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VIEWPOINT

Mitochondrial sites of contact with the nucleus

Michelangelo Campanella^{1,2,3}  and Brindha Kannan¹ 

Membrane contact sites (MCS) between mitochondria and the nucleus have been recently described. Termed nucleus associated mitochondria (NAM), they prime the expression of genes required for cellular resistance to stressors, thus offering a tethering mechanism for homeostatic communication. Here, we discuss the composition of NAM and their physiological and pathological significance.

Introduction

In eukaryotes, homeostatic regulation involves the coordinated interaction between intracellular organelles that operate in close and confined proximity. Mitochondrial contact sites (MCS) are emerging key mediators of cellular signaling determining the transfer of metabolites such as ions, proteins, and lipids (Scorrano et al., 2019). MCS contributes to the preservation of organelle identity, biogenesis, and morphology. Essential to tissue development and homeostasis, MCS govern areas of proximity between heterologous or homologous membranes that are key to the preservation of core functions. Aberrations in MCS consequently are involved in the formation and progression of malignancies as well as neuronal degeneration. The importance of understanding the composition and function of MCS is therefore pivotal to inform processes at the basis of cell physiology. MCS require molecular tethers between organelles, with abnormalities of these molecules being linked to a variety of cellular and pathophysiological processes (Scorrano et al., 2019; Voetz et al., 2024).

The initial functional relevance of MCS was attained through studies of the second messenger Ca²⁺ described to be transferred from the Sarco/endoplasmic reticulum (ER) to mitochondria through a site of juxtaposition between the two organelles (Rizzuto et al., 1998). Since then, the repertoire of known MCS has rapidly expanded with the

findings of contacts between numerous organelles including ER-mitochondria, ER-plasma membrane (PM), ER-Golgi, ER-lipid droplets, ER-endolysosomes, lipid droplets and degradative organelles, PM-mitochondria, mitochondria-lysosomes, and most recently the nucleus associated mitochondria (NAM) between mitochondria and the nucleus. Here, we will discuss recent insights into the composition and function of the MCS between mitochondria and the nucleus in mammalian cells, yeast, and pathogens like *Plasmodium falciparum* and *Toxoplasma gondii*.

The mitonuclear interaction in mammals

Past studies had hinted at the existence of mitochondria in proximity to the nucleus (see Prachar [2003]), but a physical interaction between the two had not been explicitly proposed or discussed.

The first evidence of such contacts was attained by the scrutiny of the mitochondrial redistribution in proximity of the nucleus during activation of the mitochondrial retrograde response (MRR) triggered by cellular stress (Desai et al., 2020). These sites of inter-organelle interaction, named the NAM, have a crucial role in priming pro-survival gene expression, thereby determining cellular protection against damaging cues, may these be acute or chronic (Strobbe et al., 2021).

Stabilization of the outer mitochondrial membrane (OMM) based translocator protein

(TSPO) (Gatliff and Campanella, 2016) proved to be pivotal for the mitochondrial redistribution and their subsequent contact with the nucleus (Desai et al., 2020). TSPO and its interacting partners the A-kinase anchoring protein acyl-coenzyme A binding domain containing 3 and the protein kinase A, interact with the A-kinase-anchoring protein AKAP95 on the nucleus. This complex tethers the two organelles within a range typical for MCS (>30 nm).

NAM formation is negatively regulated by the autophagic removal of mitochondria (or mitophagy), a process counteracted by TSPO (Gatliff et al., 2014). The overexpression (or stabilization) of TSPO, in response to MRR-inducing stimuli, traps cholesterol on the OMM. The juxtaposition of mitochondria and nucleus traffics the excess of cholesterol into the nucleus aiding the transcriptional activity of the NF-κB (Desai et al., 2020).

Mitochondria-to-nucleus tethering also allows a non-canonical nuclear entry pathway of the mitochondrial pyruvate dehydrogenase complex (PDC) (Zervopoulos et al., 2022). PDC is a macromolecular enzymatic complex that sits in the inner mitochondrial membrane and, in response to proliferative stimuli, crosses the nuclear envelope through the NAM, to interact with the nuclear lamina protein Lamin A in areas away from the nuclear pore complexes (NPCs). PDC redistribution into the nucleus

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is therefore independent from NPCs but requires the Lamin interaction facilitated by NAM formation. Most notably, nuclear PDC (nPDC) aids histone acetylation through acetyl-CoA (Zervopoulos et al., 2022), corroborating a direct role for NAM in the regulation of nuclear metabolism previously reported in Desai et al. (2020). Furthermore, this subsequent evidence suggested that other mitochondrial proteins, beyond TSPO, may be involved in the dynamic of organelles juxtaposition. In this very case, authors have described the OMM GTPase mitofusin-2 (MNF2) to be involved in the mitochondria and nucleus tethering required for the PDC nuclear import (Zervopoulos et al., 2022), and thus MNF2 is increased by the same proliferative stimuli that promote the nPDC.

