Expanding the spectrum of the cellular roles of spastin

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Hereditary spastic paraplegia (HSP) comprises a heterogeneous group of neurological disorders characterized by weakness and spasticity of the lower limbs, owing to progressive degeneration of the corticospinal axons. The identification of a large number of HSP genes in the recent years has highlighted a number of cellular pathways underlying the disease, involving cytoskeletal remodeling, endoplasmic reticulum morphogenesis and mitochondrial function and converging into defects of axonal transport. A central player in this intricate picture is spastin, the protein product of the *SPG4* gene. Spastin is mutated in almost half of the cases of autosomal dominant pure HSP and specifically interacts with at least other two HSP genes, Atlastin1 and REEP1, suggesting that elucidation of spastin function can potentially shed light on a larger number of HSPs. Our group was the first to demonstrate that spastin is involved in microtubule dynamics. Since our first observations, several studies have provided evidence that spastin is a microtubule-severing protein, involved in several processes such as midbody abscission, Pacman flux during mitosis, neurite branching formation, and axonal stability. We further showed that two spastin isoforms are produced through usage of alternative methionines. The long spastin isoform (M1-spastin) is predominantly expressed in neurons, is characterized by an N-terminal extension containing a hydrophobic stretch, and mediates the interaction with Atlastin1 and REEP1. We will now present data on a novel subcellular localization of the long spastin isoform, opening new functional perspectives. The relevance of our observations for axonal degeneration will be discussed.