Common cellular pathogenic themes for the hereditary spastic paraplegias

Craig Blackstone

Neurogenetics Branch, NINDS, US National Institutes of Health, Bethesda, Maryland, USA

Hereditary spastic paraplegias have been classically divided into pure and complicated forms, based on clinical symptoms. More recently, a genetic classification scheme has come into wide use, with about 50 discrete loci already identified and many more likely to come. This daunting genetic complexity has been mollified by the identification of a much smaller number of common cellular pathogenic themes. These include abnormalities in ER morphology and cytoskeletal interactions, bone morphogenetic protein signaling, lipid/cholesterol metabolism, and endocytic and membrane trafficking. The majority of patients with HSP -- in particular SPG3A, SPG4, SPG12, and SPG31 -- harbor mutations in proteins that bind one another and are involved in shaping and organizing the tubular endoplasmic reticulum (ER) network within cells. How the ER is distributed within neuronal axons as well as the functions and interorganelle interactions of smooth ER tubules are currently areas of intense investigation. Further unification of pathogenic themes may develop as the biology of these and other HSP proteins are clarified. Encouragingly, some cellular pathways are already emerging, such as the regulation of bone morphogenetic protein (BMP) signaling and microtubule dynamics, that may represent attractive targets for therapies.