The Origin of Mitochondrial Cristae from Alphaproteobacteria

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Abstract

Mitochondria are the respiratory organelles of eukaryotes and their evolutionary history is deeply intertwined with that of eukaryotes. The compartmentalization of respiration in mitochondria occurs within cristae, whose evolutionary origin has remained unclear. Recent discoveries, however, have revived the old notion that mitochondrial cristae could have had a pre-endosymbiotic origin. Mitochondrial cristae are likely homologous to the intracytoplasmic membranes (ICMs) used by diverse alphaproteobacteria for harnessing energy. Because the Mitochondrial Contact site and Cristae Organizing System (MICOS) that controls the development of cristae evolved from a simplified version that is phylogenetically restricted to Alphaproteobacteria (alphaMICOS), ICMs most probably transformed into cristae during the endosymbiotic origin of mitochondria. This inference is supported by the sequence and structural similarities between MICOS and alphaMICOS, and the expression pattern and cellular localization of alphaMICOS. Given that cristae and ICMs develop similarly, alphaMICOS likely functions analogously to mitochondrial MICOS by culminating ICM development with the creation of tubular connections and membrane contact sites at the alphaproteobacterial envelope. Mitochondria thus inherited a pre-existing ultrastructure adapted to efficient energy transduction from their alphaproteobacterial ancestors. The widespread nature of purple bacteria among alphaproteobacteria raises the possibility that cristae evolved from photosynthetic ICMs.

Key words: **endosymbiosis, ICMs, Mic60, MICOS, magnetosomes, purple bacteria.**

Introduction

Aerobic eukaryotes use their mitochondria as bioenergetic organelles to produce most of the ATP of the cell. They do so by coupling electron transport to chemiosmosis in the presence of oxygen. These ATP-generating factories have enabled eukaryotes to greatly diversify in aerobic environments and evolve complex structures and functions that have high energetic demands. The bioenergetic function of mitochondria, however, strongly depends on mitochondrial structure (Westermann 2012; Mannella et al. 2013). At the morphological level, the dynamic interaction among mitochondrial fission, fusion and the cytoskeleton (as well as diverse cellular membranes) regulate the distribution, size and overall shape of mitochondria (i.e., punctate or reticulate) in response to cellular needs (Okamoto and Shaw 2005; Galloway et al. 2012; Westermann 2012). At the finer level of mitochondrial internal architecture, the mitochondrial inner membrane invaginates into cristae to compartmentalize aerobic respiration (Mannella et al. 2001, 2013; Mannella 2006). Mitochondrial morphology and ultrastructure have evolved to optimize the efficiency of aerobic respiration (Liesa and Shirihai 2013; Cogliati et al. 2016; Jayashankar et al. 2016; Mishra and Chan 2016). How this happened is now being revealed by recent discoveries on the evolutionary cell biology of mitochondria.

Mitochondrial cristae, the structural hallmarks of mitochondria, constitute respiratory sub-compartments within mitochondria (Daems and Wisse 1966; Mannella et al. 1994; Perkins et al. 1997). They effectively limit the diffusion of molecules between the intra-cristal space and the intermembrane space, thereby: (1) localizing proton gradients (Mannella 2000; Williams 2000; Strauss et al. 2008), (2) concentrating metabolites (Mannella et al. 2001, 2013), and (3) preventing the release of signaling molecules (e.g., cytochrome *c* during apoptosis) (Olichon et al. 2003; Frezza et al. 2006; Cogliati et al. 2013; Varanita et al. 2015). This compartmentalization is achieved by means of crista junctions, which are tubular, slot- or neck-like membrane structures that differentiate the inner mitochondrial membrane (MIM) into the inner boundary membrane (IBM) and the crista membrane (CM) (Vogel et al. 2006; Wurm and Jakobs 2006) (fig. 1A). The development of cristae largely depends on the formation of crista junctions (CJs) and contact sites (CSs), which usually overlap spatially at the mitochondrial envelope (Harner et al. 2011; Hoppins et al. 2011; von der Malsburg et al. 2011; Körner et al. 2012; Ott et al. 2012; Zerbes et al. 2012) (see Zick et al. 2009 and van der Laan et al. 2016 for overviews on the different molecular determinants of crista development). A multi-protein complex named MICOS (MItochondrial Contact site and Cristae Organizing System)

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Review

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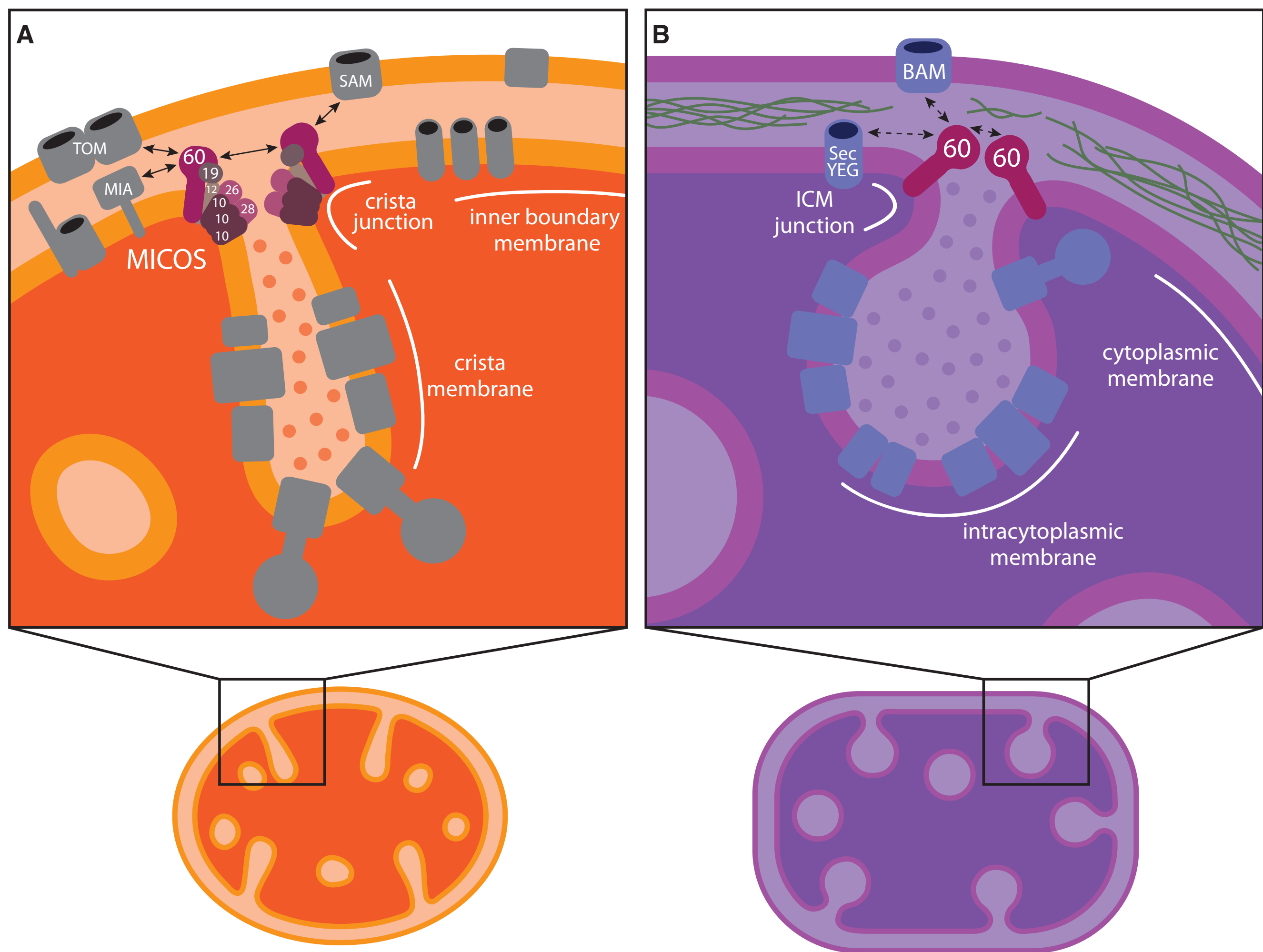

