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Review

The contribution of mitochondrial DNA alterations to aging, cancer, and neurodegeneration

Anna Picca [a,b,1], Flora Guerra [c,1], Riccardo Calvani [b,d,*], Hélio José Coelho-Júnior [d], Christiaan Leeuwenburgh [e], Cecilia Bucci [c], Emanuele Marzetti [b,d]

[a] Department of Medicine and Surgery, LUM University, 70100 Casamassima, Italy
[b] Fondazione Policlinico Universitario "Agostino Gemelli" IRCCS, 00168 Rome, Italy
[c] Department of Biological and Environmental Sciences and Technologies, University of Salento, 73100 Lecce, Italy
[d] Department of Geriatrics and Orthopedics, Università Cattolica del Sacro Cuore, 00168 Rome, Italy
[e] Department of Physiology and Aging, University of Florida, 32601 Gainesville, FL, USA

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ABSTRACT

Mitochondrial DNA (mtDNA) is as a double-stranded molecule existing in hundreds to thousands copies in cells depending on cell metabolism and exposure to endogenous and/or environmental stressors. The coordination of mtDNA replication and transcription regulates the pace of mitochondrial biogenesis to guarantee the minimum number of organelles per cell. mtDNA inheritance follows a maternal lineage, although bi-parental inheritance has been reported in some species and in the case of mitochondrial diseases in humans. mtDNA mutations (e.g., point mutations, deletions, copy number variations) have been identified in the setting of several human diseases. For instance, sporadic and inherited rare disorders involving the nervous system as well higher risk of developing cancer and neurodegenerative conditions, including Parkinson's and Alzheimer's disease, have been associated with polymorphic mtDNA variants. An accrual of mtDNA mutations has also been identified in several tissues and organs, including heart and muscle, of old experimental animals and humans, which may contribute to the development of aging phenotypes. The role played by mtDNA homeostasis and mtDNA quality control pathways in human health is actively investigated for the possibility of developing targeted therapeutics for a wide range of conditions.

1. Introduction

The mammalian mitochondrial DNA (mtDNA) is a double-stranded circular molecule of about 16.5 kb packaged in nucleoid-like structures within the mitochondrial matrix. mtDNA includes 37 DNA regions encoding for 13 subunits of the electron transport chain (ETC) complexes I, III, IV, and V, 2 rRNAs (12S rRNA and 16S rRNA), and 22 tRNAs (Attardi and Schatz, 1988). mtDNA also holds two non-coding regions (NCRs) that control mtDNA transcription and replication. One NCR is called displacement loop (D-loop). In its 900 bp of length, the D-loop hosts the two promoters of the heavy mtDNA strands (HSP1 and HSP2), the promoter of the light strand (LSP), and the origin of replication of the heavy mtDNA strand (OriH). Herein, a set of accessory regulatory proteins are recruited and compose the major site of mtDNA transcriptional regulation (Scarpulla, 2008). Another minor NCR of 30 bp is located between the two coding regions for the tRNACys and tRNAAsn and

Abbreviations: AD, Alzheimer's disease; AMPK, AMP-activated protein kinase; CaMK, Ca^{2+}/calmodulin-dependent protein kinase; CJD, Creutzfeldt-Jakob Disease; COX, cytochrome c oxidase; D-loop, displacement loop; ERR-α, estrogen-related receptor-α; ETC, electron transport chain; HSP, promoter of the heavy strand; LHON, Leber's hereditary optic neuropathy; LSP, light strand promoter; MCI, mild cognitive impairment; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; MERFF, myoclonus epilepsy with ragged-red fibers; mtDNA, mitochondrial DNA; $mtDNA^{4977}$, mtDNA deletion of 4977 bp; NRF, nuclear respiratory factor; NUMTs, nuclear-encoded mitochondrial sequences; OriH, origin of replication of the heavy mtDNA strand; OriL, origin of replication of the light mtDNA strand; PD, Parkinson's disease; PGC-1α, proliferator-activated receptor gamma coactivator 1-alpha; Sirt1, sirtuin 1; TFAM, mitochondrial transcription factor A; TFBM, mitochondrial transcription factor B.

* Corresponding author at: Centro di Medicina dell'Invecchiamento (Ce.M.I.), Fondazione Policlinico Universitario "Agostino Gemelli" IRCCS, Università Cattolica del Sacro Cuore, Largo F. Vito 1, 00168 Rome, Italy.
E-mail address: riccardo.calvani@unicatt.it (R. Calvani).
[1] These two authors contributed equally to this work.

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includes the origin of mtDNA replication of the light strand (OriL).

mtDNA exists as a multi-copy genome. Each cell contains hundreds to thousands of mtDNA copies, with large variations depending on cell metabolism and the exposure to endogenous and/or environmental stressors (Bonawitz et al., 2006). The genesis of new organelles, mitochondrial biogenesis, is triggered by replication and transcription processes that guarantee the minimum number of organelles per cell (Picca and Lezza, 2015). The primary role of mitochondria is to fuel cellular processes by supplying adenosine triphosphate (ATP) and produce metabolites for the synthesis of macromolecules (Frezza, 2017). However, the list of processes in which these organelles are involved continues to grow and include, among others, the regulation of redox balance, cell death/survival signals, and heme biosynthesis (Piel et al., 2019; Vakifahmetoglu-Norberg et al., 2017).

Mitochondria are dynamic and plastic organelles that establish homo- and heterotypic interactions with several cellular compartments (Picca et al., 2022, 2020). The optimization of mitochondrial responses to specific cell/tissue demands is achieved also via these contacts (Picca et al., 2022, 2020). Inter-organelle contact sites also serve as molecular platforms for the displacement of mitochondrial components (Picca et al., 2022, 2020). The release of mitochondrial portions at the systemic level has also been shown to hold immunostimulatory properties that can be sensed by innate immunity receptors for which circulating mtDNA may play a major role (Picca et al., 2017).

mtDNA inheritance follows a maternal lineage although bi-parental inheritance has also been reported in some species (Gyllensten et al., 1991; Kvist et al., 2003; St. John and Schatten, 2004; Zhao et al., 2004) and in the case of mitochondrial diseases in humans (Schwartz and Vissing, 2002). However, the latter case is still a matter of debate (Filosto et al., 2003; Taylor et al., 2003). Indeed, results from whole-genome sequencing analyses have identified nuclear-encoded mitochondrial sequences (NUMTs) that may represent a source of bias in the hypothesis of bi-parental inheritance. mtDNA mutations have been identified in several human diseases (Lawless et al., 2020). Both sporadic and inherited rare disorders involving the nervous system are characterized by mtDNA mutations. Polymorphic mtDNA variants have also been associated with a higher risk of developing cancer and neurodegenerative conditions, including Parkinson's (PD) and Alzheimer's disease (AD) (Coskun et al., 2012). An age-associated accrual of mtDNA mutations has also been found in several tissues and organs, which may contribute to the development of aging phenotypes (Srivastava, 2017).

The role played by mtDNA homeostasis and mtDNA quality control pathways in human health is actively investigated for the possibility of developing targeted therapeutics for a wide range of conditions.

