Membrane protein folding, misfolding, and quality control

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Key points

- Summarize the major cellular pathways that govern membrane protein biogenesis, including co-translational insertion and early quality-control mechanisms.
- Describe the physicochemical principles underlying the folding of α-helical bundles and β-barrels within lipid bilayers.
- Discuss how misfolding of membrane proteins and failures in proteostasis contribute to human diseases.
- Outline therapeutic strategies aimed at rescuing or selectively degrading misfolded membrane proteins, including pharmacological chaperones and targeted degraders.

Abstract

Membrane proteins represent nearly one-third of the cellular proteome and carry out essential functions in signaling, transport, and energy conversion. This chapter summarizes key aspects of membrane protein folding and biogenesis, including co-translational insertion, quality-control systems, folding mechanisms, and misfolding-related diseases. We also outline emerging therapeutic strategies aimed at rescuing or selectively degrading misfolded membrane proteins.

Introduction

Membrane proteins perform many of the most essential tasks in living systems (Li et al., 2021). They sense and transmit extracellular signals into intracellular responses through receptors such as G protein-coupled receptors (GPCRs) and receptor tyrosine kinases (RTKs); regulate the passage of ions and metabolites across otherwise impermeable lipid bilayers through channels, transporters, and pumps; drive energy capture and conversion in respiratory and photosynthetic pathways; and provide scaffolding for cell-cell and cell-matrix interactions. Across organisms, approximately 20–30% of proteins are membrane-associated, highlighting the evolutionary commitment to this protein class (Dobson et al., 2023; Almén et al., 2009; Krogh et al., 2001; Wallin and von Heijne, 1998).

The biomedical significance of membrane proteins is equally striking. More than half of approved drugs target membrane proteins—most notably GPCRs, ion channels, and transporters—because these proteins are both readily accessible to pharmacological agents and central to physiological control (Santos et al., 2017). Moreover, membrane protein misfolding or dysregulation contributes to diverse human diseases, including neurodegeneration, cardiac arrhythmias, metabolic disorders, cystic fibrosis, and cancer (Marinko et al., 2019; Liu and Dudley, 2018; Fraser-Pitt and O'Neil, 2015). Beyond their pharmacological importance, engineered membrane proteins and membrane-mimetic platforms are driving new frontiers in biosensing, synthetic biology, and nanotechnology (Meyer et al., 2025; Selivanovitch et al., 2024; Arya et al., 2023). Therefore, elucidating how membrane proteins fold—how they establish correct topology, pack α-helices or β-strands, assemble into functional oligomers, and remain stable within a dynamic lipid bilayer—is fundamental to both basic biology and translational research.

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Conceptual foundations of the field were laid by early models of membrane organization. The lipid bilayer concept established the membrane's structural basis, while the fluid-mosaic framework highlighted its dynamic nature and the central role of embedded proteins (Nicolson and de Mattos, 2022; Nicolson, 2014; Singer and Nicolson, 1972). Pioneering studies in the late 20th century led to the two-stage model for α-helical membrane proteins: first, transmembrane (TM) helices insert into the bilayer, and then they laterally pack and assemble into a functional fold (Popot and Engelman, 1990; Engelman et al., 2003; MacKenzie, 2006). In cells, however, the process is more intricate. In bacteria and in the eukaryotic endoplasmic reticulum (ER), most α-helical membrane proteins are inserted co-translationally through the Sec translocon, assisted by YidC/Oxa1-superfamily insertases, which facilitate proper insertion and reduce the risk of misfolding (Hegde and Keenan, 2024; Cymer et al., 2015; Osborne et al., 2005). Meanwhile, studies in Gram-negative bacteria revealed distinct pathways for β-barrel outer-membrane proteins (OMPs): these substrates are escorted across the periplasm by chaperones such as SurA and Skp, and then inserted and folded by the β-barrel assembly machinery (BAM) complex (Noinaj et al., 2013, 2015, 2017; Hagan et al., 2011; Sklar et al., 2007).

The lipid bilayer is an anisotropic and heterogeneous environment, characterized by a thin apolar core, steep polarity gradients, and lateral pressure profiles (Corin and Bowie, 2020; Ding et al., 2015; White and Wimley, 1999; Cantor, 1999). As a result, membrane protein folding entails partitioning between aqueous and hydrophobic phases, conforming to topological constraints (such as inside-outside asymmetry), and coupling strongly to bilayer mechanics, including thickness, curvature, and tension (Machin et al., 2023; Renne and Ernst, 2023; Corin and Bowie, 2020). Membrane composition further modulates folding stability and pathways: factors such as headgroup charge, acyl-chain saturation, sterol content (e.g., cholesterol), and hydrophobic mismatch influence helix packing and oligomerization equilibria (Peruzzi et al., 2024; Machin et al., 2023; Corin and Bowie, 2020; Muller et al., 2019). Moreover, certain proteins rely on specific lipid interactions, such as cardiolipin binding in bacterial and mitochondrial transporters (Senoo et al., 2024; Laganowsky et al., 2014; Hunte, 2005).

Membrane-mimetic systems—including supported bilayers, vesicles, nanodiscs, and bicelles—approximate native environments (Harris et al., 2022; Notti and Walz, 2022), but can sometimes destabilize the folded state or bias folding pathways. Nevertheless, the field advanced from early denaturant-induced (un)folding studies to denaturant-free approaches, such as the steric trapping method, which enabled detailed analysis of model systems, including bacteriorhodopsin and the rhomboid protease GlpG (Kim et al., 2025; Wijesinghe and Min, 2023; Hong et al., 2009). Membrane protein folding kinetics were further refined through single-molecule force spectroscopy methods, such as magnetic tweezers, which directly resolved folding steps and intermediate lifetimes, and enabled quantitative estimation of barrier heights (Wijesinghe and Min, 2023).

This chapter provides a concise overview of key aspects of membrane protein folding and biogenesis, and highlights how this knowledge informs therapeutic strategies. **Membrane protein biogenesis and quality control** section describes co-translational insertion and quality-control systems in bacteria and the eukaryotic ER that coordinate topology and prevent early misfolding. **Physicochemical principles of membrane protein folding** section examines the physicochemical principles that govern the energetics, kinetics, and pathways of α-helical and β-barrel membrane proteins within lipid bilayers. **Membrane protein misfolding and therapeutic approaches** section considers how perturbations in these processes give rise to misfolding-related diseases and discusses emerging pharmacological and proteostasis-based interventions aimed at restoring balance.

Membrane protein biogenesis and quality control

For many α-helical membrane proteins, folding begins co-translationally, while synthesis is still ongoing (Min, 2024). As hydrophobic segments emerge from the ribosome, the signal recognition particle (SRP) captures the ribosome-nascent chain complex (RNC) and delivers it to the protein-conducting channel: SecYEG in bacteria or Sec61 in the eukaryotic ER (**Fig. 1**A) (Sánchez et al., 2025; Hegde and Keenan, 2022). Once engaged, translation resumes, and the nascent chain is threaded into the channel, which features a lateral gate that opens into the lipid bilayer (**Figs. 1**A and **2**) (Lewis et al., 2024; Ge et al., 2014). TM segments partition laterally according to their hydrophobicity and flanking charges, establishing membrane protein topology consistent with the positive-inside rule, while folding and glycosylation of soluble domains further stabilize and refine TM orientation (Duart et al., 2024; Janoschke et al., 2021; von Heijne, 2006; van den Berg et al., 2004). Because elongation of the polypeptide chain is coupled to membrane insertion, factors such as codon usage, translation rate, and the sequential emergence of charged or reentrant segments can bias topological outcomes, thereby imprinting constraints that influence subsequent folding (Nicolaus et al., 2021; Pechmann et al., 2014).