FIG. 1. The function of MICOS is probably conserved between mitochondria and alphaproteobacteria. (*A*) In the mitochondrion of *Saccharomyces cerevisiae*, MICOS forms CSs and CJs to maintain and stabilize cristae (Harner et al. 2011; Hoppins et al. 2011; von der Malsburg et al. 2011; Körner et al. 2012; Ott et al. 2012; Zerbes et al. 2012). MICOS is composed of the Mic60–Mic19 subcomplex which establishes CSs with the MOM and marks the sites of CJ formation, and the Mic12–Mic10–Mic26–Mic28 subcomplex which differentiates and bends the MIM at CJs (Pfanner et al. 2014; Friedman et al. 2015; Muñoz-Gómez, Slamovits, Dacks, Baier, et al. 2015; Zerbes et al. 2016). The central MICOS subunit, Mic60, contacts the outer membrane through its interactions with the TOM and SAM complexes (additional interactions have also been reported with the MOM proteins porin and Ugo1), and further interacts with Mia40 to aid in the oxidative import of mitochondrial proteins (von der Malsburg et al. 2011; Körner et al. 2012; Ott et al. 2012; Zerbes et al. 2012). (*B*) In alphaproteobacteria, alphaMic60 is presumably involved in the formation of ICMJs and CSs to stabilize bioenergetic ICMs. alphaMic60 likely uses its conserved mitofilin domain to interact with the BAM complex, the bacterial homologue of SAM. alphaMICOS might therefore mark the sites of ICM invagination and keep ICMs anchored to the alphaproteobacterial envelope at CSs. Alternatively, alphaMic60 might bring together protein translocases (e.g., SecYEG and BAM) for proper envelope biogenesis (the so called Bayer's junctions) at sites of murein hypotrophy. The compartmentalization of both mitochondrial cristae and alphaproteobacterial ICMs is achieved by narrow tubules (i.e., CJS and ICMJs) likely made and stabilized by Mic60. Mitochondrial cristae and alphaproteobacterial ICMs are therefore functionally analogous. They both constitute specialized sub-compartments that optimize the efficiency of energy transduction by concentrating bioenergetic metabolism. Thick arrows indicate physical interactions between protein partners. Dashed arrows indicate hypothesized physical interactions between protein partners based on the known function of their homologues.

is in charge of creating both CJs and CSs at the mitochondrial envelope by combining the functions of its six different subunits (Harner et al. 2011; Hoppins et al. 2011; von der Malsburg et al. 2011; Pfanner et al. 2014; Friedman et al. 2015; Zerbes et al. 2016) (fig. 1A). MICOS, therefore, constitutes the molecular basis of crista development, and is ultimately responsible for the adaptive compartmentalization of cristae as respiratory sub-compartments within mitochondria.

Historically, early transmission electron microscopic investigations revealed superficial similarities between the structure of mitochondrial cristae and the intracytoplasmic membranes (ICMs) of some bacteria (Munn 1974). However, no explicit statements were made with regard to the evolutionary connection between these two kinds of structures. When the phylogenetic affiliation between mitochondria and purple nonsulfur bacteria (today's photosynthetic alphaproteobacteria) was first recognized based on the comparative biochemistry of the respiratory chain, mitochondrial cristae were interpreted as having evolved post-endosymbiotically in their specialization as respiratory organelles (John and Whatley 1975).

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It was not until 1980 that Stewart and Mattox (based on parsimony and morphological considerations) explicitly proposed that mitochondrial cristae were derived from purple nonsulfur bacterial ICMs, and therefore had a pre-endosymbiotic origin (the homology hypothesis). Stewart and Mattox drew on the pioneering phylogenetic work of Dayhoff and Schwartz on organelle origins (Schwartz and Dayhoff 1978) to suggest that mitochondria evolved polyphyletically from distinct endosymbiotic events with two purple nonsulfur bacteria, each with a different ICM morphology (Stewart and Mattox 1980, 1984). Since then, Cavalier-Smith (1981, 1983a, 1983b) has also discussed these ideas in different contexts, and has recently argued in more detail that cristae evolved from vesicular ICMs that were present in an anoxygenic photosynthetic alphaproteobacterium (Cavalier-Smith 2002, 2006, 2007). Others have also recently noted superficial morphological similarities between cristae and the ICMs developed by phylogenetically derived alphaproteobacterial methanotrophs (Moreira and López-García 1998; López-García and Moreira 2006; Degli Esposti 2014).

Other than these accounts, the evolutionary origin of mitochondrial cristae is seldom discussed in a literature that increasingly focuses on genomes and metabolism (e.g., Müller et al. 2012; Burger et al. 2013). A major reason for this is that there was, until recently, no evidence for the evolutionary connection between cristae and ICMs beyond superficial morphological resemblance. Given the important role of MICOS in crista biogenesis, knowledge about its evolutionary history could shed light on the origin of mitochondrial cristae and the structural adaptation of mitochondria to ATP production. We, and others, recently showed that MICOS is an ancient mitochondrial protein complex of eukaryotes, and that its origin traces back to Alphaproteobacteria, the bacterial progenitors of mitochondria (Muñoz-Gómez, Slamovits, Dacks, Baier, et al. 2015; Muñoz-Gómez, Slamovits, Dacks, Wideman 2015; Huynen et al. 2016). These evolutionary and comparative analyses of MICOS tested the initial predictions of the more than three-decade-old "homology hypothesis", and revive the idea that mitochondrial cristae have a pre-endosymbiotic origin. The modern resurgence of this idea has relevant implications for the phylogenetic and phenotypic nature of the mitochondrial ancestor.

Here, we review recent discoveries on MICOS and make sense of them from an evolutionary perspective. We gather disparate evidence from diverse fields and assemble a coherent theoretical framework to understand the origin of mitochondrial cristae. This framework revolves around the notion that mitochondrial cristae likely evolved from intracytoplasmic membranes (ICMs) developed by alphaproteobacteria. We also explore the implications of this new view for the nature of the mitochondrial ancestor.

MICOS Has an Alphaproteobacterial Origin

MICOS is an ancient eukaryotic protein complex (Muñoz-Gómez, Slamovits, Dacks, Baier, et al. 2015; Huynen et al. 2016). The six MICOS subunits in yeast have homologues in humans (Zerbes et al. 2012; Pfanner et al. 2014). However, the phylogenetic distribution of MICOS extends to all eukaryotic diversity. At least three MICOS subunits (i.e., Mic60, Mic10 and Mic19) are also present in the other four major eukaryotic supergroups (i.e., amoebozoans, SAR, archaeplastids, and excavates) (Muñoz-Gómez, Slamovits, Dacks, Baier, et al. 2015). This widespread distribution points to an ancient and conserved mechanism of cristae development that relies on the formation of CJs and CSs (Muñoz-Gómez, Slamovits, Dacks, Baier, et al. 2015). A MICOS complex was already in place in the eukaryotic cenancestor (or the last eukaryotic common ancestor, LECA) to regulate the development of cristae and optimize the efficiency of aerobic respiration in mitochondria.