2. Mitochondrial biogenesis and mitochondrial DNA inheritance

2.1. *Mitochondrial biogenesis: the work of an intricated machinery*

Mitochondrial biogenesis is the result of a fine coordination of multiple pathways engaging mitochondrial and nuclear genomes. These involve a set of processes, including mtDNA replication and transcription, and the synthesis, import and assembly of nuclear-encoded mitochondrial proteins.

mtDNA replication and transcription are under the control of the master regulator of mitochondrial biogenesis, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a member of the PGC-1 family proteins (Handschin and Spiegelman, 2006; Scarpulla, 2008). Upon activation, either by phosphorylation or deacetylation, PGC-1α triggers the expression of a set of transcription factors. Among these, the nuclear respiratory factor (NRF) 1 and 2, and estrogen-related receptor-α (ERR-α) upregulate the expression of the mitochondrial transcription factor A (TFAM) and the associated mitochondrial transcription factors B1 and B2 (TFB1M and TFB2M) (Handschin and Spiegelman, 2006; Rebelo et al., 2011). The increase of TFAM protein expression in the nucleus and its subsequent translocation into the mitochondrion signal at the organelle the beginning of a new replication and/or transcription process (Picca and Lezza, 2015). Herein, the binding of TFAM to mtDNA is pivotal and intervenes in the regulation of mitochondrial biogenesis (Picca and Lezza, 2015).

TFAM belongs to the high-mobility-group (HMG) family proteins and can bind to the mtDNA without sequence specificity (Parisi and Clayton, 1991). Beyond the coordination of mtDNA replication and transcription, TFAM contributes to mtDNA maintenance and participate to mitochondrial repair processes (Canugovi et al., 2010; Ekstrand et al., 2004). These activities are made possible also by architectural roles of TFAM on mtDNA (e.g., bending and unwinding) (Fisher et al., 1992). However, the best characterized function of TFAM is the coordination of mtDNA transcription and translation via recruitment of the mitochondrial initiation factors (mtIF2 and mtIF3) and the mitochondrial elongation factors (mtEFTu, mtEFTs, and mtEFG1) encoded by the nucleus (Mai et al., 2017). In addition, protein expression of the mitochondrial translational release factor 1-like (mtRF1L) and the recycling factors (mtRRF1 and mtRRF2) as well as that of the translational activator of cytochrome *c* oxidase (COX) 1 regulates the rate of mitochondrial-encoded proteins under the control of nuclear genes (Fig. 1).

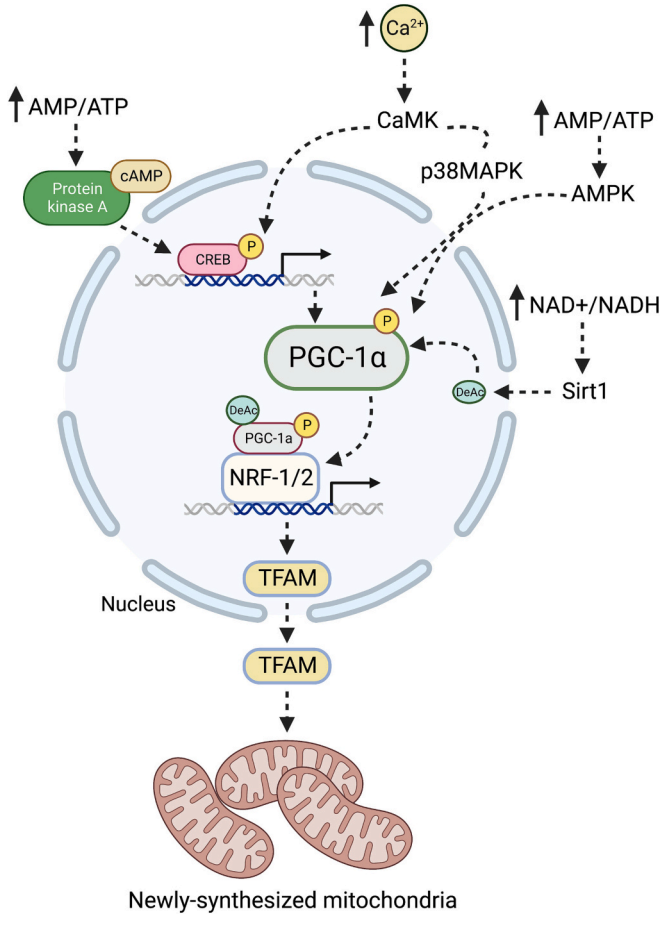

Fig. 1. Schematic representation of the events involved in mitochondrial biogenesis. Created with BioRender.com, accessed on 24 April 2023.
Abbreviations: AMPK, AMP-activated protein kinase; cAMP, cyclic AMP; CaMK, Ca^{2+}/calmodulin-dependent protein kinase; CREB, cAMP response element-binding protein; DeAc, deacetylation; NAD, nicotinamide adenine dinucleotide; NRF, nuclear respiratory factor; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; Sirt1, sirtuin 1; TFAM, mitochondrial transcription factor A.

2.2. Mitochondrial DNA inheritance: maternal lineage, homoplasmy, and heteroplasmy

Although paternal transmission of mtDNA has been documented in mammals (Gyllensten et al., 1991; Kvist et al., 2003; Zhao et al., 2004), its actual existence in humans is still a matter of debate (Filosto et al., 2003; Luo et al., 2018; Lutz-Bonengel and Parson, 2019; McWilliams and Suomalainen, 2019; Taylor et al., 2003) as it seems more the results of an experimental artifact (Annis et al., 2019; Balciuniene and Balciunas, 2019; Wei et al., 2020). Regardless, paternal transmission of mtDNA in humans is an exceptionally rare event (Rius et al., 2019). Therefore, unlike nuclear DNA (nDNA), mtDNA inheritance is considered to follow a maternal lineage (Fig. 2).

The modality of mtDNA inheritance is important for determining variant acquisition by the offspring (van den Ameele et al., 2020). mtDNA inheritance in humans has been implicated in several common and rare diseases (Wei and Chinnery, 2020). "Homoplasmy" occurs when mutations follow a germ line inheritance, while the term "heteroplasmy" denotes somatic mutations that are inherited along with wild-type molecules. In the case of heteroplasmic mutations, the proportion of heteroplasmy, reflecting the percentage of mutated alleles inherited, defines whether this would translate into a biochemical defect at the cellular level (Fig. 3). Although considered to be a rare event until the advent of deep re-sequencing techniques, mtDNA heteroplasmy is now recognized as a frequent phenomenon in mitochondrial diseases (Li et al., 2010; Payne et al., 2013).

According to the mitochondrial theory of aging, mtDNA mutations accumulate over time mainly due to a less sophisticated repair machinery than nDNA (Yakes and Van Houten, 1997) and proximity to the source of reactive oxygen species (ROS). However, the hypothesis that some of the clonally expanded mutations observed in older adults may have been inherited at a very low level of heteroplasmy and probably even held at birth is gaining support (Keogh and Chinnery, 2013). Therefore, heteroplasmic and homoplasmic mtDNA mutations can in principle both be maternally inherited and contribute to rare genetic diseases and other disorders when coupled with additional factors. The dissection of the inheritance mechanisms of these mutations is of outmost importance for their implications in mitochondrial medicine.

