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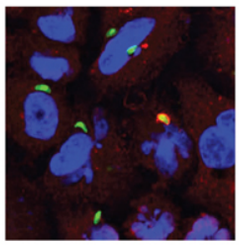

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The evolution of MICOS: Ancestral and derived functions and interactions

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The MItochondrial Contact Site and Cristae Organizing System (MICOS) is required for the biogenesis and maintenance of mitochondrial cristae as well as the proper tethering of the mitochondrial inner and outer membranes. We recently demonstrated that the core components of MICOS, Mic10 and Mic60, are near-ubiquitous eukaryotic features inferred to have been present in the last eukaryote common ancestor. We also showed that Mic60 could be traced to α-proteobacteria, which suggests that mitochondrial cristae evolved from α-proteobacterial intracytoplasmic membranes. Here, we extend our evolutionary analysis to MICOS-interacting proteins (e.g., Sam50, Mia40, DNAJC11, DISC-1, QIL1, Aim24, and Cox17) and discuss the implications for both derived and ancestral functions of MICOS.

Keywords: evolutionary cell biology, MICOS, mitofilin, MCS, membrane contact sites

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MICOS Structure and Function

Mitochondrial cristae, the sites at which aerobic respiration occurs, are specialized subcompartments derived from invaginations of the mitochondrial inner membrane (MIM).[1,2] Cristae biogenesis and maintenance have been shown to strongly depend on a protein complex called MICOS (MItochondrial Contact Site and Cristae Organizing System).[3-5] In *Saccharomyces cerevisiae* MICOS is composed of 6 subunits: Mic10, Mic12, Mic19, Mic26, Mic28 (Aim37), and Mic60.[6,7] In humans, MICOS is also composed of 6 subunits; it differs from yeast's MICOS by lacking Mic12, but containing Mic25 (a paralogue of Mic19) and Mic27 (a paralogue of Mic26).[8,9] The study of MICOS in *S. cerevisiae* and *Homo sapiens* has characterized both Mic10 and Mic60 as the 2 most functionally important subunits of MICOS.[10,11]

In mitochondria, MICOS has 2 primary functions: (i) to create/maintain crista junctions (CJs), and (ii) to anchor CJs to the mitochondrial outer membrane (MOM). These two functions synergistically control the development of cristae, and stabilize and maintain these as respiratory subcompartments. It is also hypothesized that, by localizing at CJs, MICOS dynamically differentiates the MIM into 2 functionally distinct domains: the inner boundary membrane (IBM) and the crista membrane (CM).[12,13] Mic60 is the central MICOS subunit responsible for these functions. Mic60 has an N-terminal trans-membrane domain with central coiled-coil and C-terminal Mitofilin domains, both exposed at the inter-membrane space (IMS). These IMS domains mediate homotypic and heterotypic interactions to maintain crista junction architecture and establish contact sites between the MIM and MOM, respectively.[3,14,15]

By creating tubular membrane structures (i.e., CJs), MICOS introduces membrane tension in the form of negative curvature.[16] Two recent studies demonstrated that the bending of the IBM at CJs is performed by the oligomerization of the second MICOS core subunit, Mic10.[17,18] Two MICOS subunits, Mic26 and Mic28, are apolipoproteins that bind the characteristic mitochondrial lipid cardiolipin.[19] It is suspected that MICOS regulates and distributes cardiolipin between the IBM and the CM, further differentiating these 2 MIM domains.[20] Furthermore, MICOS

exists as 2 dynamic subcomplexes, a Mic60-Mic19 (Mic60-Mic19-Mic25 in humans) subcomplex, and a Mic26-Mic10-Mic12 (Mic26-Mic10-Mic27 in humans) subcomplex.[21,22] It has also been recently shown that the interaction between these 2 subcomplexes is mediated by the peripheral IMS subunit Mic19.[21] MICOS, therefore, combines the different non-redundant functions of its subunits to create CJs and regulate the differentiation of the MIM into cristae.

We recently investigated the evolutionary history of the MICOS complex.[9] Our analyses revealed that the common ancestor of all eukaryotes made use of a MICOS comprising at least 2 subunits, Mic10 and Mic60, but probably also Mic19. The extra MICOS subunits of *S. cerevisiae* and *H. sapiens* were acquired during the evolution of opisthokonts (animals, fungi and their protistan relatives). Despite the ubiquity of MICOS across eukaryotic diversity, anaerobic lineages that exhibit reduced acristate mitochondria have lost all MICOS genes. Strikingly, we also discovered a prokaryotic homolog of Mic60 unique to the α-proteobacteria, the progenitor lineage of mitochondria.[9] This led us to suggest that MICOS has a pre-endosymbiotic origin and that mitochondrial cristae were inherited from membrane invaginations, or intracytoplasmic membranes (ICMs), present in α-proteobacteria. Furthermore, the evolutionary stasis of Mic60 structure and the sequence conservation of its Mitofilin domain suggest that the 2 primary functions of MICOS are ancestral to mitochondria in eukaryotes, and that prokaryotic Mic60 is important for the development and maintenance of α-proteobacterial ICMs and contact sites (Bayer's junctions).