Nuclear redistribution of the PDC enzyme and the transcription factor NF- κ B could also act both as end points and read-outs of the NAM (Zervopoulos et al., 2022; Desai et al., 2020). The nuclear accumulation of NF- κ B following the formation of mitonuclear contact sites occurs in cells exposed to TNF α stimulation (Wu et al., 2022) as well as in response to pro-death stimuli (Desai et al., 2020).

Altogether these findings (Desai et al., 2020; Zervopoulos et al., 2022; Wu et al., 2022) corroborate NAM as a key component in the transduction of cell signaling representing a novel conduit of communication. In addition, it seems plausible considering that more than one tethering complex may be involved in the formation of contacts and this may vary according to the regulated cellular function. Understanding form and function of the NAM may therefore become instrumental to inform the mechanisms driving the accumulation of mitochondrial DNA (mtDNA) fragments inserted into the nuclear genome, known as nuclear-mitochondrial-DNA segments and now reported in several conditions (Xue et al., 2023). Similarly, NAM, given its degree of conservation, which is below discussed, will help in understanding the process that, within the primordial eukaryotic cell, has driven the transfer and integration of genes from mtDNA into the genomic DNA.

Mitonuclear interactions in unicellular eukaryotes

Yeast

Mitonuclear tethers have also been documented in *Saccharomyces cerevisiae*

(Eisenberg-Bord et al., 2021). A screen for proteins involved in the formation of tethers between mitochondria and nucleus identified contact nucleus mitochondria (Cnm1) that when overexpressed results in mitochondrial accumulation around the nucleus. Cnm1 requires a component of the mitochondrial outer-membrane protein translocase of the outer membrane (TOM) complex Tom70 to enable the interaction between organelles. Tom70 deletion affects the nuclear distribution of Cnm1, whereas Cnm1 overexpression resulted in the localization of an artificial, soluble Tom70 to the nucleus. In the same way, an artificial and soluble Cnm1 accumulates around the mitochondria upon Tom70 overexpression. Accordingly, Tom70 and Cnm1 are proposed as terminals of the molecular bridge that brings the mitochondria and nucleus together.

However, this molecular mechanism may be species specific, as Cnm1 is not conserved in mammals. Even though the authors have speculated on the involvement of lipids at the basis of the Cnm1 mediated tethering, no hypothesis has been formulated on the function the molecular contacts between mitochondria and the nucleus may prime and regulate. Nonetheless, it is likely that in yeast, the physical interplay between mitochondria and nucleus would not exploit the MRR route of communication given the prevalent role mediated by the Rtg pathway. The Rtg pathway is activated in response to the accumulation of dysfunctional mitochondria. Rtg1 and Rtg3 are transcriptional factors that move from the cytosol to the nucleus, whereas Rtg2 is responsible for the phosphorylation between Rtg1 and Rtg3, hence forming a self-regulating complex (Sekito et al., 2002). Therefore, yeast is equipped with a dedicated set of molecules that determine and drive nuclear events because of the dysfunctional mitochondria.

Plasmodium falciparum

Another relevant study for the understanding of the functional biology of the mitonuclear interaction took place in the eukaryotic unicellular parasite *Plasmodium falciparum*, the causative agent of malaria (Connelly et al., 2021). Treating *Plasmodium falciparum* with the anti-malarial drug dihydroartemisinin results in mitochondrial morphological changes and nuclear proximity of the remodeled mitochondria

(Connelly et al., 2021). Cells bearing greater resistance to treatment present enlarged mitochondria that relocate to the nucleus. This study showed a decrease in interaction between the mitochondria and the nucleus when its mitochondria undergo morphological changes. However, they showed no indication of any tethering mechanism involved in the interaction (Connelly et al., 2021). Like mammalian cells, the resistance to stress in *Plasmodium falciparum* is mirrored by the decrease in distance between the mitochondria and the nucleus as well as an increase in reactive oxygen species (Desai et al., 2020).

Toxoplasma gondii

A contact between the nuclear envelope and the mitochondrion has recently been reported in the apicomplexan parasite *Toxoplasma gondii* (Ovcariakova et al., 2024). In this case the physical interaction appears mediated via contacts between the nuclear pore and the mitochondrial outer membrane via the TOM complex. Thus, depletion of the TOM component TgTom40 or the nuclear pore component TgNup503 reduces the nuclear mitochondrial contacts, suggesting the presence of a possible tethering mechanism relying on these two proteins. Furthermore, the authors also report that the loss of these contacts results in mitochondrial morphological defects coupled with a mild enhancement of mitochondrial membrane potential, implying the contact with the nucleus to be relevant for mitochondrial homeostasis.

Detecting MCS between mitochondria and the nucleus

The capability to progress in our understanding of NAM biology rests with the development of new methods. A valuable one is offered by the genetically encoded reporter SPLICS^{NU-MT} (Wu et al., 2022). Devised by adapting split-GFP technology, the SPLICS^{NU-MT} fluoresces when mitochondria are within contact range of the nucleus. This is the latest addition to the suite of SPLICS probes previously used to detect MCS (Cali and Brini, 2021).

