Expanding Proteostasis by Membrane Trafficking Networks

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Cold Spring Harbor Perspectives in Biology
www.cshperspectives.org

The folding biology common to all three kingdoms of life (Archaea, Bacteria, and Eukarya) is proteostasis. The proteostasis network (PN) functions as a "cloud" to generate, protect, and degrade the proteome. Whereas microbes (Bacteria, Archaea) have a single compartment, Eukarya have numerous subcellular compartments. We examine evidence that Eukarya compartments use coat, tether, and fusion (CTF) membrane trafficking components to form an evolutionarily advanced arm of the PN that we refer to as the "trafficking PN" (TPN). We suggest that the TPN builds compartments by generating a mosaic of integrated cargo-specific trafficking signatures (TRaCKS). TRaCKS control the temporal and spatial features of protein-folding biology based on the Anfinsen principle that the local environment plays a critical role in managing protein structure. TPN-generated endomembrane compartments apply a "quinary" level of structural control to modify the secondary, tertiary, and quaternary structures defined by the primary polypeptide-chain sequence. The development of Anfinsen compartments provides a unifying foundation for understanding the purpose of endomembrane biology and its capacity to drive extant Eukarya function and diversity.

We now appreciate that biological protein folding occurs in complex, protein-rich, and aggregation-prone cellular environments. De novo–synthesized proteins require constant support from the protein-folding management system, proteostasis (Fig. 1) (for term definitions, see Box 1) (Balch et al. 2008; Douglas and Cyr 2010; Gidalevitz et al. 2011; Ong and Kelly 2011), a system of chaperones, folding enzymes, and degradation components that manage the fold. Moreover, Eukarya, unlike microbes (Bacteria or Archaea) (Balch et al. 1977; Fox et al. 1980), have multiple subcellular compartments that house proteins in different environments, have different intracellular functions, and provide proteins for use outside the cell (Powers and Balch 2011). The structure and function of these compartments are managed by coat (Stagg et al. 2007; Popoff et al. 2011; Weinberg and Drubin 2012; Zanetti et al. 2012), tether (Barrowman et al. 2010; Freeze and Ng 2011; Henne et al. 2011; Munro 2011a), and fusion (Sudhof and Rothman 2009; Wickner 2010) machineries, collectively abbreviated herein as the CTF system (Box 2).

Anfinsen first taught us that the information required to fold a protein is coded in the primary polypeptide chain sequence (Anfinsen 1973).

Editors: Susan Ferro-Novick, Tom A. Rapoport, and Randy Schekman
Additional Perspectives on The Endoplasmic Reticulum available at www.cshperspectives.org

 doi: 10.1101/cshperspect.a013383
Cite this article as *Cold Spring Harb Perspect Biol* 2013;5:a013383

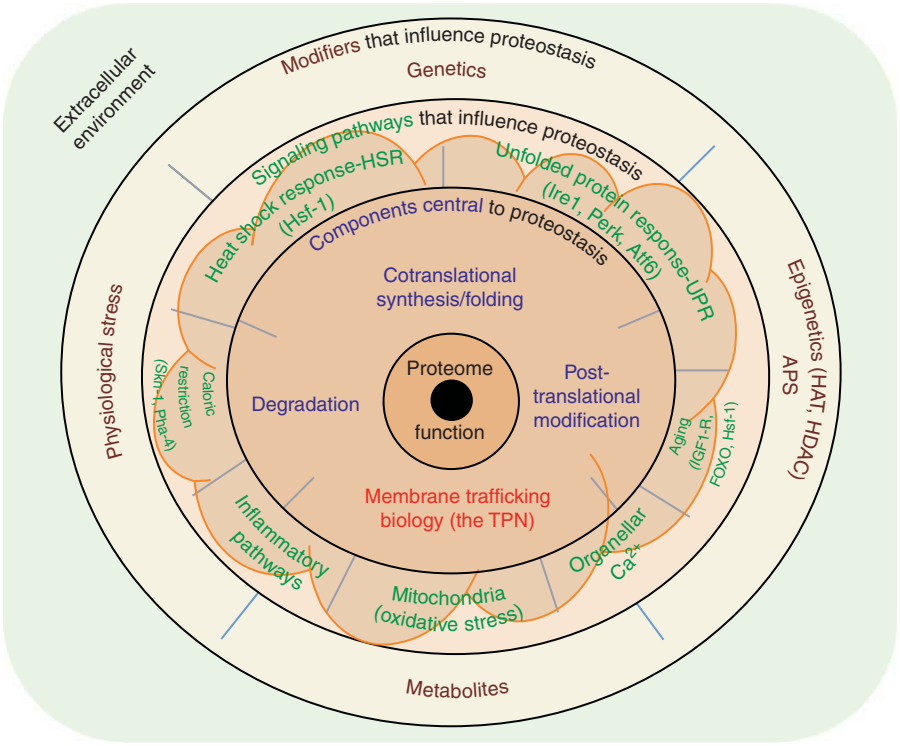

Figure 1. Proteostasis and trafficking biology. The hierarchical influence of proteostasis on proteome function (indicated by the dark orange circle with a protein represented by a black node) in a eukaryotic cell. The first layer outside the proteome lists the working components of the proteostasis network (PN; blue lettering) that we now propose includes membrane trafficking biology coat, tether, and fusion (CTF) components comprising the trafficking proteostasis network (TPN; see main text). The next layer lists the many signaling pathways (green lettering) that can influence the composition of the PN/TPN in each cell type. The outer layer (brown lettering) highlights the impact of genetics (including modifiers), epigenetics (including HATs and HDACs), metabolites, and physiological stress pathways stemming from the extracellular environment (solid green) that influence PN/TPN activity. We capture the dynamic features of these relationships as the "cloud" (light orange icon), a unique TPN/PN management system that surrounds each protein (black node) and controls its function from birth to death. (Adapted from Powers et al. 2009.)

Herein, we review emerging principles of the function of CTF components, focusing on their ability to generate folding environments that impact the biological properties of the polypeptide chain sequence as an extension of proteostasis biology. We will explore the development of CTF-based membrane trafficking pathways as an integrated trafficking proteostasis network PN (TPN) charged with managing the folding and structural properties of cargo during transit through endomembrane compartments by capitalizing on the second Anfinsen principle—that the environment strongly influences the protein fold (Anfinsen 1973). We highlight evidence that supports the view that the TPN operates as a mosaic by using CTF-based trafficking signatures (TRaCKS) to temporally and spatially create compartmentalized proteostasis activity. TRaCKS provide remarkable flexibility to the cellular folding capacity by transporting cargo through highly adaptive and diverse folding environments—rather then varying the composition of a single cytosolic environment as occurs in microbes. We emphasize how the development of this "quinary" level of protein structure control through TPN activity provides us with

