Healthy mitochondrial DNA in balanced mitochondrial dynamics: A potential marker for neuro-aging prediction (Review)

MADE PUTRA SEMADHI[1,2], DEWI MULYATY[3], ELI HALIMAH[2] and JUTTI LEVITA[2]

[1]Prodia National Reference Laboratory, Jakarta 10430; [2]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Sumedang 45363; [3]Prodia Widyahusada Co., Jakarta 10430, Indonesia

Received September 26, 2023; Accepted May 15, 2023

DOI: 10.3892/br.2023.1646

Abstract. The mitochondrial genome or mitochondrial DNA (mtDNA) is released as a response to cellular stress. In mitochondrial biogenesis, active communication between the mitochondria genome and nucleus is associated with the mtDNA profile that affects the mitochondrial quality. The present review aimed to assess the molecular mechanism and potential roles of mitochondria in neuro-aging, including the importance of evaluating the health status of mtDNA via mitochondrial dynamics. The normal condition of mitochondria, defined as mitochondrial dynamics, includes persistent changes in morphology due to fission and fusion events and autophagy-mitophagy in the mitochondrial quality control process. The calculated copy number of mtDNA in the mitochondria genome represents cellular health, which can be affected by a long-term imbalance between the production and accumulation of reactive oxygen species in the neuroendocrine system, which leads to an abnormal function of mitochondria and mtDNA damage. Mitochondria health is a new approach to discovering a potential indicator for the health status of the nervous system and several types of neurodegenerative disorders. Mitochondrial dynamics is a key contributor to predicting neuro-aging development, which affects the self-renewal and differentiation of neurons in cell metabolism. Neuro-aging is associated with uncontrolled mitochondrial dynamics, which generates age-associated diseases via various mechanisms and signaling routes that lead to the mtDNA damage that has been associated with neurodegeneration. Future studies on the strategic positioning of mtDNA health profile are needed to detect early neurodegenerative disorders.

Correspondence to: Professor Jutti Levita, Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Jl. Raya Bandung-Sumedang km 21 Sumedang, Bandung, West Java 45363, Indonesia
E-mail: jutti.levita@unpad.ac.id

Key words: cellular health, mitochondrial DNA, mitochondrial dynamics, neuro-aging

Contents

1. Introduction
2. Balance quality control role of mitochondria leads to healthy mitochondrial dynamics
3. Mitochondria serve an essential role in response to neuro-aging
4. Mitochondrial dynamics as a key factor in predicting an early neuro-aging
5. Conclusion

1. Introduction

Mitochondria serve critical biological roles in the cell, including the production and control of reactive oxygen species (ROS), preservation of Ca^{2+} ion homeostasis, and modulation of programmed cell death (1,2). As an essential organelle, mitochondria serve a role in the generation of fatty acids and integrate the cell signaling circuitry that modulates cell survival, immune response, and autophagy (3,4). Therefore, the dysfunction of mitochondria can trigger damage (5,6).

As the energy generator, the genome of mitochondria, namely mitochondrial DNA (mtDNA), encodes 37 key genes and 13 mitochondrial proteins, two RNAs and 22 transfer RNAs (3,7,8). In response to cellular stress that triggers unbalanced intracellular processes such as respiration, energy production in the form of ATP, or apoptosis, mtDNA fragments are released as cell-free mtDNA (cf-mtDNA) in the bloodstream (9-11). cf-mtDNA is smaller compared with nuclear cfDNA. Moreover, cf-mtDNA is present in large amounts in patients with hepatocellular and prostate cancer (9,12).

Mitochondria interact with organelles, such as endoplasmic reticulum, lysosomes, cytoskeleton, peroxisomes, and nucleus, to accomplish their bioenergetics, metabolism, and apoptosis roles (11,13). These processes were predicted to be fundamentally active and are not controlled by other reactions. Previous work has reported the arrangement of indiscriminate mitochondrial protein import (4). This activity represents the health of mitochondria as well as the functional condition (14). The function of mitochondria is associated with transcription in the nucleus in response to intrinsic and extrinsic signals, such as modulation of the intracellular reduction-oxidation state, nutrient deprivation and exercise (15,16).

A previous lineage tracer study reported that haplogroup U5 is the most ancient haplogroup in Europe (17). Many studies categorize mtDNA in haplogroups, which is useful to trace maternal phylogenetic lineages, and is synergistically communicated from mitochondrial genome. The U5b2c1 haplogroup is found uncommon in modern populations (17-19). The phenotypes of the disease are associated with specific sequence mutations in mtDNA variations, for example, mitochondrial encephalopathy lactic acidosis with stroke-like episodes) syndrome Clinical phenotypes are correlated with human mtDNA pathogenic mutation, e.g., in patients with Kearns Sayre syndrome). Therefore, a mismatch between the nuclear and mitochondrial genome may affect mitochondria quality and leads to cellular problems, such as respiratory dysfunction, DNA damage (20-22).

The present review aimed to assess the molecular mechanism and potential roles of mitochondria in neuro-aging, including the importance of evaluating the health status of mtDNA via mitochondrial dynamics.

2. Balance quality control role of mitochondria leads to healthy mitochondrial dynamics

The quality control process of mitochondria, which includes fission and fusion, mitophagy, transport and biogenesis, sustains its balance and supports cellular health (23). Specifically, the normal condition of mitochondria, defined as mitochondrial dynamics, involves changes of morphology due to fission and fusion events (24). During traumatic conditions, such as lack of nutrition, two mutated genes may merge and allow functional complementation by RNA, resulting in new mitochondria and maintaining its respiratory function (25). The basic concept of balanced mitochondrial dynamics that leads to healthy mitochondria is presented in Fig. 1.

