Patient-derived stem cells could improve drug research for Parkinson's

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Researchers have taken a step toward personalized medicine for Parkinson's disease, by investigating signs of the disease in patient-derived cells and testing how the cells respond to drug treatments. The study was funded by the National Institutes of Health.

The researchers collected skin cells from patients with genetically inherited forms of Parkinson's and reprogrammed those cells into neurons. They found that neurons derived from individuals with distinct types of Parkinson's showed common signs of distress and vulnerability – in particular, abnormalities in the cellular energy factories known as mitochondria. At the same time, the cells' responses to different treatments depended on the type of Parkinson's each patient had.

The results were published in *Science Translational* Medicine.

"These findings suggest new opportunities for clinical trials of Parkinson's disease, in which cell reprogramming technology could be used to identify the patients most likely to respond to a particular intervention," said Margaret Sutherland, Ph.D., a program director at NIH's National Institute of Neurological Disorders and Stroke (NINDS).

A consortium of researchers conducted the study with primary funding from NINDS. The consortium is led by Ole Isacson, M.D., Ph.D., a professor of neurology at McLean Hospital and Harvard Medical School in Boston.

The NINDS consortium's first goal was to transform the patients' skin cells into induced pluripotent stem (iPS) cells, which are adult cells that have been reprogrammed to behave like embryonic stem cells. The consortium researchers then used a combination of growth conditions and growth-stimulating molecules to coax these iPS cells into becoming neurons, including the type that die in Parkinson's disease.

Parkinson's disease affects a number of brain regions, including a motor control area of the brain called the substantia nigra. There, it destroys neurons that produce the chemical dopamine. Loss of these neurons leads to involuntary shaking, slowed movements, muscle stiffness and other symptoms. Medications can help manage the symptoms, but there is no treatment to slow or stop the disease.

Most cases of Parkinson's are sporadic, meaning that the cause is unknown. However, genetics plays a strong role. There are 17 regions of the genome with common variations that affect the risk of developing Parkinson's disease. Researchers have also identified nine genes that, when mutated, can cause the disease.

Dr. Isacson and his collaborators derived iPS cells from five people with genetic forms of Parkinson's disease. By focusing on genetic cases, rather than sporadic cases, they hoped they would have a better chance of seeing patterns in the disease process and in treatment responses. Three of the individuals had mutations in a gene called LRRK2, and two others were siblings who had mutations in the gene PINK1. The researchers also derived iPS cells from two of the siblings' family members who did not have Parkinson's or any known mutations linked to it.

Because prior studies have suggested that Parkinson's disease involves a breakdown of mitochondrial function, the researchers looked for signs of impaired mitochondria in patient-derived neurons. Mitochondria turn

oxygen and glucose into cellular energy. The researchers found that oxygen consumption rates were lower in patient cells with LRRK2 mutations, and higher in cells with the PINK1 mutation. In PINK1 mutant cells, the researchers also found increased vulnerability to oxidative stress, a damaging process that in theory can be counteracted with antioxidants.

Next, the researchers tested if neurons derived from patients and healthy volunteers were vulnerable to a variety of toxins, including some that target mitochondria. Compared to neurons from healthy individuals, patient-derived neurons were more likely to become damaged or die after exposure to mitochondrial toxins. Patient-derived neurons also suffered more damage from the toxins than did patient-derived skin cells.

Next, the researchers attempted to rescue the toxin-exposed cells with various drug treatments that have shown promise in animal models of Parkinson's, including the antioxidant coenzyme Q10 and the immunosuppressant rapamycin. All patient-derived neurons – whether they carried LRRK2 or PINK1 mutations – had beneficial responses to coenzyme Q10. However, the patient-derived neurons differed in their response to rapamycin; the drug helped prevent damage to neurons with LRRK2 mutations, but it did not protect the neurons with PINK1 mutations.

These results hint that iPS cell technology could be used to help define subgroups of patients for clinical trials. To date, interventional trials for Parkinson's disease have not focused on specific groups of patients or forms of the disease, because there have been few clues to point investigators toward individualized treatments. Although the current study focused on genetic forms of Parkinson's, iPS cell technology could be used to define disease mechanisms and the most promising treatments for sporadic Parkinson's as well.

The NINDS Parkinson's Disease iPS Cell Research Consortium is one of three such consortia funded by NINDS. One of the consortia is focused on developing iPS cells for the study of Huntington's disease, and another focuses on amyotrophic lateral sclerosis (ALS) and frontotemporal dementia.

The Huntington's disease consortium recently reported successful derivation of iPS cells and iPS-generated neurons from patients. Cells from patients with both early and later onset disease showed severe defects in physiology, metabolism, and cell viability, compared to cells from healthy volunteers. These results were reported in the June 28th issue of *Cell Stem Cell*. The consortium is led by led by Leslie Thompson, PhD, a professor of psychiatry and human behavior at the University of California, Irvine.

Skin cell and iPS cell lines developed by the consortia are available to both academic and industry researchers through the NINDS human cell line repository at the Coriell Institute. To date the NINDS repository has distributed more than 200 cell lines worldwide.

More information: Cooper, Oliver and Seo, Hyemyung et al. for the NINDS Parkinson's Disease iPS Cell Research Consortium. "Familial Parkinson's disease iPSCs show cellular deficits in mitochondrial responses that can be pharmacologically rescued." *Science Translational Medicine*, published online July 4, 2012. DOI: 10.1126/scitranslmed.3003985

Mattis, Virginia et al. for the NINDS Huntington's Disease iPS Cell Consortium. "Induced pluripotent stem cells from patients with Huntington's disease show CAG repeat expansion associated phenotypes." *Cell Stem Cell*, published online June 28, 2012. DOI: 10.1016/j.stem.2012.04.027

The Parkinson's Disease iPS Cell Research Consortium is funded primarily by grants and contracts from NINDS (NS070276, NS078338). The three disease consortia were started in 2009 with more than $11 million in NINDS grants, made possible by the Recovery Act. Funding for the consortia was recently renewed through 2013 via a public-private partnership. Future goals include increasing the number of iPS cell lines and the variety of mutations represented, and giving some lines biological tags that will enable researchers to see when the cells have transformed into specific neuronal types. NINDS is funding this next phase in collaboration with the Michael J. Fox Foundation, the Parkinson's Disease Foundation, the ALS Association, the Association for Frontotemporal Degeneration, the CHDI Foundation, the Huntington's Disease Society of America, the Hereditary Disease Foundation, and the California Institute for Regenerative Medicine.

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