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# RNA Treatments that Target the Mitochondria as a Potential Treatment for Mitochondrial Illnesses

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## Introduction

Currently, case-specific symptom management and pharmacological supplementation are used to treat mitochondrial diseases. Typically, vitamins, cofactors, coenzyme Q10, or antioxidants are recommended. A drug cocktail containing supplemental antioxidants, vitamins, and xenobiotics to partially alleviate symptoms is the most common treatment for mitochondrial disease. Even though there have been a few clinical trials of mutation-specific targeted therapies, treatments that are specifically targeted to specific genetic causes are needed. The development of therapeutic agents based on RNA has recently made significant advancements. Mitochondrion-targeted RNA therapies could be used to treat mitochondrial diseases, as we discuss here. After going over the genetics of mitochondrial disease, we discuss the most recent therapeutic options for mitochondrial disease and the state of the art in the field of mitochondrial and RNA therapies. As a possible strategy for the development of precise therapies for mitochondrial diseases, we discuss RNA delivery to mitochondria as the conclusion of this review [1].

## Description

The process of genetically defining mitochondrial diseases is intricate. There are approximately 1,200 nuclear protein-encoding genes in human mitochondria, 300 of which are associated with various mitochondrial disease pathogeneses. Each human cell has hundreds to thousands of mitochondria, each of which contains between two and ten copies of the mitochondrial genome. Heteroplasmy, in which an individual or even a single cell can have distinct mtDNA genomes, may result from mtDNA's multiple copies. Up to 61% of the population is thought to have heteroplasmy. Clinical symptoms may typically appear when the heteroplasmic load exceeds 70%–80% of all mtDNA genomes. The mitochondrial haplogroup, which is defined by ancestry-linked combinations of single nucleotide polymorphisms, can also be linked to clinical symptoms and have the potential to influence disease risk and pathology. According to a number of recent studies conducted in England, the United States, Canada, Sweden, Portugal, and Japan, the global prevalence of clinically diagnosed mitochondrial disease ranges from 10 to 20 per 100,000 people. Despite the limited number and power of studies to date, epidemiological studies of mitochondrial diseases with clinical manifestations are broadly consistent across regions. To comprehend mitochondrial disease expressed in varying forms and the true burden of mitochondrial diseases, further characterization of the genetic prevalence of disease-causing mutations and genotype-to-phenotype penetration is required [2].

The literature suggests a number of limitations for describing the genetic epidemiology of mtDNA mutations in mitochondrial disease and their contribution to various diseases. It is believed that three major stages control mtDNA maintenance: bottlenecks in oogenesis, embryos, and somatic quality control. Mitochondrial legacy examples and bottlenecks include stochastic cycles, in this manner it is hard to foresee the legacy of mitochondrial illness changes. Heteroplasmic variation and altered risk of mtDNA mutation-derived diseases may result from the resulting genetic drift. Purifying selection is less likely to remove mtDNA mutations in mt-tRNA and mt-rRNA regions during bottlenecks than it is in mt-mRNA regions. The m.3243A>G mutant mtDNA copy confers a replicative advantage [3].

Low-fidelity polymerase and cumulative stress are thought to increase mitochondrial heteroplasmy of inherited or new mutations with age. Pathogenic mtDNA blood heteroplasmy levels can be reduced through quality control, as evidenced by reports of heteroplasmic harmful mutations found in other somatic tissues but not in the blood. However, it is difficult to identify variants due to the fact that this decreasing trend is only evident in cell/tissue types with rapid proliferation. Post-mitotic tissues, on the other hand, in the elderly heart, muscle, and brain carry a higher heteroplasmic load. This suggests that tissues with a lower proliferative capacity may be more susceptible to carrying heteroplasmic levels of harmful mtDNA mutations that contribute to aging and diseases. Lastly, numerous mitochondrial diseases have been linked to pathogenic mtDNA mutations. Patients with potential mitochondrial diseases need to have their mtDNA variants and heteroplasmic load, which may be associated with the disease, carefully examined [4].

A plan to mitigate the effects of heteroplasmy is an important therapeutic need in mitochondrial disease. When mutant mtDNA accounts for more than 60%–80% of a cell's total mtDNA, phenotypic manifestations of heteroplasmic mtDNA disorders typically occur, and the severity of symptoms typically rises in tandem. Engineers have created RNA molecules that bind to mutant mtDNA loci in a specific way and halt mtDNA replication. This gives WT mtDNA an advantage in replication and saves normal mitochondrial functions. Delivered to cells in vitro, these so-called antigenomic or antireplicative RNAs were able to partially rescue mitochondrial protein expression in KSS cybrid cells and patient fibroblasts containing a deleterious point mutation, m, and reduce the amount of deleterious heteroplasmy. The ND5 gene's A13514G codon [5].

## Conclusion

Instead of altering the cell's and mitochondria's genomic composition, the three approaches to using RNA-based therapeutic agents to treat mitochondrial diseases focus on altering mitochondrial RNAs and their products. Even though they are outside the scope of this review, mitochondrial diseases can be treated with gene editing techniques. Derivatives of bacterial toxins, such as DdCBEs (DddA-derived cytosine base editors), which are capable of introducing single-base modifications, have been developed to specifically modify mtDNA. MitoTALEN and other protein-only nucleases that have been modified with mitochondrial targeting sequence (MTS) can be imported into the mitochondrial matrix and utilized to specifically edit the mtDNA. Additionally, mitoCRISPR has been adapted to target mtDNA by modifying the CRISPR-Cas machinery. DNA-editing therapeutics can also be delivered to mitochondria using a number of the mitochondrial RNA delivery strategies discussed later in this review. mRNA encoding protein-only nucleases or mitoCRISPR proteins, for instance, can be delivered directly to the mitochondrial matrix, and the sgRNA required for mitoCRISPR can be modified with endogenous

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RNA import determinants (such as the RP-stem-loop structure) to target it to the mitochondrial matrix and boost mitoCRISPR efficiency. However, we believe that RNA-targeting therapies outperform mtDNA-editing strategies due to their inability to pharmacologically control the therapeutic agent and their permanent effect on a person's genetic makeup. The delivery of RNA-targeting therapeutic agents may be hampered in vivo due to the fact that the size of some gene editing machinery is typically much larger than that of the latter.

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