038

**DISCOVERY OF A NEW ROLE FOR PINK1:
PHOSPHORYLATION OF UBIQUITIN BY PINK1
ACTIVATES PARKIN**

A Kazlauskaitė,¹ C Kondapalli,¹ R Gourlay,¹ DG Campbell,¹ MS Ritorto,¹ K Hofmann,² DR Alessi,¹ A Knebel,¹ M Trost,¹ M Muqit^{1,3}. ¹MRC Protein Phosphorylation and Ubiquitylation Unit, University of Dundee; ²Institute of Genetics, University of Cologne, Germany; ³College of Medicine, Dentistry & Nursing, University of Dundee

10.1136/jnnp-2014-309236.38

Mutations in the PINK1 and Parkin genes are associated with autosomal-recessive Parkinson's disease. PINK1 encodes a mitochondrial localized protein kinase and Parkin encodes an

ubiquitin E3 ligase. Several lines of evidence indicate that the enzymes encoded by these genes function in a common signalling pathway. For example patients bearing mutations in PINK1 or Parkin share a similar phenotype. We have previously reported that PINK1 is activated by mitochondrial depolarization and stimulates Parkin activity by phosphorylating Serine 65 (Ser65) that lies within its ubiquitin-like (Ubl) domain. In a screen for novel PINK1 substrates we unexpectedly identified an ubiquitin phosphopeptide phosphorylated at Ser65. We undertook a series of biochemical experiments that provide striking evidence that Ser65-phosphorylated ubiquitin functions as a critical activator of Parkin. We also provide evidence that optimal activation of Parkin is dependent on PINK1-mediated phosphorylation of both Parkin at Ser65 and ubiquitin at Ser65. Our study defines PINK1 as the first ubiquitin kinase and suggests that small molecules that mimic Ser65-phosphorylated ubiquitin could hold promise as novel therapies for Parkinson's.