Investigating the Structures and Functions of Key Guardians of Protein Homeostasis

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Autophagy is an evolutionarily conserved pathway for degrading long-lived cytoplasmic proteins, macromolecules, and organelles, a process critical to the maintenance of cellular homeostasis and response to stress. Malfunction of autophagy has been implicated in a wide range of human diseases from neurodegeneration, cancer, and infectious diseases. Autophagic degradation involves sequestering cytoplasmic material into a double-membrane autophagosome transport vesicle and delivering this "package" to the lysosome for breakdown. To obtain mechanistic insights into this multi-step process, our lab is characterizing different Atg (autophagy-related) and non-Atg proteins that regulate different steps of this important degradation pathway. In the first part of my talk, I will share with you our work on delineating the molecular architecture and subunit organization of the Atg1 complex that regulates autophagy initiation and autophagosome biogenesis.
As a key component of the protein synthesis machinery, tRNA is subject to different types of post-transcriptional modifications. Of these, modifications to the anticodon loop fine-tune ribosome decoding efficiency and contribute to overall translation regulation and thus protein homeostasis. Conserved from yeast to humans, Elongator is a ~850kDa, heterododecameric protein complex (Elp1-Elp6) that mediates modifications of U34 in the wobble position of the anticodon loop of multiple tRNA's. Defects in Elongator have been implicated in different human pathologies, including familial dysautonomia, bronchial asthma, intellectual disabilities, cardiac hypertrophy, and amyotrophic lateral sclerosis. In the second part of my talk, I will describe findings from our recent structural studies on this complex.