Alternative insertases provide additional routes for membrane protein insertion (**Figs. 1**A and **2**). In bacteria, YidC facilitates the integration of single-pass proteins or individual TM segments from multipass proteins by providing a hydrophilic groove and locally thinning the bilayer (Caliseki et al., 2025; Dalbey et al., 2023; Kim and Min, 2023; Chen et al., 2017). Its homologs, Oxa1 in mitochondria and Alb3 in chloroplasts, carry out analogous insertase functions (Wang and Dalbey, 2011). In the ER, the ER membrane protein complex (EMC) lowers the energetic barrier for marginally hydrophobic or tilted helices and often cooperates with Sec61 to ensure productive assembly of multipass topologies (**Fig. 2**) (Klose et al., 2025; Wu et al., 2024; Pleiner et al., 2020; Chitwood and Hegde, 2019; Chitwood et al., 2018). Tail-anchored proteins, whose C-terminal TM domain emerges only after translation terminates, are delivered post-translationally via the GET pathway in yeast or the TRC pathway in mammals, with EMC contributing to insertion in certain cases (Farkas and Bohnsack, 2021; Hegde and Keenan, 2011). Electrochemical gradients across membranes—comprising both membrane potential and proton concentration differences—further bias the insertion of charged

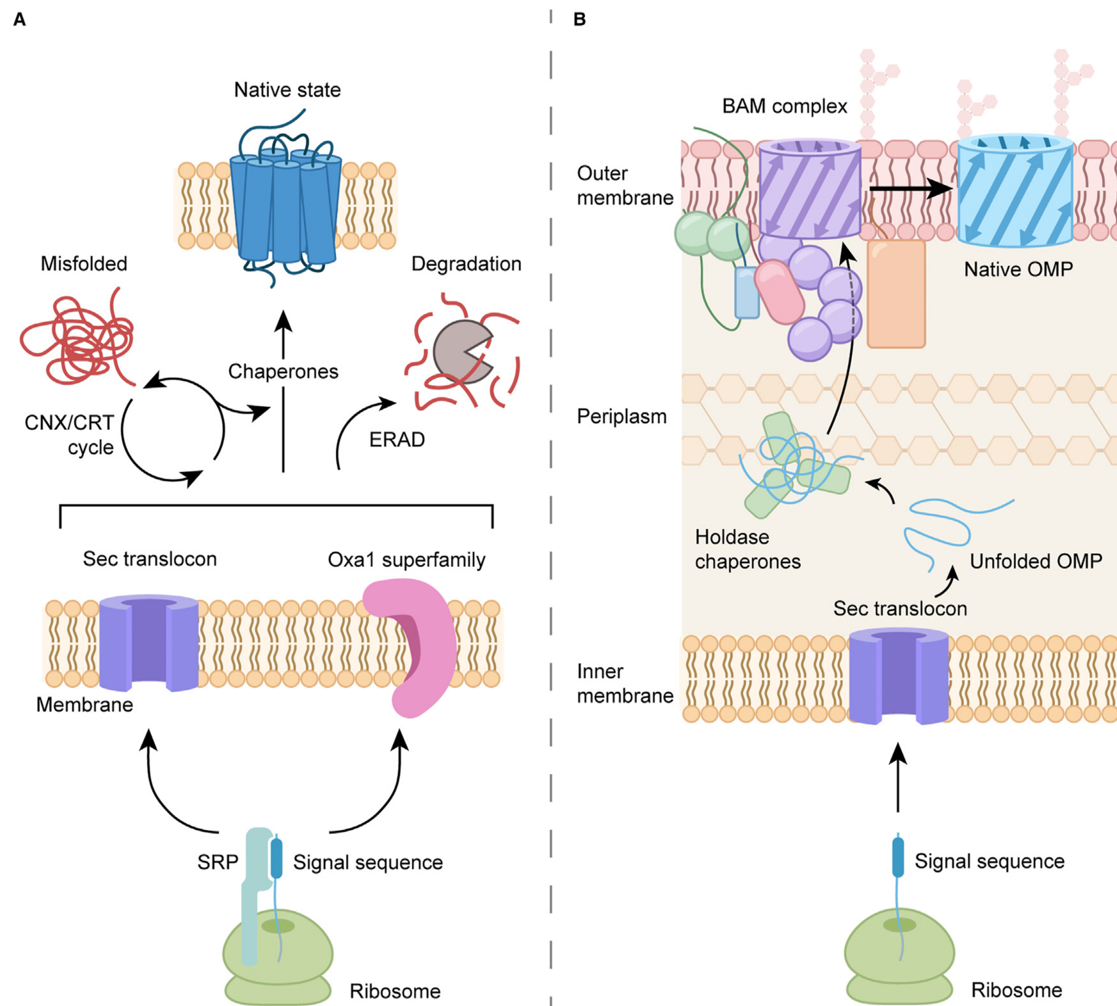

Fig. 1 Biogenesis of α-helical and β-barrel membrane proteins in cells. (A) Biogenesis of α-helical membrane proteins. Signal recognition particle (SRP) directs ribosome-nascent chain complexes (RNCs) to Sec translocons or Oxa1 superfamily insertases for co-translational insertion of membrane proteins. Upon insertion, transmembrane (TM) segments partition laterally according to their hydrophobicity and flanking charges, establishing membrane protein topology. Molecular chaperons and glycan-based quality-control systems—such as the calnexin/calreticulin (CNX/CRT) cycle—promote membrane protein folding and allow opportunities for refolding. Polypeptides that fail quality control are targeted for endoplasmic reticulum (ER)-associated degradation (ERAD), whereas correctly folded proteins are released for downstream trafficking and assembly. (B) Biogenesis of β-barrel membrane proteins (illustrated for outer membrane proteins in Gram-negative bacteria). Unfolded polypeptides of outer membrane proteins (OMPs) are exported through Sec translocons into the periplasm, where holdase chaperones capture and stabilize them in an assembly-competent state. The β-barrel assembly machinery (BAM) complex then couples folding with insertion into the outer membrane via a lateral-gate, yielding the native β-barrel architecture of OMPs.

residues (Dowhan et al., 2019; Knyazev et al., 2018; Driessen and Nouwen, 2008). Together, these mechanisms ensure that diverse membrane proteins insert with the correct topology while minimizing misfolding at early stages.

In the ER, Sec61 associates with accessory proteins such as the translocon-associated protein (TRAP) complex and the oligosaccharyltransferase (OST), enabling co-translational N-glycosylation (**Fig. 2**) (Sundaram et al., 2022; Russo, 2020). N-glycans act as both maturation timers and quality-control tags, directing monoglucosylated glycoproteins into the calnexin/calreticulin cycle (CNX/CRT cycle) (Guay et al., 2025; Caramelo and Parodi, 2008; Helenius and Aebi, 2004). The CNX/CRT cycle is an ER quality-control pathway in which the lectin chaperones CNX and CRT recognize monoglucosylated N-glycans and enable reglucosylation-dependent folding retries (**Figs. 1**A and **2**). Lumenal chaperones—including heat-shock protein 70 (HSP70; BiP in ER), heat-shock protein 40 (HSP40), and protein disulfide isomerase (PDI) family—complement this process by preventing aggregation and facilitating disulfide bond formation (**Fig. 2**) (Braakman and Bulleid, 2011; Anelli and Sitia, 2008). Together, these systems ensure that only properly folded glycoproteins exit the ER. Sec61 also collaborates with EMC and additional factors to coordinate the order of helix insertion, thereby preventing kinetic traps such as helix mispacking or premature oligomerization

