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White matter from fibroblasts

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Abstract

Myelinating oligodendrocytes are induced from mouse embryonic fibroblasts by transcription factor-mediated reprogramming.

The possibility of transplanting glial progenitor cells into the brain to replace lost oligodendrocytes has attracted the interest of translationally oriented stem-cell biologists, who view disorders of the whitematter as among the most tractable neurological conditions for cell therapy¹. Yet preparing human glial progenitor cells—also known as oligodendrocyte progenitor cells—in the numbers, homogeneity and purity needed for clinical transplantation has proven challenging, and most studies have necessarily relied upon fetal tissue as a cell source. In this issue, two teams report the direct conversion of mouse embryonic fibroblasts to glial progenitor cells capable of differentiating to myelinogenic oligodendrocytes. Tesar and colleagues² and Wernig and colleagues³ carried out combinatorial screening of transcription factors important to glial identity [to derive a core set of factors sufficient to instruct oligodendrocytic reprogramming. Notably, the gene sets identified by the two groups are only partially overlapping, and although the ‘induced’ oligodendrocyte progenitor cells generated by each protocol can restore myelin, the cells seem to differ in lineage potential. Thus, the studies may reveal fundamental differences in fate commitment that attest to the potential of reprogramming to fine-tune the production of desired phenotypes.

The white matter of the brain is the target of many of the major neurological diseases of man, ranging from multiple sclerosis, subcortical stroke and vascular dementia to the childhood leukodystrophies and cerebral palsy. All of these disorders, in some way, shape or form, involve the loss of central oligodendrocytes, the myelin-producing cells of the human brain. Oligodendrocytes are one of the two major types of macroglial cells, the other being astrocytes; together, these cells arise from bipotential glial progenitor cells, which pervade the adult as well as the developing CNS.

To meet the challenge of developing renewable sources of transplantable glia and neurons, investigators have focused on developing protocols for the neural differentiation of pluripotential stem cells, especially somatic cell-derived induced pluripotential stem cells, in light of their promise of patient-specific stem cell generation and relative non-immunogenicity^{4, 5}. More recent reprogramming efforts have focused on skipping the pluripotent stage altogether to permit the direct differentiation of one somatic phenotype, often fibroblasts, to another lineage of interest. Direct conversion of fibroblasts into

neurons^{6, 7} presaged serially more precise inductions of specific neuronal phenotypes, including dopaminergic neurons and motor neurons, among others.

Yet neurons are generated early in neural development, and much is known about their molecular ontogeny and transcription factor codes; as a result, their generation from induced pluripotent stem cells or directly from somatic cells has required relatively short differentiation protocols using well-studied transcription factors. In contrast, oligodendroglial differentiation is less well-understood and occurs much later in development; human neurogenesis begins within the first month after conception, whereas oligodendroglial production does not begin in earnest until four months later. As a result, strategies for efficiently inducing human glial progenitor cells and their derived myelin-producing oligodendrocytes from pluripotent stem cells have proven more elusive, though we have recently achieved efficiencies that may be suitable for clinical consideration⁹. It is no surprise, then, that the direct induction of astrocytes and oligodendrocytes from somatic cells has taken much longer to accomplish than that of their neuronal neighbors.

Both Tesar and colleagues² and Wernig and colleagues³ used mouse rather than human fibroblasts as their starting material, taking advantage of the more rapid development of murine oligodendroglia to more quickly derive protocols for their production. Tesar's group—using rat as well as murine fibroblasts—employed a combination of eight transcription factors, from which a core set of three genes—*Sox10*, *Nkx6.2* and *Olig2*—was subsequently defined, to drive the production of induced oligodendrocyte progenitor cells. The paper provides strong histological and ultrastructural evidence of efficient myelination by these cells in an elegant *in vitro* slice model of the congenitally hypomyelinated shiverer mouse. Remarkably, while the induced progenitor cells were able to divide and expand for at least five passages, they appeared to do so as oligodendrocyte-restricted progenitors; the authors reported little evidence of astrocyte production, even though oligodendrocyte progenitor cells typically generate both astrocytes and oligodendrocytes, and most studies have found them to be bipotential until their terminal division.

Capitalizing upon an earlier assessment of differential gene expression by oligodendrocytes¹⁰, Wernig and colleagues³ screened a set of factors different from that used by Tesar and colleagues² and identified *Sox10*, *Olig2* and *Zfp536* as sufficient to direct glial progenitor cell phenotype. Yet when fibroblasts were transduced with this combination, in which *Nkx6.2* was replaced by *Zfp536*, the cells developed as bipotential glial progenitors able to give rise to both astrocytes and oligodendrocytes. This bipotential phenotype is more reflective of that seen in development, and seems more analogous to the phenotype of oligodendrocyte progenitor cells derived by my group from both human tissue and pluripotent cells^{8, 9}. However, whether the apparently distinct phenotypes noted by these investigators merely reflect differences in how the cells were assessed, or whether they instead evidence a fundamental distinction in the differentiated state of the cells generated by the two protocols, remains unclear. If Tesar and colleagues² have indeed discovered a reprogramming protocol that avoids the bipotential glial progenitor stage and directly generates mitotic cells capable only of oligodendrocytic differentiation, then might their derived phenotype be downstream of that identified by Wernig and colleagues³? This is

certainly a real possibility, as the adult rodent brain harbors populations of mitotic oligodendroglia that seem to be downstream of the bipotential progenitor stage.

This distinction in lineage competence between the glial progenitors derived in the two studies may have significant implications as these experiments move from mice to humans, given that oligodendrocyte biology differs between rodents and primates. Whereas rodents appear to harbor populations of lineage-restricted oligodendroglial progenitors, we and others have noted that human oligodendroglia are every bit as post-mitotic as neurons, whereas their progenitors are multilineage competent¹¹ As such, might the protocol of Tesar and colleagues² yield direct oligodendroglial differentiation in humans, bypassing the bipotential stage at which astrocytes might also be generated? If so, would the cells thereby generated lose mitotic competence with oligodendrocytic fate restriction? This might have significant benefits in directing terminal differentiation, but would defeat the purpose of generating stable lines of mitotic glial progenitor cells able to be expanded for clinical transplantation. In fact, this consideration cuts to the core issue of what constitutes direct reprogramming: will the glial cells derived through directed differentiation strategies be able to divide and expand as phenotypically-stable clones of mitotic and myelinogenic glial progenitor cells, months and years after their introduced reprogramming genes have ceased transcription? If so, will the phylogenetic differences in oligodendroglial biology between rodents and humans permit the same transcription factor combinations to be effectively used in human cells, with comparable results?

Time and further modeling in human cells will allow these issues to be addressed and resolved, but the two groups have already made a giant leap forward in our ability to employ cellular reprogramming for direct oligodendrocytic induction and replacement. As such, they have accomplished not just an especially challenging bit of cellular alchemy but have done so in the service of a patient population that may be especially likely to benefit from cell-based repair strategies, and especially grateful for the efforts of these pioneering investigators.

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