BRAIN REPAIR

Gatekeeping astrocyte identity

New findings cast doubt on whether suppressing the RNA-binding protein PTBP1 can force astrocytes to become dopaminergic neurons.

ALEXIS COOPER AND BENEDIKT BERNINGER

As a cell acquires its final identity, it usually closes the door on the other cellular fates it could have adopted. Valiant guardian mechanisms ensure that this gate remains shut, even as a plethora of signals threaten to crack it open once more. These processes are particularly crucial for cells from highly related lineages – such as astrocytes and neurons, two types of brain cells that derive from the same progenitor cells.

In the past 15 years, work has shown that astrocytes, which belong to a class of non-neuronal cells that support and fine-tune the activity of nerve cells, can be converted into neurons if they are forced to express neurogenic transcription factors (Götz and Bocchi, 2021). In some brain regions such as the mouse striatum, injury can even re-activate a neurogenic programme which is otherwise suppressed (Magnusson et al., 2014). This raises the intriguing possibility that specific mechanisms help to safeguard the identity of astrocytes; these processes could also be harnessed to awaken neurogenic potential in astrocytes and help repair neural damage.

A top-selling candidate for gatekeeping the astrocyte-to-neuron conversion is the RNA-binding PTBP1 which, in vitro, inhibits neuronal fate by ensuring that a master repressor of neuronal genes remains active (Makeyev et al., 2007). The discovery of these regulatory interactions suggested that simply downregulating PTBP1 could release the brake on a neurogenic programme in non-neuronal cells (Xue et al., 2013; Figure 1A). In fact, two recent bodies of work suggest that when PTBP1 is knocked down, mouse astrocytes can turn into dopaminergic neurons with remarkable efficiency (Qian et al., 2020, Zhou et al., 2020). This class of nerve cells degenerates in Parkinson’s disease, and both studies reported a drastic amelioration of motor deficits in a mouse model of this condition, with enormous implications for new brain therapies.

Now, in eLife, Mingtao Li and colleagues at Sun Yat-sen University – including Weizhao Chen as first author – report results that question these findings (Chen et al., 2022).

The team focused on whether the seemingly converted dopaminergic cells truly derived from astrocytes, using a transgenic mouse line that faithfully reports the origin of astrocytes. PTBP1 was successfully knocked down in astrocytes by using adeno-associated viruses, viral vectors that contain the information necessary to suppress the protein only in astrocytes (Figure 1B).

Dopaminergic neurons carrying the viral label were identified, but to the team’s surprise, none of these were positive for the genetic tag that marked astrocyte origin (Figure 1C). This data strongly suggests that these neurons have not emerged from converted astrocytes, but that instead the viral vectors had lost their original specificity. This adds to recent, baffling observations, which highlighted that adeno-associated
viruses designed to activate the expression of neuronal conversion factors only in astrocytes, fail to attain the required specificity (Wang et al., 2021).

Chen et al. then checked whether the manipulation could be successful if done on a type of astrocyte that may be more prone to changing its identity. These ‘reactive’ astrocytes emerge in damaged tissues, where they start to display traits present in neural stem cells (Sirko et al., 2013). A toxin was used to kill dopaminergic neurons as PTBP1 was suppressed in reactive astrocytes, yet even this scenario failed to turn the cells into neurons (Figure 1D). Conducting this manipulation in a mouse model of Parkinson’s disease also did not lead to improvements in the animals’ motor deficits. How this negative finding can be reconciled with earlier studies showing that these symptoms were corrected upon PTBP1 deactivation will require further clarification.

