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

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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.