MICOS has even deeper evolutionary roots. The MICOS core subunit Mic60 is widespread among members of the Alphaproteobacteria—the progenitors of mitochondria. Moreover, alphaproteobacterial Mic60 (alphaMic60) exhibits the same overall structure as eukaryotic Mic60 containing an N-terminal transmembrane segment, followed by a central coiled-coil region, and a C-terminal mitofilin signature domain (Muñoz-Gómez, Slamovits, Dacks, Baier, et al. 2015; Huynen et al. 2016). These conserved features suggest that alphaMic60 localizes to the cytoplasmic membrane in alphaproteobacteria and that its function has likely been conserved as well. The alphaproteobacterial origin of Mic60 implies that MICOS predates the origin of mitochondria and therefore has a pre-endosymbiotic origin.

Mitochondrial Cristae Are Homologous to Alphaproteobacterial ICMs

Given the alphaproteobacterial origin of MICOS and its critical function in the development of mitochondrial cristae, it is possible that cristae also have a pre-endosymbiotic origin. This possibility attains particular significance with the observation that several members of the Alphaproteobacteria develop intracytoplasmic membranes (ICMs) that resemble some crista morphotypes (Drews 1992; Drews and Golecki 1995). The discovery of MICOS and its alphaproteobacterial roots now allows testing the hypothesis that mitochondrial cristae and alphaproteobacterial ICMs are homologous structures. Although direct experimental evidence for the involvement of alphaMic60 in ICM development is lacking, four main lines of evidence indicate that there has been a functional conservation in the evolution of eukaryotic Mic60 from alphaMic60. These include: (1) the presence of a mitofilin signature domain in alphaMic60 (Muñoz-Gómez, Slamovits, Dacks, Baier, et al. 2015; Huynen et al. 2016), (2) the structural conservation (same motif order and composition) between alphaMic60 and eukaryotic Mic60 (Muñoz-Gómez, Slamovits, Dacks, Baier, et al. 2015; Huynen et al. 2016), (3) the expression profile of alphaMic60 which reveals that alphaMic60 is overexpressed under conditions that promote ICM development in *Rhodobacter sphaeroides* (Callister et al. 2006), and (4) the localization of alphaMic60 to ICMs, as revealed by proteomic studies of isolated ICMs (i.e., chromatophores) of *Rhodobacter sphaeroides* (D'Amici et al.

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2010; Jackson et al. 2012), *Rhodospirillum rubrum* (Selao et al. 2011), and *Rhodopseudomonas palustris* (Fejes et al. 2003). These observations strongly suggest that MICOS performs the same general function in both mitochondria and alphaproteobacteria and that there has been a historical continuity between cristae and ICMs (fig. 1).

Alphaproteobacterial ICMs Are Functionally Analogous to Mitochondrial Cristae

A large and diverse number of alphaproteobacteria differentiate and enlarge their cytoplasmic membrane into a complex system of intracytoplasmic membranes (ICMs) that protrude into the cytoplasm (Drews 1992; Niederman 2006) (fig. 2). The general function of ICMs is to increase the surface area available for the biochemical processes that take place in them (Drews and Golecki 1995; Pinevich 1997). At least three physiological "groups" of Alphaproteobacteria develop extensive ICM systems: the anoxygenic photosynthesizers (purple nonsulfur bacteria; a strictly physiological, nonphylogenetic term), the methanotrophs, and the nitrifiers (nitrite-oxidizing alphaproteobacteria) (Drews 1992; Pinevich 1997; Niederman 2006) (fig. 2). In these "groups", ICMs allocate protein complexes or the enzymatic machinery required for diverse bioenergetic functions.

Most purple alphaproteobacteria (Rhodopirillales, Sphingomonadales, Rhodobacterales, and Rhizobiales) develop ICMs in the presence of light and the absence of oxygen (Drews 1992; Drews and Golecki 1995; Niederman 2006) (fig. 2*E* and *F*). Their ICMs house the photosynthetic apparatus and electron transport chain, which is generally composed of light-harvesting complexes 1 and 2 (LH1 and LH2), a type II reaction center (RC), a cytochrome bc_1, a periplasmic cytochrome c_2, and an ATP synthase. By means of cytochrome bc_1, which is also shared with the respiratory chain, the photosynthetic chain creates a proton motive force across the ICM that is harvested by the ATP synthase to produce energy (Niederman 2006). Methanotrophic alphaproteobacteria (Methylocystaceae and Beijerinckiaceae) use methane as a carbon and energy source (Tamas et al. 2014) (fig. 2*B*). The aerobic development of methanotrophic ICMs is strongly dependent on the expression of a particulate methane monooxygenase, the defining enzyme of methanotrophy (Hanson and Hanson 1996; Niederman 2006). The enzymes methanol dehydrogenase and formaldehyde dehydrogenase, which complete the oxidation of methane to formate, are also ICM-associated, being located in the intra-ICM space and the ICM, respectively (Zahn et al. 2001; Brantner et al. 2002). These three ICM enzymes are coupled to the methanotrophic respiratory electron transport chain and ultimately the conversion of energy to ATP (DiSpirito et al. 2004). The nitrifying alphaproteobacteria (the *Nitrobacter* genus) aerobically oxidize nitrite as their energy source (Ward et al. 2011) (fig. 2*A*). The enzyme nitrite oxidoreductase (NOR or NXR), which oxidizes nitrite into nitrate, is also membrane-bound and localizes at the cytoplasmic face of ICM membranes (Spieck et al. 1998). The reducing power derived from nitrite oxidation is subsequently funneled through the respiratory electron chain of nitrifiers to produce ATP (Yamanaka and Fukumori 1988).

The common feature of all the ICMs in these physiologically diverse groups of Alphaproteobacteria is their bioenergetic function. They all carry out processes that are tightly linked to the production of energy (ATP or reducing equivalents) (Drews and Golecki 1995). Primarily, ICMs increase the surface area to accommodate increasing numbers of components that are connected to an electron transport chain, and ultimately ATP synthesis. All ICM types, as well, sustain electron transport chains that share at least two components with a typical aerobic respiratory chain: a cytochrome *bc*1 complex, and the ATP synthase complex (Spieck et al. 1996; Zahn et al. 2001; Choi et al. 2003; DiSpirito et al. 2004); ICMs that develop aerobically (methanotorphic, nitrifying and some photosynthetic) might also harbor an oxygen-reducing cytochrome *aa*3 complex. In purple alphaproteobacteria, ICMs provide a larger surface area for capturing light through photosynthetic pigments, as well as for protein complexes of the photosynthetic machinery. In nitrifying and methanotrophic alphaproteobacteria, ICM systems harbor the enzymatic machinery required for chemolithotrophy, which is considered to give a relatively low bioenergetic yield. In summary, the development of ICMs in Alphaproteobacteria likely compartmentalizes their bioenergetic metabolism, thereby concentrating the enzymatic reactions that occur within the intra-ICM space and increasing overall bioenergetic efficiency. In this sense, ICMs are functionally analogous to the respiratory cristae of mitochondria.

