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Aging: All roads lead to mitochondria

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Abstract

Mitochondria were described as early as 1890 as ubiquitous intracellular structures by Ernster and Schatz (1981) [1]. Since then, the accretion of knowledge in the past century has revealed much of the molecular details of mitochondria, ranging from mitochondrial origin, structure, metabolism, genetics, and signaling, and their implications in health and disease. We now know that mitochondria are remarkably multifunctional and deeply intertwined with many vital cellular processes. They are quasi-self organelles that still possess remnants of its bacterial ancestry, including an independent genome. The mitochondrial free radical theory of aging (MFRTA), which postulated that aging is a product of oxidative damage to mitochondrial DNA, provided a conceptual framework that put mitochondria on the map of aging research. However, several studies have more recently challenged the general validity of the theory, favoring novel ideas based on emerging evidence to understand how mitochondria contribute to aging and age-related diseases. One prominent topic of investigation lies on the fact that mitochondria are not only production sites for bioenergetics and macromolecules, but also regulatory hubs that communicate and coordinate many vital physiological processes at the cellular and organismal level. The bi-directional communication and coordination between the co-evolved mitochondrial and nuclear genomes is especially interesting in terms of cellular regulation. Mitochondria are dynamic and adaptive, rendering their function sensitive to cellular context. Tissues with high energy demands, such as the brain, seem to be uniquely affected by age-dependent mitochondrial dysfunction, providing a foundation for the development of novel mitochondrial-based therapeutics and diagnostics.

Keywords

Mitochondria; Genomic instability; Aging; Longevity; Mitonuclear; Communication; Mitochondrial-derived peptides; Oxidative stress; Immunity; Inflammation

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1. Introduction

Dietary interventions, nutrient sensing pathways, and metabolic homeostasis have profound effects on lifespan and/or healthspan in a broad range of model organisms. Upon the discovery that reducing caloric intake, known as caloric restriction, could extend lifespan in rats, considerable advances on the effect of dietary components and feeding patterns on aging have been made in the past century. For instance, diets that are low in proteins or specific amino acids, ketogenic diets, intermittent fasting, fasting-mimicking diets, and time-restricted feeding are known to promote healthy aging. Genetic studies in *C. elegans*, *D. melanogaster*, and mice have also paved the way to the current understanding that nutrient sensing pathways also play a pivotal role in regulating aging. First discovered in *C. elegans*, single gene manipulations were shown to effectively extend lifespan [2,3]. Soon after, several other genes were also identified to regulate lifespan, many of which turned out to be interconnected in the context of insulin and insulin-like signaling pathways. Parallel pathways in *D. melanogaster* were discovered, providing a strong genetic foundation to the aging process. Meanwhile, in mice, deficiencies in the growth hormone and its downstream insulin-like growth factor 1 (IGF-1) axis were revealed as major regulators of aging in mammals [4]. These pathways reflect a conserved metabolic network with profound effects on lifespan and/or healthspan.

Mitochondria are supreme metabolic entities that evidently originated from bacteria some 2 billion years ago. The remnants of their bacterial ancestry are evident even today, including an independent genome with polycistronic genes, usage of a distinct genetic code, asexual mode of division (*i.e.* fission). They are multifunctional organelles that not only produce the great majority of cellular ATP, but also function as major regulatory hubs that coordinate essential cellular processes, including programmed cell death, immune response, macromolecular synthesis (*e.g.* steroids, heme), calcium regulation, and intracellular and endocrine signaling. The multifunctional and adaptive nature of mitochondria makes their role in aging a complex moving target. Recent advances in mitochondrial research have moved the field of aging forward in various avenues, including geroscience (Fig. 1). Yet, a coherent molecular map that integrates the various layers of mitochondrial functions during aging is far from complete. Technological advances, including mitochondrial genome editing [5–7], imaging [8,9], bioinformatics [10–12], and emerging vertebrate model organisms [13–15] hold much promise in revealing deeper and comprehensive molecular details of mitochondrial function during aging and in age-related diseases such as Alzheimer's disease (AD). In this review, we discuss some of the recent advances made on the role of mitochondria in aging and age-related diseases, with special emphasis on the brain.

