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Mitochondrial contact site and cristae organizing system: A central player in membrane shaping and crosstalk

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ABSTRACT

Mitochondria are multifunctional metabolic factories and integrative signaling organelles of eukaryotic cells. The structural basis for their numerous functions is a complex and dynamic double-membrane architecture. The outer membrane connects mitochondria to the cytosol and other organelles. The inner membrane is composed of a boundary region and highly folded cristae membranes. The evolutionarily conserved mitochondrial contact site and cristae organizing system (MICOS) connects the two inner membrane domains via formation and stabilization of crista junction structures. Moreover, MICOS establishes contact sites between inner and outer mitochondrial membranes by interacting with outer membrane protein complexes. MICOS deficiency leads to a grossly altered inner membrane architecture resulting in far-reaching functional perturbations in mitochondria. Consequently, mutations affecting the function of MICOS are responsible for a diverse spectrum of human diseases. In this article, we summarize recent insights and concepts on the role of MICOS in the organization of mitochondrial membranes. This article is part of a Special Issue entitled: Membrane Contact Sites edited by Christian Ungermann and Benoit Kornmann.

1. Introduction

Eukaryotic cells contain diverse intracellular membrane systems, termed organelles, which fulfill specific functions in cellular physiology. However, the cell as a complex system is more than the sum of these intricate subsystems, because organelles are highly interconnected with each other via metabolite flux, common regulatory circuits, and direct membrane contact sites [1]. Accordingly, intracellular membrane systems show a high degree of structural and functional plasticity and adaptability to adjust to changing environmental conditions and developmental programs. Mitochondria are intimately embedded in this organellar network [2,3]. They harbor key processes of cellular energy metabolism, such as oxidative phosphorylation for the synthesis of adenosine triphosphate (ATP), and a large number of anabolic and catabolic pathways. Moreover, mitochondria are multilateral signaling organelles that play critical roles in the control of cellular behavior, for example by impacting on intracellular calcium homeostasis and programmed cell death [4–9]. Mitochondria form a dynamic network protruding throughout the entire cell that is continuously adjusted by balanced fission and fusion events [10–13]. The tightly regulated equilibrium between fusion and fission reactions is critical for the maintenance of a healthy mitochondrial population and coordinated with the behavior of the endoplasmic reticulum via direct membrane contact sites between both organelles [14].

As a relic of their evolutionary origin as endosymbiotic α-proteobacteria, mitochondria are surrounded by two membranes, the outer membrane and the inner membrane, which encompass two separate aqueous compartments, the intermembrane space and the mitochondrial matrix [15–20]. The outer mitochondrial membrane not only separates the organelle from the cytosol but also mediates the contact to and the communication with other organelles [3]. Furthermore, outer membrane-mediated contacts between different mitochondria that are distinct from mitochondrial pre-fusion sites have been found in certain cell types [12,21]. The particularly protein-rich inner membrane shows a complex ultrastructure. It is composed of two subdomains, the inner boundary membrane and the cristae. The inner boundary membrane is connected to the outer membrane via direct physical contact sites that are visible in electron microscopy images as electron-dense bridging structures [22,23]. Cristae are extended tubular or lamellar membrane invaginations that protrude from the inner boundary membrane into

Abbreviations: MIA, mitochondrial intermembrane space import and assembly machinery; MICOS, mitochondrial contact site and cristae organizing system; MicX, Mic protein of X kDa (subunit of MICOS); OPA1, optic atrophy 1; SAM, sorting and assembly machinery; TIM23, presequence translocase of the inner mitochondrial membrane; TOM, translocase of the outer mitochondrial membrane

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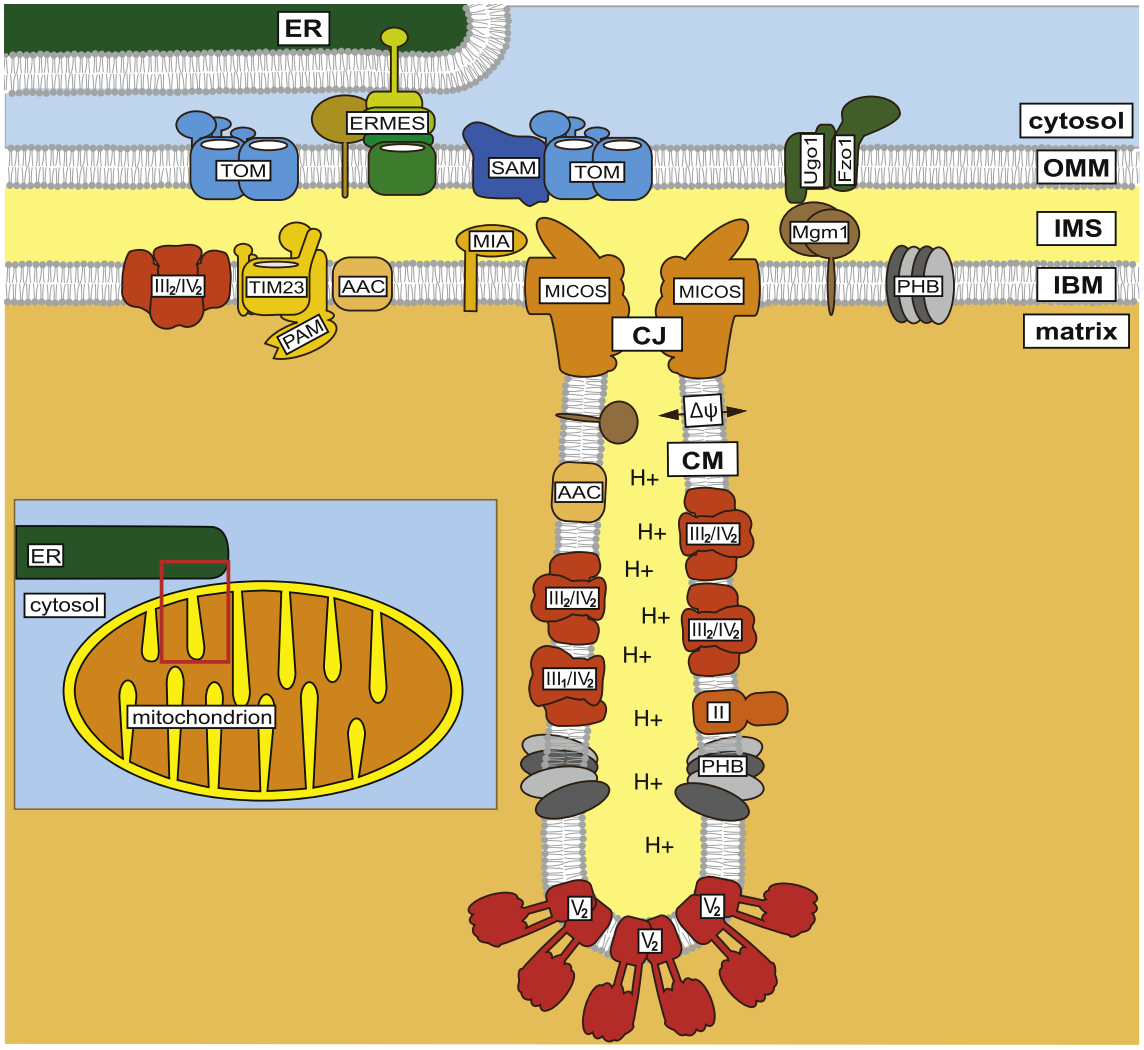