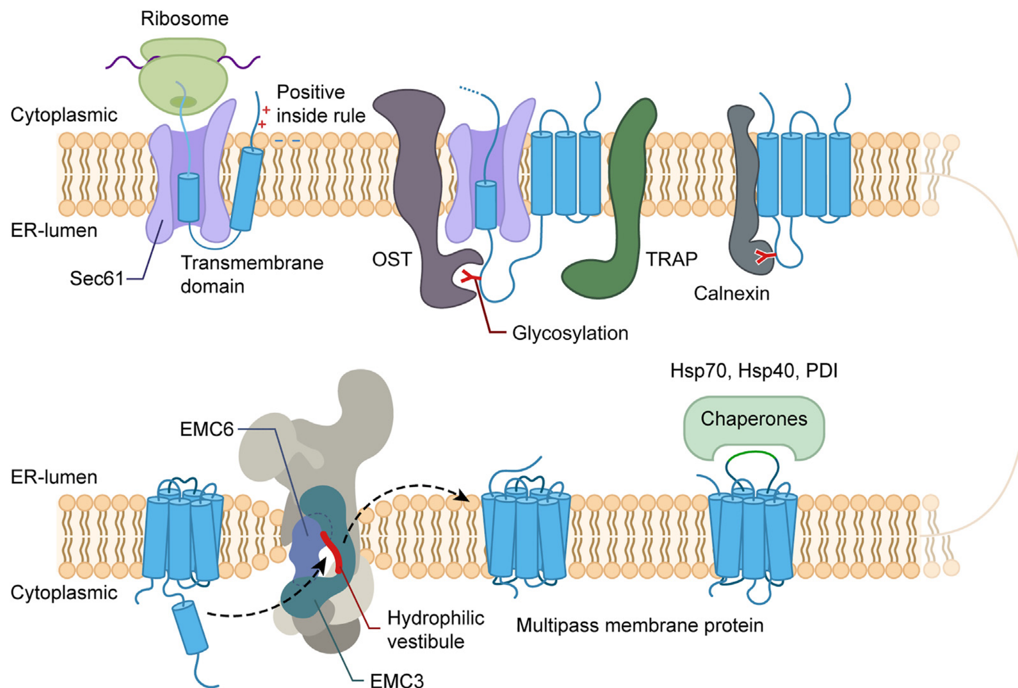

Fig. 2 Insertion and folding of multipass α-helical membrane proteins at the endoplasmic reticulum. Once the ribosome-nascent chain complex (RNC) docks at the Sec61 translocon via the signal recognition particle (SRP) pathway and translation resumes, the nascent chain is threaded into the channel, where transmembrane (TM) segments form helices and partition laterally through the Sec61 lateral gate into the lipid bilayer. Insertion of TM helices is influenced by their hydrophobicity and flanking charges, lipid composition of the endoplasmic reticulum (ER), and the membrane potential. The ER membrane complex (EMC) assists helix insertion via the EMC3-EMC6 hydrophilic vestibule and cooperates with Sec61 to ensure the proper topology of multipass membrane proteins. In our schematic, one of the EMC modes illustrates the post-translational insertion of the C-terminal helix by EMC, completing the final membrane protein topology. With topology established by Sec61 and EMC, insertion is coupled to luminal modification and folding surveillance, where oligosacharyltransferase (OST), acting in association with the translocon-associated protein (TRAP) complex, catalyzes N-glycosylation of exposed luminal loops, thereby stabilizing and refining TM orientation. These N-glycans can be monoglucosylated, recruiting calnexin (CNX) and calreticulin (CRT) for lectin chaperone-mediated folding and quality control. Additionally, luminal chaperons—including heat-shock protein 70 (HSP70; BiP in ER), heat-shock protein 40 (HSP40), and protein disulfide isomerase (PDI) family—can prevent aggregation and promote disulfide bond formation.

(Hegde and Keenan, 2022; Chitwood and Hegde, 2019; Shurtleffn et al., 2018). Thus, the ER translocon Sec61 is best understood not as a passive pore but as a dynamic assembly line that couples insertion, glycosylation, disulfide formation, and early folding quality control (Fig. 2).

In Gram-negative bacteria, β-barrel OMPs face a distinct biogenesis challenge due to their periplasmic transit. After Sec-dependent export into the periplasm, OMPs are captured and stabilized by holdase chaperones such as SurA and Skp, whereas DegP acts as a dual-function quality-control factor, transiently sequestering misfolded proteins and degrading those that fail to refold (Fig. 1B) (Devlin and Fleming, 2024; Goemans et al., 2014; Merdanovic et al., 2011; Sklar et al., 2007). Final insertion and folding are tightly coupled processes mediated by the BAM complex, composed of BamA and its associated lipoproteins (BamB—E) (Fig. 1B) (Noinaj et al., 2013, 2017; Hagan et al., 2011; Sklar et al., 2007). Structural studies support a lateral-gate model in which BamA transiently opens to locally perturb the membrane and template β-strand augmentation of nascent OMPs, enabling β-sheet closure and barrel formation (Noinaj et al., 2013, 2015, 2017; Bakelar et al., 2016; Gu et al., 2016). This process does not require ATP; instead, it is driven by the favorable free energy of β-sheet completion and bilayer partitioning, with periplasmic chaperones and BamA-mediated membrane remodeling lowering the kinetic barriers. Analogous machineries in eukaryotic organelles—including the sorting and assembly machinery (SAM) in mitochondria and outer envelope proteins (OEPs) in chloroplasts—highlight a conserved strategy for β-barrel protein biogenesis across compartments (Diederichs et al., 2021; Walther and Rapaport, 2009; Schleiff and Soll, 2005).

Because insertion and early folding are intrinsically error-prone, cells invest substantial resources in quality-control surveillance and triage mechanisms. In the ER, quality control is initiated co-translationally (Eisenack and Trentini, 2022; Ellgaard and Helenius, 2003): for example, the Sec63 J-domain recruits the heat-shock protein BiP, which then binds newly exposed luminal segments of the nascent chain as they emerge through Sec61 (Wentink et al., 2025; Otero et al., 2010). Subsequently, the lectin chaperones monitor glycoprotein folding through glucose trimming and UGGT-dependent reglucosylation, thereby providing retry signals

for incompletely folded substrates (Caramelo and Parodi, 2015). Stalled or collided ER-bound ribosomes activate ribosome-associated quality control (RQC) to eliminate defective nascent chains (Joazeiro, 2019; Brandman and Hegde, 2016). Misfolded or persistently unassembled membrane proteins are targeted to ER-associated degradation (ERAD), which is classically subdivided into ERAD-L (luminal domains), ERAD-M (TM domains), and ERAD-C (cytosolic domains) (**Fig. 1**A) (Sergejevs and Carvalho, 2025; Christianson et al., 2023; Christianson and Ye, 2014; Ruggiano et al., 2014). Substrates are captured by lectins and adaptors (e.g., OS-9 and EDEM for glycoproteins) and delivered to membrane-embedded E3 ubiquitin ligases (e.g., HRD1, gp78/AMFR, and MARCH6/TEB4) for ubiquitination. Retrotranslocation (dislocation) across the ER membrane converges on p97/VCP ATPase complexes, together with cofactors such as UFD1-NPL4, which extract ubiquitinated clients into the cytosol for proteasomal degradation. Structural and genetic data further support roles for HRD1 and Derlin family proteins in forming the retrotranslocation conduit (Guo et al., 2025; Rao et al., 2023; Schoebel et al., 2017; Greenblatt et al., 2011; Carvalho et al., 2010; Lilley and Ploegh, 2004). When ER burden exceeds capacity, the unfolded protein response (UPR) rebalances proteostatic flux by transiently reducing protein translation via the PERK signaling pathway, enhancing folding and ERAD capacities through ATF6 and IRE1α-XBP1 signaling, and—if stress remains unresolved—initiating apoptosis (Hetz et al., 2020; Karagöz et al., 2019; Walter and Ron, 2011).

Comparable protein quality control logic operates in other compartments, adapted to their energetic and structural constraints. In bacteria, envelope quality control relies on stress-response regulons (Merdanovic et al., 2011; Silhavy et al., 2010; Ruiz et al., 2006): the σ^E and Cpx pathways upregulate periplasmic chaperones and proteases; SurA and Skp buffer OMP aggregation, while DegP (HtrA) clears terminally misfolded clients. At the inner membrane, the AAA^+ protease FtsH degrades misfolded or misassembled α-helical membrane proteins (Yang et al., 2018; Ito and Akiyama, 2005). In mitochondria, the i-AAA protease YME1L and the m-AAA proteases AFG3L2/paraplegin monitor protein quality in the inner membrane, while OMA1 is activated by loss of membrane potential or related stresses to cleave OPA1 and remodel mitochondrial fusion-fission dynamics (Szczepanowska and Trifunovic, 2022; Quirós et al., 2015; Rugarli and Langer, 2012). When damage persists, mitophagy is engaged to eliminate defective organelles. In the eukaryotic ER, chronic stress triggers selective ER-phagy through dedicated receptors, providing a parallel route for clearing defective membrane proteins and remodeling stressed ER subdomains (Reggiori and Molinari, 2022; Wilkinson, 2020).

Overall, cells stabilize nascent chains, regulate the timing of insertion and assembly, and selectively remove nonproductive species, thereby restricting the accessible folding landscape to favor native outcomes (Okiyoneda et al., 2011; Walter and Ron, 2011; Hartl et al., 2011). Conversely, perturbations to translation kinetics, membrane lipid composition, cellular redox load, or electrochemical gradients can shift the folding balance, leading to long-lived off-pathway states. Thus, folding yield and fidelity are emergent properties of the entire biogenesis-quality control pipeline, rather than fixed traits of the polypeptide itself.