2. Mitochondrial genomic instability

Mitochondria generate the great majority of cellular ATP by transferring electrons harnessed from nutrients through the electron transfer chain (ETC) to oxygen during oxidative phosphorylation (OXPHOS). However, during this process, electrons can react with oxygen and generate reactive oxygen species (ROS), largely from complex I and III of the ETC [16,17]. Mitochondria are the major source of intracellular ROS production. Subsequently, mitochondrial ROS, particularly hydroxyl radicals, can react with and damage

macromolecules, including proteins, nucleic acids, phospholipids, thereby impairing their function. Whereas proteins and lipids are turned over without permanent damage, unrepaired ROS-inflicted DNA damage can persist and accumulate over time. mtDNA is thought to be more vulnerable to ROS-mediated mutagenesis, largely due to its proximity to the production site. Denham Harman, in his mitochondrial free radical theory of aging (MFRTA), postulated that aging and degenerative diseases are attributed to the progressive accumulation of ROS-mediated deleterious mtDNA mutations [18–25]. Consistently, oxidative damage to macromolecules was observed during aging in multiple organisms [26,27] and long-lived model organisms were reported to exhibit higher expression of antioxidant enzymes [28]. Multiple studies in various model organisms provide inconsistent results, indicating a complex role of antioxidants in regulating lifespan that is largely unclear [29–38]. Further, the presumably inferior DNA repair capacity of mitochondria, compared to the nucleus [39] lent weight to the MFRTA. However, more recent studies show that mitochondria are capable of repairing oxidative mtDNA lesions [40]. In addition, protection from ROS can be conferred by the nucleoid complex that binds to mtDNA [39], distancing from the respiratory chain (*i.e.* site of ROS production) [41–43], mitochondrial dynamics [44,45], and mitophagy [46]. While mtDNA mutations accumulate with age [47,48], oxidative damage in aged tissues of model organisms and humans is considerably lower than expected and rather modest [49–51]. Instead, prominent age-dependent mtDNA mutations are attributed to replication errors introduced by mitochondrial DNA polymerase γ (POLG). Indeed, mice expressing mutant POLG that are defective in proofreading during mtDNA replication have exhibit supraphysiological mtDNA mutation loads (~2500-fold in the homozygous $Polg^{mut/mut}$ and ~500-fold higher in the $Polg^{+/mut}$) and exhibited premature aging phenotypes [49,52]. Yet, despite the fact that both homo- and heterozygous mutants harbored mtDNA mutations far exceeding that observed during aging, only the homozygous mice ($Polg^{mut/mut}$) experienced shortened lifespan, indicating that mtDNA mutation load alone does not determine lifespan [53–55] and that a more complex manifestation of mitochondrial genomic instability is likely involved [56]. Although the MFRTA provided a valuable conceptual foundation for aging research its validity has been challenged [57]. Alternative roles for ROS, such as mitonuclear redox signaling [58–61], may provide further insight into their role in aging.

3. Mitochondria and inflammation

Aging is accompanied by a chronic state of low-grade inflammation referred to as ‘inflammaging’, which is interconnected with other major mechanisms of aging and age-related diseases [62]. Thought to largely result from chronic stimulation of the innate immune system, inflammaging leads to immune dysfunction characterized by impaired response to infection [63] and stimulation (vaccination) [64,65] and aberrant inflammatory signaling [66]. Mitochondria are critical mediators of innate immune response to viral infections [67,68], mitochondrial stress [69], and can signal through inflammasomes [70], toll-like receptor (TLR) signaling [71–73], and interferons [74]. The innate immune system recognizes intruding foreign organisms by pathogen-associated molecular patterns *via* pattern recognition receptors (PRRs), such as TLRs. Meanwhile, sterile inflammation can occur upon recognition of cellular damage by damage-associated molecular patterns