Fig. 1. Structural and functional organization of mitochondrial membranes in yeast. Mitochondria are composed of three distinct membrane compartments: The mitochondrial outer membrane (OMM) separates the organelle from the cytosol and establishes connections to other cellular membrane systems, such as the endoplasmic reticulum (ER). The mitochondrial inner membrane can be divided into the inner boundary membrane (IBM) and cristae membranes (CM). Inner boundary and cristae membrane domains are connected via crista junctions (CJs). Cristae membranes contain the vast majority of respiratory chain complexes. The inner boundary membrane predominantly harbors various transport machineries, such as preprotein translocases, and is in close proximity to the outer mitochondrial membrane. Formation and stabilization of cristae membranes depends on the membrane-shaping activity of certain protein complexes, such as dimeric and oligomeric F_1F_o-ATP synthase and the mitochondrial contact site and cristae organizing system (MICOS). Further abbreviations: IMS, intermembrane space; Δψ, mitochondrial inner membrane potential; ERMES, ER-mitochondria encounter structure; SAM, sorting and assembly machinery; TOM, translocase of the outer mitochondrial membrane; II, respiratory chain complex II; III_1/IV_2 and III_2/IV_2, supercomplexes of respiratory chain complexes III and IV; TIM23: presequence translocase of the inner mitochondrial membrane; PAM, presequence translocase-associated import motor; AAC, ADP/ATP carrier; MIA, mitochondrial intermembrane space import and assembly machinery; Mgm1/Ugo1/Fzo1: mitochondrial membrane fusion machinery; PHB, prohibitin complexes; V_2, dimeric F_1F_o-ATP synthase (also termed complex V).

the matrix space (Fig. 1). Their frequency and morphology shows substantial variations between different organisms and cell types as well as distinct metabolic and developmental states [13,17]. However, there is a common and pivotal architectural feature of cristae membranes: They provide an extended membrane surface for the accumulation of oxidative phosphorylation enzymes (respiratory chain complexes I to IV; F_1F_o-ATP synthase) and shape a micro-compartment that is optimized for ATP production via chemi-osmotic coupling [17,22,24–28].

The mechanism of cristae formation has remained unclear. It is generally assumed that tubular cristae form via the outgrowth of initially shallow invaginations that are induced by the accumulation of additional phospholipids and protein complexes in the inner boundary membrane when mitochondrial biogenesis is stimulated [17,28–30]. A well-known trigger of mitochondrial inner membrane expansion is the switch from glycolytic to respiratory metabolism. An elegant recent study suggested that lamellar cristae are generated via a different mechanism and result from localized mitochondrial inner membrane fusion activity in the vicinity of the outer membrane [30]. At least this pathway of cristae formation likely depends on the inner membrane fusion GTPase OPA1 (Mgm1 in yeast) (Figs. 1 and 2) [30–36]. A key player in shaping cristae membranes is the dimeric and oligomeric F_1F_o-ATP synthase that accumulates at the tips and rims of cristae. It is thought that the characteristic V-shape of ATP synthase dimers is responsible for the strong membrane curvature at cristae tips and rims (Fig. 1) [25,26,37–42].

2. Lateral heterogeneity of the inner mitochondrial membrane

Several lines of evidence indicate that the lateral diffusion of membrane proteins within the inner mitochondrial membrane is restricted. Cristae and inner boundary membranes exhibit a markedly asymmetric protein distribution: Whereas the cristae membranes contain the vast majority of respiratory chain and ATP synthase complexes, the inner boundary membrane is enriched in transporters for a wide variety of molecules ranging from metabolites to polypeptides (Fig. 1)