Membrane Proteins at the Margins: Understanding Nature's Most Frustrated Molecules

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Membrane proteins must balance the structural constraints of function against those of biosynthesis and folding. Their transmembrane domains, in particular, must accommodate functional polar residues while maintaining sufficient hydrophobicity to achieve proper solvation within the lipid bilayer. Membrane proteins navigate these trade-offs with the help of a handful of molecular chaperone and membrane insertase proteins that suppress misfolding and clear a path into the membrane. Despite their simplistic mode of action, these quality control proteins support the biosynthesis of thousands of membrane proteins that vary considerably with respect to their physicochemical properties. Our collective work shows how the failure of chaperones to consistently recognize polar segments within their clients generates inefficiencies in membrane protein biosynthesis that ultimately influence evolutionary pathways and give rise to various genetic diseases. Our investigations have also unexpectedly revealed that the manner in which nascent proteins interact with these chaperones can allosterically regulate the outcomes of protein synthesis in real time. Finally, we outline ongoing efforts to leverage our discoveries and methodological innovations to gain new insights into the actions of an emerging class of pharmaceuticals designed to restore the expression of misfolded membrane protein variants. Together, our findings reveal how the intrinsic inefficiencies associated with the process of folding proteins into membranes presents nature (and the pharmaceutical industry) with both challenges and opportunities.