Mitochondrial DNA: from forensic genetics to the origins of humanity

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Abstract: Mitochondria are cellular organelles that provide cellular energy. Along with chloroplasts of plant cells, mitochondria are the only organelles that have genetic material. These peculiarities make mitochondrial DNA (mtDNA) one of the main research topics in the field of cytology and genetics. interest shared by criminalistics, which uses mtDNA analysis for forensic identification of DNA traces in which nuclear DNA analysis is not possible. In addition to being used in forensic investigation, mtDNA analysis has also been widely used in paleoanthropological investigation through the elaboration of human phylogenies, which retroact to only one female ancestor, known as mitochondrial Eve. In this context, this manuscript aims to address the relevance of this organelle in the field of criminalistics and the sciences of origins, presenting the scientific, philosophical and theological implications arising from the in-depth analysis of this cellular structure.

Keywords: Mitochondrial DNA; Forensic sciences; Mitochondrial Eve; Science of origins.

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DNA Mitocondrial: da genética forense às origens da humanidade

Resumo: As mitocôndrias são organelas celulares que fornecem energia para o funcionamento da maquinaria celular. Juntamente com os cloroplastos das células vegetais, as mitocôndrias são as únicas organelas que possuem material genético. Essas peculiaridades tornam o DNA mitocondrial (DNAmt) um dos principais tópicos de estudo no campo da citologia e da genética. Esse interesse é compartilhado pela criminalística, que se utiliza da análise do DNAmt para a identificação forense em vestígios biológicos nos quais a análise de DNA nuclear é inviável. Além de ser empregado na investigação forense, a análise do DNAmt também tem sido amplamente utilizada na investigação paleoantropológica por meio da elaboração de filogenias humanas, as quais retroagem a apenas uma fêmea ancestral, conhecida como Eva mitocondrial. Nesse contexto, o presente artigo visa abordar a relevância dessa organela no campo da criminalística e das ciências das origens, apresentando as implicações cientificas, filosóficas e teológicas advindas do estudo aprofundado dessa estrutura celular.

Palavras-Chave: DNA mitocondrial; Ciências forenses; Eva mitocondrial; Ciências das origens.

