− | + | + | + |
| tdh   | Threonine-3-dehydrogenase | 35 | +/− | + | + | + |
| metF  | 5,10-Methylene-tetrahydrofolate reductase | 33 | + | + | + | + + |
| metK  | S-Adenosylmethionine synthetase | 42 | ++ | ++ | +++ | +++ |
| galY  | α-Tagatose-1,6-bisphosphate aldolase | 31 | + | + | + | +|
| dpaA  | Dihydropicolinate synthetase | 38 | + | + | + | ++ |
| tpiA  | Triosephosphate isomerase | 27 | + | + | + | +/− |
| thiD  | Phosphohydroxypridimine kinase | 29 | + | + | + | +/− |
| upp   | Uracil phosphoribosyltransferase | 20 | ++ | + | + | + |
| rpoA  | DNA-directed RNA polymerase α | 36 | + | ++ | ND | ND |
| mdh   | Malate dehydrogenase | 33 | + | ++ | ND | ND |
| zwf   | Glucose-6-phosphate dehydrogenase | 56 | ++ | ++ | + | − |
| ldhA  | L-Lactate dehydrogenase | 36 | ++ | + | − | + |
| dld   | L-Lactate dehydrogenase | 65 | ++ | + | ND | ND |
| malE  | Malto-binding protein (double mutant) | 41 | + | ++ | + | + |
| foulA | Dihydrofolate reductase | 18 | + | + | + | − |

a +++ , ++ , + , − , and ND mean high, medium, low, no dependency and not determined, respectively.

systems (DnaK and GroEL systems) on the solubility of these newly synthesized proteins was explored, the addition of chaperones increased the proportion of translation products in the soluble fraction. Among these proteins, products of the metK and dpaA genes, which were highly dependent on GroEL-GroES, were considered as potential GroEL-GroES substrates in translation-coupled folding. Indeed, the addition of GroEL markedly suppressed the aggregation of these proteins during translation (data not shown). metK is a structural gene for adenosylmethionine synthetase, which consists of a tetramer of identical 42-kDa subunits (24, 28). Since its enzymatic activity can be easily measured, we used MetK as the subject of further investigations.

Both the DnaK and GroEL systems increased the solubility of translated MetK, although GroEL did so more effectively (Fig. 2A). When translation-coupled folding of MetK was evaluated by analysis of its enzymatic activity, we found that the folding of MetK was remarkably GroEL-GroES-dependent (Fig. 2B). In the presence of GroEL-GroES, MetK folding was 12-fold higher than that observed in the absence of chaperones, with this effect being ATP- and GroES-dependent. In contrast, the addition of the DnaK system failed to enhance the enzymatic activity, although it did result in increased solubility. This result clearly demonstrated that GroEL-GroES assistance is essential for the production of MetK in its native state (data not shown). Since it is well known that the ATP turnover cycle of wild-type GroEL has a duration of ~10 s, we employed a mutant form of GroEL, GroEL(D398A), that can assist protein folding in a similar manner to wild-type GroEL but hydrolyzes ATP very slowly (less than ~2% of the rate of wild-type GroEL) (29, 30), in order to extend the lifetime of the GroEL-MetK complex. As expected, levels of the GroEL-MetK complex greatly increased in the presence of GroEL(D398A).

The direct association of MetK with GroEL and the strict requirement of GroES for MetK folding led us to test whether MetK polypeptides are actually encapsulated inside the GroEL-GroES cavity. The most reliable method for testing this hypothesis is the protease protection assay, in which the encapsulated protein was protected from the proteinases outside the GroEL-GroES cavity (31). Cell-free translation was performed in the presence of GroEL (D398A) alone or with GroEL (D398A) and GroES together, respectively. The resultant translation products were subsequently digested with proteinase K. Proteins synthesized in the presence of GroEL alone were completely digested by the proteinase K, whereas those synthesized in the presence of both GroEL and GroES were resistant to proteinase K (Fig. 2D). The native MetK and intermediate MetK1 forms of the protein also survived proteinase K attack, which probably reflects their stable tight conformation. This indicated that the newly translated MetK is encapsulated into the GroEL-GroES cavity.

