activity early in the lineage is an important determinant of the number of neurons that integrate the target tissue. Disruption of the EphA7–ephrin-A2 reverse signalling by infusion of soluble ephrin-A2 disinhibits proliferation and results in increased neurogenesis in the adult brain.

It will be important to determine whether there is a similar mechanism in other stem cell populations in which ephrins and Ephs are also expressed. Manipulating the ephrin–Eph signalling could be a potential therapeutic strategy in regenerative medicine and cancer treatment.

Jane Qiu

References and links

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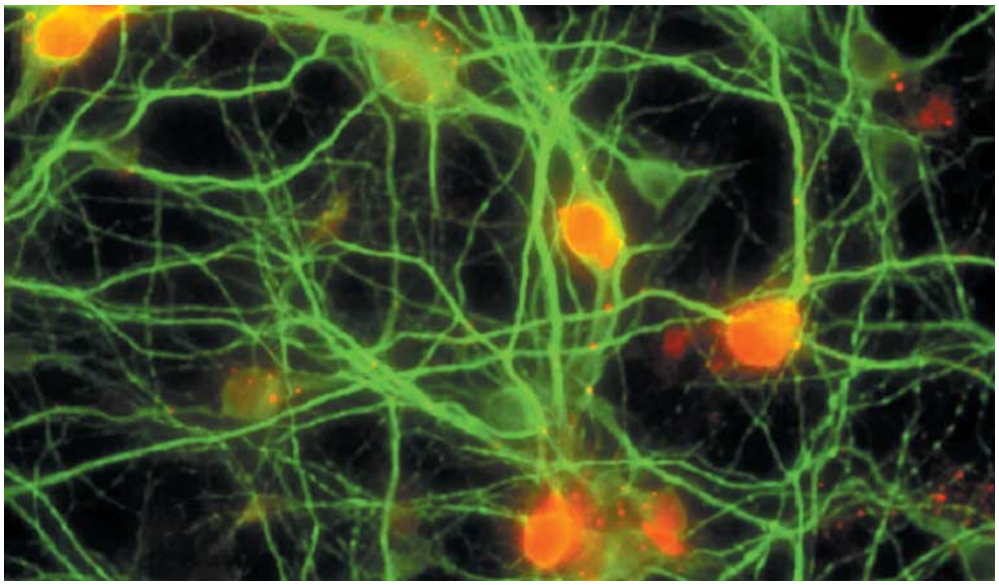
WEB SITE

Frisén's laboratory: http://www.cmb.ki.se/projektdokument/frisen3.htm



Immunofluorescence analysis of lentiviral vector-mediated β-galactosidase expression (red) and microtubule-associated protein 2 (green) in primary cortical neurons derived from mice expressing mutant human *SOD1*. Reproduced, with permission, from Ralph, G. S. *et al. Nature Med.* 13 March 2005 (doi:10.1038/nm1205).

NEURODEGENERATIVE DISEASE

ALS meets RNAi

The idea of using RNA interference (RNAi) as a therapeutic strategy is gaining momentum. Two papers in the April issue of *Nature Medicine* show that RNAi interferes with the progression of pathology in an animal model of amyotrophic lateral sclerosis (ALS) — a fatal neurodegenerative disease that attacks both upper and lower motor neurons.

RNAi is a post-transcriptional mechanism of gene silencing that is mediated by small interfering RNA molecules (siRNAs) — 19- to 23-nucleotide double-stranded RNA duplexes that promote the cleavage of specific mRNAs. Long-lasting RNAi-mediated gene knockdown can be achieved using lentiviral vectors that express the siRNAs. In the two studies, by Raoul *et al.* and Ralph *et al.*, the authors independently tested whether RNAi could be used to silence mutant forms of the human superoxide dismutase 1 gene (*SOD1*) expressed in mice. Familial forms of ALS are associated with mutations in *SOD1*, and mice that overexpress mutant *SOD1* show features of the human disease, such as motor neuron death and motor dysfunction.

Both studies showed that the injection of the lentiviral vectors led to substantial delays in the onset and progression of the disease. RNAi reduced the expression of mutant *SOD1* in culture and *in vivo*, prevented the death of spinal and brainstem motor neurons and improved the motor performance of the mice in different behavioural tasks. Raoul *et al.* also measured electromyographic responses in their animals, and found them to be preserved in the mice treated with the lentiviral vectors.

Early studies on the therapeutic use of siRNAs used vector-delivery methods that have limited potential as treatment agents: hydrodynamic delivery, intracerebral injection and other techniques. More recent papers have added credibility to the idea of using RNAi as therapy by placing extra emphasis on the way in which the vectors are administered. In this regard, the paper by Ralph *et al.* is particularly compelling, as the authors delivered the lentiviral vector through intramuscular injection, an administration method that has clear therapeutic relevance.

The therapeutic benefit reported in these two papers is among the most substantial ever seen in this animal model, raising hopes for its successful translation to the clinical domain. However, familial forms of ALS account for a very small fraction of clinical cases. So, the need for therapeutic approaches for both familial and sporadic forms of ALS is as pressing as ever.

Juan Carlos Lopez, Chief Editor,
Nature Medicine

References and links

ORIGINAL RESEARCH PAPERS Raoul, C. *et al.* Lentiviral-mediated silencing of SOD1 through RNA interference retards disease onset and progression in a mouse model of ALS. *Nature Med.* 13 March 2005 (doi:10.1038/nm1207) | Ralph, G. S. *et al.* Silencing mutant *SOD1* using RNAi protects against neurodegeneration and extends survival in an ALS model. *Nature Med.* 13 March 2005 (doi:10.1038/nm1205)

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