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Review

Structure and dynamics of the mitochondrial inner membrane cristae

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Abstract

Three-dimensional images of mitochondria provided by electron tomography reveal that the micro-compartments (cristae) defined by the inner membrane are connected to the periphery of this membrane by narrow tubular junctions, which likely restrict diffusion. The tomograms also strongly suggest that inner membrane topology represents a balance between membrane fusion and fission processes. The hypothesis being developed is that inner membrane topology is a regulated property of mitochondria. This review summarizes the evidence about how inner membrane shape influences mitochondrial function and, conversely, what is known about the factors that determine this membrane's topology.

Keywords: Mitochondria; Electron microscopy; Electron tomography; Membrane topology; Bioenergetics; Cardiolipin

The first images of the internal structure of mitochondria were provided over 50 years ago by transmission electron microscopy (TEM) of thin sections of chemically fixed and plastic-embedded specimens [1]. It was soon apparent that the mitochondrial inner membrane can assume an astounding variety of morphologies [2], even though it has the same two basic functions in every cell: to serve as the scaffold for the assembly and operation of the respiratory chain complexes, and to provide the permeability barrier across which the respiratory machinery generates its chemiosmotic gradient. In the last 10 years, the technique of electron tomography – employing advanced, higher voltage electron microscopes and computer-based reconstruction algorithms – has afforded biologists true three-dimensional images of mitochondria, first in thick plastic sections [3–8] and more recently in frozen-hydrated suspensions [8–10] or tissue sections [11,12]. While the results have underscored the tremendous pleomorphism of the mitochondrial inner membrane, they also point to conserved design principles and to an important role for membrane dynamics in maintaining membrane morphology. Moreover, these studies suggest that the diversity in inner membrane shape and the changes observed under certain conditions might not be random, but rather might reflect a novel regulatory mechanism. The growing implication is that certain mitochondrial functions are affected (or even effected) by changes in mitochondrial membrane topology, e.g., by altering the diffusion of metabolites and proteins between internal compartments [4,8,10]. This review is intended to highlight recent findings relevant to the influence of inner membrane shape on mitochondrial function and the identification of factors that, in turn, regulate this membrane's topology.

1. Morphology and implied dynamics of mitochondrial inner membranes

The mitochondrion is structurally defined, in large measure, by its two membranes: a limiting outer membrane that enwraps the energy-transducing inner membrane, which in turn encloses a dense, protein-rich matrix. The outer membrane is topologically simple, varying in shape depending on whether the mitochondrion is in a cell (usually tubular when attached to the cytoskeleton, sometimes reticulated) or isolated in suspension (ellipsoidal or spherical). The inner membrane, which has a larger surface area than the outer membrane, contains features referred to as *cristae* (literally, crests) which have long been represented as simple infoldings of this membrane [1,7]. Although this "baffle" interpretation was not universally accepted (e.g., [13]), it rapidly found its way into the textbooks. Subsequent electron tomographic analyses of a variety of

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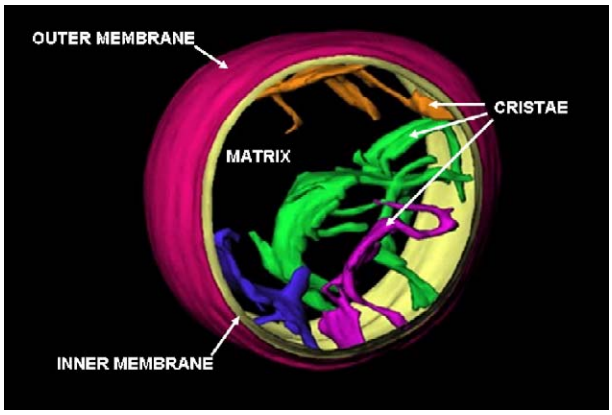

Fig. 1. Model derived from cryo-electron tomography of the membranes in an intact, frozen-hydrated mitochondrion isolated from rat liver. This mitochondrion has a diameter of 700 nm.

mitochondria, isolated and in situ, have provided overwhelming evidence that cristae are not simply random folds in the inner membrane but rather internal compartments formed by invagination of the membrane (Figs. 1 and 2). These invaginations originate at narrow neck-like segments, called *pediculi cristae* (crista feet) when first detected by conventional TEM [13] and later *crista junctions* [5].

