The mitochondrion is a highly specialized organelle, present in almost all eukaryotic cells [1] that generates energy for the cell to use, and are hence referred to as the "powerhouses" of the cell. Human mitochondria have a DNA of their own. The hereditary information in the mitochondria is entirely contained in the mitochondrial genome [2]. The mitochondria has a characteristic double membrane structure, the outer membrane is smooth while the inner membrane is thrown into folds called cristae (Figure 1). The large surface area of the inner mitochondrial membrane makes room for the oxidative phosphorylation system (OXPHOS) which is the energy generating apparatus of the mitochondria [4].

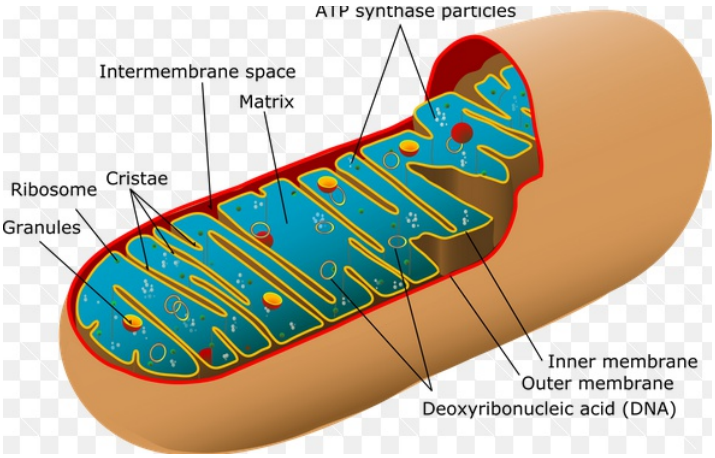


Figure.1 Mitochondria [3]

EVOLUTION

Symbiosis that happened two billion years ago between two coequal single-celled organisms resulted in the eukaryotic cell. One of the organisms became specialized in encoding the cellular and organismal structure and gave rise to nucleus-cytosol while the other became specialized in energy production and gave rise to mitochondrian. The interaction between genomes in the two organisms resulted in an organism in which the nuclear DNA (nDNA) had all the genes for structure and mitochondrial DNA (mtDNA) retained all the genes for the energy production of mitochondria [4].

INHERITANCE

The human mitochondrial DNA (mtDNA) is strictly maternally inherited. This is owing to the fact that the mammalian egg has around 100,000 mtDNA while the sperm contributes around 100 mitochondria to the fertilized egg. The sperm mtDNAs are contributed to the zygote at fertilization and will persist in interspecific crosses (eg: cross between lions and tigers; cross between different species) throughout development. But this kind of cross occurs rarely in nature. On the other hand, in intraspecific crosses (eg: cross between Bengal tiger and Siberian tiger; cross between sub-species within a species) the sperm mitochondria are selectively eliminated [4]. The sperm mitochondria are tagged by the recycling

marker ubiquitin, which appears to mark them for degradation on entrance into the oocytes [7]. The oocyte cytoplasm has a species-specific mechanism that recognizes and eliminates sperm mitochondria and mtDNA [6]. Paternal mtDNA transmission can occur only in some exceptional circumstances as highlighted in a case report of a 28-year-old man with mitochondrial myopathy due to a novel 2-bp mtDNA deletion in the ND2n gene (also known as MTND2), which encodes a sub-unit of the enzyme complex I of the mitochondrial respiratory chain. The mtDNA which had the mutation was determined to be paternal in origin and accounted for 90% of the patient's muscle mtDNA [5].