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BOX 1. GLOSSARY OF TERMS

Anfinsen cage	The space within the oligomeric, ring-like structures of the HSP60-type chaperonins in which proteins are able to fold, isolated from the aggregation- and degradation-prone environment of the cytosol.
Anfinsen compartments	The specialized folding environments comprising the membrane-enclosed trafficking compartments found in all Eukarya that are generated by sequential activity of CTF-based TRaCKS.
APS	The acetylation proteostasis system (APS) uses the activity of histone acetylases (HATs) and histone deacetylases (HDACs) to manage the balance of acetylation and deacetylation, respectively, of Lys residues of both histone and nonhistone proteins to control transcription, and the secondary, tertiary, quaternary, and quinary status of the protein fold, affecting its function.
Autophagy	Multiple PN pathways converge on the lysosome to degrade proteins including macroautophagy (that consumes large intracellular protein aggregates/organelles using ATG components), chaperone-mediated autophagy (CMA) (that uses cytosolic PN components to translocate client proteins directly across the lysosomal membrane), and phagocytic compartments that internalize extracellular content.
Chaperone	A class of proteins that aid protein folding by binding to proteins in nonnative (i.e., unfolded, misfolded, or partially folded) states. Chaperones can function as holdases by simply binding to and retaining unfolded proteins, recoverases that use ATP to convert misfolded proteins to the unfolded state, giving them another chance to fold or be degraded, and/or foldases that use ATP to enhance the folding of unfolded proteins to the native state.
Chaperonins	Multisubunit folding chambers found in all cell types, functioning as Anfinsen cages to isolate the folding pathway from the harsh and challenging aggregation- and degradation-prone environment of the cytosol.
CTF	The coat, tether, and fusion (CTF) machinery that works together to generate TRaCKS for a given cargo protein directing its path through the endomembrane system. CTFs generate Anfinsen compartments that facilitate the maturation and function of the protein by controlling the activity of the folding environment, providing a quinary level of structural information to the polypeptide sequence.
Evolvability	The capacity of a biological system for adaptive evolution in response to the environment—that is, the ability of a population to acquire adaptive genetic diversity to facilitate natural selection.
Healthspan	The ability of the proteostasis program to manage efficiently the generation of a functional, misfolding–free folding environment to promote healthy aging.
HSR	The canonical heat shock response (HSR) pathway found in extant biology that regulates the expression of proteostasis and other components through the activity of the transcription factor heat shock factor 1 (HSF1) and its related family members.
LUCA	The last universal common ancestor before the divergence of the extant (current) three kingdoms of life—the Bacteria, Archaea, and Eukarya.
Mosaic	An assemblage of pieces or components that when viewed as a collective generate an image.
Proteasome	A degradation chamber found in eukaryotic cells that uses ATP and the components of the UPS to remove proteins from the cell through degradation.
Proteostasis	An evolutionarily conserved and universal protein-folding management system that consists of the proteostasis network (PN)—a collection of more than 2500 chaperones, folding modifiers, degradative components, and signaling

Continued

BOX 1. *Continued*

	pathways that together form a "cloud" around each protein to manage its folding status (its health) and its healthspan in a given intracellular environment or outside the cell.
PRs	Proteostasis regulators are small molecules or biologicals that influence signaling pathways that control the composition of the PN.
Quinary	"Quinary" is used to describe a new level of structural interactions to the secondary, tertiary, and quaternary structures (defined by the primary polypeptide chain sequence) that are generated by compartment specific folding environments in response to the TPN biology.
TPN	The trafficking proteostasis network (TPN) composed of CTF components found in each cell type that together manage the structure and operation of endomembrane compartments in response to the cargo client.
TRaCKS	CTF-based trafficking signatures (TRaCKS) form sequentially in response to the cargo client to provide a trajectory to cargo flow through the endomembrane system. TRaCKS operate as an integrated mosaic to generate endomembrane compartments that manage cargo folding and function.
UPR	The unfolded protein response (UPR) is a signaling pathway regulating the function and composition of the endomembrane compartments directing protein traffic from the ER.
UPS/UB/UBL	The ubiquitin (UB) proteasome system (UPS) is composed of an extensive system of components that tag proteins with UB through the activity of ubiquitin ligases (UBLs) to direct the protein fold for degradation by the proteasome.

a unifying foundation for understanding the role of endomembrane trafficking in Eukarya biology.

PROTEOSTASIS BIOLOGY

Protein folding is limited by the energy landscape barriers (Oliveberg and Wolynes 2005; Hartl et al. 2011), which guide folding intermediates down favorable path(s) required to achieve a functional fold (Brown et al. 2011). The polypeptide chain frequently occupies intermediate metastable states that are necessary to achieve function. Protein-folding dynamics, therefore, offer the cell multiple opportunities for translational and/or posttranslational management of proteins. The crowded cellular environment often leads to failure of protein folding caused by the protein-rich (~300 mg/mL), aggregation-prone environment (Balch et al. 2008). An extensive support system exists to counteract these complexities and is referred to as the proteostasis network (PN) (Balch et al. 2008; Powers et al. 2009; Douglas and Cyr 2010; Gidalevitz et al. 2011; Ong and Kelly 2011). For further description of the proteostasis biology (Fig. 1), we refer the reader to Box 2 and the many excellent reviews on the topic. In brief, the PN is composed of chaperones, chaperonin folding chambers, folding enzymes, and a host of degradation components, whose levels are controlled by multiple signaling pathways (Fig. 1). We have previously described the quantitative capacity of proteostasis to globally manage protein folding and function (Wiseman et al. 2007b; Hutt et al. 2009; Powers et al. 2009, 2012). We refer to the PN as the proteostasis "cloud," to describe its dynamic folding capacity enveloping the protein throughout its life span in the cell (Fig. 1). The PN cloud is constantly changing in composition reflecting varying cellular requirements in response to development and the environment to maintain the overall composition of the PN, ensuring fidelity of the folding capacity for a particular cell type (Fig. 1) (Powers et al. 2009; Tyedmers et al. 2010; Hartl et al. 2011; Morimoto 2011).

Of particular note is that there is emerging evidence for a new proteostasis pathway linking epigenetic biology to protein structure

BOX 2. PROTEOSTASIS AND TRAFFICKING BIOLOGY

The cell offers an extensive and evolutionarily conserved support system to deal with folding complexities to ensure the acquisition and maintenance of functional proteins—referred to as proteostasis (Balch et al. 2008; Powers et al. 2009; Douglas and Cyr 2010; Gidalevitz et al. 2011; Ong and Kelly 2011). The proteostasis network (PN) is composed of a multiplicity of folding "assistants" (e.g., chaperones including Hsp40, Hsc/p70/BiP, Hsp90 and Hsp60 family chaperonin folding chambers), as well as folding enzymes (immunophilins/*cis–trans* prolyl isomerases) and a host of degradation components including the ubiquitin (UB) proteasome system (UPS), the membrane-delimited lysosome, and autophagic/phagocytic compartments. Many homologs of chaperone and degradation components are found in the lumen of the ER and other trafficking compartments. The composition of the proteostasis network (PN) is differentially controlled by multiple signaling pathways, including the unfolded protein response (UPR), heat shock response (HSR), and the APS in each cell type (Fig. 1). The PN has a high impact on phenotypic variation (evolability) and the manifestation of genetic diversity in response to environmental stress (Lindquist 2009; Jarosz and LIndquist 2010; Jarosz et al. 2010).

