News & views

Parkinson's disease

Unleashing the neuronal side of astrocyte cells

Ernest Arenas

Astrocytes are non-neuronal brain cells that express a protein called PTB. It emerges that PTB depletion unlocks the potential of astrocytes to convert to neurons in a mouse model of Parkinson's disease. See p.550

How can the neurons that degenerate in the substantia nigra region of the midbrain in Parkinson's disease be replaced? One exciting possibility would be to convert non-neuronal cells called astrocytes, which are plentiful in the brain, into neurons. On page 550, Qian *et al.*[1] report a simple strategy that harnesses this possibility and can ameliorate neurological deficits in a mouse model of Parkinson's disease[1]. Their work, along with a parallel approach recently outlined by Zhou *et al.* in *Cell*[2], holds huge promise for our ability to use cell-conversion strategies to treat neurodegenerative diseases.

Cell types such as skin cells or astrocytes can be converted – through forced expression of transcription factors, microRNAs or small molecules – to other cell types *in vitro*[3–8], including to neurons that produce the neurotransmitter molecule dopamine[5,8]; these neurons are lost in Parkinson's disease. This approach has also been used to convert mouse-brain astrocytes to neurons *in vivo*[6–8]. For instance, astrocytes in the brain's striatum have been converted to 'induced dopamine-releasing' (iDA) neurons that can partially correct motor defects in a mouse model of Parkinson's disease[8]. However, the iDA neurons generated using this approach neither formed the distant neuronal connections found in a healthy brain nor comprehensively restored motor behaviour. Qian *et al.* and Zhou *et al.* have used an alternative strategy to efficiently reprogram astrocytes into neurons: depletion of an RNA-binding protein called PTB that is expressed in astrocytes and that inhibits neuronal differentiation.

Qian *et al.* began their experiments *in vitro*, using astrocytes isolated from the cortex and midbrain of mouse brains, and from the human cortex. The authors used an RNA molecule called a small hairpin RNA to promote degradation of messenger RNA transcribed from the gene that encodes PTB, *Ptbp1*. This triggered conversion of all three types of astrocyte to neurons. Zhou *et al.* achieved the same effect using the genome-editing technique CRISPR–CasRx to deplete *Ptbp1* mRNA in astrocytes isolated from the mouse cortex.

Next, the two teams depleted PTB *in vivo* in the adult mouse brain. Qian and colleagues used mice genetically engineered such that astrocytes could be targeted by the small hairpin RNA against *Ptbp1*, which was carried into the brain in a viral construct. By contrast, Zhou *et al.* infected astrocytes in wild-type mice with a virus that carried the CRISPR–CasRx machinery. Both strategies led to conversion of the targeted astrocytes to neuronal cell types.

The groups next depleted PTB in a mouse model of Parkinson's disease. In these animals – as in people who have the disorder – dopamine-releasing neurons are depleted in the substantia nigra, and dopamine levels are abnormally low in the striatum (the area to which these neurons project), resulting in deficits in motor behaviour. Qian *et al.* depleted PTB in astrocytes in the substantia nigra of these animals; Zhou *et al.* in the striatum. Both approaches yielded the same result: conversion of some of the infected astrocytes to neurons that resembled those lost in Parkinson's disease, and restoration of motor behaviour.

The two groups demonstrated that PTB depletion causes astrocytes to convert to neuronal cell types largely appropriate to the brain region they reside in. How is this specificity conveyed? Qian *et al.* found that astrocytes in the midbrain express low levels of the transcription

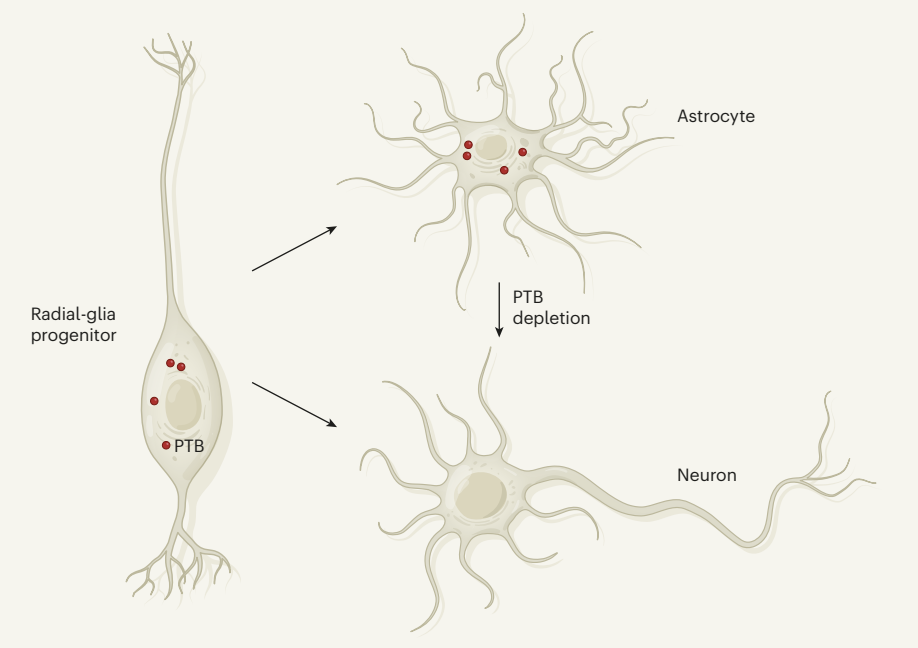

Figure 1 | A path for astrocyte-to-neuron conversion. Radial-glia progenitors are stem-cell-like cells that – in the developing mouse midbrain – express messenger RNA that encodes the protein PTB. These cells can give rise to non-neuronal cells called astrocytes, which also express this mRNA, and to neurons, which do not. Two groups[1,2] report that depletion of PTB in adult astrocytes leads to the cells' conversion to neurons. In a mouse model of Parkinson's disease, PTB depletion produced the type of dopamine-releasing neuron that is lost in Parkinson's disease, and restored motor behaviour (not shown).

