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Review

Integrative functions of the mitochondrial contact site and cristae organizing system

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ABSTRACT

Mitochondria are complex double-membrane-bound organelles of eukaryotic cells that function as energy-converting powerhouses, metabolic factories and signaling centers. The outer membrane controls the exchange of material and information with other cellular compartments. The inner membrane provides an extended, highly folded surface for selective transport and energy-coupling reactions. It can be divided into an inner boundary membrane and tubular or lamellar cristae membranes that accommodate the oxidative phosphorylation units. Outer membrane, inner boundary membrane and cristae come together at crista junctions, where the *mitochondrial contact site and cristae organizing system* (MICOS) acts as a membrane-shaping and –connecting scaffold. This peculiar architecture is of pivotal importance for multiple mitochondrial functions. Many elaborate studies in the past years have shed light on the subunit composition and organization of MICOS. In this review article, we summarize these insights and then move on to discuss exciting recent discoveries on the integrative functions of MICOS. Multifaceted connections to other major players of mitochondrial biogenesis and physiology, like the protein import machineries, the oxidative phosphorylation system, carrier proteins and phospholipid biosynthesis enzymes, are currently emerging. Therefore, we propose that MICOS acts as a central hub in mitochondrial membrane architecture and functionality.

Contents

1. Introduction: Endless forms most beautiful

Eukaryotic cells contain a fascinating variety of structurally and functionally distinct intracellular membrane systems, termed organelles. This intricate inner organization allows to delineate specialized subcompartments dedicated to distinct biochemical processes, which would often be conflicting within the same compartment. In this way, the functional repertoire of eukaryotic cells is tremendously expanded compared to prokaryotes. Concentration gradients of ions and other compounds may be explored for energy conversion or signal transmission. Anabolic and catabolic pathways

Abbreviations: CL, cardiolipin; ERMES, ER-mitochondria encounter structure; ERMIONE, ER-mitochondria organizing network; MCU, mitochondrial calcium uniporter; MIA, mitochondrial intermembrane space import and assembly; MICOS, mitochondrial contact site and cristae organizing system; MicX, Mic protein of X kDa (subunit of MICOS); OPA1, optic atrophy 1; PA, phosphatidic acid; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PS, phosphatidylserine; SAM, sorting and assembly machinery; TIM23, presequence translocase of the inner mitochondrial membrane; TOM, translocase of the outer mitochondrial membrane; VDAC, voltage-dependent anion channel.

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may be segregated and coordinated to achieve an unprecedented metabolic plasticity. However, compartmentalization also comes with a burden: the coordination of cellular functions now requires the transport of macromolecules, like proteins, metabolites and information between organelles across one or more selectively permeable membranes. Earlier research in organelle biology has focused on the assignment of discrete biochemical and physiological functions and the mechanisms of transport into and out of membrane-bound compartments. More recently, substantial efforts have been made to better understand the interaction and communication of organelles and the functional implications of the intriguing organellar membrane architecture [1–5].

A prime example of this development is the ongoing advancement in our understanding of the structural and functional organization of mitochondria [6–11]. These large organelles of endosymbiotic origin form extensive and highly ramified tubular networks that in most cell types propagate throughout the entire cytosol [12]. They contain a small circular genome that is organized into nucleoids and encodes for a few mitochondrial proteins as well as ribosomal and transfer RNAs [13,14]. The ultrastructure of mitochondria is particularly complex, because they are made up of two membrane systems that are termed outer and inner mitochondrial membrane, respectively. The outer mitochondrial membrane is much more than just a simple physical perimeter with large metabolite-conducting pores. Instead it assures the selective targeting and entry of more than thousand different proteins encoded by nuclear genes into mitochondria [15–20]. The outer membrane constitutes a versatile signaling platform and guides the communication of mitochondria with other organelles, like the endoplasmic reticulum [21]. The signal-dependent permeabilization of the outer mitochondrial membrane sends cells to their apoptotic doom [22,23]. The inner membrane is composed of two morphologically distinguishable domains with particular, yet tightly linked, functions in mitochondrial physiology [24–26]. The inner boundary membrane is enriched in transport machineries for metabolites and proteins. It mostly huddles against the outer membrane confining the narrow intermembrane space. Particularly protein-dense, tubular or lamellar membrane structures sprout from the inner boundary membrane into the central matrix compartment that may occupy a substantial part of the mitochondrial volume in heavily respiring cells [9,24–30]. These cristae membranes contain the oxidative phosphorylation machinery that produces ATP, the universal cellular energy currency, from ADP and phosphate via a sophisticated chemi-osmotic coupling of the proton-pumping respiratory chain complexes to the proton-gradient-consuming F_1F_o-ATP synthase. The ultrastructure of the narrow cristae tubules and discs appears to be perfectly tweaked for this process (24,25). Thus, cristae membranes are the actual biochemical reactors within mitochondria, the power plants of eukaryotic cells.

