AMYOTROPHIC LATERAL SCLEROSIS

Early involvement of grey matter oligodendrocytes in amyotrophic lateral sclerosis

Abnormalities in oligodendrocytes in grey matter could be a crucial early step in the pathogenesis of amyotrophic lateral sclerosis (ALS), according to a study in mice and patients. The results provide an important advance in our understanding of this fatal motor neuron disease and highlight new therapeutic targets.

In the current study, Jeffery Rothstein and colleagues began by using *in vivo* genetic fate tracing of oligodendrocytes and their precursors in superoxide dismutase 1

(*SOD1*)-mutant ALS mice. “The core element of this study was to understand what was happening to oligodendrocytes in ALS,” says Rothstein.

The researchers found enhanced proliferation of NG2⁺ cells—progenitor cells that can differentiate into oligodendrocytes—in the ventral grey matter of ALS mice compared with controls, beginning prior to onset of disease symptoms. These changes coincided with increased generation of oligodendrocytes, but in the absence of oligodendrocyte accumulation. Cell-fate analysis in *SOD1*-mutant mice confirmed progressive degeneration of newly formed oligodendrocytes in lumbar spinal cord.

Next, the investigators selectively removed the *SOD1* mutation from NG2⁺ cells in *SOD1*-mutant mice. This intervention significantly delayed disease onset and prolonged survival, highlighting the key role of defective oligodendrocytes in initiation and propagation of disease.

In agreement with the studies in mice, immunohistochemistry in motor cortex and spinal cord samples from patients with ALS revealed NG2⁺ cell abnormalities and focal myelin loss compared with control tissue. “Injury to oligodendroglia was seen not only in patients with sporadic ALS, but also in those with the newly identified *C9orf72* mutation. Thus, the injury is common to sporadic and genetic forms of the disease,” says Rothstein.

The new findings suggest that drugs to enhance oligodendrocyte survival and function, which are currently in development for treatment of multiple sclerosis, could have clinical utility in ALS.

Katie Kingwell

Numerous apoptotic oligodendrocytes in spinal cord grey matter of an ALS mouse. Permission obtained from NPG © Kang, S. H. et al. *Nat. Neurosci.* doi:10.1038/nn.3357.

Original article Kang, S. H. et al. Degeneration and impaired regeneration of gray matter oligodendrocytes in amyotrophic lateral sclerosis. *Nat. Neurosci.* doi:10.1038/nn.3357

Further reading Ferraiuolo, L. et al. Molecular pathways of motor neuron injury in amyotrophic lateral sclerosis. *Nat. Rev. Neurol.* 7, 616–630 (2011)