Trafficking components (Allan et al. 2000; Barrowman et al. 2010; Koulov et al. 2010; Miller and Barlowe 2010; Balch et al. 2011; Lord et al. 2011; Coppinger et al. 2012; Zanetti et al. 2012) that manage compartment structure and function to provide special environments to manipulate the protein fold are largely cytosolic proteins and fall into three categories: the coat protein complexes and their adaptors including the COPII, COPI, clathrin, adaptor proteins (APs) (Stagg et al. 2007; Dancourt and Barlowe 2010; Routledge et al. 2010; Lord et al. 2011; Popoff et al. 2011; Weinberg and Drubin 2012; Zanetti et al. 2012); the tether complexes including PGGM (p115-Grasp-GM130), ESCRT, COG, GOLGINs, and TRAPP complexes, among others, that serve as scaffolds to transiently link compartments in response to the activity of coat and fusion components (Allan et al. 2000; Barrowman et al. 2010; Nakamura 2010; Freeze and Ng 2011; Henne et al. 2011; Munro 2011a); and the fusion system that consists of the *N*-ethylmaleimide-sensitive factor (NSF) attachment protein (SNAP) receptors (SNARE) components and multiple supporting SNARE assembly and disassembly factors including AAA ATPase NSF (Sudhof and Rothman 2009; Wickner 2010). We now appreciate that these integrated coat, tether, and fusion (CTF) scaffolds, although evolutionarily conserved (Gurkan et al. 2007; Dacks et al. 2009; Brighouse et al. 2010; Klute et al. 2011; Elias et al. 2012), are often unique and/or highly specialized for each cell type (Gurkan et al. 2005).

In addition to the CTF components, the TPN uses the properties of the lipid bilayer as a solvent for folding of transmembrane cargo (Wiseman et al. 2007a), to create spatial boundaries to catalog their transient compositions and to maintain identity and function (Lippincott-Schwartz and Phair 2010; Santiago-Tirado and Bretscher 2011). In particular, the steady-state assembly of compartments appears highly sensitive to specific phosphoinositide pools (PIs) whose relative abundance is controlled by membrane-anchored PI-specific kinases and phosphatase cargo coupled to TPN biology (Allan et al. 2000; Kutateladze 2010; Santiago-Tirado and Bretscher 2011). The operation of CTF components is also tightly coupled to the operation of cytoskeletal components through adaptor trafficking components, which in the case of actin involve Rab GTPases (Goud and Gleeson 2010; Hunt and Stephens 2011; Hutagalung and Novick 2011).

biology—referred to as the acetylation proteostasis system (APS) (Fig. 1) (Bouchareilh et al. 2012). The APS is managed by histone acetyl transferases (HATs) and histone deacetylases (HDACs) mediating the posttranslational acetylation/deacetylation state of proteins (Choudhary et al. 2009; Wagner et al. 2011). These enzymes regulate the activity of the PN through diverse mechanisms, in some cases, directly competing with degradative PN pathways (Wagner et al. 2011). APS regulates chromatin transcriptional activity by controlling nucleosome structure and function through acetylation of histones and directs the posttranslational

modification of more than 800 nonhistone proteins found in the cytosol to modify their activities (Fig. 1). For example, the APS has been shown to control the function of key proteostasis components (Westerheide et al. 2009; Zeng et al. 2009; Hutt et al. 2010; Bouchareilh et al. 2012) such as Hsp90 (Aoyagi and Archer 2005) and the central HSR transcription factor, heat shock factor 1 (HSF1) (Fig. 1) (Westerheide et al. 2009; Zeng et al. 2009; Morimoto 2011). The APS also regulates protein degradation through its links to the UPS (Box 2) (Canettieri et al. 2010; Du et al. 2010; Alamdari et al. 2012) as well as autophagy (Yi et al. 2012). Moreover, it plays a critical role in managing membrane trafficking through regulation of cytoskeletal components (Gao et al. 2010). Consistent with the importance of the acetylation/deacetylation balance in proteostasis biology, HDAC inhibitors (HDACi) have been shown to have a corrective impact on multiple human trafficking misfolding diseases including α-synuclein aggregation (Donmez et al. 2012), α1-antitrypsin deficiency (Bouchareilh et al. 2012), Gauchers disease (Lu et al. 2011), and cystic fibrosis (CF) (Hutt et al. 2010; Balch et al. 2011; Calamini et al. 2012). Thus, by providing a "set point" for the proteostasis cloud to operate through global adjustment of acetylation (Fig. 1), the APS has a significant impact on protein folding and membrane trafficking.

TRAFFICKING BIOLOGY AS AN ARM OF PROTEOSTASIS BIOLOGY

Given the impact of the local environment on protein folding (Anfinsen 1973), what does proteostasis biology tell us regarding the role of the endomembrane compartments in managing protein biogenesis and function? Folding in vitro (Fig. 2A, column 1) relies on the polypeptide sequence and is sensitive to rather arbitrary folding environments chosen to generate the structure (Baker 2010). To address this problem biologically, microbes evolved a single folding compartment, the cytosol (Fig. 2A, column 2) with cell surface and extracellular proteins exported into or through the limiting lipid bilayer. The addition of a single, ER-like subcellular compartment, an ancestral state that no longer exists (Fig. 2A, column 3, gray rectangle), as a separate, specialized folding environment for transmembrane and secreted proteins, defines the enabling event for the evolution of Eukarya (Fig. 2A, column 3). In essence, it provided a mechanism to manage protein folding without the need to alter the entire cytosolic PN yet be protected by the cytosol (Balch et al. 1977; Fox et al. 1980). The evolutionary development of a separate folding compartment presented the advantage through compartmentalization to (1) optimize folding through environment control (Anfinsen 1973); (2) use the energetics of the two-dimensional (2D) bilayer template to fold a cohort of proteins

Figure 2. (*See following page.*) The contribution of compartmentalization to proteostasis biology. (*A*, *upper* panels) Illustrated is the relationship between protein (black sphere) folding in vitro (column 1) and biological protein folding in vivo (columns 2–4), the latter requiring the assistance of PN/TPN components (*lower* panels). In column 1, protein folding in vitro is limited to the chemical information contained in the polypeptide chain sequence and is strongly influenced by the choice of the folding buffer. In the simplest case in vivo, illustrated by column 2 (such as found in extant Bacteria and Archaea), one cytosolic PN (the orange cloud) manages all intracellular folding and the export of proteins to and through the cell surface, although specialized chaperones can manage folding in the environment immediately outside the cell (Evans et al. 2011; Powers and Balch 2011; Quan et al. 2011). The small gray cloud icon surrounding the protein (dark circle) defines the select PN components used by a particular protein to facilitate its own structure/function relationships. In column 3, the addition of an intracellular folding compartment (e.g., the ER found in eukaryotic cells) generates a specialized folding environment that now requires trafficking biology found in the cytosol (hazy red cloud) to facilitate cargo movement between the compartment and the cell surface. (Gray rectangle) Indicates that this is only an ancestral state found in the last universal common ancestor (LUCA). In column 4, the presence of multiple compartments (>2) found in extant eukaryotic cells is accompanied by the evolution of CTF-based trafficking pathways (hazy red cloud icon) found in the cytosol that manage both compartment identity and itinerant cargo flow between compartments.

