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NEURODEGENERATIVE DISEASE

EPHA4 inhibition rescues neurodegeneration in ALS

Amyotrophic lateral sclerosis (ALS), which is characterized by the progressive degeneration of motor neurons, is one of the most common neuromuscular disorders, but there is just one approved therapy, riluzole, and it only modestly increases survival. A study in *Nature Medicine* now shows that ephrin type A receptor 4 (EPHA4) can modulate motor neuron degeneration and disease progression in ALS, suggesting that EPHA4 inhibition could be developed as a therapeutic strategy.

Although the average survival of patients with ALS is ~3–5 years, there can be substantial variability in age of onset and disease progression, even among patients in whom the disease is caused by the same mutation. Based on this observation, Robberecht and colleagues investigated potential genetic modifying factors by conducting a screen using translation-blocking morpholinos in a zebrafish model of ALS induced by mutations in superoxide dismutase 1 (SOD1). This screen revealed a protective effect of inhibition of the zebrafish homologue of human EPHA4 — one of a family of receptor tyrosine kinases that are involved in many processes within the developing and adult nervous system, including regeneration and

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repair. Pharmacological inhibition of EPHA4 with 2,5-dimethylpyrrolyl benzoic acid also rescued the disease phenotype in the zebrafish model.

Subsequently, the authors investigated the effects of genetically and pharmacologically inhibiting EPHA4 in rodent models of ALS. Genetic deletion of one *Epha4* allele in a mouse model of ALS (based on overexpression of human mutant SOD1) improved survival and slowed motor neuron deterioration after the onset of disease. In an analogous rat model of ALS, intracerebroventricular administration of an EPHA4-blocking peptide delayed the onset of disease and enhanced survival.

Large motor neurons are more susceptible to degeneration in ALS. In line with this, EPHA4 expression in the ALS mouse model was higher in large motor neurons compared to small motor neurons, and the protective effect of *Epha4* deletion was also more prominent in large motor neurons. Furthermore, higher levels of EPHA4 expression inhibited re-innervation after sciatic nerve axotomy. Together, these observations suggest that EPHA4 is a determinant of the re-innervation capacity of motor neurons.

The authors also investigated the link between ALS and EPHA4

in patients with the disease. Lower EPHA4 expression was correlated with later disease onset, and direct sequencing of *EPHA4* in 192 patients identified two previously unknown coding variants that were associated with uncharacteristically long survival and whose functional effect was either to decrease EPHA4 expression or impair EPHA4 signalling.

Collectively, these findings indicate that lowering EPHA4 expression or inhibiting EPHA4 signalling could reduce disease severity in patients with ALS (for example, by promoting neuromuscular re-innervation in late stages of ALS), delay the onset of disease and improve survival, although potential side effects will need to be further investigated. Furthermore, the authors found that inhibiting EPHA4 expression rescued axonopathy in an alternative zebrafish model of ALS (induced by expression of mutant TAR DNA-binding protein 43) and a zebrafish model of spinal muscular atrophy, suggesting that the protective effect of targeting EPHA4 is independent of the cause of neurodegeneration.

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ORIGINAL RESEARCH PAPER Van Hoecke, A. et al. EPHA4 is a disease modifier of amyotrophic lateral sclerosis in animal models and in humans. *Nature Med.* **18**, 1418–1422 (2012)