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When mitochondrial ultrastructure matches function: A role for OPA1 and MIC60 complexes

Maria Eugenia Soriano
University of Padua, Italy

The pleotropic roles of mitochondria in energy conversion, cell death, calcium homeostasis, intermediary metabolism, cell differentiation and even immunity are matched by their morphological and ultrastructural complexity. In particular, the formation and shape of the cristae, structures that host the oxidative phosphorylation are crucial aspects that dictate mitochondrial functionality. Moreover, during apoptosis the cristae undergo morphological changes that allow the release of proapoptotic proteins, normally confined in the cristae lumen, through the cristae junctions to the intermembrane space and cytosol. Therefore, the understanding of the molecular mechanism underlying cristae biogenesis and morphology has become an important aim to control mitochondrial diseases which are phenotypically characterized by an abnormal mitochondrial ultrastructure. Two main proteins have been described to regulate the later are: MIC60 as part of the mitochondrial contact site and cristae organizing system (MICOS) and Optic atrophy 1 (OPA1) but whether and how they interact physically and functionally is unclear. Here we investigate the relative role of OPA1 and MICOS in cristae morphology and we provide evidence that OPA1 is epistatic to MICOS in the regulation of width and junctions of cristae. Multiple MICOS components are retrieved by proteomics in native OPA1-containing high molecular weight complexes targeted during cristae remodeling and the core MICOS protein MIC60 physically interacts with OPA1. A genetic epistatic analysis combined with electron tomography of cristae and cristae junctions shows that OPA1 defines width of cristae and of cristae junction independently of MIC60 and places OPA1 upstream of MIC60 in the control of cristae junction number and stability. We provide a unifying model for mammalian cristae biogenesis where OPA1 specifies width of cristae and cristae junctions and MIC60 requires OPA1 to define cristae junction number and stability.

mariaeugenia.soriano@unipd.it