

## Protein Folding in the Cell

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### ABSTRACT

*In vitro* refolding studies are considered as a good model to understand the mechanism by which polypeptide chain acquires unique three dimensional structure in the cell. However, the intracellular environment is highly crowded containing about 300-400 mg/ml of macromolecules. These conditions would promote improper associations among protein molecules leading to aggregation. This eventually led to the discovery of molecular chaperone that revolutionized the concept of protein folding in the cell. Molecular chaperone is defined as any protein that interacts, stabilizes or helps a non-native protein to acquire the native structure but is not a part of the final structure. Chaperones that participate in protein biogenesis primarily recognize exposed hydrophobic surface of protein and promote their folding through ATP-regulated cycles of binding and release. Failure of the chaperone network to maintain proteostasis, i.e. the conformational integrity of the cellular proteome, may results in the manifestation of pathological states including Parkinson's disease, Huntington's disease, Alzheimer's disease and Amyloid lateral Sclerosis disease, in which proteins misfold and are deposited as aggregates. In view of above, in this review, I have discussed current status of protein folding in the cell with special reference to chaperone pathways in *de novo* folding, chaperones acting downstream of the ribosome, proteostasis network and proteostasis network as drug target.

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**Key words:** Molecular Chaperones; Protein folding in the cell; Protein Disulfide Isomerase; Peptidyl Prolyl Isomerase; proteostasis; proteostasis network

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### Abbreviations

ATP: Adenosine Tri-Phosphate;  
CCT: Chaperonin-Containing TCP-1;  
CFTR: Cystic Fibrosis Transmembrane Conductance Regulator;  
ER: Endoplasmic Reticulum;  
ERAD: Endoplasmic Reticulum-Associated Degradation;  
FKBP: FK506-binding proteins;  
GimC: Gim Complex;  
Hsc70: Heat shock cognate 70;  
HSR: Heat Shock Response;  
NAC: Nascent-chain-Associated Complex;  
NEFs: Nucleotide Exchange Factors;  
PDI: Protein Disulfide Isomerase;  
PN: Proteostasis Network;  
PPI: Peptidyl-Prolyl Isomerase;  
PR: Proteostasis Regulator;  
RAC: Ribosome-Associated Complex;  
TCP-1: Tailless Complex Polypeptide-1;  
TF: Trigger Factor;  
TriC: TCP-1 Ring Complex;  
UPR: Unfolded Protein Response.

### INTRODUCTION

Protein folding is a complex process in which the neighboring and distant amino acid residues of a polypeptide chain adhere to each other to give rise native structure in which protein exhibits

distinct biological activity. The main processes that underlie protein folding have been mainly deduced from *in vitro* studies. Thus, *in vitro* refolding is considered as a good model to understand the mechanism by which polypeptide chain acquires unique three dimensional structure in the cell. However, the intracellular environment is highly crowded containing about 300-400 mg/mL of macromolecules<sup>[1]</sup>. The crowded environment affords many opportunities for improper associations. To overcome these hurdles, cell has evolved molecular chaperones and enzymes [peptidyl-prolyl isomerase (PPI) and protein disulfide isomerase (PDI)] for preventing misassociations among protein molecules and catalyzing proper folding reaction respectively. Molecular chaperone is defined as any protein that interacts, stabilizes native conformation or helps a non-native protein to acquire native state but is not an integral part of the final structure. Chaperones that participate in protein biogenesis primarily recognize exposed hydrophobic surface of protein and promote their folding through ATP-regulated cycles of binding and release. The molecular chaperone networks have several more important functions in maintaining protein quality control by stabilizing protein conformation in the native state under stress and unfold misfolded protein; disaggregate aggregated protein and target terminally misfolded proteins for the proteolytic degradation<sup>[2]</sup>. The enzymes including PPI catalyzes the cis/trans isomerization of proline residues<sup>[3]</sup> while PDI catalyzes the otherwise slow disulfide bond interchange that is important for the folding of many small and secreted polypeptides<sup>[4]</sup>. Besides possessing enzymatic activity, PDI may also function as a chaperone<sup>[5]</sup>.