Physicochemical principles of membrane protein folding

Protein folding in membranes is governed by the same fundamental physicochemical principles as water-soluble proteins, yet the lipid bilayer reshapes their relative contributions and constrains the accessible conformational space (Corin and Bowie, 2020). In other words, membrane protein folding cannot be decoded from sequence alone; rather, it arises from a contextual co-code between amino acid chemistry and the physicochemical properties of the lipid bilayer, which together determine topology, folding routes, and ultimately function (Levental and Lyman, 2023; Dowhan et al., 2019; Marsh, 2008; Bogdanov and Dowhan, 1999). Structurally, the lipid bilayer is only a few nanometers thick but highly anisotropic, providing a low-dielectric medium in which polarity decreases steeply from the aqueous interface, through the headgroup region, to the hydrocarbon core (**Fig. 3**) (Corin and Bowie, 2020; Nagle and Tristram-Nagle, 2000). The transfer of nonpolar side chains from water into the bilayer core yields a strong thermodynamic drive for hydrophobic burial (Moon and Fleming, 2011; Hessa et al., 2005; White and Wimley, 1999). However, desolvation of the peptide backbone is energetically unfavorable unless compensated by intramolecular hydrogen bonding (Bowie, 2011). Therefore, the formation of regular secondary structures such as α-helices or β-sheets within the membrane is essential, as these motifs internally satisfy backbone hydrogen-bonding requirements and thereby offset the energetic cost of desolvation (Bowie, 2011; Moon and Fleming, 2011; White, 2005).

Lipid membranes are not passive solvents but active participants in membrane protein folding and function (Dowhan et al., 2019; Hong, 2015; Ding et al., 2015; Phillips et al., 2009). Bilayer properties—including thickness, headgroup charge, acyl-chain length and saturation, and sterol content—collectively define the lateral pressure profile and elastic moduli to which proteins must adapt (Andersen and Koeppe, 2007; Lee, 2004). Hydrophobic mismatch between a protein's effective hydrophobic length and the surrounding bilayer thickness imposes energetic penalties that can be relieved by helix tilt, local bilayer deformation, or lipid rearrangement (**Fig. 3**) (Andersen and Koeppe, 2007; Kandasamy and Larson, 2006; Hong and Tamm, 2004; Killian, 1998). See also chapter 6.12 on Membrane Protein-Lipid Match and Mismatch by O.G. Mouritsen in this volume. Cholesterol typically thickens and orders lipid bilayers, increasing their elastic moduli and promoting tighter molecular packing, although this effect diminishes in lipid bilayers enriched in polyunsaturated acyl chains (Doole et al., 2022; Pan et al., 2008, 2009; Rog et al., 2009; Lundbaek et al., 2003). In contrast, polyunsaturated lipids disorder and soften membranes, enhancing flexibility and lowering energetic barriers between conformational states (Baccouch et al., 2023). Beyond these generic effects, specific lipids can bind at non-annular sites to stabilize membrane proteins (Abramsson et al., 2025; Mukhaleva et al., 2024; Hedger et al., 2019; Guixà-González et al., 2017; Pan et al., 2008). Notable examples include cardiolipin bound to bacterial and mitochondrial transporters (Abramsson et al., 2025; Yi et al., 2022; Ruprecht et al., 2014; Pfeiffer et al., 2003), phosphatidylinositol-4,5-bisphosphate (PIP_2) interacting

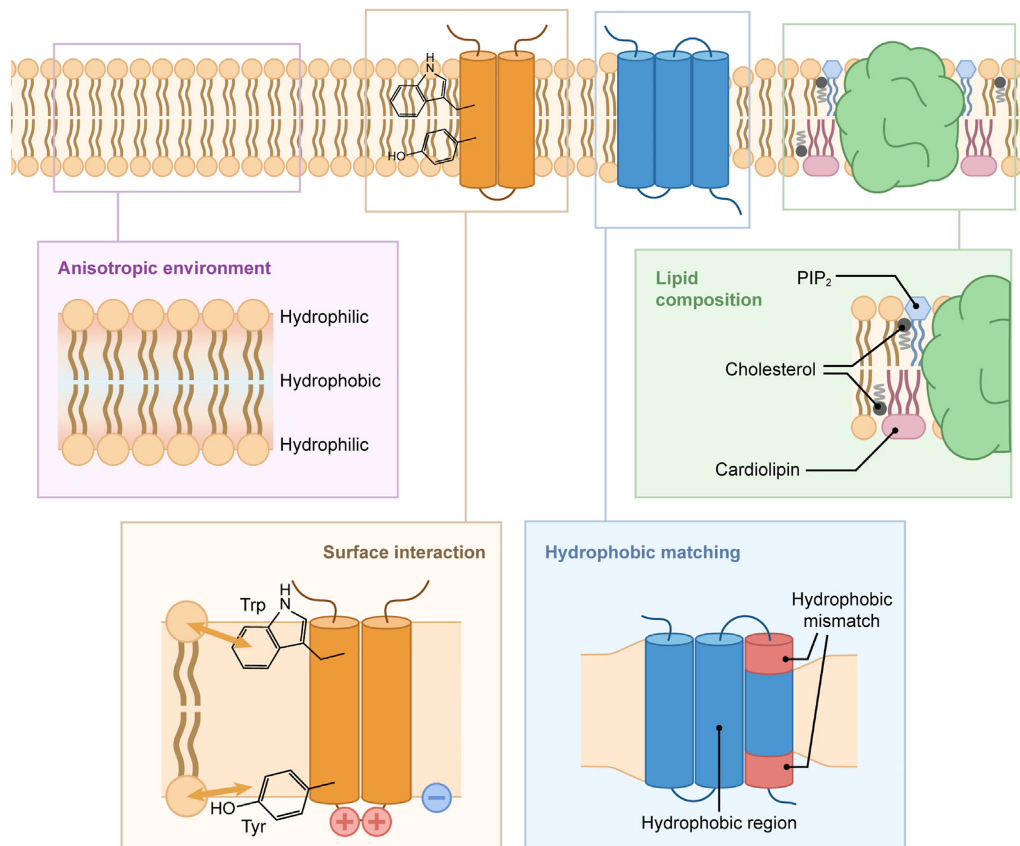

Fig. 3 Physicochemical properties of lipid bilayers influencing membrane protein folding and stability. The lipid bilayer is an anisotropic medium with hydrophilic headgroup regions and a hydrophobic hydrocarbon core. At the water-bilayer interface, aromatic residues such as tryptophan (Trp) and tyrosine (Tyr) typically act as molecular anchors that stabilize membrane proteins. Through surface interaction with lipid headgroups while simultaneously contacting the hydrocarbon core, these aromatic residues help secure the placement of transmembrane (TM) helices. Lipid composition is heterogeneous across membranes and microdomains. Specific lipids such as phosphatidylinositol-4,5-bisphosphate (PIP_2), cholesterol, and cardiolipin can stabilize particular conformations via site-specific binding, whereas the overall composition tunes membrane thickness, stiffness, and interfacial chemistry, thereby influencing membrane protein folding and stability. Hydrophobic matching refers to the condition in which the hydrophobic span of TM helices closely matches the hydrophobic thickness of the surrounding bilayer, minimizing energetic strain. Under hydrophobic mismatch (a disparity between helix span and bilayer hydrophobic thickness; indicated in red), helices may tilt and the membrane may remodel locally by thickening or thinning, thereby altering protein conformation and stability.

with basic interfacial patches of channels and transporters (Logothetis et al., 2007; Suh and Hille, 2005), and cholesterol molecules occupying defined cavities in GPCRs and ion channels (Hedger et al., 2019). Such specific lipid-protein interactions can tune equilibrium stabilities and modulate allosteric transitions (Fig. 3).

