PINK1

PINK1 and parkin constitute a mitochondrial quality control system mutated in Parkinson's disease. PINK1, a kinase, phosphorylates ubiquitin to recruit parkin, an E3 ubiquitin ligase, to mitochondria. PINK1 controls both parkin localization and activity through phosphorylation of both ubiquitin and the ubiquitin-like (Ubl) domain of parkin. Here, we observed that phospho-ubiquitin can bind to two distinct sites on parkin, a high-affinity site on RING1 that controls parkin localization and a low-affinity site on RING0 that releases parkin autoinhibition. Surprisingly, ubiquitin vinyl sulfone assays, ITC, and NMR titrations showed that the RING0 site has a higher affinity for phospho-ubiquitin than phosphorylated Ubl in trans. We observed parkin activation by micromolar concentrations of tetra-phospho-ubiquitin chains that mimic mitochondria bearing multiply phosphorylated ubiquitins. A chimeric form of parkin with the Ubl domain replaced by ubiquitin was readily activated by PINK1 phosphorylation. In all cases, mutation of the binding site on RING0 abolished parkin activation. The feedforward mechanism of parkin activation confers robustness and rapidity to the PINK1-parkin pathway and likely represents an intermediate step in its evolutionary development [1)].

McLelland et al. described the involvement of parkin and PINK1 in a vesicular pathway regulating mitochondrial quality control. This pathway is distinct from canonical mitophagy and is triggered by the generation of oxidative stress from within mitochondria. Wild-type but not PD-linked mutant parkin supports the biogenesis of a population of mitochondria-derived vesicles (MDVs), which bud off mitochondria and contain a specific repertoire of cargo proteins. These MDVs require PINK1 expression and ultimately target to lysosomes for degradation. We hypothesize that loss of this parkin- and PINK1-dependent trafficking mechanism impairs the ability of mitochondria to selectively degrade oxidized and damaged proteins leading, over time, to the mitochondrial dysfunction noted in PD [2)].

1)
Sauvé V, Sung G, MacDougall EJ, Kozlov G, Saran A, Fakih R, Fon EA, Gehring K. Structural basis for feedforward control in the PINK1/Parkin pathway. EMBO J. 2022 May 2:e109460. doi: 10.15252/embj.2021109460. Epub ahead of print. PMID: 35491809.
2)
McLelland GL, Soubannier V, Chen CX, McBride HM, Fon EA. Parkin and PINK1 function in a vesicular trafficking pathway regulating mitochondrial quality control. EMBO J. 2014 Jan 20. [Epub ahead of print] PubMed PMID: 24446486.