MICOS Secondary Interactors and Functions

The discovery of interactions between MICOS and several protein partners/complexes at the mitochondrial envelope suggests additional roles for MICOS in mitochondrial biogenesis. These interacting proteins include Tom40 of the TOM (Translocase of the Outer Mitochondrial membrane) complex, Sam50 of the SAM (Sorting and Assembly Machinery) complex, VDAC (Voltage-Dependent Anion Channel), Mia40, and Ugo1.[3-5,23-25] The interaction of MICOS with TOM and Mia40 positions both complexes in close proximity for the correct oxidative folding of translocated proteins.[3,25,26] Similarly, the interaction of MICOS with both TOM and SAM is presumed to bring together both translocases for the efficient transfer of β-barrel proteins from one complex to the other.[23-25] By interacting with VDAC, MICOS is hypothesized to enrich it in the vicinity of CJs, therefore increasing the diffusion of metabolites into the intracristal space.[5,27] Finally, the interaction of MICOS with Ugo1 suggests the involvement of MICOS in mitochondrial fission, although the precise function of this interaction remains uncertain.[4] This multiplicity of interactions has recently led to the view that MICOS also functions as the protein scaffold of a larger network of protein complexes termed ERMIONE (ER-mitochondria organizing network) that controls mitochondrial function and biogenesis in *S. cerevisiae*.[27]

Several other proteins have been shown to physically interact with MICOS. These proteins include DNAJC11,[28] DISC-1,[29] and QIL1 in humans;[30] and Aim24,[31] and Cox17 in *S. cerevisiae*.[32] Some of these might be lineage-specific *bona fide* members of MICOS, although most of them are probably transient interactors. The functional context for some of these interactions remains unknown (e.g., DNAJC11, DISC-1), whereas some of these protein partners appear to be MICOS stabilizing/modulating subunits or factors (e.g., QIL1, Aim24, and Cox17).

In order to infer whether these interactions are ancestral or derived features of MICOS, we investigated the phylogenetic distribution of these MICOS-interacting proteins (**Fig. 1**). We show that Sam50, Mia40, Cox17, and DNAJC11 are widely distributed among eukaryotic diversity, suggesting their ancestral nature. Sam50 is ubiquitous among mitochondria, but was not detected in *Giardia intestinalis*. This distribution is largely congruent with that of other mitochondrial β-barrels, Tom40 and VDAC, previously analyzed by some of us.[33] Mia40 is also widespread, but absent from most acristate eukaryotes, as well as from members of SAR (i.e., stramenopiles, alveolates, and rhizarians) and discicristates (e.g.,, *Naegleria gruberi*, *Bodo saltans*, *Trypanosoma brucei* and *Leishmania major*). Cox17 and DNAJC11 are similarly widespread, but show more irregular distributions. On the other hand, Aim24, Ugo1, QIL1, and DISC1 have more restricted phylogenetic distributions. Both Aim24 and Ugo1 are specific to the Holomycota (fungi and their amoeboid relatives, e.g., *Fonticula* and nucleariids), only absent from the divergent microsporidians and Cryptomycota (*Rozella allomycis*). DISC1 appears to be present among animals and some of their single-celled relatives (e.g., choanoflagellates), whereas QIL1 is only found among animals (**Fig. 1**). Interestingly, with the exception of *Piromyces* sp., lineages that lack MICOS (i.e., microsporidians, *Entamoeba histolytica*, *G. intestinalis*, and *Trichomonas vaginalis*) also lack all MICOS-interacting proteins (with the exception of the ubiquitous and essential Sam50).

