Abstract

Spastizin in hereditary spastic paraplegia type 15: a large and complex protein with different functions

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Hereditary spastic paraplegias (HSPs) are neurodegenerative disorders characterized by progressive weakness and spasticity of the lower limbs due to degeneration of upper motoneuron axons. SPG15 is a recessively inherited HSP subtype characterized by cerebellar ataxia, intellectual disability and progressive thinning of the corpus callosum caused by mutations in the ZFYVE26 gene which encodes spastizin. Spastizin is a large protein of 2539 amino acid residues harbouring three functionally recognized domains, a FYVE domain flanked by a Zinc-finger and a leucine zipper domains. Spastizin protein has a diffuse cytoplasmic distribution and co-localises partially with early endosomes, the endoplasmic reticulum, microtubules and vesicles involved in protein trafficking. From the functional point of view, spastizin has been demonstrated to be involved in cytokinesis and is was found associated with the newly discovered adaptor protein 5 (AP5) complex. Spastizin interacts with Beclin1, a protein required for cytokinesis and autophagy, which is the major lysosome-mediated degradation process in the cell. Starting from this data we demonstrated that Spastizin interacts with the autophagy related Beclin1-Uvrag-Rubicon multiprotein complex and is required for autophagosome maturation. In cells lacking Spastizin or with mutated forms of the protein, Spastizin interaction with Beclin1 is lost although the formation of the Beclin1-Uvrag-Rubicon complex can still be observed. However, in these cells we demonstrate an impairment of autophagosome maturation and an accumulation of immature autophagosomes. These findings were replicated in different cell types and were also observed in cells lacking spatacsin the protein involved in the SPG11 subtype. Based on these types of protein interactions we are now analysing the role of spastizin protein in the endolysosomal system .