PARKIN dependent regulation of the MCU complex component MICU1

A.Matteucci[1], T.Calì[2], A.Raffaello[3], M.Brini[2], R.Rizzuto[3] and S.Amoroso[1]

[1]Department of Biomedical Sciences and Public Health, University 'Politecnica delle Marche,Ancona, Italy
[2]Department of Biology, University of Padova, Padova, Italy.
[3]Department of Biomedical Sciences, University of Padova and CNR Neuroscience Institute, Padova, Italy

The mitochondrial Ca^{2+}uniporter machinery is a multiprotein complex composed by the Ca^{2+}selective pore-forming subunit mitochondrial uniporter (MCU) and accessory proteins, including MICU1, MICU2 and EMRE. Their concerted action at the inner mitochondrial membrane is required to fine-tune the uptake of Ca^{2+}into the matrix to sustain cell bioenergetics and to regulate the apoptotic response. To fulfill such requirements, and to avoid the many cell-type dependent pathological conditions associated with impaired mitochondrial Ca^{2+}handling, the intracellular turnover of all the components must also be tightly regulated. However, the mechanism(s) and the players involved in this process are still unknown. Here we show that the MCU complex regulator MICU1 is rapidly and selectively turned-over by the Ubiquitin Proteasome System (UPS). Moreover, we identified the multifunctional E3 ubiquitin ligase Parkin (*PARK2*), whose mutations cause autosomal recessive early-onset Parkinson's disease (PD), as a potential candidate involved in this regulation since its upregulation strongly decreases the MICU1 basal levels. Parkin was also found to interact with MICU1 and, interestingly, the presence of the Ubl-domain is required for the Parkin-mediated degradation of MICU1, suggesting that it may play a role in the basal auto-inhibited state. Our findings support a model in which the PD-related E3 ubiquitin ligase Parkin participates in the selective regulation of the MCU complex regulator MICU1, thus contributing to shape the mitochondrial Ca^{2+}signals and supporting the notion that impairments in the ability of mitochondria to take up Ca^{2+}might contribute to the pathogenesis of PD.