MICOS Functional Evolution

MICOS' functions that depend on components present in both mitochondria and α-proteobacteria are inferred to have a pre-endosymbiotic origin. These include the formation of neck-like membrane structures that depend on homotypic interactions between Mic60 subunits, and the creation of contact sites between enveloping membranes that depend on heterotypic interactions between Mic60 and the POTRA domain of Sam50.[9] In bacteria, the core component of the BAM complex, BamA, comprises POTRA domains and a β-barrel domain and is a homologous to Sam50.[34] The BAM complex is required for β-barrel assembly in the outer membrane of bacteria.[35] Since MICOS-mediated contact sites in mitochondria facilitate the transfer of proteins from TOM to SAM during β-barrel protein import and assembly, it is attractive to hypothesize that α-proteobacterial Mic60 could be similarly involved in β-barrel export by positioning appropriate secretion complexes in the cytoplasmic membrane near BAM complexes in the outer membrane. Our current experimental

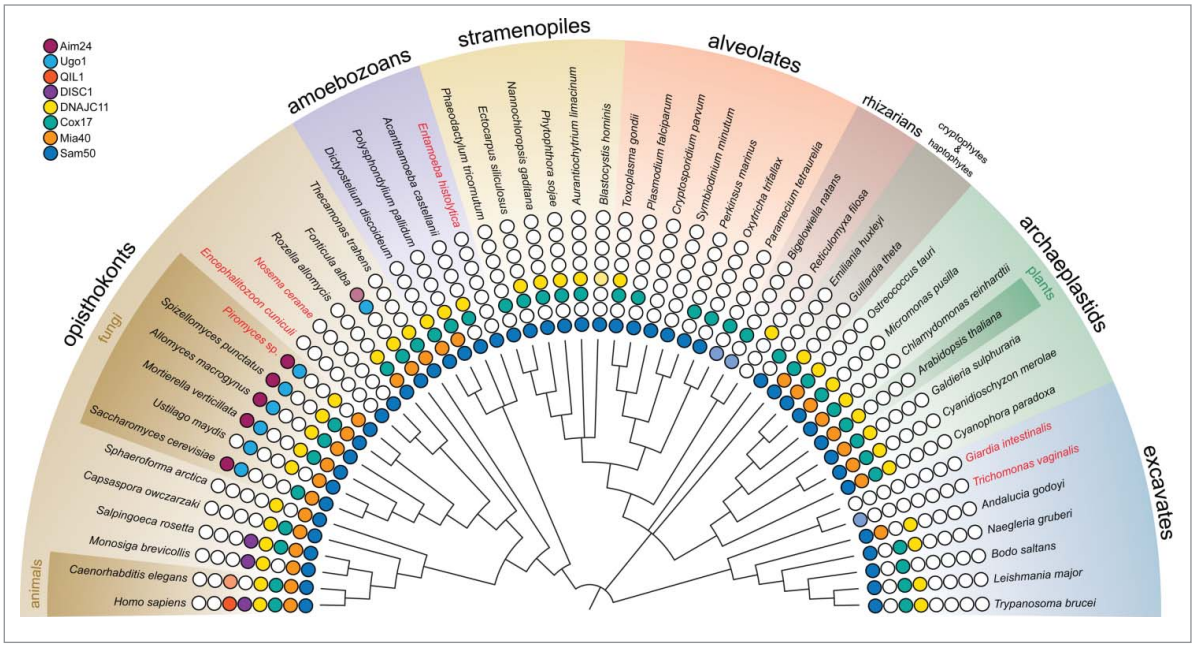

Figure 1. Phylogenetic distribution of MICOS-interacting proteins. Homology searching was performed as previously described (Muñoz-Gómez et al. 2015). Briefly, MICOS-interacting proteins Aim24, Ugo1, QIL1, DISC1, DNAJC11, Cox17, Mia40 and Sam50 from *S. cerevisiae* and/or *H. sapiens* were used as BLAST queries in searches into predicted proteomes of diverse eukaryotes. Sequences were retained as putative orthologues only if, when used as BLAST queries in searches into *S. cerevisiae* or *H. sapiens* protein databases, the original query sequences were retrieved as the best hit. The collected sequences were used to construct hidden Markov models (HMMs) that were used to search eukaryote protein databases for divergent homologues. All sequences that were hit with an e-value lower than 0.05 were then used in reciprocal pHMMER searches into protein databases from organisms with bioinformatically validated orthologues. If a validated sequence was retrieved as the best hit in any organism, then the sequence was retained. Species in red are those that have lost MICOS.[9] Light color circles indicate potential orthologues with weaker sequence similarity. In the case of Sam50, highly divergent ciliate candidate orthologues were found using PsiBLAST with the closest available Sam50 gene sequence (e.g., *Chromera velia* Cvel_14064). Although we could not detect a Sam50 ortholog in *Trichomonas vaginalis* with our bioinformatics methods, its presence in *T. vaginalis* hydrogenosomes is supported by experimental data previously reported.[41,42].

research aims to understand the function of Mic60 in α-proteobacteria, and therefore whether CJ and CS formation, and Mic60-mediated β-barrel assembly, predates the evolution of mitochondria or represent derived eukaryotic functions.

