Abstract

Hereditary spastic paraplegias (HSPs) are characterized by progressive weakness and spasticity of the legs because of the

degeneration of cortical motoneuron axons. SPG15 is a recessively inherited HSP variant caused by mutations in the

ZFYVE26 gene and is additionally characterized by cerebellar ataxia, mental decline, and progressive thinning of the corpus

callosum. ZFYVE26 encodes the FYVE domain-containing protein ZFYVE26/SPASTIZIN, which has been suggested to be

associated with the newly discovered adaptor protein 5 (AP5) complex. We show that Zfyve26 is broadly expressed in

neurons, associates with intracellular vesicles immunopositive for the early endosomal marker EEA1, and co-fractionates

with a component of the AP5 complex. As the function of ZFYVE26 in neurons was largely unknown, we disrupted Zfyve26

in mice. Zfyve26 knockout mice do not show developmental defects but develop late-onset spastic paraplegia with

cerebellar ataxia confirming that SPG15 is caused by ZFYVE26 deficiency. The morphological analysis reveals axon

degeneration and progressive loss of both cortical motoneurons and Purkinje cells in the cerebellum. Importantly, neuron

loss is preceded by accumulation of large intraneuronal deposits of membrane-surrounded material, which co-stains with

the lysosomal marker Lamp1. A density gradient analysis of brain lysates shows an increase of Lamp1-positive membrane

compartments with higher densities in Zfyve26 knockout mice. Increased levels of lysosomal enzymes in brains of aged

knockout mice further support an alteration of the lysosomal compartment upon disruption of Zfyve26. We propose that

SPG15 is caused by an endolysosomal membrane trafficking defect, which results in endolysosomal dysfunction. This

appears to be particularly relevant in neurons with highly specialized neurites such as cortical motoneurons and Purkinje

cells.