MITOCHONDRIAL ENERGY PRODUCTION

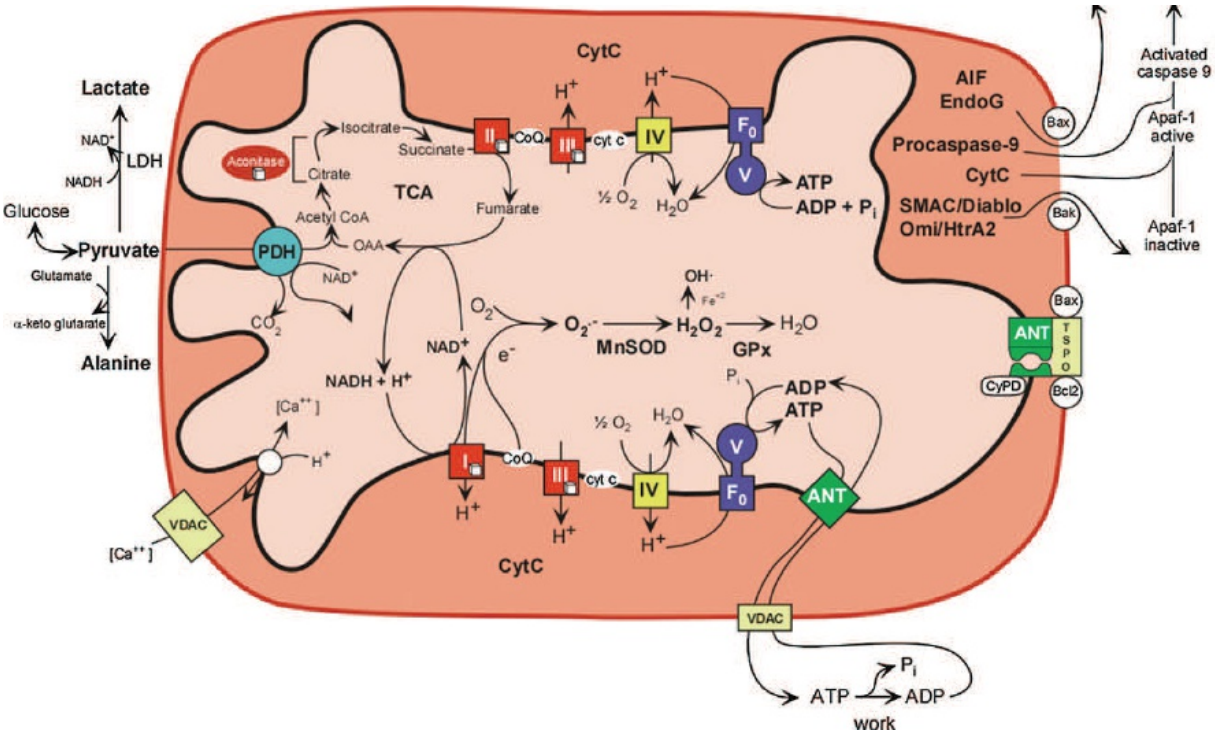


Figure.2 Mitochondrial energy production system

The mitochondria performs four central functions in the cell that are relevant to the pathophysiology of disease: They (*a*) provide the majority of the cellular energy in the form of ATP through oxidative phosphorylation (OXPHOS), (*b*) generate and regulate reactive oxygen species (ROS), (*c*) buffer cytosolic calcium (Ca^{2+}), and (*d*) regulate apoptosis through the mitochondrial permeability transition pore (mtPTP)[8].

OXPHOS

OXPHOS is composed of five multi-polypeptide enzyme complexes. Complexes I, II, III, and IV make up the electron transport chain (ETC), while complex V is the ATP synthase (ATPsyn). The OXPHOS complexes, designed I to V (Figure.2), are complex I (NADH: ubiquinone oxidoreductase) encompassing a flavin mononucleotide (FMN) and six Fe-S centers (designated with a cube); complex II (succinate: ubiquinone oxidoreductase) involving a flavin adenine dinucleotide (FAD), three Fe-S centers, and a cytochrome b; complex III (ubiquinol: cytochrome c oxidoreductase) encompassing cytochromes b, c1 and the Rieske Fe-S center; complex IV (cytochrome c oxidase) encompassing cytochromes a+a3 and CuA and CuB; and complex V (H+-translocating ATP synthase). Energetics in animals is based on the availability of reducing equivalents, consumed as carbohydrates and fats. Controlled oxidation of the electrons takes place with the help of complexes I, II, III, IV. The energy that is released is used to pump protons from the mitochondrial matrix across the inner membrane through the 4 complexes into the intermembrane space. ATP is synthesized by complex V which contains three distinctive components: the base, the stalk (F0) and the hexagonal head (F1). As protons move back through the proton channel in F0, they cause the central axle of the complex to spin causing them to change their conformation. This causes ADP and Pi to bind, be condensed into ATP, and be released into the matrix. Matrix ATP is exchanged for cytosolic ADP by the adenine nucleotide translocator (ANT).

OXPHOS is a major factor in regulating the cellular REDOX state which in turn mediates a wide variety of gene expression and cellular metabolic functions [4]. However, OXPHOS is also a major source of endogenous toxic free-radicals including hydrogen peroxide (H_2O_2), hydroxyl($HO^{\bullet}$) and superoxide($O_2^{-\bullet}$) radicals that are products of normal cellular respiration [17].

REACTIVE OXYGEN SPECIES (ROS)

Mitochondria are the primary source of endogenous ROS. The first of the ROS, superoxide anion (O_2^-) is generated by the transfer of one electron from the ETC to O_2. Mitochondrial O_2 is converted to H_2O_2 by manganese superoxide dismutase (MnSOD) and the resulting H_2O_2 is reduced to water in the brain, liver, kidney and heart muscle. However H_2O_2 in the presence of reduced transition metals is converted to highly reactive hydroxyl radical (OH), the most potent oxidizing agent of the ROS .The Fe-S centers of the tricarboxylic acid cycle and the ETC are the major targets of ROS reactivity. The mitochondria are particularly sensitive to oxidative stress [4]. The lack of histones in mitochondrial DNA (mtDNA) and the

diminished capacity for DNA repair render the mitochondria an easy target to oxidative stress events. ROS can damage cellular proteins, lipids, and nucleic acids. Hence, excessive mitochondrial ROS production can exceed the antioxidant defenses of the cell, and the cumulative damage can ultimately destroy the cell [8].