3. Mitochondrial DNA mutations in human diseases

3.1. Mitochondrial DNA copy number variations in mitochondrial diseases

Mitochondrial diseases include a wide range of hereditary disorders characterized by deficiency in oxidative phosphorylation in several tissues and organs (La Morgia et al., 2020). These disorders arise either from mutations in nuclear genes encoding for proteins involved in mtDNA expression or primary mtDNA mutations impacting the abundance and/or function of proteins encoded by the mtDNA (La Morgia et al., 2020; Rahman, 2020) (Fig. 4). Different clinical phenotypes have been observed depending on the type of mutations (La Morgia et al., 2020; Rahman, 2020).

Mutations in genes involved in mtDNA maintenance (e.g., mtDNA replication, nucleotide metabolism, mitochondrial quality control mechanisms) have been identified in the so-called mtDNA depletion syndromes, a class of autosomal recessive disorders characterized by heavy tissue-specific mtDNA depletion (Viscomi and Zeviani, 2017).

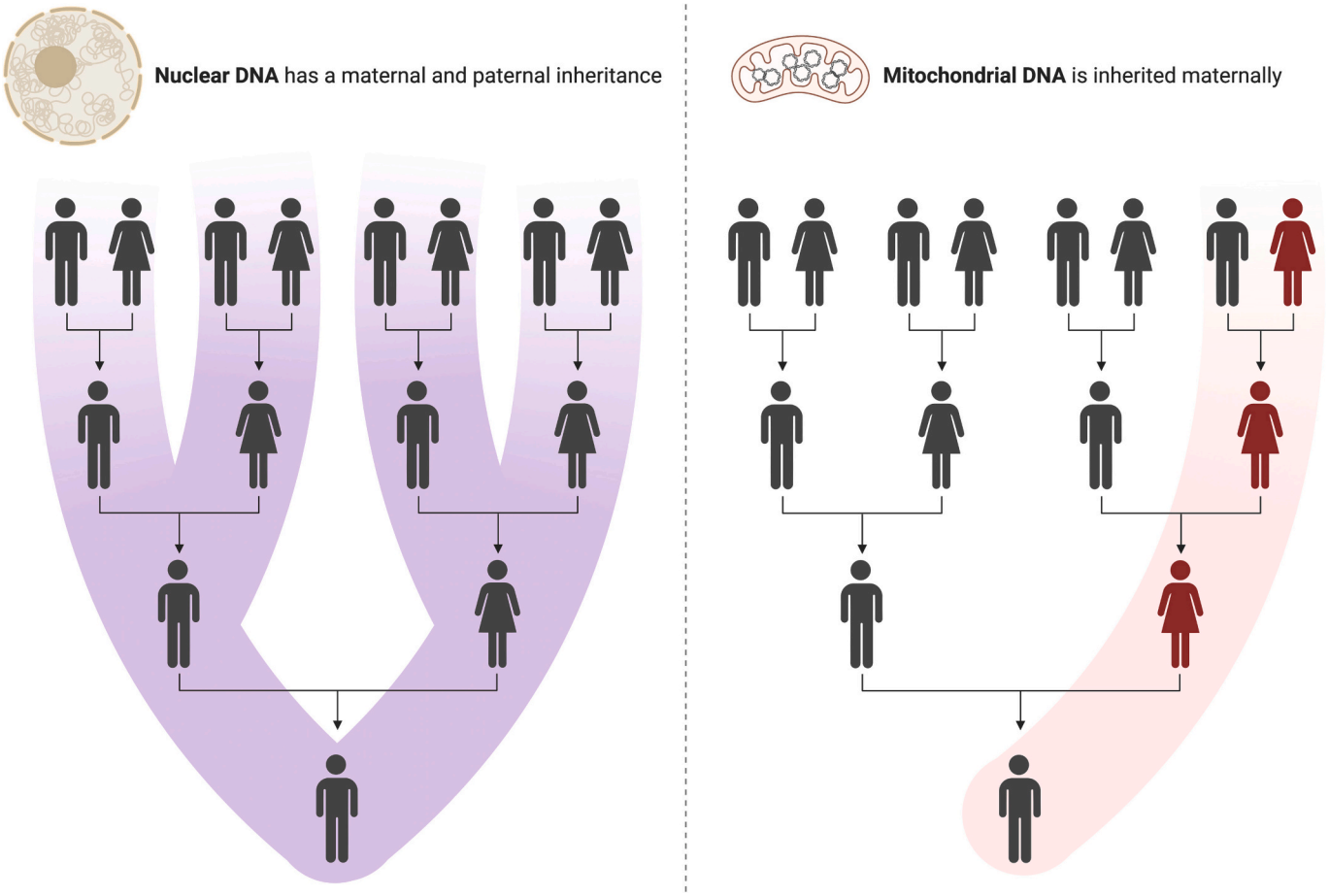

Fig. 2. Nuclear and mitochondrial DNA inheritance in humans. Nuclear DNA follows a biparental inheritance while mitochondrial DNA is inherited maternally. Adapted from "Mitochondrial Inheritance", by BioRender (2021a).

