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Mitochondrial manipulation by intracellular pathogens: Energy theft and apoptosis avoidance.

Chang Kate*

Department of Microbiology, University of Baghdad, Iraq

***Correspondence to:** Chang Kate, Department of Microbiology, University of Baghdad, Iraq, E-mail: katechang@yahoomail.com

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Introduction

Mitochondria, often referred to as the "powerhouses" of the cell, are central to energy production, cellular metabolism, and programmed cell death (apoptosis). Their unique evolutionary origin from an ancestral alphaproteobacterium makes them particularly vulnerable to manipulation by intracellular pathogens. These pathogens have evolved sophisticated strategies to exploit mitochondrial functions, hijacking energy production and evading host immune responses by interfering with apoptosis. Future research should focus on identifying pathogen-specific mitochondrial targets and developing precision therapies. Advances in mitochondrial imaging and proteomics will aid in mapping host-pathogen interactions at the organelle level. This article explores the molecular mechanisms by which intracellular bacteria and viruses manipulate mitochondria to promote their survival and replication [1].

Mitochondrial manipulation has profound effects on host immunity. By suppressing ROS production and apoptosis, pathogens evade detection and clearance. This contributes to chronic infections and inflammation. Moreover, altered mitochondrial function can impair antigen presentation and cytokine production, weakening adaptive immune responses. Understanding these mechanisms is crucial for developing therapies that restore mitochondrial integrity and enhance immune defense. Targeting pathogen effectors or boosting mitochondrial resilience may offer novel treatment strategies. Beyond ATP generation via oxidative phosphorylation (OXPHOS), mitochondria regulate calcium homeostasis, lipid metabolism, and innate immunity. They are also key players in apoptosis, particularly through mitochondrial outer membrane permeabilization (MOMP), which leads to cytochrome c release and caspase activation. Their dynamic nature and central role in cellular signaling make them prime targets for intracellular pathogens seeking to establish a replicative niche [2].

Some pathogens prevent mtDNA leakage to avoid triggering inflammatory pathways. This fine-tuned control of mitochondrial signaling underscores the strategic importance of these organelles in host-pathogen interactions. Pathogens use specialized secretion systems to deliver effector proteins into host cells. These proteins often localize to mitochondria, altering their function. *Legionella pneumophila* uses the Dot/Icm Type IV secretion system to inject effectors like MitF, which disrupt mitochondrial fission and fusion dynamics. Intracellular pathogens often reside in nutrient-poor environments within host cells. To survive and replicate, they must secure access to energy. Some pathogens, such as *Chlamydia trachomatis*, form close associations with mitochondria to siphon ATP directly. Others, like *Legionella pneumophila*, secrete effector proteins that rewire host metabolism, redirecting resources toward bacterial replication. *Mycobacterium tuberculosis* has been shown to alter host mitochondrial dynamics, reducing ATP output and increasing glycolysis—a metabolic shift that favors bacterial persistence. These manipulations not only provide energy but also suppress mitochondrial reactive oxygen species (ROS), which are toxic to pathogens [3].

Apoptosis is a defense mechanism that limits pathogen spread. To counter this, intracellular microbes deploy strategies to inhibit mitochondrial-mediated apoptosis. *Salmonella enterica* secretes AvrA, a protein that stabilizes anti-apoptotic Bcl-2 family members, preventing cytochrome c release.

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Similarly, *Listeria monocytogenes* produces listeriolysin O, which disrupts mitochondrial membranes without triggering apoptosis. Viruses also manipulate mitochondrial apoptosis pathways. The hepatitis C virus (HCV) core protein interacts with mitochondrial membranes to inhibit MOMP, while Epstein-Barr virus (EBV) encodes BHRF1, a viral homolog of Bcl-2 that blocks apoptosis [4].

For instance, *Chlamydia trachomatis* induces mitochondrial elongation by inhibiting the fission protein Drp1, thereby enhancing energy availability and suppressing cell death. This morphological manipulation is a hallmark of chronic infections. Mitochondria communicate with the nucleus to regulate gene expression and stress responses. Pathogens interfere with this crosstalk to suppress immune signaling. *Listeria monocytogenes* and *Mycobacterium tuberculosis* inhibit mitochondrial antiviral signaling protein (MAVS), dampening interferon responses and allowing immune evasion. Additionally, mitochondrial DNA (mtDNA) release during infection can activate innate immunity. *Rickettsia* species, which share evolutionary ancestry with mitochondria, exploit host mitochondrial membranes to facilitate replication. Their effector proteins mimic host regulators of mitochondrial dynamics, promoting elongation and reducing fragmentation—conditions favorable for pathogen survival. Mitochondrial shape is tightly regulated by fission and fusion processes. Pathogens manipulate these dynamics to create a cellular environment conducive to infection. Elongated mitochondria are associated with increased ATP production and reduced apoptosis—beneficial traits for intracellular pathogens [5].

Conclusion

Intracellular pathogens have evolved intricate strategies to manipulate mitochondria, stealing energy and evading apoptosis to ensure their survival. These interactions highlight the dual role of mitochondria as both metabolic hubs and immune sentinels. The central role of mitochondria in infection makes them attractive targets for therapeutic intervention. Drugs that restore mitochondrial dynamics or enhance apoptosis could limit pathogen survival. For example, BH3 mimetics that activate pro-apoptotic pathways are being explored in viral and bacterial infections. Decoding the molecular tactics used by pathogens offers new insights into infection biology and opens avenues for innovative treatments aimed at restoring mitochondrial function and host immunity.

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