APOPTOSIS

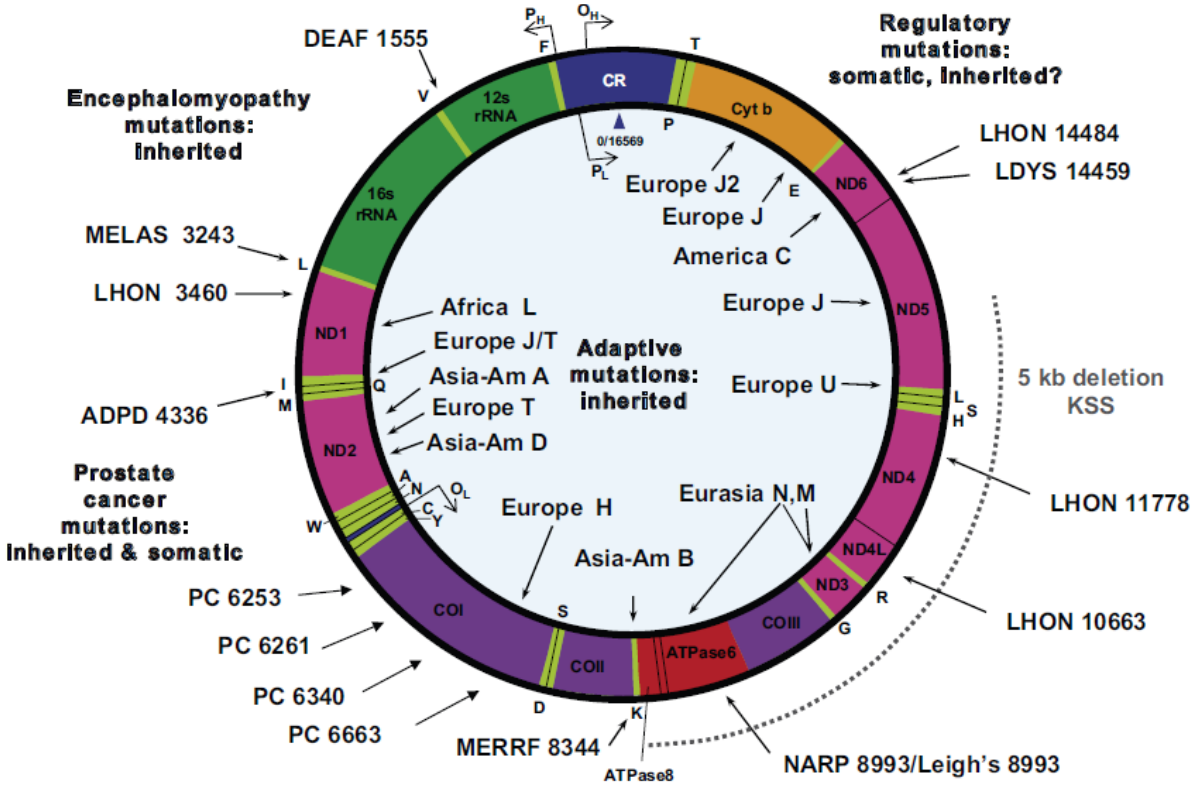
The mitochondria are also the major regulators of apoptosis, which is initiated through the opening of the Mitochondrial Permeability Transition Pore (mtPTP)**.** The mtPTP is activated when the biochemical health of the mitochondria and cell decline, specifically when mitochondrial energy production declines, ROS generation increases, and excessive Ca++ is released into the cytosol and taken up by the mitochondrion. When the mtPTP is activated, it opens a channel in the mitochondrial inner membrane, the potential energy stored as ΔP which is used to synthesize ATP in the matrix collapses, and programmed cell death (apoptosis) is initiated [8]. The VDAC (voltage-dependent anion channel) together with ANT, Bax, and the cyclophilin D (CD) protein are thought to come together at the mitochondrial inner and outer membrane contact points to create the mtPTP. The opening of the mtPTP is associated with the release of several pro-apoptotic proteins. Cytochrome c (cytc) interacts with and activates cytosolic Apaf-1, which then binds to and activates procaspase-9. The activated caspase-9 then initiates the proteolytic degradation of cellular proteins. Apoptosis initiating factor (AIF) and endonuclease G (EndoG) have nuclear targeting peptides that are transported to the nucleus and degrade the chromosomal DNA (see Figure2). Disease states that inhibit OXPHOS and increase ROS production make the cell highly susceptible to apoptosis [4].