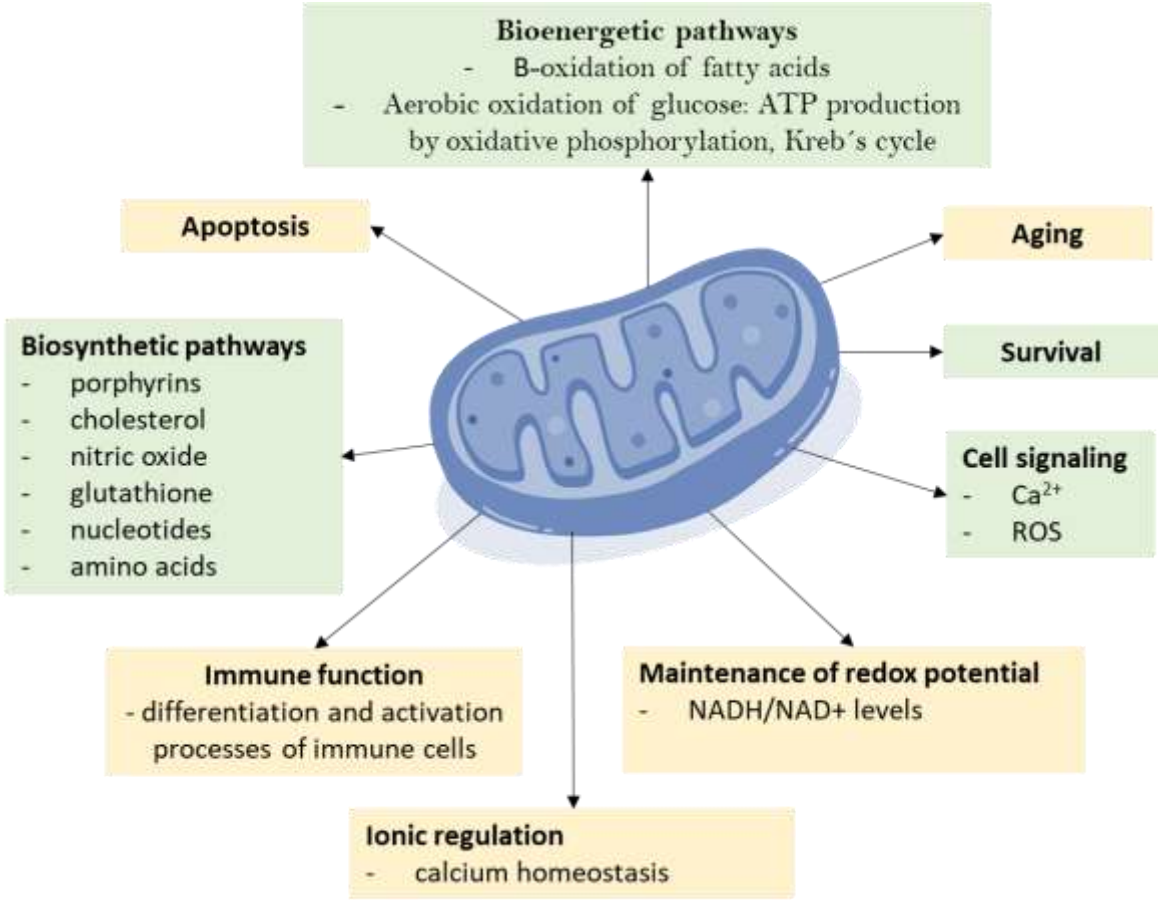
Introduction

Mitochondria

The discovery of the basic biological units that constitute living beings was only possible thanks to the invention of rudimentary microscopes during the 17th century. In this period, Robert Hooke (1635-1703) and Antonie van Leeuwenhoek (1632-1723) stand out as the responsible for coining the term “cell” and observing living cells for the first time, respectively. In 19th century, the recurrence of cellular structures in all organisms led Theodor Schwann (1810-1882) and Matthias Schleiden (1804-1881) to elaborate the cellular theory which stated that all organisms and their respective organs and systems were formed by cells (BOLSOVER *et al.*, 2004; KARP *et al.*, 2016). During the 20th century, the structure and functioning dynamics of organelles were elucidated. Mitochondria, for example, were initially described by the physiologist Albert von Koliker (1817-1905) who designated them as the “powers of the cell”. The term “mitochondria” was coined more than a decade later by Carl Benda (1857-193) (BENDA, 1898).

The importance of mitochondria for energy metabolism, was described in 1946 and its basic structure in 1950. These organelles have a cylindrical shape, can reach up to 10 µm in length and are found in algae, protozoa, fungi, animals and higher plants (SOUZA, 2005). The number mitochondrias varies according to the cell subtype and is directly associated with the cell's metabolic activity. Human striated muscle cells, for example, can contain up to 10,000 mitochondria while they are absent in erythrocytes. Each cell has an average of 500 to 2000 mitochondria (ALBERTS *et al.*, 2002; NARDIN & JOHNS, 2001). Mitochondria perform several functions related with bioenergetic pathways, aging, survival, cell signalling, maintenance of redox potential, ionic regulation, imune function, biosynthetic pathways and apoptosis (Figure 1) (KOKLESOVA *et al.*, 2021; SOUZA, 2005).

Figure 1 – Mitochondrial cell functions. Modified from KOKLESOVA *et al.*, 2021.



Mitochondrial DNA

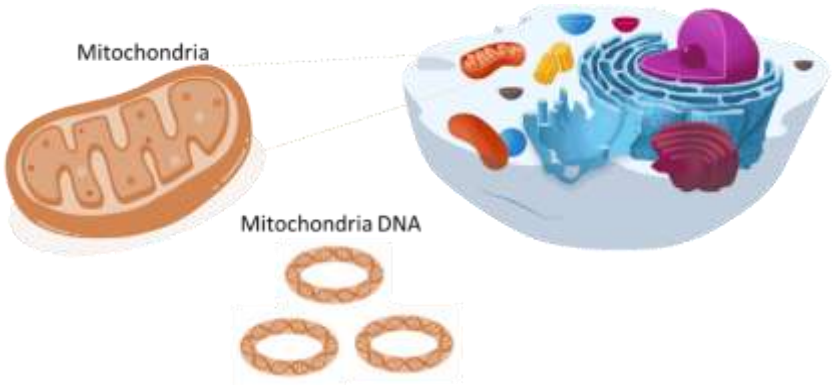
The vast majority of the cell's genes reside in the nucleus, but within the mitochondria we find a double-stranded, circular, intronless DNA molecule containing a H heavy chain