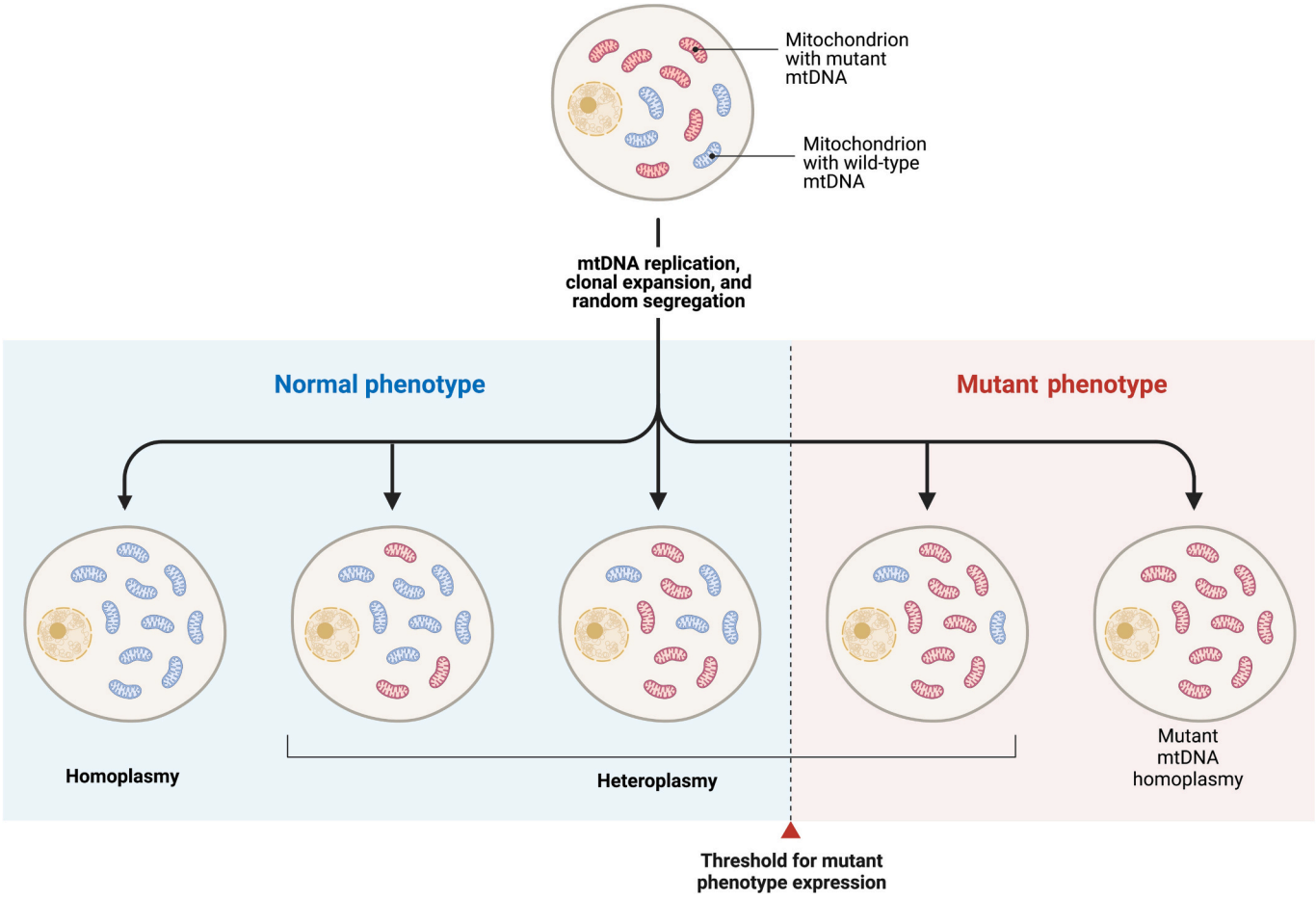

Fig. 3. Mechanisms of mitochondrial DNA (mtDNA) clonal expansion, heteroplasmy, and mutant phenotype expression. Adapted from "mtDNA heteroplasmy", by BioRender (2021b).

Mutations in the nuclear *POLGA* gene, encoding for the catalytic subunit of the mitochondrial polymerase-γ (PolgA), is a major contributor to these syndromes (Rahman and Copeland, 2019). Over 300 *POLGA* gene mutations have been identified and associated with a variety of mtDNA alterations (e.g., reduced mtDNA copy number, accrual of mtDNA mutations and deletions) and related disorders manifesting from infancy to late adulthood (Dimmock et al., 2010). However, a direct relationship between *POLGA* mutations, phenotypic manifestations, and mtDNA copy number variations has not always been verified (Tzoulis et al., 2006). In fact, the knock-in mouse for *POLGA* showed premature aging and high levels of mtDNA point mutations and deletion, but no variations in mtDNA copy number (Trifunovic et al., 2004). However, copy number variations have been identified in people with mitochondrial syndromes carrying homoplasmic and heteroplasmic mtDNA mutations. In individuals with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), levels of heteroplasmic m.3243A>G mutations and mtDNA copy number were associated with disease severity (Grady et al., 2018). Levels of mtDNA copy number were also associated with different phenotypes in people with myoclonus epilepsy with ragged-red fibers (MERFF) (Liu et al., 2006). An association between mtDNA copy number and disease penetrance was observed in people with Leber's hereditary optic neuropathy (LHON) carrying homoplasmic mutations (Bianco et al., 2018, 2017; Giordano et al., 2014). Finally, people with Pearson's syndrome or Kearns–Sayre syndrome, bearing heteroplasmic single mtDNA deletions, have a high mtDNA copy number that is not correlated with the size or the position of the mtDNA deletion (Bai and Wong, 2005).

Taken as a whole, these findings indicate that mtDNA copy number may be involved in the onset and progression of mitochondrial diseases. In this setting, an increase in mtDNA copy number may be interpreted as a compensatory mechanism to sustain mitochondrial bioenergetics deficits, delay disease onset, and attenuate phenotypic expression (Filograna et al., 2019; Kauppila et al., 2016).

3.2. Mitochondrial DNA mutations and cancer

More than 80 years ago, Otto Warburg (1956) demonstrated that cells from solid cancer were characterized by a phenomenon known as "aerobic glycolysis" highlighting the role of mitochondria in cancer. Metabolic reprogramming is one of the hallmarks of cancer biology (Hanahan and Weinberg, 2011) and the role of mitochondria in this phenomenon is supported by the identification of several mtDNA mutations in cancer cells (Bartoletti-Stella et al., 2011; Brandon et al., 2006; Chinnery et al., 2002; Copeland et al., 2002; Gasparre et al., 2008; Guerra et al., 2017b; Pereira et al., 2012; Wallace, 2012). In 2006, the results of a meta-analysis indicated that most significant mtDNA variants identified in cancer cells consisted in the same polymorphisms in different human populations (Brandon et al., 2006). Following this finding, mtDNA mutations were classified in two types of variants: 1) de novo mutations that act as "inducers" of carcinogenesis, and 2) functional variants, that act as carcinogenesis "adaptors" allowing cancer cells to adapt to and survive in different environments (Kopinski et al., 2021).

The mechanisms by which mtDNA mutations determine tumorigenesis have not yet been completely clarified. It is known that mtDNA mutations are associated with ROS production and altered redox status,