Rat-liver mitochondria display highly variable crista morphology, even within a single organelle. In the frozen-hydrated mitochondrion shown in Fig. 1, the inner membrane comprises curved, tubular regions that co-exist or merge with flattened lamellar segments. The overall impression is one of a highly fluid, interconnected membrane continuum. Hackenbrock [14] defined two morphologic states in chemically fixed mitochondria, *condensed* and *orthodox*, which differed primarily in the relative states of expansion or contraction of the matrix and intracristal compartments. Three-dimensional analyses of rat-liver mitochondria in these states indicate major differences in inner membrane topology (Fig. 2). Cristae in the orthodox (matrix expanded) state tend to be tubes or short flat lamellae with one or two openings (junctions) in the peripheral region of the inner membrane. Condensed (matrix compacted) mitochondria (Fig. 2, also Fig. 1) have larger internal compartments with multiple tubular connections to the peripheral region and to each other. Interconversion of these states can only be achieved by the inner membrane undergoing fusion and fission [8]. Matrix compression is accompanied by fusion of individual cristae into larger compartments, while matrix expansion requires fissioning of the large cisternae into individual tubes or lamellae and (with extreme matrix swelling) recruitment of membrane from the interior to the periphery. Analyses of a variety of mitochondria reveal inner membrane morphologies that appear to represent extreme states of membrane fusion or fission (Fig. 3). Thus, the 'typical' crista morphology represented by mitochondria like those of Figs. 1 and 2 likely represents a balance between intra-mitochondrial membrane fusion and fission processes [10]. As discussed below, this raises the possibility that inner membrane morphology is regulated, at least in part, by the same types of proteins that control inter-mitochondrial fission and fusion.

2. Sites of inner membrane invagination: crista junctions

Tubular connections between cristae and the peripheral or boundary region of the mitochondrial inner membrane have been observed in mitochondria from protozoa (amoeba), fungi, and metazoa from nematodes to flies to mammals [3–9,15–17]. The junctions have been shown to form spontaneously in yeast mitochondria after extreme osmotic swelling and re-contraction of the inner membrane, indicating that their formation is energetically favored [8]. However, while crista junctions are ubiquitous, they are not structurally constant. Perkins et al. reported that crista junctions in neuronal mitochondria have uniformly circular cross-sections with diameters of ~28 nm [5]. However, in rat-liver mitochondria the cross-section of the junctions can vary from circular to elliptical (short slots) with openings typically in the range 20–50 nm [3,4,8]. The crista junctions in *Neurospora* mitochondria have been reported to be exclusively slot-like

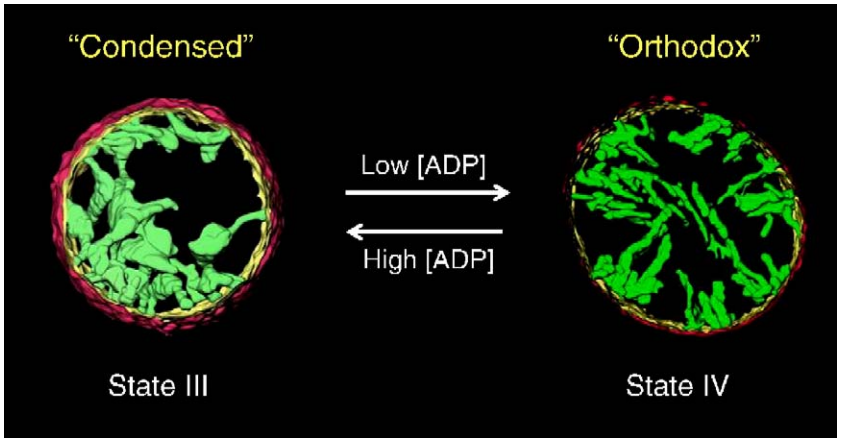

Fig. 2. Change in mitochondrial inner membrane topology associated with the orthodox-condensed transition. Model on left reproduced from [4] with permission of Elsevier Science. Model on right reproduced from C.A. Mannella, (2004) Mitochondrial Membranes, Structural Organization, in *Encyclopedia of Biological Chemistry* (W.J. Lennarz and M.D. Lane, eds), vol. 2, pp. 720–724, with permission of Elsevier Science. Mitochondria (left to right) have diameters of 1500 nm and 500 nm.

