

## Abstract

Disturbances in the morphology and function of mitochondria cause neurological diseases, which can affect the central and peripheral nervous system. The *i*-AAA protease YME1L ensures mitochondrial proteostasis and regulates mitochondrial dynamics by processing of the dynamin-like GTPase OPA1. Mutations in human *YME1L* cause a multi-systemic mitochondriopathy associated with neurological dysfunction and mitochondrial fragmentation but pathogenic mechanisms remained enigmatic. This study reports on striking cell-type specific defects in mice lacking YME1L exclusively in the nervous system. YME1L-deficient mice manifest congenital ocular dysfunction with microphthalmia and cataracts. Later in life these mice develop deficiencies in locomotor activity due to specific degeneration of long spinal cord axons, which relay proprioceptive signals from the hind limbs to the cerebellum. Furthermore, this study demonstrates that YME1L is essential for efficient mitochondrial transport in axons of cultured neurons and ensures mitochondrial proteostasis in neurons *in vivo*. Mitochondrial fragmentation occurs throughout the nervous system of YME1L-deficient mice but does not correlate with the degenerative phenotype. Surprisingly, despite mitochondrial fragmentation being also present in the brain, YME1L-deficient mice did not show signs of neurodegeneration or inflammation in different brain regions. Additional deletion of *Oma1* restores tubular mitochondria but deteriorates axonal degeneration in the spinal cord, demonstrating that (1) OMA1 activation plays a pro-survival role in spinal cord tissue and (2) impaired mitochondrial proteostasis rather than mitochondrial fragmentation causes disturbed mitochondrial trafficking and the observed neurological defects in YME1L-deficient mice.