2. Formation and maintenance of mitochondrial cristae membranes

Different views on the mechanisms of mitochondrial cristae formation have been discussed (summarized in: [26]). In the unicellular eukaryotic model organism baker's yeast (*Saccharomyces cerevisae*), mitochondria contain only few, small cristae, when cells are grown in the presence of the fermentable carbon source glucose. Under these conditions, yeast cells produce ATP mainly via glycolysis in the cytosol. When cells are then transferred into a medium only containing non-fermentable carbon sources, like glycerol or lactate, expression of a plethora of (glucose-repressed) genes is induced. Nuclear and mitochondrial encoded components of the oxidative phosphorylation machinery are synthesized and inserted into the mitochondrial inner membrane. The surface of the inner membrane expands and because the outer membrane does not grow to the same extent, invaginations of the inner membrane towards to matrix appear inevitable [31]. Moreover, membrane protein crowding supports membrane bending [32]. It is well established that dimers and oligomers of the F_1F_o-ATP synthase are crucial factors for shaping the inner mitochondrial membrane [33–38]. ATP synthase dimers have an angular shape imposing curvature on the resident membrane. Long rows of ATP synthase dimers line up at the tips and rims of cristae membranes and are required for their formation and/or stability. Thus, initially shallow invaginations of the inner mitochondrial membrane may be stabilized and shaped into cristae-like structures by the accumulation of ATP synthase dimers and oligomers. Respiratory chain (super-)complexes and other cristae-resident proteins likely contribute to this process. The outgrowth of cristae membrane domains consequently generates a strong membrane curvature at the origin, where the cristae remain connected to the inner boundary membrane. In electron micrographs, these neck regions present as regularly shaped narrow tubular membrane domains that have been termed crista junctions [24–26]. The formation of crista junctions is critical for the ultrastructure and functionality of mitochondria. These structures not only stabilize the strong membrane curvature at the base of the cristae, but also act as diffusion barriers for proteins and likely also metabolites [39]. They are crucial for the asymmetric protein distribution between inner boundary and cristae membranes [26].

The molecular nature of crista junctions and their protein composition was long enigmatic. Early studies had implicated the conserved dynamin-like GTPase OPA1 (Mgm1 in yeast) in the regulation of crista junctions and, hence, the mobilization of cytochrome *c* from intracristal pools at the onset of apoptosis [40–43]. However, a strict requirement for OPA1/Mgm1 for the formation of crista junctions has been refuted recently [44]. OPA1/Mgm1 was initially identified as an essential factor for inner membrane fusion and several lines of evidence suggest that the contributions of OPA1 in higher eukaryotes and Mgm1 in yeast to cristae architecture and remodeling may differ [3,45]. A recent seminal paper by Walter Neupert and colleagues [46] has put forward an appealing and very elegant model for the interplay of mitochondrial fusion and cristae formation. They propose that two pathways of cristae formation exist. Tubular cristae are formed by membrane outgrowth and ATP synthase-dependent membrane shaping as described above. Alternatively, lamellar cristae may be formed by an incomplete inner membrane fusion event. The authors argue that Mgm1 fusion activity in yeast depends on its interaction with the outer membrane fusion complex Fzo1/Ugo1 [47,48]. Thus, inner membrane fusion occurs at contact sites between inner and outer mitochondrial membranes. At late stages of the fusion reaction a narrow tubular structure will remain which resembles a crista junction. Stabilization of this structure will lead to the formation of a disc-shaped crista domain [46]. The molecular mechanisms of such a process and the crosstalk of the protein machineries involved remain unclear. However, the model would explain several earlier observations regarding the mutual relationship between mitochondrial dynamics and cristae biogenesis. Follow-up studies based on this intriguing hypothesis will certainly lead to novel insights into mitochondrial architecture and homeostasis.

3. Mitochondrial contact site and cristae organizing system (MICOS)

Independent of the question how cristae formation is initiated, crista junction structures obviously need to be stabilized by a protein machinery given their regular shape and immense membrane curvature. This serious gap in previous models was closed a cou-

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