(Heavy and H-strand), and a L light chain (Light or L-strand), complementary to the heavy chain. The mtDNA has approximately 16,569 base pairs (bp) distributed in a coding region and a non-coding region. The coding region is formed by 37 genes that code for: (i) ribosomal RNAs (rRNA) (12S rRNA and 16S sRNA); (ii) Transfer RNAs (F, V, L1, I, Q, M, A, W, N, C, Y, S1, D, K, G, R, H, S2, L2, E, P, T); (iii) 13 proteins (ND1, ND2, COI, COII, ATP8, ATP6, COIII, ND3, ND4, ND4L, ND5, ND6 and CYT B) and (iv) the replication origins of the heavy and light strands of mtDNA (NONIN-LECOMTE; DARDEL; LESTIENNE, 2005; TANAKA; OZAWA, 1994).

The non-coding region of mtDNA is formed by 1,122 bp and is known as a hypervariable region (HV). The gene promoters of the coding region are located in the non-coding region, also called control region (HOLLAND & PARSONS, 1999). Considering that the control region has a large number of polymorphisms, it has become a widely studied area for human identification. More specifically, three highly polymorphic segments of the control region are studied for human identification purposes: (i) HV1; (ii) HV2 and (iii) HV3 (ANDERSON *et al.*, 1981).

The mtDNA molecule is highly polymorphic due to high mutation rates, which are much higher than those observe in nuclear DNA, which occur due to replication failures and the absence of repair mechanisms. It is estimated that mtDNA undergoes six to ten times more mutations than nuclear DNA (BROWN; GEORGE; WILSON, 1979; BROWN *et al.*, 1982; BUDOWLE *et al.*, 2003; JOHNSON & JOHNSON, 2001; UNDERHILL & KIVISILD, 2007; WALLACE *et al.*, 1987).

Figure 2 – Mitochondrial DNA.



MTDNA Analysis in Forensic Sciences

Nowadays, DNA analysis of biological traces collected in forensic sites has become a routine practice in criminalistics. DNA analysis alone is not sufficient to incriminate a suspect,

but it unequivocally establishes a connection between the forensic site and the suspect (MARQUEZ, 2012; PENA, 2005).

Although mtDNA is not as informative as nuclear DNA, it has some peculiarities that make it essential for human identification in certain samples. As the zygote only has the mitochondria of the mother, previously present in the egg, the mtDNA inheritance is uniparental, that is, exclusively maternal (THOMPSON & WILLARD, 1993). Therefore, the mtDNA is very important to establish family relationships of the examined individual. Mitochondrial DNA does not undergo recombination and the entire set is passed from mother to her offspring with the exception of selected point sequences. In this case, the maternal lineage can be used effectively for human identification in the occurrence of accidents and missing persons (BUDOWLE *et al.*, 2003; WILSON *et al.*, 1995).

Furthermore, mtDNA copies are abundant in cells and more resistant to degradation than nuclear DNA, so the analysis of these molecules is essential in scarce, old, degraded and/or contaminated samples (KOCH, 2008). The mtDNA regions of forensic interest are the hypervariable segments HV1 and HV2 of the control region due to the high mutation rate they present and the ease of analysis procedures. Furthermore, as they are short segments, they can be easily amplified using PCR (Polymerase Chain Reaction) and subsequently sequenced. Finally, as it is monoclonal and haploid, mtDNA provides results that allow an easy interpretation, however, it requires prior knowledge of nomenclatures, heteroplasmies and terms that refer to the various existing population data bases (BUDOWLE *et al.*, 2003; MORAIS, 2013).

The mtDNA analysis allows relating individuals through female ancestors but has no power of individualization, being considered an accessory technique, whose results are always disclosed in relation to a reference sequence (GARRIDO *et al.*, 2014).

