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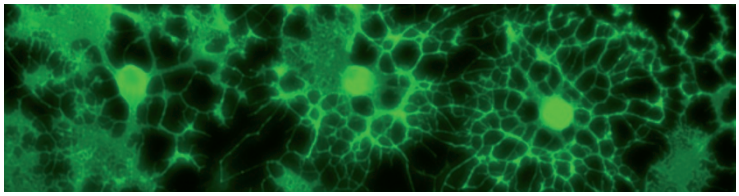
NEURAL REPAIR AND REHABILITATION

Fibroblast-derived OPCs—hope for remyelination therapy?



Immunofluorescent image showing induced oligodendrocyte precursor cells expressing the Plp1-eGFP reporter (green). Image courtesy of F. Najm and A. Lager.

In two new studies, published in *Nature Biotechnology*, researchers have shown that a panel of three transcription factors can be used to reprogramme rodent fibroblasts into oligodendrocyte precursor cells (OPCs) that can successfully remyelinate axons both *in vivo* and *in vitro*. "Millions of people worldwide are affected by disorders of myelin," says Paul Tesar, principal investigator of one of the studies, "and therapies for these disorders are heavily reliant upon a source of autologous OPCs for study and development of transplantation strategies."

Studies in rodent models of demyelinating disease have suggested a benefit of transplantation of OPCs derived from foetal brain tissue or embryonic stem cells, but issues with technology and tissue availability have limited further developments. "The direct cell-fate switch from one cell type to another provides one way to generate inaccessible cells from a more obtainable cell type—in this case, fibroblasts—for cell replacement treatments," says Nan Yang, lead author of the other study.

Tesar and colleagues used microarray data to identify 50 transcription factors that are expressed specifically in the oligodendrocyte lineage, and expressed these factors in mouse fibroblasts with the use of doxycycline-inducible lentiviral vectors. Through a screening process, combined expression of just three of these transcription factors (Sox10, Olig2 and Nkx6.2) was found to be necessary and sufficient to drive conversion of fibroblasts into OPCs that successfully remyelinated axons *in vitro*.

Yang *et al.* took a similar approach: using their previously defined method of cell-fate switching, the researchers initially screened 10 transcription factors linked to the oligodendrocyte lineage, and narrowed this selection down to three factors (Sox10, Olig2 and Zfp536) that were capable of instructing rat fibroblasts to become OPCs. *In vitro*, the induced OPCs colonized and myelinated axons in forebrain slice cultures obtained from shiverer mice—animals that lack endogenous expression of myelin basic protein (MBP) and, therefore, compact myelin.

In both studies, the *in vivo* myelinating capacity of induced OPCs was assessed following their transplantation into the CNS (either the brain or spinal cord) of live shiverer mice. 2–3 weeks after transplantation, tissue sections were obtained and immunostained for myelin. Both groups reported presence of MBP^+ cells at the transplanted sites, and the cells seemed to form compact myelin sheaths around axons.

Tesar and Yang both note that the next step will be to translate their findings to human cells, with the hope that this technology will lead to novel therapies for patients with myelin-related disorders.

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Original articles Najm, F. J. *et al.* Transcription factor-mediated reprogramming of fibroblasts to expandable, myelinogenic oligodendrocyte progenitor cells. *Nat. Biotech.* doi:10.1038/nbt.2561 | Yang, N. *et al.* Generation of oligodendroglial cells by direct lineage conversion. *Nat. Biotech.* doi:10.1038/nbt2564