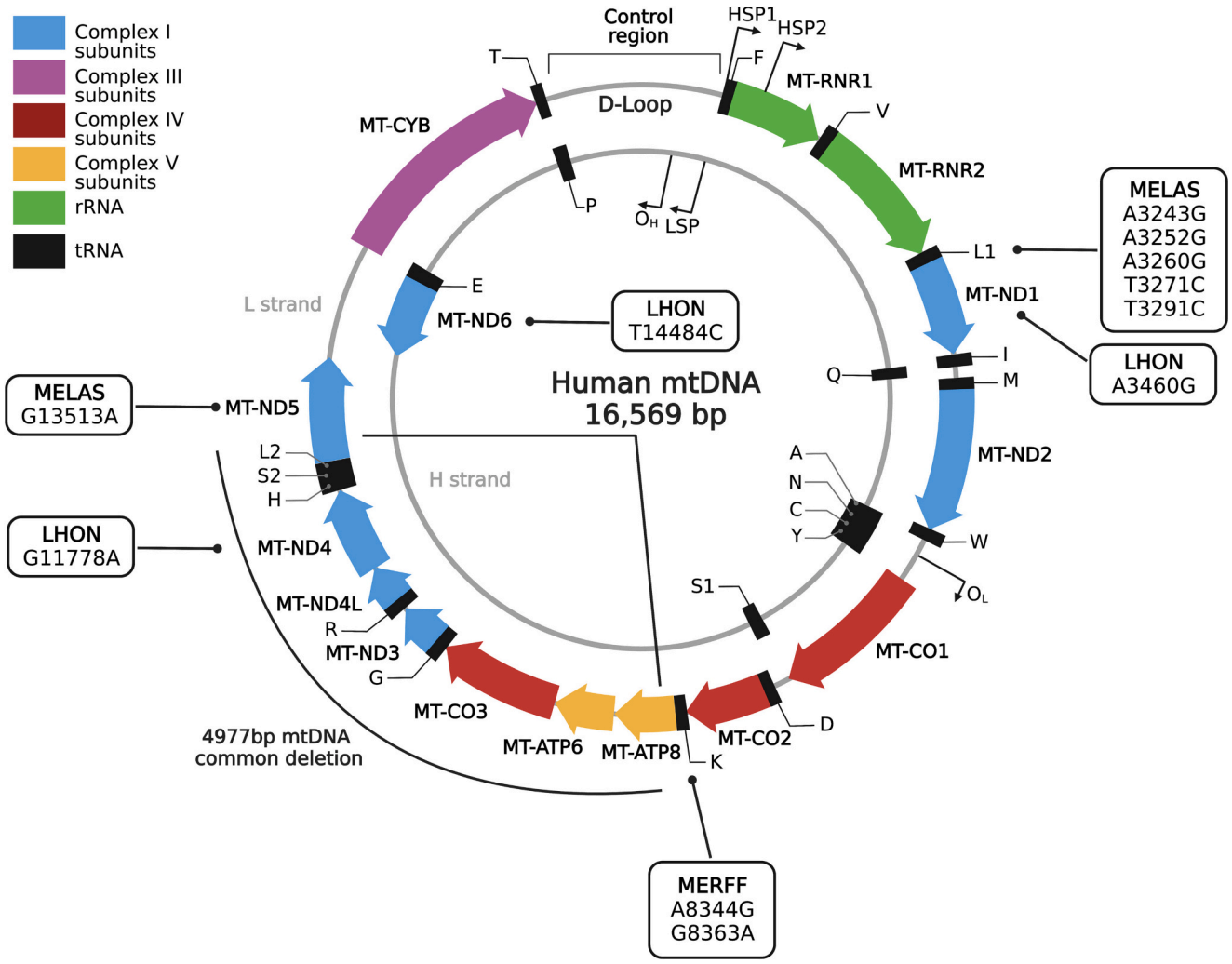

Fig. 4. Schematic representation of the human mitochondrial DNA (mtDNA), mtDNA mutations, common deletion, and associated disorders. Abbreviations: ATP, ATP synthase subunit; CO, cytochrome *c* oxidase subunit; CYB, cytochrome *b*; D-Loop, displacement loop; HSP, promoter of the heavy strand; LSP, promoter of the light strand; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; LHON, Leber's hereditary optic neuropathy; MERFF, myoclonus epilepsy with ragged-red fibers; MT, mitochondrial; ND, NADH-ubiquinone oxidoreductase chain; OH, replication origin of the heavy strand; OL, replication origin of the light strand; RNR, ribonucleotide reductase.
Adapted from "Human mtDNA Sequence Map", by Kim (2021) BioRender.

whose role in cancer cell growth has been widely described (Arnold et al., 2013; Petros et al., 2005; Wallace et al., 2010). Furthermore, mtDNA mutations can change mitochondrial metabolism, which in turn can induce modifications in the expression of nDNA and the epigenome (Dang et al., 2009; Wallace et al., 2010; Wallace and Fan, 2010). In fact, mutations in genes responsible for nDNA-encoded mitochondrial enzymes of the tricarboxylic acid cycle have been indicated to induce cancers by modifying the epigenome (Dang et al., 2009; Letouzé et al., 2013; Lu et al., 2012), while mutations in the mtDNA can result in epigenome modifications in osteosarcoma cells (Kopinski et al., 2019; Picard et al., 2014).

It has also been clarified that mtDNA variants can have three distinct origins with different clinical relevance: 1) inherited variants, which run in families; 2) somatic mutations, which occur in individuals or cell and can accumulate with age also contributing to the aging clock; and 3) variants associated with ancient mtDNA lineages, known as haplogroups and responsible for adaptation to changing tissue or geographic environments. Alterations of several processes related to mitochondrial bioenergetics, including aerobic glycolysis (Courtney et al., 2018; De Berardinis and Chandel, 2016), ROS production, regulation of calcium levels (Huang et al., 2000; Petros et al., 2005; Stewart et al., 2015), and inter-organelle interaction (Herrera-Cruz and Simmen, 2017) occur during tumorigenesis and cancer progression. Both nDNA and mtDNA mutations, but also changes in mtDNA copy number and altered gene expression, can contribute to these changes. Neoplastic transformation can be due to all three classes of clinically relevant mtDNA variants (Kopinski et al., 2021).

mtDNA mutations in tumors have been mostly reported in protein subunits of complex I (Gaude and Frezza, 2014). In this setting, a glycolytic switch of cancer cells and ROS-driven metastatization has been reported (Calabrese et al., 2013; He et al., 2013; Ishikawa et al., 2008). Tumorigenesis has also been shown to be influenced by mutations in complex III, IV, and V (Dasgupta et al., 2009).

Cancer cell growth has been associated with mutations in complex III genes via increases in ROS production and apoptotic resistance (Dasgupta et al., 2009). Mutations in mitochondrial and nuclear genes of complex IV subunits seem to have different roles in cancer progression. In leukemia cells, an upregulation of nuclear-encoded subunits of complex IV has been observed via increased oxidative phosphorylation and ROS production (Chen and Pervaiz, 2010). Instead, mutations in mitochondrial-encoded subunits of complex IV determined a decrease in oxidative phosphorylation and higher ROS production in prostate and

ovarian cancers, respectively (Petros et al., 2005). Therefore, an oncogenic role has been proposed for the nuclear-encoded complex IV subunits, while cancer growth suppressor has been ascribed to the activity of mtDNA-encoded complex IV subunit (Gaude and Frezza, 2014). Mutations in complex V, which carries out the final step of the oxidative phosphorylation process and participates in the formation of permeability transition pore for calcium efflux and apoptosis, are associated with apoptosis resistance of cancer cells (Shidara et al., 2005).

Experiments in cytoplasmic hybrid (cybrid) with different degree of heteroplasmy of m.8993 T >G mutation in the MT-ATP6 gene showed that high levels of heteroplasmy for this mutation were associated with glycolytic switch, increased cell proliferation, and migration (Gaude et al., 2018). Therefore, high levels of heteroplasmic mtDNA mutations can promote an oncogenic metabolic phenotype. Instead, a switch towards an oncogenic behavior was lost when the mutation was present at a low heteroplasmy level (Gaude et al., 2018). Along with tumor growth and proliferation, mitochondrial activity is also required for the multistep process of metastatic disease progression (Guerra et al., 2017b). During epithelial to mesenchymal transition, a process through which cancer cells acquire the ability to metastasize, mitochondrial biogenesis and metabolism, oxidative phosphorylation, and dynamics (Caino et al., 2016; Lebleu et al., 2014; Sciacovelli et al., 2016) support the invasive potential of cancer cells. Mitochondrial ROS bursts and related signaling have been associated with the promotion of metastatic dissemination (Porporato et al., 2014). Conversely, higher glucose flux through the pentose phosphate pathway leads to antioxidant production, thus protecting cancer cells against ROS and promoting survival (Schafer et al., 2009). However, beyond a certain threshold, ROS levels may also inhibit metastasis (Piskounova et al., 2015). A recent study indicated that dissemination of metastatic cancer cells was enhanced by reduced mitochondrial capacity and reliance on glycolysis for ATP production. Thus, if this is prevented, it may be possible to boost ROS production and trigger cancer cell death to inhibit metastatic spread (Labuschagne et al., 2019).

A comparison of mtDNA sequences of cancer samples from 31 different types of cancers and matched controls led to the identification of 1907 somatic base substitutions, the vast majority of which being transitions (Ju et al., 2014). It was then demonstrated that mtDNA mutations can be due to replication errors caused by oxidative inactivation of the proofreading exonuclease activity of PolgA (Anderson et al., 2020). The genetic inactivation of the exonuclease (PolgAD257A/D257A) increases the incidence of mtDNA substitutions and deletions (Kujoth et al., 2005; Trifunovic et al., 2004).