Aromatic residues such as tryptophan and tyrosine are enriched at the membrane interface, where their amphipathic character enables them to serve as aromatic anchors that stabilize TM helices at the water-lipid boundary (Fig. 3) (Hong et al., 2007; Killian and von Heijne, 2000; Yau et al., 1998). These residues interact simultaneously with the hydrocarbon core and interfacial headgroups, thereby minimizing the energetic penalty imposed by the steep polarity gradient across the membrane interface (Khemaissa et al., 2021; de Jesus and Allen, 2013; MacCallum et al., 2008). Likewise, basic residues such as lysine and arginine often snorkel toward the phospholipid headgroups, extending their charged side chains into the aqueous phase (MacCallum et al., 2008; Chamberlain et al., 2004; Strandberg and Killian, 2003). This behavior underlies the well-established positive-inside rule, which biases cytoplasmic loop orientation and exerts a strong influence on overall membrane protein topology (von Heijne, 2006; Vonheijne, 1989). These interfacial side-chain preferences act as sequence-encoded cues that link local chemical environments to the global processes of membrane insertion, folding, and topology determination (MacCallum et al., 2008; Hessa et al., 2005).

Interfacial water molecules and ions transiently sample the headgroup region, where local fluctuations can generate packing defects within the membrane (Alam et al., 2025; Karathanou and Bondar, 2018; Friedman, 2018; Pasenkiewicz-Gierula et al., 2016; Melcrová et al., 2016). Such defects can lower the energetic barriers for helix insertion and rearrangement, thereby facilitating conformational sampling and topological reorganization (Tripathy and Srivastava, 2023; Steinkuhler et al., 2022; Sikdar et al., 2021). At the same time, they can leave backbone desolvation incompletely compensated, creating nucleation sites for non-native interactions and potential misfolding (Fernández and Berry, 2003). Reactive oxygen species (ROS) and lipid peroxidation

products exacerbate these effects by disrupting lipid order and producing highly disordered interfacial regions (Balakrishnan and Kenworthy, 2024; Ferreira et al., 2016; Van der Paal et al., 2016; Jarerattanachat et al., 2013; Jurkiewicz et al., 2012; Wong-Ekkabut et al., 2007). These processes underscore the delicate balance at the membrane interface, where modest perturbations can steer folding outcomes toward either stable bilayer incorporation or, conversely, destabilization and aggregation.

Two principal architectures—α-helical bundles and β-barrels—dominate membrane protein structure, each following distinct folding principles (MacKenzie, 2006; Engelman et al., 2003; White and Wimley, 1999; Tomasek and Kahne, 2021; Horne et al., 2020; Danoff and Fleming, 2017; Kleinschmidt, 2015; Noinaj et al., 2015; Hagan et al., 2011). In β-barrel OMPs of bacterial and mitochondrial membranes, the alternating polar and nonpolar sequence pattern of β-strands imparts amphipathicity that drives insertion into the bilayer and promotes barrel closure through the formation of an extensive inter-strand hydrogen-bonding network (Dhar et al., 2021; Tamm et al., 2004). Their stability depends on structural parameters such as barrel radius, strand tilt, and loop architecture (Hermansen et al., 2022; Pali and Marsh, 2001; Murzin et al., 1994). Barrel closure typically makes β-barrels more tolerant to hydrophobic mismatch than α-helical bundles, although they remain sensitive to interfacial electrostatics, curvature stress, and lipid composition (Machin et al., 2023; Horne et al., 2020; Srivastava et al., 2018; Danoff and Fleming, 2015; Hong and Tamm, 2004). In Gram-negative bacteria, for example, lipopolysaccharide (LPS) interacts electrostatically and through hydrogen bonding with basic residues in extracellular loops, thereby stabilizing β-barrel structures and promoting proper folding (Horne et al., 2020).

In α-helical membrane proteins of the bacterial inner membrane and the eukaryotic ER, the lipid bilayer promotes helix formation because intramolecular hydrogen bonds within TM segments compensate for backbone desolvation in the low-dielectric core (Corin and Bowie, 2022; Hong, 2014). Subsequent steps—helix packing and oligomeric assembly—are governed largely by short-range van der Waals complementarity, often mediated by small-residue motifs such as GxxxG that enable tight helix-helix association (Teese and Langosch, 2015; Walters and DeGrado, 2006; Russ and Engelman, 2000; Javadpour et al., 1999). TM helices typically associate in pairs as helical hairpins, forming the fundamental unit of higher-order assemblies (**Fig. 4**a) (Kim et al., 2023; Corin and Bowie, 2022; Choi et al., 2019; Krainer et al., 2018; Engelman and Steitz, 1981). Helical hairpin formation in membranes occurs on a timescale of at least ~20 ms which is about four orders of magnitude slower than the rapid folding of comparably sized soluble proteins (Kim et al., 2023). This kinetic slowdown arises from the high viscosity and limited lateral diffusivity of the lipid bilayer, which reduce the frequency of productive helix-helix encounters (Min, 2024; Kim et al., 2023). Interfacial salt bridges and hydrogen bonds function as molecular latches that stabilize established helical topologies, whereas reentrant loops and half-helices fine-tune ion or substrate permeation pathways (Pruitt et al., 2013; Romo et al., 2010; Jensen et al., 2003).

Folding of α-helical membrane proteins, such as the *E. coli* rhomboid protease GlpG and the human β_2-adrenergic receptor, typically proceeds in an N-to-C direction, matching the vectorial emergence of the nascent chain into the lipid bilayer (**Fig. 4**a) (Choi et al., 2019; Min et al., 2015). As TM helices are synthesized and inserted via the Sec translocon, they are expected to fold locally—often as helical hairpins—soon after membrane insertion (Kim et al., 2025; Min, 2024). Because the lipid bilayer stabilizes secondary structure but resists large-scale rearrangements, early-formed helices can serve as nucleation sites that bias subsequent packing and template the folding of downstream helices (Paslawski et al., 2015). Once a folding nucleus forms, the bilayer helps lock in its structure, rendering early folding events kinetically persistent and difficult to reverse (Min, 2024; Kim et al., 2023; Choi et al., 2022; Min et al., 2018). This intrinsic folding asymmetry reflects built-in stability differences, topological constraints imposed by the translocon, and the vectorial nature of protein synthesis. This feature is also evident in many repeat-containing or multi-domain membrane proteins, including transporters (Choi et al., 2022; Min et al., 2018). For example, in the human glucose transporter GLUT3 and the *E. coli* Cl^-/H^+ antiporter ClC-ec1, the N-terminal domain reliably folds first and serves as a structural template for the C-terminal half, with final interdomain assembly strongly influenced by lipid identity (**Fig. 4**b) (Choi et al., 2022; Min et al., 2018). Evolutionary analyses of GLUT family proteins suggest that sequence-encoded asymmetry and controlled metastability together define folding order, balancing foldability with functional optimization (Choi et al., 2022).

Many α-helical membrane proteins achieve full functional stability only as dimers or higher-order oligomers (Ni and Hong, 2024; Hrmova, 2024; Corin and Bowie, 2022; Sleno and Hébert, 2018; Cymer and Schneider, 2012; Clarke and Gulbis, 2012). Molecular dynamics (MD) simulation studies suggest that their assembly can proceed through multiple TM domain association steps rather than a simple two-state on-off transition (Blazhynska et al., 2023; Lamprakis et al., 2021; Itaya et al., 2021; Domanski et al., 2017, 2020; Milligan et al., 2019; Dunton et al., 2014). A single-molecule tweezer platform has recently been adapted for studying membrane protein interactomes, allowing for the resolution of the post-diffusion dimerization dynamics of TMHC2, a designed TM helix homodimer without a defined physiological function (Sadongo et al., 2025). This work revealed three discrete dimerization domains that assemble sequentially during association, providing the first experimental evidence for a multi-step process for TM domain dimerization (**Fig. 4**c) (Sadongo et al., 2025). The overall dimer stability is governed by the TM-core domain, which exhibits extremely slow dissociation kinetics and thereby dominates the kinetic stability of the complex. These findings suggest that hidden, transient intermediates in TM helix association may be more common than previously appreciated and highlight a powerful single-molecule approach for probing TM protein-protein interactions in native-like membrane environments.