MITOCHONDRIAL DNA

Mitochondrial DNA is a closed circular double stranded molecule located within the mitochondrial matrix. It spans about 16,500 DNA building blocks (base pairs), representing a small fraction of the total DNA in cells. It contains 37 genes, all of which are essential for normal mitochondrial function. Thirteen of these genes provide instructions for making enzymes involved in oxidative phosphorylation. The remaining genes codes for 22 transfer RNA (tRNA) molecules and ribosomal RNA (rRNA) including the small (12S) and large (16S) rRNAs. The 13 polypeptides of the mtDNA include 7 (ND1, 2, 3, 4, 4L, 5, and 6) of the 45 subunits of complex I, 1 (cytochrome *b*) of the 11 subunits of complex III, 3 (COI, II, and III) of the 13 subunits of complex IV, and 2 (ATP6 and 8) of the 16 subunits of complex V. The mtDNA also contains an approximately 1121-np control region that encompasses the heavy (H)- and light (L)-strand promoters (P_H and P_L) and the H-strand origin of replication (O_H). The L-strand origin (O_L) is located on the other side of the circle in a cluster of five tRNA genes (WANCY).

The most widely accepted model for mtDNA replication is that it starts at O_H using a RNA primer generated using L-strand transcript. The replication is bidirectional and asynchronous. However, recent

studies have suggested that the mtDNA may also replicate symmetrically from alternative origins [25]. mtDNA transcription initiates from the two promoters in the control region, one for each strand: P_L and P_H. P_H is responsible for transcribing the 2 rRNA genes,13 tRNA genes, and 12 of the protein coding genes. P_L transcribes the ND6 protein gene and nine tRNAs, and also generates the primers for H-strand replication at O_H. Both promoters are associated with a binding site for a nuclear-encoded mitochondrial transcription factor (Tfam). Tfam is a high-mobility-group DNA-binding protein with two DNA-binding domains and a carboxyterminal tail essential for transcription. Transcription from both promoters proceeds around the mtDNA circle, creating a polycistronic RNA. The mtDNA mRNAs are translated on mitochondrial 55S ribosomes (mitoribosomes) composed of a large 39S and small 28S subunit. These ribosomes have a smaller amount of rRNA than bacterial or eukaryotic ribosomes but a larger number of ribosomal proteins. Translation is thought to initiate with the binding of the small subunit to a 40-base region of the mRNA. The ribosome then moves back to the 5' end to initiate translation. Because they have their own self-replication genome and associated replicating, transcription and translation systems, mitochondrial DNA behave like semi-autonomous organisms within the cytoplasm of the cell [4].



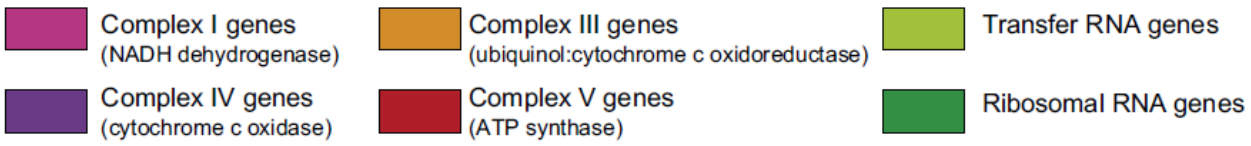


Figure.3.Human mitochondrial DNA map showing representative pathogenic and adaptive base substitution mutations. D-loop =CR (Control region). Letters around the outside perimeter indicate cognate amino acids of the tRNA genes. Arrows followed by continental names and associated letters on the inside of the circle indicate the position of defining polymorphisms of selected region-specific mtDNA lineages. Arrows associated with abbreviations followed by numbers around the outside of the circle indicate pathogenic mutations, the number being the nucleotide position of the mutation. Abbreviations: DEAF, deafness; MELAS, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes; LHON, Leber hereditary optic neuropathy; ADPD, Alzheimer and Parkinson disease; MERRF, myoclonic epilepsy and ragged red fiber disease; NARP, neurogenic muscle weakness, ataxia, retinitis pigmentosum; LDYS, LHON + dystonia; PC, prostate cancer[4].

MITOCHONDRIAL DYNAMICS

The mitochondria within a mammalian cell are in constant motion and undergoing repeated rounds of fission and fusion. Mitochondrial fusion and fission not only merges the mitochondrial inner and outer membranes but also mixes mitochondria matrices and redistributes the mtDNAs. The mammalian mitochondrial fusion machinery involves three major proteins: mitofusin 1 (Mfn1), 2 (Mfn2), and the Optic Atrophy-1 Protein (Opa1), while the mitochondrial fission machinery involves dynamin-related protein 1 (Drp1), Fis1, and Mff[8]. Each mammalian cell contains hundreds of mitochondria and thousands of mtDNAs. When a mutation arises in a mtDNA, it creates a mixed population of normal and mutant mtDNAs as some of them are affected while others are not. This state is known as heteroplasmy. When a heteroplasmic cell divides, the two types of mtDNAs (mutant and wild type) are randomly distributed into the daughter cells. This replicative segregation results in genetic drift towards either pure mutant or wild type populations, termed homoplasmic cells. As the percentage of mutant mtDNAs increases, mitochondrial energetic function decreases. When energy output is insufficient for normal tissue function, a threshold is crossed, symptoms appear, and apoptosis or necrosis may be initiated and clinical symptoms ensue [8].

