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Review article

The role of molecular chaperone CCT/TRiC in translation elongation: A literature review

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ABSTRACT

Protein synthesis from mRNA is an energy-intensive and strictly controlled biological process. Translation elongation is a well-coordinated and multifactorial step in translation that ensures the accurate and efficient addition of amino acids to a growing nascent-peptide chain encoded in the sequence of messenger RNA (mRNA). Which undergoes dynamic regulation due to cellular state and environmental determinants. An expanding body of research points to translational elongation as a crucial process that controls the translation of an mRNA through multiple feedback mechanisms. Molecular chaperones are key players in protein homeostasis to keep the balance between protein synthesis, folding, assembly, and degradation. Chaperonin-containing tailless complex polypeptide 1 (CCT) or tailless complex polypeptide 1 ring complex (TRiC) is an essential eukaryotic molecular chaperone that plays an essential role in assisting cellular protein folding and suppressing protein aggregation. In this review, we give an overview of the factors that influence translation elongation, focusing on different functions of molecular chaperones in translation elongation, including how they affect translation rates and post-translational modifications. We also provide an understanding of the mechanisms by which the molecular chaperone CCT plays multiple roles in the elongation phase of eukaryotic protein synthesis.

1. Introduction

Protein synthesis is a fundamental process that is conserved across all domains of life. It is controlled by ribosomes, which are RNA-protein complexes responsible for the biosynthesis of proteins. The accurate folding of newly synthesized proteins are the final critical step in the conversion of genetic information into functional proteins. Protein translation elongation is a process that ensures the efficient folding of newly translated peptides to convert one-dimensional genetic information into functional three-dimensional structures [1]. Recent research has demonstrated that translation elongation is influenced by a considerable portion of factors, including the presence of molecular chaperones. Molecular chaperones are nano-machines that facilitate protein folding by undergoing energy-dependent (ATP) motions that are temporally and spatially coordinated due to complex allosteric regulation. Among

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these, Chaperonin-containing tailless complex polypeptide 1 or tailless complex polypeptide 1 ring complex (CCT/TRiC) (Hereafter, the unified use of this complex will be abbreviated as CCT) is an essential heterodimer required for the folding of various essential proteins [2]. Because of the unique structure, CCT/TRiC directly interacts with emerging peptides to protect them from degradation or aggregation, and facilities the proper folding program [3].

CCT is necessary for the folding of the abundant cytoskeletal proteins actin and tubulin, which in turn form the assembly of microfilaments and microtubules. CCT is also involved in the folding of a number of other protein substrates, and some CCT subunits have been shown to function as monomers [4]. Since observations using RNAi screening in worms more than a decade ago, linking the CCT subunit to the aggregation of polyglutamine bundles, the role of CCT as a potential regulator of protein aggregation has begun to emerge [5]. CCT is also involved in human diseases such as cancer and viral infections, making it a valuable potential therapeutic target.

In this review, we will discuss the structure and the role of the CCT in translation elongation. We will also explore the impact of CCT on translation rates and post-translational modifications (Fig. 1). Understanding the role of molecular chaperones in translation elongation will provide insights into the mechanisms of protein synthesis and folding, as well as their implications in cellular processes and disease.

CCT is a key molecule to maintain the balance between protein synthesis, folding, assembly and degradation, and can promote the correct translation folding and translation extension of proteins through its structural function and post-translational modification.

2. Translation elongation

Gene expression is a multi-step process involving transcription, mRNA degradation, translation, and protein degradation. In cellular systems, the acquisition of functional protein products is a tightly regulated process that is accomplished by the ribosome in conjunction with a large number of protein factors and associated ribosomal protein factors. To sustain life, the information encoded in genetic material needs to be correctly decoded. Therefore, the translation process is an important studying object in molecular biology.

The protein translation process consists of four major stages: initiation, elongation, termination, and ribosome recycling [6]. Translation elongation also known as translation extension is a complex process that requires the synergistic action of multiple components such as mRNA templates, tRNAs, ribosomes, and many *trans*-acting factors and regulators, which are also dynamically regulated by cellular state and environmental determinants [7,8]. Recent paradigm-shifting studies using ribose sequences in combination with other methods have highlighted the importance of translation extension in protein synthesis [9]. Post-transcriptional modifications such as mRNA methylation are known to modulate translation. M^6A related proteins YTHDF1 and METTL3 improve translation efficiency by recruiting mRNA translation initiation factors [10,11]. Studies using prokaryotic systems have shown that this modification also affects translational extension dynamics. In this review, we will first address the primary criteria as molecular chaperone CCT that determine translation extension.