Membrane protein misfolding and therapeutic approaches

Misfolding of membrane proteins contributes to pathology along two broad axes: loss of native function and the emergence of toxic gain of function (**Fig. 5**) (Marinko et al., 2019; Winklhofer et al., 2008). One major route in the loss-of-function mode is that

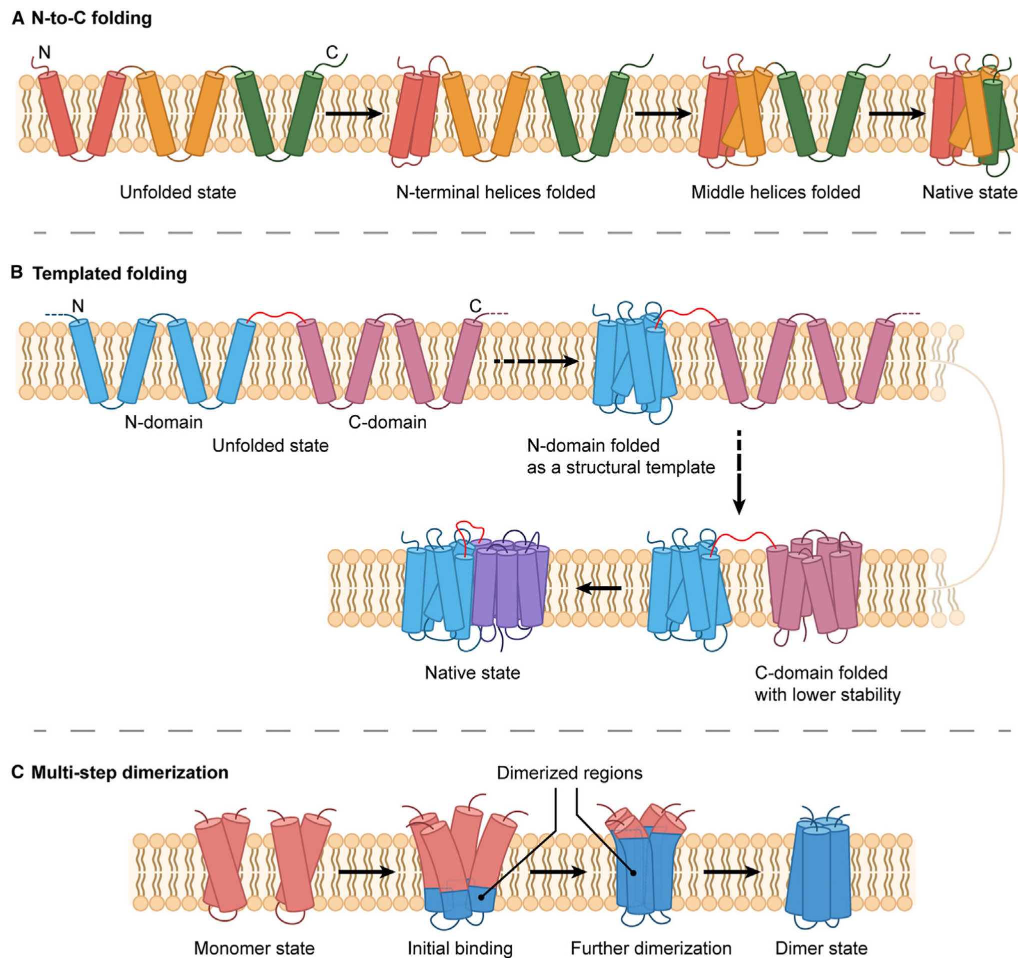

Fig. 4 Folding and assembly mechanisms of α-helical membrane proteins within lipid bilayers. Biophysical studies using single-molecule magnetic tweezers reveal key features of α-helical membrane protein folding and assembly, including N-to-C folding, templated folding, and multi-step dimerization. (A) N-to-C folding. Following bilayer insertion of transmembrane (TM) helices, the N-terminal segment often folds first and can bias subsequent packing and folding toward the C-terminus, leading to the native state. This N-to-C folding direction matches the direction of protein translation, supporting co-translational folding. During each folding step, a TM helix harpin typically serves as a stable structural unit, representing a folding intermediate. Example proteins include the *E. coli* rhomboid protease GlpG and the human β_2-adrenergic receptor. (B) Templated folding. For multi-domain membrane proteins such as those in the major facilitator superfamily (MFS) that follow the N-to-C folding pathway, the N-terminal domain (N-domain) similarly folds first, followed by folding of the C-terminal domain (C-domain). Once both domains are folded, interdomain assembly brings them together into the native structure. The N-domain can sometimes be more stable than the C-domain, acting as a structural template and thereby facilitating the interdomain assembly. The dashed arrows indicate that multiple intermediates may exist during the folding of each domain. Example proteins include the human glucose transporter GLUT3 and the *E. coli* Cl^-/H^+ antiporter ClC-ec1. (C) Multi-step dimerization. Separated monomers first encounter one another by lateral diffusion within the lipid bilayer. Once initial binding occurs, post-diffusion dimerization proceeds through a series of discrete, short-lived intermediates that reflect the stepwise engagement of distinct TM association domains. The fully assembled dimer state is ultimately established through this multi-step dimerization process. Example proteins include the designed TM helix homodimer TMHC2.

unstable variants are retained in the ER and targeted for ERAD, thereby reducing surface expression, even though properly folded states would have been functional (Marinko et al., 2019; Denny et al., 2013; Guerriero and Brodsky, 2012; Vembar and Brodsky, 2008). The cystic fibrosis transmembrane conductance regulator (CFTR), an ATP-gated chloride channel of the ATP-binding cassette (ABC) transporter family, provides a prime example: the ΔF508 mutation destabilizes nucleotide-binding domain interactions, leading to excessive ER retention and degradation while impairing trafficking and chloride transport—molecular hallmarks of cystic fibrosis (Lukacs and Verkman, 2012). Mutations in members of the ClC chloride channel family can disrupt helix-packing interfaces, leading to misassembly or gating defects that cause myotonia congenita (Jentsch and Pusch, 2018). Variants in KCNQ voltage-gated potassium channels that destabilize the voltage-sensor domain or impair gating can give rise to long-QT syndromes and epilepsies (Huang et al., 2018; Wu et al., 2016; Orhan et al., 2014). Destabilization of ABC lipid transporters (e.g., ABCA1, ABCG1, and ABCG5/8) and of the NPC1/NPC2 cholesterol-handling system underlies Tangier disease (ABCA1) and