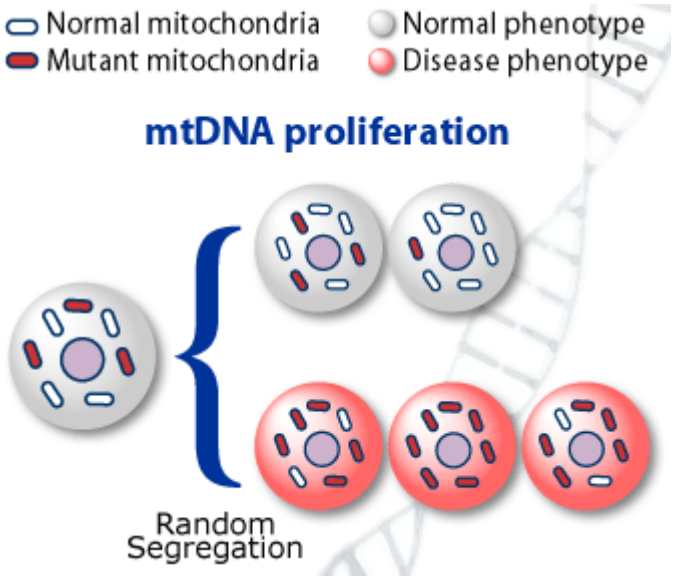


Figure.4 Replication and random segregation of heteroplasmic mutant mtDNA mutations [9]

MITOCHONDRIAL PROTEIN IMPORT

The mitochondrion is assembled from 13 mtDNA encoded polypeptides and ~1000–2000 nuclear-encoded polypeptides. These polypeptides are synthesized on cytosolic 80S ribosomes and vectorally transported into the mitochondrion via receptor binding to the outer membrane and transfer through a mitochondrial inner membrane import pore. Once inside the mitochondrial matrix, the proteins are folded and assembled by the mitochondrial heat shock protein 70 (mtHsp70) and mtHsp60. The mitochondrial protein import apparatus encompasses a set of outer and inner membrane complexes. The Tom complexes function to transport proteins across the outer membrane, while the Tim complexes function to transport proteins across the inner membrane. Proteins to be imported into the mitochondrion have embedded into their structure, specific mitochondrial targeting sequences. Most proteins to be imported into the mitochondrial matrix have an amino-terminal targeting peptide that is amphiphilic and basic. These amino-terminal targeting peptides are cleaved from the protein on import. Other proteins can have internal targeting sequences. Shown in figure 5 are various receptor complexes that bind specific protein and transport them through the intermembrane space of the mitochondria [4].