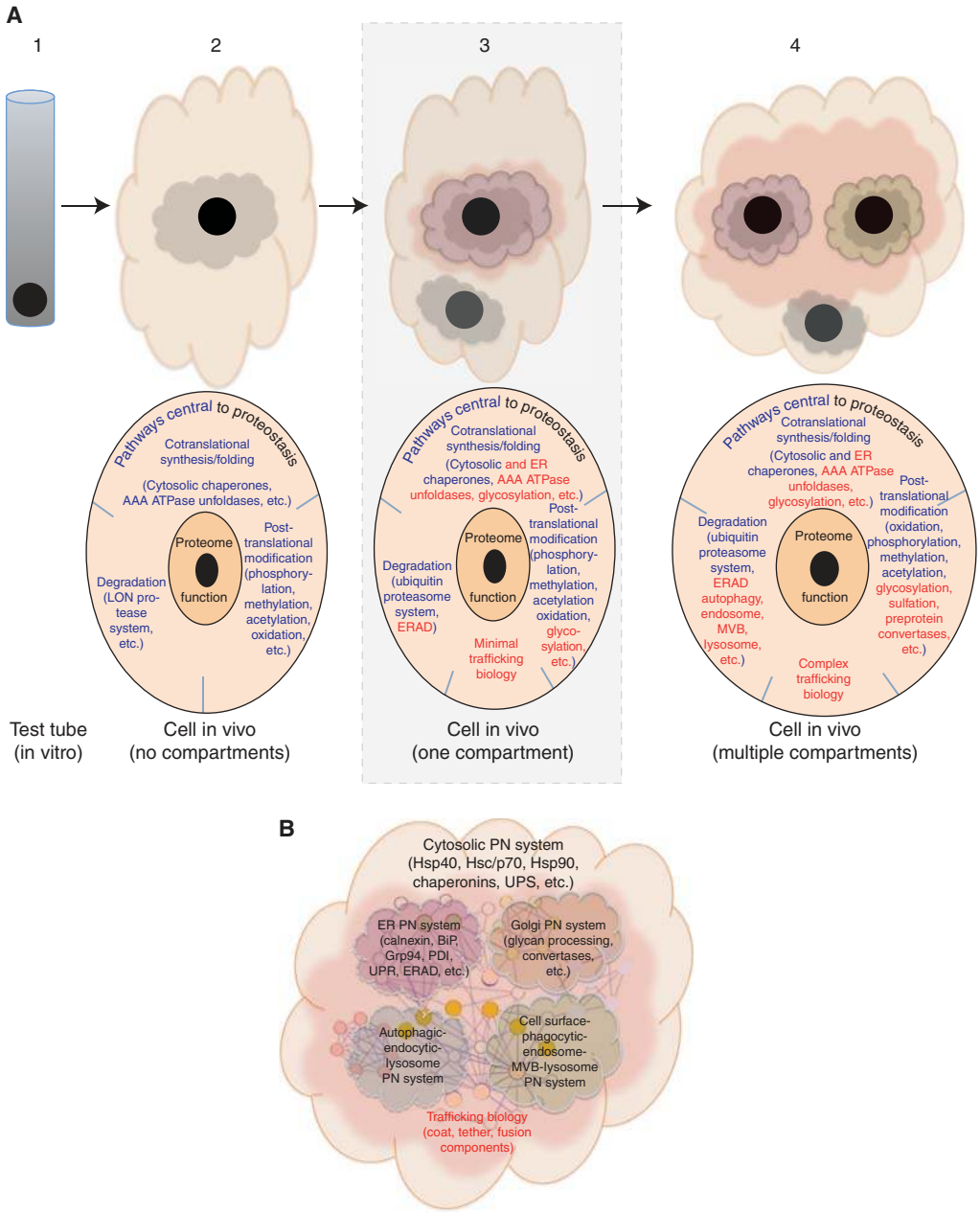

Figure 2. (*Continued*) (*B*) Illustrated are prominent CTF-defined compartments that can affect the structure/function relationships of the protein fold in eukaryotic cells. The large orange cloud icon highlights cytosolic-localized PN. Trafficking components (hazy red cloud) that manage compartment composition, structure, and function are localized to the cytosol with the exception of the fusion machinery components that are often associated with the membrane. The dashed boundary around the ER (purple) highlights the fact that it can physically exchange content with the cytosol. The dashed boundary around the autophagic-phagocytic-lysosome (red) cloud icon highlights the ability of the autophagic systems to sample intra- and extracellular cargo directly.

within a common, structured environment (Wiseman et al. 2007a); and (3) inform the polypeptide chain sequence when and how it should fold to achieve function. However, with these benefits came the major challenge of preserving compartment identity while promoting cargo flow between compartments.

MEMBRANE TRAFFICKING BIOLOGY: THE TRAFFICKING PROTEOSTASIS NETWORK (TPN)

Just as we now recognize that the ER compartment manages protein synthesis and folding (Walter and Ron 2011), we also recognize that Eukarya have generated a multiplicity of additional bilayer-delimited compartments (Fig. 2A, column 4) (Gurkan et al. 2005). We suggest that all subcellular compartments have evolved to provide special environments to allow cells to diversify their ability to manage the protein fold (Fig. 2B) (Hutt et al. 2009), an advancement that necessitated the parallel development of membrane trafficking components. Our understanding of these endomembrane trafficking pathways has come from biological, biochemical, biophysical, and structural analysis of trafficking machineries that includes the coat systems that generate nascent compartments, the tethers that link diverse trafficking compartments together, and fusion components that direct content mixing (Box 2). These integrated coat, tether, fusion (CTF) scaffolds, although evolutionarily conserved (Gurkan et al. 2007; Dacks et al. 2009; Brighouse et al. 2010; Klute et al. 2011; Elias et al. 2012), are often unique and specialized for each cell type (Gurkan et al. 2005). Moreover, the CTF system forms dynamic complexes that control the temporal and spatial features of endomembrane architecture and function through the information encoded by the primary polypeptide sequence, but presented in the context of the fold (the secondary, tertiary, and quaternary structural features) of each cargo (Nishimura et al. 1999; Miller and Barlowe 2010; Kelly and Owen 2011). The dynamic properties of CTF biology are illustrated by (1) the collapse of the Golgi into the ER in response to brefeldin A-mediated inhibition of COPI coat assembly; (2) the role of diverse cargo in managing CTF-based compartment identity (Springer and Schekman 1998; Aridor et al. 1999; Mettlen et al. 2010); (3) the role of small GTPases in regulating the trajectories of CTF complexes (Hutagalung and Novick 2011; Mizuno-Yamasaki et al. 2012); and (4) the sensitivity of compartment architecture to diverse physiologically and environmentally triggered signaling pathways.

Given that the first compartment of eukaryotic cells, the ER, was based on the ancient rules governing proteostasis (Fig. 2A, column 3), we suggest that trafficking components evolved based on the same evolutionarily conserved principles. By also serving as folding managers, trafficking components offered the opportunity to generate diverse, tunable folding environments that we now refer to as the trafficking proteostasis network (TPN). As in proteostasis, the protein client uses the local PN to manage its genesis and folding. Likewise, in TPN biology, the cargo traversing the endomembrane compartments uses its encoded information to selectively interact with specific CTF components to generate trafficking signatures (TRaCKS) to define and/or redefine its biological destiny (Fig. 3A). Cargo management of TRaCKS, therefore, differentially localizes cargo to a given compartment in response to unique developmental and physiological cues (Fig. 3A, left panel, dotted circle). As a collective, cargo proteins manage compartment architecture by generating in a given cell type a unique mosaic of TRaCKS interactions (Fig. 3B) (Gurkan and Balch 2005). By managing CTF activity, cargo-specific TRaCKS solve the challenge highlighted above—a mechanism for building temporally and spatially regulated folding environments—yet permitting the variable flow of cargo within the mosaic (Fig. 3B). Thus, TRaCKS biology contributes a new "quinary" level of structural interactions to the secondary, tertiary, and quaternary structures defined by the primary polypeptide chain sequence (Fig. 3A, right panel).

