New Parkinson's disease chemical messenger discovered

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A new chemical messenger that is critical in protecting the brain against Parkinson's disease has been identified by scientists at the Medical Research Council (MRC) Protein Phosphorylation and Ubiquitylation Unit at the University of Dundee.

The research team led by Dr Miratul Muqit had previously discovered that mutations in two genes – called PINK1 and Parkin – lead to Parkinson's.

Now they have made a completely unexpected discovery about the way the two genes interact, which they say could open up exciting new avenues for research around Parkinson's and offer new drug targets. The results of their research are published in *Biochemical Journal*.

"Understanding the fundamental mechanisms of how brain cells die in Parkinson's is likely to uncover new insights into how to treat this progressive disorder," said Dr Muqit, a Wellcome Trust Senior Clinical Fellow and Consultant Neurologist at the MRC Protein Phosphorylation and Ubiquitylation Unit at Dundee.

"Our previous research had mapped out a key pathway involving the PINK1 and Parkin genes that when disrupted by mutations led to Parkinson's disease. However, we still did not understand the molecular details of how this pathway was controlled.

"Our new work suggests a chemical messenger called phospho-ubiquitin,

is protective and can't be made in Parkinson's patients with genetic mutations in PINK1. This leaves their brain cells vulnerable to stress and likely to trigger cell death."

Dr Muqit's team had already found that the PINK1 and Parkin genes encode for important enzymes that protect brain cells. In patients with mutations in PINK1 and Parkin the protective effects of these enzymes is lost and brain cells controlling movement are damaged, resulting in Parkinson's.

Previous work revealed that the PINK1 enzyme protects survival of brain cells by switching on Parkin, but how this occurred was unknown and in itself formed a major area of research.

Now they have worked out how the two genes interact. They have uncovered that the role of the PINK1 enzyme is to generate a novel chemical messenger molecule termed `phospho-ubiquitin'.

Their research shows that phospho-ubiquitin then functions to directly switch on the Parkin enzyme.

"The data suggests that phospho-ubiquitin molecules will play a critical role in protecting brain cells and thus patients from developing Parkinson's disease," said Dr Muqit.

"This research opens up new exciting avenues for future research that include studying whether low levels of the phospho-ubiquitin molecule are a common feature and cause of Parkinson's. The new data also suggests that it might be possible to develop drugs to better treat Parkinson's that can switch on the Parkin enzyme by mimicking phospho-ubiquitin."

Professor Dario Alessi, Director of the MRC unit at Dundee and a co-

author on the study, added, "Now that we have identified this new chemical messenger, it will be important to determine its role in Parkinson's patients. Whilst more work is needed, our findings suggest that designing drugs that mirror phospho-ubiquitin could represent an exciting approach to develop an urgently needed novel therapy for Parkinson's patients."

Claire Bale, Research Communications Manager at Parkinson's UK, said, "This exciting research has revealed the 'missing link' between two key proteins known to be important in Parkinson's.

"We have known for some time that the PINK1 and Parkin proteins work together to protect the precious brain cells that are lost in Parkinson's, but we weren't sure how.

"This new study is the first to reveal that PINK1 produces a vital chemical messenger called 'phospho-ubiquitin' which is essential for switching on Parkin's protective effects.

"This discovery provides a completely new avenue for developing treatments that can tackle the root causes of brain cell death and could ultimately take us closer to a cure for Parkinson's."

David Carling, Deputy Chair of the *Biochemical Journal* Editorial Board, said, "The study by Dr Muqit and colleagues provides a breakthrough in understanding how two proteins, previously shown to play important roles in Parkinson's disease, interact with one another. This new work opens up a number of avenues for further research and will help in identifying drugs aimed at combatting this devastating disease. We are pleased to be able to publish this exciting study in the *Biochemical Journal*."