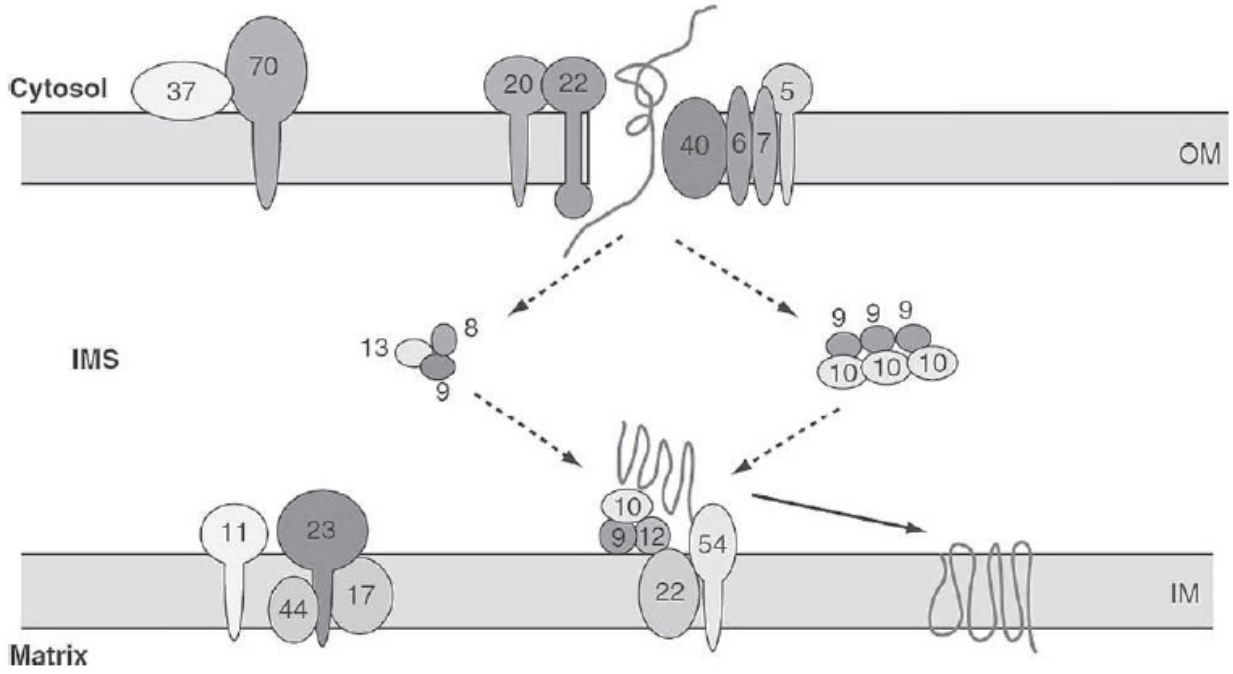


Figure.5 Import of cytosolically synthesized polypeptides through the inner and outer membrane. Shown in the figure are various protein complexes that aid in the import process.

mtDNA MUTATIONS

As modern humans migrated out of Africa, mtDNA mutations accumulated along radiating maternal lineages. When a mtDNA acquired a functional mutation beneficial in a particular environment, then that mtDNA became enriched by selection and radiated within that environment to give a cluster of related mtDNA haplotypes, known as a haplogroup. However, if the mutation disrupts an important mitochondrial function and are deleterious, they are removed by natural selection as disease [4]. Various mtDNA haplogroups have been associated with neurodegenerative diseases, diabetes and metabolic syndrome, infectious diseases, longevity and cancer [8]. The mtDNA mutation rate is much higher than that of nuclear genes. The reason could be that a nuclear gene, called DNA polymerase gamma (*POLG*), encodes the DNA polymerase responsible for replicating the mitochondrial genome. The POLG protein consists of two domains: a catalytic domain that exhibits polymerase activity and an exonuclease domain that is involved in the recognition and removal of DNA base-pair mismatches that occur during DNA replication. A recent study suggests that mitochondria may have a nucleotide imbalance that leads to decreased POLG fidelity and higher mitochondrial DNA mutation rates [10]. mtDNA pathogenic mutations include both rearrangement and base substitution mutations. Rearrangement mutations (intergenic mutations) can be either de novo deletion mutations or maternally transmitted insertion mutations that are unstable and generate deletion mutations in postmitotic cells. Most deletion mutations remove at least one tRNA and thus affect protein synthesis. MtDNA-rearrangement syndromes are invariably heteroplasmic and can result in a range of clinical manifestations and severities. Base-substitution mutations (intragenic

mutations) can alter either polypeptide genes (polypeptide mutations) or rRNAs and tRNAs (protein-synthesis mutations). Pathogenic polypeptide mutations encompass a broad spectrum of multisystem diseases, including LHON, Leigh syndrome and mitochondrial myopathy. Mitochondrial tRNA and rRNA protein-synthesis mutations can result in multisystem diseases such as Alzheimer disease, Parkinson disease, etc. Mutations in the mtDNA have been observed to accumulate with age in a variety of post-mitotic tissues in a wide range of species, and in a spectrum of complex of age-related diseases. Increasing this somatic mtDNA mutation rate in mice increases their aging rate while decreasing the somatic mtDNA mutation rate by introducing catalase into the mitochondrial matrix extends mouse life span. Therefore, the accumulation of somatic mtDNA mutations provides an aging clock that helps define an animal's life span and contributes to the delayed-onset and progressive course of complex diseases. Moreover, both somatic and germline mtDNA mutations have been associated with cancer [8]. Mutations in the nDNA-encoded genes for mitochondrial biogenesis result in the destabilization of the mtDNA with symptoms ranging from mild neurological complications to lethal symptoms. Milder nDNA mutations may also interact with milder mtDNA mutations to create a severe disease [11].

MITOCHONDRIAL ETIOLOGY FOR NEURODEGENERATIVE DISEASES:

Alzheimer's and Parkinson's disease

Mitochondria play a pivotal role in neuronal cell survival or death as they are the major regulators of both energy metabolism and cell death pathways. The origins of neurons themselves: their spatially-extended structure, having been evolved largely by and for their mitochondria, provides both refuge from a potentially hostile nuclear environment where they are continually threatened with lysosomal degradation, and also a way to select and deliver mitochondrial derivatives and mtDNA nucleoids to parts unknown[22]. Mitochondrial dysfunction is the major factor in the etiology of Alzheimer Disease (AD), Parkinson Disease (PD), Amyotrophic lateral Sclerosis (ALS), Huntington's disease and several other psychiatric disorders. These diseases preferentially affect the central nervous system, which is the tissue with the highest mitochondrial energy demand [12]. This report briefly summarizes how mitochondria are involved in the pathogenesis of both AD and PD.