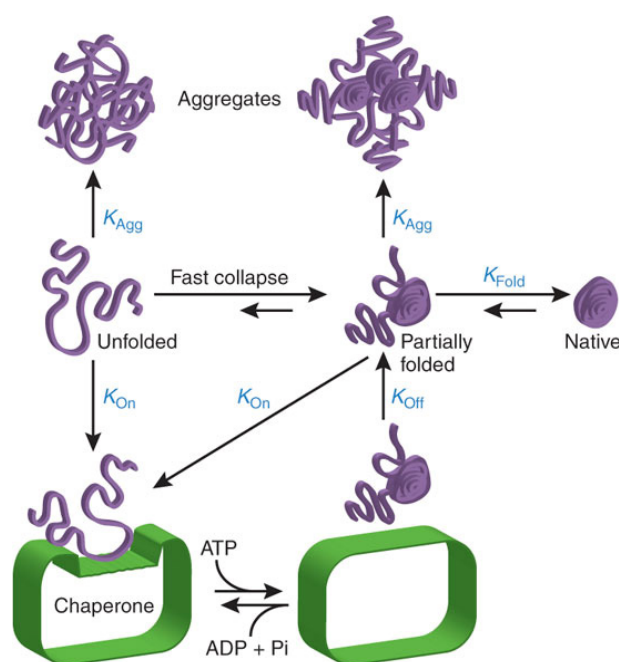
In the cytosol chaperones including Trigger factor and Hsp70, stabilize elongating polypeptide chains on ribosomes and maintain in a non-aggregated state. Folding occurs either on polypeptide chain release from these factors or following polypeptide transfer to downstream chaperones, such as the cylindrical chaperonins, GroEL and TRiC. The latter contains nano-compartments for the folding of polypeptide chain in isolation, unimpaired by aggregation<sup>[2]</sup>. Failure of the chaperone network to maintain proteostasis, i.e. the conformational integrity of the cellular proteome, may results in the manifestation of pathological states including Parkinson's disease, Huntington's disease, Alzheimer's disease and Amyloid lateral Sclerosis disease, in which proteins misfold and are deposited as aggregates<sup>[2]</sup>. A decline in proteostasis capacity occurs during aging, which presumably explain why age is a major risk factor for the development of neurodegenerative diseases<sup>[2]</sup>.

In this review the current status of protein folding in the cell have been discussed in respect to chaperone pathways in *de novo* folding, chaperones acting downstream of the ribosome and proteostasis network. The proteostasis network as drug target also forms the theme of the review.

## PROTEIN FOLDING IN THE CELL

As mentioned above that the intracellular environment is massively crowded containing about 300-400 mg/mL of macromolecules<sup>[1]</sup>. This condition differs markedly from that of the test tube where protein folds at low concentration. There are several problems associated with macromolecular crowding. For instance, macromolecular crowding results in excluded volume effect thus limiting entropic freedom of the polypeptide chain thereby favors compact non-native states<sup>[6]</sup>. Besides this, macromolecular crowding enhances protein aggregation by increasing interactions among partially folded intermediates. Protein folding in the cell is further complicated by coupling with translation. Further proteins must be transported to

the endoplasmic reticulum (ER) and mitochondria prior to folding. In spite of these problems protein fold with remarkable ease in the cell. This eventually led to the discovery of molecular chaperone that assists protein folding in the cell. Molecular chaperone is defined as any protein that interacts, stabilizes or helps a non-native protein to acquire the native state but is not a part of the final structure<sup>[7]</sup>. Chaperones primarily recognize exposed hydrophobic surface of protein and promote their folding through ATP-regulated cycles of binding and release (Figure 1)<sup>[7]</sup>. In fact many of these chaperones are stress proteins as their synthesis are induced under stress (heat shock). For instance, synthesis of chaperones including Hsp70, Hp90 and GroEL/Hsp60 are induced by heat shock. Nevertheless, the majority of family members are expressed constitutively and abundantly in the absence of any stress and genetic studies have shown that many of these proteins are essential for the viability of the cell under the normal condition of growth. However, it has been found that these proteins are induced under other stress conditions. When chaperone binds to protein it blocks aggregation and reduces the concentration of folding intermediates. There are several proteins that possess extremely low intrinsic folding efficiencies or do not fold at all in the absence of chaperones. For example, actins and tubulins do not fold easily because they have a high energy barrier which can be overcome only through assistance by chaperones<sup>[7]</sup>. Moreover, mutations often disrupt protein's ability to fold; therefore chaperone system is also important in buffering the effects of deleterious mutations<sup>[8,9]</sup>. This buffering function is implicated in the evolution of new protein functions and phenotypic traits<sup>[8,10,11]</sup>. These chaperones not only assist *denovo* protein folding, but are also involved in various aspects of proteome maintenance, including assistance in macromolecular complex assembly, protein transport and degradation and aggregate dissociation and refold stress-denatured proteins. Mammalian Hsps have been mainly classified into four families according to their molecular weight: Hsp100, Hsp90, Hsp70, Hsp60, and small Hsps (15-30 kDa). They are also divided into three categories based on their interactions with client proteins including