3. Molecular chaperone CCT

A class of proteins known as molecular chaperones serves a common purpose but are not sequentially related to one another. The molecular chaperone family is made up of massive ketone double rings that bind to non-natural proteins in the central cavity they create. They rely on ATP to release the substrate protein which they have wrapped in the lumen and fold, effectively interacting with other proteins and assisting other structures containing polypeptides to complete correct assemble and achieve functional conformation [12]. When assembled, chaperones are separated from the proteins they interact with and do not constitute components of the

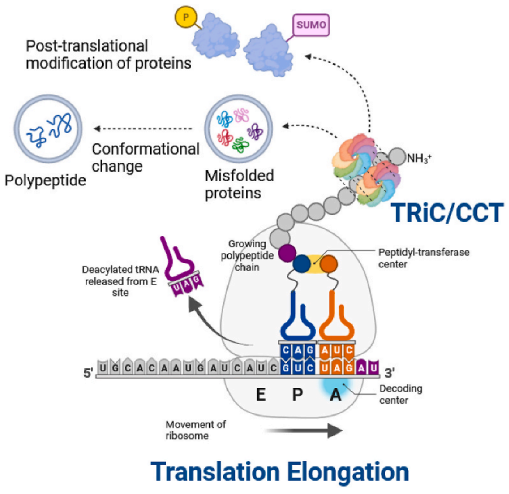

Fig. 1. Overview of the role of chaperone CCT in translation elongation.

interacting proteins when performing their functions [13]. Molecular chaperones are important for the formation of functional proteins. When proteins are folded incorrectly, they no longer doing their job, they can even clump together into useless clumps, which lead to a host of diseases such as Alzheimer's and Parkinson's [14]. Molecular chaperones help proteins fold correctly, inhibit protein aggregation and precipitation, and mediate the degradation of misfolded proteins so that proteins can successfully complete the folding and become functional proteins [15].

The chaperone proteins are divided into two subfamilies: molecular chaperone I group, which includes the mitochondrial and chloroplast-specific HSP60 and HSP10 as well as the bacterial chaperone GROEL and its helper chaperone GroES. The chaperonins from archaea and eukaryotic cytosol belong to the second, distantly related chaperonin family, also known as group II.

The eukaryotic chaperone protein CCT is the main object of this discussion. The eukaryotic chaperone CCT is a highly conserved and essential chaperone protein that is essential for cell survival. Molecular chaperone CCT is an ATP-dependent bicyclic protein machine. It is able to use ATP to hydrolyze about 10% of the proteome, which contains many essential proteins such as cell cycle regulators and cytoskeletal components and cell cycle regulators, thereby mediating the folding of members of the eukaryotic cytoskeletal protein family [16]. The CCT chaperone protein is a 1-MDa polymeric complex made up of 16 CCT1-CCT8 subunits arranged in a double-loop barrel shape [17]. Table .1 displayed the physicochemical properties of each subunit of the molecular chaperone CCT. The complex is characterized by a stacked structure of two eight-membered rings that gives it a flexible overall coverage and is opened and closed by ATP binding and hydrolysis cycles [18,19]. Each subunit of CCT and other chaperone proteins can be divided into three regions: the equatorial region, which is where most intra-ring and inter-ring interactions occur; the apical region, which is thought to be in charge of substrate binding; and an intermediate region, which serves as a linker between the other two regions. Protein folding is facilitated by conformational changes in the CCT structure brought about by ATP binding and hydrolysis on the CCT subunit [20]. The nucleotide binds to the cavity while the unfolded peptide binds to the folded cavity when the CCT is in the open conformation. The chamber closes as a result of the motion of each subunit's lengthy alpha helical process when ATP binds and reaches the ATP hydrolytic transition state, trapping the protein inside [21]. This trap assists in folding by limiting the conformational degrees of freedom and affecting the folding trajectory of the peptide. After ATP hydrolysis, the compartment opens, and if the protein reaches a natural fold and loses contact in the compartment, it is released. Thus, CCT plays an important role in assisting the folding of structural domain proteins and in the assemble of folded proteins in complexes.

