Converging endolysosomal pathways for autosomal recessive HSP pathogenesis

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The identification of cellular themes common among the HSPs is important for understanding disease pathogenesis. We investigated SPG15-related cellular changes in patient fibroblasts, seeking to identify shared pathogenic themes between SPG15 and SPG11. These are the most common autosomal recessive forms of HSP, and they are similarly characterized clinically by progressive spastic paraplegia along with thin corpus callosum, white matter changes, ocular abnormalities, cognitive impairment, and sometimes early-onset parkinsonism. Using cell lines prepared from patients with SPG15, we found a clear, selective enlargement of lysosomal size, and fibroblasts from different patients consistently showed abnormal lysosomal storage by electron microscopy. Lysosomal enlargement was also observed in cell lines from multiple patients with the clinically-similar disorder SPG11, though prominent abnormal lysosomal storage was not observed. The stability of the SPG15 protein spastizin and the SPG11 protein spatacsin were highly dependent upon one another's presence.

Similar abnormalities in the sizes of lysosomes in SPG15 and SPG11 fibroblast lines are consistent with emerging studies implicating these two proteins in interactions with the late endosomal/lysosomal adaptor protein complex AP-5. This suggests a converging lysosomal disease mechanism for these two disorders. SPG15 and SPG11 are particularly notable among HSPs because they can also present with juvenile parkinsonism, and this lysosomal pathogenesis is likely relevant for other forms of parkinsonism related to lysosomal dysfunction.