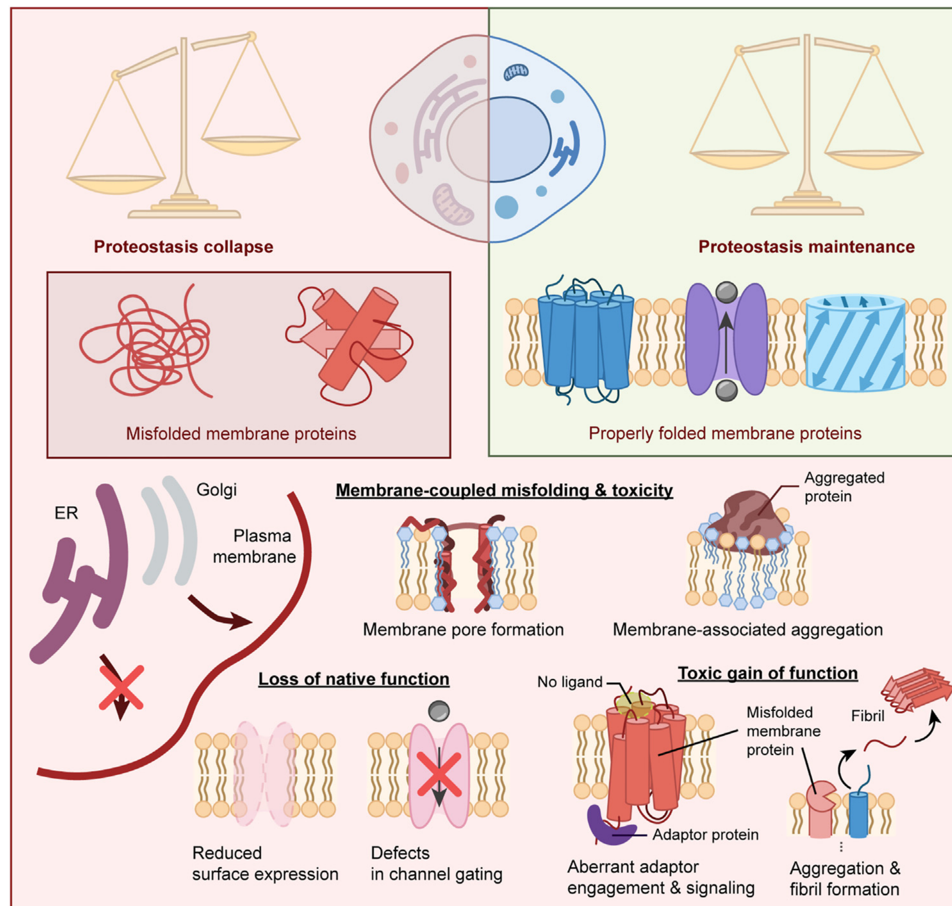

Fig. 5 Consequences of proteostasis collapse in membrane proteins. Under balanced proteostasis, folding, trafficking, and degradation are tightly coordinated to maintain cellular homeostasis. When this network collapses, however, misfolded or misassembled membrane proteins can accumulate. Moreover, in the collapsed state, trafficking between the endoplasmic reticulum and Golgi apparatus (ER-Golgi trafficking) can fail, reducing delivery to the plasma membrane and thereby decreasing surface expression. This contributes to a loss-of-function phenotype. More broadly, three major pathological outcomes of proteostasis collapse in membrane proteins can arise: (i) loss of native function, including reduced surface expression or defects in channel gating; (ii) toxic gain of function, including signaling dysregulation by aberrant adaptor engagement or aggregation and fibril formation triggered by aberrant enzymatic processing; and (iii) membrane-coupled misfolding and toxicity, including membrane-permeabilizing pore formation or membrane-associated aggregation.

Niemann-Pick type C disease (NPC1/NPC2), respectively (Vanier, 2010; Oram and Vaughan, 2006; Baldan et al., 2006; Scott and Ioannou, 2004).

Misfolded or misassembled membrane proteins can acquire aberrant activities that compromise cellular integrity (**Fig. 5**) (Marinko et al., 2019). For example, the γ-secretase complex, with presenilin as its catalytic core, requires assisted assembly in the bilayer, with dedicated factors and precise stoichiometry guiding the formation of a functional enzyme (Almén et al., 2009; Sato et al., 2007; Edbauer et al., 2003). However, pathogenic variants destabilize the complex and shift amyloid precursor protein (APP) processing toward amyloid-β42 (Aβ42), thereby increasing the Aβ42/40 ratio characteristic of familial Alzheimer's disease (Szaruga et al., 2017; Chávez-Gutiérrez et al., 2012; Shen and Kelleher, 2007). Misassembled subunits can also exert dominant-negative effects by trapping wild-type partners in nonfunctional complexes, as observed in dimeric ion channels and ABC transporters (Rinne et al., 2015, 2024; Jentsch and Pusch, 2018; Graf et al., 2004; Kubisch et al., 1998). Likewise, GPCR variants can aberrantly engage cytosolic scaffold or adaptor proteins in a ligand-independent manner, promoting receptor desensitization and internalization and thereby disrupting downstream signaling (Kocan et al., 2009).

In many cases, loss of native function and toxic gain of function are not mutually exclusive but operate concurrently within the same system (Balendra and Isaacs, 2018; Winklhofer et al., 2008). In the retina, for example, P23H rhodopsin mutants misfold in the ER and are largely eliminated by ERAD, reducing surface expression and impairing phototransduction (Griciuc et al., 2010; Illing et al., 2002). Yet, residual species that evade quality control can accumulate at the membrane, where they misassemble and exert toxic gain of function in retinitis pigmentosa (Sakami et al., 2014; Haeri and Knox, 2012). Within mitochondria, oxidative stress destabilizes the proteome at multiple levels: cardiolipin peroxidation compromises respiratory-chain supercomplexes and reduces oxidative phosphorylation capacity, while misfolding of transporters and assembly factors activates mitophagy and drives

bioenergetic collapse (Schlame and Greenberg, 2017; Paradies et al., 2014a). These primary losses of function are further amplified by secondary toxic outputs, notably ROS and lipid peroxidation (Paradies et al., 2014a, 2014b). While ROS broadly oxidize proteins and lipids, lipid peroxidation specifically generates hydroperoxides and reactive carbonyl species (RCS; e.g., 4-HNE and 4-HHE), which soften and thin membranes while covalently modifying residues such as Lys, His, Cys, Met, and Trp (Gaschler and Stockwell, 2017; Runas and Malmstadt, 2015; Wong-Ekkabut et al., 2007; Yamada et al., 2004; Doorn and Petersen, 2002). Such membrane modulation and residue modifications can destabilize helix-helix packing interactions, thereby promoting misfolded or misassembled states (Wiczew et al., 2021; Van der Paal et al., 2016; Liu et al., 2008).

Interactions with lipid membranes constitute another critical dimension of misfolding pathology (**Fig. 5**) (Mirdha, 2024; Hong, 2015). Although Aβ and α-synuclein are not canonical TM proteins, their oligomers associate with and remodel membranes, generating Ca^{2+}-permeable defects that exemplify toxic gain of function at the bilayer and contribute to the pathogenesis of Alzheimer's and Parkinson's diseases (Fusco et al., 2017; Demuro et al., 2005, 2011; Lashuel et al., 2002). Likewise, the prion protein (PrP), tethered to the outer leaflet of the plasma membrane by a glycosylphosphatidylinositol (GPI) anchor, undergoes conformational conversion from an α-helix- to a β-sheet-rich state within cholesterol- and sphingolipid-rich microdomains, where altered membrane composition can promote PrP aggregation and drive transmissible prion diseases (Conceicao et al., 2023; Puig et al., 2014; Baron et al., 2002; Taylor and Hooper, 2006). Beyond these protein-specific interactions, the physical properties of the bilayer itself constitute additional determinants of misfolding (Vendruscolo, 2022). The effective hydrophobic length of TM segments must match membrane thickness: deviations can bias helices toward nonnative packing or oligomeric stoichiometries (Bernhardt et al., 2025; Chadda et al., 2021; Marinko et al., 2019; Andersen and Koeppe, 2007; Jensen and Mouritsen, 2004). Cells normally tune bilayer thickness (e.g., via cholesterol and sphingolipid enrichment) to support their membrane proteome, but an imbalance imposes elastic penalties that misdirect folding pathways (Holthuis and Menon, 2014; van Meer et al., 2008). Accumulation of ceramides or lysolipids can introduce packing defects that promote misfolding and aberrant protein-protein associations (Lima et al., 2025; Lai et al., 2023; Kurzawa-Akanbi et al., 2021; Sheikh and Nagai, 2011).

Pharmaceuticals have conventionally targeted membrane protein function via agonists, antagonists, and channel blockers (Zhang et al., 2024; Santos et al., 2017; Bagal et al., 2013). A complementary strategy is to reshape the folding landscape to increase the fraction of molecules that reach and remain in the native basin (Marinko et al., 2019; Beerepoot et al., 2017; Wang et al., 2014; Leidenheimer and Ryder, 2014; Tao and Conn, 2014; Mendre and Mouillac, 2010; White et al., 2009; Bernier et al., 2004; Morello et al., 2000a). This can be pursued through several key levers, the first involving small-molecule stabilizers that thermodynamically favor native or near-native conformations (**Fig. 6**) (Van Goor et al., 2011; Bernier et al., 2004; Morello et al., 2000a; Sato et al., 1996). Orthosteric ligands mimic endogenous ligands—or occupy the same binding site—and can stabilize the bound conformation, thereby rescuing trafficking of otherwise unstable variants (Van Goor et al., 2011; Mendre and Mouillac, 2010; Bernier et al., 2004; Morello et al., 2000a; Sato et al., 1996). Classic examples include retinal analogs such as 9-cis-retinal, which stabilize misfolded opsins and restore trafficking in models of retinitis pigmentosa (Chen et al., 2014; Mendes and Cheetham, 2008; Noorwez et al., 2004; Saliba et al., 2002); vasopressin V2 receptor (V2R) antagonists such as SR121463 and VPA-985, which recover surface expression of V2R mutants associated with nephrogenic diabetes insipidus (Robben et al., 2007; Wüller et al., 2004; Morello et al., 2000b); and small-molecule orthosteric ligands such as propranolol for the β_2-adrenergic receptor and IN3 for the gonadotropin-releasing hormone receptor (GnRHR), both of which enhance folding and trafficking efficiency in misfolded variants (Parmar et al., 2017; Conn and Janovick, 2009; Janovick et al., 2002, 2003).

