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Protein folding in membranes

By virtue of their immersion into the hydrophobic membrane environment and the strong coupling between secondary structure formation and membrane partitioning, membrane proteins typically fold into extremely stable structures. Unlike the situation for water soluble proteins, the "denaturation" of membrane proteins by temperature, pH or chemical denaturants rarely leads to an unfolded protein chain. This means that equilibrium denaturation studies on membrane proteins are challenging in the laboratory and are rare in the literature. Thus, our understanding of the detailed principles of folding and unfolding of proteins in membranes is still fragmentary; only the parts of the folding/unfolding process that are amenable to experimental study are described in much detail. Many of the same issues are at play in the living cell where a series of special protein machines are essential for the sorting and folding of membrane proteins. For this Special Issue of BBA Biomembranes, I have brought together a group of researchers from a broad cross-section of the field to describe what is known about membrane protein folding, and perhaps more importantly, to highlight the questions in the field that remain unanswered.

The issue is grouped by area into four sections: Fundamental principles, helix–helix interactions, membrane protein folding *in vitro* and membrane protein folding *in vivo*.

The first section contains a group of articles that set the tone of the membrane protein folding problem by providing information on some of the fundamental principles. Jie Liang and colleagues describe the state of computational studies on membrane proteins and Nicoleta Bondar and Steve White describe the contribution of hydrogen bonding to membrane protein function. Articles by Drake Mitchell and Richard Epand describe the critical contribution of lipids and protein–lipid interactions to folding and function of membrane proteins.

The second section focuses on the special case of membrane protein folding that involves the lateral interactions between membrane-spanning α-helices. Such studies have long been some of the most quantitative and detailed in the membrane protein folding field. The increasing sophistication of the experimental and computational techniques available to study helix–helix interactions is described by Yechiel Shai and colleagues. Dirk Schneider and colleagues also describe the relevance of the rapidly increasing number of three dimensional structures of helical dimers to our understanding of the field. Lars Schaffer and his co-authors describe the effect of transmembrane helices on lipid organization. Rounding out the second section, Lijuan He and Kalina Hristova describe the contributions of helix–helix interactions to the activation of receptor tyrosine kinases in living cell membranes. These articles provide a reason to hope that a coherent description of helix–helix interactions in membranes, with predictive power, could arise in the near future. This has long been considered as a potential "Rosetta Stone" for solving the membrane protein folding problem.

In the third section of this special issue, the folding and function of complex membrane proteins *in vitro* are described. These articles include discussions by Alexey Ladokhin, David Eliezer, Daniel Otzen and their co-authors on membrane protein folding that takes place mostly on membrane surfaces. Rod Tweten describes the folding and assembly of bacterial pore-forming cytolysins, while John Tomich and colleagues write about engineered ion channel peptides as a possible treatment for cystic fibrosis, a disease that arises due to the misfolding of the cystic fibrosis transmembrane regulator, a membrane protein. Finally Jim Bowie, Paula Booth, and their co-authors discuss membrane protein folding in the more classical terms of thermodynamic stability, describing special experimental methods needed to study the stability of membrane proteins.

Finally, in the fourth section, articles describe the folding and misfolding of membrane proteins in the living cell. Dante Ricci and Tom Silhavy describe the bacterial Bam machine as a "molecular cooper" while Doron Rappaport and Kai Dimmer outline the remaining mysteries in the folding and assembly of mitochondrial membrane proteins. Although mitochondrial membrane protein folding is highly complex, it is also one of the most intensively studied systems. A sophisticated understanding of the molecular machinery is at hand. Articles by Daniel Daley, William Dowhan and their co-authors describe the results of experimental manipulation of proteins and lipids, respectively, on membrane protein folding. Membrane protein folding *in vivo* finishes with membrane protein folding gone wrong; Scott Houck and Douglas Cyr describe cellular quality control systems for membrane protein folding, and Charlie Deber and colleagues describe the role of membrane protein misfolding in disease.

In the pages of this special issue, the authors have provided a broad cross section of the rapidly growing knowledge in the field of membrane protein folding. Yet they also articulate the unanswered questions that continue to drive the field forward. While some parts of the membrane protein folding puzzle are becoming well-resolved, others remain poorly understood. With the continued efforts of these scientists and others like them, we can be sure that the sophistication with which we can describe membrane protein folding will continue to improve.

I dedicate this special issue to those scientists who have the courage, tenacity and creativity required to study the folding of membrane proteins. My special thanks to all the authors for the hard work required to write these excellent articles. My personal thanks to the editors of BBA Biomembranes as I am honored to have been invited to be Guest Editor for this Special Issue. Finally, many thanks to the Editorial Staff at BBA Biomembranes who made this whole complex endeavor come together.

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William C. Wimley, PhD, grew up in Monroe, Connecticut, USA, where he decided at a very early age to become a scientist, eventually earning a B.S. in Biophysics from the University of Connecticut. He obtained a PhD in Biochemistry at the University of Virginia in 1990 where he studied the biophysics of lipid–lipid interactions in multicomponent bilayers. His postdoctoral studies were conducted at the University of California, Irvine where he investigated the interactions between peptides and membranes. In 1998, Dr. Wimley joined the faculty of the Biochemistry Department at the Tulane University School of Medicine in New Orleans, where his studies on peptide–membrane interactions have taken on a translational flavor. He currently focuses on the use of high-throughput methods to identify peptides that have potentially useful membrane activities, including antimicrobial activity, pore formation and membrane translocation.

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