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Mitochondrial contact site and cristae organizing system

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Mitochondria possess two membranes of different architecture. The outer membrane surrounds the organelle, whereas the inner membrane consists of two domains. The inner boundary membrane that is adjacent to the outer membrane harbors many protein translocases. The inner membrane cristae form deep invaginations that carry respiratory chain complexes and the ATP synthase. It has remained enigmatic how crista junctions that connect inner boundary membrane and cristae are formed. The identification of a large protein complex, the mitochondrial contact site and cristae organizing system (MICOS), provided important insights. MICOS is a multi-subunit machinery with two core components, Mic10 and Mic60, organized into subcomplexes. The Mic10-containing subcomplex forms the structural basis of crista junctions, whereas the Mic60-containing subcomplex is crucial for connecting mitochondrial inner and outer membranes at contact sites. Numerous diseases have been directly or indirectly linked to MICOS. MICOS forms a network of interactions with further mitochondrial machineries and can be seen as an organizing center of mitochondrial architecture and biogenesis.

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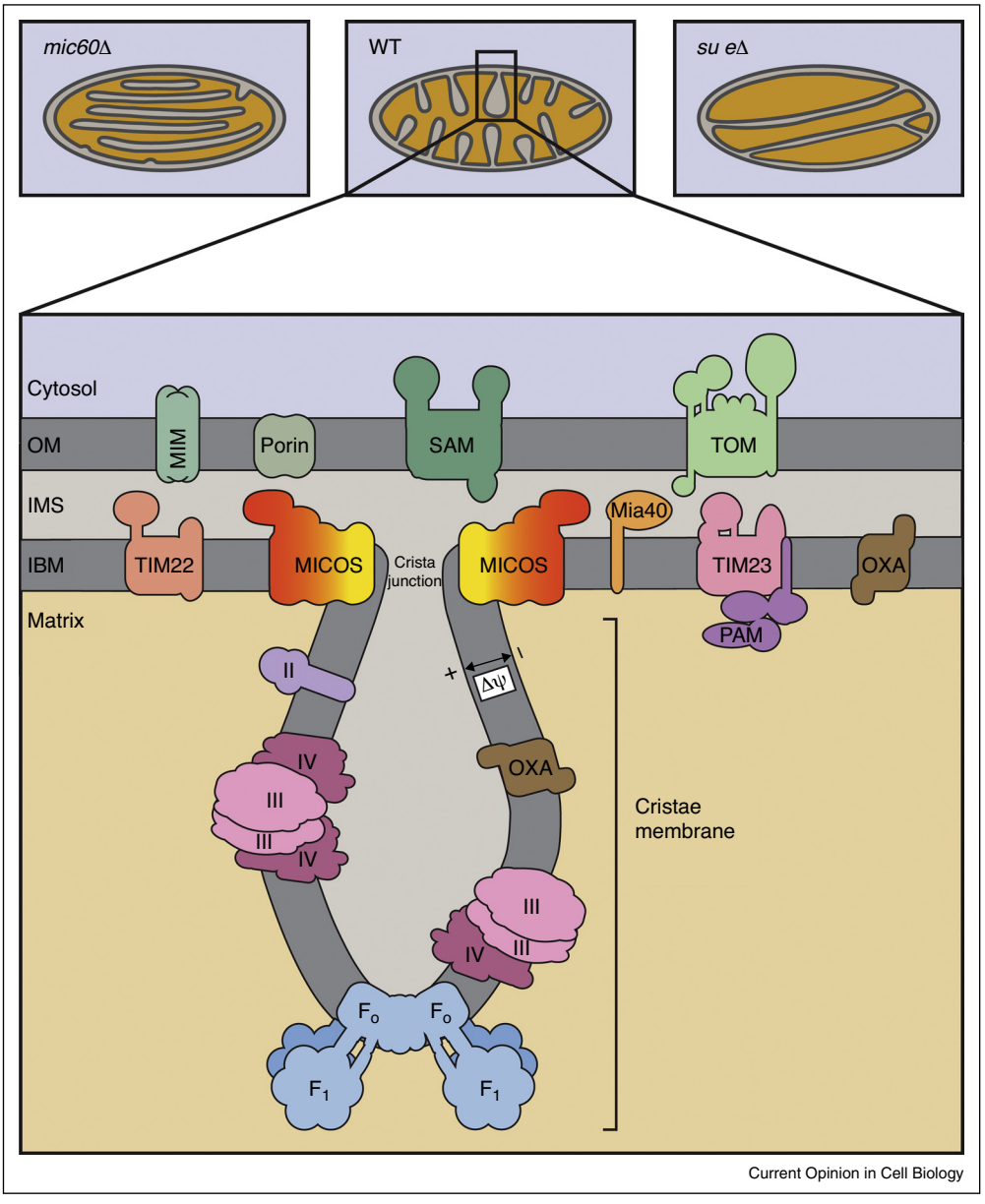
Introduction