By contrast, the fission process triggers the breakdown of mitochondria into smaller fragments to facilitate transport and autophagy (13). Fission often induces dissociation of damaged components, thus, the ability of mitophagy is impacted by impaired fission (26). Mitophagy is key to remove any malfunctioning or unneeded mitochondria and direct them to autophagosomes to sustain quality control (27).

To manage organelle and protein turnover within cells, autophagy and apoptosis perform mitochondria quality control (5,17). Autophagy works by recycling selective intracellular organelles, while apoptosis works by removing damaged cells. In certain conditions, e.g., in severe cell damage, autophagy induces apoptosis or necrosis by degrading the cytoplasm excessively. There is a unique cellular response which induces autophagy and the mechanisms of cell death that leads to normal removal of dead cells, as well as immune recognition of antigens (28). Mitochondria serve an essential role in the connection between autophagy and apoptosis that influences pathological conditions (29).

Mitochondria manage damaged proteins or remove abnormal organelles to maintain their function (27). Impairment of quality control decreases of the balance of normal cellular function and lead to decreased survival and general cell health associated with aging (30). Thus, mitochondrial impairment and dysregulation are associated with neurodegenerative disorders (Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis), metabolic syndromes, and cancer (5).

In addition, mitochondria fission increases the number of organelles to activate biogenesis and remove injured organelles for autophagic degradation (31). The balance between fusion and fission regulates distribution of mtDNA, mitochondrial biogenesis and proteins (11). Abnormal function of chaperones and proteases may lead to accumulation of unfolded/misfolded/damaged proteins/protein aggregates and orphaned subunits (7,4,27). Quality control of impaired mitochondria is a therapeutic approach in many types of neurodegenerative disease, e.g., Parkinson's disease, Huntington's disease, and Alzheimer's disease. It is hypothesized that these neurodegenerative diseases associated with mitochondrial genetic improvement are also associated with mitochondrial disease and disorder (28,32).

3. Mitochondria serve an essential role in response to neuro-aging

In relation to cellular health, mitochondria are actively studied; mitochondrial impairment due to cellular senescence is associated with certain types of neurodegenerative diseases (33,34). Mitochondrial-associated disorder or mitochondrial dysfunctions such as neurodegenerative disorders, neurometabolic diseases, neuroaging, have a prevalence of 1:2,000 individuals (17,13). Mitochondrial-associated disorders mostly are caused by the mutations of genes that alter mtDNA replication and transcription and mitochondrial mRNA translation, thus decreasing the mitochondrial oxidative phosphorylation (OXPHOS). The inhibition of OXPHOS process may also be caused by dysfunction of respiratory chain enzyme complexes and ATP synthase in the mitochondrial inner membrane folds. This dysfunction leads to cell-specific stress responses and health problems, e.g., neuroaging or neurodegenerative disorders (10).

Copy number of mtDNA (mtDNA-cn) in mitochondria genome represents cellular health. cn can be measured in peripheral blood mononuclear cells (7,35). Studies have shown that mtDNA is liberated in small amounts in the blood under cellular stress and can be detected in plasma in the form of circulating cf-mtDNA (ccf-mtDNA) (6,9). Furthermore, imbalance between production and accumulation of ROS in cells and tissue may lead to the movement of mtDNA into the cytoplasm and the extracellular region. This is triggered by long-term neuroendocrine, inflammatory, oxidative and metabolic stress and may result in mitochondrial dysfunction and mtDNA damage (6,9). The effect of unbalanced mitochondrial dynamics on mitochondria is presented in Fig. 2.

cfDNA derived from mtDNA has been widely investigated in cancer and inflammatory, cardiovascular, and metabolic disease (10,11,36). Therefore, mitochondrial health is a novel approach to discover potential indicators for neurological and brain health in conditions such as depressive disorders, Alzheimer's disease, dementia and Parkinson's disease (35,37). Levels of ccf-mtDNA and cellular mtDNA-cn may be associated with oxidative stress and cellular senescence. mtDNA is vulnerable to oxidative stress due to lack of protective histones and limited DNA repair mechanisms. Glutathione peroxidase,

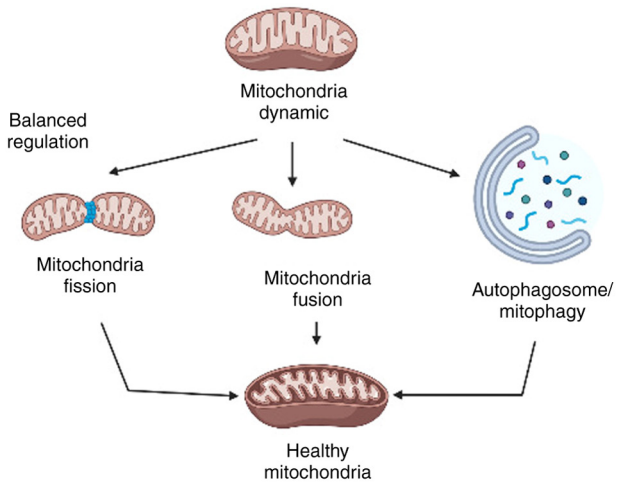


Figure 1. Balanced mitochondrial dynamics leads to healthy mitochondria. Figure is created using Biorender (biorender.com/).

