Interaction Between AP-5 and the Hereditary Spastic Paraplegia Proteins SPG11 and SPG15

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Adaptor proteins form part of a vesicle coat machinery involved in sorting transmembrane proteins to different destinations in the cell. Using structural homology searching we identified a fifth adaptor complex, AP-5 (**Hirst J** et al., 2011 PLoS Biol. Oct;9(10):e1001170). It is associated with two proteins that are mutated in patients with hereditary spastic paraplegia, SPG11 (spatacsin) and SPG15 (FYVE-CENT/ ZFYVE26/spastizin). Using quantitative immunoprecipitation we show that the four AP-5 subunits can be coimmunoprecipitated with SPG11 and SPG15 in a stable complex, with a stoichiometry of ~1:1:1:1:1:1. Using a number of different antibodies we were able to localize AP-5 along with SPG11 and SPG15 to a compartment that can be defined biochemically, enzymatically and morphologically as an endolysosome. Fibroblasts from 2 HSP patients, which are nulls for AP-5ζ protein, accumulate morphologically aberrant endolysosomes. Both SPG11 and SPG15 have predicted secondary structures containing α-solenoids related to those of clathrin heavy chain and COPI subunits. SPG11 also has an N-terminal, β-propeller–like domain, which interacts in vitro with AP-5. We propose that AP-5, SPG15, and SPG11 form a coat-like complex, with AP-5 involved in protein sorting, SPG15 facilitating the docking of the coat onto membranes by interacting with PI3P via its FYVE domain, and SPG11 (possibly together with SPG15) forming a scaffold.