**GroEL Assists the Folding of MetK in the Cavity Formed by GroES**—The direct association between MetK and GroEL was investigated by native PAGE. Cell-free translated products, into which [35S]methionine was incorporated, were loaded onto native gradient (5–10%) gels. Several bands with different mobility were observed when translation was performed in the presence of either GroEL or GroEL-GroES (Fig. 2C). We confirmed that all of these radio-labeled bands were derived from full-length MetK polypeptides by analyzing excised bands under two-dimensional SDS-PAGE (data not shown). In addition, the observed mobility of purified recombinant MetK and the GroEL tetradecamer further clarified the locations of the native tetramer MetK4 and the GroEL-MetK complex. Other bands were assigned as an intermediate (possibly a MetK1 dimer) and a denatured MetK2 form. In the absence of GroES, neither the native form nor the intermediate appeared. The enzyme assay results were consistent with the PAGE data, confirming that both GroEL and its co-chaperonin GroES were necessary to produce newly synthesized MetK in its native state.
tion methods. The presence of GroEL in translating ribosome fractions confirms the in vivo analysis (Fig. 1), which indicated that GroEL interacts with nascent peptides.

To obtain more solid evidence that GroEL complexes with TC through nascent peptides, the mRNA in GroEL-bound TC was evaluated in a series of experiments shown in Fig. 3. The metK mRNA was translated in a RF-free translation system and was amplified by RT-PCR after immunoprecipitation of the GroEL-bound TC using anti-GroEL-coated beads. RT-PCR indicated that metK mRNA was extensively amplified when the translation was performed in the presence of GroEL, but it scarcely accumulated in the eluted fraction and was only faintly amplified when translation was performed in the absence of GroEL (Fig. 3D). It appeared that without GroEL, the TC comprising the translating mRNA was almost entirely washed away during the wash steps. Obviously, these observations further indicated that GroEL is associated with the TC, thereby confirming its co-translational participation.

Overproduction of GroEL-GroES Increases the Solubility of MetK in Vivo—Finally, the requirement of GroEL for the in
**Fig. 4. Contribution of GroEL-GroES to MetK in vivo.** A, SDS-PAGE (12%) of cells in which MetK was co-expressed with or without GroEL-GroES. **MW** molecular weight marker; **S**, supernatant; **P**, pellet. **B**, gradient fractions of the cytoplasm in which metK gene expression was detected. **C**, GroEL was immunodetected in the translating ribosomal fractions (monosome and polysome fractions), which were prepared from cells overexpressing the metK gene (**A**, left lanes of S and P).

**Fig. 5. Schematic model of the chaperonin-assisted folding pathway.**

**DISCUSSION**

Here, we provide in vivo and in vitro evidence for the co-translational involvement of the chaperonin, GroEL, in the folding of emerging polypeptides on ribosomes. Our model for co-translational involvement of GroEL is illustrated schematically in Fig. 5. In this model, GroEL or GroEL-GroES binds to the nascent peptide on the ribosome probably at its apical domain, thereby preventing the aggregation and/or misfolding of emerging polypeptides. After termination of translation, full-length proteins can be encapsulated with the aid of ATP and GroES and folded in the cavity of the GroEL-GroES complex. Currently, it is unclear whether GroES participates in this pathway before or after the peptide release from ribosomes. In comparison with its co-translational addition, the post-translational addition of GroEL to the cell-free translation system was rather inefficient in preventing the aggregation of newly synthesized proteins (data not shown). Furthermore, in preliminary experiments, the addition of GroEL and GroES increased the rate of MetK translation, whereas GroEL alone had little effect on translational productivity. This result confirms the co-translational involvement of the GroEL-GroES system in the protein folding pathway as well as implying a co-translational role for GroES in this process. This model may provide a plausible explanation as to how and why the GroEL-GroES system compensates in the co-translational folding process under conditions in which the TF/DnaK systems are double-deleted. Moreover, GroEL is essential for cell viability, suggesting that these chaperones are required for quality control of nascent proteins in cells. It is likely that GroEL plays a pivotal role in the co-translational folding pathway in which DnaK and TF are involved, at least in the case of stringent substrates.