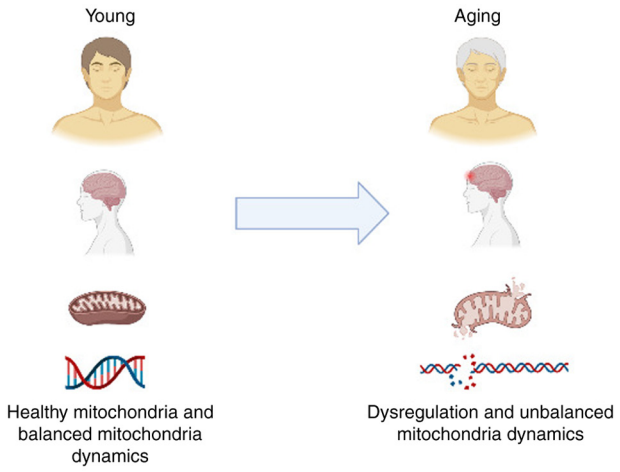


Figure 2. Balanced mitochondrial dynamics leads to healthy mitochondria. Figure is created using Biorender (biorender.com/).

an antioxidant enzyme, is required to protect the mitochondria and prevent dysfunction (38).

Studies have shown that mtDNA mutations are positively related with aging, depression and Parkinson's and Alzheimer's disease (11,15). Evidence has shown that dysregulated mitochondrial dynamics and mutations due to mtDNA replication induce aging and increased mtDNA mutation rates is correlated with the aging rate (11,15). High levels of mtDNA deletion are found in the substantia nigra neurons of aging patients with Parkinson's disease. mtDNA deletion cause human disease and their accumulation play a role in the aging process (39). Parkinson's disease is a neurodegenerative disease characterized by a depletion of dopamine neurons in the basal ganglia in the midbrain and the accumulation of synuclein (13,30).

Studies on Parkinson's disease have indicated a defect in Parkin RBR E3 ubiquitin-protein ligase and PTEN-induced kinase 1 (PINK1) (30,38). An autosomal recessive mutation at two genes (PARK2 and PARK6) that encode outer mitochondrial membrane kinase PINK1 and the cytosolic Parkin E3 ubiquitin-protein ligase, lead to the reduction of mitochondrial damage (30,38). Impairment of these processes leads to loss of muscle and dopaminergic neurons and affects male infertility in a way that can be fixed by inducing mitochondrial fission (40). As a novel biomarker of depression, ccf-mtDNA levels exhibit a positive correlation with inflammatory symptoms of depression (41). A recent cohort study of patients with depressive disorder (n=281; 36% with a personality disorder and 13% with bipolar; 93% receiving mono- or multi-psychotropic drugs), demonstrated a significant difference in mean ccf-mtDNA levels between patients with a current (n=236) or remitted depressive episode (n=45) and healthy participants (n=49); treatment using mood stabilizers, such as lamotrigine, valproic acid or lithium, was associated with decreased ccf-mtDNA proportion (41). The aforementioned study hypothesized that mtDNA is recognised as a damage-associated molecular pattern (DAMP), activating the innate immune response primarily by attaching to the toll-like receptor 9. The aforementioned study suggested that ccf-mtDNA may be differentially regulated in different subtypes of depression. ccf-mtDNA in inflammatory depression subtype is correlated with worse treatment response to conventional selective serotonin reuptake inhibitors and a more prospective anti-inflammatory agent, such as omega-3 fatty acids (41). The mitochondrial studies in patients with neurodisorders are summarized in Table I.

Alzheimer's disease is associated with heteroplasmic mtDNA mutations. This disease is characterized by the formation of amyloid-β (Aβ) plaques in the extracellular space, which exhibits substantial neuronal loss (4). Accumulation of Aβ plaques increases oxidative damage in neurons, is associated with the accumulation of reactive oxygen species in the mitochondrial (42), and induces the severity of mtDNA damage. Eventually, this condition steers to the rise of oxidized nucleic acid in mtDNA (43).

4. Mitochondrial dynamics as a key factor in predicting an early neuro-aging

Mitochondrial dynamics are critical contributors in predicting the development of neuro-aging (44). Mitochondrial dynamics influence the self-renewal and differentiation of neuron in cell metabolism (13,44). In neurons of neonates, small mitochondria fission is observed, which size increases during maturity process. By contrast, the developing brain exhibits more fused and fragmented mitochondria (33,43). In neurogenesis, mitochondrial dynamics is associated with cell cycle; there is increased escalated fusion during G1/S phase, followed by fission during G2 and mitosis (5,45). Mitochondrial fission occurs during neural stem progenitor cell (NSPC) mitosis, which exhibits dichotomic behaviour of the daughter cells: Those destined to remain NSPCs display high levels of mitochondrial fusion, whereas prospective neuronal cells maintain higher levels of mitochondrial fission (24,46).

With aging, mitochondria will accumulate oxidative damage with reduced reparative ability leading to impairment and dysfunction (26). Escape of electrons during the electron transport cascade in OXPHOS may generate oxidative stress and disrupt the cellular metabolic and signalling routes (16). Mitochondrial fission and fusion are associated with mitochondrial activity. These activities, (such as programmed cell death regulation, haem complexes biosynthesis, calcium signalling,

Table I. Mitochondrial biomarkers for neuro-aging prediction.

