Ackert Hall, Room 120
Wednesday, November 19 2025
4:00 P.M.

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

Biochemistry & Molecular Biophysics Seminar

Causes and consequences of tRNA splicing disorders in neurological disease

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Although protein aggregates are a hallmark of neurodegenerative diseases, their roles in pathogenesis remain controversial. Recently, aggregation-prone polyglycine-containing proteins produced from expanded GGC repeats have been implicated in an emerging family of neurodegenerative disorders. We found that polyglycine itself forms intracellular aggregates that incorporate endogenous glycine-rich proteins, including FAM98B, a component of the tRNA ligase complex (tRNA-LC) that harbors the single most glycine-rich sequence in the human proteome. Through sequestration and accelerated proteasome-dependent turnover mediated by the FAM98B glycine-rich intrinsically disordered region (IDR), polyglycine depletes the tRNA-LC and disrupts tRNA processing. Accordingly, brains of affected patients reveal aggregate-associated sequestration and depletion of the tRNA-LC as well as accumulation of aberrant tRNA species. Furthermore, Fam98b depletion in adult mice caused progressive motor coordination deficits and hindbrain pathology. Notably, Mendelian tRNA splicing defects cause severe forms of neurodegeneration that phenotypically overlap with GGC repeat disorders. The FAM98B glycine-rich IDR thus mechanistically links previously disparate neurodegenerative disorders of protein aggregation and tRNA processing. Ongoing work in our laboratory is exploring the molecular basis for the selective vulnerability to these and related RNA processing disorders observed in the central nervous system.