Over the past ten years, increasing amounts of evidence have shown that the issue of protein folding has grown more complex. Cells have evolved a complex mechanism to ensure that proteins can efficiently arrive at their inherent state, and through this complex molecular chaperone cellular mechanism and the input of metabolic energy to help the newly synthesized peptides fold, to some extent avoiding stress-induced degradation of existing proteins [22]. At present, new ideas of protein folding are emerging, that is, from the ribosome to the master chaperone system, new proteins may interact with some factors that regulate their folding pathway. The translation system (ribosomes and related factors) is the cell factory for synthesizing proteins. Ribosome play a key role in this process as they ensure the translation of mRNA into linear polypeptides [23]. But the newly altered peptide still needs to be folded into a distinct three-dimensional structure. Hence, knowing what elements are essential to the development of the new proteins become an intriguing question.

4. Structure of CCT affects the dynamic process of translation elongation

Anfinsen's pioneering research in the 1950s demonstrated that a tiny protein could spontaneously fold in the absence of additional stimuli in vitro [24,25]. Recent research has provided extensive insights into the general principles of protein folding throughout the last 50 years. The unifying mechanism of protein folding, however, remains difficult [26,27]. As far as we know, Protein folding is a complex process during translation elongation that requires the assistance of molecular chaperones.

In recent decades, numerous biochemical studies have shown that ribosomes cannot remain static, but are dynamic. Recent

Table 1
Physicochemical properties of each subunit of the molecular chaperone CCT.

	Formula	Number of amino acids	Theoretical pI	Instability index	Aliphatic index	GRAVY
CCT1	C5057H8448N1668 O2120S303	1668	5.01	36.65	30.94	0.726
CCT2	C4847H8091N1605 O2031S303	1605	5.01	40.13	30.16	0.731
CCT3	C4809H7985N1635 O1984S380	1635	4.96	40.48	28.32	0.833
CCT4	C4882H8149N1617 O2040S324	1617	5.00	38.49	38.49	0.756
CCT5	C4804H7987N1623 O1992S342	1623	4.98	37.86	29.57	0.794
CCT6	C4760H7929N1593 O1986S306	1593	5.01	42.20	30.38	0.752
CCT7	C4801H7975N1629 O2005S378	1629	4.96	37.49	25.48	0.764
CCT8	C4988H8334N1644 O2089S297	1644	5.01	42.19	31.33	0.732

advances in the study of ribosome structure have begun to reveal the remarkable conformational flexibility of ribosomes. Major conformational changes are recognized to be associated with each phase of translational expansion [28,29]. Emerging peptides appear as carriers during synthesis and are prone to misfolding and aggregation, thus lacking the information needed to complete the folding until the end of translation. Eukaryotes, however, have a complex and conserved ribosome-associated partner network called CLIPS (chaperones linked to protein synthesis), the partner network associated with protein synthesis, which bind and process new strands as they emerge from the ribosome exit tunnel [30,31]. CCT is the structurally diverse primary chaperone protein in the CLIPS network. CCT is an essential hetero-oligomer chaperone protein that contributes to the folding and maturation of about 10% of cytoplasmic proteins. Post-translational CCT is capable of co-binding to a specific set of substrates and plays a key role in the folding of cytoskeletal proteins, actin and tubulin, as well as several proteins essential for the orderly progression of the cell division cycle [32–34]. Meanwhile, CCT also plays an important role in maintaining protein homeostasis [4,35,36].