via PRRs, such as mitochondrial DNA (mtDNA) and formyl peptides that are bacterial-like due to the prokaryotic origin of mitochondria and released during cellular stress [74,75]. Notably, the release of mtDNA from mitochondria is a regulated process that communicates the damage to other subcellular compartments or to distal cells. Deficiencies in mitochondrial transcription factor A cause considerable mitochondrial stress and triggers the ejection of mtDNA [74,76]. Oxidative stress also causes mtDNA to be released into the cytoplasm through pores formed by VDAC (voltage-dependent anion channel) oligomers in the mitochondrial outer membrane [77]. Further, apoptosis leads to mtDNA release following mitochondrial outer membrane permeabilization (MOMP) driven by the activation pro-apoptotic BCL-2 proteins (*e.g.* BAX and BAK) [78]. The mitochondrial inner membrane extrudes into the cytosol and becomes permeabilized following the widening of BAX/BAK-mediated MOMP, allowing mitochondrial export of mtDNA [79]. Another mechanism for mtDNA transport across the mitochondrial inner membrane is through the mitochondrial permeability transition pore (mPTP), which spans the mitochondrial inner membrane in response to mitochondrial calcium concentration and cellular stress [80–82]. mtDNA that is released into the cytosol can then bind to cGAS (cyclic guanosine monophosphate–adenosine monophosphate synthase) and relay an immune response *via* the activation of STING (stimulator of interferon genes), such as type I interferons (IFNs) and IFN-stimulated genes [71,74,83,84]. Notably, the cGAS/STING pathway is involved in cellular senescence and is strongly linked to the pro-inflammatory senescence-associated secretory phenotype [85–87], indicating an immunological role of mitochondria in cellular senescence. In addition to cGAS-STING activation, stress-induced damage and release of mtDNA also promotes nuclear DNA repair, indicating a role for mtDNA as a sensor and communicator of genotoxic stress that guards the nuclear genome [69]. mtDNA is also exported out of the cell and detected as circulating cell-free mtDNA (ccf-mtDNA) in extracellular fluid [88,89] and cerebrospinal fluid (CSF) [90,91]. ccf-mtDNA provides an novel mechanism for mitochondrial communication between distal tissues [92] and are implicated in neurological disorders [93–95] and systemic inflammatory conditions [96]. Further, psychological stress [97–101] and age [102] increase ccf-mtDNA levels, suggesting the possibility that mtDNA may connect the aging mind and inflammation. Mitochondrial cytokines (mitokines), including growth differentiation factor 15, fibroblast growth factor 21, and mitochondrial-encoded humanin, have been suggested to mediate age-dependent adaptive mitochondrial anti-inflammatory responses [103].

4. Mitochondrial communication

Mitochondria communicate in a variety of ways to coordinate cellular processes, including metabolism, stress response, and adaptive nuclear gene expression. The mode and scope of mitochondrial communication is continuously being unveiled and has shown to be involved in key intra- and inter-cellular processes. To maintain cellular homeostasis under a continuously changing cellular context, mitochondria communicate to the nucleus to relay proteotoxic and metabolic stress and inflammatory signals. Several mediators of mitochondrial communication have been identified, including nuclear-encoded proteins, mitochondrial-encoded peptides, metabolites, inorganic molecules, and mtDNA itself. Here, we discuss some aspects of mitochondrial communication, particularly to the nucleus.

4.1. Mitochondrial signaling and proteostasis

The observation that mitochondrial stress triggers an adaptive transcriptional response in the nucleus was first reported in mammalian cells; the loss of mtDNA [104] or the accumulation of unfolded proteins in the mitochondrial matrix [105] triggered the expression of nuclear-encoded mitochondrial-targeted heat shock chaperones. Such mitochondria-to-nucleus proteotoxic signaling that induces a nuclear transcriptional program is largely known as the mitochondrial unfolded protein response (UPR^{mt}). Considerable advances in understanding the molecular mechanisms of UPR^{mt} were made using the model organism *C. elegans*, including the transcription factors ATFS-1 and DVE-1 [106–112]. UPR^{mt} induces adaptive nuclear gene expression, in part, through chromatin remodeling *via* histone H3K9 methylation by MET-2 and LIN-65 [113] and H3K27 demethylation by histone demethylases (*jmjd-1.2* and *jmjd-3.1*) [111]. Notably, UPR^{mt} in *C. elegans* is not confined to intracellular signaling but can also act on distal cells; neuronal OXPHOS perturbation can activate UPR^{mt} in the intestine and extend lifespan in *C. elegans* [114].