Just as chaperonin and proteasomal chambers evolved their specialized environments through gene duplication (Yebenes et al. 2011), the development of TRaCKS-based compartments also arose as a consequence of gene

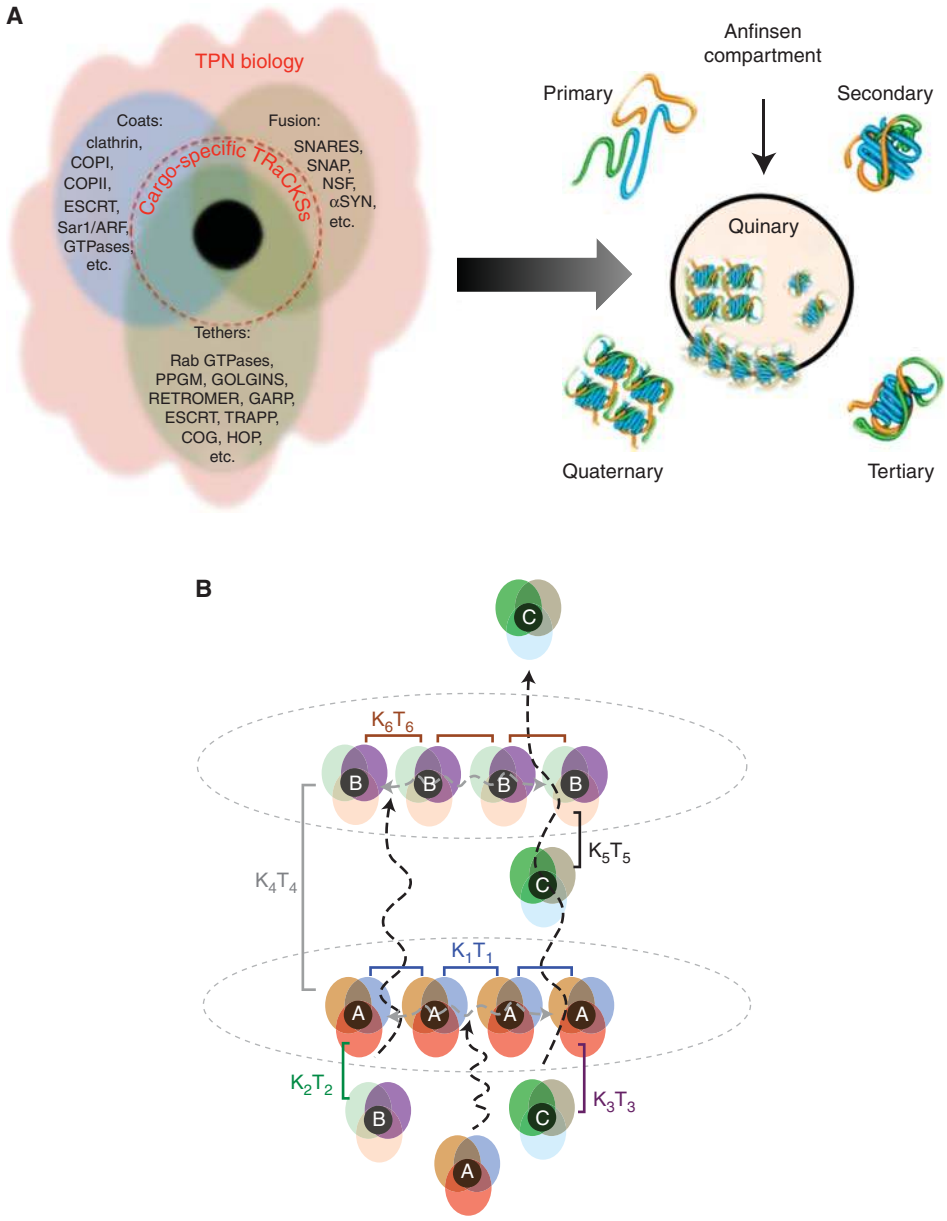

Figure 3. The TPN and TRaCKS. (*A*) C, T, and F components work together to form the TPN (hazy red cloud icon). The TPN is unique for each cell type, and temporally and spatially generates endomembrane compartments (Gurkan et al. 2005). In response to cargo (black circle), select CTF components generate TRaCKS (dotted circle) that specifically manage the trajectory and function of cargo in maintaining or transiting through endomembrane compartments. The mosaic composition of TRaCKS (*right* panel) can be viewed as contributing to an additional "quinary" level of structural interactions to the secondary, tertiary, and quaternary structures defined by primary sequence of the polypeptide chain. (*B*) Speculative snapshot of a mosaic arrangement of TRaCKS used to generate compartment (dotted gray lines) identities or to facilitate flow between compartments based on the kinetic (K) and/or thermodynamic (T) properties of the cargo client interaction with PN and TPN components (K_1T_1, K_2T_2, . . .). A and B are compartment-generating TRaCKS (e.g., glycosyl transferases), and C is an itinerant TRaCKS (e.g., CFTR) permitting rapid transit through compartments (Stagg et al. 2007; Powers et al. 2009).

duplication and specialization of the CTF machineries (Gurkan et al. 2005; Yebenes et al. 2011; Liu et al. 2012). Chaperonin complexes are often referred to as Anfinsen cages because of the special environment they provide by sequestering nascent polypeptide chains from the cytosol to promote productive protein folding. By analogy, we now suggest that TPN components generate "Anfinsen compartments" that provide specialized folding milieus to manipulate cargo client stability and function specific for each cell type. But, unlike cytosolic chaperonins and proteasomes that have relatively stable Anfinsen cage structures (Zhang et al. 2010), Anfinsen compartments are temporally and spatially dynamic in composition and organization in response to the CTF composition (Gurkan et al. 2005) and cargo content of each cell type (Fig. 3A) (Springer and Schekman 1998; Aridor et al. 1999; Mettlen et al. 2010). This is evident in, for example, the sequential CTF-based TRaCKS transiently engaged by the cystic fibrosis transmembrane conductance regulator (CTFR) to provide a precise trajectory for its trafficking from the ER to the plasma membrane (Tang et al. 2011a), a process that is disrupted in disease (Balch et al. 2011). As might be expected, CFTR TRaCKS biology is different from the sequential TRaCKS generated by glycosylation enzymes to generate Golgi compartments (see below).

In summary, we suggest that the TPN evolved as a new function based on the ancient proteostasis language found in the last universal common ancestor (LUCA). The TPN dramatically extended the folding capacity of Eukarya through the principle of environment diversification (Fig. 2) (Anfinsen 1973). The development of membrane-delimited Anfinsen compartments (Fig. 3) expanded the use of the information encoded in the polypeptide chain sequence (Anfinsen 1973) over that available to the single compartment folding environment found in Bacterial and Archaeal lineages (Gurkan et al. 2005; Yebenes et al. 2011; Liu et al. 2012) by application of a quinary level of structure guidance. TPN biology, as an addition to proteostasis cloud biology (Fig. 1), provides a unifying explanation for the evolution and operation of the eukaryotic endomembrane system (Fig. 3).

THE OPERATION OF TRaCKS WITHIN THE PROTEOSTASIS PARADIGM

Above we introduced proteostasis and the logic behind the genesis of the ER as an initiating event for the use of TRaCKS-based compartmentalized folding environments. However, TPN-mediated protein folding must also work seamlessly with cytosolic PN components (Fig. 2B). There is substantial evidence that the PN cloud engages all aspects of TPN biology.