Interestingly, 58% of analyzed cancers harbor at least one somatic mitochondrial mutation and 31% are characterized by multiple mutations (Ju et al., 2014). Of 1907 substitutions, 1153 (60.5%) were in the 13 protein-coding genes. These include 63 nonsense mutations, 4 loss of stop codon, 878 missense, 110 insertion-deletion (indel) mutations, and 208 silent substitutions (Ju et al., 2014). Presumably numerous low-heteroplasmy mutants, initially phenotypically masked, are generated in cancer cells with subsequent drift into higher heteroplasmy levels conferring these cells the ability to survive in specific environments (Wallace, 2018, 2015).

In another study 1916 tumors and matched control tissues across 24 different cancer types were analyzed and displayed mtDNA mutations (Grandhi et al., 2017). In this study, 2350 cancer-specific somatic mtDNA mutations were found in 64% of patients compared to normal cells in which heteroplasmic variants were identified in 40% of individuals. In particular, heteroplasmic variants of normal cells occurred within the non-coding D-loop region, while cancer-specific somatic mutations were distributed across both coding and non-coding mtDNA regions. Interestingly, according to the adaptive roles of mtDNA for disseminating cancer cells, mutations in the mitochondrial coding region are more abundant than those in D-loop regions in metastatic and recurrent cancers (Grandhi et al., 2017). Furthermore, differences in the frequency of functional mtDNA variants were observed between cancer types. For instance, a high number of somatic mtDNA mutations was described in chromophobe renal cell carcinoma and thyroid cancers (Yuan et al., 2020). Specifically, it was observed that these mutations occurred with heteroplasmic allele frequencies in positive correlation with the severity of the mutation class, indicating a positive selection (Yuan et al., 2020). Moreover, it was demonstrated that normal tissues were characterized by non-synonymous heteroplasmic mutations at low frequency which increased in cancer tissues. Grandhi et al. (2017) have demonstrated that, in patients with thyroid and kidney cancer, it is frequent to observe a shift of frameshift mutations from a low degree of heteroplasmy in normal tissue to quasi homoplasmy in the tumors. These findings suggest that disruptive mutations of mtDNA are at a low level in normal cells but undergo a positive selection in cancer tissues. This observation confirms the critical role of mtDNA in tumorigenesis.

Several studies have analyzed mtDNA mutations in specific cancers (Bartoletti-Stella et al., 2011; Brandon et al., 2006; Chinnery et al., 2002; Copeland et al., 2002; Gasparre et al., 2008; Pereira et al., 2012; Wallace, 2012). In prostate cancer, the occurrence of mtDNA mutations was associated with an increase of tumorigenic potential (Kalsbeek et al., 2016), and, because they coexist with nuclear somatic driver events (Hopkins et al., 2017), it was emphasized their role as co-initiators of cancer (Hopkins et al., 2017; Kalsbeek et al., 2016; Xiao et al., 2018). Indeed, it was suggested that for thyroid Hüthle cell carcinoma (Gopal et al., 2018), breast cancer (Jiménez-Morales et al., 2018; Weerts et al., 2018), pancreatic cancer (Hardie, 2007), gynecological malignancies (Musicco et al., 2018; Perrone et al., 2018), lung adenocarcinoma metastases (Li et al., 2018; Yuan et al., 2015), and acute myeloid leukemia (Kim et al., 2018; Tyagi et al., 2018) mtDNA may act as a tumor initiator.

The role of mtDNA mutations has been well characterized especially in prostate cancer (Kalsbeek et al., 2017). Interestingly, several nDNA gene loci that show mutational events and epigenomic modulation are related to genes that influence mitochondrial functions. Furthermore, a significant number of somatic mtDNA mutations were described in the non-coding control region and gene-coding regions of mtDNA (Hopkins et al., 2017; Kalsbeek et al., 2017, 2016; Petros et al., 2005). In a work by Arnold et al. (2015), the recurrence of the adaptative MT-ND3 m. 10398 A>G in bone metastasis of prostate cancer has been reported. Furthermore, it has been demonstrated that prostate cancer tissue is enriched in several types of de novo mtDNA mutations. For instance, Petros et al. (2005) identified a de novo MT-COI mutation (5949G>A) responsible for impairment of complex IV assembly existing in homoplasmic degree in cancer tissue and not in the surrounding healthy tissue (Petros et al., 2005). This finding indicates a positive selection of cancer cells towards mtDNA complex IV deficiency (Petros et al., 2005). In the same work, the authors demonstrated that the transfer of mtDNA mutation MT-ATP6 variant m.8993T>G into PC3 prostate cancer cells as transmitochondrial cybrids induced the growth of seven-fold larger tumor masses and increased ROS production compared with PC3 cybrids obtained with wild-type allele.

Similarly, 143B mtDNA deficient (ρ0) cell line, variant MT-COI m.6124T>C was transferred in osteosarcoma cells to generate parallel homoplasmic mutants and wild-type clones. Arnold et al. (2013) described a partial defect of complex IV, increased ROS production, enhanced growth rate, and tumor growth in nude mice in mutant cybrids. After the transfer of mtDNA mutation in PC3 cells, the ability of mutant cybrids to induce the formation of larger tumors and increased resistance to apoptosis after statin treatment were described compared with normal cybrids (Howell and Sager, 1978). Similar experiments were conducted in other cancer cell types, reinforcing the hypothesis of a tumorigenic role of mtDNA mutations (Ishikawa et al., 2008; Sablina et al., 2005; Shidara et al., 2005) and the importance of ROS production (Gasparre et al., 2007; Nieborowska-Skorska et al., 2012).

The role of mtDNA mutations is oncocytoma offers further insights on the subject (Xiao et al., 2018). Oncocytoma is characterized by mitochondrial hyperplasia and a benign behavior (Gasparre et al., 2008). Several studies revealed numerous mtDNA mutations at high

heteroplasmic degree particularly in mitochondrial genes encoding subunits of complex I (Gasparre et al., 2007; Guerra et al., 2012), allowing to conclude that these mutations are markers of this type of cancer (Gasparre et al., 2007). A study described the occurrence of multiple mtDNA mutations at high heteroplasmy level in nine oncocytoma patients (Gasparre et al., 2008). Most mutations were in complex I genes causing complex deficiency and cell's inability to grow on obligatory oxidative metabolites (Gasparre et al., 2008). In all cases, mtDNA mutations were classified as somatic, and only in one case were maternally inherited. This last mutation occurred also in normal tissue at a low heteroplasmy level and shifted to homoplasmy in the cancer tissue of the patient, indicating tumor selection for this mitochondrial variant (Gasparre et al., 2009).

The study of oncocytoma was extremely useful to describe a dual role of mtDNA mutations in cancer. Accordingly, beyond a specific threshold, mtDNA mutations may acquire an anti-tumoral function and induce benign cancer behavior (Gasparre et al., 2011). The term of oncojanus genes was proposed to refer to the degree of heteroplasmy of certain mtDNA mutations able to contribute either oncogenic or suppressive functions in the setting of mitochondrial-driven tumorigenesis (Gasparre et al., 2011). Oncojanus functions have also been described ex vivo in ovarian cancer tissue from patients treated with cisplatin, demonstrating a role for mtDNA variants in chemoresistance (Guerra et al., 2017a, 2012).