In mammals, a more general adaptive stress response program exists. The integrated stress response (ISR) is activated by various insults including proteotoxicity, nutrient deprivation, oxidative stress, and viral infection [115]. ISR is induced during aging and is implicated in age-related functional decline and diseases of the brain [116]. Age-dependent activation of ISR is, in part, driven by increased protein misfolding and reduced protein synthesis, which impedes brain functions (*e.g.* long-term memory) and contributes to pathology (*e.g.* AD [117]). ISR is mediated by 4 sensor kinases (PERK, GCN2, PKR, and HRI) that relay stress signals by converging on a single phosphorylation site (Ser51) of the eukaryotic translation initiation factor 2 (eIF2) protein [115]. Phospho-eIF2 ultimately leads to a global reduction of protein synthesis, while selectively promoting the expression of specific stress-responsive proteins that contain upstream ORFs (uORFs), such as ATF4 [118]. Notably, ISR is necessary for UPR^{mt} in metazoans but not in *C. elegans*, suggesting conserved and distinct mitochondrial protein stress signaling between the two organisms. The accretion of recent evidence indicates the involvement of other nuclear-encoded mitochondrial stress sensors that signal to the nucleus, which may feed into mitochondrial ISR. GPS2 (G-Protein Pathway Suppressor 2) is a nuclear-encoded mitochondrial-resident protein that translocates to the nucleus upon mitochondrial depolarization to activate multiple transcriptional programs that overlaps with those induced by UPR^{mt} [119,120]. GPS2 is involved in chromatin remodeling *via* the H3K9me2/3 histone demethylase JMJD2A/KDM4A [119]. Further, multiple nuclear-encoded proteins that reside in mitochondria translocate to the nucleus upon stimulation [111,121], indicating a regulatory network that maintains mitochondrial homeostasis.

4.2. Mitochondrial metabolites and nuclear gene regulation

Mitochondria communicate to the nucleus using metabolites to provide a metabolic context for nuclear gene regulation. The relative abundance of specific metabolites directly reflects nutrient availability, metabolic demand, cellular redox state and/or mitochondrial function, which can be modulated by diet and exercise. The metabolites serve as substrates and cofactors for various enzymatic modifications that regulate chromatin remodeling and consequent transcriptional regulation of multiple genes [122]. Many of

the metabolites are intermediates from the tricarboxylic acid (TCA) cycle, including ATP, acetyl-CoA, α-ketoglutarate (α-KG), fumarate, succinate, and 2-hydroxyglutarate (2-HG), which regulate enzymes that write, read, and erase the post-translational modifications on histones or modify DNA and RNA. Interestingly, mitochondrial metabolites relay actionable information regarding the state of mtDNA heteroplasmy, which increases with age and is linked with aging phenotypes [123–125], to the nucleus [126]. High levels of heteroplasmy lead to reduced, mitochondrial-derived acetyl-CoA levels and subsequent reduction in histone H4 acetylation [126]. mtDNA heteroplasmy also alters mitochondrial nicotinamide adenine dinucleotide (NAD^+/NADH) ratio, which likely affects histone acetylation. Midlevel heteroplasmy causes an increase in α-ketoglutarate concentration that may negatively regulate histone H3 methylation. Here, we discuss the mechanisms by which metabolites mediate mitonuclear communication *via* epigenetic modification.

Histone methylation and acetylation are key post-translational modifications that regulate epigenetics based on the canonical “histone code” [127]. The methylation of histone tails, which occurs at lysine and arginine residues [128], assists as a docking site for chromodomain epigenetic readers on histone [122]. Histone methylation is associated with both repression and activation of transcription depending on the genomic context. Histone methyltransferases (HMTs) and demethylases (HDMs) allow for the enzymatic transfer or removal of a methyl group to and from lysine and arginine residues. HMT utilizes S-adenosylmethionine (SAM) as a cofactor, which is derived from methionine and ATP through the one-carbon folate cycle that shuttles between the cytoplasm and mitochondria [129,130]. Conversely, S-adenosyl-homocysteine (SAH), a byproduct of HMT activity, inhibits HMT activity [131]. HDM utilizes mitochondrial-derived metabolites as cofactors [122,132,133]. Lysine-specific histone demethylase (LSD) and Jumonji C domain-containing protein (JMJD) families are two major conserved families of HDM [111,134]. LSD utilizes flavin adenine dinucleotide (FAD) as a cofactor, which is generated *de novo* in mitochondria and cytoplasm from the essential vitamin riboflavin (vitamin B2) [135]. JMJD proteins use iron (Fe^{2+}) and the TCA cycle intermediate α-KG as cofactors. This type of HDM can be inhibited by other TCA intermediates such as fumarate, succinate, and the onco-metabolite 2-hydroxyglutarate (2-HG) [136,137].

