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The emerging role of immune dysfunction in mitochondrial diseases as a paradigm for understanding immunometabolism

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ABSTRACT

Immunometabolism aims to define the role of intermediary metabolism in immune cell function, with bioenergetics and the mitochondria recently taking center stage. To date, the medical literature on mitochondria and immune function extols the virtues of mouse models in exploring this biologic intersection. While the laboratory mouse has become a standard for studying mammalian biology, this model comprises part of a comprehensive approach. Humans, with their broad array of inherited phenotypes, serve as a starting point for studying immunometabolism; specifically, patients with mitochondrial disease. Using this top-down approach, the mouse as a model organism facilitates further exploration of the consequences of mutations involved in mitochondrial maintenance and function. In this review, we will discuss the emerging phenotype of immune dysfunction in mitochondrial disease as a model for understanding the role of the mitochondria in immune function in available mouse models.

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Contents

Abbreviations: MD(s), mitochondrial disease(s)); OXPHOS, oxidative phosphorylation; FAO, fatty acid oxidation; SIRS, systemic inflammatory response syndrome; KD, knockdown; ChIP, chromatin immunoprecipitation; CD4-Cre, CD4 *cre* recombinase; DAMPs, damage associated molecular patterns; TH1, T helper 1 cells; TH2, T helper 2 cells; TH17, T helper 17 cells; TREG, T regulatory cells; ROS, reactive oxygen species; KO, knockout; EAE, experimental autoimmune encephalomyelitis; MNGIE, mitochondrial neurogastrointestinal encephalopathy; SANDO, sensory ataxic neuropathy, dysarthria, and ophthalmoparesis; SCAE, spinocerebellar ataxia with epilepsy; CRISPR, clustered regularly interspaced short palindromic repeats; PS, phosphatidylserine; PEO, progressive external ophthalmoplegia; IOSCA, infantile-onset spinocerebellar ataxia; STAT, signal transducer and activator of transcription; PRR, proline-rich region; RIPK3, receptor-interacting serine/threonine protein kinase 3; NFAT, nuclear factor of activate T cells; NKT, natural killer T cell; BMDC, bone marrow-derived dendritic cell; MEF, mouse embryonic fibroblast.

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1. Introduction

> "The human system […] comes equipped with an astonishingly broad array of characterized mutant phenotypes; thousands of human genes have been identified by virtue of the phenotype they confer when inherited in mutant form."
> Ray White and C. Thomas Caskey, The Human as an Experimental System in Molecular Genetics [1]

Mitochondria arose only once in evolution, approximately 2.5 billion years ago, via endosymbiosis during the evolution of eukaryotic cells [2]. The persistence of this arrangement is due to the mutual benefit derived from the ability of mitochondria to convert organic molecules from the environment to energy. Over time, the mitochondria developed an ultrastructure characterized by a double membrane composed of phospholipids and protein with an intermembrane space between the outer and inner membranes. Residing in the center is the matrix which is surrounded by the inner membrane. The inner membrane has numerous folds, or cristae, that increase its surface area and house the chemiosmotic machinery that facilitates cellular respiration.

The matrix of each mitochondrion contains multiple copies of a double-stranded, circular mitochondrial DNA (mtDNA). Approximately 17 kb, each mtDNA contains 37 genes: 22 transfer RNAs, and 2 ribosomal RNAs, and 13 protein-coding genes. During evolution, many genes required for mtDNA replication and maintenance, and other functions, were transferred to the nucleus [3]. To date, >1100 nuclear-encoded genes have been identified to be involved in sustaining mitochondrial function [4], further emphasizing the importance of coordination between the nuclear and mitochondrial genomes.

Mitochondrial diseases (MDs) are a group of clinically heterogeneous disorders that can arise from heritable mutations in either mtDNA or nuclear DNA (nDNA). Mutations in genes involved in mitochondrial function lead to disorders of oxidative phosphorylation (OXPHOS), mtDNA integrity, and mitochondrial maintenance, among others. MDs due to mtDNA mutations are inherited in a matrilineal fashion, whereas MDs arising from mutations in nuclear genes are inherited in an autosomal dominant, autosomal recessive, or X-linked manner. For MDs due to mtDNA mutations, the proportion of mutant mtDNA molecules within a tissue determines both the penetrance and severity of the phenotype in that tissue. This phenomenon of mixed populations of mtDNA (i.e. mutated and wildtype), known as heteroplasmy, serves to modify the phenotypic expression of MDs. In addition, the phenotype of mtDNA and nDNA mutations in MDs may also be modified by tissue specific expression of the gene, modifier genes, and epigenetics [5].

Since most cells contain mitochondria, the clinical effects of mitochondrial disease are potentially multisystemic, and involve organs with large energy requirements including the heart, skeletal muscle, and brain [6]. The burgeoning field of immunometabolism aims to define the role of intermediary metabolism in immune cell function [7], cells which also have potentially large energy requirements during innate and adaptive responses to insult or injury. Based on recent medical literature and advances in profiling technologies, there has been renewed interest in the bioenergetics of immune cells, with the mitochondria and OXPHOS taking center stage. In addition to performing the critical function of energy production, which is the basis of life, additional roles of mitochondria include heat production, calcium storage, apoptosis, cell signaling, and biosynthetic roles (e.g. heme, sterols), all important for cell survival and function [3,8–10]. In the spirit of the seminal article by White and Caskey [1], extolling the virtues of the human as an experimental system, here, we explore a patient centered approach to understand the role of mitochondria in immune cell function using MDs as a guide (Fig. 1). In the sections to follow, we review the emerging clinical phenotype of immune dysfunction in MDs, which is generally absent from textbooks and reviews on MD, and discuss existing mouse model systems for mitochondrial disease genes that have expanded, or have the potential to expand, our understanding of multiple aspects of mitochondrial function in the context of MDs.

2. Methods

In this review, we provide a blueprint for studying mitochondrial function in immune cells. Patients with MD serve as the starting point. Clinical and experimental findings in patients are then followed up in physiologically relevant mouse models. Overall this approach is critical for revealing the interplay between the mitochondria and immune cell function. Research was performed by employing combinations of the terms 'mitochondrial disease', 'mitochondria, immune', 'immunodeficiency', and 'mouse models', in PubMed.