“Dynamic phosphorylation of WIPI2B is required to counteract an age-related decline in autophagosome biogenesis in neurons”

Autophagy defects are implicated in multiple late-onset neurodegenerative diseases including Amyotrophic Lateral Sclerosis (ALS) and Alzheimer’s, Huntington’s, and Parkinson’s diseases. Since aging is the most common shared risk factor in neurodegeneration, we assessed rates of autophagy in mammalian neurons during aging. We identified a significant decrease in the rate of constitutive autophagosome biogenesis during aging and observed pronounced morphological defects in autophagosomes in neurons from aged mice. While early stages of autophagosome formation were unaffected, we detected the frequent production of stalled LC3B-negative isolation membranes in neurons from aged mice. While these stalled structures recruited the majority of the autophagy machinery, they failed to develop into LC3B-positive autophagosomes. Importantly, ectopically expressing WIPI2B effectively restored autophagosome biogenesis in aged neurons. This rescue is dependent on dynamic phosphorylation of WIPI2B at the isolation membrane, suggesting a novel therapeutic target in age-associated neurodegeneration.