ALZHEIMER'S

AD is the most commonly recognized form of late-onset dementia. It is a progressive neurodegenerative disease that has been associated with the deposition of amyloid beta peptide plaques, a condition termed as amyloidosis and neurofibrillary tangles in the brain. Clinically, AD has been split into early-onset and late-onset forms, divided roughly at age 65. Early-onset AD has been associated with mutations in several autosomal dominant loci, including the amyloid precursor protein (APP) gene on chromosome 21, presenilin 1 (PS1) on chromosome 14 and PS2 on chromosome 1[4]. PS1 gene provides instructions for making presenilin 1. This protein is part of a complex called gamma- (γ-) secretase and carries out the major function of the complex, which is to cut apart (cleave) other proteins into smaller pieces called

peptides. The γ-secretase complex is involved in processing APP, which is made in the brain and other tissues into smaller peptides, including soluble amyloid precursor protein (sAPP) and several versions of amyloid-beta (Aβ) peptide. But mutations in this gene produce an abnormal protein which interferes with the function of the γ-secretase and results in a longer, toxic version of Aβ peptide. Copies of this protein fragment stick together and build up in the brain, forming clumps called amyloid plaques which lead to the death of neurons and are a characteristic feature of AD [15].

Few of several mitochondrial defects linked to AD:

Synapses are sites for memory storage in brain, and are packed with mitochondria. Synaptic mitochondria are involved in regulation of neurotransmitter release during intense neuronal activity [14]. Synaptic damage is the best pathologic correlate of cognitive decline in AD [13]. AD is associated with neurofibrillary tangles, which are composed of hyperphosphorylated Tau. The N-terminal 20–22 kDa of the Tau protein is enriched in the synaptosome mitochondria of AD patients and correlates with Aβ multimeric species. Therefore, Aβ interacts with 20–22 kDa N-terminal Tau and the complex may impair mitochondrial function. Aβ is known to enter mitochondria where it inhibits mitochondrial function by increasing mitochondrial membrane viscosity, causing a decrease in ATP/O ratio, reducing electron transport chain (ETC) activity, increasing ROS production, and facilitating cytochrome c release[12].

Azide-induced COX (complex IV) inhibition has been shown to change the processing of the APP and induce production of an amyloidogenic derivative of APP. Hence, mitochondrial dysfunction could contribute to the amyloidosis observed in AD. Amyloidosis could further destabilize calcium homeostasis and facilitate excitotoxicity(neurons are damaged and killed by the overactivations of receptors for the excitatory neurotransmitter glutamate). Exposure to Aβ causes ultrastructural damage to both the mitochondria and golgi apparatus. Epidemiological data suggests that inheriting AD from the mother is 1.7–3.6 times more likely than inheriting the disease from the father. This strong maternal bias in transmission of AD suggests that some mtDNA variants may be risk factors for AD [4]. A novel mitochondrial DNA transfer RNA mutation (tRNATrp) at position 5549 was identified in a dementia patient. Postmortem analysis of the brain revealed diffuse and moderate neuronal loss in the cortex and basal ganglia with gliosis present throughout the brain. Ragged Red fibre(RRFs)and cytochrome c oxidase-negative-staining(COX) fibers were evident on skeletal muscle analysis, as were morphologically abnormal mitochondria on electron microscopy of skeletal muscle. A complex I defect was detected in mitochondrial respiration assays. Hence, this tRNATrp mutation demonstrates that mitochondrial defects can cause dementia [4].

Late-onset AD cases are commonly associated with the apolipoprotein gene ε4 allele (ApoE ε4). This association has been linked to mitochondrial dysfunction by demonstrating that transgenic mice which over-express ApoE ε4 have reduced levels of complexes I, IV, and V. Apolipoprotein (apo) E4, a 299-aa

protein is a major risk factor as the lipid(aa 241-272) and receptor-binding regions(aa135-150) in apoE4 fragments act together to cause mitochondrial dysfunction and neurotoxicity[12][18].

An interesting study has found that levels of dynamin-like protein 1 (DLP1), a regulator of mitochondrial fission and distribution, were decreased significantly in sAD (Sporadic AD) fibroblasts. The study also concluded that elevated oxidative stress and increased Aβ production are likely the potential pathogenic factors that cause DLP1 reduction and abnormal mitochondrial distribution in AD cells.