Cristae and ICMs Follow Parallel Developmental Routes

The development of both alphaproteobacterial ICMs and mitochondrial cristae share similarities (fig. 3). The first steps of their development require the accumulation of the protein complexes that the two membrane systems harbour, i.e., photosynthetic complexes in purple alphaproteobacteria (Woronowicz et al. 2013; Niederman 2016), and respiratory complexes in mitochondria (Horvath et al. 2015) (fig. 3*A* and *D*). Some of these protein complexes serve as morphogenetic factors, e.g., RC-LH1, LH2 (Chandler et al. 2008; Qian et al. 2008) and mitochondrial ATP synthase (Paumard et al. 2002; Strauss et al. 2008; Davies et al. 2012), that introduce membrane curvature upon their oligomerization (fig. 3*A* and *D*). Concomitantly, the outgrowth of the inner (or cytoplasmic) membrane relative to the outer membrane contributes to the initial membrane invagination (Renken et al. 2002). The organization of diverse morphogenetic factors and the interaction between these and the lipid composition (e.g., cardiolipin and phosphatydilethanolamine in both mitochondria and alphaproteobacteria; McAuley et al. 1999; Kwa et al. 2008) of their surrounding membranes determine the overall morphology of the membrane system (fig. 3*B* and *E*). Mutants that do not express the whole photosynthetic machinery ($RC^{-}LH1^{-}LH2^{-}$ *Rba. spheroides* mutants), or the respiratory

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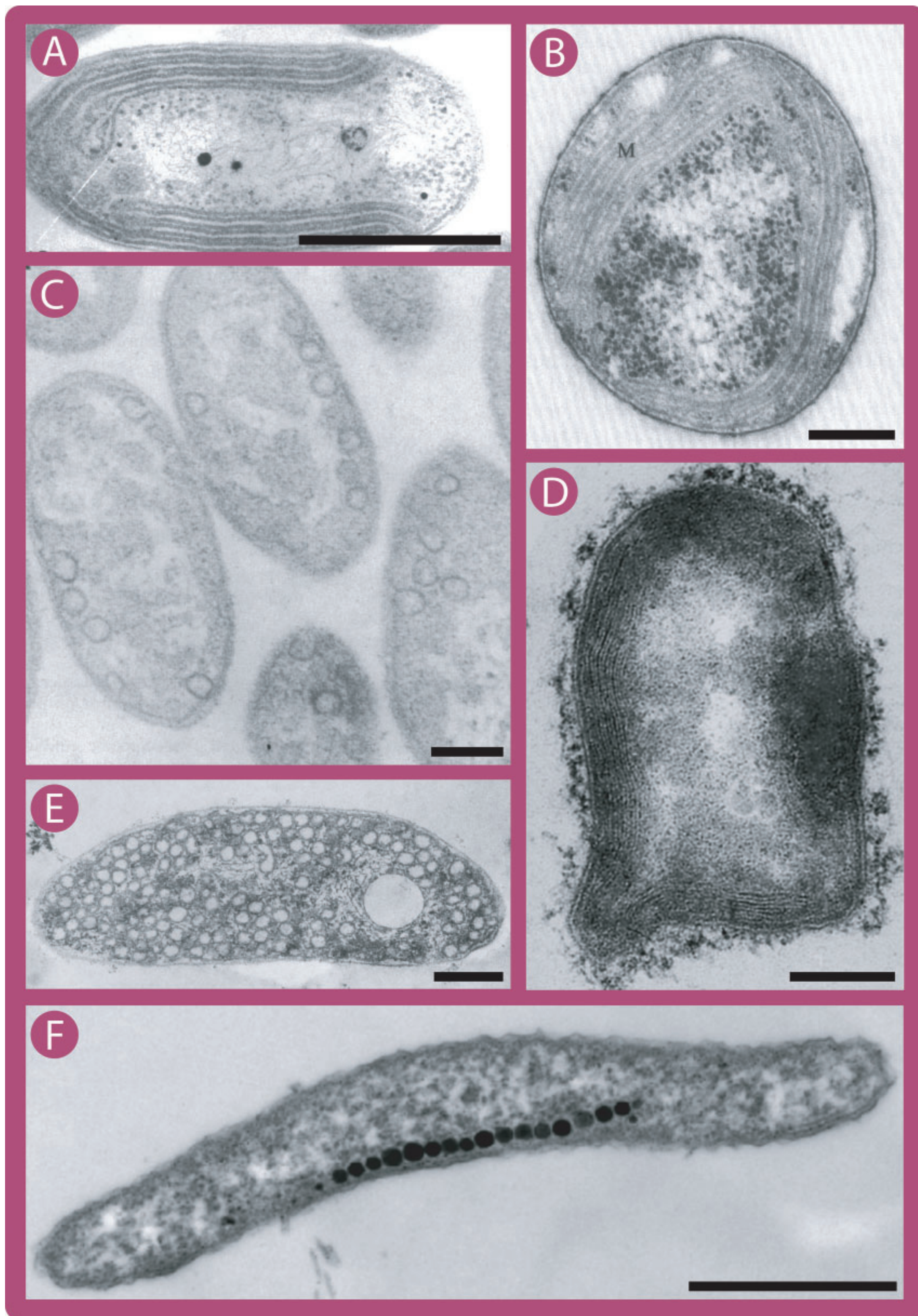

Fig. 2. Members of the Alphaproteobacteria develop morphologically diverse ICMs to carry out different bioenergetic functions. (*A*) *Nitrobacter winogradski* NB-255, a nitrifying alphaproteobacterium from the order Rhizobiales that develops flat ICMs at the cell periphery (scale bar: 1 μm; modified from Watson and Mandel 1971). (*B*) *Methylosinus trichosporium* OB3b, a methanotrophic alphaproteobacterium from the order Rhizobiales that develops flat ICMs at the cell periphery (scale bar: 0.2 μm; modified from Scott et al. 1981). (*C*) *Erythrobacter* sp. OCh114, an aerobic anoxygenic photosynthesizer from the order Rhodobacterales that develops few irregular and vesicular ICMs (scale bar: 0.2 μm; modified from Iba et al. 1988). (*D*) *Rhodoblastus sphagnicola*, an anaerobic anoxygenic photosynthesizer from the order Rhizobiales that develops flat ICMs at the cell periphery (scale bar: 0.5 μm; modified from Kulichevskaya et al. 2006). (*E*) *Rhodobacter capsulatus* (formerly *Rhodobacter capsulata*), an anaerobic anoxygenic photosynthesizer from the order Rhodobacterales that develops abundant vesicular ICMs (scale bar: 0.2 μm; modified from Kaufmann et al. 1982). (*F*) *Magnetospirillum gryphiswaldense*, a magnetotactic alphaproteobacterium from the order Rhodospirillales that develops ICMs in the form of magnetosomes to align itself along a geomagnetic field (scale bar: ~0.5 μm; modified from Schüler 2008).