More specifically, the analysis involves the study of frequency of polymorphisms markers identified in a sample in their representative population. For this purpose, a search should be carried out in population databases of mtDNA profiles. The most used of these databases is EMPOP (www.empop.org) (GARRIDO *et al.*, 2014; PARSON *et al.*, 2004).

In some cases, there may be more than one mitochondrial genome in the same cell, a phenomenon known as heteroplasmy. The frequency with which this phenomenon occurs is also used for forensic purposes (MONNAT; LOEB, 1985; SALAS; LAREU; CARRACEDO, 2001). The mtDNA analysis was employed, for example, to identify the American soldiers' bones who died in the Vietnam War and it was also widely used to identify the victims of the World Trade Center (LEWIS, 2004).

MTDNA Phylogeny

Through the use of mtDNA it is possible to carry out ancestry studies focused on paleoanthropology. In the human species, for example, specific haplogroups have been identified for certain ethnically described peoples. These haplogroups are made up of subsets of haplotypes that share common characteristics. Therefore, through the analysis of these haplogroups it is possible to reconstruct the migratory trajectories, perform phylogenetic analyzes and determine the degree of miscegenation of a given population. By analyzing the differences between the different haplogroups, it is possible to analyze the mutations accumulated throughout the history of maternal lineages in search of a common ancestry (ALLARD *et al.*, 2006; ALVAREZ, 2007; ALVES-SILVA, 2000; BUDOWLE *et al.*, 2003; VAN OVEN & KAYSER, 2009).

Haplogroups are designated following the sequence of the alphabet letters. As the haplogroups of native americans were the first to be described, being named A, B, C and D. The oldest haplogroups, designated as L, are africans, which corroborates the hypothesis that humanity would have been originated in the african continent. The antiquity of these haplogroups is supported by genetic studies in fossils, which also demonstrate that haplogroup L3 originated the macrohaplogroups M, N and R throughout human history (PAKENDORF; STONEKING, 2005; VAN OVEN & KAYSER, 2009). Over time, the nomenclature evolved combining letters and numbers and some haplogroups came to be framed within other haplogroups. The only letter of the alphabet not used in this nomenclature is "O" (HUDJASHOV *et al.*, 2007; VAN OVEN & KAYSER, 2009).

By definition, haplogroups are ethnically specific and can be correlated with specific regions. The seven haplogroups (L0, L1, L2, L2, L3, L4, L5, L6) of the macrogroup L are the oldest and belong to the african continent. The letters A, B, C, D, E, F, G and M represent the haplogroups that encompass most of the lineages described for native populations of America, Asia and Oceania. On the other hand, haplogroups H, HV, I, J, K, T, U, V, W and X represent the north african, european and east asian caucasian lineages. There are currently 25 haplogroups defined (FINNILA *et al.*, 2001; KIVISILD *et al.*, 2002; KONG, 2003; MACAULAY *et al.*, 1999; RICHARDS *et al.*, 2000; ROMERO *et al.*, 2014; SCHLEBUSCH *et al.*, 2009; TORRONI *et al.*, 1994).

MTDNA and the Sciences of Origins

The use of mtDNA to investigate the origins of humanity dates back to studies performed in the 1980s. These studies demonstrated that the greatest mtDNA variations occurred in african haplogroups. Several studies of uniparental lineages have been carried out, mainly analyzing the mtDNA in order to analyze historical events, evolutionary processes of different ethnicities, migrations, demographic past and other aspects related to the history of humanity. In 1987, Cann, Stoneking and Wilson discovered that, in fact, all humans alive today have a common female ancestor who probably lived hundreds of thousands of years ago in Africa, and they named this ancestor "mitochondrial Eve". From these studies, mtDNA started to appear in a large number of population studies that addressed the topic of human evolution (CARRACEDO *et al.*, 2005; HOLLAND, 1995; PAKENDORF; STONEKING, 2005; LADOUKAKIS; ZOUROS, 2017; VIGILANT *et al.*, 1991).