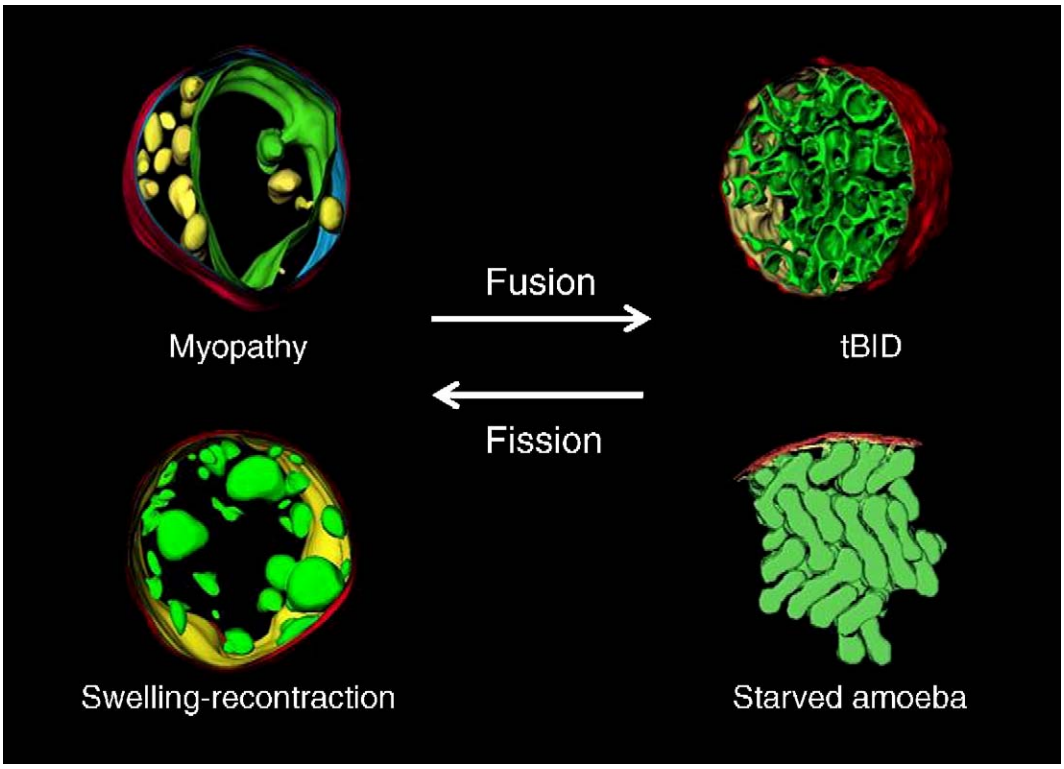

Fig. 3. Extreme mitochondrial inner membrane topologies reflecting an imbalance of membrane fusion and fission. Upper left: heart muscle mitochondrion (1000 nm diameter) with "vesicular" cristae from a patient with Senger's syndrome. (Reproduced with permission from M. Huizing, PhD thesis, University of Nijmegen, 1998.) Lower left: yeast mitochondrion (1200 nm diameter) with "vesicular" cristae formed following extreme osmotic swelling and recontraction. (Reproduced from [8] with permission of IUBMB Life, Taylor Francis Group.) Upper right: mouse liver mitochondrion (900 nm diameter) after brief exposure to tBid [25]. (Reproduced from [10] with permission of Elsevier Science.) Lower right: segment of a fasting amoeba mitochondrion showing paracrystalline arrangement of cristae. Length of outer membrane segment is 800 nm. (Reproduced from [7] with permission of Elsevier Science).

[9,16]. However, intact frozen-hydrated *Neurospora* mitochondria have both circular and slot-like crista junctions (Mannella, Marko, Hsieh, unpublished results).