**Figure 1** Chaperone mechanism in promoting folding through kinetic of partitioning. Reprinted with permission from Hartl FU, Hayer-Hartl M 2009. Copyright 2009 Nature Structural and Molecular Biology.

disaggregase, holdase and foldase (Table 1)<sup>[12]</sup>. Disaggregases are ATP-dependent proteins that disentangle aggregated polypeptides and transfer them to holdase and/or foldase for refolding. Holdases are chaperones that are ATP independent and can recognize, bind and stabilize unfolded polypeptides avoiding aggregation and foldases provide energy to assist the folding and refolding of client proteins through ATP-dependent mechanism.

## PROTEIN DISULFIDE ISOMERASE

Protein disulfide isomerase (PDI) is important cofactors involved in the folding of many proteins in the cell. They are found in the ER<sup>[13-16]</sup>. Many secreted proteins have multiple disulfide bonds, thus presenting potential problems for correct disulfide pairing during folding. Therefore, catalysis of oxidative folding is necessary *in vivo* to rapidly generate the correct disulfide bonds in newly synthesized proteins. In the eukaryotic ER, PDI serve this role. The PDI is present in the cell at millimolar concentrations. Besides showing strong affinity for unfolded proteins and peptides, it binds many hydrophobic molecules including steroid and thyroid hormones. Hence, it

possesses chaperone-like activity thereby inhibits aggregation which is independent from its ability to catalyze disulfide bond formation<sup>[17-19]</sup>. Protein disulfide isomerase has two distinct catalytic sites which are located in the two domains that are homologous to thioredoxin. One domain is located near the N--terminus while other domain is present near the C-terminus. The thioredoxin domains are capable of catalyzing disulfide bond formation.

## PEPTIDYL PROLYL ISOMERASE

PPI catalyzes cis/trans isomerization of proline residues<sup>[3]</sup>. The crystallographic data show that approximately 6.5% of the proline residues are in the cis isomeric form<sup>[20]</sup>. Since the rate constant for the isomerization is slow in comparison to the rate of protein folding in the cell, PPI plays an important role in accelerating folding *in vivo*. Peptidyl prolyl isomerases are ubiquitous enzymes that are found in virtually all organisms and subcellular compartments. Three unrelated families are now known including cyclophilins, the FK506-binding proteins (FKBP), and the parvulins<sup>[21]</sup>. The former two families are also known as immunophilins.

