Unlocking another piece of the Parkinson's puzzle—scientists reveal workings of vital molecular switch

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Scientists at the University of Dundee have uncovered the inner relay of a molecular switch that protects the brain against the development of

Parkinson's disease.

The research provides new potential strategies to develop drugs that may benefit patients with Parkinson's. Parkinson's is the fastest growing brain disorder in the world; however, there are currently no treatments that can slow or arrest the condition.

Previous research conducted at the University had found a gene called PINK1 is central to protecting brain cells against stress. In patients who carry PINK1 mutations, this protective effect is lost, leading to the degeneration of cells controlling movement that in turn lead to Parkinson's symptoms.

PINK1 encodes a class of enzyme known as a kinase and acts as a sensor of damage to the "power generators" of cells known as mitochondria. PINK1 then switches on a protective pathway by targeting two key proteins, ubiquitin and Parkin, that clears the damage. But how PINK1 was switched on was not previously known.

In research that has just been published in the journal *Science Advances*, a team of Dundee scientists, working with colleagues in the UK, Netherlands and Germany, used biological and artificial intelligence methods to uncover a model of the inner workings of how the PINK1 enzyme is switched on.

The model reveals how the PINK1 switch is activated by binding to key parts of a complex machine at the surface of mitochondria known as the Translocase of outer membrane (TOM) complex.

The new findings show that PINK1 uses unique elements not found in other enzymes. These make up a relay switch by which PINK1 is activated to enable it to target ubiquitin and Parkin to exert its protective function against Parkinson's.

"As a clinician who treats Parkinson's patients, the goal of our research is to discover fundamental mechanisms that may point to new ways to better treat the disease in the future," said Professor Miratul Muqit, Consultant Neurologist at the Medical Research Council Protein Phosphorylation and Ubiquitylation Unit (MRC-PPU), in the School of Life Sciences at Dundee.

"Our new findings add to a number of emerging treatment strategies targeting the PINK1 pathway, some that are now entering clinical trials for Parkinson's patients this year. This work provides a framework to undertake future studies directed at finding new drug-like molecules that can target PINK1 at the TOM complex."

Professor Dario Alessi, Director of the MRC-PPU, added, "This is bold and painstaking molecular research which allows us to better understand the biology that underlies Parkinson's disease, and provides new ideas on how PINK1-controlled Parkinson's disease could be better diagnosed and treated, opening the door for further important research."

The study involved an international multi-center collaboration with Professor Karim Labib at the University of Dundee; Professor Rubén Fernández Busnadiego at University Medical Center Göttingen / Cluster of Excellence "Multiscale Bioimaging: From Molecular Machines to Networks of Excitable Cells (MBExC)"; Professor Neil Ranson at the University of Leeds; and Dr. Sebastian Mathea at Goethe-Universität, Frankfurt.

More information: Olawale Raimi et al, Mechanism of human PINK1 activation at the TOM complex in a reconstituted system, *Science Advances* (2024). DOI: 10.1126/sciadv.adn7191. www.science.org/doi/10.1126/sciadv.adn7191

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