It is unclear whether the formation of crista junctions is dependent on or supported by specific mitochondrial protein or lipid components. On the one hand, membrane invaginations with short neck-like junctions are predicted to occur when a flexible spherical membrane increases in area while nested inside a second, rigid sphere [18]. Thus, formation of tubular crista junctions might be a spontaneous lipid-mediated process requiring nothing more than the rate of inner membrane biogenesis exceeding that of the outer membrane. On the other hand, certain mutations and pathological conditions are associated with unattached cristae, suggesting derangement in mechanisms that normally stabilize the crista junctions (Fig. 3 and below). One of the rare cases of total absence of crista junctions is associated with the relict mitochondrion of the anaerobic pathogen, *Cryptosporidium parvum* [19]. This organism lacks a functioning respiratory chain but has a single mitochondrion, probably retained for iron–sulfur metabolism. The inner membrane of the relict mitochondrion is highly convoluted but does not have crista junctions (Fig. 4).

Overexpression of membrane proteins in *E. coli* can cause expansion and infolding of the inner, cytoplasmic membrane. In one case, the infoldings of the bacterial inner membrane were shown by electron tomography to be random, lacking the tubular junctions typical of mitochondrial cristae [20]. By contrast, magnetotactic bacteria contain so-called magnetosomes, linear

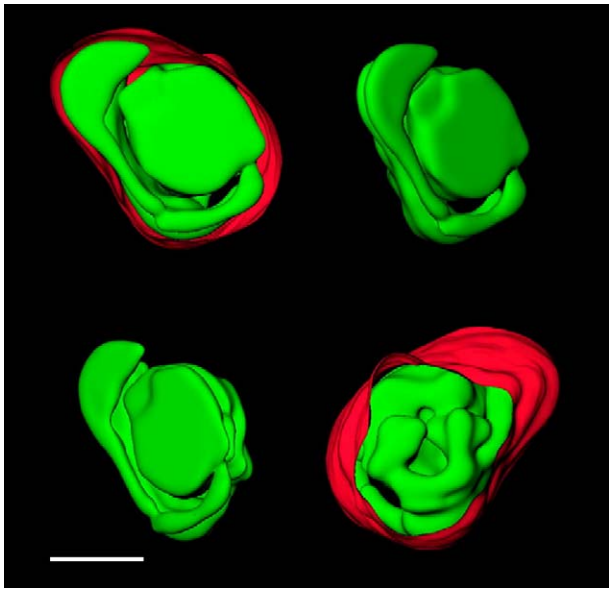

Fig. 4. Relict mitochondrion from the anaerobic pathogen *Cryptosporidium parvum*, having a highly folded inner membrane that lacks crista junctions. Scale bar = 100 nm. (Reproduced from [19] with permission of Blackwell Publishing, Inc.).

arrays of ~50-nm magnetite crystals contained inside membrane vesicles formed by invagination of the inner membrane. These invaginations have been shown, by cryo-electron tomography, to occur at short, neck-like membrane junctions that form in the membrane even in the absence of the magnetic particles [21]. Thus, it is possible, perhaps likely, that mitochondrial crista junctions are formed and stabilized by specific, conserved mechanisms shared with the mitochondrion's bacterial ancestors.

3. Functional implications of inner membrane topology

An early inference from the 3D images of mitochondria provided by electron tomography was that narrow tubular junctions might restrict diffusion between intracristal compartments and the peripheral intermembrane space [4]. Williams [22] and Tedeschi [23] have commented separately on the bioenergetic implications of the new model for inner membrane organization: localized, kinetically controlled proton flow as opposed to the original description of delocalized chemiosmosis of Mitchell [24]. In fact, there are several indications in the recent literature that the topology of the mitochondrial inner membrane might directly affect specific mitochondrial functions and, therefore, that changes in inner membrane morphology might represent a novel form of metabolic regulation.