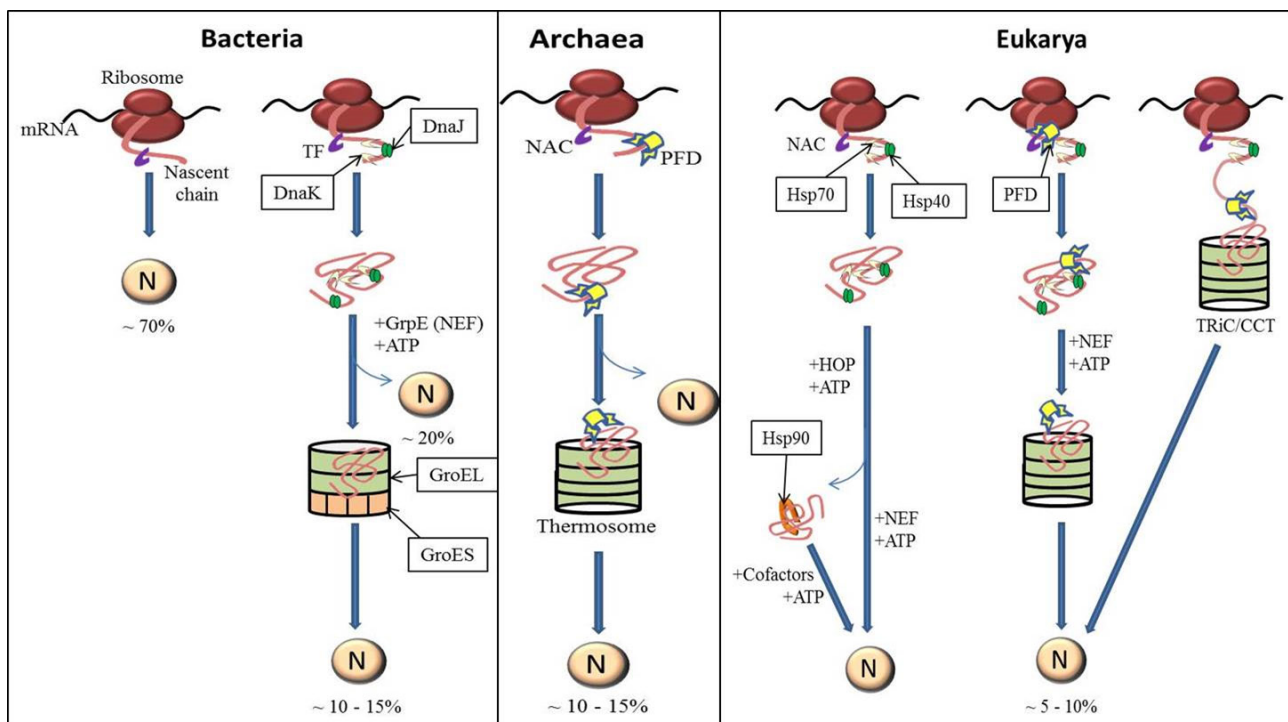
**Table 1** Heat Shock Proteins Classification\*.

Hsp family	Molecular mass	Oligomer	Classification
Hsp100	100 kDa	Hexamer	Disaggregase
Hsp90	90 kDa	Dimer	Foldase
Hsp70	70 kDa	Monomer	Foldase
Hsp60	60 kDa	Heptamer	Foldase
Hsp40	40 kDa	Dimer	Foldase
Small Hsps	15-30 kDa		Foldase

\*Adapted from reference [12].

## CHAPERONE PATHWAYS IN DE NOVO FOLDING

The organization of cytosolic chaperone pathways is highly conserved throughout evolution (Figure 2). In all three domains of life including bacteria, archaea, and eukaryotes, the ribosome binding chaperones [e.g., trigger factor (TF), nascent-chain-associated complex (NAC), and specialized Hsp70s] interact with



**Figure 2** Organization of chaperone pathways in the cytosol. In bacteria, archaea, and eukarya, ribosome-bound chaperones [trigger factor (TF) in bacteria, nascent-chain-associated complex (NAC) in archaea and eukarya] aid folding cotranslationally by binding to hydrophobic segments of the emerging nascent chains. For longer nascent chains, members of the heat shock protein (Hsp)70 family (DnaK in bacteria and Hsp70 in eukarya), together with Hsp40s and nucleotide exchange factors (NEFs), mediate co- and posttranslational folding. In archaea lacking the Hsp70 system, prefoldin (PFD) assists in folding downstream of NAC. Partially folded substrates may also be transferred to the chaperonins [GroEL-GroES in bacteria, thermosome in archaea, and tailless complex polypeptide-1 (TCP-1) ring complex (TRiC)/chaperonin-containing TCP-1 (CCT) in eukarya]. The Hsp90 system also binds substrates of heat shock cognate 70 (Hsc70) and mediates their folding in presence of additional cofactors. Percentages indicate the approximate protein flux through the various chaperones. Adapted from reference 2.

the nascent polypeptide. This is followed by binding of a second set of chaperones that do not interact with the ribosome (the classical Hsp70 system). Under these conditions, folding begins cotranslationally and terminates posttranslationally upon chain release from the ribosome or after transfer to downstream chaperones (e.g., the chaperonins and Hsp90 system) (Figure 2)<sup>[2]</sup>. The nascent polypeptide chain is conformationally restricted until a complete protein domain is synthesized and emerges from the ribosomal tunnel. Ribosome binding chaperones prevent polypeptide chain from non-native interactions during translation. This occurs by masking exposed hydrophobic segments. The examples of ribosome-associated molecular chaperones are TF (in prokaryotes) and Hsp70 complexes which include ribosome-associated complex (RAC; in *Saccharomyces cerevisiae*), MPP11 and Hsp70L1 (in mammals), and NAC (in archaea and eukaryotes) (Figure 2)<sup>[22-24]</sup>.