First author, year	Mitochondrial biomarker	Clinical results	(Refs.)
Park *et al*, 2022	Peripheral and CSF ccf-mtDNA of neuropsychiatric patients	No significant difference in levels of peripheral ccf-mtDNA in neuropsychiatric studies between cases and controls. CSF ccf-mtDNA levels in non-psychiatric neurological disease decreased compared with controls	(1)
Peng *et al*, 2019	CSF cf-mtDNA of patients with NMDAR	Significantly higher levels of CSF cf-mtDNA and inflammation-associated cytokines in patients with NMDAR	(2)
Lindqvist *et al*, 2018	ccf-mtDNA of patients with MDD	Significantly elevated levels of ccf-mtDNA in patients with MDD	(7)
Newell *et al*, 2018	Plasma mtDNA of patients with mitochondrial disease	Full mitochondrial genome presents in the cf plasma fraction of human blood	(36)
Castellazzi *et al*, 2019	Autophagy (ATG5 protein) and mitophagy marker (Parkin protein) in patients with AD and MCI	Patients with AD and MCI showed significantly decreased circulating levels of both ATG5 and Parkin compared with healthy controls	(38)
Kageyama *et al*, 2018	Plasma mtDNA of patients with MDD, BD and SZ	Patients with MDD and BD showed significantly lower plasma mtDNA levels than controls. Plasma mtDNA is associated with cytokines; GM-CSF, IL-2, and IL-4 in patients with MDD mtDNA levels were lower in the depressive state than in the remission state in patients with MDD	(39)
Trumpff *et al*, 2019	Serum ccf-mtDNA of healthy midlife adults exposed to acute psychological challenge	Acute psychological stress increased ccf-mtDNA levels. Neuroendocrine signaling triggered mtDNA extrusion in living cells	(62)
Silzer *et al*, 2019	Plasma ccf-mtDNA, cf-mtDNA, mtDNA copy number in patients with T2DM and AD	Cf-mtDNA levels are higher in individuals with T2DM but not significantly in those with cognitive impairment compared with controls	(63)

CSF, cerebrospinal fluid; ccf-mtDNA, circulating cell free-mitochondrial DNA; NMDAR, N-methyl-D-aspartate receptor; MDD, major depressive disorder; ATG5, autophagy-related protein 5; AD, Alzheimer's disease; MCI, mild cognitive impairment; BD, bipolar disorder; T2D, type 2 diabetes mellitus; SZ, schizophrenia.

fatty acids oxidation, and, a platform for signal transduction in the innate immune response, are modulated in mitochondria cristae, in which OXPHOS molecular effectors and electron transport chain components are concentrated (45). Mitochondrial damage may cause cognitive impairment, increased aggregation and neural disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and ischemic stroke (46).

In neurogenesis, mitochondria activity plays an essential role in the amplification and differentiation of neurogenic precursors (47). During mitosis, mitochondria of the neural stem cells (NSCs) are present mainly in the form of fragmented mitochondria, and during the G0/early G1 phase (1 h after mitosis) these fragmented mitochondria undergo differentiation and progressive fusion in neurogenic precursors or form immature neuron (44). It is hypothesized that the association between mitochondria morphology, dynamics and function serve an essential role in neurogenesis as a response to neuro-aging (48,49). OXPHOS in human neurogenesis is to facilitate the renewal of NSC and the acquisition of neuronal fate by generating ATP in cells (37). More than 98% of essential proteins for mitochondrial function are encoded in the nucleus, translated in the cytoplasm based on the presence of encoded mitochondrial targeting sequences. These proteins are imported to specific sub-compartments to stimulate the physiological activity of mitochondrial enzymes, such as translocases, proteinase and chaperones (50). This process is the most important character of mitochondrial dynamics, by which cellular homeostasis is coordinated via communication between the mitochondria and the nucleus, thus modulating adaptive responses to stress (31,45).

Mitochondrial dynamics determines the distribution and maintenance of mtDNA in the mitochondrial network (50). Studies have shown an association between mtDNA, dynamin related protein-1 and endoplasmic reticulum in mitochondrial replication and fission, which lead to equal distribution of mtDNA in mitochondria and cells (7,43). Lack of fission and fusion in mitochondria lead to genetic dysfunction such as severe or multiple deletion, increased levels and unequal distribution of mtDNA (51). Impairment of mitochondrial fission induces disorganization of inner mitochondrial structure membranes, such as cristae junctions, which maintain proper internal membrane compartmentalization; loss of these

junctions leads to clustering and mis-segregation of mtDNA nucleoids (48,52). When disorganization of the mitochondrial structure occurs, the ability of mtDNA to repair cellular damage will decrease, leading to the false protection to neuro-aging process (16).

During aging, the aperture of the mitochondrial permeability transition pore (mPTP) is associated with depolarization of mitochondria and OXPHOS uncoupling. Smaller molecules (<1,500 Da) enter mitochondria via the mPTP (29). Under physiological conditions, the mPTP serves as an efflux channel for calcium ions. mPTP is activated by ROS, which causes the release of cytochrome-C oxidase and the initiation of the caspase-9 cascade, which activates the apoptotic pathway (22,33). The nod-like receptor pyrin domain 3 (NLRP3) inflammasome may also be activated as a result of mPTP activation and subsequent ROS generation. This is key because neuronal loss in nigrostriatal neurons is caused by NLRP3 activation in brain microglia and astrocytes; this activation is a fundamental mechanism by which Parkinson's disease and other illnesses display motor impairments and cognitive abnormalities (30,32).

