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Review

Mitochondrial Cristae: Where Beauty Meets Functionality

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Mitochondrial cristae are dynamic bioenergetic compartments whose shape changes under different physiological conditions. Recent discoveries have unveiled the relation between cristae shape and oxidative phosphorylation (OXPHOS) function, suggesting that membrane morphology modulates the organization and function of the OXPHOS system, with a direct impact on cellular metabolism. As a corollary, cristae-shaping proteins have emerged as potential modulators of mitochondrial bioenergetics, a concept confirmed by genetic experiments in mouse models of respiratory chain deficiency. Here, we review our knowledge of mitochondrial ultrastructural organization and how it impacts mitochondrial metabolism.

Trends

Mitochondria adapt their shape to sustain necessary cellular functions.

Cristae are functional dynamic compartments whose shape and dimensions modulate the kinetics of chemical reactions and the structure of protein complexes.

Cristae shape is maintained by the cooperation of mitochondrial-shaping proteins.

Perturbations of mitochondrial-shaping proteins disrupt cristae shape and affect the structure of the OXPHOS system, impairing cellular metabolism and growth.

Cristae shape could be an interesting and promising therapeutic target for modulating metabolic dysfunction.

The Dynamic Functional Form of Mitochondria

'Form ever follows function' is a famous quote from the American architect Louis Sullivan. He reached this conclusion by observing nature, where function is determined by specific and defined structures. Mitochondria are an extraordinary example of this axiom: they are dynamic organelles that have crucial roles in many cellular processes, including apoptosis, metabolism, reactive oxygen species (ROS) detoxification, and ATP production through OXPHOS. Such a variety of functions is coupled to a highly defined but plastic structure that continuously changes according to the needs of the cell (Box 1).

Mitochondria can switch from an elongated and interconnected network to a fragmented state via fusion and fission events during the so-called 'mitochondrial life cycle' [1]. Through these transitions, mitochondria modulate their functions and status and allow complex quality control. Recent discoveries shed light on the correlation between the modulation of mitochondrial shape and network and the energetic state of the cell. For example, activation of the recycling autophagy pathway triggers mitochondrial elongation [2,3], protecting mitochondria from degradation and promoting mitochondrial ATP production to increase the efficiency of energy conversion during nutrient deprivation [2]. Even upon exposure to other acute stressors, such as oxidative stress, mitochondria elongate [4,5]. The opposite situation is found under nutrient excess, where mitochondria fragment by uncoupling OXPHOS from ATP production [6]. Oxygen tension can also modify the structure and mobility of mitochondria, especially in neurons [7]. Taken together, these recent discoveries show that mitochondrial shape and bioenergetics are intimately linked, providing a defined framework to study the crucial biological problem of the relation between form and function.

Mitochondrial Cristae: Dynamic Biochemical Reactors

Mitochondria reorganize their internal structure by modifying the shape of the cristae. Nearly 50 years ago, Hackenbrock noted that, in response to low ADP concentrations, the inner membrane morphology changed from a 'condensed' state, characterized by a contracted and dense

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Box 1. Mitochondrial Structure

Mitochondria were first described in 1857 by the Swiss anatomist Rudolf von Koelliker, who called them 'sarcosomes' while studying human muscle. Then, in 1898, Carl Brenda coined the name 'mitochondrion' from the Greek word *mitos* (thread) and *chondros* (granule). Their structure and number vary among different tissues and under different metabolic conditions. Advances in light and electron microscopy and biochemical fractionation of submitochondrial membrane resulted in the description of mitochondrial structure. Mitochondria are embedded by two membranes with different structures and functions. The outer membrane (OM) and the inner membrane (IM) can be further organized into specialized regions.

The OM separates the mitochondria from the cytosol, yet it allows the passage of metabolites through the voltage-dependent anion channel (VDAC) [92] and of nuclear-encoded proteins through the translocase of the OM TOM [93]. Moreover, it is the platform where the β-barrel protein-sorting and assembly machinery (SAM), as well as mitochondrial-shaping proteins (Mfn1,2, Fis1) and proteins of apoptotic pathway (e.g., BAK), are located. In addition, at least two specialized regions of the OM have been described to interact with other organelles: (i) mitochondria-associated endoplasmic reticulum membrane (MAMs), which interact with the endoplasmic reticulum; and (ii) intermitochondrial junctions (IMJ), which interact with other mitochondria.

The IM can be subdivided into the inner boundary membrane (IBM) and the cristae. The IBM contains the translocase inner membrane (TIM), which shuttles proteins into the matrix [94], and proteins, such as Mia40 and Oxa1 [95], which are essential for the correct assembly and localization of IM proteins. Cristae are fundamental structures for mitochondria and are not simply invaginations of the IM, as originally described by Palade in 1952. Indeed, during the 1990s, Mannella and colleagues used 3D image reconstruction of electron tomography to show that the cristae are bag-like structures, separated from the intermembrane space by narrow tubular junctions. This new structural organization suggested that cristae are specialized compartments for limiting the diffusion of molecules that are important for the OXPHOS system. A plethora of proteins that are not fully characterized regulate cristae biogenesis and structure. Among them, OPA1 and the MICOS complex are the masters of cristae dynamics [10,27].

matrix compartment and wide cristae, to an 'orthodox' state, with an expanded, less dense matrix and a more compact cristae compartment [8]. However, these pioneering observations remained confined to the aficionados of mitochondrial bioenergetics and were considered to be an *in vitro* artifact of isolated organelles incubated in nonphysiological sugar-containing media, until the discovery of the dynamic rearrangement of cristae shape that occurs during programmed cell death. This so-called 'cristae remodeling' occurs during apoptosis to allow the complete release of cytochrome *c* [9]. This occurs through the proapoptotic members of the B cell lymphoma (BCL)-2 family, which widen cristae junctions and invert cristae curvature [9,10], ultimately impacting mitochondrial bioenergetics [11]. The discovery of this cristae-remodeling process showed that dynamic ultrastructural mitochondrial changes occur in pathophysiology and paved the way to discover the molecular mechanism controlling cristae shape. Moreover, it resulted in the hypothesis that the cell and the organelle can exploit changes in mitochondrial ultrastructure to modulate enzymatic activity. This concept has precedent in cell biology; for example, cells use swelling and shrinking processes to regulate their anabolic and metabolic functions, such as glycogen synthesis, maintenance of pH, and activation of Cdc42 [12]. In a crucial proof-of-principle study, Orwar and colleagues used a solitary-vesicle model with the same size volume of mitochondria to demonstrate that the shape and volume of vesicles affects the reaction rate of several enzymes in the Krebs cycle [13], providing a biophysical basis for how changes in mitochondrial compartments can regulate the embedded biochemical reactions.

Biological examples of this process exist: in the amoeba *Chaos carolinensis*, upon fasting, the cristae transition from random tubular to ordered (paracrystalline) larger cubic structures [14], perhaps to protect the membrane from oxidants and prevent mitochondrial damage, as demonstrated in the large vesicles [15]. In addition, upon different energetic states in mouse heart and muscle, adjacent mitochondria form intermitochondrial junctions (IMJs), where cristae density is higher and cristae are aligned in the same orientation. The authors hypothesized that IMJs allow exchange between mitochondria. Although more work is needed to understand the