From: Faculty Description of Research Project
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Project title:

Defining the role of Rab proteins in Neurodegeneration

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Research Project Description

Many neurodegenerative diseases are characterized by pathologic protein deposits and multiple lines of evidence support the assertion that these diseases are proteinopathies triggered by the accumulation of normal proteins in abnormal aggregation states. Tau and amyloid accumulate in Alzheimer disease, whereas Lewy bodies enriched with the protein alpha-synuclein (aS) are found in Parkinson disease and related disorders. Abnormal accumulation of aS results in endoplasmic reticulum (ER) stress, intracellular protein/vesicular trafficking deficits, and toxicity that contributes to neurodegeneration in Parkinson disorders. Increasing evidence suggests that aS interacts with Rab GTPase proteins that have critical functions in intracellular trafficking, membrane transport, and exocytosis. In PD models, aS-related trafficking deficits, accumulation of intracellular vesicles, and toxicity can be rescued by expression of specific Rab GTPase proteins such as Rab8a, which localizes to the trans-Golgi network. We have recently shown that Rab8a expression potently reduces aS levels and oligomer formation, and rescues Golgi fragmentation, supporting a potential neuroprotective role. In contrast, the role of Rabs in tau disorders such as Alzheimer's or FTD is less well understood. However, recently we have demonstrated that Rab8a expression also potently reduces tau and pathological phospho-tau, suggesting a novel role for Rab GTPases.

Based on this data plan to test whether viral expression of Rab proteins, such as Rab8a, can protect against aS or tau accumulation and prevent "seeding" of pathology in mammalian models of Parkinsonism or FTD. Interested students will help with animal studies and processing data.