

Opinion

Mitochondria: A Covert Chronic Infection Masquerading as a Symbiotic Partner?

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Abstract

Mitochondria, ubiquitous in eukaryotic cells, evolved from an ancestral aerobic alpha-proteobacterium that had been phagocytosed by a primordial archaeal cell. Numerous factors link mitochondria to current-day bacteria, notably the facultative pathogens that are phagocytosed and survive within the host as a chronic infection. Despite these parallels, we typically refer to mitochondria as “symbionts” and rarely consider them as perhaps the most successful example of long-term chronic infection. Here, we will explore critical aspects of mitochondrial structure and function and consider what we might learn by refocusing our attention on mitochondria as bacteria that are uniquely adapted to their host cell, i.e., as a chronic infection tolerated by its eukaryotic host.

Keywords: mitochondria; chronic infection; symbiosis; evolution; eukaryotic cell

1. Introduction

Mitochondria are membrane-bound intracellular organelles that replicate independently within virtually all eukaryotic cells and generate energy via a series of biochemical reactions collectively known as oxidative phosphorylation. Although several competing theories exist [1–4], the most widely accepted is that mitochondria arose approximately 1.5 billion years ago in a primordial archaeal cell that had phagocytosed an ancestral aerobic alpha-proteobacterium, most likely a predecessor of the marine iodide-oxidizing bacterial genus, *Iodidimonas* [5]. Upon escaping the phagosome, the intracellular bacterium adapted within the cytoplasm to exist in symbiosis within its anaerobic host [6]. Among these adaptations, most of the bacterial genes were eventually transferred to the newly formed eukaryotic cell nucleus [7]. Mitochondria in human cells maintain a single double-stranded ~16.5 kB circular DNA that encodes 13 polypeptides that are essential components of the electron transport chain, as well as two ribosomal RNAs and 22 transfer RNAs necessary for their translation. In addition to energy production, mitochondria evolved to support several additional roles, including macromolecular synthesis and intracellular signaling (reviewed in [8]).

Most textbooks state that mitochondria live in symbiosis with their eukaryotic cell hosts. In its simplest terms, *symbiosis* describes a relationship between two entities that is mutually beneficial (i.e., mutualism), although other types of arrangements exist (e.g., commensalism, parasitism). By contrast, the term *infection* typically infers specific harm to the host, although the distinction between these terms blurs when considering the pathogenesis of chronic infections. Despite their evolutionary history, mi-

tochondria are rarely considered to represent an infection. This is likely because mitochondria in their current form are considered critical elements of the eukaryotic host cell, and not infectious or pathologic agents [9]. Likewise, although mitochondrial dysfunction can lead to serious disease, in their healthy state, they are not perceived to function as pathogens. However, and despite these ongoing perceptions, mitochondria share numerous characteristics with bacteria, reflecting their evolutionary origin from an ancestral endosymbiotic bacterium, which may have entered by an infective process [10–12]. In this manuscript, we will explore various features of current-day mitochondria and consider what we might learn by refocusing our attention on mitochondria as bacteria that are uniquely adapted to their host cell, i.e., tolerated as chronic pathogens in their eukaryotic hosts.

1.1 Structure

Mitochondria are roughly the same size and shape as free-living coccobacilli, and many of their metabolic components, such as those in the electron transport chain and oxidative phosphorylation, are structurally and functionally conserved with those found in current-day bacterial systems [13]. Both mitochondria and bacteria are enveloped in double membranes, with the inner membranes of both bacteria and mitochondria sharing similar lipid compositions and embedded transport proteins [14]. For example, cardiolipin, a phospholipid abundant in bacterial membranes, can be found only in the inner mitochondrial membrane of eukaryotic cells [15]. Likewise, and similar to bacteria, the mitochondrial genome, which contains 37 genes, exhibits high gene density and no introns [16].



1.2 Phagocytosis

As noted above, mitochondria are believed to have developed within the cytoplasm of a primordial archaeal cell of the *Asgard* superphylum that had phagocytosed an ancestral aerobic alpha-proteobacterium. Notably, this interaction resembles the initial events of an intracellular infection, in which bacteria avoid destruction largely by remaining inside a phagosome and thus physically and immunologically sequestered from the host environment. Over time, interdependence between these two previously independent life forms increased through membrane integration, shared signaling, and gene transfer [17,18].

