Hereditary spastic paraplegia: Disruption of microtubule pathways?

Molon et al. compared RNA expression profiles in clinically unaffected muscle of patients with hereditary spastic paraplegia (SPG-4 linked) vs normal muscle. They found evidence of disruption of microtubule pathways. They suggest that the study of unaffected tissue may provide important insights into the pathophysiology of neurologic disease.

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Does skeletal muscle reflect neuronal pathology in SPG4, or are we in a house of mirrors?

Commentary by Peter Hedera, MD

SPG4 is caused by mutations in the *SPAST (SPG4)* gene, encoding spastin. The normal function of spastin remains poorly understood, even though the analysis of functional domains has suggested several possible roles. Spastin is a member of a diverse AAA (ATPases Associated with various cellular Activities) superfamily of proteins, characterized by the presence of the ATP binding cassette. It also contains the MIT (microtubule interacting and trafficking) domain, and is predicted to shuttle to the nucleus based on the presence of putative nuclear localization signal. Recent in vitro studies have suggested that it functions as a microtubule-severing protein, and mutated spastin may disrupt an axonal transport by constitutive binding to the microtubules.[1,2]

Spastin is expressed in many tissues, including skeletal muscle, but the most constant and profound pathologic abnormality in SPG4 is distal degeneration of the long axons. Understanding a mechanism that underlies a selective axonal pathology remains a challenge. One possibility is that long motor axons may be particularly susceptible to any disruption of the microtubular dynamics, thus accounting for their vulnerability to spastin mutations.[3]

In the Molon et al. report of gene expression analysis in muscle from SPG4 patients, muscle histology was normal but the gene expression profile by DNA microarray analysis showed reduced expression of several genes involved in microtubule maintenance and vesicle trafficking, together with downregulation of a number of other genes involved in transcription. They suggest that spastin haploinsufficiency results in changes in microtubule dynamics but many cells, including myocytes, can fully compensate for these changes without any obvious dysfunction.

These results lend support to the leading hypothesis that SPG4 (and many other types of hereditary spastic paraplegia) is a consequence of disrupted axonal transport. However, one must first ask whether gene expression in skeletal muscle adequately reflects neuronal pathology in SPG4. Although spastin is expressed ubiquitously, the levels of expression are highest in neuronal tissue.[4] Furthermore, spastin undergoes alternative splicing that is highly tissue specific. The transcriptome of skeletal muscle and neurons is not identical and myocytes may express or lack additional proteins, rendering them resistant to abnormal spastin levels and function; this might mean that the cascade of molecular events in muscle is different from those in neurons.

The Molon et al. study also found that several genes encoding transcriptional and translational proteins are dysregulated in muscle. Although abnormal axonal transport is likely to be an important part of HSP pathophysiology, these other genes are candidates deserving further investigation in SPG4. The importance of pursuing mechanisms other than axonal transport is further underscored by a persisting controversy over the cellular localization of spastin, where there is strong evidence for its shuttling to the nucleus.[4]

These results need to be confirmed by similar analysis of neuronal tissues. Murine and nonvertebrate animal models of SPG4 will soon be available. If confirmed, the analysis of muscle tissue may provide us with exciting possibilities to monitor future treatments directed at the molecular pathogenesis of SPG4.

References

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