Cellular Brain Repair for Parkinson's Disease: Is the Answer in the (Biomaterial) Matrix?

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Résumé

Title:

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Abstract:

Cell-based brain repair is a promising option for Parkinson's disease whereby the nigrostriatal dopaminergic neurons that have degenerated over the course of the disease are replaced by transplantation of healthy neurons into the brain. However, the clinical roll-out of this approach has been limited by several factors including the poor survival of the implanted neurons, heretofore of fetal origin, in the diseased adult brain. Injectable biomaterial hydrogels offer significant potential to improve this approach through provision of a more favourable, supportive and protective microenvironment for the transplanted neurons in the Parkinsonian brain(1-3). In this context, the aim of our recent work has been to determine if a collagen-based hydrogel can improve the survival, integration and function of cell-based brain repair in rat models of Parkinson's, as well as the mechanism underlying any benefits.

For this work, we used type I collagen which naturally contains the tripeptide Arg-Gly-Asp (RGD) cell adhesion motif allowing for cell-matrix adhesion during and after the transplantation process. This was cross-linked with poly(ethylene glycol) ether tetrasuccinimidyl glutarate (4s-StarPEG) to control the rate and degree of gelation. To optimise the hydrogel for neurotrophin loading/release and cell encapsulation, we completed a series of *in vitro* and *ex vivo* studies, using SH-SY5Y cells and embryonic day 14 (E14) ventral mesencephalic (VM) cultures, as well as E14 VM whole tissue explants. These were followed by a series of *in vivo* studies to assess the biocompatibility of the hydrogel *in situ*, the suitability of the

*Intervenant

hydrogel as a cell transplantation matrix, and the kinetics of hydrogel-mediated neurotrophin delivery and retention in the brain. Finally, we completed several studies to determine if neurotrophin-loaded collagen hydrogels could improve the survival, integration and function of fetal VM transplants in the hemi-Parkinsonian (6-hydroxydopamine-lesioned) rat brain.

The collagen hydrogels cross-linked with low concentrations of 4s-StarPEG were highly biocompatible and did not affect the overall, neuronal or dopaminergic viability when preformed and seeded onto SH-SY5Y or VM cultures, or VM tissue explants. The hydrogels could also be efficiently loaded with neurotrophins, and the released neurotrophins remained functionally neuroprotective against 6-hydroxydopamine neurotoxicity in SH-SY5Y cultures and VM tissue explants. When assessed *in vivo*, the hydrogels were biocompatible in that they did not induce an overt innate immune response after implantation in the rat striatum; they were also compatible with the fetal VM cells encapsulated within them (indeed they reduced the host innate immune response to these cells); and they were capable of enhanced retention of neurotrophins in the brain (relative to bolus). Finally, we found that when fetal rat VM cells were encapsulated within a GDNF-loaded collagen hydrogel, the hydrogel significantly improved the survival and striatal integration of the dopaminergic neurons (tyrosine hydroxylase immunopositive) with the graft, as well as their ability to reverse the motor imbalance caused by the 6-hydroxydopamine lesion as assessed by amphetamine-induced rotation(4-5).

Taken together, this data shows that neurotrophin-enriched collagen hydrogels can improve the outcome of fetal cell-based brain repair in the Parkinsonian rodent brain. The hydrogel provided the transplanted neurons with a physical scaffold for cell-matrix adhesion, a neurotrophin reservoir for sustained neurotrophin exposure after transplantation, and shielding from the deleterious effects of the host microglial and astroglial innate immune response.

Given that cell-based brain repair is rapidly accelerating towards the clinic, with the ongoing TRANSEURO trial(6) using fetal tissue and the recently initiated Takahashi trial(7) using iPSC-derived dopaminergic progenitors, but that the margin for improvement of such approaches is great, it is critical to continue rigorous preclinical studies to identify potential methods of improving the outcome of cell-based brain repair for patients. Improving the safety and efficacy of such approaches, using this minimally invasive and injectable hydrogel that offers a neuroprotective and immune shielding microenvironment to the transplanted cells, could dramatically improve the reparative capacity of cell therapy for Parkinson's, and ultimately lead to an improved therapy for patients.

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References:

• Moriarty N, Parish CL, Dowd E. Primary tissue for cellular brain repair in Parkinson's disease: Promise, problems and the potential of biomaterials. The European Journal of Neuroscience. 2019;49(4):472-86.

• Moriarty N, Dowd E. Brain repair for Parkinson's disease: Is the answer in the matrix? Neural Regen Res. 2018;13(7):1187-8.

• Bruggeman KF, Moriarty N, Dowd E, Nisbet DR, Parish CL. Harnessing stem cells and biomaterials to promote neural repair. British Journal of Pharmacology. 2019;176(3):355-68.

• Moriarty N, Pandit A, Dowd E. Encapsulation of primary dopaminergic neurons in a GDNF-loaded collagen hydrogel increases their survival, re-innervation and function after intra-striatal transplantation. Sci Rep. 2017;7(1):16033.

• Moriarty N, Cabre S, Alamilla V, Pandit A, Dowd E. Encapsulation of young donor age dopaminergic grafts in a GDNF-loaded collagen hydrogel further increases their survival,

reinnervation, and functional efficacy after intrastriatal transplantation in hemi-Parkinsonian rats. The European Journal of Neuroscience. 2019;49(4):487-96.

- Barker RA (and TRANSEURO Consortium). Designing stem-cell-based dopamine cell replacement trials for Parkinson's disease. Nature Medicine. 2019;25(7):1045-53.
- Takahashi J. Preparing for first human trial of induced pluripotent stem cell-derived cells for Parkinson's disease: an interview with Jun Takahashi. Regen Med. 2019;14(2):93-5.

Mots-Clés: biopolymers, intrastriatal graft, Parkinson