In contrast, allosteric stabilizers engage structurally privileged sites—including interhelical grooves, lipid-facing pockets, and seam interfaces—providing stabilization without requiring similarity to endogenous ligands (**Fig. 6**) (Fiedorczuk and Chen, 2022; Kruse et al., 2013; Janovick et al., 2009). In the calcium-sensing receptor (CaSR), the positive allosteric modulator cinacalcet—clinically used for hyperparathyroidism and chronic renal disease—rescues misfolded receptor mutants associated with familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism by promoting folding and surface trafficking (Huang et al., 2011; Reh et al., 2011). Likewise, positive allosteric modulators of the γ-aminobutyric acid type B (GABAB) receptor, such as CGP7930, facilitate maturation and plasma-membrane trafficking of misfolded subunits, while simultaneously enhancing receptor signaling (Adams and Lawrence, 2007). Lumacaftor (VX-809), typically classified as a CFTR corrector, also functions as an allosteric stabilizer of ΔF508-CFTR, improving folding and ER export, albeit without fully correcting the gating defect (Van Goor et al., 2011). Interestingly, certain pharmacological chaperones—regardless of whether they bind at orthosteric or allosteric sites—can act dually as negative modulators of receptor activity and positive modulators of protein biogenesis. For example, YC-001 suppresses basal rhodopsin signaling while promoting its proper folding and forward trafficking to the plasma membrane (Chen et al., 2018).

Proteostasis modulators alter the capacity and stringency of cellular protein quality control networks (**Fig. 6**) (Yang et al., 2024; Balch et al., 2008). By tuning the UPR, ER chaperone activity, ERAD flux, or autophagy, cells can influence how marginal folding intermediates are triaged between rescue and degradation, thereby increasing the overall folding yield and improving surface delivery (Wiseman et al., 2022; Wang and Kaufman, 2016; Anelli and Sitia, 2008). For example, celastrol, a natural triterpene that induces the heat-shock response, has been shown to enhance ER export of ΔF508-CFTR by upregulating molecular chaperones and thereby augmenting the folding capacity of the ER (Mu et al., 2008). Conceptually, this lever also includes regulating translocon and insertase assistance during co-translational insertion, which is particularly important for multipass GPCRs and ion channels whose folding efficiency depends on ribosome-Sec61 dynamics (Smalinskaite and Hegde, 2023). Small molecules such as eeyarestatin I, CAM741, and CADA illustrate how pharmacological perturbation of Sec61 gating can alter the insertion and maturation of

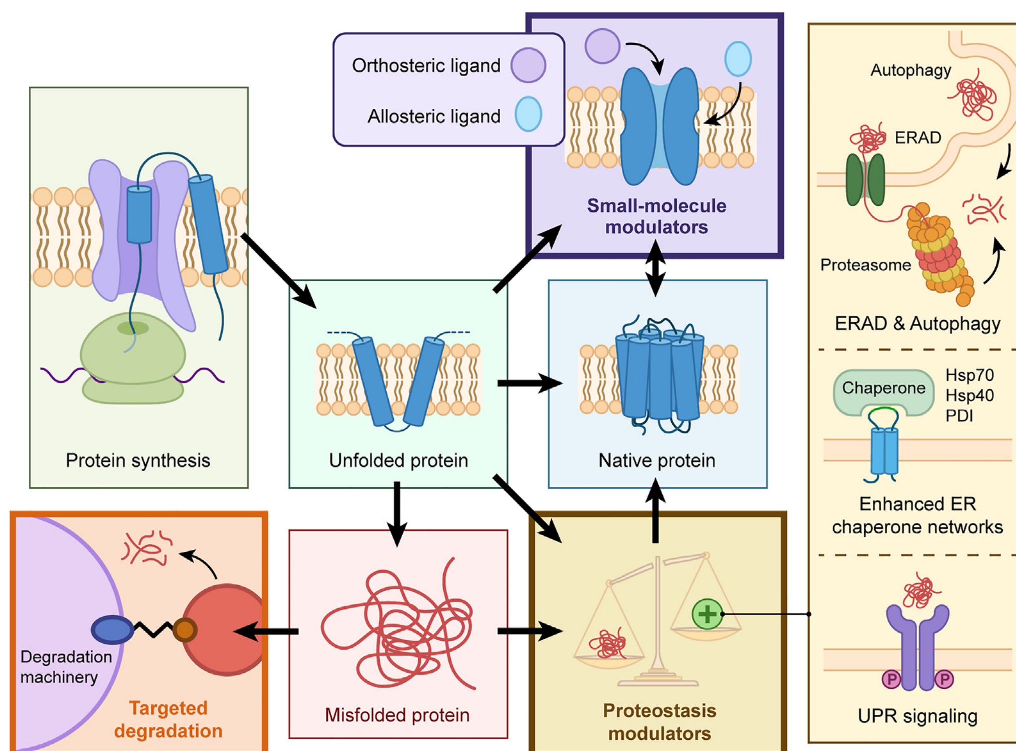

Fig. 6 Therapeutic intervention in membrane protein proteostasis. During protein synthesis, nascent polypeptides emerge in a fully or partially unfolded state and ultimately reach their native conformation through co- and post-translational folding. Therapeutic strategies can intervene at multiple points along this pathway. Small-molecule modulators—including orthosteric ligands and allosteric ligands—can remodel the folding energy landscape to favor the native conformation, thereby enhancing surface expression and functional activity. Proteostasis modulators can act on unfolded protein response (UPR) signaling, augment endoplasmic reticulum (ER) chaperone networks, and enhance ER-associated degradation (ERAD) or autophagy, thereby increasing folding efficiency and promoting forward trafficking. Targeted degradation strategies selectively eliminate pathogenic protein species by recruiting endogenous degradation machinery—proteasome engagement via proteolysis-targeting chimeras (PROTACs) or lysosomal uptake via lysosome-targeting chimeras (LYTACs)—while minimizing effects on native functional protein populations.

membrane proteins, underscoring early biogenesis steps as a potential therapeutic target (Xin et al., 2025; Hassdenteufel et al., 2018; Linxweiler et al., 2017).

Targeted degradation emerges as a critical therapeutic approach, prioritizing elimination over folding rescue (Fig. 6) (Zhao et al., 2022; Alabi and Crews, 2021). Platforms such as proteasome-targeting chimeras (PROTACs), lysosome-targeting chimeras (LYTACs), and related targeted degraders are being extended to membrane proteins, including GPCRs and RTKs (Keen et al., 2024; Xie et al., 2023; Bekes et al., 2022; Huber et al., 2022; Burslem et al., 2018a, 2018b; Powell et al., 2018; Santos et al., 2017; Sakamoto et al., 2001). ARV-110 and ARV-471 represent first-in-class PROTACs that degrade nuclear hormone receptors and have advanced to clinical trials, establishing proof of the modality (Ma and Zhou, 2025; Arnold, 2024; Mullard, 2019, 2021). In parallel, preclinical PROTACs directed against membrane proteins such as epidermal growth factor receptor (EGFR) and c-Met receptor demonstrate feasibility for therapeutic downregulation of RTKs (Ruffilli et al., 2025; Burslem et al., 2018a). Likewise, EGFR-directed LYTACs, including antibody-glycoprotein conjugates such as cetuximab-based constructs, have been shown to induce lysosomal degradation of EGFR and effectively deplete pathogenic receptor pools (Ahn et al., 2021, 2023; Banik et al., 2020). The therapeutic goal in these cases is not to rescue folding but to selectively eliminate pathogenic protein populations while sparing—and in some cases indirectly enhancing—the functional wild-type pool (Alabi et al., 2021). Future therapeutic strategies will likely integrate folding rescue with targeted degradation to finely tune membrane protein homeostasis.

Outlook

This chapter has outlined how membrane proteins fold within the complex environment of the lipid bilayer, covering cellular folding pathways, their physicochemical principles, the pathological consequences of misfolding, and emerging therapeutic interventions. Overall, these perspectives emphasizes that the fidelity of membrane protein folding is not determined by sequence alone but arises from dynamic interactions among proteins, lipids, and quality-control systems. Future advances are likely to come from the integration of high-resolution single-molecule biophysics, multiscale computational approaches, and cell-based folding assays,

which together can capture co-translational and lipid-dependent influences on membrane protein folding in real time. A deeper understanding of these processes will, in turn, help elucidate the mechanisms of misfolding-related diseases and guide the development of therapeutic strategies.

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