Abstract

Cell function depends on the proper protein and lipid composition of its organelles. Mitochondria possess elaborate mechanisms to adjust their membrane features in order to facilitate a wide variety of functions like cellular energy supply. Mitochondrial phospholipid synthesis is important to ensure functional lipid composition of the two mitochondrial membranes. Also, mitochondria exert critical functions in cellular lipid metabolism and promote the synthesis of major constituents of other cellular membranes, such as phosphatidylethanolamine (PE) and phosphatidylcholine (PC). The synthesis of phospholipids in mitochondria requires coordinated transfer of lipids between membranes. For example, the synthesis of PE in the mitochondrial inner membrane by phosphatidylserine decarboxylase 1 (Psd1) is preceded by the import of the endoplasmic reticulum (ER) derived precursor lipid phosphatidylserine (PS) across the intermembrane space. Moreover, synthesized PE can be exported and converted to PC in the ER. Although these transport steps of PS and PE between membranes are known, most of the molecular components responsible for the transport within mitochondria remain elusive.

In this study, two pathways promoting PE synthesis within the mitochondria of *Saccharomyces cerevisiae* were characterized. The intermembrane space protein Ups2 was shown to function together with Mdm35 as a PS-specific lipid transfer protein complex transporting PS through the mitochondrial intermembrane space, thus promoting PE synthesis in the inner mitochondrial membrane. Loss of Ups2 led to a reduced PE level in mitochondria but surprisingly did not affect the synthesis of PC from mitochondria-derived PE. In fact, a second pathway existed, whereby Psd1 required the apposition of mitochondrial membranes and the mitochondrial contact site and cristae organizing system (MICOS). This pathway is important for the availability of mitochondrial PE for PC synthesis in the ER. Thus, this study demonstrates how a soluble lipid transfer protein complex and a contact site ensure efficient lipid trafficking and synthesis in mitochondria. Remarkably, limiting mitochondrial PE accumulation by deleting *UPS2* preserved respiratory growth and cristae formation in MICOS-deficient cells. This highlights the combining functions of protein and lipid homeostasis to preserve mitochondrial structure and function.