CCT is ring-shaped, with a central folding chamber that encapsulates its substrate [37,38]. In the open state, CCT binds to unfolded polypeptides through apical domains; Atp-induced cap formation releases the substrate into the closed chamber where folding is thought to occur [39]. While the determinants of substrate selectivity in vivo for CCT remain unclear, recent studies have revealed a critical role for subunit diversity in substrate binding and folding. The H11-PL interface of each subunit apex domain of CCT has a unique combination of polar, charged, and hydrophobic residues, resulting in a diversity of substrate motif types recognized in its substrates. Due to the plasticity of apical domain-substrate motif interactions, different substrates can bind to the same apical domain in different configurations, and unique substrate binding motifs enable different substrates with no similar sequences to bind, so that a wider range of substrate sequences can be recognized [40]. Through the interaction of a specific combination of polar and non-polar contacts between a specific sequence or structural element and the eight subunits, substrates recruited to the surface of the apical domain will also orient the substrate polypeptides in the cavity and promote a specific topology that may produce folding. The division of the substrate binding surface by charge and non-polar contact may also play a role in substrate recruitment by regulating the rate of association and dissociation [41,42]. Thus, these eight subunits are thought to coordinate multivalent interactions with the substrate, thereby preventing aggregation and initiating the substrate conformation for subsequent folding.

Since many CCT substrates have complex topologies, a key aspect of CCT-assisted folding may be to facilitate the formation of high-contact order interactions that are difficult to form with simpler chaperones, or with chaperones that expose a range of the same hydrophobic binding sites [43]. Depending on the topological properties of the nascent chain, CCT can be specifically recruited to the coding region of the nascent chain at a later stage, and CCT binds to domain-specific folded intermediates, exposing a hydrophobic patch consisting of discontinuously translated hydrophobic beta chains. Binding CCTs at the ends of these domains can stabilize these intermediates in a protected CCT compartment environment by promoting the folding of intact domains. After completing the translation of the folded element, the CCT separates and buries the hydrophobic surface within the core of the folded domain [44]. In addition, in organisms containing CCT-like chaperone proteins, subunit diversity was positively correlated with the size of its proteome, suggesting that subunit diversity of CCT was associated with proteome amplification in eukaryotes [45]. This raises the possibility that folding mechanisms determine the size of the proteome. Once the substrate is released into the chamber, the CCT can assist in folding. The asymmetric charge distribution in the room may also aid in folding, for example, by separating the charged regions of peptides that are normally exposed on the surface, while allowing the formation of a collapsed hydrophobic core. Constraints within the GroEL-ES cavity have been shown to enhance folding by providing geometric constraints on possible folding paths [46]. Theoretical studies have also shown that confined water in the polarized cavity leads to an increase in the hydrophobic effect, which drives production folding [47]. Since most of the above mechanisms come from the study of bacterial chaperone proteins, we hypothesized that the structural conformation of CCT affects the dynamic process of translation extension, but the specific mechanisms driving folding in the CCT cavity remain to be determined.

5. Molecular chaperone CCT affects translation elongation rates

Gene expression requires ribosomes to translate mRNA sequences into peptides. Although many features of this process have been well described, there are still some mechanisms that control the rate of translation waiting to be discovered, especially at the genomic scale [48,49]. The rate of protein translation is mainly determined by the rate of translation initiation and translation extension. The translation elongation rate is influenced by many factors, such as codon preference, mRNA secondary structure, and SD-like sequence. If there are more rare codons and SD-like sequences in genes, and rich in mRNA secondary structure, translation will be slowed down or even paused, thus affecting the expression of proteins. However, the optimal expression effect is not achieved with high translation rate, which may increase the possibility of misfolding peptide chains to form inactive and insoluble inclusion bodies. This is because the maintenance of protein activity is closely related to its spatial structure and the secondary bonds that maintain these structures, and the elongation of peptide chains directly affects the formation of protein secondary structures.

Most proteins must maintain a well-defined two-dimensional and three-dimensional structure in order to function. It is well known that there is a conserved genome-wide codon use-dependent negative correlation between protein abundance and length, suggesting that optimal codon use is a mechanism that allows efficient production of large proteins essential for cellular function [50]. The folding pathway that induces the three-dimensional structure of proteins has been characterized primarily through the use of model substrates that fold rapidly spontaneously and reversibly in vitro [51]. However, ribosome effects, polypeptide elongation, molecular crowding, and co-translational interactions with cellular companions can influence folding energy patterns and folding outcomes [52]. Thus, molecular chaperons and their binding partners regulate cellular protein homeostasis under all growth conditions and constitute protein homeostasis networks.

