Targets for astrocyte-based treatments of Parkinson’s disease (PD)

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Parkinson’s disease (PD) is the second most common neurodegenerative condition worldwide, and the number of cases is expected to rise as the population ages (1). It is defined pathologically by the loss of dopaminergic (DA) neurons in the ventral midbrain (VM) and their projection into the dorsal striatum, especially posterior putamen (2). This degeneration of the nigrostriatal pathway is accompanied by the presence of pathological protein inclusions called Lewy bodies and neurites whose main component is α-synuclein (α-syn). α-syn is found at high concentrations in the normal adult brain, but in PD, it changes into a toxic oligomeric form that not only causes dysfunction within the cell where it is generated but also, may affect neighboring cells through cell-to-cell spread and seeding in the “infected” cell (reviewed in ref. 3). Consequently, much preclinical work, as well as a number of clinical trials, has been undertaken based on the premise that stopping α-syn spread will slow down disease progression in PD, and this publication by Yang et al. (4) explores this.

α-syn pathology:

It is well known that α-syn is not restricted to the neuronal compartment but is also found in most glial cell populations. The glial expression can even define the pathology in another α-synucleinopathy: multiple system atrophy with its pathognomonic glial cytoplasmic inclusions. In PD, on the other hand, there is a clear link established between α-syn pathology, reactive gliosis, and the inflammatory response, possibly through pathogenic species of α-syn directly activating toll-like receptors on microglia (5–8). Moreover, astrocytes have been shown to play a critical role in preventing neuronal α-syn accumulation by phagocytosis, endocytosis, and proteolysis, and it is speculated that it may also prevent α-syn transfer between neurons (9). However, the exact role that astroglia and microglia play in the development of α-syn pathology in PD still needs to be defined (10). Indeed, in this new study (4), Lee and colleagues have sought to investigate the mechanism by which rodent astrocytes take up and degrade α-syn employing various in vitro and in vivo models of PD. Their results have implications for also using glial cell therapies to treat this condition, in contrast to current therapeutic strategies that focus mainly on the dopaminergic neurons themselves (11).

Astrocytes:

Astrocytes are a type of glia that exists in all levels of the Central Nervous System (CNS), where they exert important roles in maintaining extracellular homeostasis, regulation of blood flow, brain metabolism, and regulation of synaptic transmission. Upon brain insult, astrocytes undergo molecular, cellular, and functional changes in a process called reactive astrogliosis. It is also becoming recognized that astrocytes can have both neurotoxic and neuroprotective effects in neurodegenerative diseases, such as PD, amyloid lateral sclerosis (ALS), Alzheimer’s disease, and Huntington’s disease (12, 13).

Mechanistic action of astrocytes in α-syn pathology

In the current study by Lee et al. (4), developed an in vitro model system based on neural stem/precursor cultures isolated from the developing ventral midbrain (VM) of mice and rats at a time point when the DA neurons normally arise. α-syn pathology was subsequently generated in the cells using viral vector-mediated transfer of α-syn combined with pathogenic preformed α-synuclein fibrils (PFFs) based on a method specifically developed for studies of α-synucleinopathy in the DAergic system (14). In this cellular model, α-syn aggregations could be detected in a substantial number of cells within 2 wk (but without cell death), which is a time frame suitable for mechanistic studies and evaluation of therapeutic interventions. When grown in cocultures with astrocytes from the mouse brain, the proportion of neurons with α-syn pathology was reduced when the astrocytes were derived from the VM, suggesting that these cells were having some effect on the α-syn aggregation process. Combined with previous findings reported from the same group, it was concluded that the astrocytes inhibit intraneuronal α-syn aggregation, regulate α-syn aggregation/disassembly, and eliminate monomeric and aggregate forms of α-syn in the neurons via both cell-autonomous and paracrine activities.