Beside the balance between fission and fusion of mitochondria, another option to maintain healthy mitochondria is to release toxic substances, including oxidized cardiolipin, protein and mtDNA, into extracellular vesicle (EVs), which are subsequently degraded. EV generation rises with aging and is correlated with mtDNA release and pro-inflammatory cytokine production (48). The components of EV, such as mtDNA, ROS and cardiolipin, serve as DAMPs, disrupt nearby molecular patterns and trigger inflammatory responses that lead to neuro-aging (Fig. 3) (50,52). Cardiolipin and mitochondrial dysfunction are required for NLRP3 activation. Caspases 1 and 2 are activated as a result of NLRP3 induction, cleaving Parkin to stop mitophagy (53). When fission and fusion are no longer possible, oxidized macromolecules accumulate and activate IL-1 and IL-18 to cause pyroptosis, an inflammation-mediated cell death (42). Following cell death, mtDNA and ROS are released and interact with other inflammasomes to exacerbate the inflammatory response (53).

Any changes to mtDNA that codes for cytochrome C oxidase or direct protein oxidation of the enzyme may cause early T cell death and loss of function, which may explain immune system impairment in the elderly (25,27). Microglia in the brain and immuno-senescence of T cells have both been connected to mitochondrial dysfunction. This could lead to aberrant activation in response to damage. However, mitochondrial malfunction in microglia inhibits the ability of T cells and microglia to adopt a neuroprotective role (27,53). It is hypothesized that aging-associated neuroinflammatory processes in microglia alter the synaptic plasticity of the brain and impair memory by causing downstream changes (27,53). Astrocytic activation is stimulated by microglial activation and serves a crucial part in both neuroinflammation and the aging of the brain (25,53).

Due to limited intracellular glycogen stores in the brain and the high energy needs of neurons, age-associated hypoperfusion has notable effects on mitochondrial energy metabolism and cognitive functioning (39,53). The association between aging brain, hypoperfusion, hypoxia (due to neuroinflammation) and BBB dysfunction that leads to decreased glucose uptake and mitochondrial dysfunction, is depicted in Fig. 4. Age-associated cognitive impairment is linked to hypometabolism, which is

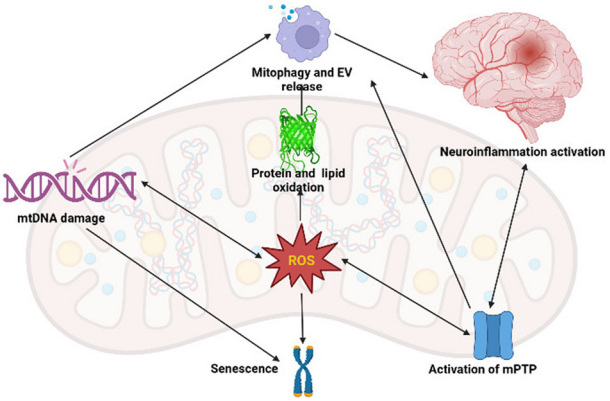


Figure 3. Effects on mtDNA and mitochondrial function of production of ROS, which is associated with aging. Figure is created using Biorender (biorender.com/). mt, mitochondrial; ROS, reactive oxygen species; EV, extracellular vesicle; mPTP, mitochondrial permeability transition pore.

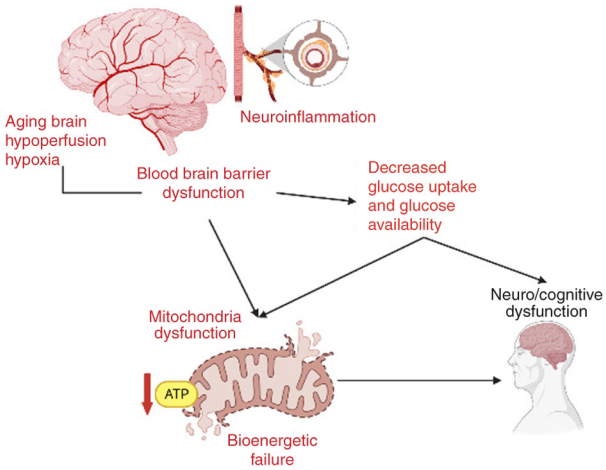


Figure 4. Association between aging brain, hypoperfusion, hypoxia (due to neuroinflammation) and BBB dysfunction that leads to decreased glucose uptake and mitochondrial dysfunction. Figure is created using Biorender (biorender.com/).

characterized by decreased oxidative respiration efficiency, ATP generation and expression of genes implicated in mitochondrial biogenesis, oxidative respiration and dysregulation (42,46). Using directly reprogrammed neurons (iN) from elderly donors to study mitochondrial function in aging shows decreased energy output and significant downregulation of genes involved in the electron transport chain complexes I, III, IV and V, accounting for 70% of all mitochondrial genes when compared with iN from young donors; proteins encoded by genes for mitochondrial phosphorylation decreased along with mRNA and protein expression (53).

To confirm that abnormality of mitochondrial dynamics promote ageing in neurons, physiological factors in cellular functions and processes related to mitochondrial fitness must be maintained (45). The depletion of mitofusin-2 (MFN-2) a fusion GTPase, in mitochondria in human cells stimulates mitochondrial dysfunction, characterized by decreased ATP synthesis, increased proton leak, reduced mitochondrial membrane potential and elevated production of ROS (38). MFN-2 modulates mitochondria cristae, which are associated

with decreased mitophagy and impact mitochondria quality control ability (54). Impairments in mitochondrial quality control are associated with impaired neuronal development, plasticity and function, and therefore are involved in several neurodegenerative diseases, such as Parkinson's, Alzheimer's and Huntington's disease (55).

