Neuroaxonal dystrophy of dopaminergic neurons in a mouse model of mitochondrial membrane protein-associated neurodegeneration

Wenzhang Wang, Fengqin Wu, Sandra L. Siedlark, Sabina Bhatta, Changjuan Shao, Sandy Torres

Department of Pathology, Case Western Reserve University, Cleveland, OH, USA

Neurodegeneration with brain iron accumulation (NBIA) is a group of rare diseases associated with genetic mutations in several genes including C19orf12. To explore the underlying mechanism of NBIA pathogenesis, we investigated a mouse model by knocking out the mouse homolog of human C19orf12 gene. In the brains of knockout mice, we observed age-dependent accumulation of abundant axonal spheroids, alongside brain iron accumulation, neuroinflammation, α-synuclein and ubiquitin pathology. Axonal spheroids were featured with abnormal ER and damaged mitochondria in knockout mice. These abnormal spheroids were decorated with tubular ER proteins RTN3, which preceded the onset of motor symptoms. The abnormal localized expansion of axonal ER underlies swollen axon terminals of dopaminergic neurons. The accumulated neuroaxonal swellings likely impair functioning of the dopaminergic system in the substantia nigra, striatum, and other brain regions, which ultimately led to motor function deficits in knockout mice. Altogether, the absence of C19orf12 in mouse brains recapitulates cardinal features of neuropathology in human NBIA, suggesting that C19orf12 is essential to maintain the tubular ER homeostasis in neuronal axon in vivo.

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Presenter Name and contact information:
Wenzhang Wang, Ph.D., Assistant Professor
Department of Pathology, Case Western Reserve University, Cleveland, OH, 44106
Phone: 216-368-3753
Email: wxw157@case.edu