We used an essential protein, MetK, as a model to study the involvement of an essential molecular chaperone, GroEL, in its folding. Of course, here we demonstrated only that GroEL-GroES attached the nascent peptides on ribosomes to conduct the proper folding of active subunits. MetK is composed of four identical subunits. The oligomerization, which is not the issue we addressed in this paper, may take place spontaneously in consequence of the emergence of the active monomers. Although MetK was previously identified as a GroEL-associated protein (6), its GroEL-GroES-dependent folding had never been studied. In vitro experiments using a reconstituted translation system and the exogenous addition of individual chaperones revealed that MetK is a stringent substrate of GroEL-GroES and that GroEL-GroES participates not only in preventing its aggregation but also in enhancing its folding. This role of GroEL-GroES is definitely coupled with the translation process and is crucial for tetramer formation, thereby endowing MetK with enzymatic activity. It was known that metK is an essential gene (26), and since here we found that GroEL-GroES is strictly required for the maturation of its product MetK, GroEL must be indispensable for cell viability. In contrast, the DnaK system increased the solubility of MetK but failed to facilitate its folding, which is consistent with the observation that deletion of DnaK does not induce cellular lethality. We assume that the results obtained in this study point to GroEL-GroES as
being an essential factor in cells, and they also provide an explanation for the growth survival observed upon overexpression of GroEL-GroES in vivo.

The hypothesis that GroEL interacts with polypeptides only after the termination of translation is based on reconstituted biochemical analysis (4), in which the sequential actions of the DnaK and GroEL systems were revealed, as well as on the architecture of the GroEL-GroES complex, which indicates that GroES caps the GroEL cage for substrate encapsulation. Here, using the PURE system, we identified a co-translational interaction between GroEL and its stringent substrate MetK and observed GroEL to be present as a complex with nascent polypeptides released from ribosomes in a puromycin-dependent manner. Although GroEL needs its co-chaperonin, GroES, to accomplish the effective folding of arrested non-native proteins, emerging polypeptides could be held co-translationally by GroEL alone. The Group II eukaryotic chaperonin TRiC/CCT was reported to bind de novo polypeptides in a co-translational manner (33–35). Other than the existence of co-factors, Group I (eubacterial GroEL family) and Group II chaperonins resemble each other structurally, suggesting that they would have similar potential to associate with nascent polypeptides. Moreover, co-translational folding in prokaryotes is considered somewhat unlikely given that bacterial translation occurs at a higher rate than the eukaryotic process (5, 17, 38, 39). Comparison of the endogenous GroEL concentration in the prokaryotic cytosol with that of TRiC in eukaryotes reveals that GroEL is much more abundant than TRiC in cells, although both chaperonins assist in folding a similar amount of proteins (39). Although the translation speed in prokaryotes (15–20 residues/s) (34, 39), the concentration of GroEL (~3 μM) (14, 37) is ~10-fold higher than that of TRiC (0.3–0.5 μM) (34, 39). Indeed, our in vitro translation experiments, in which 0.1–1 μM GroEL was present, strongly suggested the interaction of GroEL with the growing polypeptide on the ribosome. Thus, the post-translational participation of GroEL that was proposed previously on the basis of its limited cytosolic concentration might warrant reconsideration. In addition, if only one GroES molecule binds to GroEL, one of the two polypeptide binding regions in GroEL remains accessible. Therefore, in this model, the interaction between GroEL and a nascent polypeptide on the ribosome would not be hindered.

Of the more than 4000 proteins encoded on the E. coli genome, there is little information on the relationship between substrates and their chaperones. For example, how are natural proteins identified and subjected to distinct folding pathways? Which features of the natural substrates are recognized by each chaperone? How many proteins are folded with the assistance of GroEL-GroES co- or post-translationally? Clearly, many questions still remain. Nevertheless, we believe that the combination of the reconstituted system and in vivo approaches will provide a technology platform for the genome-wide screening of stringent chaperone-dependent substrates and will significantly contribute to the elucidation of chaperone networks and their roles in cell maintenance.

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