factors Lmx1a and Foxa2; these are expressed in the progenitors of dopamine-releasing neurons during midbrain development and are required for the maturation of these progenitors into neurons[9]. PTB depletion further increased the expression of these factors in midbrain astrocytes. By contrast, in cortical astrocytes, the treatment led to increased levels of transcription factors associated with cortical neurons, such as Ctip2 and Cux. In addition, reprogramming of astrocytes in the substantia nigra, or in the neighbouring ventral tegmental area, produced different subtypes of iDA neuron that express subtype-specific transcription factors and proteins: Sox6 and Aldh1a1 in the substantia nigra, Otx2 in the ventral tegmental area.

Qian and colleagues' results indicate that brain-region-specific transcription factors contribute to the astrocyte-to-iDA conversion. However, such a mechanism cannot explain why Zhou *et al.* were able to convert striatal astrocytes to iDA neurons, given that striatal astrocytes express a different set of region-specific transcription factors. What might be the mechanism leading to iDA conversion in the striatum?

Zhou and colleagues show an almost threefold increase in iDA conversion efficiency in the mouse model of Parkinson's disease compared with control mice one month after treatment. These results suggest that astrocytes themselves, or cells in their environment, respond to the loss of endogenous dopamine-releasing neurons by expressing factors that promote the conversion of astrocytes to iDA neurons. And Qian *et al.* found higher conversion efficiency in the mouse midbrain than in isolated midbrain astrocytes, indicating a role for local brain-derived factors in iDA conversion. Identifying local and damage- or disease-specific factors, intrinsic or extrinsic to cells, holds the key to further improving the efficiency of astrocyte-to-neuron conversion.

One intriguing question to arise from these studies is why astrocytes are constantly repressing neuronal genes. One explanation might lie in the cells' developmental origin. Astrocytes and neurons have common ancestors called radial-glia progenitors — stem-cell-like cells that first give rise to neurons and then differentiate into astrocytes and other neuron-supporting glial cells[10]. In the developing mouse midbrain, all radial-glia cell types express *Ptbp1*, whereas differentiating neuron precursors and neurons do not[11]. Perhaps midbrain astrocytes — as descendants of radial glia — have inherited a program to generate neurons that lies dormant unless PTB is depleted (Fig. 1). *Ptbp1* is also expressed in other midbrain cell types[11], including endothelial and pericyte cells in the blood vessels, ependymal cells lining the ventricular cavity and immune cells called microglia. Future studies should examine whether PTB depletion can also convert these cells to iDA neurons in animal models of Parkinson's disease.

For this strategy to be useful in the clinic, its efficiency might need to be improved. For instance, 60–65% of the infected astrocytes do not become iDA neurons. This percentage must decrease, either through more-focused targeting of astrocytes in the substantia nigra, or by introducing factors that enable non-nigral astrocytes to convert to iDA neurons. It will also be important to determine the quality and authenticity of the converted iDA cells at single-cell level, and to investigate whether unwanted cells are generated. Both Qian *et al.* and Zhou *et al.* provide evidence that astrocytes are converted to other neuron types, besides iDA cells. Moreover, Qian *et al.* show that converted iDA neurons mainly project to the septum, rather than the striatum, and that only 8% of the fibres that project to the septum come from iDA neurons. However, on a positive note, more than half of the fibres reaching the striatum were contributed by iDA neurons. This finding — together with the demonstration that the conversion process restored striatal dopamine levels and motor activity — provides evidence for a remarkable functional reconstitution of the nigrostriatal pathway by iDA neurons.

In a final set of experiments, Qian *et al.* explore a way in which their approach might be used in the clinic: using short nucleic acids called antisense oligonucleotides that bind to an mRNA and prevent its translation into protein. The authors show that local transient delivery of antisense oligonucleotides against PTB led to the generation of iDA-like neurons and to motor recovery in the mouse model of Parkinson's disease, demonstrating the validity of the approach.

Future experiments will need to examine whether human midbrain or striatal astrocytes can also be converted to iDAs, and whether the converted cell types and their targets are correct and stable over long periods. The safety of PTB depletion and the strategies used to deliver the treatment will also have to be carefully assessed, to rule out any collateral damage to bystander host brain cells or to the converted cells, or any damage resulting from the strategy's depletion of astrocytes. Although many questions remain to be answered, the simplicity and efficiency of this gene-therapy approach to cell replacement makes it very attractive. The current studies promise to open a new chapter in the development of regenerative medicine for neurological disorders such as Parkinson's disease.

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Archaeology

Large-scale early Maya sites revealed by lidar

Patricia A. McAnany

Archaeology is transforming our view of how ancient Maya societies developed. Use of lidar technology has now led to the discovery that large, monumental structures that aid naked-eye astronomy were built unexpectedly early. **See p.530**

In archaeology, there are few watershed moments, when a technological breakthrough changes everything. But the invention of radiocarbon dating in the 1940s brought one such revolution, by providing a consistent, worldwide system for placing archaeological material in chronological order. A more-recent transformative innovation is the airborne application of a remote-sensing technique called light detection and ranging (lidar) to create a model (also known as a digital-elevation model) of the bare-surface terrain that is hidden by trees in forested areas[1]. Lidar is changing archaeological study of the ancient Maya in Mexico and Central America. It is increasing the speed and scale