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Parkinson's disease: Study of live human neurons reveals the disease's genetic origins

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Parkinson's disease researchers at the University at Buffalo have discovered how mutations in the parkin gene cause the disease, which afflicts at least 500,000 Americans and for which there is no cure.

The results are published in the current issue of *Nature Communications*.

The UB findings reveal potential new drug targets for the disease as well as a screening platform for discovering new treatments that might mimic the protective functions of parkin. UB has applied for patent protection on the screening platform.

"This is the first time that human dopamine neurons have ever been generated from Parkinson's disease patients with parkin mutations," says Jian Feng, PhD, professor of physiology and biophysics in the UB School of Medicine and Biomedical Sciences and the study's lead author.

As the first study of human neurons affected by parkin, the UB research overcomes a major roadblock in research on Parkinson's disease and on neurological diseases in general.

The problem has been that human neurons live in a complex network in the brain and thus are off-limits to invasive studies, Feng explains.

"Before this, we didn't even think about being able to study the disease in human neurons," he says. "The brain is so fully integrated. It's impossible to obtain live human neurons to study."

But studying human neurons is critical in Parkinson's disease, Feng explains, because animal models that lack the parkin gene do not develop the disease; thus, human neurons are thought to have "unique vulnerabilities."

"Our large brains may use more dopamine to support the neural computation needed for bipedal movement, compared to quadrupedal movement of almost all other animals," he says.

Since in 2007, when Japanese researchers announced they had converted human cells to induced pluripotent stem cells (iPSCs) that could then be converted to nearly any cells in the body, mimicking embryonic stem cells, Feng and his UB colleagues saw their enormous potential. They have been working on it ever since.

"This new technology was a game-changer for Parkinson's disease and for other neurological diseases," says Feng. "It finally allowed us to obtain the material we needed to study this disease."

The current paper is the fruition of the UB team's ability to "reverse engineer" human neurons from human skin cells taken from four subjects: two with a rare type of Parkinson's disease in which the parkin mutation is the cause of their disease and two healthy subjects who served as controls.

"Once parkin is mutated, it can no longer precisely control the action of dopamine, which supports the neural computation required for our movement," says Feng.

The UB team also found that parkin mutations prevent it from tightly controlling the production of monoamine oxidase (MAO), which catalyzes dopamine oxidation.

"Normally, parkin makes sure that MAO, which can be toxic, is expressed at a very low level so that dopamine oxidation is under control," Feng explains. "But we found that when parkin is mutated, that regulation is gone, so MAO is expressed at a much higher level. The nerve cells from our Parkinson's patients had much higher levels of MAO expression than those from our controls. We suggest in our study that it might be possible to design a new class of drugs that would dial down the expression level of MAO."

He notes that one of the drugs currently used to treat Parkinson's disease inhibits the enzymatic activity of MAO and has been shown in clinical trials to slow down the progression of the disease.

Parkinson's disease is caused by the death of dopamine neurons. In the vast majority of cases, the reason for this is unknown, Feng explains. But in 10 percent of Parkinson's cases, the disease is caused by mutations of genes, such as parkin: the subjects with Parkinson's in the UB study had this rare form of the disease.

"We found that a key reason for the death of dopamine neurons is oxidative stress due to the overproduction of MAO," explains Feng. "But before the death of the neurons, the precise action of dopamine in supporting neural computation is disrupted by parkin mutations. This paper provides the first clues about what the parkin gene is doing in healthy controls and what it fails to achieve in Parkinson's patients."

He noted in this study that these defects are reversed by delivering the normal parkin gene into the patients' neurons, thus offering hope that these neurons may be used as a screening platform for discovering new drug candidates that could mimic the protective functions of parkin and potentially even lead to a cure for Parkinson's.

While the parkin mutations are only responsible for a small percentage

of Parkinson's cases, Feng notes that understanding how parkin works is relevant to all Parkinson's patients. His ongoing research on sporadic Parkinson's disease, in which the cause is unknown, also points to the same direction.

Provided by University at Buffalo