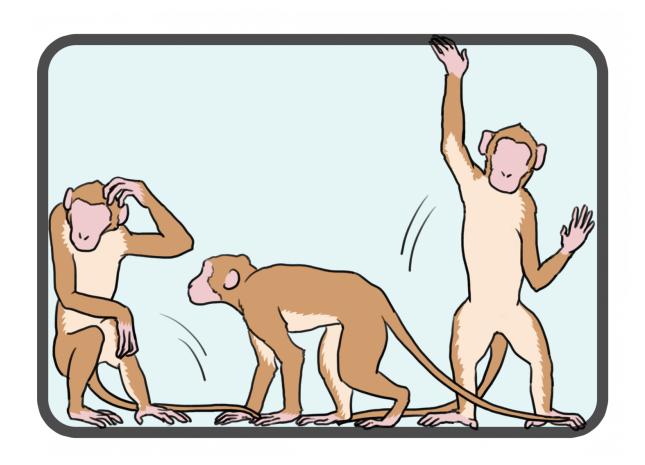


Monkeys with Parkinson's disease benefit from human stem cells

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Monkeys show reduced Parkinsonian symptoms following a donor-matched iPS cell-based therapy. Credit: Misaki Ouchida, Center for iPS Cell Research and Application, Kyoto University



One of the last steps before treating patients with an experimental cell therapy for the brain is confirmation that the therapy works in monkeys. Today, scientists at the Center for iPS Cell Research and Application (CiRA), Kyoto University, Japan, report monkeys with Parkinson's disease symptoms show significant improvement over two years after being transplanted neurons prepared from human iPS cells. The study, which can be read in *Nature*, is an expected final step before the first iPS cell-based therapy for neurodegenerative diseases.

Parkinson's disease degenerates a specific type of <u>cells</u> in the brain known as dopaminergic (DA) neurons. It has been reported that when symptoms are first detected, a patient will have already lost more than half of his or her DA neurons. Several studies have shown the transplantation of DA neurons made from <u>fetal cells</u> can mitigate the disease. The use of fetal tissues is controversial, however. On the other hand, iPS cells can be made from blood or skin, which is why Professor Takahashi, who is also a neurosurgeon specializing in Parkinson's disease, plans to use DA neurons made from iPS cells to treat patients.

"Our research has shown that DA neurons made from iPS cells are just as good as DA neurons made from fetal midbrain. Because iPS cells are easy to obtain, we can standardize them to only use the best iPS cells for therapy, "he said.

To test the safety and effectiveness of DA neurons made from human iPS cells, Tetsuhiro Kikuchi, a neurosurgeon working in the Takahashi lab, transplanted the cells into the brains of monkeys.

"We made DA neurons from different iPS cells lines. Some were made with iPS cells from healthy donors. Others were made from Parkinson's disease patients," said Kikuchi, who added that the differentiation method used to convert iPS cells into neurons is suitable for clinical trials.



It is generally assumed that the outcome of a cell therapy will depend on the number of <u>transplanted cells</u> that survive, but Kikuchi found this was not the case. More important than the number of cells was the quality of the cells.

"Each animal received cells prepared from a different iPS cell donor. We found the quality of donor cells had a large effect on the DA neuron survival," Kikuchi said.

To understand why, he looked for genes that showed different expression levels, finding 11 genes that could mark the quality of the progenitors. One of those genes was Dlk1.

"Dlk1 is one of the predictive markers of cell quality for DA neurons made from embryonic stem cells and transplanted into rat. We found Dlk1 in DA neurons transplanted into monkey. We are investigating Dlk1 to evaluate the quality of the cells for clinical applications."

Another feature of the study that is expected to extend to clinical study is the method used to evaluate cell survival in the host brains. The study demonstrated that magnetic resonance imaging (MRI) and position electron tomography (PET) are options for evaluating the patient post surgery.

"MRI and PET are non-invasive imaging modalities. Following cell transplantation, we must regularly observe the patient. A non-invasive method is preferred," said Takahashi.

The group is hopeful that it can begin recruiting patients for this iPS cell-based therapy before the end of next year. "This study is our answer to bring iPS cells to clinical settings," said Takahashi.

More information: Tetsuhiro Kikuchi et al. Human iPS cell-derived



dopaminergic neurons function in a primate Parkinson's disease model, *Nature* (2017). DOI: 10.1038/nature23664

Provided by Kyoto University

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