

Protein folding is an amazing molecular process that occurs by sorting out an astronomical number of possible conformations down the free energy landscape. In a crowded cellular environment, however, environmental stresses or mutations can mislead polypeptide chains to misfolded or catastrophic aggregate states (**Fig. 1**). Therefore, these unnecessary proteins have

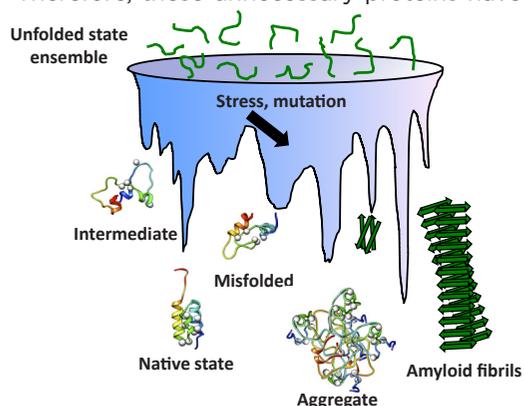


Fig. 1. Ruggedness of free-energy landscape in protein folding (modified from Hartl et al., *Nature* 2011, 475, 324-332.)

to be selectively cleared from cells for quality control and regulatory purposes. For the past decades, there have been remarkable advances in understanding these phenomena and related diseases. However, efforts have been largely limited to water-soluble proteins excluding the other major class of proteins that reside in cell membranes.

Our research focuses on a fundamental biological question, how membrane proteins are made and destroyed in cells (**Fig. 2**). Membrane proteins comprise approximately 30% of all proteins encoded in genes and carry out numerous critical cellular functions. Approximately 60% of all drug developments target membrane proteins. The folding problem of membrane proteins is directly connected to human health. Indeed, accumulation of misfolded or misprocessed membrane proteins causes serious diseases such as Alzheimer's disease, cystic fibrosis, and cancer. To answer

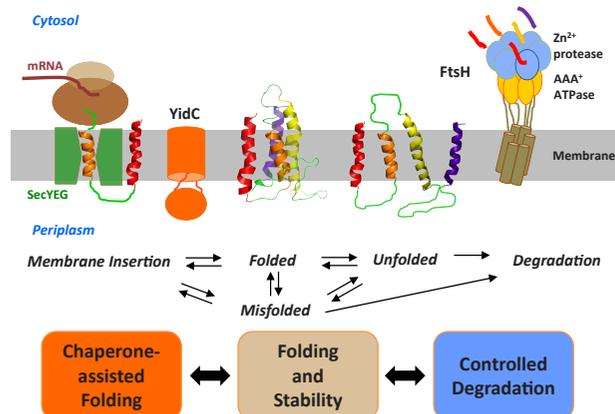


Fig. 2. From the cradle to the grave: overall scheme of membrane protein research in the Hong lab.

our cardinal question, we investigate two conceptually connected biological processes by multi-disciplinary approaches including biochemical, biophysical, and chemical methods.

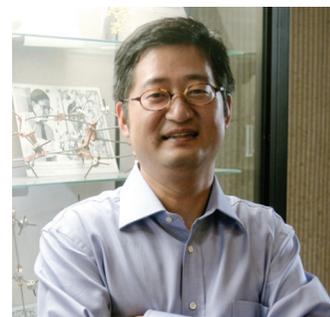
Chaperone-assisted membrane protein folding: YidC/Oxa1/Alb3 is a membrane protein family that plays a critical role in folding and assembly of membrane proteins in the inner membranes of bacteria, mitochondria, and chloroplasts. In *E. coli*, YidC forms a membrane insertion pore independent of SecYEG complex, major protein translocation machinery. YidC also has a chaperone activity: it facilitates the folding of a variety of SecYEG-dependent proteins. To understand how YidC acts as chaperone, we will tackle three specific problems:

- What are the driving forces in YidC-substrate interaction?
- What mechanism does YidC use to facilitate folding of membrane proteins?
- How are the structure and dynamics of YidC related to the function?

Controlled degradation of membrane proteins: Rapid protein degradation is a crucial cellular process that enables the clearance of misfolded proteins and regulatory proteins that are no longer needed. In all cells, this process is mediated by AAA⁺-protease superfamily. FtsH is the only membrane-localized AAA⁺-protease, which degrades both membrane and cytosolic proteins. To understand the principles of the quality control mechanism of membrane proteins, we focus on three specific questions using FtsH from *E. coli* as model.

- What sequence or structural features of substrates are subject to degradation?
- What is the role of the FtsH trans-membrane domain in recognition and translocation of substrates?
- How is the proteolytic activity modulated by other membrane-bound cofactors?

Graduate students will gain a training opportunity in DNA manipulation, expression and purification of membrane proteins, biophysics of lipid bilayers, protein labeling, and various biophysical tools such as fluorescence, EPR, and X-ray crystallography. 🍷



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Biophysical Chemistry of Membrane Protein Folding and Stability

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