DNA methylation also modifies chromatin structure and inhibits gene expression by single nucleotide structural modification. DNA methyltransferases (DNMTs) also use SAM as a methyl donor to convert naked cytosine to 5-methylcytosine (5mC) [138]. DNA methylation can be passively reversed by replication-dependent dilution if not maintained or actively reversed through stepwise oxidation of 5mC by the ten-eleven translocation (TET) enzymes, coupled with or thymine DNA glycosylase (TDG)-mediated excision and based excision repair (BER) of the oxidized 5mC forms [139,140]. TET enzymes use Fe^{2+} and α-KG as cofactors and are inhibited by fumarate, succinate, and 2-HG, similar to the HDM JMJD [136].

Histone acetylation is associated with chromatin opening (*i.e.* euchromatin) and is therefore associated with active transcription [141,142]. Histone acetyltransferases (HATs) and deacetylases (HDACs) are enzymes that add or remove an acetyl group, respectively. Acetyl-CoA provides the acetyl group necessary for HAT activity. Acetyl-CoA exists both in

and out of mitochondria. Mitochondrial-derived acetyl-CoA typically results from complex metabolic activities, including ATP generation through OXPHOS. Cytoplasmic acetyl-CoA serves as building blocks for lipids, steroids, amino acids, and cofactor for HATs. Besides acetyl-CoA, acyl-CoA derivatives such as propionyl-CoA, butyryl-CoA, crotonyl-CoA, and succinyl-CoA also contribute to the activity of HATs [143]. Enzymes that produce acyl-CoAs are linked to fatty acid β-oxidation in mitochondria [144]. There are two different families of HDACs, of which one is Zn^{2+}-dependent histone deacetylases (HDACs) and the other one being NAD^+-dependent sirtuin deacetylases (SIRTs). The sirtuin family of HDACs use NAD^+ as a cofactor, which provides reducing equivalents (*i.e.* NADH) for OXPHOS, thus reflects the metabolic state of a cell [145]. In addition to metabolites, metabolic enzymes can reside in the nucleus for direct on-site generation of substrates and co-factors (*e.g.* acetyl-CoA) for epigenetic regulation [146]. Notably, RNA is also subject to modification, which is relatively recently identified compared to histone and DNA modification [147] and known to undergo ~150 different alterations [148]. RNA-modifying enzymes are reported to travel between mitochondria and nucleus, thereby offering a direct link of nucleus and mitochondrial communication [149]. For example, nuclear-encoded tRNA-modifying enzyme, pseudouridine synthase 1 (PUS1), modify both mitochondrial and cytoplasmic RNAs.

The ability of a cell to sense its metabolic state is key to maintaining homeostasis under an ever-changing environment. This is consistent with the fact that, as mentioned above, nutrient sensing pathways can regulate the aging process. Here, we highlight the fact that the nucleus is directly under the influence of mitochondrial metabolites that fluctuate depending on the rate of metabolic processes and cause chemical modifications to key regulatory components of gene expression. In other words, the nucleus fine-tunes gene regulation based on the cellular fuel gauge (*i.e.* metabolites) to effectively mount adaptive responses and promote cellular fitness.