Besides mtDNA mutations, alterations in mtDNA copy number have also been found in cancer cells. In particular, lower levels of mtDNA copy number were found in seven tumor types (bladder, breast, oesophageal, head and neck squamous cell, clear cell and papillary kidney, and liver) compared with surrounding non-cancer tissue (Brandon et al., 2006). Conversely, an increase in mtDNA copy number was shown in lung adenocarcinoma (Reznik et al., 2016), but also in low-grade gliomas harboring phosphatase and tensin homolog or isocitrate dehydrogenase 1 mutations, and in endometrial carcinomas with tumor protein 53 mutations compared with wild-type samples (Reznik et al., 2016).

Transcriptional profile analyses also indicated that mtDNA copy number correlated with the transcript levels of enzymes of the tricarboxylic acid cycle, fatty acid β-oxidation, branched-chain amino acid catabolism pathways, and ETC complexes. Instead, in prostate cancer, mtDNA content was inversely correlated with the expression of mitochondrial genes. The reason for such a variability in copy number changes is unknown, but the hypothesis is that the directionality of the change may result from the type of mutations as well as the tumor type. For instance, in thyroid and kidney tumors harboring mtDNA variants inactivating mtDNA genes, a marked increase in mtDNA copy number occurs in cancer cells compared with adjacent normal tissue cells (Grandhi et al., 2017). In endometrial cancer, a high mtDNA copy number has been reported as a compensatory effect to mtDNA mutations (Cormio et al., 2009; Guerra et al., 2011). In certain tumor types, alterations in mtDNA abundance can also represent an adaptive response and a secondary effect of a mutation that confers proliferation advantage. Cancer severity is also correlated with changes in mtDNA copy number. Indeed, it was observed that breast cancer at stage IV characterized by at least one metastatic site had the lowest mtDNA copy number (Guha et al., 2018). In tumor samples of triple-negative breast cancer, a significantly lower mtDNA copy number was detected compared with non-tumor tissue (Guha et al., 2018). In line with this observation, triple-negative breast cancer cell lines had markedly reduced mitochondrial respiration and increased glycolysis (Guha et al., 2018).

3.3. Mitochondrial DNA mutations in aging and neurodegeneration

Mitochondrial dysfunction is a feature of the aging process (Schmauck-Medina et al., 2022). Among other alterations, somatic mtDNA mutations, including large mtDNA deletions and point mutations, have been identified in several tissues from old people (Corral-Debrinski et al., 1992; Larsson, 2010; Yen et al., 1991). Causality between the presence of these mutations and an aging phenotype has also been inferred. Mice bearing a proofreading-deficient PolgA accumulate mtDNA mutations to a large extent and age prematurely with a phenotype characterized by reduced fertility and cell stemness, anemia, hair greying and loss, and hearing impairment (Kujoth et al., 2005; Trifunovic et al., 2004). In a second mutator mouse model obtained by inducing double-strand breaks ubiquitously in the mtDNA, an accelerated ROS-dependent aging phenotype, preferentially affecting proliferating tissues, was also observed (Pinto et al., 2017).

In the early '90s, a mosaic pattern of COX deficiency was reported for the first time in human heart and muscle (Müller-Höcker, 1990, 1989). An accrual of clonally expanded mtDNA point mutations and deletions was also identified in COX-deficient fibers, which was hypothesized to cause focal mitochondrial dysfunction (Fayet et al., 2002). mtDNA deletions have also been detected in post-mortem brain samples of older adults (Corral-Debrinski et al., 1992). The mtDNA deletion of 4977 bp ($mtDNA^{4977}$), so-called common deletion, removes mtDNA between the nucleotide positions 8470 to 8482 and 13,447 to 13,459 encompassing five tRNA genes and seven genes encoding subunits of ETC complex (i.e., subunits of cytochrome *c* oxidase, complex I and ATPases) (Cortopassi et al., 1992). This large mtDNA mutation was identified among the germline mtDNA deletions responsible for Kearns–Sayre syndrome (Schon et al., 1989), with tRNA depletion and consequent impaired mtDNA translation (Nakase et al., 1990). However, this can only occur when heteroplasmy is beyond ~80% (Moraes et al., 1992) due to a compensatory effect of wild-type mtDNA. A "biochemical threshold effect" exists whereby mtDNA mutations need to reach a critical threshold before mitochondrial bioenergetics are impacted (Rossignol et al., 1999).

The role of mtDNA copy number variations in aging and associated diseases is still unclear. mtDNA content in tissues of old individuals has been widely investigated and most studies reported a decrease in mtDNA content with age (Ding et al., 2015) with more dramatic declines in older people (Knez et al., 2016; Mengel-From et al., 2014) and loss of small percentages of mtDNA copies per decade of age (Zhang et al., 2017). In older people, a lower mtDNA copy number was associated with mortality and decline in cognition and physical performance (Mengel-From et al., 2014). However, the relationship between low mtDNA content and longevity is not yet completely clear. Indeed, mtDNA quantification in nonagenarians and centenarians have shown contradictory results with lower (Van Leeuwen et al., 2014) or higher (He et al., 2014) mtDNA content compared with middle-aged controls.

Genetic mtDNA variants and somatic mtDNA mutations have also been related to age-associated neurodegenerative conditions and indicated as pathophysiological contributors (Keogh and Chinnery, 2015). More specifically, population variants that allow identifying geographical clusters of mtDNA in humans called "haplogroups" (Torroni et al., 2000), have been associated with a higher risk of developing neurodegeneration (e.g., AD, PD) (Hudson et al., 2013; Maruszak et al., 2009). Experiments in cybrids have also shown that some mtDNA variants (i.e., m.A10398G (MT-ND3 p.T114A) and m.G8584A (MT-ATP6 p.A20T)) of the B5 haplogroup protect against PD (Liou et al., 2016). Cybrids bearing "protective" mtDNA variants were found to be more resistant to rotenone and less susceptible to apoptosis and autophagy-induced degradation compared with those carrying wild-type B4 mitochondrial genome (Liou et al., 2016). In line with this finding, a study by Strobbe et al. (2018) indicated that the haplogroup K1 provided a protective background to cybrids exposed to rotenone by enhancing mitochondrial biogenesis and supporting ATP production through glycolysis. Cybrids have also been used to investigate the possible role of mitochondrial dysfunction in familial PD. For instance, cell lines generated from individuals with familial autosomal dominant PD bearing mutations in the synuclein gene (SNCA) do not show complex I deficiency relative to those derived from patients with idiopathic PD (Swerdlow et al., 2001).

However, mitochondrial-related oxidative stress was still documented in SNCA-mutated cells (Swerdlow et al., 2001).

