Biogenesis, transport and degradation of mitochondrial proteins

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Mitochondria play an important role in variety of metabolic and regulatory processes and their dysfunction leads to life threatening disorders. About 1000-1500 proteins are needed to build this essential organelle. The large majority of mitochondrial proteins is synthesized on the cytosolic ribosomes, and after completion of their synthesis must be properly targeted to mitochondria. After synthesis, precursors of mitochondrial proteins are directed to the TOM complex and subsequently to specific mitochondrial import machineries that are responsible for their sorting. Proteins destined to the intermembrane space of mitochondria follow the mitochondrial intermembrane space import and assembly (MIA) pathway. The MIA pathway provides an efficient and redox-dependent mechanism for trapping substrate proteins in the intermembrane space of mitochondria. The cytosolic steps that precede mitochondrial import have not been well understood. We identified a role for the ubiquitin-proteasome system in the biogenesis of the intermembrane space proteins. The ubiquitin-proteasome system persistently removes a fraction of intermembrane space proteins under physiological conditions, acting as a negative regulator in the biogenesis of this class of proteins. Moreover, based on unbiased proteomic approaches, we discovered that mitochondria play a role in the regulation of cellular protein homeostasis.