Recent studies using SERPs have identified about 500 proteins in yeast that co-translate with CCT. They are primarily cytoplasmic

and nucleoproteins with complex folding intermediates that can be difficult to fold. Once an almost complete domain emerges from the ribosome exit site, CCT binds to these substrates. CCT is an essential heterooligomeric chaperone protein that binds jointly or post-translative to a selected set of substrates and is required for folding of many essential proteins.

In the neonatal polypeptide chain, chaperone proteins CCT and Hsp70 can be sequentially recruited to specific sites within the domain coding region of the selected neonatal polypeptide. Hsp70 first binds to selected binding sites of the entire domain, while CCT binds later after the emergence of an almost complete domain that exposes the unprotected hydrophobic surface [53]. This suggests that the transient topological properties of newly folded intermediates drive the association of sequential partners. Co-translation recruitment of CCT and Hsp70 is associated with slower translation elongation. However, CCT and Hsp70 balance chaperone binding dynamics through co-translation of folded intermediates and optimize the local elongation of the nascent polypeptide chain [54]. The slowing down of the elongation stage also contributes to the quality control of cotranslational proteins, helps to reduce the co-translational ubiquitination and degradation of new peptide, and ensures stability; Sometimes "less is more" in protein synthesis [55]. Further comparisons with Hsp70/Ssb cotranslational binding sites suggest that CCT is associated with newborn chains and functions after Hsp70 binding, thus providing a bridge between cotranslational folding and post-translational folding events. This suggests that CCT recruitment is coordinated by the integration of translation dynamics with the specific properties of folding intermediates produced by cotranslation. Due to the formation of specific types of topologically complex folding intermediates, CCT usually correlates as soon as an almost complete domain appears.

Translation dynamics have become an important, though poorly understood, determinant of the fate of nascent chains. Variations in local elongation were determined by analyzing the abundance of ribosome protective readings during translation on transcripts, since an increase in ribosome occupancy relative to adjacent codons indicates a slowing of elongation. In vivo extension kinetics optimizes the production of protein folding. This local deceleration may contribute to the recruitment of CCTs, or it may balance the dynamics of mate recruitment and the formation of folded intermediates. Disrupting this balance may impair partner-mediated folding, providing a mechanical explanation for codon optimality increasing the likelihood of misfolding of the new chain. Thus, folding the nascent chains can generate the power to overcome the ribosomal block [56], conjugation or domain folding may also alter the translation rate [57].

CCT is recruited on the polypeptide chain during translation extension, optimizing the codon encoding rate to ensure that the protein can be translated correctly. It is essential for promoting the folding of nascent polypeptide chains and maintaining protein quality control.

6. Effect of CCT interaction with translation factors affects translation elongation fidelity

In cells, many proteins begin to fold as they attach to the ribosome [58,59]. Even some secondary elements or small protein domains may be fully folded within the ribosomal exit tunnel [60]. It is not clear how ribosomes affect the folding, thermodynamic stability, and net charge of protein domains of different sizes. Since polypeptide chains emerge from ribosomal vectors, chain linkage may have important effects on co-translational folding. By studying the separation region, it was found that changing the separation of residues on the polypeptide chain while maintaining their spatial contact may affect the stability and folding pathway of the protein [61]. The initiation of cotranslational folding in the MATH region of the ribosome can be influenced by polypeptide chain linkage. Small intact beta domains often form part of larger multi-domain proteins, and in the case of flaky foldability, initiation of co-translational folding may occur in MATH to prevent the accumulation of partially folded structures that can lead to misfolding or aggregation [62]. Thus, there is a direct correlation between the size of the protein and the location of the ribosome exit tunnel during protein folding, as well as the thermodynamic stability and tension generated on the nascent chain during folding. The co-translational

