Project Leader **Noriyuki Matsuda** Ubiquitin Project

Ubiquitin-Mediated Mitochondrial Quality Control: A shield against Parkinson's disease

Ubiquitin is well-known as a signal for proteasome-dependent degradation; however, it also functions in autophagic degradation. Increasing evidence indicates that selective autophagy functions in intracellular quality control by using ubiquitin tags to delineate aggregated proteins and damaged organelles for degradation.

In 2000, Dr. Mizuno and Dr. Hattori (Juntendo Univ.) collaboration with Dr. Suzuki and Dr. Tanaka (TMIMS) reported for the first time that Parkin, which is a causative gene product of familial Parkinson's disease (PD), is an ubiquitin-protein ligase (Nat. Genet. 2000). In addition, the identification of another gene PINK1 that linked to the familial forms of hereditary recessive early-onset PD (Science 2004) has revealed that phosphorylation, ubiquitylation, and mitochondrial integrity are key factors in disease pathogenesis. Nevertheless, the exact mechanism underlying the functional interplay between Parkin and PINK1 remained an enigma. We thus have investigated how PINK1 and Parkin cooperate to keep mitochondrial integrity against mitochondrial stresses.

"We found that low-quality mitochondria are marked with ubiquitin for selective degradation, and the key factors in this process are PINK1 (a mitochondrial kinase) and Parkin (a ubiquitin ligase), two proteins implicated in Parkinson's disease."

PINK1 is a mitochondrial Ser/Thr kinase whereas Parkin is a ubiquitin-protein ligase that catalyzes ubiquitylation of diverse mitochondrial outer membranous proteins (J. Cell Biol. 2010). We revealed that PINK1 is rapidly and constitutively degraded under steady-state conditions in a mitochondrial membrane potential-dependent manner but that a loss in mitochondrial membrane potential stabilizes PINK1 mitochondrial accumulation (J. Cell Biol. 2010). Previously our and other groups found that PINK1 acts as an upstream factor for Parkin, but how PINK1 activates latent Parkin and recruits cytoplasmic Parkin to damaged mitochondria were still obscure.

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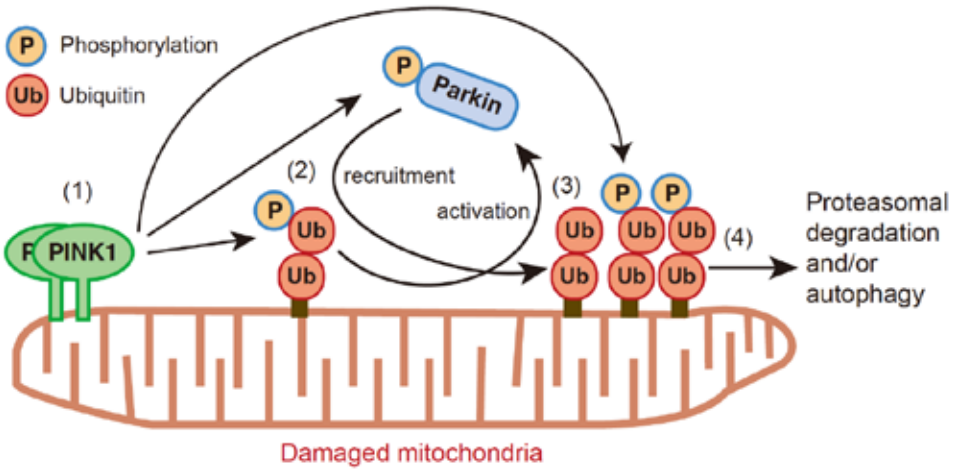
Ubiquitin

We found that PINK1 phosphorylates both Parkin and ubiquitin at Ser65 that are sufficient for full activation of latent Parkin E3 activity, and that the S65 phosphorylated ubiquitin is a Parkin activator (Nature 2014). Subsequently we unveiled that the phosphorylated ubiquitin chain functions as the genuine Parkin receptor for its recruitment to depolarized mitochondria (J. Cell Biol. 2015). Ubiquitin phosphorylation enables us to understand comprehensively how PINK1 regulates Parkin to prevent predisposition to Parkinson's disease.

Our study has revealed that PINK1 and Parkin cooperate in the recognition, labeling, and clearance of damaged (i.e., depolarized) mitochondria by selective mitochondrial autophagy (mitophagy). To date, ubiquitylation has been a well-known post-translational modification; however, it is becoming increasingly clear that modified ubiquitin itself plays a critical cellular function as S65-phosphorylated ubiquitin functions in mitochondrial quality control.

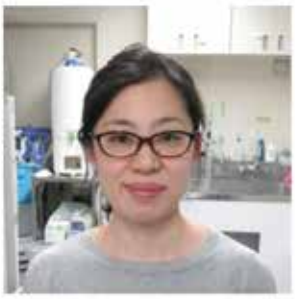
"We believe that big mystery in mitochondrial quality control has been unraveled, and our work can establish new principles of how a simple ubiquitin tag plays more varied roles than expected."



Our model for PINK1- and Parkin-catalyzed ubiquitylation for mitochondrial quality control.
We have revealed that accumulated PINK1 on damaged mitochondria (1) phosphorylates Parkin and ubiquitin, which (2) induces Parkin activation and its recruitment to the phosphorylated ubiquitin chain. Activated Parkin produces more ubiquitin chain (3), and the resultant ubiquitin is phosphorylated by PINK1 in a feed forward cycle. Parkin thus functions as an amplifier of the ubiquitin chain on depolarized mitochondria (4) for degradation.

Members

Yukiko Yoshida
Organellophagy via glycoprotein-specific ubiquitin ligase



Fumika Koyano
Molecular mechanism underlying Parkin-catalyzed ubiquitylation

Koji Yamano
Membrane dynamics upon mitochondrial quality control

Ubiquitin