This first set of experiments was carried out in a reductionist culture model with limited cell type diversity and lack of microglia, and the relevance to the process underlying what happens in the human PD brain remains to be established. However, the key findings were confirmed in vivo using a PD mouse model where pathology was established by bilaterally injecting α-syn PFF + adenovirus into the terminal site of the DA nigrostriatal pathway. In this paradigm, it was shown that transplantation of VM astrocytes increased the number of surviving DA neurons and

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reduced the degree of nigrostriatal DA denervation as well improved behavioral deficits, thus supporting the data from the cell culture model and suggesting that astrocyte transplantation may be a useful therapeutic strategy in PD working to modify disease progression (13).

Of particular interest is the mechanistic insights these studies report. In the cell culture model, the work suggests that the astrocytes not only directly affect the intracellular pathology of α-syn but also, prevent its spread by phagocytosing and removal of extracellular α-syn (which provides the source for propagation of the pathology between neurons). This is further explored in a transplant study, with the hypothesis that astrocytes could reduce or block transfer of host-to-graft pathology to grafted VM DA cells. This part of the study is especially timely given that stem cell therapies for PD are now entering first in human (FIH) trials (10) following decades of experimental and clinical work using fetal tissue (15), which has shown the presence of Lewy body-like pathology within some of the transplanted neurons (16, 17). For these fetal VM transplants, the percentage of neurons containing α-syn pathology was low (2 to 12%) and appears to have had no significant impact on graft function. Thus, while of interest, this spread of pathology is unlikely to represent a major deterrent in the development of such allogeneic therapies should they show safety and efficacy in these FIH trials. This of course may change in autologous grafting paradigms where the patients’ own cells are used, given that such DA cells already possess a vulnerability to developing PD pathology (18). The data in this study by Yang et al. (4) suggest that one strategy to try and overcome this problem of α-syn spread into the autologous transplants is to cograft astrocytes. This has been considered previously with DA transplants for treating PD, but in these cases, the rationale has been that these cells provide critical trophic factors to support the differentiating dopamine cells (e.g., ref. 19) rather than protecting them for the α-syn pathology.

**Future therapies:**

Astrocytes are increasingly being recognized to play important roles in neurodegenerative disorders. They have previously been shown to help protect motor neurons in models of ALS (20) as well drive the development of a Huntington’s disease phenotype in a chimeric model of disease (21). This study, therefore, adds to this literature, and while of great interest, it should be noted that such therapies for PD are still in their infancy and that a number of critical steps remain to be taken, including performing studies using human glia and their capacity to abrogate α-syn pathology. Indeed, it is curious that the VM astrocytes in this rodent study perform so well in preventing α-syn pathology when the midbrain is the primary site of pathology in PD, suggesting at least that their function in the adult human PD brain is not that effective. Moreover, as both fetal- and stem cell–derived DAergic transplants mature, they contain a high proportion of glia even without cotransplantation, and it should be investigated why these glia, which also have a midbrain identity, do not seem to protect the graft in the same way (22, 23). Nevertheless, this study, as well as others in the field, clearly shows that a better understanding of the role of glia in neurodegenerative disorders is much needed, including the regional properties of different astrocytes (24, 25) and their interaction with microglia—all of which may provide important avenues of therapeutics in PD.