TF binds to the large ribosomal subunit at the opening of the ribosomal exit tunnel<sup>[25-27]</sup> and interacts with most of the newly synthesized cytosolic proteins as well as subset of secretory proteins<sup>[28,29,23,24]</sup>. *In vitro*, TF binds to stretch of ~60 amino acid residues when the first hydrophobic segment of the chain emerges from the ribosome<sup>[23,30]</sup>. Release of TF from the nascent chain occurs in an ATP independent manner and permits folding or polypeptide transfer to downstream chaperones such as DnaK, the major Hsp70 in bacteria. Although, deletion of the genes encoding TF and DnaK are lethal at temperatures above 30°C, but it has been found that *E. coli* cells can tolerate single deletion, TF or DnaK, indicating that these proteins are functionally redundant<sup>[29,23,31]</sup>. In eukaryotes the ribosome binding chaperone RAC and NAC may fulfill this role, although they are not homologous to TF. The RAC comprises the Hsp70-like protein Ssz1 (also known as Pdr13) and the Hsp70 co-chaperone zotin (Hsp40) (Figure 2)<sup>[23,32-36]</sup>. In fungi, RAC cooperates with ribosome-binding isoforms of Hsp70, Ssb1, or Ssb2. The NAC is a heterodimeric complex of  $\alpha$ - (33 kDa) and  $\beta$ - (22 kDa) subunits that also associate with ribosomes (via the  $\beta$ - subunit) and short nascent chains<sup>[37-40]</sup>. However, the exact role of NAC in folding or protein quality control is not yet established.

## CHAPERONES ACTING DOWNSTREAM OF THE RIBOSOME

In bacteria and eukaryotic cells, the Hsp70s play a central role in assisting folding co and post-translationally<sup>[41,22]</sup>. These chaperones interact with nascent and newly synthesized polypeptide chains but not with ribosome<sup>[29,42]</sup>. The Hsp70 chaperones homolog in bacteria and some archaea include DnaK, in yeast Ssa1-4, and in metazoan and mammalian cells heat shock cognate 70 (Hsc70)<sup>[43,23]</sup>. The Hsp70 chaperones function with co-chaperones of the Hsp40 family (also known as DnaJ proteins or J proteins) and nucleotide exchange factors (NEFs) (Figure 2)<sup>[44]</sup>. The Hsp70-Hsp40 chaperone systems assist folding either co- or posttranslationally through ATP-regulated cycles of substrate binding and release and thereby transfer the polypeptide chain to downstream chaperones. Strikingly, most species of archaea lack the Hsp70 chaperone system instead they contain protein prefoldin also known as the Gim complex, GimC<sup>[45]</sup>. The prefoldin binds in an ATP-independent manner to nascent polypeptide chains and mediates their transfer to the cylindrical chaperonin complex for carrying out final stages of folding. In eukaryotes, prefoldin participates in the chaperonin-assisted folding of actin and tubulin<sup>[41,46]</sup>. Proteins that are unable to utilize Hsp70 for folding are transferred to the chaperonin or the Hsp90 system. Chaperonins (also referred as Hsp60s) are

large double-ring complexes of 800-1,000 kDa containing central cavities where protein molecules fold protected from the cytosolic environment which are highly aggregation promoter<sup>[43,46]</sup>. The chaperonins are basically classified into two distinct groups including group I and group II<sup>[47,48]</sup>. The Group I chaperonins include GroEL in bacteria, Hsp60 in mitochondria, and Cpn60 in chloroplasts. These chaperonins cooperate with lid-shaped cochaperones (GroES, Hsp10, and Cpn10/20) for the encapsulation of substrates. The examples of group II chaperonins are the archaeal thermosome and its eukaryotic homolog tailless complex polypeptide-1 (TCP-1) ring complex (TRiC), also known as chaperonin-containing TCP-1 (CCT), which have a built-in lid. The GroEL-GroES assist folding posttranslationally, whereas TRiC may assist folding both co and posttranslationally<sup>[41]</sup>. The TRiC binds to nascent chains and cooperates with Hsp70 in the cotranslational folding of multidomain proteins<sup>[49]</sup>. In these two chaperones a direct interaction occur<sup>[50]</sup>. The substrates of GroEL are proteins with complex domain folds<sup>[11,51]</sup>. The TRiC substrates comprise proteins such as actin and tubulin as well as several proteins with  $\beta$ -propellers/WD40 repeats<sup>[52,53]</sup>. In the eukaryotic cell, many signaling proteins are transferred from Hsp70 to the ATP-dependent Hsp90 chaperone system for the completion of folding (Figure 2)<sup>[54-56]</sup>. The Hsp90 stabilizes the nuclear hormone receptors conformation thereby facilitates hormone binding and activation. In the yeast and other fungi, the cytosolic Hsp70 system cooperates with the AAA+ (ATPases associated with various cellular activities) chaperone Hsp104 and dissociates and refolds aggregated proteins. The Hsp104 is homologous to bacterial ClpB and with cooperation of DnaK disaggregates protein<sup>[57]</sup>. Similarly, a variety of cochaperones of Hsp70 and Hsp90 carry terminally misfolded proteins to protein degradation machinery for the degradation<sup>[58]</sup>.