To maintain a healthy mitochondrial population, the removal of damaged mitochondria via autophagy and mitophagy and stimulation of mitochondrial biogenesis must be controlled (48,56). During aging, autophagy and mitophagy are commonly impaired, resulting in alteration of several types of protein, e.g., PINK-1 (37,55). The impairment of mitophagy is related to aging and age-associated disease (51,52). Changes in mitochondrial fusion or fission proteins trigger intrinsic mitochondrial defects that result in a decrease in mitochondrial activity and an increase in mitochondrial damage (47,57). Impaired autophagy and/or mitophagy and decreased elimination of damaged mitochondria are influenced by unbalanced mitochondrial dynamics (26,58).

Abnormal mitochondrial dynamics may induce damaged mitochondria (59). Mitochondrial dysfunction and decreased autophagy and/or mitophagy are promote dysregulation of mitochondrial dynamics during aging (60,61). Dysfunction in mitochondrial dynamics is correlated with age-related disease and health span, particularly in humans (46). Neuro-aging is associated with the dysregulation of mitochondrial dynamics, triggered by age-related disorders via various mechanisms and signalling routes (54,62). Accumulation of damaged mitochondria that cannot be processed by autophagy or mitophagy may result in the dysfunction of mtDNA, which is associated with neurodegeneration (55,63).

This review is in the framework of the first author's dissertation project which concerns to finding an early detection of mild cognitive impairment and its progression in elderly patients. In this article we did not specify the technical issue as organelles separation and preservations.

5. Conclusion

Previous studies (27,54,55,52,63) have investigated the role of mtDNA to find potential early markers to predict and evaluate neurodegenerative processes related to aging. Approaches to evaluate healthy mitochondria include mitochondria dynamics, which is associated with mitochondria quality control. It is hypothesized that mitochondrial functions (fusion, fission, mitophagy and DNA repair) should be assessed as complete indicators to determine health status of mitochondria in aging. However, research on the role of mtDNA to find an early marker to predict neurodegeneration associated with aging is needed.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

DM and MPS were responsible for the conception and design of the study. MPS performed the literature review and wrote the manuscript. JL, MPS and EH were responsible for reviewing and revising the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Park SS, Jeong H and Andreazza AC: Circulating cell-free mitochondrial DNA in brain health and disease: A systematic review and meta-analysis. World J Biol Psychiatry 23: 87-102, 2022.
2. Peng Y, Zheng D, Zhang X, Pan S, Ji T, Zhang J, Shen HY and Wang HH: Cell-free mitochondrial DNA in the CSF: A potential prognostic biomarker of Anti-NMDAR encephalitis. Front Immunol 10: 103, 2019.
3. Chang CY, Liang MZ and Chen L: Current progress of mitochondrial transplantation that promotes neuronal regeneration. Transl Neurodegener 8: 17, 2019.
4. Moya GE, Rivera PD and Dittenhafer-Reed KE: Evidence for the role of mitochondrial DNA release in the inflammatory response in neurological disorders. Int J Mol Sci 22: 7030, 2021.
5. Cai Q and Tammineni P: Alterations in mitochondrial quality control in Alzheimer's disease. Front Cell Neurosci 10: 24, 2016.
6. Valenti D, Braidy N, De Rasmo D, Signorile A, Rossi L, Atanasov AG, Volpicella M, Henrion-Caude A, Nabavi SM and Vacca RA: Mitochondria as pharmacological targets in Down syndrome. Free Radic Biol Med 114: 69-83, 2018.
7. Lindqvist D, Wolkowitz OM, Picard M, Ohlsson L, Bersani FS, Fernström J, Westrin Å, Hough CM, Lin J, Reus VI, *et al*: Circulating cell-free mitochondrial DNA, but not leukocyte mitochondrial DNA copy number, is elevated in major depressive disorder. Neuropsychopharmacol 43: 1557-1564, 2018.
8. Aryaman J, Bowles C, Jones NS and Johnston IG: Supplemental Material for Aryaman *et al*., 2019. Figshare; 2019 [cited 2022 Sep 11]. p. 1311221 Bytes. Available from: https://gsajournals.figshare.com/articles/Supplemental_Material_for_Aryaman_et_al_2019/8343830.
9. An Q, Hu Y, Li Q, Chen X, Huang J, Pellegrini M, Zhou XJ, Rettig M and Fan G: The size of cell-free mitochondrial DNA in blood is inversely correlated with tumor burden in cancer patients. Precision Clinical Medicine 2: 131-139, 2019.
10. Wu B, Ni H, Li J, Zhuang X, Zhang J, Qi Z, Chen Q, Wen Z, Shi H, Luo X and Jin B: The impact of circulating mitochondrial DNA on cardiomyocyte apoptosis and myocardial injury after TLR4 activation in experimental autoimmune myocarditis. Cell Physiol Biochem 42: 713-728, 2017.
11. Yan C, Duanmu X, Zeng L, Liu B and Song Z: Mitochondrial DNA: Distribution, mutations, and elimination. Cells 8: 379, 2019.
12. Gambardella S, Limanaqi F, Ferese R, Biagioni F, Campopiano R, Centonze D and Fornai F: ccf-mtDNA as a potential link between the brain and immune system in neuro-immunological disorders. Front Immunol 10: 1064, 2019.
13. Gao J, Wang L, Liu J, Xie F, Su B and Wang X: Abnormalities of mitochondrial dynamics in neurodegenerative diseases. Antioxidants 6: 25, 2017.
14. Wang AS and Dreesen O: Biomarkers of cellular senescence and skin aging. Front Genet 9: 247, 2018.
15. Pugazhenthi S: Metabolic syndrome and the cellular phase of Alzheimer's disease. Prog Mol Biol Transl Sci 146: 243-258, 2017.