Role of UPS in Cargo-Specific TRaCKS Biology

The UPS is a central feature of proteostasis biology that targets proteins for unfolding and degradation through the proteasome, or through lysosome-mediated degradation (Box 2) (Finley 2009; Yang and Klionsky 2010; Weissman et al. 2011). For many years, the UPS has been known to play a critical role in cargo recognition by the cell-surface-localized endocytic clathrin–adaptor complexes (Eyster et al. 2011; Piper and Lehner 2011; Lukacs and Verkman 2012; Macgurn et al. 2012). Here, mono- or poly-UB tagging of the cargo alters client recognition by specific clathrin–adaptor TRaCKS to redirect cargo from early recycling endosomes to late-endosome-linked lysosomal degradation. Of particular note, is the contribution of arrestin-related trafficking adaptors (ART) (MacGurn et al. 2011) to CTF-based TRaCKS that couples cargo to the UPS machinery. In the exocytic pathway, initiated by the COPII TRaCKS coat components directing ER export (Box 2), recent evidence now suggests that the assembly of the COPII vesicles for certain types of cargo such as collagen requires the action of the UPS (Jin et al. 2012; Malhotra 2012; Zanetti et al. 2012). Here, the mono-ubiquitination of Sec31 by the ER-associated UB ligase (UBL) CUL3-KLHL12 facilitates the formation of an expanded SEC31 scaffold that can capture large collagen oligomers (Jin et al. 2012), although it has no effect on the formation of conventional COPII vesicles harboring other cargo (Jin et al. 2012; Malhotra 2012). Moreover, the UBL Ubdx1 is required for ERGIC53-mediated formation of pre-Golgi intermediates (Nagahama et al. 2009) and the

trafficking of α1-antitrypsin (α1AT) (Nyfeler et al. 2008; Haines et al. 2012). Additionally, the Golgi-localized PGGM (p115-Grasp-GM130) tether complex is extensively managed by the UPS during mitosis (Wang and Seemann 2011). Here, tagging of the PGGM with UB disrupts exocytic trafficking during the mitotic cycle, triggering Golgi fragmentation into ministacks and vesicles. Indeed, multiple UBLs are localized to the Golgi (Lauwers et al. 2010; Chen et al. 2011; Litterman et al. 2011; Tang et al. 2011b), raising the specter of an unanticipated level of UPS-mediated management of the early exocytic pathway. UB conjugating pathways have also been shown to play a critical role in macroautophagy (Krick et al. 2010; Yi et al. 2012) generated by ATG components originating from the ER (Behrends et al. 2010). Overall, it is evident that TPN function involves close coupling of TRaCKS components with the UPS arm of the PN and likely APS-linked events (Hutt et al. 2010)—either through direct cargo modification or through regulation of individual TRaCKS to modulate compartment architecture (Fig. 3).

Integration of the TPN with the Hsp40, Hsc/p70, and Hsp90 Proteostasis Components

Numerous homologs of cytoplasmic chaperones and cochaperones (Box 2) are found in the lumen of the ER and in other compartments, where they manage protein folding in response to UPR (Walter and Ron 2011), HSR (Akerfelt et al. 2010; Morimoto 2011), and antioxidant stress signaling pathways (Laurindo et al. 2012). Cytosolic Hsc/p70 and Hsp90 and their many cochaperones also play an important role in the recognition of cargo clients by COPII TPN components, where they manage, for example, CFTR recruitment to COPII vesicles (Wang et al. 2008; Routledge et al. 2010; Balch et al. 2011; Coppinger et al. 2012; Hutt et al. 2012). Moreover, chaperone-mediated autophagy (CMA) uses the Hsc/p70 system to translocate cytosolic proteins into the lysosome (Kaushik and Cuervo 2012).

Although the above are cargo client-specific folding activities, the cytosolic chaperones directly affect the operation of TRaCKS components. Given the role of Hsp90 in regulating kinases (Sharma et al. 2012a), some of which regulate CTF components (Clague et al. 2009; Vergne and Deretic 2010; Sharpe et al. 2011; Campelo and Malhotra 2012), it is anticipated that Hsp90 will frequently affect endomembrane compartment structure and function through phosphorylation events. Beyond kinases, Hsc70 and its J-domain-containing cochaperones auxilin and cyclin G-associated kinase (GAK) (McMahon and Boucrot 2011) are central to the function of the clathrin coat by promoting clathrin cage disassembly and recycling (Schmid and Rothman 1985; Bocking et al. 2011; Rothnie et al. 2011). Moreover, genetic evidence suggests a role for Hsp90 in the assembly and function of the tether "congenital disorders of glycosylation" (COG) TRaCKS components, which regulate the compartmentalization of Golgi glycosylation biology (see below) (Banfield 2011; Freeze and Ng 2011; Geller et al. 2012; Rosnoblet et al. 2012). Finally, increasing evidence implicates a general role for Hsc/p70 and Hsp90 in vesicle tethering and fusion, mediated by sequential RAB GTPase and SNARE TRaCKS found in the Golgi (Chen and Balch 2006) and at the synapse (Sakisaka et al. 2002; Sharma et al. 2012b). In the latter case, we have a snapshot of integration of synapse-specific TRaCKS (Fig. 4A) involving the SNARE fusion components syntaxin1 (STX1), vesicle-associated membrane proteins 2 (VAMP2) with the the cytosolically oriented PN component cysteine string protein (CSP) through α-synuclein (αSYN) (Chandra et al. 2005; Burre et al. 2010; Sharma et al. 2011, 2012b; Sudhof and Rizo 2011), and the PN component Hsp90 (Sakisaka et al. 2002). When defective, αSYN triggers neurodegenerative disease, implicating a role for TRaCKS in Parkinson's (Auluck et al. 2010; Chua and Tang 2011).

TPN Biology and AAA ATPase Function

AAA ATPases comprise a large family of cytosolic proteostasis machines with unfoldase/disaggregase activity that correct protein-folding missteps and target proteins for degradation by the UPS and autophagy (Buchberger et al. 2010;