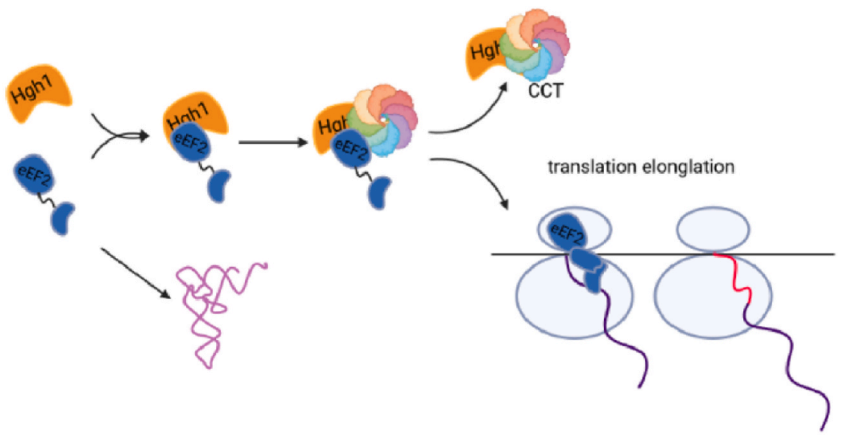

Fig. 2. The structure of CCT promotes translation elongation. With the help of chaperone protein Hgh1, CCT and Hgh1 form a multi-partner complex with eEF2, and CCT and Hgh1 are involved in eEF2 folding. When folded properly, eEF2 can fulfill the role of translation extension. In the absence of this complex component, eEF2 is unstable and forms aggregates in the cell.

folding process provides a further level of protein regulation [63].

CCT interacts with a variety of peptides that play a role in many cellular processes. With the help of CCT, misfolding and toxic protein aggregation can be effectively avoided [64,65]. Since the translated cell environment has a significant impact on CCT specificity and the chaperone can recognize a wide variety of structural conformations, it is possible that CCT works to aid in the folding of various structural protein families [42,66]. Eukaryotic elongation factor 2 (eEF2) is an abundant and essential component of the translation machinery. It is a 93 kDa protein consisting of six domains and a highly conserved GTPase that controls mRNA translocation during translation through GTP hydrolysis [67]. CCT is capable of assisting eEF2 folding. 136 CCT substrates have been identified in yeast through proteomic analysis and genomic approaches, among which, eEF2 is the most abundant CCT client. The highly conserved protein Hgh1 in yeast cells (FAM203 in humans) is a chaperone protein that binds to the dynamic central domain III of eEF2 via a bipartite interface and cooperates with CCT in eEF2 folding. In the absence of Hgh1, much of the newly synthesized eEF2 is degraded or aggregated [68]. Proteomic screening showed interactions with eEF2 and CCT subunits Cct6 [69], and ternary complexes were formed between eEF2, CCT and Hgh1, supported by co-chaperones Hgh1. Hgh1 binding recruits CCT to the C-terminal eEF2 module for encapsulation folding and prevents ineffective interactions of domain III, thus allowing efficient folding of the N-terminal GTPase module. The folding of eEF2 is completed upon dissociation of CCT and Hgh1, thus improving the translation fidelity problem [70] (Fig. 2).

EIF3 (Eukaryotic Initiation factor 3) is the most abundant and complex factor in eukaryotic mRNA translation factors. In mammals, eIF3 is composed of 13 distinct peptide subunits, of which 5 subunits A, B, C, G, and I are conserved and required from yeast to mammals. Electron microscopy (CRYO-EM) studies have shown that the conformational change of eIF3 occurred during the initial reaction, which is consistent with the persistence on 80S ribosome [71,72]. On 80S ribosomes, EIF3 enables vertical expansion of the function of selected mRNA-encoding membranes through physical interactions with ribosomes, and translational expansion of eIF3e functions is essential for mitochondrial physiology and skeletal muscle health in the elongation phase of eukaryotic protein biosynthesis, the structure and conformation of several acting factors are integral [73]. CCT effectively promotes the correct folding of eIF3h and eIF3i by binding to newly synthesized eIF3b. CCT, which is required for the correct folding of the eIF3h and eIF3i subunits, indirectly affects gene expression through eIF3i overexpression, enhancing CAP and IRES (internal ribosome entry fragments) - dependent translation initiation, while eIF3h overexpression selectively increases IRES-dependent translation initiation [74].

CCT can bind tightly or reversibly to misfolded or aggregated proteins by acting on multiple translation-related factors. After CCT binding, the wrong proteins will be degraded and depolymerized. Therefore, CCT interacts with these translation initiation factors and translation extension factors to promote proper folding of peptides, as well as promoting translation extension, maintaining protein homeostasis and preventing protein aggregation [75–77].

