Overview of Mitochondrial Diseases and the Path to Progress

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Introduction

Mitochondria - commonly known as the chief producers of ATP energy supply in cells - also perform various other specialized homeostatic functions for our bodies. Both nuclear DNA (nDNA) and mitochondrial DNA (mtDNA) genetically contribute to mitochondrial form and function. Mutations within both DNA may lead to fatal genetic conditions that affect children and adults alike. MtDNA is also more prone to mutations due to oxidative damage from metabolism. The short, double-stranded, and circular 16.6 kb mtDNA contains 37 genes and no introns, and exists in multiple copies within a single mitochondrion. Hundreds or even thousands of mitochondria can be in one human cell. Complex cellular interactions have made it difficult for rapid progress.

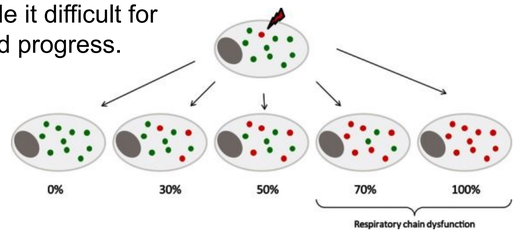

Figure 1. A specific example of mutant mtDNA percentages that can be detected. Green - wild type mtDNA. Red - mutated mtDNA.

Challenges

Modern therapies and treatments are few, and remain largely in development due to the nature of mtDNA. Undetected mutant phenotypes beneath threshold levels due to mtDNA heteroplasmy - as seen in figure 1 - plus cellular genetic codependence of mtDNA and nDNA makes it difficult to analyze patterns and mechanisms of mtDNA *(1, 5)*. Moreover, while mtDNA inheritance is primarily through maternal transmission, other sources may also be important to consider, such as, paternal leakage *(2)*.

Ongoing Research of Diseases & Conditions Linked to MtDNA

A broad spectrum of mtDNA diseases are the result of phenotypic blending within mutations. Of these, mtDNA-linked advanced aging and neurodegenerative disorders are a common focus in research. In figure 2, three point mutations and a large scale deletion along with their possible corresponding symptoms are shown *(5)*. A specific mutation in one person may not show the exact phenotypic effect in others.

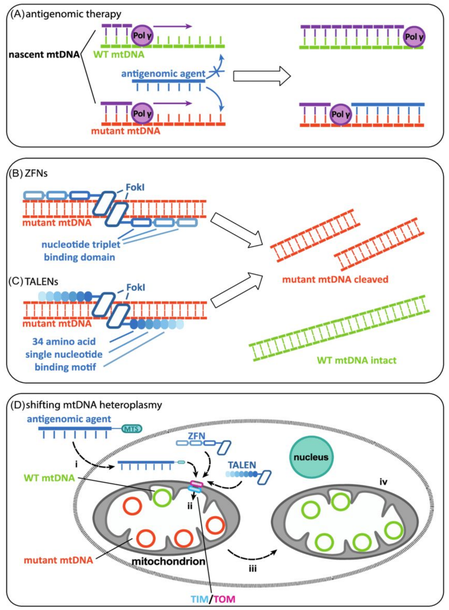

Figure 3. Approaches to shifting heteroplasmy: (A) Targeted inhibition of Pol γ replication of mutant mtDNA by a short gene treatment. (B) Binding and cleavage of mutant mtDNA by ZFNs or (C) TALENs. (D) Summary of the approaches: (i) delivery of an antigenomic agent into the cell, (ii) translocation into matrix, (iii & iv) Result: almost completely wild type mtDNA.

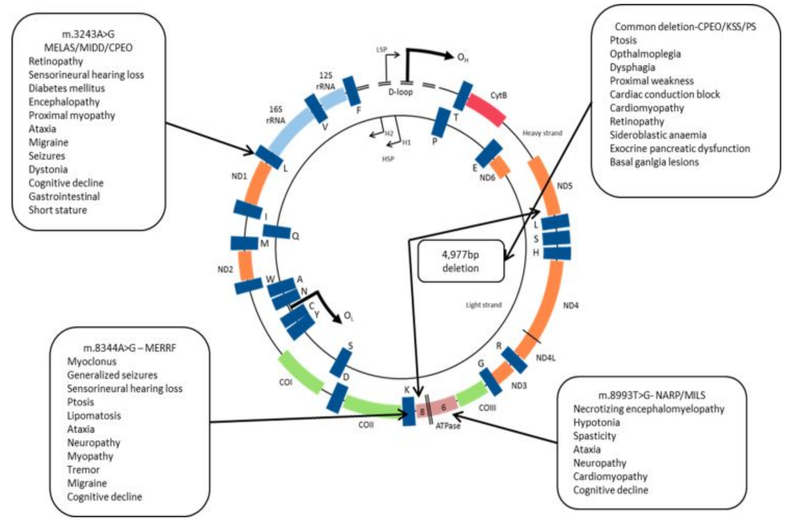

Figure 2. Map of mitochondrial genome and four mutations with their corresponding phenotype groups.

The "Cure"

Currently, keeping symptoms under control with supplemental remedies exists as the primary treatment; although, it is not quite effective. Heteroplasmic shifting seems to be a potential therapy that inhibits mutant genomes, therefore restoring healthy wild type phenotypes. With a gene or protein treatment that targets specific genetic sequences, indicated by figure 3, mutant mtDNA replication can be prevented *(4)*. Another research development is preventing maternal transmission and refining preimplantation techniques to select embryos free of mtDNA disease. However, these approaches do not come without controversy. Greater understanding of mtDNA mechanisms will pave the way for efficient personalized treatments since these diseases vary in severity case-by-case.

Diagnosis

Productive treatments rely on accurate, well-rounded genetic testing. Extensive tissue analyses have established guidelines when diagnosing certain organs. Generally, liver screenings, rather than muscle, seem to provide the most dependable results. Also, southern blot analyses can find mtDNA deletions. PCR and sequencing helps determine heteroplasmic levels. Enzymatic analysis may also be used to study mitochondrial activity and function. *(3)*

Future Focus

- Classification of mtDNA diseases
- MtDNA mutations, pathways, and evolutionary history
- Collaboration between groups globally, as well as between clinicians and researchers
- Overcoming diagnosis limitations

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