In this context, phylogenetic studies analyzing the mtDNA mutations of different haplogroups find convergences pointing to only one ancestral female. According to the mitochondrial Eve theory, all of humanity's haplotypes would have originated from a single ancestral female that supposedly lived 150,000 years ago on the african continent (SNUSTAD & SIMMONS, 2001; WILSON, 1992). mtDNA is inherited through the maternal lineage and, unlike nuclear DNA, they are not affected by homologous recombination during the process of gamete formation. Mitochondrial DNA mutations observed in reproductive system cells are passed directly to the offspring which makes possible to organize the human population into groups of individuals who share a set of mtDNA variants. Ultimately, all these groups can be unified in a common ancestry from a single ancestral female, known as mitochondrial Eve (MIURA *et al.*, 2022, WALLACE, 2005).

Interestingly, there is a certain convergence between the thinking held by scientists who hold an evolutionary view with those scientists who reconcile the biblical account of origins with the scientific evidence related to the Mitochondrial Eve Theory. Both proposals give this maternal ancestor the same name, and agree that modern mtDNA haplogroup differences arose throughout human history due to mutations and replication errors which were not initially in mitochondrial Eve. However, there are profound disagreements regarding the identity of this mitochondrial Eve and the timeline scale adopted. From an evolutionary perspective, this ancestral female would have lived approximately 150,000 to 180,000 years ago, while from a biblical perspective Eve would have lived a few thousand years ago (SNUSTAD; SIMMONS, 2001; WILSON, 1992). In order to verify which of the

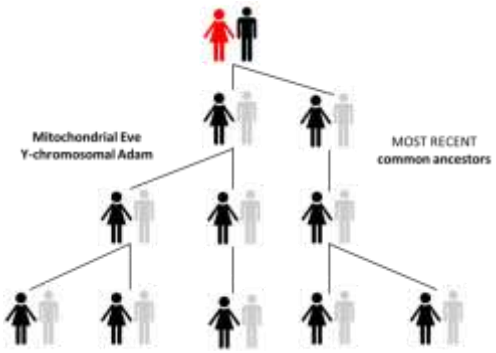
proposals fits the objective data, it is necessary to verify the mtDNA mutation rate and perform calculations to estimate the divergence time from this ancestral female.

The dates of hundreds of thousands of years attributed to mitochondrial Eve are calculated based on the time of phylogenetic divergence between humans and chimpanzees, which would have occurred approximately 5 million years ago. The data obtained is then calibrated with ages attributed to archaeological finds. That is, the basis for the calculations lies in the assumption that humans share a common ancestor with great apes. When these assumptions were ignored and the age of this female ancestor was calculated taking into account exclusively the mitochondrial DNA mutation rates, the age of "mitochondrial Eve" was revise from the previously theorized 180,000 years to only 6,000 years (GIBBONS, 1998).

This data is compatible with the useful life of DNA samples considering many studies that demonstrated the impossibility of existing DNA traces in natural environments for more than 10,000 years. In this context, DNA recovery from insects in amber, human fossils and even dinosaurs (CANO *et al.*, 1993; CHERFAS, 1991; KRINGS *et al.*, 1997) can be used to question the chronological age usually attributed to them.

Although not the focus of this manuscript, the inheritance of Y chromosome markers, as well as those present in mtDNA, lead us to only one male ancestor of humanity, known as Y-chromosomal Adam. From both a biblical and a naturalistic perspective, modern mtDNA and Y chromosome differences have emerged among the global human population. The two models explain these differences through mutations since the beginning of the human race and produce the same family tree (LUO *et al.*, 2018) (Figure 3). However, there is a clear incompatibility between a literal reading of edenic couple story portrayed in the Bible and the concept of mitochondrial Eve and Y-chromosomal Adam adopted by the evolutionary theory. In this sense, some christian scientists seek to reconcile the biblical account with evolutionary chronology and narrative by adopting a theistic evolutionary worldview.

Figure 3 – Mitochondrial Eve and y-chromosome Adam.



The publication of the book "The origin of species by means of natural selection, or the preservation of favored races in the struggle for life" in 1859 by Alfred Wallace and Charles Darwin proposed the evolution of species through natural selection and generated controversy both in the scientific and religious fields (DARWIN, 1859). One of the main obstacles to the acceptance of Darwin's theory by the 19th century clergy resided in the clear incompatibility of this theory with the creation account present in the first Genesis chapters.

