

## **Axonal Transport Deficits and Pathogenic Mechanisms in Hereditary Spastic Paraplegias**

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An increasing number of neurodegenerative diseases have been shown to follow a “dying-back” pattern, in which neurons begin to degenerate at the synapse and axon, and then slowly die back towards the cell body. Dying-back neuropathies are characterized by a loss of synaptic and axonal connectivity, development of axonal swellings and abnormal accumulation of transported organelles (MBOs). These early pathological events precede neuronal cell death, but correlate well with the onset of early symptoms of disease (Morfini et al., 2009). This pattern of cell degeneration suggests that early pathological events in the synaptic and/or axonal compartments may be central to the pathogenesis of disease.

One instructive example of dying-back neuropathy is seen in the hereditary spastic paraplegias (HSPs). HSPs are a genetically diverse group of disorders where mutations in one of over 40 different genes result in degeneration of the corticospinal tracts and dorsal column fibers (Fink, 2006). Patients exhibit adult-onset progressive muscle weakness and spastic paralysis of the lower limbs and often require a walker or wheelchair. There is currently no medical treatment, and pathogenic mechanisms are poorly understood. Recent insights into the role of axonal transport deficits, however, may be central to understanding pathogenesis in HSPs and other dying-back neuropathies.

Autosomal dominant mutations in the SPG10 gene encoding kinesin-1a (also known as KIF5A), one of three isoforms of kinesin-1, results in one such form of HSP (Reid et al., 2002). The significance of this mutation is manifold. First, patients are heterozygotic for the mutation, so only one allele of kinesin-1a is affected, leaving intact the expression of the other SPG10 allele as well as the other two isoforms of kinesin-1. The kinesin-1a-null mouse dies at birth

(Xia et al., 2003). This expression pattern suggests that a partial reduction in fast axonal transport is sufficient to cause neurodegeneration. Second, SPG10-HSP is an adult-onset disease. This suggests that a partial reduction in axonal transport may not produce clinical symptoms in affected neurons for years or even decades. Third, although kinesin-1a is expressed throughout the brain, only upper motor neurons degenerate. This selective degeneration suggests that reductions in specific components of axonal transport can produce degeneration of specific neuronal populations while leaving other neuronal populations relatively unaffected. More recent data have given further insight into the role of axonal transport in neurodegeneration. The SPG10 mutation affects the ability of kinesin1-a to bind to microtubules, suggesting that alterations in kinesin function may play a central role in SPG10 pathogenesis (Ebbing et al., 2008).

Axonal transport deficits have been implicated in other forms of HSP as well. Mutations in the microtubule-severing protein spastin are the most common cause of HSP, accounting for over 40% of diagnoses. Recent data show an inhibitory effect of pathogenic spastin mutations on both anterograde and retrograde fast axonal transport (Solowska et al., 2008), raising the possibility that additional forms of HSP may involve changes in axonal transport.

Deficits in axonal transport have been implicated in other forms of dying back neuropathy (Morfini et al., 2009). Recent data has implicated axonal transport deficits in the pathogenesis of the motor neuron diseases amyotrophic lateral sclerosis (ALS) and Huntington's disease. Similarly, both Alzheimer's and Parkinson's diseases display a dying-back pattern as well as evidence of alterations in axonal transport. More work is needed to more clearly elucidate the role of axonal transport in the pathogenesis of these and other dying-back neuropathies, but the common features shared among these various neurodegenerative diseases may provide an avenue for therapeutic intervention based on an understanding of the prominent

role played by defects of axonal transport in neurodegeneration.

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