GLIA

A time code for myelin

Combinatorial codes are a recurring theme in neural development — a *Hox* gene code specifies different cell types along the anteroposterior axis of the neural tube, and distinct combinations of transcription factors determine neuronal fate along the dorsoventral axis. Now, in the *Journal of Neuroscience*, Farhadi *et al.* describe a new combinatorial code that temporally controls the expression of a single gene. They show that glia use different combinations of regulatory sequences to control the expression of myelin basic protein (MBP) at various stages during and after the onset of myelination.

Farhadi *et al.* examined the region upstream of the MBP coding sequence, and they identified four regulatory modules — M1–M4 — that are conserved between mice and humans. The authors made DNA constructs in which various combinations of regulatory elements were linked to a reporter gene. These reporter constructs were inserted in single copy into the mouse genome using a controlled transgenesis strategy that allowed direct comparisons of both qualitative and quantitative expression phenotypes.

In the central nervous system, Farhadi *et al.* showed that M1 and M2 upregulated reporter gene expression in oligodendrocytes in the early postnatal period during primary myelination. M3, on the other hand, drove continuous reporter expression throughout primary myelination and adulthood, and the authors proposed that M3 is required for myelin maintenance. M3 also seems to be required during myelin repair in the CNS after a demyelinating injury. In the peripheral nervous system, both myelinating and remyelinating Schwann cells used elements within M3 and M4 to drive reporter gene expression.

These findings indicate that different phases in myelin development and maintenance are characterized by the use of different combinations of regulatory elements to control *MBP* expression. By finding out which factors bind to these elements, it should be possible to identify the upstream signalling pathways that control myelination and remyelination. This could have important implications for myelin repair. Remyelination in the injured adult nervous system produces comparatively thin myelin sheaths, and this tends to limit the degree of functional recovery. If the signalling pathways that promote robust myelination can be identified and harnessed, this problem might be overcome.

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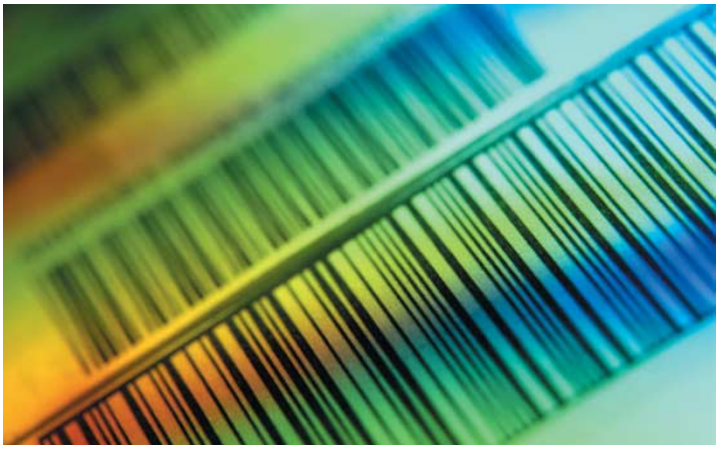
References and links

ORIGINAL RESEARCH PAPER Farhadi, H. F. *et al.* A combinatorial network of evolutionarily conserved *myelin basic protein* regulatory sequences confers distinct glial-specific phenotypes. *J. Neurosci.* **23**, 10214–10223 (2003)

FURTHER READING Franklin, R. J. Why does remyelination fail in multiple sclerosis? *Nature Rev. Neurosci.* **3**, 705–714 (2002)



IN BRIEF

CELL BIOLOGY OF THE NEURON

AMPA receptor tetramerization is mediated by Q/R editing.

Greger, I. H. *et al. Neuron* **40**, 763–774 (2003)

The channel properties and trafficking of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors depend largely on their subunit composition. RNA editing of the GluR2 subunit at the 'Q/R site' controls trafficking of AMPA receptors from the endoplasmic reticulum to the synapse, and this study shows that RNA editing at this site also regulates tetramerization of AMPA receptor subunits. Edited GluR2 subunits are retained in the endoplasmic reticulum (ER) and do not readily tetramerize, whereas most unedited subunits are exported from the ER to the synapse and assemble into receptor tetramers.

NEURODEGENERATIVE DISORDERS

Dietary Cu stabilizes brain superoxide dismutase 1 activity and reduces amyloid Aβ production in APP23 transgenic mice.

Bayer, T. A. *et al. Proc. Natl Acad. Sci. USA* **100**, 14187–14192 (2003)

In vivo reduction of amyloid-β by a mutant copper transporter.

Phinney, A. L. *et al. Proc. Natl Acad. Sci. USA* **100**, 14193–14198 (2003)

In APP23 transgenic mice, a model of Alzheimer's disease, overexpression of the amyloid precursor protein (APP) is associated with reduced activity of superoxide disumutase 1 (SOD1) and deposition of amyloid plaques. Bayer *et al.* find that dietary copper restores SOD1 activity in these mice, and also lowers levels of amyloid-β in the brain. In the second of these papers, Phinney and colleagues use another mouse model of Alzheimer's disease in which amyloid-β accumulates. When these mice are homozygous for a mutant copper transporter that causes accumulation of copper in the cytoplasm, levels of amyloid-β and deposition of amyloid plaques are reduced. These studies contrast with previous *in vitro* results, which indicated that copper increased amyloid-β assembly and toxicity, and indicate that treatment with copper might be useful in the early stages of Alzheimer's disease.

NEUROPSYCHOLOGY

Altered awareness of voluntary action after damage to the parietal cortex.

Sirigu, A. *et al. Nature Neurosci.* 30 November 2003 (10.1038/nn1160)

In electroencephalographic studies, the human experience of wanting to move is reported after, rather than before, the 'readiness potential', which indicates preparation for a movement. Sirigu *et al.* find that patients with damage to the parietal cortex cannot report awareness of an intention to move. They propose that activity in the parietal cortex is important for the generation of an internal model of a planned movement, and that this model might be necessary for awareness of motor planning.