16. Hood S and Amir S: The aging clock: Circadian rhythms and later life. J Clin Invest 127: 437-446, 2017.
17. Malyarchuk B, Derenko M, Grzybowski T, Perkova M, Rogalla U, Vanecek T and Tsybovsky I: The peopling of Europe from the mitochondrial haplogroup U5 perspective. PLoS One 5: e10285, 2010.
18. Meiliana A, Dewi NM and Wijaya A: Mitochondria in health and disease. Indones Biomed J 11: 1-15, 2019.
19. Richards M, Macaulay V, Hickey E, Vega E, Sykes B, Guida V, Rengo C, Sellitto D, Cruciani F, Kivisild T, *et al*: Tracing European founder lineages in the Near Eastern mtDNA pool. Am J Hum Genet 67: 1251-1276, 2000.
20. de Goede P, Wefers J, Brombacher EC, Schrauwen P and Kalsbeek A: Circadian rhythms in mitochondrial respiration. J Mol Endocrinol 60: R115-R130, 2018.
21. Oliver D and Reddy P: Dynamics of dynamin-related protein 1 in Alzheimer's disease and other neurodegenerative diseases. Cells 8: 961, 2019.
22. Dunham-Snary KJ and Ballinger SW: GENETICS. Mitochondrial-nuclear DNA mismatch matters. Science 349: 1449-1450, 2015.
23. Hummel EM, Hessas E, Müller S, Beiter T, Fisch M, Eibl A, Wolf OT, Giebel B, Platen P, Kumsta R and Moser DA: Cell-free DNA release under psychosocial and physical stress conditions. Transl Psychiatry 8: 236, 2018.
24. Chakravorty A, Jetto CT and Manjithaya R: Dysfunctional mitochondria and mitophagy as drivers of Alzheimer's disease pathogenesis. Front Aging Neurosci 11: 311, 2019.
25. Sebastián D, Palacín M and Zorzano A: Mitochondrial dynamics: Coupling mitochondrial fitness with healthy aging. Trends Mol Med 23: 201-215, 2017.
26. Bhatia D, Chung KP, Nakahira K, Patino E, Rice MC, Torres LK, Muthukumar T, Choi AM, Akchurin OM and Choi ME: Mitophagy-dependent macrophage reprogramming protects against kidney fibrosis. JCI Insight 4: e132826, 2019.
27. Schrepfer E and Scorrano L: Mitofusins, from mitochondria to metabolism. Mol Cell 61: 683-694, 2016.
28. Gómez-Serrano M, Camafeita E, Loureiro M and Peral B: Mitoproteomics: Tackling mitochondrial dysfunction in human disease. Oxid Med Cell Longev 2018: 1435934, 2018.
29. Leung K, Chakraborty K, Saminathan A and Krishnan Y: A DNA nanomachine chemically resolves lysosomes in live cells. Nature Nanotech 14: 176-183, 2019.
30. Zhang CW, Hang L, Yao TP and Lim KL: Parkin regulation and neurodegenerative disorders. Front Aging Neurosci 7: 248, 2016.
31. Nicolas E, Tricarico R, Savage M, Golemis EA and Hall MJ: Disease-associated genetic variation in human mitochondrial protein import. Am J Hum Genet 104: 784-801, 2019.
32. Truban D, Hou X, Caulfield TR, Fiesel FC and Springer W: PINK1, Parkin, and mitochondrial quality control: What can we learn about Parkinson's disease pathobiology? J Parkinsons Dis 7: 13-29, 2017.
33. Misgeld T and Schwarz TL: Mitostasis in neurons: Maintaining mitochondria in an extended cellular architecture. Neuron 96: 651-666, 2017.
34. Clark A and Mach N: The crosstalk between the gut microbiota and mitochondria during exercise. Front Physiol 8: 319, 2017.
35. Nicholas D, Proctor EA, Raval FM, Ip BC, Habib C, Ritou E, Grammatopoulos TN, Steenkamp D, Dooms H, Apovian CM, *et al*: Advances in the quantification of mitochondrial function in primary human immune cells through extracellular flux analysis. PLoS One 12: e0170975, 2017.
36. Newell C, Hume S, Greenway SC, Podemski L, Shearer J and Khan A: Plasma-derived cell-free mitochondrial DNA: A novel non-invasive methodology to identify mitochondrial DNA haplogroups in humans. Mol Genet Metab 125: 332-337, 2018.
37. Martin LJ: Biology of mitochondria in neurodegenerative diseases. Prog Mol Biol Transl Sci 107: 355-415, 2012.
38. Castellazzi M, Patergnani S, Donadio M, Giorgi C, Bonora M, Bosi C, Brombo G, Pugliatti M, Seripa D, Zuliani G and Pinton P: Autophagy and mitophagy biomarkers are reduced in sera of patients with Alzheimer's disease and mild cognitive impairment. Sci Rep 9: 20009, 2019.
39. Kageyama Y, Kasahara T, Kato M, Sakai S, Deguchi Y, Tani M, Kuroda K, Hattori K, Yoshida S, Goto Y, *et al*: The relationship between circulating mitochondrial DNA and inflammatory cytokines in patients with major depression. J Affect Disord 233: 15-20, 2018.
40. Jin SM and Youle RJ: PINK1- and Parkin-mediated mitophagy at a glance. J Cell Sci 125: 795-799, 2012.
41. Fernström J, Ohlsson L, Asp M, Lavant E, Holck A, Grudet C, Westrin Å and Lindqvist D: Plasma circulating cell-free mitochondrial DNA in depressive disorders. PLoS One 16: e0259591, 2021.
