Spichthyin, The *Drosophila* homolog of spastic paraplegia protein SPG6, inhibits BMP signalling, and reveals a role for BMP signalling in maintaining axonal microtubules

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Hereditary Spastic Paraplegias (HSPs) are a heterogeneous set of diseases characterized by degeneration of corticospinal tract axons and spasticity of the lower extremities. The mechanisms of degeneration in HSPs are unknown, but the causative genes may affect a limited number of cellular processes, including membrane traffic, and axonal microtubule function. However, it is unknown whether any of the membrane-associated SPG proteins have common functions, or affect common cellular pathways, and how mutations in them can lead to disease.

One HSP protein, SPG6, a predicted nine-transmembrane domain protein, is also homologous to ichthyin (mutated in autosomal recessive congenital ichthyosis). The *Drosophila* homolog of SPG6 and ichthyin, which we have named spichthyin (Spict) is found preferentially in early endosomes, with a lumenal N-terminus and a cytosolic C-terminus. We generated *spict* loss-of-function mutations, and showed that Spict is necessary for normal organisation of the Rab5 early endosomal compartment. *spict* mutations cause excessive growth of the neuromuscular junction (NMJ), and this overgrowth requires BMP signaling. They also increase levels of BMP receptors and BMP signaling in presynaptic boutons of the NMJ. Spict has a punctate distribution that overlaps with that of BMP receptors at the NMJ, and interacts biochemically with the BMP type II receptor Wit. Overexpression of Spict in S2 cells leads to relocalization of BMP receptors from the plasma membrane to early endosomes.

How can altered function of an endosomal protein cause axonal pathology? Spict overexpression leads to loss of axonal microtubules and impairment of axonal transport, suggesting a possible mechanism for axonal degeneration in the human disease. This phenotype is suppressed by activation of BMP signalling and enhanced by its inhibition, and is also found in BMP loss-of-function signalling mutants, suggesting that BMP signalling is required for a normal axonal microtubule cytoskeleton.

Therefore, Spict is a novel endosomal protein that inhibits BMP signalling in *Drosophila* neurons. Spict might either make BMP receptors inaccessible to ligands, or regulate their traffic to favour degradation in lysosomes. This is the first demonstration of a role for an SPG protein or ichthyin family member in a specific signalling pathway, and suggests mechanisms by which mutations affecting these proteins can lead to either disease. It also suggests a wider role for impaired BMP signalling in other neurodegenerative diseases.