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NEURODEGENERATION

Selective vulnerability

> *Sil1* was expressed at higher levels in fatigue-resistant and slow motor neurons than in fast-fatigable motor neurons

Motor neuron subtypes degenerate at different rates in amyotrophic lateral sclerosis (ALS), but the molecular mechanisms underlying this selective vulnerability are not known. A new study by Filézac de L'Etang *et al.* suggests that the most vulnerable motor neurons are prone to endoplasmic reticulum (ER) stress, owing to low levels of the ER-associated protein SIL1.

Low-excitable, fast-fatigable motor neurons degenerate early during the course of ALS, whereas medium-excitable, fatigue-resistant and highly excitable, slow motor neurons degenerate at later disease stages. To gain insight into why this happens, the authors looked for differences in gene expression in the different motor neuron subtypes from wild-type mice. They focused their search on genes associated with ER homeostasis, a process known to be dysregulated in neurodegeneration.

The authors identified various differentially expressed genes, including *Sil1*, which encodes a co-chaperone protein that is involved in sensing ER stress. Indeed, *Sil1* was expressed at higher levels in fatigue-resistant and slow motor neurons than in fast-fatigable motor neurons. Interestingly, mutations in *SIL1* are responsible for Marinesco–Sjögren syndrome, a rare neurodegenerative disorder, and the authors found that mice lacking one copy of *Sil1* displayed hallmarks of ER stress in fast-fatigable motor neurons. Together, these findings suggest that fast-fatigable motor neurons may be more prone to develop ER stress because of their low levels of SIL1.

Mutations in the gene encoding superoxide dismutase 1 (SOD1) can cause familial ALS. Here, the authors found that, in a SOD1-mutant mouse model of ALS, SIL1 levels decreased over time in fast-fatigable motor neurons but increased over time in slow motor neurons. Moreover, they showed that virus-mediated overexpression of *Sil1* in SOD1-mutant mice prevented degeneration of fast-fatigable neurons and improved muscle strength, coordination and survival time. Thus, decreased SIL1 levels may be a key factor in the degeneration of susceptible neurons in ALS.

This study suggests that the specific vulnerability of the fast-fatigable motor neuron subtype in ALS is partly mediated by low levels of SIL1 and impaired ER homeostasis. SIL1 may therefore be a promising therapeutic target for this disease.

Fiona Carr

ORIGINAL RESEARCH PAPER Filézac de L'Etang, A. *et al.* Marinesco-Sjögren syndrome protein SIL1 regulates motor neuron subtype-selective ER stress in ALS. *Nature Neurosci.* http://dx.doi.org/10.1038/nn.3903 (2015)
FURTHER READING Robberecht, W. & Philips, T. The changing scene of amyotrophic lateral sclerosis. *Nature Rev. Neurosci.* **14**, 248–264 (2013)

Jennie Vallis/NPG