Movement Disorders
CLINICAL PRACTICE

Brain Alchemy: Transforming Astrocytes into Neurons for Neurodegenerative Disease

Qian H, Kang X, Hu J, et al. *Reversing a model of Parkinson's disease with in situ converted nigral neurons*. *Nature* 2020;582 (7813):550–556.

Repair or replacement of neurons lost as a result of neurodegenerative disease has been a long-sought goal. The discovery of cellular reprogramming methods, recognized by the Nobel Prize in Physiology or Medicine awarded to Drs. John Gurdon and Shinya Yamanaka in 2012, opened the door to new ways of overcoming the unique hurdle of the central nervous system's overall lack of spontaneous neuroregenerative ability. Therapeutic progress with this approach so far, however, has been relatively limited. The main focus of reprogramming efforts for neurodegenerative disease to date has been on producing cells that could be transplanted into the brain using neurosurgical interventions. There are many challenges with this approach, including the feasibility of restoring a complete neural circuit with transplanted neurons as well as the potential for harmful immunological responses to either the reprogramming vectors or transplanted tissue.[1] The study by Qian and colleagues[2] reports on an entirely new approach to the problem, using conversion of existing brain astrocytes into neurons to repair the nigrostriatal circuit that is damaged in Parkinson's disease (PD).

In their manuscript, Qian and colleagues[2] expanded on the capability of reprogramming somatic cells into neurons via the depletion of the RNA-binding protein polypyrimidine tract-binding protein (PTB), previously shown to be a key neuronal lineage transcriptional regulator in transforming fibroblasts into functional neurons.[3] Here, Qian and colleagues[2] demonstrate that adeno-associated virus mediated knockdown of PTB in midbrain astrocytes leads to their conversion into cells with properties of functional dopamine neurons. Surprisingly, when this reprogramming is conducted in vivo, newly converted dopamine neurons in the mouse nigra are able to develop working synapses in the striatum. Using the 6-hydroxydopamine model of PD to deplete dopamine neurons in the substantia nigra, the authors show that their astrocyte-to-neuron conversion is not only able to restore lost dopamine function in the nigrostriatal circuit but also can reverse the motor phenotype associated with dopamine depletion. For the group's concluding experiment, they show that reprogramming does not require the use of viral vectors; they are able to use short-term administration of antisense oligonucleotides directed toward PTB alone to alleviate 6-hydroxydopamine motor symptoms.

This work provides an exciting glimpse of the future of neurodegenerative disease treatment. The reprogramming of cells already present in the brain could become a preferred approach for targeting not only PD but also a wide range of other disorders. Similar success has recently been reported by another group in the same PD model as well as another model for glaucoma using the same PTB knockdown strategy.[4]

There are important questions about in situ reprogramming that remain to be examined. Key issues will be the durability of the effect (the experiments here were limited to a few months), the extent of reprogramming, and reinnervation that can be obtained (only a small fraction of the astrocytes were converted) as well as screening for any potentially off-target or tumorigenic effects of this type of therapy. Nevertheless, this work marks an important milestone in the search for a cure for PD and other neurodegenerative disorders.

Author Roles

(1) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

G.P.W.: 1A, 1B

D.P.S.: 1A, 1B

Disclosures

Ethical Compliance Statement: : The approval of an institutional review board and informed patient consent were not necessary for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflict of Interest: : There are no specific funding sources applicable here, and there are no conflicts of interest to report.

Financial Disclosures for the Previous 12 Months: : Dr. Standaert is a member of the faculty of the University of Alabama at Birmingham and is supported by endowment and University funds. Dr. Standaert is an investigator in studies funded by Abbvie, Inc.,

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Keywords: astrocytes, neurodegeneration, Parkinson's disease, neuroregeneration.
Relevant disclosures and conflicts of interest are listed at the end of this article.
Received 24 August 2020; accepted 27 August 2020.
Published online 25 September 2020 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.13090

Avid Radiopharmaceuticals, the American Parkinson Disease Association, the Michael J. Fox Foundation for Parkinson Research, Alabama Department of Commerce, the Department of Defense, and National Institutes of Health Grants P01NS087997, P50NS108675, R25NS079188, P2CHD086851, P30NS047466, and T32NS095775. He has a clinical practice and is compensated for these activities through the University of Alabama Health Services Foundation. In addition, since January 1, 2019, he has served as a consultant for or received honoraria from Axovant Sciences, Inc., Censa Pharmaceuticals, Abbvie Inc., Grey Matter Technologies, Theravance Inc., the Kennedy Krieger Institute, McGraw Hill Publishers, Sanofi-Aventis, RTI Consultants, Cerevance Inc., Yale University, and Michigan State University. ■

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References

1. Barker RA, Gotz M, Parmar M. New approaches for brain repair-from rescue to reprogramming. *Nature* 2018;557(7705): 329–334.
2. Qian H, Kang X, Hu J, et al. Reversing a model of Parkinson's disease with in situ converted nigral neurons. *Nature* 2020;582(7813): 550–556.
3. Xue Y, Ouyang K, Huang J, et al. Direct conversion of fibroblasts to neurons by reprogramming PTB-regulated microRNA circuits. *Cell* 2013;152(1–2):82–96.
4. Zhou H, Su J, Hu X, et al. Glia-to-neuron conversion by CRISPR-CasRx alleviates symptoms of neurological disease in mice. *Cell* 2020; 181(3):590–603. e516.