1.3 Replication

Although many proteins required for full mitochondrial function are synthesized in the cell nucleus, mitochondria maintain their own circular DNA and can replicate independently of the host cell through a process similar to binary fission [19,20]. Mitochondria use prokaryotic-type ribosomes (55S vs. 70S) and initiate translation with the amino acid N-formyl methionine, a feature typical of most bacterial species [21–23]. The results of recent studies suggest that mitochondria can exist and function in extracellular environments, analogous to the life cycle of facultative intracellular bacterial pathogens. Cell-free mitochondria found in human blood are respiration competent (i.e., utilize oxygen) [24,25] and may modulate host inflammation and immune responses [26] and sensory functions [27].

1.4 Mitophagy

Mitophagy, the process used by eukaryotic cells to remove damaged mitochondria, in many ways resembles microbial clearance [28]. Damaged mitochondria are tagged with ubiquitin chains; engulfed in autophagosomes, and delivered to lysosomes for degradation and clearance. Intracellular pathogens (e.g., *Mycobacteria* and *Salmonella* spp.) are cleared by similar mechanisms [29].

1.5 Mitoviruses and Bacteriophages

Virus pathogens also serve to link mitochondria to their bacterial predecessors [30–33]. Mitoviruses (family *Narnaviridae*) are non-enveloped viruses with non-segmented, linear, positive-sense, single-stranded RNA genomes that encode a single protein (RNA-dependent RNA polymerase) and specifically target and replicate within mitochondria. Although most characterized mitoviruses infect mitochondria in fungi, recent evidence suggests that several members of this family target contemporary plants and insects [34,35]. Interestingly, mitoviruses are believed to have evolved from leviviruses (family *Leviviridae*), which are RNA bacteriophages that target Gram-negative bacteria.

1.6 Antibiotic Susceptibility

Antibiotics are used widely to treat and, in some cases, prevent bacterial infection. Despite their perceived safety and efficacy, antibiotics also target host mitochondria. Prolonged use of beta-lactams, quinolones, and/or aminoglycosides can lead to overproduction of reactive oxygen species, oxidative damage, and mitochondrial dysfunction [36]. While several studies have highlighted the impact of antibiotic use on metabolic, neurodegenerative, and/or psychiatric disease [37–40], additional research will be needed to improve our understanding of the precise mechanisms underlying this effect.

2. Discussion

Thus, mitochondrial endosymbiosis may be interpreted as an initially infective process that evolved into mutualism, driven by molecular compatibility favored by environmental selection. While compatibility, or conformational matching [41], may have masked the origin of protomitochondria; this process may ultimately have presented specific liabilities. Under stress or aging, mitochondria become dysfunctional (from the perspective of their role as eukaryotic symbionts), triggering apoptosis or necrosis and altering cellular and organismic behavior [42–44]. Some researchers suggest that subtle conflicts persist between mitochondrial and nuclear genomes (e.g., mitonuclear incompatibility), a condition that becomes particularly visible in aging or interspecies hybrids [45,46]. From this perspective, the cost of retaining the ancestral symbiont may include eventual cellular decline [47,48]. A full exploration of the implications of this hypothesis may lead to a novel understanding of disorders such as diabetes and neurodegeneration among others, i.e., those coupled to energy metabolism.

Furthermore, mitochondria demonstrate an exceptional degree of immunologic compatibility with their eukaryotic host cells. Mitochondria elicit minimal immune responses when transplanted into different cell types or even across species [49–51]. This tolerance probably emerged as the protomitochondria became integrated into host cell signaling pathways and interacted with other cellular components. An improved understanding of the mechanisms underlying the nature of their immunological “invisibility” has critical implications for the development of novel strategies to combat transplant rejection and treat autoimmune disorders.

3. Conclusion

The evolutionary history of mitochondria suggests that the most successful pathogens are those that can adapt to their host and environment, evade detection, and reproduce efficiently while providing specific benefits to their host cells. The development of mutualistic symbiosis has permitted protomitochondrial “intruders” to thrive in part-

nership with evolving eukaryotic cells and organ tissues. Further consideration of mitochondrial biology as the most successful example of long-term chronic infection may provide us with new insights into strategies to prevent age-related neurodegeneration and related metabolic disorders.

Author Contributions

The single author was responsible for the conception of ideas presented, writing, and the entire preparation of this manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The author declares no conflict of interest.

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