3.1. Bioenergetics: the condensed to orthodox morphological transition

Computer simulations by Moraru and colleagues indicate that ADP depletion could occur inside large intracristal compartments of condensed mitochondria connected by long narrow tubular segments to the inner boundary membrane [8]. The simulations predict that restricted diffusion of ADP cannot keep up with its utilization inside these micro-compartments, leading to diminished local production of ATP. Isolated rat-liver mitochondria were first shown by Hackenbrock to switch from condensed to orthodox state when [ADP] drops during the conversion from respiratory state 3 to state 4 [14]. Thus, this familiar but poorly understood morphological transition (Fig. 2) may have a functional basis: elimination of diffusion bottlenecks that would otherwise reduce efficiency of ATP production [10].

3.2. Apoptosis: tBid-induced remodeling of the inner membrane

Isolated mouse liver mitochondria undergo a dramatic change in inner membrane morphology after incubation for a few minutes with the truncated form of the pro-apoptotic protein Bid (Fig. 3) [25]. This remodeling, marked by a reversal in curvature of the cristae membranes, results in increased interconnectivity of the intracristal spaces and a widening of cristae junctions. Concomitantly, there is a mobilization and more complete release of internal stores of cytochrome *c*, suggesting that the tBid-induced inner-membrane remodeling is an integral step in the apoptotic pathway.

3.3. Oxidative stress: cubic transition in mitochondrial membranes of amoeba

The mitochondrial cristae of many protozoa are tubular. In the case of the amoeba, *Chaos carolinensis*, fasting induces a remarkable morphological transition in the cristae, resulting in formation of a paracrystalline labyrinth of wide interconnected compartments with cubic symmetry (Fig. 3) [15]. This structural transition coincides with increased intracellular production of reactive oxygen species (ROS) associated with breakdown of internal carbon stores [26], suggesting that this type of membrane remodeling – also observed in other membrane systems associated with oxidative stress (see discussion in [26]) – might represent a protective mechanism to help clear ROS from the organelles.

4. Factors that affect inner membrane topology

The topology of a membrane is a complex function of intrinsic and extrinsic factors, including: spontaneous curvature (protein and lipid composition), dynamics (ability to undergo fusion and fission), and binding to other cellular constituents (such as membrane-bending proteins, cytoskeletal filaments, and even other membranes). In the case of the mitochondrial inner membrane, its physical interactions with the outer membrane likely have a major effect on its shape. For example, as noted above, the very existence of a volume-constraining outer membrane may play an important role in initiating crista invagination; and contacts or attachments of the two membranes, through ~10 nm bridging particles detected by cryo-electron tomography [8,10], may serve to keep the inner membrane extended. Likewise, there are obvious effects of the protein-rich matrix on inner membrane shape, in terms of setting a minimum volume below which the space bounded by the membrane can collapse. Whether there are more direct interactions, such as binding of the inner surface of cristae to a "mitoskeleton" (analogous to the interactions of endoplasmic reticulum with the cytoskeleton) is unknown.

The intrinsic factors involved in the formation of crista junctions and in the structural transitions (remodeling) described in the previous section have, until recently, been largely a matter of conjecture. However, new findings are beginning to implicate several mitochondrial inner membrane components as regulators of this membrane's topology.

4.1. tBid, adenine nucleotide translocator, and cardiolipin

As noted above, tBid triggers a remodeling of mouse liver mitochondria, involving reversal of curvature of the crista membranes [25]. Epand et al. have observed that tBid induces reversed curvature in cardiolipin-containing membrane phases [27], suggesting that the remodeling of the cardiolipin-rich mitochondrial inner membrane might be lipid-mediated, i.e., a direct effect of tBid on the organization of lipids in these membranes. Further evidence in support of this hypothesis has been provided by studies involving the adenine nucleotide translocator (ANT), the inner membrane carrier protein which

