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Review

Evolutionary perspectives on the links between mitochondrial genotype and disease phenotype☆

Damian K. Dowling

School of Biological Sciences, Monash University, Clayton 3800, VIC Australia

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ABSTRACT

Background: Disorders of the mitochondrial respiratory chain are heterogeneous in their symptoms and underlying genetics. Simple links between candidate mutations and expression of disease phenotype typically do not exist. It thus remains unclear how the genetic variation in the mitochondrial genome contributes to the phenotypic expression of complex traits and disease phenotypes.
Scope of review: I summarize the basic genetic processes known to underpin mitochondrial disease. I highlight other plausible processes, drawn from the evolutionary biological literature, whose contribution to mitochondrial disease expression remains largely empirically unexplored. I highlight recent advances to the field, and discuss common-ground and -goals shared by researchers across medical and evolutionary domains.
Major conclusions: Mitochondrial genetic variance is linked to phenotypic variance across a variety of traits (e.g. reproductive function, life expectancy) fundamental to the upkeep of good health. Evolutionary theory predicts that mitochondrial genomes are destined to accumulate male-harming (but female-friendly) mutations, and this prediction has received proof-of-principle support. Furthermore, mitochondrial effects on the phenotype are typically manifested via interactions between mitochondrial and nuclear genes. Thus, whether a mitochondrial mutation is a pathogenic in effect can depend on the nuclear genotype in which is it expressed.
General significance: Many disease phenotypes associated with OXPHOS malfunction might be determined by the outcomes of mitochondrial–nuclear interactions, and by the evolutionary forces that historically shaped mitochondrial DNA (mtDNA) sequences. Concepts and results drawn from the evolutionary sciences can have broad, but currently under-utilized, applicability to the medical sciences and provide new insights into understanding the complex genetics of mitochondrial disease. This article is part of a Special Issue entitled Frontiers of Mitochondrial Research.

1. Introduction

The mitochondria are cornerstones to eukaryote life, providing the cell with a highly efficient means of converting biochemical energy stored in food, through the oxidation of nutrients to produce adenosine-5′-triphosphate (ATP). This process occurs via the metabolic pathway known as oxidative phosphorylation (OXPHOS), during which redox reactions, which take place over a series of five enzyme complexes (the mitochondrial respiratory chain), release energy that is used to form ATP [1]. This ability to harness energy via OXPHOS is likely to have been salient in enabling the evolution of complex and energy-demanding forms of life [2]. In addition to their central role in energy conversion, the mitochondria are heavily involved in other vital biological processes including thermogenesis via mitochondrial uncoupling [3], cellular apoptosis [4], calcium storage and signaling [5], and reactive oxygen species (ROS) production (used in signaling [6], albeit highly toxic when at surplus levels [7]).

As a legacy of their ancient endosymbiotic origin, the mitochondria retain their own diminutive genome (around 16 000 nucleotides, 37 genes in the typical metazoan) of mitochondrial DNA (mtDNA) [8]; although many of the genes essential for mitochondrial respiration have been translocated across to the nuclear genome throughout the course of evolutionary history [9]. As a result, of the more than 80 protein subunits that comprise the enzyme complexes of the mitochondrial respiratory chain, 13 are encoded by the mtDNA, and the remainder by genes within the nuclear genome [8]. Given their pivotal role in regulating essential biological function, one would logically infer that if mutations were to arise in these genes, then the phenotypic consequences would be serious. Thus, by implication, these genes will be subjected to the intense and perpetual force of natural selection to ensure their optimization. Yet, despite the prediction of strong and effective selection to remove such mutations, it is well known that mutations to OXPHOS-encoding genes do persist and can cause mitochondrial disease in humans. However, the link between these mutations and the expression of disease is complex [10], and for instance likely to be mediated by interactions between alleles spanning both mitochondrial and nuclear genomes (mito-nuclear interactions) [11], and predicting

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the presence or severity of mitochondrial disease of patients based on their genetic profile remains a major challenge in many cases.

In this review, I draw on insights from evolutionary theory and empiricism to suggest new avenues for exploring the complex genetics underlying human mitochondrial disease. Research into mitochondrial genome evolution and research into mitochondrial disease share fundamental common ground, because both center on the study of mutations. While each field is undoubtedly driven by a different set of conceptual questions and end goals, a central shared aim is to understand the effects and role that mutations within the mitochondrial–nuclear (mito-nuclear) complexes of the respiratory chain have on expression of the organismal phenotype (Fig. 1). I start by introducing human mitochondrial disease (Section 1.1), and then outline the primary genetic factors that are well known by medical researchers to affect the expression and severity of disease symptoms (Section 2). I then discuss other genetic peculiarities and processes relevant to the mitochondrial genome (Sections 3 and 4), which have received focused attention from evolutionary theorists and empiricists, but for which the realized implications to mitochondrial disease expression remain elusive and not at the frontline of the biomedical mitochondrial research agenda, despite their potential key relevance.