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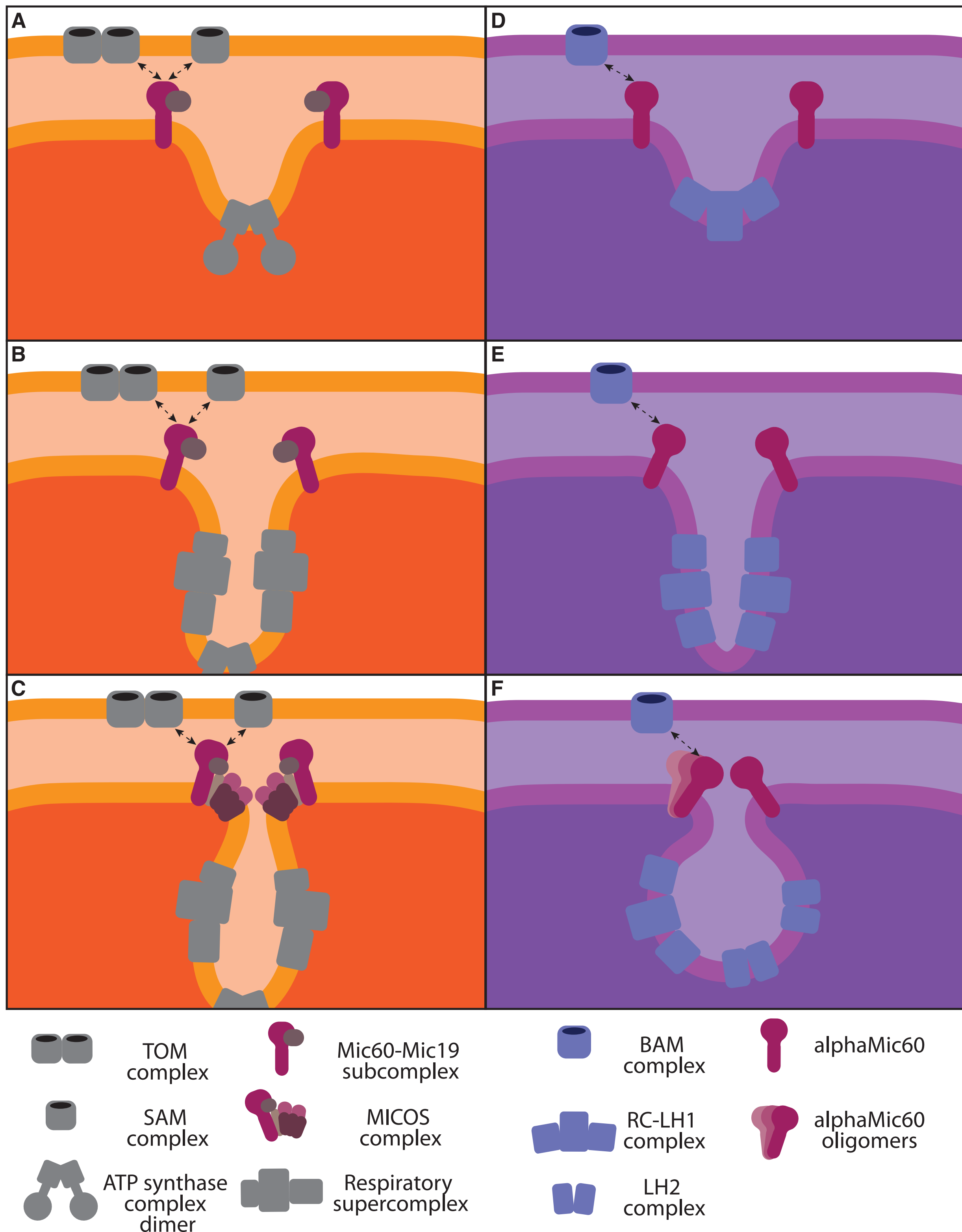

Fig. 3. Similar developmental routes lead to the compartmentalization of bioenergetic metabolism in mitochondrial cristae and alphaproteobacterial ICMs. (*A*) The Mic60–Mic19 subcomplex forms discrete foci at the mitochondrial envelope independently of other MICOS subunits. By its interaction with TOM and SAM at CSs, Mic60 initially marks the sites of crista development. Continuous insertion of new lipids (e.g., cardiolipin) and respiratory complex subunits, together with the oligomerization of ATP synthase complexes at nascent CMs, drive the initial invagination of cristae from the IBM. (*B*) The assembly of increasing numbers of respiratory complexes subsequently leads to an expansion of the CM surface area for respiratory purposes. Simultaneously, the redistribution of ATP synthase oligomers to cristal rims, and of respiratory complexes to flat CMs, start the compartmentalization of cristae and allow these sub-compartments to start assuming their final shape. (*C*) Crista development culminates with the formation and further stabilization of CJs by the MICOS complex. Once respiratory complexes have assembled at CMs,

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chain (mtDNA^{-} *rho* mutants), do not develop ICMs (Kwa et al. 2008) or cristae (Friedman et al. 2015), respectively. Finally, thin tubules (e.g., crista junctions and ICM junctions) connecting cristae to the mitochondrial inner membrane (Mannella et al. 1994), and ICMs to the cytoplasmic membrane (Konorty et al. 2009; Tucker et al. 2010), are formed to perform important structural and functional roles (fig. 3C and *F*). These thin tubules are stabilized and maintained by MICOS in mitochondria (John et al. 2005; Rabl et al. 2009; Harner et al. 2011; van der Laan et al. 2016), and hypothetically by alphaMic60 (alphaMICOS) in alphaproteobacteria (fig. 3C and *F*).

AlphaMic60 Likely Compartmentalizes Bioenergetic ICMs in Alphaproteobacteria

In order to create cristae, eukaryotic Mic60 engages in homotypic interactions with itself at CJs, and in heterotypic interactions with Sam50 and Tom40 at CSs between MIM and MOM (John et al. 2005; von der Malsburg et al. 2011; Körner et al. 2012; Ott et al. 2012) (fig. 1*A*). The structural conservation of alphaMic60 relative to eukaryotic Mic60 suggests that alphaMic60 possesses all the elements required for the formation of ICM junctions (ICMJs) and CSs at the cytoplasmic membranes of alphaproteobacteria (Muñoz-Gómez, Slamovits, Dacks, Baier, et al. 2015; Muñoz-Gómez, Slamovits, Dacks, Wideman 2015). A main function of alphaMic60 could then be the formation of ICMJs. These junctions between ICMs and the cytoplasmic membrane of alphaproteobacteria are functionally analogous to CJs in mitochondria and likely play a role in restricting the diffusion of metabolites between the ICM lumen and the periplasm (fig. 1*B*). Interestingly, the development of vesicular ICMs in *Rba. sphaeroides* and *Rsp. rubrum* necessarily requires the formation of tubular regions between the ICM and the cytoplasmic membrane (Tucker et al. 2010; Scheuring et al. 2014). The lamellar ICMs of *Blastochloris viridis* have been shown to be connected to one another and the cytoplasmic membrane by tubular structures similar to mitochondrial CJs (Konorty et al. 2008, 2009). Moreover, ICMJs can also aid in the differentiation of the ICM from the cytoplasmic membrane by limiting the lateral diffusion of protein complexes between these two membrane domains (fig. 1*B*). Similarly to CMs in mitochondria, ICMs clearly differ in composition, function and structure from the cytoplasmic membrane of alphaproteobacteria (Niederman 2006) (fig. 1). By creating ICMJs, alphaMic60 might compartmentalize the diverse bioenergetic metabolisms that take place in alphaproteobacterial ICMs (fig. 1*B*).

