Commentary

Mitochondria: Starving to reach quorum?

Insight into the physiological purpose of mitochondrial fusion

Martin Picard[1)*] *and Yan Burelle*[2)]

Why might mitochondria fuse? Mammalian mitochondria continuously undergo fusion in vivo, a process accomplished by an elaborate machinery of energy-dependant GTPase proteins. These proteins are extensively post-translationally regulated and the fusion process involves actively merging both inner and outer mitochondrial membranes to shape extensive networks. Executing this energetically costly process must hold an essential physiological function. Recent reports demonstrate that cells with fusion-incompetent mitochondria fail to thrive, especially under challenging conditions. Bacteria, the ancestors of mitochondria, also undergo life-promoting networking under challenging conditions. Here, we consider evolutionarily conserved behavioral similarities among mitochondria and their bacterial counterparts, as well as recent exciting discoveries in mitochondrial dynamics. We propose that the hunger of mitochondria to undergo fusion results in interconnected mitochondrial networks that establish a life-sustaining unity and coherence within cells, allowing them to thrive in times of energetic hardship.

Insight from bacteria: Communicating for survival

Insight into why mitochondria undergo fusion can be gained from observing the mitochondrion's ancestors: the bacteria. Under normal circumstances where energetic substrates are highly available, bacteria typically exhibit solitary behaviors. However, when bacterial population density increases and energy supply decreases, individual bacteria engage in cell-to-cell communication. This allows the synchronization of gene expression among members of the whole colony [1, 2], a process termed *quorum sensing*. Through quorum sensing, bacteria can act in unison by coordinating certain behaviors, which if performed in isolation would be in vain. One culminating result of coordinated bacterial behavior is the ability to form a larger complex multicellular structure called the biofilm [3]. This intercellular communication involves the production of cytokines and elaborate signal transduction pathways, and is therefore an energetically costly process. Nevertheless, quorum sensing and biofilm formation enhance bacterial survival and promote colonization of host organisms [3]. Thus, for the bacterium to behave as a coordinated unit, it must be starved (i.e. the population density increased). In short, conditions leading to nutrient deprivation initiate cell-to-cell communication, allowing a population of individual bacteria to reach quorum and "agree" on a communal direction to be taken. Once quorum is reached the bacteria behave as a united community working towards a common goal: survival. Could the purpose of fusion in the domesticated bacteria-derived mitochondria serve a similar goal?

Mitochondrial fusion: Physiological roles

The dynamic fusion of mammalian mitochondria is highly regulated by post-translational modifications of the nuclear-encoded proteins, the mitofusins Mfn1 and Mfn2, and optic atrophy 1 (OPA1) [4] (Fig. 1). OPA1 is cleaved within mitochondria at two different sites S1 and S2 by the matrix-processing peptidase OMA1. This gives rise to short and long forms that heterodimerize to induce inner membrane fusion. Mfn1 and Mfn2 are ubiquitinylated by the E3-ligase MARCH5, and probably also experience other function-defining post-translational modification (reviewed in ref. [4]). That post-translational modifications are indeed the key element in the regulation of this process is also suggested by the time frame – minutes to hours – within which mitochondria can undergo global fusion.

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[1)] Department of Kinesiology, McGill University, Montreal, Canada
[2)] Faculty of Pharmacy, Université de Montreal, Montreal, Canada

***Corresponding author:**
Martin Picard
E-mail: martin.picard@mail.mcgill.ca

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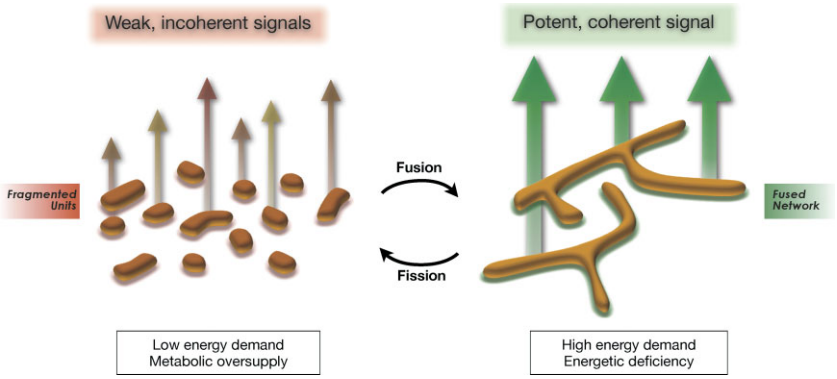

Figure 1. The potential role of mitochondrial morphology in controlling cellular function and retrograde signaling. Mitochondria undergo continuous dynamic processes of fusion and fission, and oscillate between extensively fragmented units (fission) and highly fused networks (fusion). Compared to individual fragmented mitochondria, fused mitochondria are larger in volume and can exchange functional molecules (e.g. mtDNA) and membrane potential ($\Delta\Psi$) within the tubular network. Intrinsic functional differences between fragmented and fused mitochondria exist. Changes in mitochondrial morphology can thus significantly influence energy metabolism, redox signaling, Ca^{2+} homeostasis, gene expression, and, thus, overall cellular function. We hypothesize that mitochondrial fusion fulfills a need for mitochondria to communicate among themselves, allowing synchronous quorum-type behavior among the interconnected network. Mitochondrial networks are possibly better suited than isolated units to generate potent (strength) and coherent (quality) retrograde signals to neighboring and distant cellular compartments such as the nucleus.

