Ribosome-Associated Protein Quality Control (RQC) and Neurodegeneration

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Our laboratory is interested in understanding how cells know when their macromolecular or structural components are aberrant or damaged, and then decide on ways to either correct or eliminate them. We study this issue in the context of protein quality control, a process critical to ensure proteome integrity and cellular fitness; further underscoring its relevance, defective protein quality control is implicated in several "proteinopathies", and is a hallmark of neurodegenerative diseases.

In eukaryotes, key factors conferring specificity to protein quality control are molecular chaperones and E3 ubiquitin ligases. We had previously discovered that the Listerin/Ltn1 E3 ligase functions in a novel pathway of protein quality control, now known as Ribosome-Associated Quality Control (RQC). Listerin binds to ribosomes and marks aberrant nascent chains that become stuck in the 60S ribosomal subunit for proteasomal degradation (Bengtson & Joazeiro 2010, Nature 467:470-3). We also found that Listerin mutation causes neurodegeneration in mice (Chu et al 2009, PNAS 106:2097-103), suggesting that elucidation of the RQC pathway may provide new clues on mechanisms underlying neurodegenerative diseases. We will present data on fundamental mechanisms of RQC and their relevance to disease.