binds cardiolipin and requires it for activity [28,29]. Gonsalvez et al. recently have reported that tBid inhibits ANT activity of yeast mitochondria in a cardiolipin-dependent manner, consistent with this inhibition being an indirect effect of tBid on cardiolipin organization [30]. Interestingly, Klingenberg and coworkers reported three decades earlier that ANT ligands, such as the inhibitor atractyloside (ATR), induce a morphological change in beef heart mitochondria [31] that, in retrospect, appears equivalent to the tBid induced remodeling of rat liver mitochondria (Fig. 3). Klingenberg et al. recognized the change in inner membrane shape as a reversal in membrane curvature and attributed it to a ligand-induced "re-orientation" of a mobile carrier protein to the matrix side of the membrane. However, Klingenberg later questioned whether the stoichiometry of ANT could be sufficient to cause so dramatic a change in inner membrane structure [32]. An alternative explanation might be that ligand-induced conformational changes in ANT cause a reorganization of the cardiolipin in the inner membrane, similar to that attributed to tBid, which, in turn, triggers the inner membrane remodeling. Of course, the possibility cannot be excluded that tBid (like ATR) directly interacts with ANT and that the reversal of curvature that both induce in the mitochondrial inner membrane is protein-mediated, i.e., due to a conformational change in the carrier protein, as originally suggested by Klingenberg et al. Distinguishing between these possibilities will require a better understanding of the nature of the interactions of tBid with cardiolipin and with ANT. It is worth noting, in this context, another inducer of reversed mitochondrial inner membrane curvature, cytochalasin B. This polycyclic antibiotic, best known for its inhibition of actin polymerization, was found by Coleman and Hermina in 1974 to induce a change in the inner-membrane morphology of rat-liver mitochondria very similar to that caused by ATR (and later tBid), which they attributed to interaction of the antibiotic with ANT [33]. In fact, the effects of cytochalasin-B and tBid on ADP-stimulated (state 3) respiration and respiratory control were both shown to be similar to those of ATR [30,33].

4.2. ATP synthase

The mitochondrial F_1F_0-ATP synthase complex has been strongly implicated in contributing to the curvature of the inner membrane as a result of its oligomerization. Paumard et al. have shown that mutations in ATP synthase subunit e (also called Atp21p and, formerly, Tim11p) inhibit formation of the ATP synthase dimer (the first step in formation of larger oligomers) and results in appearance of concentric onion-like cristae [34]. More recently, single-particle electron microscopic studies from two laboratories [35,36] have revealed the likely basis for the membrane bending ability of ATP synthase. Since the lateral dimension of the membrane-embedded F_0 domain (at which dimer binding occurs) is considerably less that that of the extrabilayer F_1 domain, lateral close-packing causes the complexes to be tilted with respect to each other and so imparts a local bend to the membrane of 40° in the case of beef heart ATP synthase [35] and 70° for the algal complex [36]. A mitochondrial DNA mutation in the gene encoding subunit 6 (F_0 domain) of the ATP synthase recently has been described in *Drosophila* [17]. This mutation ($ATP6^1$) causes marked reduction in ATP production in neuronal mitochondria and very unusual inner membrane topology: rounded crista compartments contiguous with flattened lamellar regions of the same membrane (Fig. 5). A possible explanation for this highly unusual topological transition is that ATP synthase dimerization is normally inhibited in flat, lamellar cristae and that the $ATP6^1$ mutation somehow weakens the inhibition, allowing complex dimerization and, consequently, increased membrane curvature.

4.3. Mitofilin

Mitofilin is a 90-kDa inner-membrane protein, with predicted membrane anchor and coiled-coil domains, that is present at high levels in heart mitochondria but which, until recently, had no obvious function. John et al. recently have reported that down-regulation of mitofilin in HeLa cells by siRNA results in the formation of concentric onion-like inner mitochondrial membranes [37]. The mitofilin-deficient mitochondria tend to form progressively larger membrane sworls, which were analyzed by electron tomography. The larger inner-membrane structures were found to be composed of a complex, interconnected network of membranes totally lacking tubular