4.3. Mitochondrial-Derived Peptides (MDPs)

The mtDNA has been long considered to encode 13 proteins that are key components of the electron transport chain complexes [1]. However, the recent identification of short genes in the mtDNA and nDNA reveals a more complex proteome of mitochondrial basis. Peptides derived from short open reading frames (sORFs) that are encoded in the mtDNA are collectively referred to as mitochondrial-derived peptides (MDPs). The selection pressure that drove the retention of two independent genomes, while the entire mtDNA can be found scattered across the nuclear genome [150], indicates that genomic consolidation was technically possible. Thus, a surpassing benefit(s) of choosing a dual-genomic system, over a single consolidated genomic system, likely increased cellular and/or organismal fitness. MDPs may reflect an ancient communication method that was retained based on the benefit of possessing inherent mitochondrial messengers. A lingering question lies regarding the role mtDNA, which divides asexually and is prone to higher mutation frequency, in influencing the genetics of aging. Currently, there are eight published MDPs, including humanin [151–153], six small humanin-like peptides (SHLP1-6) [154], and mitochondrial ORF of the 12S ribosomal RNA type-c (MOTS-c) [155]. Notably, MDPs are detected in cells/tissues and in circulation, indicating dual intracellular and endocrine roles.

Humanin is the first MDP that was identified, which was initially discovered as a neuro-protective factor from unaffected brain fractions of an autopsy-diagnosed AD patient [151–153]. Indeed, humanin has been shown to protect neurons from multiple cytotoxic insults, including those related to AD (*e.g.* familial AD genes and β-amyloid) [151–153,156–159]. Humanin is encoded within the mitochondrial 16S rRNA gene as a 75 bp sORF. Later, six additional MDPs were also identified within the 16S rRNA and named SHLP1–6. Humanin and SHLP expression is dynamic and alters with age, which reflects its role in adaptive stress response. In mice, humanin levels in tissues and in circulation have been shown to decline with age (2 *vs* 13 mo.) [160]. In humans, circulating humanin levels during aging have been reported to decline [(45–65 *vs* 65–80 *vs* 81–110 yrs.) [160]; (39 *vs* 60 yrs.) [161]] and increase (21–113 yrs.) [162]. The underlying reason for the varying reports on humanin levels is likely complex, but considering that humanin is a stress-responsive factor that adapts to physiological contexts, further studies in healthy subjects that control for biological and technical variables (*e.g.* genetic background, sex, physical status, sample collection time/methods) are needed to better interpret the significant of circulating peptide levels.

Central administration of humanin or SHLP2 improves insulin sensitivity in mice [160], indicating a role for regulating neuronal and/or glial function. As discussed below, MOTS-c also acts in the brain [163]. Notably, circulating humanin levels were decreased in AD and MELAS (Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes) patients, suggesting that further studies on peptide levels from patients with age-related diseases will likely provide additional insight [164]. Further, circulating humanin levels were considerably higher in centenarian offsprings compared to their age-matched counterparts [164].

Considerable expression of transcripts from the mitochondrial rRNA loci (*i.e.* 12S and 16S rRNA) have been reported previously in mononuclear cells under interferon-inducing conditions, but the originating genes were not identified nor annotated [165]. Whereas humanin and SHLPs are derived from the 16S rRNA, MOTS-c is encoded within the 12S rRNA [155]. MOTS-c is detected in various tissues (*e.g.* brain, liver, skeletal and cardiac muscle) and in circulation [155], thus has been dubbed a mitochondrial hormone [166] or a mitochondrial cytokine (mitokine) [167,168]. MOTS-c acts as a regulator of metabolic homeostasis, in part, by targeting the skeletal muscle and enhancing insulin sensitivity. In fact, MOTS-c prevented diet-induced and reversed age-dependent insulin resistance in mice. Notably, MOTS-c translocates to the nucleus in response to metabolic stress and directly regulates adaptive nuclear gene expression to promote homeostasis [169]. This indicates that the co-evolved mitochondrial and nuclear genomes cross-regulate each other and coordinate cellular responses [170,171].