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1. E. R. Dosey, T. Sheer, M. S. Okun, B. B. Bloem, The emerging evidence of the Parkinson pandemic. J. Parkinsons Dis. 8 (s1), 53-58 (2018).
2. D. J. Surmeier, J. A. Obeso, G. M. Halliday, Selective neuronal vulnerability in Parkinson disease. Nat. Rev. Neurosci. 18, 101-113 (2017).
3. Y. C. Wong, D. Kainz, α-synuclein toxicity in neurodegeneration: Mechanism and therapeutic strategies. Nat. Med. 23, 1-13 (2017).
4. Y. Yang et al., Therapeutic functions of astrocytes to treat α-synuclein pathology in Parkinson’s disease. Proc. Natl. Acad. Sci. U.S.A., 10.1073/pnas.2110746119 (2022).
5. A. Kouli, C. B. Horne, C. H. Williams-Gray, Toll-like receptors and their therapeutic potential in Parkinson disease. Int. J. Mol. Sci. 18, 41-51 (2019).
6. W. Zhang et al., Aggregated alpha-synuclein activates microglia: A process leading to disease progression in Parkinson’s disease.FASEB J. 19, 533-542 (2005).
7. V. Sanchez-Guajardo, N. Tentillier, M. Romero-Ramos, The relation between α-synuclein and microglia in Parkinson’s disease: Recent developments. Neuroscience 302, 47-58 (2015).
8. M. F. Duffy et al., Lewy body-like α-synuclein inclusions trigger reactive microgliosis prior to nigral degeneration. J. Neuroinflammation 15, 129 (2018).
9. F. Li et al., α-Synuclein transfer between neurons and astrocytes indicates that astrocytes play a role in degradation rather than in spreading. Acta Neuropathol. 134, 789-808 (2017).
10. P. Mavroeidi, M. Xilouri, Neurons and glia interplay in α-Synucleinopathies. Int. J. Mol. Sci. 22, 4994 (2021).
11. R. A. Barker, M. Parmar, L. Studer, J. Takahashi, Human trials of stem cell-derived dopamine neurons for Parkinson’s Disease: Dawn of a new era. Cell Stem Cell 21, 569-573 (2017).
12. S. A. Libedov et al., Neurotoxic reactive astrocytes are induced by activated microglia. Nature 541, 481-487 (2017).
13. J. T. Hinkle, V. L. Dawson, T. M. Dawson, The AT astrocyte paradigm: New avenues for pharmacological intervention in neurodegeneration. Mov. Disord. 34, 959-969 (2019).
14. M. A. Cenci, A. Bjorklund, Animal models for preclinical Parkinson’s research: An update and critical appraisal. Prog. Brain Res. 252, 27-59 (2020).
15. O. Lindvall, Neural transplantation. Cell Transplant. 4, 393-400 (1995).
16. J. H. Kordower, Y. Chu, R. A. Hauser, T. B. Freeman, C. W. Olanow, Lewy body-like pathology in long-term embryonic signal transplants in Parkinson’s disease. Nat. Med. 14, 504-506 (2008).
17. J. Yu et al., Lewy bodies in grafted neurons in subjects with Parkinson’s disease suggest host-to-graft disease propagation. Nat. Med. 14, 501-503 (2008).
18. M. Parmar, S. Greath, C. Heschl, The future of stem cell therapies for Parkinson disease. Nat. Rev. Neurosci. 21, 103-115 (2020).
19. N. S. Roy et al., Functional engagement of human ES cell-derived dopaminergic neurons enriched by coculture with telomerase-immortalized midbrain astrocytes. Nat. Med. 12, 1259-1268 (2006).
20. K. Yamanka, O. Komine, The multi-dimensional roles of astrocytes in ALS. Neurosci. Res. 128, 31-38 (2018).
21. A. Biervest et al., Human glia can both induce and rescue aspects of disease phenotype in Huntington disease. Nat. Commun. 7, 11758 (2016).
22. K. Tókárová et al., Single cell transcriptomics identifies stem cell-derived graft composition in a model of Parkinson’s disease. Nat. Commun. 11, 2434 (2020).
23. S. Greath et al., Human ESC-derived dopamine neurons show similar preclinical efficacy and potency to fetal neurons when grafted in a rat model of Parkinson’s disease. Cell Stem Cell 15, 653-665 (2014).
24. L. Ben Haim, D. H. Rowitch, Functional diversity of astrocytes in neural circuit regulation. Nat. Rev. Neurosci. 18, 31-41 (2017).
25. B. S. Khakh, B. Deneen, The emerging nature of astrocyte diversity. Annu. Rev. Neurosci. 42, 187-207 (2019).