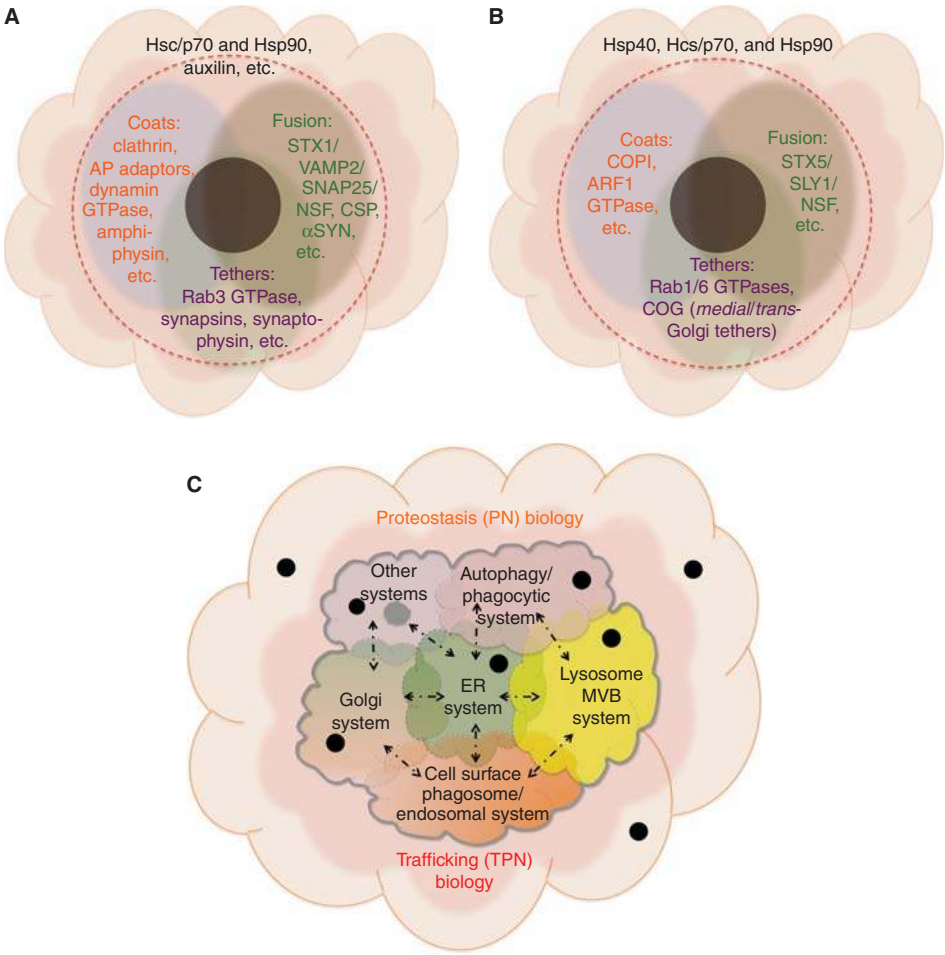

Figure 4. Management of glycan structure and neurotransmission by TRaCKS. (*A*) Snapshot of a specific collection of coat (purple oval), tether (green oval), or fusion (brown oval) components (ovals) contributing to the TRaCKS (dotted red line) mediating synaptic vesicle docking and fusion at the synapse. The activity of these TRaCKS components (hazy red cloud icon) are coupled to the activity of cytosolic Hsp40, Hsc/p70, and Hsp90 protein-folding components (orange cloud icon). (*B*) Snapshot of select CTF components (ovals) contributing to TRaCKS (dotted red circle) involved in glycosyl transferase localization (black circle) to *medial-trans* Golgi compartments as described in *A*. (*C*) Currently recognized "morphological" compartments (ER, Golgi, endosomes, etc.) are temporally and spatially managed by the TPN (hazy red cloud icon) to form an integrated endomembrane system (multicolored, overlapping cloud icons outlined by a solid gray line). In this view, the ER forms a central, multitasking proteostasis hub that is linked to most (if not all) endomembrane trafficking pathways through the TPN—including mitochondria and peroxisomes (other; small gray cloud) (Friedman et al. 2011; Westermann 2011; Grimm 2012; Dimitrov et al. 2013). Boundaries between compartments are blurred (dotted lines around cloud icons) to illustrate the transient organization of the compartment-specific mosaic of TRaCKS that define temporal and spatial role(s) in proteostasis biology.

Tyedmers et al. 2010). The valosin-containing protein (VCP)/p97 complex (VCP/p97) AAA ATPase is integral for protein dislocation from the ER and targeting to the proteasome (Stolz et al. 2011; Claessen et al. 2012; Guerriero and Brodsky 2012; Wolf and Stolz 2012), and its unfoldase activity also affects the activity of many TPN pathways (Wang and Seemann 2011; Dargemont and Ossareh-Nazari 2012; Kloppsteck et al. 2012; Meyer 2012; Yamanaka et al. 2012)

such as TRaCKS containing the RAB1 GTPase-regulated PGGMs tethers that control Golgi structure and function (Meyer 2005; Uchiyama and Kondo 2005; Uchiyama et al. 2006; Haines et al. 2012). VSP4 and, importantly, *N*-ethylmaleimide-sensitive factor (NSF) are specialists in membrane remodeling (Fig. 4B) (Diefenbacher et al. 2011; Chang et al. 2012). Vps4 promotes abscission of inward budding vesicles at the multivesicular body through the activity of the ESCRT tether system (Babst et al. 2011). On the other hand, NSF is a central player in all aspects of TPN biology directing cargo flow and compartment architecture by managing membrane fusion trajectories. Like classical AAA ATPases involved in protein disaggregation and unfolding (Doyle and Wickner 2009), NSF uses its ATP-dependent unfoldase activity as a specialist activity to disassemble complexes responsible for SNARE-dependent bilayer fusion. Moreover, NSF uses special cochaperones that operate in a similar vein to the Hsp70 cochaperone Hsp40 to facilitate NSF recognition of SNAREs (Burgalossi et al. 2010; Zhao et al. 2010; Chang et al. 2012). The AAA unfolding ATPase activity of NSF (Zhao et al. 2012) clearly illustrates that TPN biology is based on the same general principles underpinning the ancient proteostasis program preceding the LUCA (Balch et al. 2008).

TPN BIOLOGY AND ANFINSEN COMPARTMENTS

The ability of CTF-based TRaCKS to generate specialized quinary folding environments (Fig. 3A,B) is evident, for example, from the existence of compartments such as (1) the sarcoplasmic reticulum, a specialized ER subdomain that manages Ca^{2+}-sensitive folding and signaling pathways in muscle (Zhao et al. 2011); (2) peroxisomes that are specialized for managing oxidative stress (Lam et al. 2011; Dimitrov et al. 2013; Grimm et al. 2012). Moreover, endosomal/lysosomal compartments generate a reduced pH environment to promote destabilization and metastability of the protein fold for recycling and/or degradation by the lysosome (Wickner 2010). Here, for example, major histocompatibility complex (MHC) class II-based antigen presentation is largely a task for TRaCKS that respond to the compartment-specific proteolytic processing of MHC class II substrates (Angeles et al. 2012; Watts 2012).

The structure and function of the Golgi is a particularly striking example of TRaCKS biology. It not only manages the activity of many preprotein convertases (proteases that are critical for the processing of peptide hormones and central to organismal endocrine and neuroendocrine biology) (Seidah and Prat 2012) but is a specialist in protein glycan processing. Glycan biology has ancient origins and was operational well before the LUCA. Glycans appear to function as conserved modifications that stabilize and/or protect the protein fold. In eukaryotic cells, glycan management was expanded significantly by the invention of the TPN (Varki 2011). *O*-linked glycans, such as those found contributing to the highly abundant extracellular glycoproteins such as mucins (Thornton et al. 2008) and proteoglycans (Hynes and Naba 2012), are particularly interesting examples of the use of the Anfinsen compartment strategy to confer new structural, functional, and solubility properties to a polypeptide chain sequence, modifications that are crucial for multicellular, higher Eukarya function. On the other hand, the management of proteins containing *N*-linked glycans starts in the ER through the activity of the evolutionarily conserved dolichol-linked glycosylation pathway involving the PN-folding components such calnexin, BiP, protein disulfide isomerases, and ER-associated degradation (ERAD) pathways (Ellgaard and Helenius 2003; Sifers 2010). The addition of only the first three residues of the *N*-linked high mannose glycan motif during nascent synthesis is necessary and sufficient to stabilize the fold (Culyba et al. 2011; Price et al. 2011), leaving the remaining glycan structure with chemical features that are amenable to management of the protein fold properties by the TPN. For example, following COPII capture for export, COPI-containing pre-Golgi and Golgi TRaCKS are thought to redirect metastable cargo to degradation by facilitating Golgi to ER recycling (Aridor et al. 1995; Kimata et al. 2000; Taxis et al. 2002; Sifers 2010; Pan et al. 2011).