42. Cai Q and Jeong YY: Mitophagy in Alzheimer's disease and other age-related neurodegenerative diseases. Cells 9: 150, 2020.
43. Wang W, Zhao F, Ma X, Perry G and Zhu X: Mitochondria dysfunction in the pathogenesis of Alzheimer's disease: Recent advances. Mol Neurodegeneration 15: 30, 2020.
44. Iwata R and Vanderhaeghen P: Regulatory roles of mitochondria and metabolism in neurogenesis. Curr Opin Neurobiol 69: 231-240, 2021.
45. Blagov AV, Grechko AV, Nikiforov NG, Borisov EE, Sadykhov NK and Orekhov AN: Role of impaired mitochondrial dynamics processes in the pathogenesis of Alzheimer's disease. Int J Mol Sci 23: 6954, 2022.
46. Apaijai N, Sriwichaiin S, Phrommintikul A, Jaiwongkam T, Kerdphoo S, Chansirikarnjana S, Thongmung N, Mahantassanapong U, Vathesatogkit P, Kitiyakara C, *et al*: Cognitive impairment is associated with mitochondrial dysfunction in peripheral blood mononuclear cells of elderly population. Sci Rep 10: 21400, 2020.
47. Starkov AA: An update on the role of mitochondrial α-ketoglutarate dehydrogenase in oxidative stress. Mol Cell Neurosci 55: 13-16, 2013.
48. Shamsi TN, Athar T, Parveen R and Fatima S: A review on protein misfolding, aggregation and strategies to prevent related ailments. Int J Biol Macromol 105: 993-1000, 2017.
49. Stephan BCM, Hunter S, Harris D, Llewellyn DJ, Siervo M, Matthews FE and Brayne C: The neuropathological profile of mild cognitive impairment (MCI): A systematic review. Mol Psychiatry 17: 1056-1076, 2012.
50. Ding WX and Yin XM: Mitophagy: Mechanisms, pathophysiological roles, and analysis. Biol Chem 393: 547-564, 2012.
51. Sas K, Szabó E and Vécsei L: Mitochondria, oxidative stress and the kynurenine system, with a focus on ageing and neuroprotection. Molecules 23: 191, 2018.
52. Jagannathan R, Thapa D, Nichols CE, Shepherd DL, Stricker JC, Croston TL, Baseler WA, Lewis SE, Martinez I and Hollander JM: Translational regulation of the mitochondrial genome following redistribution of mitochondrial MicroRNA in the diabetic heart. Circ Cardiovasc Genet 8: 785-802, 2015.
53. Kaliszewska A, Allison J, Martini M and Arias N: Improving Age-related cognitive decline through dietary interventions targeting mitochondrial dysfunction. Int J Mol Sci 22: 3574, 2021.
54. Moehle EA, Shen K and Dillin A: Mitochondrial proteostasis in the context of cellular and organismal health and aging. J Biol Chem 294: 5396-5407, 2019.
55. Xu ZP, Yang SL, Zhao S, Zheng CH, Li HH, Zhang Y, Huang RX, Li MZ, Gao Y, Zhang SJ, *et al*: Biomarkers for early diagnostic of mild cognitive impairment in type-2 diabetes patients: A multicentre, retrospective, nested Case-control study. EBioMedicine 5: 105-113, 2016.
56. Trumpff C, Anna LM, Carla BA, James LM, Judith EC, Gabriel S, Amy EV, Eugene VM, Zhenglong G, Brett AK and Martin P: Acute psychological stress increases serum circulating cell-free mitochondrial DNA. Psychoneuroendocrinology 106: 268-276, 2019.
57. Labbadia J, Brielmann RM, Neto MF, Lin YF, Haynes CM and Morimoto RI: Mitochondrial stress restores the heat shock response and prevents proteostasis collapse during aging. Cell Rep 21: 1481-1494, 2017.
58. Silzer T, Robert B, Jie S, Gita P, Leigh J, Sid O'B and Nicole P: Circulating Mitochondrial DNA: New indices of type 2 diabetes-related cognitive impairment in Mexican Americans. PLoS One 14: e0213527, 2019.
59. Horejs CM: Lysosomes uncovered. Nat Rev Mater 4: 2, 2019.
60. Holstege H, van der Lee SJ, Hulsman M, Wong TH, van Rooij JG, Weiss M, Louwersheimer E, Wolters FJ, Amin N, Uitterlinden AG, *et al*: Characterization of pathogenic SORL1 genetic variants for association with Alzheimer's disease: A clinical interpretation strategy. Eur J Hum Genet 25: 973-981, 2017.
61. Forlenza OV, Diniz BS, Teixeira AL, Stella F and Gattaz W: Mild cognitive impairment (part 2): Biological markers for diagnosis and prediction of dementia in Alzheimer's disease. Rev Bras Psiquiatr 35: 284-294, 2013.
62. Klaips CL, Jayaraj GG and Hartl FU: Pathways of cellular proteostasis in aging and disease. J Cell Biol 217: 51-63, 2018.
63. Giau VV, Bagyinszky E and An SSA: Potential fluid biomarkers for the diagnosis of mild cognitive impairment. Int J Mol Sci 20: 4149, 2019.

Copyright © 2023 Semadhi et al. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.