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Implications of Mitochondrial DNA

Author: Jennifer Gaither
Major: Microbiology and Zoology
Department of Microbiology and Molecular Genetics, Oklahoma State University, Stillwater, OK 74078, USA

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Mitochondria are often referred to as the powerhouse of the cell because they provide the energy needed for the cell to perform necessary cellular functions. Mitochondria also have their own source of DNA, although not all genes needed for mitochondrial function are encoded by the mitochondrial genome. While mitochondria have many important roles in the cell such as the site of the tricarboxylic acid cycle (TCA cycle) and providing the cell with energy in the form of adenosine triphosphate (ATP) through oxidative phosphorylation, mitochondrial DNA (mtDNA) can be associated with rapid evolution, disease, and aging. This review looks at different aspects of mtDNA, and explores the implications associated with evolution, diseases, and causes of aging related to mtDNA. In addition, this paper provides a brief overview of mtDNa.

Introduction

Mitochondrial DNA (mtDNA) has many implications, which are important to understand because "[m]itochondria contain the only extranuclear source of DNA in animal cells" (Greaves et al. 2012). To better understand, it is first necessary to understand mtDNA, how it is different from nuclear DNA, and how mtDNA is inherited. Every cell has only one copy of nuclear DNA, but can contain several hundred or thousand copies of mtDNA (Greaves et al. 2012) depending on the type of cell. Like nuclear DNA, mtDNA is double-stranded; however, mtDNA is circular, much like the nuclear DNA derived from bacteria. In addition mtDNA do not have any introns and most genes have no base pairs between them, which is also characteristic of bacterial DNA. These discoveries helped provide evidence that gave rise to the theory of endosymbiosis, which explains the evolution of multicellular organisms from unicellular organisms.

The human mitochondrion encodes very few genes (approximately 37 genes and about 16,569 base pairs) compared to the human nuclear genome which encodes approximately 30,000 genes and consists of 3 x 10^9 base pairs (Alberts et al. 2010). Among the 13 genes encoded by mtDNA are genes for oxidative phosphorylation, ribosomal RNAs (rRNAs), and transfer RNAs (tRNAs) (Greaves 2012). These rRNAs and tRNAs are important for translating proteins encoded by the mitochondrial genome.

Additional differences include the packaging of DNA and the lack of recombination in mtDNA. Nuclear DNA employs the use of proteins called histones, which package the DNA into nucleosomes and help condense the molecule. Mitochondrial DNA, on the other hand, is histone free. It is still unclear why mtDNA do not undergo recombination like nuclear DNA, however it is thought to be a result of maternal inheritance. Interestingly, recombination was once observed in a rare case of a human with both maternal and paternal mtDNA (Pakendorf and Stoneking 2005). Furthermore, mtDNA is usually strictly maternally inherited, with few extremely rare exceptions of paternal inheritance. This is because sperm mitochondria are marked by a protein called ubiquitin, which tags it for destruction in the oocyte (Pakendorf and Stoneking 2005)..

Recent Progress

One recent study by Brown et al. (2012) found that animal mtDNA evolves many times more rapidly than nuclear DNA. In order to compare evolutionary rates, one of the things this study performed was comparisons of sequence divergence rates between nuclear DNA and mtDNA in closely related primate species. Upon doing this Brown et al. found that "the mtDNA difference exceeds the nuclear DNA difference by an average of 5-fold, based on m, and 10-fold, based on p" (2012). Where m and p are the minimum and estimated number of base substitutions and are given by the equations used in

Brown et al. (2012) to estimate sequence divergence. The sequence divergence between nuclear DNA and mtDNA implies the evolutionary rates. This is due to the understanding that the rate of sequence divergence (for example, divergence in primary structure between nuclear DNA and mtDNA) can imply a rate of change from one organism to another, thus also implying an evolutionary rate. Since the divergence rate for mtDNA is much higher than that of nuclear DNA it is said that mtDNA evolves much more rapidly. According to Brown et al. (2012) several factors such as high mutation rate may be the cause for rapid evolution in mtDNA. Likewise, Pakendorf and Stoneking (2005) point out that mtDNA mutation rates are significantly higher than mutation rates of nuclear DNA. Therefore, it can be inferred that these high mutation rates can cause high sequence divergence rates, which implies faster rates of evolution in mtDNA.

A study conducted by Schaefer et al. (2008) looks at mtDNA and its association with disease. They estimated the prevalence of mtDNA disease with clinical manifestations to be about 9.18 in 100,000 people. The most common disease was identified to be due to one adenine to guanine point mutation, whereas large scale deletions in the mitochondrial genome were identified as the rarest type of mutation. However, diseases associated with mtDNA may be difficult to identify based solely on clinical signs because these diseases may have great overlap in symptoms with more common diseases. In addition, they seem to have a high degree of phenotypic variation, even those associated with the same mutation (Schaefer et al. 2008). Many of the clinical manifestations affect tissues that have a high energy demand such as the heart, skeletal muscle, or the central nervous system (Greaves et al. 2012). On a cellular level, "a chronic state of energy failure" (Greaves et al. 2012) is thought to be a fundamental sign of mutations in the mtDNA genome. However, it is important to note that not all diseases associated with mitochondria are due to mutations in the mtDNA genome. Some diseases of the mitochondria are due to mutations in the nuclear genome. The study by Schaefer et al. focused on disease associated with mutations in the mtDNA genome. Therefore, some may consider their prevalence estimate to be considerably underestimated.

Although still a debated topic, mitochondrial DNA has also been found to be associated with aging. A study by Das and Guha (2011) suggests that accumulations of point mutations and deletions can occur in the mitochondrial genome due to reactive oxygen species such as superoxide radicals and hydrogen peroxide, which are by-products produced during oxidative phosphorylation. Since mtDNA do not have any introns, any mutation or deletion can be detrimental to the protein product of the gene where the mutation occurs. "Oxidation-induced mtDNA mutagenesis produces a progressive deterioration throughout life in the respiratory capacity of an organism" (Das and Guha, 2011). However, this study also points out that the use of antioxidants, a supplementation that reduces the build-up of reactive oxygen species, can help with age-associated effects of oxidative phosphorylation on mtDNA

Discussion

While mitochondria play many important roles in the cell, mitochondrial DNA can be associated with rapid evolution, disease, and aging. It is important to take these implications into consideration because knowing things like the prevalence of disease and how it occurs can help us to make better diagnosis, treatments, and therapies for future generations. In addition, if disease prevalence is known, we can better assess the patients who may be at risk for disease by applying our knowledge of mitochondrial inheritance and associating it with family history. However, since these diseases tend to be hard to diagnose due to similar symptoms of more common diseases and phenotypic variation, there is a growing need to apply molecular techniques when analyzing diseases. Likewise, we may not be able to stop aging from occurring, however expanding our knowledge on aging associated with mtDNA could help slow some of the undesirable effects. Our knowledge of implications of the mitochondrial genome is still relatively young, and many more studies must be implemented to further our understanding of the underlying causes associated with mtDNA.

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