Synergistically with the formation of ICMJs, alphaMic60 might also be involved in the formation of CSs between the cytoplasmic membrane and the OM of the alphaproteobacterial envelope. This function would be analogous to the formation of CSs at the mitochondrial envelope, which requires Sam50 at the MOM as an interaction partner of eukaryotic Mic60 (Körner et al. 2012; Ott et al. 2012). In support of this hypothesis, Sam50 is homologous to the ubiquitous outer membrane (OM) protein BamA of Gram-negative bacteria (Heinz and Lithgow 2014). In addition, alphaproteobacterial BamA homologues harbor N-terminal POTRA domains responsible for their interactions with diverse protein partners (Simmerman et al. 2014), consistent with the interaction of Mic60 with the POTRA domain of Sam50 at mitochondrial CSs (Bohnert et al. 2012; Körner et al. 2012; Zerbes et al. 2012). CSs formed by alphaMic60 therefore anchor ICMJs to the alphaproteobacterial envelope and stabilize ICMs (fig. 1*B*). The maintenance and stability of alphaproteobacterial ICMs might therefore rely on the formation of CSs and ICMJs by alphaMic60 at the alphaproteobacterial envelope (fig. 1*B*).

Alternatively, alphaMic60 might play a more general role as the molecular basis of the CSs formed between the cytoplasmic membrane and the OM (also called Bayer's junctions) required for the proper biogenesis of the alphaproteobacterial envelope (Bayer 1991). Under this scenario, alphaMic60 would function in facilitating protein export by bringing together translocases of the cytoplasmic membrane (e.g., SecYEG) in contact with BamA or other OM complexes (fig. 1*B*). In modern mitochondria, Mic60 works similarly by interacting with the TOM (Tom40), MIA (Mia40) and SAM (Sam50) complexes to aid in protein import (von der Malsburg et al. 2011; Ott et al. 2012) (fig. 1*A*). Furthermore, Mic60 binds cardiolipin and, in partnership with Tom40, is involved in lipid transport between the MOM and MIM in *Arabidopsis thaliana* (Michaud et al. 2016). If this represents an ancestral function, then alphaMic60 could also be involved in the biogenesis of the alphaproteobacterial envelope by facilitating lipid transport between the cytoplasmic membrane and the OM at Bayer's junctions. The propensity of alphaMic60 to participate in protein–protein interactions (John et al. 2005; Rabl et al. 2009) through its coiled-coil

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Fig. 3. Continued
the assembly of the MICOS subcomplex Mic12–Mic10–Mic26–Mic28 proceeds by its coordination with both respiratory complexes and the lipid cardiolipin. Mic10 multimers bend the MIM at CJs, thereby stabilizing the strong negative curvature created at CJs. Both Mic19 and Mic12 act at the interface between the two MICOS subcomplexes and regulate their interaction. (*D*) Photosynthetic ICM development in purple nonsulfur bacteria initiates by the invagination of the cytoplasmic membrane induced by the increased assembly of membrane-deforming RC-LH1 complexes. It is hypothesized that the sites of ICM invagination are marked by CSs created by the interaction between alphaMic60 and the Sam50 homologue BamA. These CSs might primarily play a role in envelope biogenesis (i.e., Bayer's junctions). (*E*) The continuous assembly of RC-LH1 complexes leads to the expansion of the ICM area, and drives the tubulation of ICMs as demonstrated by *R. sphaeroides* LH2^{-} mutants that lack vesicular ICMs. (*F*) The subsequent insertion and assembly of LH2 antenna complexes introduce further positive curvature and produce the characteristic vesicular shape of *Rba. sphaeroides* ICMs (prokaryotic ATP synthase complexes do not dimerize; Kühlbrandt 2015). The final stage in ICM development is the formation of small membrane tubules (ICM junctions) that keep the ICM connected to the cytoplasmic membrane. We hypothesize that ICM junctions are maintained and stabilized by alphaMic60 oligomers and their interactions with OM complexes such as BamA at Bayer's junctions.

and mitofilin domains could have facilitated its exaptation to form CJs during the endosymbiotic origin of mitochondria.

Several of the functions reported for mitochondrial MICOS in yeast and mammalian cells (e.g., regulation of overall mitochondrial morphology, nucleoid transcription and maintenance, protein import and assembly; see Itoh et al. 2013; Friedman et al. 2015; Höhr et al. 2015; Horvath et al. 2015; Li et al. 2015; Yang et al. 2015) appear to be derived and specific to either fungi or animals, or all eukaryotes. This inference is based on the fact that most of them require protein interaction partners that have restricted phylogenetic distributions among eukaryotes (Muñoz-Gómez, Slamovits, Dacks, Wideman 2015). For this reason, we have instead focused on MICOS as a tether because this key function is most easily extrapolated to alphaproteobacterial envelopes. It assumes a structural role for alphaMic60 in aiding ICMJ formation, and/or making CS between the cytoplasmic membrane and the OM. These structural roles would function to (1) stabilize and maintain bioenergetic ICMs, or (2) serve in envelope biogenesis at Bayer's patches. Although logically separate hypotheses, they are not mutually exclusive and both functions might occur simultaneously in the same cell.

Photosynthetic ICMs Gave Rise to Other Types of ICMs during Alphaproteobacterial Diversification

The primary divergence in the phylogeny of Alphaproteobacteria appears to be between the endosymbiotic rickettsialeans and a large assemblage of alphaproteobacteria with diverse lifestyles and physiologies (the "free-living" alphaproteobacteria) (fig. 4A). Whereas rickettsialeans evolved by reduction as they adjusted to an endosymbiotic lifestyle inside eukaryotic cells, the basal radiations among the "free-living" alphaproteobacteria gave rise to diverse lineages of purple nonsulfur bacteria (as inferred from the distribution of photosynthesis in all the other major alphaproteobacterial orders; Williams et al. 2007; Wang and Wu 2015). This phylogenetic pattern points to a free-living alphaproteobacterial cenancestor that may have been capable of performing anoxygenic photosynthesis (see Swingley et al. 2009 and Koblížek et al. 2013 for evidence on the vertical inheritance of photosynthesis in Alphaproteobacteria). In addition, this ancestral alphaproteobacterium very likely developed bioenergetic ICMs to increase the efficiency of anoxygenic photosynthesis, as this is a ubiquitous adaptation among purple nonsulfur bacteria (Drews and Golecki 1995) (fig. 4A and B). The diversification of the "free-living" alphaproteobacteria from a photosynthetic ancestor likely produced the methanotrophic and nitrifying alphaproteobacteria (both of which have close photosynthetic relatives) within the Rhizobiales, which modified the ancestral photosynthetic ICMs to perform new bioenergetic roles (Tamas et al. 2014; Spieck and Bock 2015) (fig. 4A and B).

A subgroup of magnetotactic alphaproteobacteria, namely the *Magnetospirillum* genus, also evolved from purple nonsulfur bacteria (within the order Rhodospirillales; see fig. 4A). These bacteria develop magnetosomes, which are vesicular invaginations of the cytoplasmic membrane that biomineralize magnetite in their lumen that allow these bacteria to orient themselves within their microhabitats (fig. 2F). The development of magnetosomes among the magnetospirilla follows the same general pattern as that of the morphologically similar vesicular ICMs of purple nonsulfur bacteria like *Rba. sphaeroides* and *Rsp. rubrum* (Uebe and Schüler 2016; and fig. 3A–C). Magnetosomes probably evolved by recruiting part of the developmental machinery used by photosynthetic alphaproteobacteria to create ICMs (fig. 4B). In support of this inference, the magnetosome gene island (MAI) of the magnetospirilla (*Msp. gryphiswaldense* MSR-1, *Msp. magneticum* AMB-1 and *Msp. caucaseum* SO-1), which clusters the genes necessary for the formation of magnetosomes, includes a paralogoue of the *mic60* gene (Supplementary Material 1, Supplementary Material online), and its product is associated with the magnetosome membrane (Lohße et al. 2011). Moreover, the disruption of this gene leads to an increase in magnetosome size and a reduction in the number of magnetosomes (Lohße et al. 2014). These observations constitute strong evidence for a causal role of alphaMic60 in facilitating ICM development.

