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## Title: Novel regulatory mechanisms of PINK1, the guardian of mitochondria

Mitophagy refers to a selective form of autophagy for clearance of damaged or dysfunctional mitochondria via the autophagy-lysosome pathway. PINK1 (PTEN-induced kinase 1) is a key Ser/Thr kinase that stabilizes and accumulates at mitochondria to initiate the mitophagy process, together with Parkin, an E3 ligase. Thus, PINK1 is considered as the guardian of mitochondria. In recent years, we have focused on PINK1, from its transcriptional regulation to its post-translational modifications (PTMs). First, we found that a specific autophagy inhibitor, Spautin-1, is capable of promoting mitophagy, mainly via promoting PINK1 stabilization and activation at outer mitochondrial membrane (OMM) by direct binding to the TOM complex. Second, we discovered O-GlcNAcylation as a novel form of PTMs in regulation of PINK1 stability and activity. Third, via both bioinformatics analysis and cellular-biochemical analysis, we identified SMAD3 as a novel nuclear transcriptional factor of PINK1, via a non-canonical pathway independent of TGF- $\beta$ . Taken together, our work provides deeper insights into the molecular mechanisms of mitophagy and lays foundation for discovery of new interventional strategy for mitophagy-related human diseases such as neurodegenerative disorders.

HOSTED BY: DR TSAI SHIH-YIN

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