The role of the *m*-AAA protease in axonal degeneration: insights from mouse models

E. Rugarli; Division of Biochemistry and Genetics, Istituto Neurologico Besta and DNTB, Università Milano-Bicocca, ITA

Hereditary spastic paraplegia (HSP) is a progressive neurological disorder characterized by retrograde degeneration of the corticospinal tracts. The gene responsible for the autosomal recessive form linked to chromosome 16q (SPG7) encodes paraplegin, a subunit of the *m*-AAA protease, involved in protein quality control in the inner mitochondrial membrane. The *m*-AAA protease exists in a hetero-oligomeric form, composed by paraplegin and the homologous protein AFG3L2 (Afg3 like 2), and in a homo-oligomeric complex containing only AFG3L2. We previously generated a mouse model by inactivation of the Spg7 gene. Paraplegin-deficient mice show focal axonal swellings in the distal axons of the fasciculus gracilis and of descending spinal tracts, consistent with a retrograde axonopathy, starting at about 7 months. This phenotype is slowly progressive, with signs of axonal degeneration becoming prominent at 12 month of age. Ultrastructural studies of affected axons demonstrate that, long before degeneration, the distal regions of axons are filled with mitochondria with abnormal size and morphology. Axonal degeneration can be reverted by restoration of paraplegin expression in the mitochondria, providing a proof-of-principle for gene therapy in this disorder. Recently, two different Afg3l2 mouse mutants have been described, pointing to an involvement of Afg3l2 in spinal cord and peripheral nerve development. We will describe recent data obtained in double paraplegin-Afg3l2 mutants, underlying the requirement of the *m*-AAA protease in different neuronal populations.