Ackert Hall, Room 120
Wednesday, September 13, 2017
4:00 P.M.

Coffee and Cookies
Chalmers Hall, Room 168
3:45 P.M.

Biochemistry & Molecular Biophysics Seminar

Endoplasmic Reticulum Associated Degradation (ERAD) and Protein Conformational Diseases: Lessons from Model Systems and Therapeutic Opportunities

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Numerous proteins that play critical roles in cellular physiology transit through the secretory pathway. In fact, approximately one-third of all proteins in eukaryotes enter the secretory pathway via endoplasmic reticulum (ER) prior to their delivery to other cellular compartments or prior to being secreted. Although most of these proteins fold efficiently, a significant percentage folds slowly or inefficiently, particularly when cells are stressed. Because unfolded proteins can aggregate and compromise cellular homeostasis—and in some cases trigger apoptosis—it is critical that aberrant proteins in the secretory pathway are recognized and then destroyed. Fortunately, once selected by chaperones and chaperone-like lectins, proteins in the ER can be removed via a process we termed ER associated degradation (ERAD). During ERAD, defective polypeptides are delivered from the ER to the cytoplasm, are ubiquitinated at the ER membrane, and are destroyed by the proteasome. Many of the critical players in the ERAD pathway have been identified and their functions discerned. However, a growing number of substrate-specific modifiers of ERAD have been identified. Moreover, some misfolded proteins escape the ERAD pathway but are selected for lysosome-mediated degradation. Because the ERAD pathway has been associated with nearly 70 human diseases, we propose that ERAD modifiers might, in turn, be disease modifiers. We also propose that the correction of misfolded, disease-linked secreted proteins will require ERAD-targeted drugs. To these ends, we have used yeast-based expression systems to dissect the ERAD pathway for proteins linked to human diseases and to identify previously uncharacterized factors and pathways that modulate ERAD. Candidates from these efforts are then tested in mammalian cell models. In parallel, we have identified small molecule modulators of the ERAD pathway and examined these in combination with clinically relevant protein folding correctors. These studies have been complemented by in vitro assays that have allowed us to dissect at which step in the ERAD pathway specific factors and small molecules act.