MedicalXpress

Researchers make key improvements to Parkinson's disease cell therapies

July 13 2023

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Cell therapy holds promise as a new treatment for Parkinson's disease but, in many trials to date, most transplanted dopamine cells have failed to survive, raising a fundamental obstacle. Recent advancements led by

researchers at Mass General Brigham could change this. Investigators used regulatory T cells to supplement neuronal cell therapy and decrease adverse effects of the surgical procedure in rodent models. Results from the team, which includes investigators from McLean Hospital and Massachusetts General Hospital, are published in *Nature*.

"We have been investigating personalized, stem-cell based therapies that reprogram a patient's own cells to treat their Parkinson's," said corresponding author Kwang-Soo Kim, Ph.D., of the Molecular Neurobiology Laboratory at McLean Hospital. "We have now made a major breakthrough using immune cells to improve delivery, survival, and recovery for neuronal cell therapies. Our findings show the power and flexibility of cell therapy to be modified and enhanced to become a realistic modality to treat conditions like Parkinson's."

In the United States, only Alzheimer's disease is a more common neurodegenerative disorder than Parkinson's disease, which is characterized by loss of midbrain dopaminergic neurons. The current standard of care is dopamine replacement therapy, which addresses only symptoms like tremors or stiffness with substantial side effects.

Since the 1980s, cell therapies have faced a significant barrier: poor graft survival. Researchers have proposed diverse mechanisms to explain the cell death and added various modifications to improve cell survival. Three years ago, Kim's team demonstrated that personalized cell therapy could be used to replace dopamine neurons in the first personalized cell therapy in a sporadic Parkinson's disease patient. However, their results were restricted to a single patient and limited graft survival remained a key challenge.

In their current study, Kim and colleagues hypothesized that regulatory T cells—which maintain immune homeostasis, contain inflammation, and prevent immune rejection —could be co-transplanted with the neurons

to mitigate needle trauma and improve cell survival and disease recovery. To test this, the researchers first transplanted midbrain dopaminergic neurons in previously validated mouse and rat models of Parkinson's disease. They observed how the surgical procedure resulted in acute inflammation and an adverse immune response in the brain tissue, which they termed "needle-trauma."

Next, they co-transplanted regulatory T cells with the dopaminergic neurons. They measured the survival of grafted neurons over two weeks. After five months, they reassessed this finding and observed how the grafted area was recovering.

"Initially, just one or two weeks after transplantation, the majority of the dopamine neurons died, rendering the cell therapy unsuccessful," said Kim. "But when we added regulatory T cells to the transplant, survival of the grafted dopamine neurons increased. Also, behavior recovery was faster and more robust."

Regulatory T cells not only improved the survival of grafted dopaminergic neurons but also significantly suppressed the outgrowth of non-dopaminergic cells, including reactive inflammatory cells, in host brains.

"This finding is very significant because a potential hazard associated with cell transplantation is often the outgrowth of undesirable, potentially harmful cells," Kim said. "The most important criterion for cell therapy is safety."

The needle trauma induced significant brain cell death. However, the regulatory T cells were able to suppress the death, along with the adverse neuroinflammation and unwanted peripheral immune cells entering the injury site.

"Needle trauma is a universal issue in cell therapies in the nervous system, not just for dopaminergic neurons or Parkinson's disease," said Bob Carter, MD, Ph.D., the chief of Neurosurgery at the Mass General Hospital and a co-author of the current paper. "Our principles can be applied widely to any cell therapy for other (neuro)degenerative disorders such as Alzheimer's, ALS, or Huntington's."

Limitations of the study include being constrained to rodent models. Kim says the next steps are to understand the safety of these transplants, exactly how regulatory T cells improve the survival of dopaminergic neurons, and how to optimize their function.

Recently, Mass General Brigham launched its Gene and Cell Therapy Institute to help translate scientific discoveries made by researchers like Kim into first-in-human clinical trials and, ultimately, life-changing treatments for patients.

More information: Tae-Yoon Park et al, Co-transplantation of autologous Treg cells in a cell therapy for Parkinson's disease, *Nature* (2023). DOI: 10.1038/s41586-023-06300-4

Provided by Mass General Brigham