Taken together, the work by Chen et al. strongly argues against PTBP1 being the sole gatekeeper between astrocyte and neuronal fates, while also stressing the importance of rigorous genetic lineage tracing when conducting in vivo reprogramming. Still, given the powerful control that PTBP1 exerts on the molecular switch that represses neuronal genes, it would be premature to fully move away from studying the impact of this protein on astrocyte identity and function.
Alexis Cooper is in the Centre for Developmental Neurobiology, King’s College London and the Francis Crick Institute, London, United Kingdom
alexis.cooper@kcl.ac.uk
http://orcid.org/0000-0002-2182-0046

Benedikt Berninger is in the Centre for Developmental Neurobiology and the MRC Centre for Neurodevelopmental Disorders, King’s College London, the Francis Crick Institute, London, United Kingdom and the University Medical Center of the Johannes Gutenberg University, Mainz, Germany
benedikt.berninger@kcl.ac.uk
http://orcid.org/0000-0003-2652-2782

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References
Chen W, Zheng Q, Huang Q, Ma S, Li M. 2022. Repressing PTBP1 fails to convert reactive astrocytes to dopaminergic neurons in a 6-hydroxydopamine mouse model of Parkinson’s disease. eLife 11:e75636. DOI: https://doi.org/10.7554/eLife.75636, PMID: 35535997

Götz M, Bocchi R. 2021. Neuronal replacement: Concepts, achievements, and call for caution. Current Opinion in Neurobiology 69:185–192. DOI: https://doi.org/10.1016/j.conb.2021.03.014, PMID: 33984604

Magnusson JP, Göritz C, Tatarishvili J, Dias DO, Smith EMK, Lindvall O, Kokaia Z, Frisén J. 2014. A latent neurogenic program in astrocytes regulated by Notch signaling in the mouse. Science 346:237–241. DOI: https://doi.org/10.1126/science.346.6206.237, PMID: 25301628

Makeyev EV, Zhang J, Carrasco MA, Maniatis T. 2007. The MicroRNA miR-124 promotes neuronal differentiation by triggering brain-specific alternative pre-mRNA splicing. Molecular Cell 27:435–448. DOI: https://doi.org/10.1016/j.molcel.2007.07.015, PMID: 17679093

Qian H, Kang X, Hu J, Zhang D, Liang Z, Meng F, Zhang X, Yue Y, Maimon R, Dowdy SF, Devaraj NK, Zhou Z, Mobley WC, Cleveland DW, Fu X-D. 2020. Reversing a model of Parkinson’s disease with in situ converted nigral neurons. Nature 582:550–556. DOI: https://doi.org/10.1038/s41586-020-2388-4, PMID: 32581380

Sirko S, Behrendt G, Johansson PA, Tripathi P, Costa M, Bek S, Heinrich C, Tiedt S, Colak D, Dichgans M, Fischer IR, Plesnila N, Staufenbiel M, Haass C, Snapyan M, Saghatelian A, Tsai LH, Fischer A, Grobe K, Dimou L, et al. 2013. Reactive glia in the injured brain acquire stem cell properties in response to sonic hedgehog. Cell Stem Cell 12:426–439. DOI: https://doi.org/10.1016/j.stem.2013.01.019, PMID: 23561443

Wang LL, Serrano C, Zhong X, Ma S, Zou Y, Zhang CL. 2021. Revisiting astrocyte to neuron conversion with lineage tracing in vivo. Cell 184:5465–5481. DOI: https://doi.org/10.1016/j.cell.2021.09.005, PMID: 34582787

Xue Y, Ouyang K, Huang J, Zhou Y, Ouyang H. 2013. Direct conversion of fibroblasts to neurons by reprogramming PTB-regulated microRNA circuits. Cell 152:82–96. DOI: https://doi.org/10.1016/j.cell.2012.11.045

Zhou H, Su J, Hu X, Zhou C, Li H, Chen Z, Xiao Q, Wang B, Wu W, Sun Y, Zhou Y, Tang C, Liu F, Wang L, Feng C, Liu M, Li S, Zhang Y, Xu H, Yao H, et al. 2020. Glia-to-neuron conversion by CRISPR-CasRx alleviates symptoms of neurological disease in mice. Cell 181:590–603. DOI: https://doi.org/10.1016/j.cell.2020.03.024, PMID: 32272060