Mitochondria apart from generating energy in the form of ATP also generate free radicals and if the amount of free radical species produced overwhelms the neuronal capacity to neutralize them, oxidative stress occurs, followed by mitochondrial dysfunction and neuronal damage. Many preventive measures such as antioxidants and mitochondrial dynamics protectors will only help prior to the onset of dementia. The development of drugs that are able to reduce and clear Aβ, to stabilize the tau and microtubule proteins, to protect the mitochondrial membrane potential and to prevent excitotoxicity ideally will halt the cascade that leads to the development of AD. However, a majority of therapeutics will require a long process of clinical development [20].

PARKINSON'S

About 20% of AD patient brains also show the neuropathologic features of PD. Idiopathic PD is a progressive movement disorder characterized by bradykinesia, rigidity, and tremor associated with the death of dopaminergic neurons in the substantia nigra. Clinical symptoms generally become apparent when ~80% of the dopaminergic neurons are lost. Neuropathologically, PD patients' neurons contain characteristic cellular inclusions known as Lewy bodies composed of α-synuclein and ubiquitin [4]. Both genetic susceptibility and environmental risk factors contribute to the sporadic form of this disease.

Mutations in 4 nuclear genes have been identified which are involved in encoding proteins (PINK1, PARKIN, Omi/HtrA2, DJ-1) that are either transported to or into the mitochondria. Loss of function mutations in the PARK2 gene encoding Parkin, a multifunctional E3 ubiquitin protein ligase, and the PARK6 gene encoding the 581 amino acid protein PTEN-induced kinase 1 (PINK1) together represent the most frequent cause for early onset PD[21]. Parkin is expressed in the brain, skeletal muscle, and other tissues, and muscle and cells lacking parkin are more sensitive to intracellular Aβ toxicity. Increased levels of parkin are protective of both mitochondrial toxins and Aβ. Mutations in Leucine-rich repeat kinase2 (LRRK2) account for 1-2% of spontaneous cases. LRRK2 is a serine-threonine protein kinase as well as a GTPase, and the most common PD mutation causes a G2019S codon change. Patient fibroblasts harboring a mutant LRRK2 have reduced mitochondrial membrane potential, reduced ATP production using complexes I, II, or IV-lined substrates and increased mitochondrial elongation and interconnectivity [4].

Macro-autophagy is a general process to degrade proteins and cellular components and organelles. Products determined for degradation are engulfed by the autophagosome which fuses with lysosomes and the included proteins or cellular organelles are subsequently degraded by hydrolytic enzymes. Degradation of mitochondria by this process is referred to as mitophagy. Mitophagy is key to keeping the cell healthy. It promotes turnover of mitochondria and prevents accumulation of dysfunctional mitochondria which can lead to cellular degeneration and neurodegenerative disorders. Mitochondrial clearance mechanisms are controlled by PD-associated genes PINK1, Parkin, DJ-1 and Omi/HtrA2. Loss of function mutations in these genes result in reduced lysosomal activity and impaired mitophagy with accumulation of dysfunctional mitochondria [21].

mtDNA are packaged in nucleoids. Mitochondrial fission continuously isolates nucleoids packed with mutant mtDNA in a surrounding membrane vesicle so that their defect can be recognized by PINK1 and removed by PARKIN and ATP13A2. Therefore, fission is essential for PINK1 and PARKIN activation. Overexpression of α-synuclein which is characteristic of Parkinson's disease inhibits mitochondrial fission. Overexpression or triplication of α-synuclein results in long mitochondria which would inhibit the separation and removal of mutant mtDNAs. This effect can only be compensated by overexpression of PINK1, PARKIN or DJ-1[4].

Conclusions

Mitochondrial dynamics in combination with mitophagy is a beneficial process especially when the extent of molecular damage is low. However, when a certain threshold of damage is reached (during aging or under pathological conditions) it is counterproductive to further propagate or mix this damage. It is more beneficial to keep healthy mitochondria apart from the damaged ones. A deceleration of fusion-fission cycles delays reaching thresholds of damage that lead to the degeneration of the system. This reduction of fusion-fission cycles, however, make mitochondria more vulnerable to newly acquired random molecular damage. Researchers currently are unable to manipulate the mitochondrial genome with the same facility that they can manipulate nuclear sequences. However, as their ability to insert mutation reporters or selectable markers into the mitochondrial genome increases [22], solutions will be found to protect these power houses of the cell. A recent step forward in the field of reproductive medicine has been to legalize mitochondrial DNA transfers which involve 3 sets of DNA (couple and donor) to create an embryo. If the mother had damaged mitochondria, only the nucleus was removed from the unfertilized egg and transferred to the donor's cell after removing the donor's nucleus and then fertilized to create an embryo. This approach is however embroiled in ethical concerns as many view it as a death of two embryos to create a third one [24]. A question that hangs without an answer is if the mother had nuclear DNA mutation which could harm the mitochondria in the long run, then it would eventually damage the healthy one too.

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