Data on rare mtDNA polymorphisms also indicate an association with neurodegenerative disorders (Hudson et al., 2014). Early evidence of a causal role of inherited mtDNA variants in PD was reported in a family with maternally inherited parkinsonism (Swerdlow et al., 1998). A lower activity of complex I, higher ROS levels, and dysmorphic mitochondria were observed in cybrids containing mitochondria of maternal descendants, but not in those generated with paternal descendants (Swerdlow et al., 1998). A pathogenic role of mtDNA variants in parkinsonism was further shown in a young patient carrying high levels of a frameshift mutation in the mitochondrial cytochrome *b* gene (MT-CYB) (Rana et al., 2000). This mutation induced metabolic and mitochondrial respiratory deficiency in cybrids (Rana et al., 2000). Inheritance of the heteroplasmic mtDNA variant m.T1095C of the mitochondrial encoded 12S ribosomal RNA gene (MT-RNR1) was also reported in a family with neuropathy, deafness, and maternally inherited parkinsonism (Thyagarajan et al., 2000). Cybrid lines generated from a member of this family and treated with the aminoglycoside antibiotic gentamicin showed selective depletion of mitochondrial glutathione, ETC complexes II and III, and enhanced apoptosis (Muyderman et al., 2012). Finally, an association with PD was identified for the A4336G mtDNA variant of the tRNAGlu mitochondrial gene (Tan et al., 2000). Collectively, these findings suggest that specific mtDNA variants might contribute to the pathogenesis of PD by impinging on mitochondrial function and cell viability. However, the available evidence does not allow a primary role for mtDNA mutations in PD to be conclusively established (Area-Gomez et al., 2019).

An early study by Lin et al. (1992) identified point mutations in the NADH dehydrogenase 2 (ND2) subunit of complex I in the brain of 19 patients with AD. However, subsequent studies seeking associations between specific mtDNA variants and AD reported inconclusive results (Coskun et al., 2004; Onyango et al., 2006). Furthermore, no evidence of maternal inherited mitochondrial defects was found in familial AD (Payami and Hoffbuhr, 1993). However, findings in AD cybrids cell lines still point to mitochondrial dysfunction as a crucial pathogenic factor in AD (Swerdlow et al., 2017). AD cybrid cell lines show reduced mitochondrial membrane potential, ATP production, dynamics, calcium internalization, and ability of buffering calcium-mediated signaling compared with controls (Cassarino et al., 1998; Silva et al., 2013a, 2013b; Thiffault and Bennett, 2005). Cybrid cell lines generated from individuals with mild cognitive impairment (MCI), a possible precursor of AD, show changes in metabolic parameters that are distinct from AD and control cybrids (Gan et al., 2014; Silva et al., 2013a, 2013b). Taken as whole, existing findings strongly suggest a role for mitochondrial abnormalities in AD. However, causation between specific mtDNA variants and neurodegeneration still needs to be determined.

Among mtDNA mutations, the accrual of mtDNA deletions has been identified in the brain of older adults with a preferential accumulation in regions that are more susceptible to neurodegeneration (Bender et al., 2006; Ross et al., 2013). Conversely, the presence of point mutations or insertion-deletion mutations is controversial (Chinnery et al., 2001; Lin et al., 2012). Finally, cell-free mtDNA in the cerebrospinal fluid (CSF) and/or mtDNA copy number variations in the brain of people with neurodegenerative diseases have been documented and proposed as biomarkers of neurodegeneration (Pyle et al., 2016, 2015). Studies in PD showed a selective reduction in mtDNA levels in neurons of the substantia nigra, but not in the caudate nucleus or frontal and cerebellar cortex (Dölle et al., 2016; Frahm et al., 2005). In particular, the reduction of wild-type mtDNA molecules despite an increase in mtDNA deletions in dopaminergic neurons of the substantia nigra may be the mechanism driving the bioenergetic deficit observed in PD patients (Dölle et al., 2016). The quantification of mtDNA copy number in brains of patients with AD has led to more coherent results showing a 30 to 50% reduction in mtDNA levels in neurons of the frontal cortex compared with controls (Coskun et al., 2004). mtDNA depletion and altered mitochondrial biogenesis signaling was also identified in the pyramidal neurons of the hippocampus (Rice et al., 2014).

To conclusively establish whether an association between mtDNA variants and the development and progression of neurodegenerative diseases exists, and to investigate the dynamics of mtDNA mutations and copy number variations in brain aging, whole mitochondrial exome sequencing was carried out in 1,363 post-mortem brains from people with AD, PD, amyotrophic-frontotemporal dementia, dementia with Lewy bodies, and Creutzfeldt-Jakob disease (CJD), and compared with age-matched controls (Wei et al., 2017). The authors did not find any evidence of rare inherited polymorphisms or degrees of mtDNA heteroplasmy associated with disease pathogenesis (Wei et al., 2017). However, in keeping with previous reports, a significant reduction in mtDNA copy number was identified in AD and CJD brains (Coskun et al., 2004; Wei et al., 2017). Although requiring additional investigations, findings of altered mtDNA copy number in age-related neurodegeneration may help gain insights into disease mechanisms. The quantification of mtDNA copy number, mtDNA deletion of 4.8-kb, and TFAM protein levels in several tissues of young and old rats, including the frontal cortex, allowed proposing possible mechanisms of regulation of mtDNA variations during aging (Picca et al., 2014, 2013b, 2013a). In particular, higher protein levels of TFAM and 4.8-kb deletion, and a decrease in mtDNA content was found in the frontal cortex of old rats compared with young controls (Picca et al., 2013a). Furthermore, results from immunoprecipitation assay of TFAM binding to mtDNA indicated that two sub-regions of mtDNA involved in replication had less TFAM-bound mtDNA in old than young rats (Picca et al., 2013a). This decrease in TFAM binding may explain, at least partly, the mtDNA decline observed during aging despite a compensatory increase in TFAM expression (Picca et al., 2013a).

Taken as a whole, these findings support the hypothesis of a role of mtDNA copy number variations in the pathogenesis of neurodegeneration. However, it is difficult to generalize these results to brain aging, because these abnormalities may be restricted to specific brain regions. Also, an altered mtDNA copy number may be a consequence of PD rather than the cause. Indeed, the variations observed in PD may represent an indirect effect of changes in the proportion of cell types composing the tissue homogenate consequent to neurodegeneration. However, the association of mtDNA copy number variations with age in post-mortem brains of people with CJD still supports the hypothesis of a causal role for changes in mtDNA content in neurodegeneration and requires further investigation.

The urge of diagnostic and prognostic biomarkers of neurodegeneration has ignited a great deal of research. Among other candidate molecules, the level of mtDNA in peripheral blood and CSF as a marker of brain metabolism and disease pathology and progression has been widely characterized. Encouraging results towards the reliability of cell-free mtDNA as biomarker for the early detection of age-related neurodegenerative conditions have been reported, but further investigation is needed.

4. Conclusions

Polymorphic mtDNA variants have been identified in sporadic and inherited disorders of the nervous system as well as in cancer, neurodegenerative diseases, and “normal” aging. The role of mtDNA quality control pathways in human health is actively investigated for the possibility of identifying diagnostic and prognostic biomarkers and targeted therapeutics for a wide range of conditions. Among other candidate molecules, mtDNA in CSF and peripheral blood, which mirrors tissue/organ metabolism and disease progression, is increasingly investigated. Encouraging results on cell-free mtDNA levels and associated mutations as a biomarker of early detection for cancer and age-related conditions have been reported. However, results are preliminary and further investigation is warranted.

Declaration of competing interest

The authors declare no competing interests.

Data availability

No data were used for the research described in the article.

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