Hereditary spastic paraplegia and lipid droplet function

Chrisovalantis Papadopoulos, Giuseppe Mancuso, Simon Schumacher, Elena. I. Rugarli

Institute of Zoology and Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany

Hereditary spastic paraplegia (HSP) and Charcot-Marie-Tooth (CMT) neuropathies are genetic diseases characterized by the progressive degeneration of long motor and/or sensory axons. One key difference is the target axons that are primarily affected in these conditions: the cortico-spinal motor axons and dorsal columns of the central nervous system in HSPs or the motor and sensory axons of peripheral nerves in CMTs. The identification of causative genes for these conditions has shown a considerable clinical overlap, hinting to common pathogenic pathways. For example, dominant mutations in *BSCL2*, encoding seipin, are responsible for a variety of axonopathies, which manifest as spastic paraplegia 17, distal hereditary motor neuropathy type V, and CMT disease type 2 with predominant hand involvement. Patients carrying mutations in spastin (*SPAST)* are usually affected by a pure form of HSP, but sometimes display symptoms of peripheral sensory motor neuropathy. We recently found that spastin is recruited to lipid droplets (LDs), independent organelles that are composed of a lipid ester core surrounded by a phospholipid monolayer. Furthermore, we have evidence that the seipin mutants involved in CMTs decorate a compartment of the endoplasmic reticulum in close proximity to LDs. Here we will discuss these findings and their relevance for axonal degeneration.