Another way to detect and interpret the presence of MCS between mitochondria and the nucleus is offered by the changes in morphology when they are juxtaposed. Cataloguing such changes—as shown by Desai et al. (2020) and Kosmider et al.

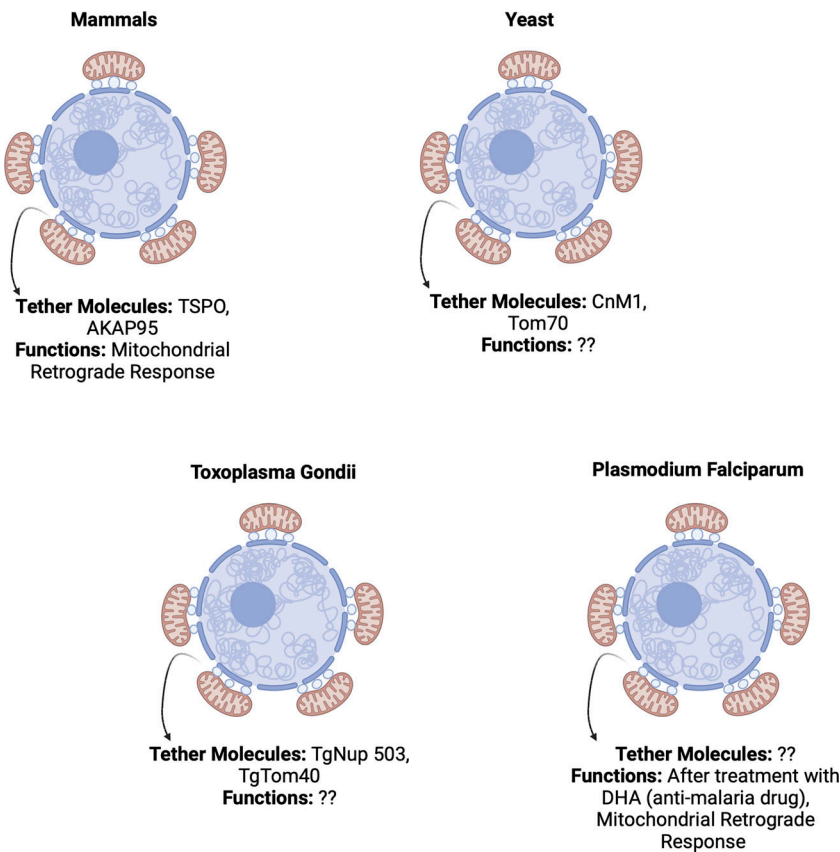


Figure 1. **The contacts between mitochondria and nucleus in mammalian cells, yeast, *Plasmodium falciparum*, and *Toxoplasma gondii*.** The figure depicts the proteins proposed to take part in the formation of contacts between mitochondria and nuclei in mammalian cells, yeasts, *Plasmodium falciparum*, and *Toxoplasma gondii*. Along with the molecular mediators of the physical interaction, the physiological function of each contact is also reported. DHA, dihydroartemisinin. This figure was created using BioRender.

(2019)—and using them to score the shortening in distance between the organelles could per se be a means to detect NAM. However, this would solely be valuable if access to ultrastructural imaging is possible, and it would not be scalable.

Along with the direct visualization of contacts, functional readouts can be utilized to assess the physical interplay between mitochondria and the nucleus. The degree of nuclear accumulation of NF- κ B could represent a suitable one in mammals according to the evidence so far collected (Desai et al., 2020; Wu et al., 2022). Whether a transcription factor (or a network of them) could work as a readout for the formation of NAM in yeast is yet to be explored; the homology between Rtg1/3 and Myc-Max (Jazwinski and Kriete, 2012) per se hints to the hypothesis that nuclear accumulation of transcription regulators may well act as readout in this organism too.

Monitoring second messengers and their redistribution between the organelles could also represent a method to read the physical interplay of mitochondria with the nucleus. Hitherto, the nuclear accumulation of unmetabolized cholesterol—passed on from redistributed mitochondria—has been indicative of the MCS formation between these two organelles (Desai et al., 2020).

Without a doubt, an advanced understanding of the NAM proteomic will unveil post-transcriptional modifications in the molecular repertoire involved in their tethering, thus allowing for more precise and robust methods of detection.

Conclusions

In rapid succession since the initial findings, contacts between mitochondria and the nucleus have been reported both in mammals and single-celled eukaryotes including parasites (Fig. 1). This advocates for a

conduit of intracellular communication worthy of general attention for the role they may cover in homeostasis, dys-homeostasis, and evolution. An exhaustive understanding of the NAM proteome and the type of signaling exploited by this new MCS will detail the function of what emerges as a new conduit of communication in cell biology.

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