Accumulation of LRRK2-associated phospho-Rab12 degenerative lysosomes in tauopathies

Silas A. Buck[1,2,3], Tuyana Malankhanova[3,4], Eileen B. Ma[1,2,3], Sarah Yim[1,2,3], Harrison W. Pratt[1,2,3], John Ervin[1,2,5], Shih-Hsiu J. Wang[1,2,5], Todd J. Cohen[6,7,8,9], Andrew B. West[1,3,4], Laurie H. Sanders[1,2,3*]

[1]Department of Neurology, Duke University School of Medicine, Durham, NC, 27710, USA . [2]Department of Pathology, Duke University School of Medicine, Durham, NC, 27710, USA . [3]Duke Center for Neurodegeneration and Neurotherapeutics, Duke University, Durham, NC, 27710, USA. [4]Department of Pharmacology and Cancer Biology, Duke University School of Medicine, Durham, NC, 27710, USA. [5]Duke/UNC Alzheimer's Disease Research Center, Durham, NC, 27710, USA. [6]Department of Neurology, University of North Carolina, Chapel Hill, NC, 27599, USA. [7]Department of Cell Biology and Physiology, University of North Carolina, Chapel Hill, NC, 27599, USA. [8]Department of Biochemistry and Biophysics, University of North Carolina, Chapel Hill, NC, 27599, USA. [9]UNC Neuroscience Center, University of North Carolina, Chapel Hill, NC, 27599, USA

Parkinson's disease (PD) pathogenic mutations in *leucine-rich repeat kinase 2* (*LRRK2*) are associated with endolysosomal dysfunction across cell types, and carriers of *LRRK2* mutations often present with phosphorylated tau and α-synuclein deposits across the brain. *LRRK2* mutations increase the phosphorylation of Rab substrates including Rab12. Rab12 is expressed in neuronal and non-neuronal cells with localization to membranes in the endolysosomal compartment. Under lysosomal stress, LRRK2 interaction with Rab12 upregulates LRRK2 kinase activity. We tested whether aberrant LRRK2 phosphorylation is associated with tau and/or α-synuclein pathology across clinically distinct neurodegenerative diseases. Analysis of brain tissue lysates and immunohistochemistry of pathology-susceptible brain regions demonstrate that pS106-Rab12 levels are increased in Dementia with Lewy bodies (DLB), Alzheimer's disease (AD), and Parkinson's disease (PD), and in *LRRK2* mutation carriers. In early pathological stages within neurons, phosphorylated Rab12 localizes to granulovacuolar degeneration bodies (GVBs), which are proteolytically active lysosomal structures. These pS106-Rab12-positive GVBs accumulate with pathological tau stage across brain tissues from subjects with DLB, AD, or PD, including *LRRK2* mutation carriers. In a mouse model of tauopathy, pS106-Rab12 localizes to GVBs formed in the process of initial tau aggregation in an age-dependent manner. While GVBs are largely absent in neurons with mature protein pathology, subsets of both tau and α-synuclein inclusions appear to incorporate pS106-Rab12 at later pathological stages in human neurodegenerative diseases. These results implicate LRRK2 kinase activity and Rab phosphorylation within the endolysosomal compartment as an early event in the pathological process of tau and α-synuclein in neurodegenerative diseases.

Sponsored By: National Institutes of Health (NIH) R01NS119528 to L.H.S., NIH R21AG084216 to L.H.S. and T.J.C., NIH R01NS064934 to A.B.W., Parkinson's Foundation PF-PRF-1244721 to S.A.B., NIH P30AG072958 to the Duke-UNC Alzheimer's Disease Research Center (ADRC), NIH P30AG066509 and NIH U19AG066567 to the University of Washington, and NIH P30AG072979, NIH P01AG066597, and NIH P01AG084497 to the University of Pennsylvania Center for Neurodegenerative Disease Research Brain Bank.

Presenter Name and contact information:
Laurie Sanders, Ph.D. Associate Professor
Department of Neurology
Duke University School of Medicine
Durham, North Carolina, USA
Email: laurie.sanders@duke.edu