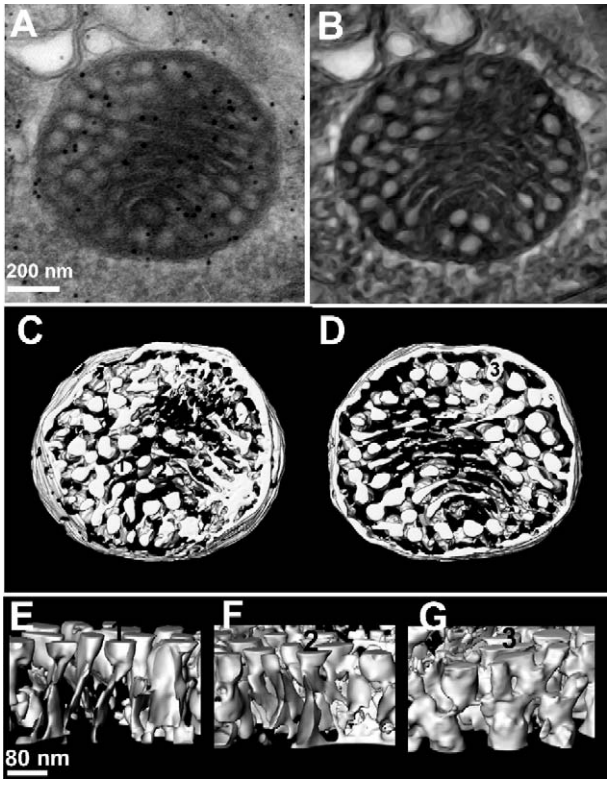

Fig. 5. Brain mitochondrion from *Drosophila* bearing a mutation in the mitochondrial DNA gene for subunit 6 of ATP synthase. (A) Projection image from a 200-nm-thick plastic section of brain. (B) Single 2-nm-thick slice from the tomographic reconstruction. (C, D) Front and back views of the membrane surfaces in the tomogram. (E–F) Zoom-in views of cristae, showing flat lamellar regions contiguous with dilated compartments. (Reproduced from [17] with permission of the Society of Neuroscience).

connections to each other or to the peripheral inner membrane. John et al. have proposed that mitofilin's physiological role is to maintain normal crista morphology, in particular, the formation or stabilization of crista junctions.

4.4. Mitochondrial dynamin-like proteins

As mentioned, three-dimensional images provided by electron tomography strongly suggest that the topology of the inner mitochondrial membrane represents a balance between membrane fusion and fission processes [10]. Studies are ongoing in several laboratories of mitochondria from organisms in which proteins involved in mitochondrial dynamics are mutated, knocked out, or up/down regulated. One such protein, mgm1 (called OPA1 in humans), is a member of the dynamin family of GTP-binding proteins. It is found on the outer surface of the mitochondrial inner membrane and generally considered to be involved in mitochondrial fusion [38,39]. Griparic et al. found that reduced expression (by siRNA) of OPA1 in HeLa cells causes cristae "disorganization", with indications of local matrix dilation and mitochondrial constrictions [40]. Continuity between different membrane regions (as in the case of the ATP6[1] mutant) was not determined. However, tomographic analyses are in progress for a *C. elegans* mgm1 mutant and for yeast mitochondria in which expression of mgm1p has been down-regulated (Van der Bliek, Pain and Mannella, unpublished results). Interestingly, Amutha et al. have reported that mgm1p is required for oligomerization of ATP synthase [41]. Thus, it might be informative to use tomography to directly compare the effects of mgm1 deficiency and ATP synthase dimer inhibition on the topology of mitochondrial inner membranes in the same organism.

5. Conclusions

The 3D images of mitochondria provided by electron tomography have led to a re-examination of standard concepts about mitochondrial membrane organization and even rekindled some old (and, frankly, unsettled) arguments about the basic tenets of chemiosmosis. The growing likelihood that many of the topological changes undergone by the inner membrane reflect alterations to internal diffusion pathways with functional impact is spurring on the search for the molecular determinants (intrinsic and extrinsic) of inner membrane shape. Likewise, visualization of the interesting and complex micro-compartments inside mitochondria is sharpening the realization that ultimate modeling of cellular energy metabolism will have to include the effects of mitochondrial inner membrane topology. Technological developments in instrumentation and computation are in progress that promise to improve the resolution in electron tomographic reconstructions of native (frozen-hydrated) organelles, cells and tissue. Sorting out the molecular signatures on mitochondrial membranes and inside the different compartments (matrix, intermembrane and intracristal) is a daunting challenge but one which, if successfully met, could provide important information needed for a complete description of mitochondrial energy metabolism.

Acknowledgments

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