7. CCT influence translational elongation by post-translational modifications

Among the different biological macromolecules, proteins show the greatest functional and structural changes. Proteins determine most cellular and physiological processes such as metabolism, catalysis as well as signaling and movement, and they are important players in homeostasis and disease development. However, alternative splicing of transcripts and extensive post-translational modifications (PTMs) greatly enrich this basic framework [78]. Current studies have shown that the total number of protein types generated by splicing and PTMs is at least tens of millions. PTMs are covalent, enzymatic or non-enzymatic attachments to specific chemical groups and amino acid side chains. The total number of different types of PTMs has exceeded 300, and the most studied non-protein PTMs remain enzyme-catalyzed phosphorylation, acetylation, methylation, glycosylation and palmitoylation, as well as non-enzyme-catalyzed glycosylation and nitrosylation. In addition to classical ubiquitination, modifications of other ubiquitin-like molecules are also receiving increasing attention.

PTMs are also consist of individual polypeptides or protein domains coupled by isopeptide bonds. PTMs can occur on specific amino acids located in the regulatory domain of the target protein that control the stability of the protein [79]. During translation, PTMs can act as signals to accelerate protein degradation or to prevent degradation and stabilize proteins. Evidence accumulated in recent years suggests that the amount of mRNA modification increases, leading to translational output. mRNA modifications affect direct translation machines by affecting translation initiation, extension, and termination, or by altering mRNA levels and subcellular localization. All biomolecules (proteins, RNA, DNA, sugars and lipids) are covalently modified after synthesis, and a large number of downstream signaling pathways are affected by PTMs [80,81]. Therefore, PTMs plays an important role in the translational extension of proteins.

In recent years, Some proteins include the cytoskeletal proteins alpha - and beta-actin, actin associated proteins (central elements), alpha -, beta - and γ-tubulin, von hipel - lindau tumor suppressors, histone deacetylases (HDAC3, Set3p, and Hos2p), and cell cycle regulators (Cdc20p and Cdc55p) have been shown to depend on the biogenesis of chaperone CCT [82]. Proteomic and genomic approaches identified 136 protein/gene CCT interaction networks, including linkages to nuclear pore complexes, chromatin remodeling, and protein degradation [83]. CCT has previously been shown to contribute to the biogenesis of the SET3 histone deacetylase complex, thus identifying the role of CCT in chromatin modification. Therefore, CCT may contribute to biosynthesis of several histone deacetylase complexes [84]. This suggests that chaperone proteins influence chromatin biology and epigenetics to a previously unrecognized extent, similar to the recently discovered Hsp90 [85].

CCT participates in histone methylation (COMPASS complex; Paf1-rnapii complex), histone acetylation (SAGA complex), histone deacetylation (Rpd3 complex; Set3 is complex; Type II HDAC complex), chromatin remodeling (i.e., Swr1 complex; SWI/SNF complex) interacts with proteins involved in telomere maintenance, such as Yku80p and Pif1p [86]. Proteins involved in chromatin modification are usually located within the nucleus, meaning that CCTs perform the assembly function of protein complexes within the nucleus, or assist in the folding or assembly of nuclear proteins within the cytoplasm before they pass through the nuclear pore. Therefore, CCT

may be involved in the folding/assembly of the nuclear pore components themselves, thereby indirectly promoting the occurrence of protein translation extension. CCT can guide the nucleoprotein on the ribosome to the NPC and release it directly into the pore in a state suitable for nuclear transport, or CCT can transport the NPC to perform protein folding/assembly functions within the nucleus, which is consistent with the reported nuclear localization of the CCT subunits [87].

mRNA output is a key step in gene expression and directly affects the development of eukaryotic cells [88]. The transcriptional output (TREX) complex mainly mediates the transport of mature mRNA from the nucleus to the cytoplasm. As a component of the TREX complex, the THO complex (THOC) is involved in the splicing, extension, and nuclear export of nascent RNA. Relevant studies have shown that CCT interacts with THOC3, and CCT8, CCT6A, and CCT2 are the first three proteins associated with THOC3. Abnormal expression of THOC can alter the quality control of mRNA output and affect transcription [89]. Further studies will reveal the exact role of CCT in nuclear protein folding, transport, and/or nuclear pore function, as well as the interaction of CCT with epigenetic modified proteins of the nascent polypeptide chain, thereby promoting the extension of the nascent polypeptide chain, i.e. maintaining the correct formation of 3D proteins.