The purpose of mitochondrial fusion can be gleamed from observing the consequences of the absence of fusion. Undeniably, cells with fusion-incompetent mitochondria fail to thrive [5]. These cells have reduced growth rates and can only perform oxidative phosphorylation to limited levels [6]. Mice completely lacking Mfn1 and Mfn2 fail to develop and die early in embryonic stage [7]. Mice completely lacking OPA1 develop past embryonic stages and live to adulthood, but they die early. Mice lacking only Mfn2 in skeletal muscle have fusion-incompetent mitochondria. They do live to adulthood but exhibit a 50% reduced body growth, impaired thermogenesis, and reduced oxidative capacity; they also accumulate high levels of mitochondrial DNA (mtDNA) mutations [8]. Excessive mitochondrial fragmentation in cells or organisms in which fusion is disabled impairs mitochondrial bioenergetics, renders host cells more susceptible to apoptotic death [9, 10], and promotes accumulation of respiratory chain deficiency secondary to mtDNA abnormalities [11]. Impaired mitochondrial fusion thus leads to changes in function of the organelle itself, and of the cell as a whole.

It is a fundamental biological principle that survival of the whole depends on interactions between its parts. Braschi and McBride [12] have argued that, to act towards the greater good of the cell and the organism, mitochondria must act as a unified coordinated network. This is accomplished by active fusion of mitochondria into a relatively interconnected reticulum, or mitochondrial network [13]. Microscopic evidence demonstrates that mitochondrial fusion is necessary to allow sharing of mtDNA and large proteins [8, 14]. Some have argued that the effect of mitochondrial fusion-fission dynamics on mtDNA plays a determinant role in cellular aging [15]. In addition, several reports indicate that cells with fused elongated mitochondria might exhibit greater bioenergetic efficiency and have pro-survival effects both in vivo [9, 16] and in vitro [17, 18]. Thus, adequate mitochondrial fusion is required for the function of the organelle, of the cells that contain them, and of the organism as a whole [19].

From a global perspective, it therefore appears that both bacteria and mitochondria can adopt a networking behavior promoting survival under challenging conditions. In the case of bacteria, this is achieved through the releases of soluble factors that mediate communication between individual bacteria. In addition to these well-established mechanisms, recent evidence indicates that bacteria can also transfer information through secreted vesicles [20, 21], bacterial conjugation channels [22], and express proteins (in particular DynA) that can tether membranes and mediate nucleotide-independent membrane fusion in vitro [23]. This suggests that bacterial quorum-sensing mechanisms may involve contact between membranes. In the case of mitochondria, quorum sensing has not been explicitly considered. But here we suggest that this phenomenon does occur, and that one of the primary mechanisms involves fusion of individual mitochondria into elaborated networks. Such community building behavior among mitochondria could have profound implications in determining how eukaryotic cells will fare during metabolic perturbations.

Implications for retrograde signaling and cellular coherence?

Mitochondria do indeed respond to changes in energetic substrate levels by undergoing substantial and rapid morphology changes. More specifically, low energy levels (i.e. starvation) triggers mitochondrial fusion into elongated tubules [16, 17], whereas exposure to high glucose and lipids levels has the opposite effect, fragmenting the mitochondrial network [24, 25]. In addition to these changes in morphology, substrate levels and ATP/ADP levels also induce important allosteric control of oxidative phosphorylation components that regulate mitochondrial function [26]. Due to their extreme sensitivity to energetic substrate levels, mitochondria are exquisite sensors of the cellular energy status. Details about this energy status represent crucial information for the nucleus where epigenetic mechanisms modulate gene expression and ultimately dictate cell function [27]. So, does effective retrograde signaling from mitochondria to the nucleus necessarily require potent and coherent signals involving the coordinated function of most mitochondria behaving in unison?

As with bacteria, could mitochondrial fusion also represent a means by

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which total mitochondrial population size is monitored? Besides the increased bioenergetic efficiency of fused mitochondria, longer organelles exhibit resistance to depolarization and permeability transition pore (PTP) opening. They also produce fewer reactive oxygen species (ROS) than their fragmented counterparts [28, 29]. ROS and other mitochondrial molecules released during reversible PTP opening (e.g. Ca^{2+}, ATP, acetyl coenzyme a, NAD^{+}, and Cyt *c*) act as cellular signaling molecules that can affect signal transduction pathways and ultimately modulate gene expression of mitochondrial genes [27, 30]. This may partly explain why in most cell types mitochondria tend to cluster more densely around the nucleus. Therefore, morphology regulation – via its effect on mitochondrial outputs – could represent a potent mean of monitoring and transducing signals about mitochondrial mass and energetic status to the cytoplasm and nucleus of the cell.

Conclusions

Like bacteria, might mitochondria communicate to reach quorum? Does mitochondrial fusion constitute an essential community check that enables population-wide behavior among these organelles? Mitochondrial fusion is an energetically costly process but nevertheless appears essential to promote cell survival and adaptation to shortage of energy supplies. Mitochondria have preserved many fossil features of their ancestors, the bacteria, including a double membrane and circular DNA. Cell-cell or mitochondrion-mitochondrion communication might be one more evolutionarily conserved feature to be added to this list. Consideration of the functional consequences incurred by mitochondrial morphology transitions, as well as of their impact on cell function and survival, may enable the discovery of yet additional layers of regulation for this fantastically complex organelle.

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