Alphaproteobacterial ICMs Transformed into Cristae after the Endosymbiotic Origin of Mitochondria

Given that the majority of alphaproteobacteria (with the possible exception of rickettsialeans) have a photosynthetic ancestry (Swingley et al. 2009; Koblížek et al. 2013; Wang and Wu 2015), and that most of their early evolution was dominated by this lifestyle (based on the wide distribution of phototrophs in Alphaproteobacteria), it is plausible that the ancestor of mitochondria was a purple nonsulfur bacterium with photosynthetic ICMs (fig. 4). Others have previously suggested that mitochondria could have had a photosynthetic ancestry based on different grounds (Woese 1977; Searcy 1992; Fenchel and Bernard 1993; Martin and Müller 1998; Cavalier-Smith 2006). The evolutionary history of MICOS is most compatible and best fits the notion that the mitochondrial ancestor was an ICM-developing alphaproteobacterium. And among the ICM-bearing alphaproteobacteria, the phylogenetic evidence points to a photosynthetic, rather than a methanotrophic or nitrifying, physiology for the ancestor of mitochondria and their cristae (see below). If mitochondria evolved from a purple nonsulfur bacterium, this was likely facilitated by the inheritance of a complex system of bioenergetic ICMs that increased the production of ATP (fig. 4B). In this sense, purple alphaproteobacteria are "pre-adapted" to become bioenergetic organelles, as they compartmentalize bioenergetic metabolism into their ICMs. Furthermore, the endosymbiosis between a heterotrophic host and a photosynthetic endosymbiont would have provided a stronger selective advantage for the initial symbiosis, as photosynthetic bacteria exude photosynthate (Smith and Wiebe 1976; Storrø et al. 1981; Wagner-Döbler et al. 2009; Seyedsayamdost et al. 2011; see also Cavalier-Smith 2006 and Cavalier-Smith 2007 for a detailed account

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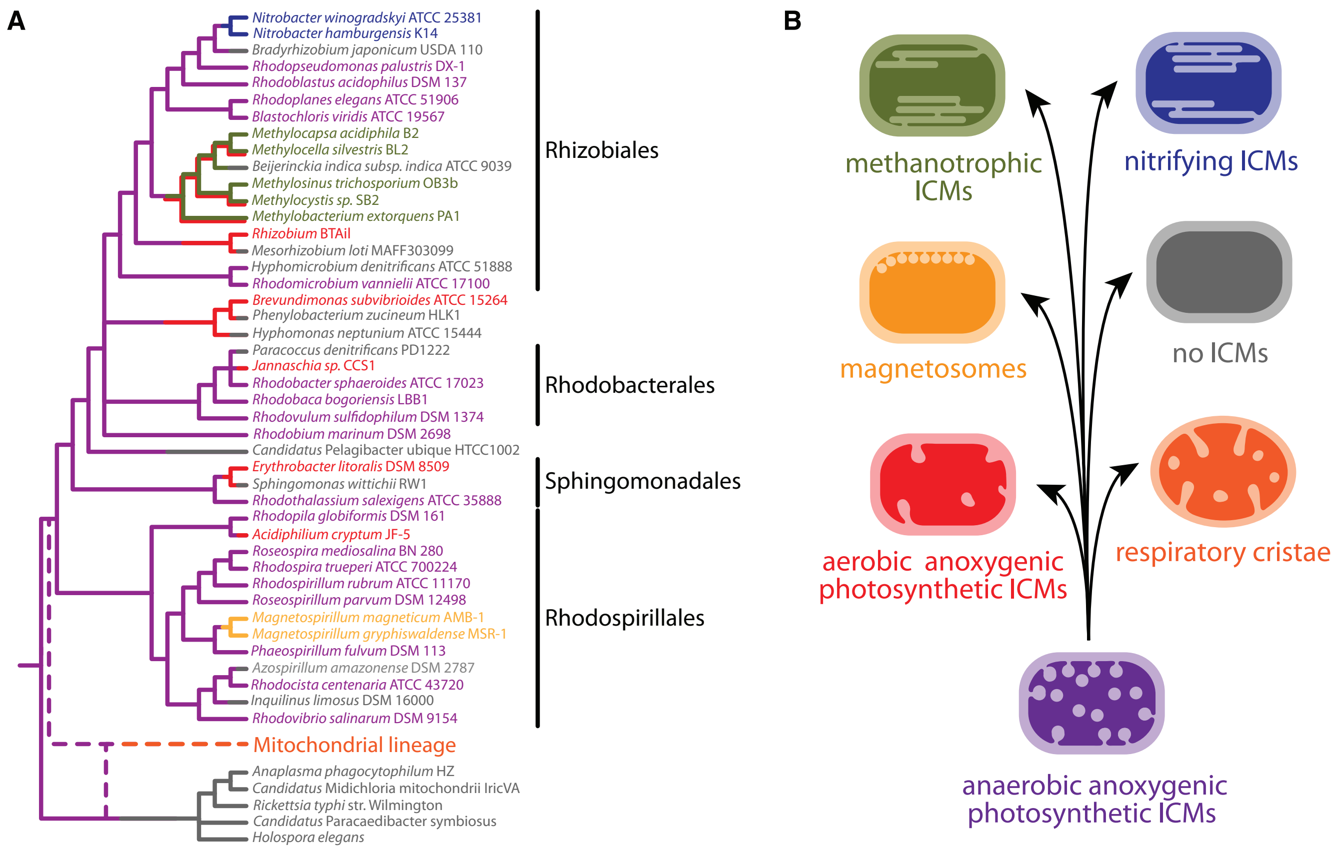

Fig. 4. Mitochondrial cristae could have evolved from photosynthetic ICMs. (*A*) The great diversification of the Alphaproteobacteria has given rise to a diverse array of ICM types. Colours indicate lineages that develop aerobic photosynthetic ICMs (red), anaerobic photosynthetic ICMs (purple), methanotrophic ICMs (green), nitrifying ICMs (blue), magnetosomes (light orange), respiratory mitochondrial cristae (dark orange), or no ICMs at all (grey). Phylogenetic relationships represent a consensus derived from the literature featuring all genera of purple nonsulfur bacteria within Alphaproteobacteria. Deep relationships between major lineages were drawn based on Wang and Wu (2013) and Wang and Wu (2015), whereas more shallow relationships followed 16S rRNA gene trees reported by Imhoff et al. (2005). During alphaproteobacterial diversification, anoxygenic photosynthesis was lost on numerous occasions (see main text). Both methanotrophy (e.g., *Methylocella silvestris*) and nitrification (e.g., *Nitrobacter winogradskyi*) evolved within the order Rhizobiales, whereas aerobic anoxygenic photosynthetic bacteria evolved several times independently from purple nonsulfur bacteria (anaerobic anoxygenic photosynthetic bacteria). Aerobic phototrophs are found in the orders Rhizobiales (e.g., *Methylobacterium extorques*), Rhodobacterales (e.g., *Jannaschia* sp.), Sphingomonadales (e.g., *Erythrobacter litoralis*), and Rhodospirillales (e.g., *Acidiphylium cryptum*) (see also fig. 2*C*). Although the exact phylogenetic placement of the mitochondrial lineage within Alphaproteobacteria is still uncertain (shown as dashed lines), it has deep roots within the group. (*B*) Photosynthetic ICMs gave rise to functionally diverse ICMs and mitochondrial cristae. Whether the mitochondrial lineage evolved from a basal purple alphaproteobacterium, or an ancestral endosymbiotic rickettsialean, the nature of the pre-mitochondrion could have been photosynthetic. Photosynthetic ICMs (in purple) could have directly been transformed into the respiratory cristae (in dark orange) of mitochondria. As alphaproteobacteria diversified, photosynthetic ICMs were exapted to support other bioenergetic metabolisms, such as methane oxidation (in green) and nitrification (in blue), which similarly require an increased membrane area. The ancestral ICMs were lost several times when anoxygenic photosynthesis (or any other intensive bioenergetic metabolism) was abandoned during evolutionary specialization to a new niche (in grey). Anaerobic photosynthetic ICMs also gave rise to the poorly developed ICMs with the decreased bacteriochlorophyll content (in red) observed in some aerobic anoxygenic photosynthetic bacteria (see also fig. 2*C*). Furthermore, the magnetospirilla that evolved from rhodospirillalean photosynthetic ancestors co-opted *mic60* to aid in the development of magnetosomes (light orange).