After the endosymbiotic origin of cristae, and prior to the diversification of modern eukaryotes, MICOS acquired both Mic10 and Mic19 as new subunits.[9] The addition of Mic10 to MICOS as a morphogenetic factor that creates curvature at CJs further increased the differentiation of the bioenergetic membranes (i.e., CM) from the IBM, effectively creating 2 MIM domains. Mic19 likely evolved to mediate the interaction between Mic60 and Mic10 oligomers. However, it must not be overlooked that Mic19 has not been identified in several eukaryote groups, which brings forth the possibility that Mic10 and Mic60 do not interact in some lineages. Nonetheless, the newly discovered functions of Mic10 and Mic19, namely the curving of the MIM at CJs and the linking of both MICOS subcomplexes,[17,18,21,22] respectively, highlight their functional importance in MICOS, and further validate our original evolutionary analyses that concluded their presence in the ancestral eukaryotic MICOS. Moreover, the presence of Mic10 in *Cryptosporidium parvum* explains the convoluted morphology of its MIM in the absence of CJs (i.e., in the absence of structurally defined cristae).

MICOS' functions in mitochondrial protein import can be inferred to have evolved after the origin of mitochondria. In support of this, TOM and Mia40 are considered eukaryotic inventions present in diverse eukaryote lineages (**Fig. 1**).[33,36-38] Interestingly, although Tom40 is a virtually ubiquitous mitochondrial feature, Mia40 is absent in SAR and discicristates, potentially indicating that MICOS lost its interaction with this system more than once. This divergence of character has yet to be explained. It is conceivable that Mia40 has been replaced by an analogous protein in these lineages or that the interaction of MICOS and Mia40 is an opisthokont-specific phenomenon.

Finally, DNAJC11 and Cox17 are widespread among eukaryotes, but their functional significance and interaction with MICOS requires further investigation. Other MICOS-interacting proteins and functions evolved more recently. For example, MICOS connection with the mitochondrial fusion machinery evolved after the divergence of animals and fungi, as Ugo1 is restricted to *Fonticula alba* and fungi. Similarly, the MICOS stabilizing factor Aim24 is a fungal innovation (eukaryotic Aim24 homologues exist outside fungi, but are more similar to bacterial homologues than the fungal proteins), whereas the metazoan-specific protein

QIL1 likely evolved to perform a similar function among animals. These lineage-specific MICOS-interacting proteins point to the inherent evolvability of MICOS and suggest that numerous other interactions likely evolved in other understudied eukaryote lineages.

Conclusions

Interactions between MICOS and protein partners are inferred based on their phylogenetic co-occurrence. However, the co-existence of protein interactors in a compartment does not guarantee that they have co-evolved to interact in another eukaryotic lineage. It is possible that some of these interactions are derived, having been only recently established in a specific eukaryotic lineage. These proteins have to be functionally investigated in other eukaryotes to validate their predicted mitochondrial localization and interaction with MICOS. Moreover, derived MICOS-interacting proteins or functions restricted to within animals and fungi suggest that several uncharacterized MICOS functions and interactions have evolved across eukaryotic diversity. Again, we stress that to understand MICOS and cristae evolution in eukaryotes, MICOS structure and function must be investigated in diverse eukaryotes beyond animal and fungal models.

The progressive integration of mitochondria with cellular functions has led to an expanded protein interaction network, and the establishment of MICOS as a major protein scaffold for mitochondrial biogenesis.[27,39] MICOS, and its multiple interactors, highlight the co-evolution of protein complexes at the mitochondrial envelope during the integrative evolution of mitochondria.[40-43] As new protein interactions were gained in a lineage-specific manner, new MICOS functions evolved. These new interactions could have evolved by a combination of adaptive and non-adaptive (ratchet-like) processes.[44,45] The presence of paralogous MICOS subunits in vertebrates and Saccharomycetales supports the latter evolutionary mode.[9] In *S. cerevisiae*, as should be the case for any other eukaryote lineage, MICOS combines both ancestral and more recently acquired functions. The functional evolution of MICOS in eukaryotes, therefore, tells a story of inheritance of conserved ancestral functions from α-proteobacteria, followed by the acquisition of ancient derived mitochondrial functions before the diversification of modern eukaryotic lineages, and then finally, the subsequent gain of lineage-specific functions and interactions.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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