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SMALL RNAS

Unwrapping glial differentiation

Oligodendrocytes — specialized glia that wrap neuronal axons with myelin — develop from rapidly proliferating oligodendrocyte precursor cells (OPCs). Two papers in *Neuron* reveal that microRNAs (miRNAs) in maturing OPCs have a key role in the post-transcriptional repression of genes involved in OPC proliferation and thus in the promotion of oligodendrocyte differentiation.

Previous studies have shown that miRNA levels are particularly high in the brain and that they have many roles in the development and function of the nervous system. Now, two studies show that disruption of miRNA processing in OPCs, by inactivation of the endoribonuclease Dicer, prevents the development of oligodendrocytes and disrupts CNS myelination *in vivo*.

PHOTODISC

Barres and colleagues identified three miRNAs that are strongly upregulated in OPCs during oligodendrocyte differentiation in mice: miR-219, miR-138 and miR-338. They focused on miR-219, which they showed was necessary and sufficient to promote oligodendrocyte differentiation. Moreover, it partially rescued the effect of conditional deletion of Dicer *in vitro*.

microRNAs prevent the translation of mRNAs with sequences that are complementary to their own. Identification of these transcripts sheds light on the mechanism through which miRNAs exert their effects. Barres and colleagues showed that miR-219 targets the expression of genes known to promote OPC proliferation and inhibit oligodendrocyte differentiation, such as platelet-derived growth factor receptor-α and SOX6, respectively. miR-219 also targets forkhead box protein J3 and zinc finger protein 238, transcription factors that were shown for the first time to repress oligodendrocyte differentiation.

In agreement with these findings, an independent study from Lu and colleagues indicated that miR-219 and miR-338 are strongly upregulated in the mouse spinal cord at the onset of oligodendrocyte differentiation and that exogenous expression of these miRNAs in the developing chick neural tube or the cortex of mouse embryos promoted premature oligodendrocyte specification and differentiation. Furthermore, specific knockdown of endogenous miR-219 or miR-338 blocked oligodendrocyte maturation *in vitro* and in zebrafish embryos. Lu's group found other targets of miR-219 and miR-338 in addition to SOX6: HES5, another transcription factor implicated in the inhibition of oligodendrocyte differentiation, and several genes involved in neuronal differentiation — such as neurogenic differentiation factor 1, ISL1 and OTX2.

These studies not only highlight a general role for miRNAs in the development of oligodendrocytes and identify novel mediators of oligodendrocyte differentiation, but also raise the intriguing possibility of using miRNAs to treat the aberrant proliferation of cells in glioblastoma or to promote myelin repair.

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ORIGINAL RESEARCH PAPERS Dugas, J. C. *et al.* Dicer1 and miR-219 are required for normal oligodendrocyte differentiation and myelination. *Neuron* **65**, 597–611 (2010) | Zhao, X. *et al.* MicroRNA-mediated control of oligodendrocyte differentiation. *Neuron* **65**, 612–626 (2010)
FURTHER READING Schratt, G. microRNAs at the synapse. *Nature Rev. Neurosci.* **10**, 842–849 (2009) | Li, X. & Jin, P. Roles of small regulatory RNAs in determining neuronal identity. *Nature Rev. Neurosci.* **11**, 329–338 (2010)