

Mitochondrial Crosstalk with the Immune System: A Biological Frontier in Disease Research

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Introduction

Mitochondria, long regarded as the “powerhouses of the cell,” are indispensable organelles that generate ATP through oxidative phosphorylation and maintain cellular energy homeostasis. However, this traditional bioenergetic perspective has evolved dramatically over the past two decades. Beyond their canonical role in metabolism, mitochondria have emerged as central regulators of innate and adaptive immunity. These organelles act as signaling hubs, integrating metabolic cues with immune pathways, thereby shaping host defense, inflammation, and tissue homeostasis. The mitochondrial genome, dynamics, and metabolites collectively influence the activation, differentiation, and effector functions of immune cells.

Mitochondria also participate in immunological surveillance by releasing Danger-Associated Molecular Patterns (DAMPs), such as mitochondrial DNA (mtDNA), formyl peptides, and Reactive Oxygen Species (ROS), which activate Pattern Recognition Receptors (PRRs). At the same time, immune signaling cascades feed back into mitochondrial function, modulating metabolism, fission–fusion dynamics, and apoptosis. Dysregulation of this crosstalk underlies a spectrum of diseases, including autoimmune disorders, neurodegeneration, metabolic syndrome, cardiovascular disease, and cancer [1].

Description

Structurally similar to bacterial DNA, mtDNA contains unmethylated CpG motifs recognized by innate immune receptors. When released into the cytosol or extracellular space during stress or cell death, mtDNA activates cGAS–STING pathways and TLR9, leading to type I interferon (IFN) production and inflammatory cytokine release. Mitochondrial ROS act as second messengers in immune signaling. Moderate ROS levels enhance T-cell receptor signaling and pathogen killing by macrophages, whereas excessive ROS trigger oxidative damage, chronic inflammation, and cell death. Located on the outer mitochondrial membrane, MAVS is a pivotal adaptor in antiviral defense. Together, these components highlight mitochondria as not merely passive energy providers but dynamic signaling platforms for immune responses [2].

Mitochondria undergo continuous cycles of fission and fusion, mediated by proteins such as DRP1, MFN1/2, and OPA1. These dynamics influence immune signaling and cell fate decisions. Facilitates rapid energy distribution during immune activation and promotes apoptosis in damaged cells. Excessive fission is associated with inflammation and tissue injury. A selective form of autophagy, mitophagy removes damaged mitochondria to prevent excessive ROS and DAMP release. Failure of mitophagy is implicated in autoimmune diseases and neuroinflammation. The immune system closely monitors mitochondrial dynamics, with dysregulation predisposing cells to chronic inflammation and immune dysfunction [3].

Mitochondrial ROS and mtDNA activate the NLRP3 inflammasome, a key mediator of IL-1 β and IL-18 secretion. Excessive inflammasome activation contributes to autoinflammatory and metabolic diseases. Cytosolic mtDNA acts as a ligand for cyclic GMP-AMP synthase (cGAS), activating STING and inducing type I interferons. This pathway is critical in antiviral defense but is also implicated in autoimmune disorders such as lupus. Mitochondrial molecules act as DAMPs, stimulating TLRs and NOD-like receptors. This molecular mimicry between mitochondria and bacteria underscores their evolutionary origins and immunogenic potential [4].

Dysregulated mtDNA release and defective mitophagy activate innate immunity inappropriately, driving systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis. For instance, anti-mtDNA autoantibodies are detected in lupus patients, linking mitochondria to autoimmunity. Mitochondrial dysfunction in neurons triggers chronic microglial activation and neuroinflammation, hallmarks of Alzheimer’s and Parkinson’s disease. Damaged mitochondria release DAMPs, perpetuating neurodegeneration. Tumor cells exploit mitochondrial–immune interactions by reprogramming metabolism and inducing T-cell exhaustion. At the same time, mitochondrial ROS and metabolites can either suppress or promote anti-tumor immunity, depending on context. Mitochondria-targeted drugs are being investigated to improve immunotherapy outcome. Conversely, enhanced mitochondrial immunity is protective against viral and bacterial pathogens [5].

Conclusion

Mitochondria are far more than cellular powerhouses—they are immunological sentinels and regulators that orchestrate the balance between health and disease. Their crosstalk with the immune system involves a complex interplay of metabolic signals, dynamic remodeling, and danger signals that shape both innate and adaptive immunity. When functioning properly, this crosstalk equips the body to respond effectively to infection, injury, and stress. However, its dysregulation drives a wide spectrum of diseases, from autoimmunity and neurodegeneration to metabolic syndrome, cardiovascular pathology, and cancer. The recognition of mitochondria as central players in immunity has transformed biomedical research, positioning mitochondrial-immune interactions as a biological frontier. Therapeutic strategies that target this interface are already showing promise, ranging from antioxidants and mitophagy inducers to metabolic reprogramming in cancer immunotherapy. Importantly, these approaches underscore the need for systems-level thinking, integrating metabolism, immunity, and organelle biology in disease research.

Acknowledgement

None.

Conflict of Interest

None.

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