Furthermore, TRaCKS build Golgi compartments that can generate novel complex oligosaccharide structures affecting protein function (Stanley 2011; Varki 2011). Here, for example, glycosyl transferases (GTs) manage the mosaic organization of TRaCKS (Fig. 3B) that create Golgi compartments using COG complex tethers (Fig. 4B) (Pokrovskaya et al. 2011; Reynders et al. 2011). COG complex subunits, when mutated, result in specific glycosylation defective diseases (Freeze and Ng 2011; Rosnoblet et al. 2012), yet do not perturb the general flow of cargo. The ability of GT components to self-organize relative to other cargo was recognized by Warren and colleagues as "kin recognition" (Nilsson et al. 1993)—illustrating the principle of affinity/avidity-based construction of a specific Golgi mosaic (Fig. 3B). Moreover, cargo-specific TRaCKS explains the controversial observation that the trafficking of itinerant cargo though the Golgi can be best described by single exponential kinetics (Patterson et al. 2008), where it would be anticipated that itinerant cargo does not interact strongly with GT-based TRaCKS, but rather behaves according to its own TRaCKS-based scheduling (Fig. 3B). This observation is consistent with the fact that both viruses and bacteria often usurp TRaCKS biology for their own benefit (Ligeon et al. 2011; Youngsaye et al. 2011; Geller et al. 2012). The necessity for TRaCKS management in disease exposes an Achilles heel of viruses and pathogens that renders them highly sensitive to inhibitors that block cytosolic PN activity linked to TPN function (Geller et al. 2012).

Overall, the above results suggest that, from a proteostasis perspective, there are no fixed boundaries in the endomembrane system (Fig. 4C). Rather, the TPN generates a dynamic mosaic of operationally integrated trajectories (Fig. 3B) that are temporally and spatially driven by the folding status of the cargo through the activity of CTF-based TRaCKS.

INTEGRATING PROTEOSTASIS AND MEMBRANE TRAFFICKING BIOLOGY

From the perspective of our proteostasis-centric cloud biology (Figs. 1–3), we have combined the conventional view of the role of membrane trafficking components in endomembrane function with a proposed role in building Anfinsen compartments to manage diverse protein folds. By generating a mosaic of TRaCKS, the TPN can (re)configure endomembrane compartments to confer an unprecedented level of function to the polypeptide chain—yet maintain efficient cargo flow through these compartments (Fig. 3B). TPN-managed compartments provide a new dimension that can expand the coded information encrypted in the polypeptide chain sequence. Indeed, the flexibility of TPN-based TRaCKS suggests that the plethora of emerging "unconventional" pathways may have a common framework that simply reflects the versatility of TPN function—and, thus, may not be so unconventional. These now include, for example, the genesis of autophagic membranes from the ER (Gee et al. 2011; Deretic et al. 2012) and the identification of multiple unanticipated compartment linkages including ER–phagosome (Hubber and Roy 2010; Huang et al. 2011), ER–mitochondrial (Friedman et al. 2011; Westermann 2011), Golgi–cell surface (Golgi–bypass) (Nickel 2010; Grieve and Rabouille 2011), ER–peroxisome (Lam et al. 2011; Dimitrov et al. 2013), preGolgi–endosome (Saraste et al. 2009), and intranuclear–cytoplasmic trafficking pathways (Montpetit and Weis 2012; Speese et al. 2012). In this regard, Golgi structure/function relationships have been a particularly acute area of controversy with many models (Morre and Ovtracht 1977; Emr et al. 2009; Papanikou and Glick 2009; Pfeffer 2010; Glick and Luini 2011; Mironov and Beznoussenko 2011; Munro 2011b). We suggest that in the context of the TPN, these diverse explanations for Golgi function are all appropriate. They simply reflect the unanticipated capacity of TPN biology to solve folding problems through Anfinsen compartment building.

How TRaCKS mechanistically operate as a mosaic to generate temporal and spatial identity to compartments yet support itinerant cargo flux (Fig. 3B) remains to be determined. For example, COPII and clathrin "see" thousands of cargo clients during recruitment from the ER or plasma membrane, respectively, yet each

cargo ultimately programs its own destiny in the TPN mosaic through directed interaction with the TPN biology using trafficking codes embedded in its primary sequence, but presented in the context of its higher-order secondary, tertiary, and quaternary structure. Indeed, TRaCKS likely direct membrane compartment architectures through the same basic rules that facilitate the energetics of protein folding (Oliveberg and Wolynes 2005; Wiseman et al. 2007b; Hutt et al. 2009; Powers et al. 2009, 2012), where the kinetic and thermodynamic properties of the cargo fold will dictate the steady-state formation of endomembrane boundaries (Fig. 3B) (Hutt et al. 2009; Powers et al. 2009). However, and unique to the TPN compared with the PN, is the central role of GTPases to manage the construction of quinary folding environments by regulating sequential TRaCKS assembly and disassembly (Allan et al. 2000; Hutagalung and Novick 2011; Lord et al. 2011; Mizuno-Yamasaki et al. 2012). This "directed maturation" (Allan and Balch 1999) reflects the need for global integration of TPN biology through the activity of cargo-based TRaCKS (Springer and Schekman 1998; Aridor et al. 1999; Mettlen et al. 2010).

Last, but not least, is the problem of the TPN and misfolding disease management. Misfolded proteins are a major concern of proteostasis biology (Broadley and Hartl 2009; Powers et al. 2009; Douglas and Cyr 2010; Taipale et al. 2010; Voisine et al. 2010; Ong and Kelly 2011) and a key concern for TPN biology (Saksena and Emr 2009; Miller and Barlowe 2010; Routledge et al. 2010; Roth and Balch 2011; Mizuno-Yamasaki et al. 2012; Zanetti et al. 2012). In addition to the more than 7000 rare misfolding disorders defective in folding and trafficking responsible for disease, their are numerous examples of mutations in the CTF TPN components that affect trafficking and contribute to a diversity of inherited diseases. Common misfolding diseases affected by the TPN include, among others, neurodegenerative (Alzheimer's, Parkinson's, Huntington's) (Ong and Kelly 2011) and systemic (Johnson et al. 2012) amyloid diseases, chronic obstructive pulmonary disease (COPD) (Bodas et al. 2010; Bouchecareilh and Balch 2012), type II diabetes (Scheuner and Kaufman 2008; Rowland et al. 2011; Westermark et al. 2011), cancer (Powers et al. 2009; Trepel et al. 2010), and cystic fibrosis (Balch et al. 2011). An understanding of the mechanisms that the cell uses to continuously adjust the function of the PN and the TPN in the context of the proteostasis cloud (Fig. 1) could have a major impact on understanding how to manage these diseases therapeutically (Balch et al. 2008).

In summary, we suggest that the development of the TPN (Fig. 3) (Gurkan and Balch 2005; Dacks et al. 2008) as a quinary feature of proteostasis folding biology is used by the eukaryotic cell to manage when and where a protein folds, when the fold should or should not be functional, and when it should be removed through degradation. The invention of the TPN as a unifying theme for eukaryotic membrane biology was a pivotal advance accelerating the evolability of unicelluar and multicellular Eukarya to not only optimize and integrate cell and organismal function for a particular niche, but to promote survival and fitness through natural selection (Darwin 1856, 1867).

ACKNOWLEDGMENTS

Support is provided by grants from the National Institutes of Health (GM42236, GM33301, AG03109, HL079442, HL095524) and the Cystic Fibrosis Foundation.

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Cold Spring Harb Perspect Biol 2013; doi: 10.1101/cshperspect.a013383 originally published online February 20, 2013

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