## PROTEOSTASIS NETWORK

Protein folding and maintenance of their conformation are essential for the integrity of protein structure. The levels of protein in the cell, their localization, and biological activity must also be carefully controlled in response to intrinsic and extrinsic stimuli in order to maintain proteome integrity. Protein homeostasis or 'proteostasis' is referred to the process that regulates the concentration of protein within the cell for maintaining the health of both the cellular proteome and the organism itself. The proteostasis involves highly complex interconnected pathways that influence the fate of a protein from biosynthesis to degradation. These integrated pathways include protein synthesis, folding, trafficking, and degradation that are dynamically regulated by a variety of proteostasis regulators (PR). These regulators enable the polypeptide chain to achieve native functional state in the cell by coordinating transcriptional and translational programs. The proteostasis network (PN) refers to the collection of cellular components involved in proteostasis maintenance<sup>[59]</sup>. Failure of proteostasis is implicated in disease and aging<sup>[60]</sup>. Molecular chaperones have multiple roles in the PN. The PN is regulated by interconnected pathways that respond to specific forms of cellular stress, including the cytosolic heat shock response (HSR)<sup>[61]</sup>, the unfolded protein response (UPR) in the endoplasmic reticulum<sup>[62]</sup>, and the mitochondrial UPR<sup>[63]</sup>. Additionally, PN regulation is linked with pathways involved in inflammation. PN regulation is affected by oxidative stress, caloric intake. The PN of mammalian cells consists of ~1,300 different proteins among them around ~400 are involved in protein biogenesis, ~300 in conformational maintenance, and ~700 in degradation, with many proteins being part of more than one pathway<sup>[2]</sup>. Different cell types

may also vary in their proteostasis capacity and thus to heat shock or other stress and vulnerability to protein aggregation<sup>[64,65]</sup>.

Even after initial folding and assembly, many proteins remain dependent on molecular chaperones throughout their lifetime for maintaining their functional native state. Many of the chaperone systems mentioned above function not only in *de novo* folding but also in conformational maintenance, i.e., they prevent aggregation of misfolded proteins and mediate their refolding. Interestingly, in yeast some proteins may interact with as many as 25 different types of chaperones throughout their lifetime<sup>[66]</sup>. Experimental studies have shown that bacterial Hsp70 and chaperonin systems are involved in conformational maintenance<sup>[11,26]</sup>. Up regulation of chaperones by heat shock or oxidative stress prevent aggregation of protein. Failure of conformational maintenance gives rise to aggregation<sup>[67]</sup> which occurs particularly in age-related neurodegenerative diseases.

## PROTEOSTATIS NETWORK AS A DRUG TARGET

There exist a close relationship between folding and PN activity and any alterations in polypeptide chain (e.g., mutation, co- or post-translational modifications) or change in the PN composition can lead to either partial or complete alteration or breakdown of the proteostasis network resulting in the manifestation of disease development and progression. Thus, targeting PN is emerging as a promising therapeutic strategy for the treatment of a wide variety of conformational diseases. In principle, we might achieve this by stabilizing the conformation of misfolding prone proteins thereby promote refolding, increase their trafficking to the final compartment; upregulation of molecular chaperone can also increase folding of protein. Degradation of terminally misfolded proteins is also important to prevent toxicity of the cell.

