Mitochondrially-localized Parkin and Its Role in Innate Immune Response

Seong-Jun Kim, PhD

Principal Researcher

Center for Virus Research and Testing, Division of Bio & Drug Discovery

Korea Research Institute of Chemical Technology

Mitochondria play a central role in innate immune signaling and are primarily targeted by many viruses which have evolved elaborate mechanisms to evade host antiviral response. Recent studies demonstrate that viruses explicitly alter mitochondrial dynamics and mitophagy to evade innate immunity and maintain viral persistence. Here, we show that Parkin and an upstream regulator, PTEN-induced putative kinase 1 (PINK1), beyond their recognized role in mitochondrial quality control and Parkinson's disease, also serve as modulators of mitochondrial antiviral signaling protein (MAVS)-mediated host innate immune response. MAVS serves as a mitochondrial platform for transduction of signal from various RIG-I-like receptors (RLRs) that sense pathogen-associated molecular patterns (PAMPs) to orchestrate type I interferon (IFN)-α/β production in response to viral infection. We show that the synthetic double-stranded (ds) RNA mimics, poly(I:C) and 5'ppp-dsRNA, potently induce Parkin translocation to the mitochondria, leading to Parkin-dependent K63-linked polyubiquitination of MAVS eventually resulting in the attenuation of type I IFN production. Interference of Parkin and PINK1 expression led to a distinct elevation of type I IFN production on stimulation with viral RNA mimics or infection with RNA viruses. In agreement, primary mouse embryonic fibroblasts (MEFs) derived from PINK1 knockout mice (*PINK1*$^{-/-}$) staged more robust type 1 IFN response compared to wild type PINK1 MEFs on stimulation with viral RNA mimics. This study unravels the yet unidentified function of Parkin and PINK1 in the modulation of MAVS-dependent innate immune signaling and depicts how the RNA viruses exploit them to evade innate immunity.