1.1. Mitochondrial disease

Mitochondrial disease in humans encompasses a broad range of metabolic disorders that result in a range of disease phenotypes, from myopathies, to visual and hearing impairment, organ failure, respiratory and neurological disorders, dementia, aging [1,12–16] and even male infertility [17]. Mitochondrial genetics have furthermore been linked to several other common human diseases, including diabetes [18], autism spectrum disorders [19], cancer [16,20], Alzheimer's [21] and Parkinson's [22] disease. The first case of mitochondrial disease was not identified until the early 1960s [23], followed by the first identified mtDNA disease-causing mutations in the 1980s [24,25]. The present estimate is that mutations to genes affecting OXPHOS function cause mitochondrial disease in around one in every five thousand human births [26]. A caveat is that this number could well be much higher, since mitochondrial OXPHOS disorders are clinically heterogeneous in their symptoms, as well as genetically heterogeneous (pathogenic mutations at 30 of the 37 mtDNA encoded genes, and at more than 30 nuclear genes alone, have been linked to OXPHOS malfunction), making their accurate diagnosis difficult. It has been suggested that over 100 nuclear-encoded OXPHOS disorders might still await identification [26]. This estimate seems plausible, in light of recent estimates that at least one in every 200 humans in the general population harbors a pathogenic mutation in the mtDNA alone [27] (i.e. not including the possible suite of mutations at nuclear-encoded sites), and are hence at risk of developing mitochondrial disease.

2. Mitochondrial disease is governed by distinct mitochondrial genetics

There are many factors, acting synergistically, which can account for the difficulty that researchers and clinicians face in establishing clear and consistent linkages between pathogenic mutations in the mtDNA and resulting disease phenotypes. These factors can be directly ascribed to the distinct genetics of the mitochondrial genome [28,29], and while some of the factors have been the subject of intense research by biomedical researchers (e.g. heteroplasmy, mitochondrial bottlenecks, and critical energy thresholds), the details of others remain nearly completely elusive (sex-specific mutation accumulation, mitochondrial–nuclear interactions, environmental-dependent mitochondrial genetic effects). These factors are the focus of this review.

The peculiarities of mitochondrial genetics render it not only possible, but actually commonplace, for individuals to harbor known pathogenic point mutations in the mtDNA without actually expressing a disease phenotype at all [27], or alternatively expressing disease at just one of numerous possible tissues or organs known to be associated with that particular mutation [10]. In short, the fundamental principles of mitochondrial genetics are markedly different from the Mendelian principles governing the inheritance of nuclear genes and their associated phenotypic effects. To start with, in diploid metazoans such as humans, each somatic cell generally harbors two copies of the nuclear genome, and germ cells carry a single copy. This contrasts to the intra-cellular

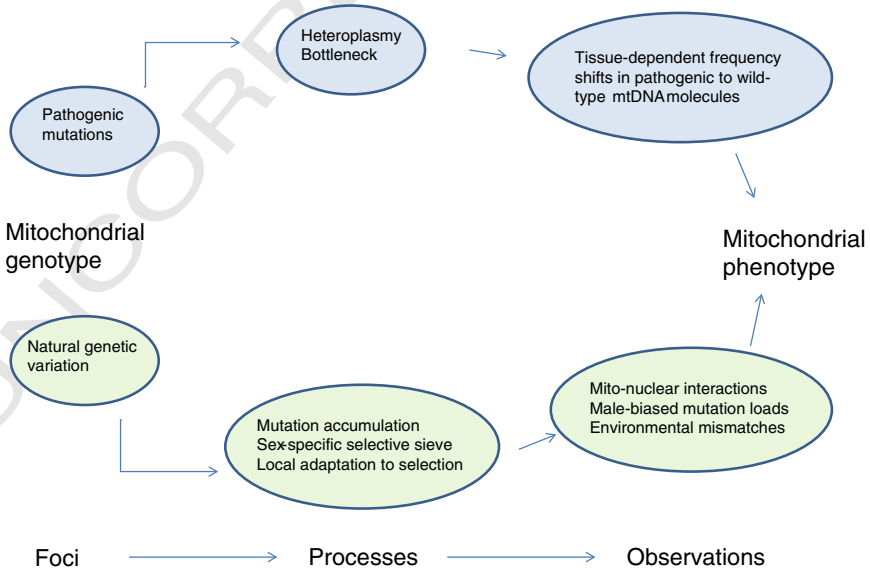

Fig. 1. Prospective routes to mitochondrial disease. The figure illustrates the general field-specific focus of researchers studying the link between mitochondrial genotype and phenotype. In the biomedical domain (top half of figure — blue bubbles), research has focused on known pathogenic mtDNA mutations, and effects of frequency changes of mutant relative to healthy mtDNA molecules under heteroplasmy (i.e. intra-individual mtDNA variation). Such frequencies can change rapidly as a consequence of the mitochondrial bottleneck during oogenesis, and these dynamics determine incidences and expression of mitochondrial disease. In the evolutionary biological domain (bottom half of figure — green bubbles), research has focused on adaptive (selection) and non-adaptive (mutation accumulation, drift) processes shaping naturally-occurring mitochondrial genetic variation (i.e. inter-individual mtDNA variation), across generations. These studies have highlighted the ubiquity by which mitochondrial effects on phenotype are manifested via mito-nuclear interactions, uncovered empirical evidence for a set of male-harming mutations within the mtDNA sequence, and provided evidence that mtDNA mutations beneficial in one environment (e.g. arctic climates), may be harmful in another (e.g. tropical climates).

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