## CONFORMATIONAL STABILIZATION OF MISFOLDING-PRONE PROTEINS AND UPREGULATION OF CELLULAR CHAPERONES

Pharmacological chaperones are a special subset of chemical chaperones that selectively bind and reversibly stabilize the misfolding-prone proteins thereby promoting refolding, thus preventing their degradation and enhancing their trafficking to the final compartments<sup>[68]</sup>. For instance, deoxygalactonojirimycin prevents defective folding, degradation and trafficking of mutants  $\alpha$ -galactosidase A in Fabry disease<sup>[69]</sup>. In a similar vein, pharmacological chaperones have been developed for Pompe and Gaucher type I diseases and are currently under various phases of clinical trials<sup>[70-72]</sup>. The pharmacological chaperone including polyaromatic compounds have been shown to bind CFTR and promote their folding into native state for the export from the ER<sup>[73]</sup>. In this regard, Wang *et al* (2006) have shown that pharmacological chaperones rescue mutant CFTR (DF508CFTR) and thereby increase the channel activity<sup>[74]</sup>. Further, it has also been suggested that combination of multiple classes of pharmacological chaperones could be more effective in treating the fibrosis disease<sup>[74]</sup>. Boosting cellular chaperone capacity is another way of increasing the efficiency of folding or degradation of proteins carrying destabilizing mutations and for the inhibition of aggregation<sup>[75]</sup>. For example, small molecules (e.g., geldanamycin) activate heat shock factor 1 and consequently increase the effective concentration of cytosolic chaperones and suppress the aggregation of various disease proteins<sup>[59,76-78]</sup>. This

approach is based on multiple lines of evidence that overexpression of chaperones such as Hsp70 and Hsp40 prevent aggregation and toxicity of huntingtin and  $\alpha$ -synuclein<sup>[7,79-82]</sup>. Similarly, increasing the levels of chaperones and folding enzymes, UPR could be effective in improving the folded state of mutant proteins. Recently, it has been reported that combination of celastrol and proteasome inhibitor MG132 up-regulate the three arms of UPR and as a consequence it increase the folding of mutant enzymes associated with lysosomal storage diseases<sup>[77]</sup>. The two inhibitors, diltiazam and verapamil, of L-type  $Ca^{2+}$  channels up-regulate several molecular chaperones which results in the rescue of mutant  $\beta$ -glucocerebrosidase folding, trafficking in Gaucher's disease<sup>[83]</sup>.

## ENHANCEMENT OF PROTEIN FOLDING BY DOWN-MODULATING DEGRADATIVE PATHWAYS

Degradative systems are involved in the removal of misfolded or aggregated toxic proteins. Thus, interfering degradative pathways for enhancing productive folding, trafficking, and function represent a promising therapeutic strategy to restore proteostasis. In this regard, Vij *et al* (2006 ) have demonstrated that selective inhibition of ERAD rescues functional mutant CFTR to the cell surface<sup>[84]</sup>. These findings were further supported by Park *et al.* (2009 ) that adamantyl sulfogalactosyl ceramide antagonizes the Hsp70-40 degradation pathway and results in an increased ERAD escape of DF508CFTR protein<sup>[85]</sup>.

## CONCLUSIONS

Protein folding in the cell occurs in highly crowded environment. Under these *in vivo* conditions molecular chaperone assists in *de novo* folding of protein. Chaperones that participate in protein biogenesis recognize exposed hydrophobic surface of protein and promote their folding via ATP-regulated cycles of binding and release. Beside this, molecular chaperone networks have several more important functions in maintaining protein quality control by stabilizing protein conformation in the native state under stress and unfold misfolded protein; disaggregate aggregated protein and target terminally misfolded proteins for the proteolytic degradation. Protein homeostasis or 'proteostasis' is important for maintaining the health of both the cellular proteome and the organism itself. The proteostasis involves highly complex interconnected pathways that influence the fate of a protein from biosynthesis to degradation. The proteostasis network (PN) refers to the collection of cellular components involved in proteostasis maintenance<sup>[56]</sup>. Failure of proteostasis is implicated in disease and aging<sup>[57]</sup>. Therefore, proteostasis network has emerged as novel drug targets for treating conformational diseases. This can be achieved by reversibly stabilizing the conformation of misfolding prone proteins and thereby promote refolding and increase their trafficking to the final compartment, upregulation of molecular chaperone can also increase folding of protein and by degrading terminally misfolded proteins that are toxic to cell. In future, detail studies on cellular proteome could unravel more about molecular mechanisms underlying conformational diseases and thereby could add knowledge to the researchers in the proteomics field for treating diseases.

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## CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare.

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