Parkin and Parkinson Disease

Hideki Shimura,1,2,3* Yoshikuni Mizuno,1,4 and Nobutaka Hattori1


Since the 1970s, Japanese neurologists have described patients with autosomal recessive forms of familial Parkinson disease (PD), which have been termed “autosomal recessive juvenile parkinsonism” and “early-onset parkinsonism with diurnal fluctuation,” both of which have become known as “PARK2.” We attempted to identify the gene responsible for autosomal recessive familial PD. In 1997, we identified, along with our collaborators, an autosomal recessive familial PD gene between D6S437 and D6S264 (1), and in 1998 we found that mutations in that gene were linked to autosomal recessive familial PD. We designated the gene, formerly known as parkin, as PARK2 (2). Parkin is a 465-amino-acid protein containing an N-terminal ubiquitin-like domain linked to a C-terminal RING box. A year later, we demonstrated that parkin was produced in the substantia nigra and localized in Lewy bodies (3). The function of parkin remained unknown, however. In 2000, in collaboration with Keiji Tanaka, Toshiaki Suzuki, Tomoaki Chiba, Shin-ichiro Kubo, Kauzihiro Iwai, Shuichi Asakawa, Shinsei Minoshima, and Nobuyoshi Shimizu, we were able to identify parkin as a ubiquitin-protein ligase that facilitates the degradation of proteins that interact with ubiquitin-conjugating enzyme UbcH7. We reported our results in the Nature Genetics article featured here. Ubiquitin is an interesting protein that acts against a wide range of toxic insults, including those that are not part of the ubiquitin-proteasome system. Parkin also associates with mitochondrial membranes and interacts with the phosphatase and tensin homolog–induced putative kinase gene to protect mitochondrial function. Clarifying the relationships between parkin, ubiquitination, and mitochondrial membranes may provide insights into PD pathogenesis.

To date, >100 parkin mutations have been identified. Various reported substrates of parkin include CDC-rel-1, O-glycosylated α-synuclein, the parkin-associated endothelin-like receptor, the α-synuclein–binding protein synphilin-1, actin filaments, the poly(Q) expanded mutant of ataxin-3, Huntington disease polyglutamine proteins, the amyloidogenic Alzheimer disease Aβ 1–42 peptide (amyloid-β peptide 1–42), and aβ-tubulin. In support of these findings, parkin-linked animal models have shown a dysregulation of dopaminergic cells. Additionally, parkin activity is decreased in sporadic PD. Parkin is considered to play an important role in familial PD and other neurodegenerative disorders. Parkin is a broad neuroprotective agent that acts against a wide range of toxic insults, including those that are not part of the ubiquitin-proteasome system. Parkin also associates with mitochondrial membranes and interacts with the phosphatase and tensin homolog–induced putative kinase gene to protect mitochondrial function. Clarifying the relationships between parkin, ubiquitination, and mitochondria may provide insights into PD pathogenesis.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design,
acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures or Potential Conflicts of Interest: Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:

Employment or Leadership: None declared.
Consultant or Advisory Role: Yoshikuni Mizuno, Kyowa Hakko Kirin Pharmaceutical Company, Medtronic, Boehringer Ingelheim, FP Pharmaceutical Company, and Otsuka Pharmaceutical Company.
Stock Ownership: None declared.
Honoraria: None declared.
Research Funding: None declared.
Expert Testimony: None declared.

References