Adaptation of Proteins to Evade Premature Degradation by the Ubiquitin-Proteasome System

Cell differentiation and development, stress conditions, and environmental factors continually threaten the integrity of proteins in every eukaryotic cell. Maintaining protein homeostasis (proteostasis) requires the degradation of damaged or unwanted proteins. It plays a critical role in cell function, organism growth, and ultimately, viability. The ubiquitin-proteasome system (UPS) is a major pathway that removes damaged and unwanted proteins. However, the UPS must effectively eliminate only undesirable proteins while leaving the functional and essential ones intact. Despite advances in the study of the mechanism of protein degradation, little is known about how the functional proteome can avoid premature proteolysis through the UPS.

The proteasome recognizes ubiquitinated proteins – tagged with a small protein named ubiquitin and degrades them. Ubiquitin is mainly attached to lysine (Lys) positions of the protein destined for degradation in a process termed ubiquitination. Our bioinformatic screen indicates that in organisms equipped with the proteasome, the fraction of proteins with extensive regions lacking Lys residues (Lys deserts) has increased over evolutionary time. Lys deserts have appeared in bacteria utilizing the pupylation pathway, a functional analog of eukaryotic ubiquitination, and are widespread in many eukaryotic proteins operating within the UPS. I propose that this feature allows them to function within the UPS without the risk of premature degradation. The first goal of our research is to decipher the role of Lys deserts in protein turnover.

Ubiquitin chains on residues like serine may be intertwined with classical Lys ubiquitination. Still, the physiological significance of this type of ubiquitination is unclear and systematic studies are lacking. Our preliminary data suggest that Lys-deficient proteins may be subject to non-canonical ubiquitin labeling. Therefore, the second goal of our research is to develop an analytical method to catalog and study the role of non-Lys ubiquitination/pupylation by applying biochemical and proteomic approaches and a deep learning method.

I propose a complementary research plan that aims to break new grounds in understanding how the cellular proteome has adapted to degradation networks and may identify novel modulators of protein turnover in health and disease.