Critical step forward in understanding Parkinson's disease and how to treat it

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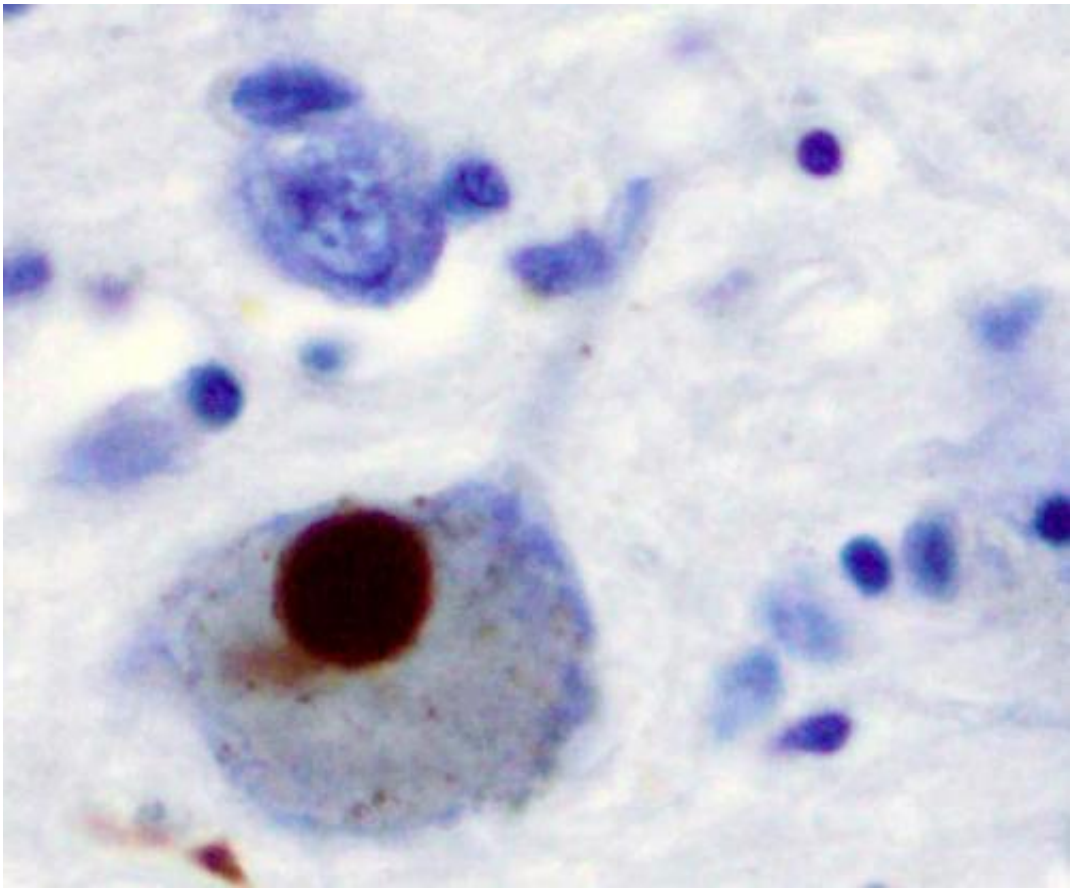

Immunohistochemistry for alpha-synuclein showing positive staining (brown) of an intraneural Lewy-body in the Substantia nigra in Parkinson's disease. Credit: Wikipedia

A new study led by a researcher in the Jacobs School of Medicine and

Biomedical Sciences at the University at Buffalo has important implications for developing future treatments for Parkinson's disease (PD), a progressive nervous system disorder that affects movement and often includes tremors.

"In this study, we find a method to differentiate human induced pluripotent stem cells (iPSCs) to A9 dopamine neurons (A9 DA), which are lost in Parkinson's disease," says Jian Feng, Ph.D., professor of physiology and biophysics in the Jacobs School and the senior author on the paper published May 24 in *Molecular Psychiatry*.

"These neurons are pacemakers that continuously fire action potentials regardless of excitatory inputs from other neurons," he adds. "Their pacemaking property is very important to their function and underlies their vulnerability in Parkinson's disease."

"This exciting breakthrough is a critical step forward in efforts to better understand Parkinson's disease and how to treat it," says Allison Brashear, MD, UB's vice president for health sciences and dean of the Jacobs School. "Jian Feng and his team are to be commended for their innovation and resolve."

Loss of neurons causes Parkinson's movement symptoms

Feng explains there are many different types of dopamine neurons in the human brain, and each type is responsible for different brain functions.

Nigral dopamine neurons, also known as the A9 DA neurons, are responsible for controlling voluntary movements. The loss of these neurons causes the movement symptoms of Parkinson's disease, he says.

"Scientists have been trying hard to generate these neurons from human pluripotent stem cells to study Parkinson's disease and develop better

therapies," Feng says. "We have succeeded in making A9 dopamine neurons from human induced pluripotent stem cells. It means that we can now generate these neurons from any PD patients to study their disease."

Feng notes that A9 DA neurons are probably the largest cells in the human body. Their volume is about four times the volume of a mature human egg.

"Over 99 percent of the volume is contributed by their extremely extensive axon branches. The total length of axon branches of a single A9 DA neuron is about 4.5 meters," he says. "The cell is like the water supply system in a city, with a relatively small plant and hundreds of miles of water pipes going to each building."

Quest to develop better treatment therapies

In addition to their unique morphology, the A9 DA neurons are pacemakers—they fire action potentials continuously regardless of synaptic input.

"They depend on Ca2+ channels to maintain the pacemaking activities. Thus, the cells need to deal with a lot of stress from handling Ca2+ and dopamine," Feng says. "These unique features of A9 DA neurons make them vulnerable. Lots of efforts are being directed at understanding these vulnerabilities, with the hope of finding a way to arrest or prevent their loss in Parkinson's disease."

"Pacemaking is an important feature and vulnerability of A9 DA neurons. Now that we can generate A9 DA pacemakers from any patient, it is possible to use these neurons to screen for compounds that may protect their loss in PD," Feng notes. "It is also possible to test whether these cells are a better candidate for transplantation therapy of

PD."

To differentiate human iPSCs to A9 DA neurons, the researchers tried to mimic what happens in embryonic development, in which the cells secrete proteins called morphogens to signal to each other their correct position and destiny in the embryo.

Feng notes the A9 DA neurons are in the ventral part of the midbrain in development.

"Thus, we differentiate the human iPSCs in three stages, each with different chemicals to mimic the developmental process," he says. "The challenge is to identify the correct concentration, duration, and treatment window of each chemical."

"The combination of this painstaking work, which is based on previous work by many others in the field, makes it possible for us to generate A9 DA neurons," Feng adds.

Feng points out there are a number of roadblocks to studying Parkinson's disease, but that significant progress is being made.

"There is no objective diagnostic test of Parkinson's disease, and when PD is diagnosed by clinical symptoms, it is already too late. The loss of nigral DA neurons has already been going on for at least a decade," he says. "There was previously no way to make human dopamine neurons from a PD patient so we could study these neurons to find out what goes wrong."

Scientists have been using animal models and human cell lines to study Parkinson's disease, but these systems are inadequate in their ability to reflect the situation in human nigral DA neurons, Feng says. "Just within the past 15 years, PD research has been transformed by the ability to

make patient-specific dopamine neurons that are increasingly similar to their counterparts in the brain of a PD patient."

More information: Hong Li et al, Generation of human A9 dopaminergic pacemakers from induced pluripotent stem cells, *Molecular Psychiatry* (2022). DOI: 10.1038/s41380-022-01628-1

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