Tubules, microtubules and axonal degeneration

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In this talk I discuss our characterisation of the role of spastin at endosomes. We showed that cells lacking the microtubule-severing protein spastin had increased tubulation of, and defective receptor sorting through, endosomal tubular recycling compartments. Spastin required the ability to sever microtubules and to interact with ESCRT-III (a complex controlling cargo degradation) proteins to regulate endosomal tubulation. Cells lacking IST1, an ESCRT component to which spastin binds, also had increased endosomal tubulation. These results suggest that inclusion of IST1 into the ESCRT complex allows recruitment of spastin to promote fission of recycling tubules from the endosome. Zebrafish spinal motor axons depleted of spastin or IST1 also had abnormal endosomal tubulation, so we propose this phenotype is important for axonal degeneration. I also discuss our characterisation of spastin MIT domain mutations, and suggest that at least some of these are pathological, as they cannot effectively rescue endosomal tubulation phenotypes in HeLa cells lacking spastin.