At the beginning of the 20th century, as a way of seeking a reconciliation between the biblical Creation account and evolutionary theory, some scientists and theologians began to defend an evolutionary theism. Among them stands out the catholic theologian and paleontologist Pierre Teilhard de Chardin (1881-1955) and some scientists responsible for the modern synthesis of evolution such as Ronald Fisher (1890-1962) and Theodosius Dobzhansky (1900-1975).

Currently, one of the main advocates of evolutionary theism in the scientific community is the geneticist Francis Collins. According to Collins, evolutionary theism would defend the following ideas (COLLINS, 2007):

(i) despite immeasurable improbabilities, the properties of the universe appear to have been fine-tuned for the creation of life;

(ii) the universe came into being approximately 14 billion years ago by the imposition of God's laws;

(iii) although the exact mechanism of the origin of life on Earth remains unknown, once life emerged, the process of evolution and natural selection allowed the development of biological diversity and complexity over long periods of time;

(iv) once evolution took its course, no supernatural intervention was necessary (but some believe that evolution is "accompanied and guided by God", like Spinoza's idea of God-present-in-the-Universe);

(v) humans are part of this process, sharing a common ancestor with apes;

(vi) humans are unique in characteristics that defy evolutionary explanation of the Moral Law (the knowledge of right and wrong) and the search for God, which characterize all human cultures."

The theistic evolutionist view can be well exemplified by a quote from the essay titled “Nothing in biology makes sense except in the light of evolution” by Theodosius Dobzhansky (DOBZHANSKY, 1973):

> I am a creationist and an evolutionist. Evolution is God's or Nature's method of creation. Creation is not an event that took place in 4004 BC; it is a process that began about 10 billion years ago and is still ongoing··· Does evolutionary doctrine clash with religious faith? Not. It is a mistake to confuse the Holy Scriptures with elementary books on astronomy, geology, biology and anthropology. Only if the symbols are interpreted as meaning what they are not intended to mean do imaginary, unresolvable conflicts arise… the blunder that leads to blasphemy: the Creator is accused of systematic fraud.

However, to be possible the dialogue between the evolutionary theory and the Genesis account it is necessary that the narrative present in the first eleven chapters of Genesis be considered as symbolic or allegorical. In this context, its important to analyze the literary structure and terms used to describe divine creative activity in Genesis.

In the Genesis account of creation, the Hebrew word for day is *yom*. In fact, it can refer to a period of more than 24 hours. But in the case of the creation days, this is not the case, for when this word (*yom* – day) is accompanied by a "definite number", it indisputably refers to a twenty-hour day. This occurs on the days of the week mentioned in Genesis (Gen 1:5, 8, 13, 19, 23, 31). Interestingly, in Exodus 20:8-11 God commanded the israelites to work six literal "days" and rest on the seventh because He created in six "days" (using the same hebrew word "*yom* – day") (KAISER, 1970).

Moreover, the literary genre of Genesis 1-11 indicates the intentionally literal nature of the narrative. The entire book of Genesis is structure in terms of generations and the hebrew word *toledoth* is employed thirteen times to introduce each generation. Therefore, when the Genesis author use the term *toledoth* in Genesis 2:4, he intented the Creation narrative to be as literal as the rest of the Genesis narratives (KAISER, 1970).

Conclusion

The narrative structure of the first chapters of Genesis clearly points to literal historical events. Considering the genealogical records present in Genesis and throughout the books of the Bible, it can be concluded that creation portrayed in Genesis 1 and 2 would have occurred a few thousand years ago (HAY, 2013), which is in line with the age empirically attributed to mitochondrial Eve (GIBBONS, 1998). Therefore, the present manuscript demonstrated that the same differences, accumulated over time in mitochondrial DNA, used in forensic sciences, can be effectively employed to unravel some of the mysteries related to the origin of humanity. Finally, the evidence provided by the genetic material of this small organelle have philosophical and theological implications that allow building a bridge

between scientific and biblical knowledge. This bridge is most effectively built by considering the literalness of Genesis rather than the evolutionary theism worldview.

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