Mitochondria are essential organelles with central functions in cellular energetics, metabolism and regulation [1–4]. They possess a peculiar architecture with two membranes. The mitochondrial outer membrane forms the envelope of the organelle and is crucial for the exchange of molecules with the cytosol and other cell organelles such as the endoplasmic reticulum (ER) [5,6]. The mitochondrial inner membrane possesses a several-fold larger surface than the outer membrane. The inner membrane can be divided in two domains: the inner boundary membrane that is in close proximity to the outer membrane; and the folded cristae membranes that form invaginations of variable size and shape (Figure 1). Inner boundary membrane and cristae membranes have a different protein composition [7,8]. Protein translocases that import nuclear-encoded proteins into mitochondria are enriched in the inner boundary membrane, whereas respiratory chain complexes and the F_1F_o-ATP synthase are enriched in cristae membranes. However, the two inner membrane domains and their resident proteins are not strictly separated but are in a dynamic exchange with each other. The localization of proteins can shift between inner boundary membrane and cristae membranes in dependence on the physiological needs. An interesting example is the oxidase assembly (OXA) translocase. Its distribution between the two membrane domains is regulated by the growth conditions of cells (respiratory *versus* non-respiratory growth) and the availability of different types of substrate proteins [9].

Cristae can be heterogeneous in their appearance depending on the cell type as well as the developmental and metabolic states of the cell. In contrast, the connection between cristae and inner boundary membrane is formed by a rather homogeneous structure that has been named crista junction. Crista junctions are narrow, neck-like structures that are characterized by a high degree of negative membrane curvature. They are thought to represent a diffusion barrier for proteins as well as small molecules. Cristae and the intracristal space likely form a micro-compartment that provides optimal conditions for chemi-osmotic coupling [10–12]. Crista junctions limit the diffusion of ATP [11,13] and of proteins like cytochrome *c*. The release of cytochrome *c* from mitochondria during apoptosis involves an opening of the crista junctions [14–16].

The mitochondrial components controlling cristae architecture have long been unknown. Two machineries have been identified that play crucial roles in maintaining the characteristic architecture of the mitochondrial inner membrane. The mitochondrial contact site and cristae

Figure 1



Architecture of the mitochondrial inner membrane. The inner membrane consists of the inner boundary membrane (IBM) and the folded cristae membranes. Crista junctions connect IBM and cristae. The MICOS complex is enriched at crista junctions. Protein translocases of the inner membrane (TIM22 and TIM23) are preferentially located in the IBM, whereas respiratory chain complexes (II, III, IV) and the F_1F_o-ATP synthase are enriched in cristae membranes. The preferential location of the OXA translocase depends on growth conditions and the availability of substrate proteins. MICOS and oligomers of the F_1F_o-ATP synthase play in part antagonistic roles in shaping the inner membrane. In cells lacking the MICOS core component Mic60, most crista junctions are lost and internal membrane stacks are formed (upper left). In cells lacking subunit e (Atp21) of the F_1F_o-ATP synthase (*su e*Δ), dimerization and oligomerization of the ATP synthase are impaired; in these mutants, cristae membranes can span the entire interior and are connected to the IBM on two sides (upper right). $\Delta\psi$, membrane potential; IMS, intermembrane space; MIM, mitochondrial import complex of the outer membrane; OM, outer mitochondrial membrane; PAM, presequence translocase-associated motor; WT, wild-type mitochondrion.

organizing system (MICOS) is required for the formation of crista junctions and oligomers of the F_1F_o-ATP synthase promote the generation of cristae rims and tubules.

Oligomeric ATP synthase promotes the formation of cristae tips and rims

An initial step toward a molecular characterization of mitochondrial inner membrane architecture was the discovery