Spastin's role at endosomes: not just tubules

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Mutations in the gene encoding the microtubule severing enzyme spastin are a major cause of axonopathy in the neurodegenerative condition Hereditary Spastin Paraplegia (HSP), however the mechanism by which spastin mutation causes axonal degeneration remains poorly understood. Previously we have reported that spastin has a role in the coordination of endosomal degradation recycling mediated by its ability to regulate fission of recycling tubules from the endosome. Here we further investigate the consequences of defective endosomal tubule fission upon the endocytic pathway. We show that cells lacking spastin have enlarged, abnormal lysosomal compartments and defective receptor sorting from the endosome to golgi. Spastin requires the ability to sever and bind microtubules and to interact with ESCRT-III (a complex controlling cargo degradation) to regulate lysosome size. We show that fibroblasts from a spastin disease mouse model also have abnormally enlarged lysosomes. Thus we reveal the consequences of abnormal receptor traffic in spastin HSP and demonstrate it's relevance in a disease model of spastin HSP.