Elucidating the Pathomechanism of HSP, what's new

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Abstract

Spastin, a member of the ATPases associated with various cellular activities (AAA) family of proteins, is the most frequently mutated in hereditary spastic paraplegia (HSP). The defining feature of the AAA proteins is a structurally conserved AAA domain which assembles into an oligomer. By chemical cross-linking and gel filtration chromatography, we show that spastin oligomerizes into a hexamer. Furthermore, to gain a comprehensive overview of the oligomeric structure of spastin, we generated a structural model of the AAA domain of spastin using template structure of VPS4B and p97/VCP. The generated model of spastin provided us with a framework to classify the identified missense mutations in the AAA domain from HSP patients into different structural/functional groups. Moreover, through colocalization studies in mammalian cells, we show that E442Q mutant spastin acts in a dominant negative fashion and causes redistribution of wild type spastin.

Considerable insights into molecular function of spastin were derived from the identification and characterization of spastin binding proteins. Over-expression of spastin binding protein; ZFYVE27 (protrudin) promotes neurite extension in cells. We show that ZFYVE27 forms an oligomer and gradient-centrifugation analysis indicates that ZFYVE27 forms either a dimer or tetramer.

Collectively from our studies, it appears that during the oligomerization state of spastin, it is the relative abundance of a specific interacting protein in the oligomeric state, which will determine the intracellular compartment to which spastin will be recruited. The regional localization of spastin enables it severe microtubule locally and promote neurite extensions.