on the benefits of a photosynthetic over a heterotrophic endosymbiont). This situation parallels the origin of plastids, which also originated by the endosymbiosis between a heterotrophic host and a photosynthetic cyanobacterium (although oxygenic instead of anoxygenic), which was capable of developing extensive ICM systems (i.e., thylakoids) for energy harvesting.

Under the scenario that a purple nonsulfur alphaproteobacterium gave rise to mitochondria, we surmise that photosynthetic ICMs were transformed into mitochondrial cristae during the co-evolutionary integration of the alphaproteobacterial endosymbiont (fig. 4*B*). This change required the loss of the photosynthetic machinery (the RC-LH1, and LH2 complexes) and the relocation of dehydrogenases and terminal oxidases to the newly evolving respiratory cristae (the cytochrome bc_1 complex and ATP synthase already had an ICM localization)—some purple nonsulfur bacteria, e.g., *Rhodocista centenaria*, might fully express an aerobic respiratory chain along their photosynthetic machinery because they can exceptionally develop extensive ICMs under high oxygen pressures (Yildiz et al. 1991; Nickens et al. 1996).

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This alteration probably occurred during the increased specialization of the ancestral eukaryote to an aerobic lifestyle, which also led to the loss of facultative components of the respiratory chain, such as the *bd* and *cbb*$_3$ terminal oxidases (Degli Esposti et al. 2014). As the expression pattern of alphaMICOS was already the same as that of heme biosynthesis genes (Huynen et al. 2016), it simply needed to be slightly adjusted to meet the need of an increasingly overexpressed respiratory chain. During the specialization of the alphaproteobacterial endosymbiont as a respiratory organelle, cristae were further refined in their role as bioenergetic subcompartments, and MICOS was expanded and acquired new roles in the biogenesis of mitochondria (van der Laan et al. 2012; Wideman and Muñoz-Gómez 2016).

Although the exact phylogenetic placement of the mitochondrial lineage within Alphaproteobacteria is still uncertain (mostly because of the propensity for phylogenetic artefacts when using mitochondrial sequence data, e.g., see Rodríguez-Ezpeleta and Embley 2012; Ferla et al. 2013), there seems to be little doubt that mitochondria have deep roots within Alphaproteobacteria (Rodríguez-Ezpeleta and Embley 2012; Thiergart et al. 2012; Wang and Wu 2015). A deep phylogenetic origin from within Alphaproteobacteria is compatible with either a free-living (photosynthetic) or an endosymbiotic (parasitic?) ancestry of mitochondria, but less harmonious with a methanotrophic or nitrifying ancestry (fig. 4). Some recent phylogenetic analyses have allied the mitochondrial lineage with the order Rickettsiales, which is entirely composed of endosymbiotic alphaproteobacteria of diverse eukaryotes (Sassera et al. 2011; Wang and Wu 2014, 2015). If this phylogenetic pattern is further corroborated, it would become more likely that the ancestor of mitochondria was an intracellular endosymbiont that did not develope ICMs for energy production, as these have not been observed among rickettsialeans.

Under the scenario that mitochondria evolved from an endosymbiotic rickettsialean, mitochondrial cristae did not evolve directly from alphaproteobacterial ICMs, but are deeply homologous to them. That is, both structures evolved separately by independently recruiting alphaMic60, which was performing a related, but more general function at alphaproteobacterial envelopes (i.e., the formation of CSs). This is plausible given that alphaMic60 is found in alphaproteobacteria not known to develop ICMs (Supplementary Material 2, Supplementary Material online), but is also clearly enriched in the photosynthetic ICMs of purple alphaproteobacteria (Fejes et al. 2003; D'Amici et al. 2010; Selao et al. 2011; Jackson et al. 2012). Due to its capability to engage in homotypic interactions and create CSs between apposing membranes, alphaMic60 likely stabilizes the development and facilitated the evolution of both cristae and ICMs.

Conclusions and Prospects

MICOS is a major multi-protein complex of mitochondria that is responsible for creating efficient respiratory subcompartments. By serving a structural role at the mitochondrial envelope, MICOS creates CSs and CJs to stabilize and maintain mitochondrial cristae. The evolution of this important multiprotein complex, specifically its core subunit Mic60 (containing a signature mitofilin domain), can be traced back to the common ancestor of the Alphaproteobacteria. This evolutionary innovation appears to coincide with the origin of photosynthesis among alphaproteobacteria, and therefore also the origin of extensive ICM systems for anoxygenic photosynthesis. alphaMic60 might have evolved to facilitate the development of photosynthetic ICMs among purple alphaproteobacteria, or more generally, the biogenesis of the alphaproteobacterial envelope. Photosynthetic ICMs would have later diversified to perform different bioenergetic functions among other alphaproteobacteria. During the early evolution of eukaryotes, mitochondria might have evolved from a purple nonsulfur bacterial ancestor (i.e., a photosynthetic alphaproteobacterium) that made use of ICMs to improve its bioenergetic efficiency. Mitochondrial cristae thus could have evolved by the transformation of ancestrally photosynthetic ICMs, and therefore have had a pre-endosymbiotic origin.

We synthesize the evidence for the involvement of alphaMic60 in the development of alphaproteobacterial ICMs. More specifically, we have argued that alphaMic60 likely creates ICMJs and CSs at the alphaproteobacterial envelope to anchor, stabilize and compartmentalize bioenergetic ICMs. These new ideas make testable predictions which, we hope, will guide future experimental research in the field. They predict that the disruption of alphaMic60 would lead to the detachment of ICMs from the cytoplasmic membrane and the loss of ICMJs, in analogy to the disruption of MICOS in mitochondria. Alternatively, MICOS disruption would result in the loss of CSs at the alphaproteobacterial envelope, or the impairment in the export and assembly of envelope proteins and lipids. The functional dissection of alphaMic60 in a model alphaproteobacterium such as *Rba. spheroides* or *Rps. palustris* will eventually test whether alphaproteobacterial ICMs are homologous to mitochondrial cristae. Filling in these details will greatly enhance our understanding of the evolution of the mitochondrion, and ultimately, the evolution of eukaryotes.

Supplementary Material

Supplementary data are available at *Molecular Biology and Evolution* online.

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