CCT has been found to interact with PTMs and influence translation elongation. CCT can be involved in histone modification, chromatin remodeling, and other processes that affect gene expression. The interaction between CCT and PTMs can regulate translation elongation, influence mRNA levels and subcellular localization.

8. Discussion

Translating mRNA into protein and folding the resulting protein into its active form is a process in almost every cell and represents the cell's single largest energy investment. Methods based on ribosome analysis have revolutionized our ability to monitor protein synthesis in vivo, enabling us to determine the start, stop, and readout of almost all encoded mRNA and protein frameworks, chaperone participation, subcellular targeting, and translation rates per cell. Nevertheless, important technical and conceptual issues remain. How chaperones participate in the process of peptide folding, protein synthesis, and how they play the important role in protein homeostasis is still unclear.

The eukaryotic solute chaperone protein CCT binds to newly synthesized eIF3b and promotes the correct folding of eIF3h and eIF3i. Three interatomic studies have suggested a linkage between eIF3 and CCT. In vitro associated novel translated proteins identified eIF3i bound to TAP (tandem affinity purification) -tagged CCT complex for MS analysis. RNA-seq on *Saccharomyces cerevisiae* has identified several translation initiation components, including eIF3a and eIF3i. Recently, evaluation of the eIF3 interatomic identified six of the eight CCT subunits with "high confidence" associations with eIF3. In addition, in vitro recombination of eIF3 suggests that molecular chaperones may also be required for complete correct assembly of the eIF3 complex in eukaryotic cells [90]. These studies demonstrate the requirement of the chaperone machinery for the correct folding of essential components of the translational machinery and provide further evidence for the close interplay between the cellular environment, cell signaling, cell proliferation, chaperone machinery, and translational apparatus.

At the same time, some CCT subunits have been proved to function in their monomer state, so the expression level of eight CCT subunits and the assembly state of chaperone oligomers will be important factors to determine the degree of CCT influence on translation elongation [91]. Stacking nascent strands can create forces to overcome ribosome stalling, and chaperone binding or domain folding may also alter translation rates [56]. The slight acceleration at the initial point of the CCT and Ssb binding sites may indicate that initial chaperone recognition may help pull the nascent strand and accelerate translation.

Co-translational misfolding events may also disrupt this equilibrium by accumulating intermediates with enhanced chaperone binding, which may deplete the pool of available folding capacity. These considerations may prove crucial for understanding protein homeostasis dysfunction in the context of aging or disease. Changes in CCT subunit expression also occur in aging and several neurodegenerative diseases [92].

In this literature review, we have discussed the role of molecular chaperone CCT in translation elongation. CCT plays a crucial role in protein folding and maintaining protein homeostasis. It interacts with nascent polypeptide chains and assists in their folding, thereby promoting the correct translation folding and translation extension of proteins. The interaction between CCT and polypeptide chains is influenced by various factors, including the cellular environment and the specific properties of the folding intermediates. CCT can also influence translation elongation through RNA modification. Therefore, not only does molecular chaperone CCT play a role in translation elongation, but the study of the subunits of CCT also greatly increases the potential of using CCT-mediated therapy to treat targeted protein misfolding diseases [93,94]. Understanding the role of CCT in translation elongation and RNA modification will provide insights into the mechanisms of protein synthesis and folding, as well as their implications in cellular processes and disease.

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Ethics approval and consent to participate

Review and/or approval by an ethics committee was not needed for this study, because this work is a review of the literature and does not address the ethical considerations of animal, cell, and human experimentation.

Data availability statement

This is a systematic review; therefore, all data are include in the manuscript.

CRediT authorship contribution statement

Yueyue Que: Writing – review & editing, Writing – original draft, Visualization, Validation. **Yudan Qiu:** Data curation. **Zheyu Ding:** Formal analysis. **Shanshan Zhang:** Validation. **Rong Wei:** Funding acquisition. **Jianing Xia:** Methodology. **Yingying Lin:** Writing – review & editing, Visualization, Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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