MOTS-c was predicted to enhance physical performance and mediate some of the physiological benefits of exercise, in part, based on its effect on skeletal muscle, glucose metabolism, and AMPK signaling [155,172–175]. Indeed, exercise increases MOTS-c levels in skeletal muscle and in circulation in humans [176] and mice [177]. Further, MOTS-c injections can significantly extend the running capacity of mice on a treadmill, regardless of their age [176]. RNA-seq analyses revealed that MOTS-c promotes proteostasis in

skeletal muscle in a HSF-1-dependent manner [176]. Further, exercise induces MOTS-c actions in the brain. Regular exercise and intracerebroventricular (ICV) treatment with the exerkine IL-6 can both induce the expression of MOTS-c in hypothalamic POMC neurons in an ROS-dependent manner [163], consistent with exercise-induced increase in skeletal muscle and in circulation [176,177]. MOTS-c mediates mitohormetic responses in the brain that connect with peripheral tissues, such as fat. Mild mitochondrial ribosomal stress specifically in the hypothalamic POMC neurons, induced by heterozygous deletion of the nuclear-encoded mitochondrial ribosome component CRIF1 (Pomc-Cre; $Crif1^{f/+}$), increases the expression of MOTS-c and β-endorphin [163]. In these mice, mild mitoribosomal stress in the hypothalamic POMC neurons triggers UPR^{mt} in distal adipose tissue, promotes browning of white adipose tissue (WAT), increases metabolic turnover, and protects from obesity. Consistently, central MOTS-c administration (ICV injections) recapitulates the adipose phenotype of Pomc-Cre; $Crif1^{f/+}$ mice, including the distal induction of UPR^{mt} and WAT browning [163]. Systemic MOTS-c treatment (intraperitoneal (IP) injections) has been shown to induce similar physiological effects [155,176–178], but whether such responses are mediated by direct neuronal regulation is yet to be determined. Further, although MOTS-c is detected in whole brain samples, it is unclear whether they are synthesized by neurons and glia and/or represent circulating peptides that crossed the blood brain barrier [155]. In neurons, MOTS-c entered the nucleus [163] and regulated POMC expression in coordination with STAT3 [163]. Finally, exercise and ICV treatment with the exerkine IL-6 both induced the expression of MOTS-c in hypothalamic POMC neurons in an ROS-dependent manner [163], consistent with exercise-induced increase in skeletal muscle and in circulation [176,177].

sORF that encode for bioactive peptides are continuously being identified from both mitonuclear genomes, and more sORFs are expected to be annotated followed by functional analyses [179–182]. The fact that MOTS-c can directly regulate nuclear gene expression and that nuclear-encoded factors are known to regulate mitochondrial function indicates our mitonuclear genomes have co-evolved to coordinate gene expression to establish a dynamic yet unified cellular network. The advent of mtDNA engineering technologies, it may not be far before targeted mutagenesis could provide powerful genetic tools for basic research and clinical correction of age-dependent and hereditary mtDNA alterations.

5. Mitochondria in the aging brain

The brain is a major consumer of energy thus is heavily reliant on mitochondria for survival and function. Mitochondria have key roles in neurons, including the biosynthesis of neurotransmitters and their regulation through ATP production and calcium handling [183–187]. The number and morphological status of mitochondria at the synapse affect brain function by changing synaptic strength with age as demonstrated using 3D electron microscopy reconstructions of the brain area linked with working memory in monkeys [188]. The variability of presynaptic strength is also affected by axonal mitochondrial motility, which regulates the release of neurotransmitters [189]. Although neuronal mitochondria exist abundantly in axons, its turnover and biogenesis largely occur in the soma, which requires active mitochondrial transport [190], which is coordinated with axonal growth [191]. Mitochondria can dock or pause in areas with high metabolic demands

(*e.g.* dendritic spines) and resume movement depending on cellular cues [190]. Aging is associated with reduced mitochondrial transport with respect to total movement duration, distance, and duty cycle (portion of time spent in transit) in old mice (23–25 mo.) [192]. Further, mitochondria-free regions increase in axons and lengths of transported mitochondria along the axon decrease with aging in rats [192]. Mitochondria are transported *via* motor proteins (*i.e.* kinesins and dyneins) across microtubules that can be destabilized by tau hyperphosphorylation. Such microtubule disruption would negatively impact mitochondrial mobility and provide a connection between mitochondrial dysfunction and Alzheimer's disease (AD) [193,194]. Further, mitochondria may be involved in the aberrant processing of amyloid precure protein (APP), providing an amyloid connection to the pathogenesis of AD [195,196]. Also, mitochondria may influence the sex dimorphic nature of AD [197] as estradiol, upon binding to estrogen receptors (ER), localizes to mitochondria and modulates mtDNA gene expression, respiratory capacity, mitochondrial antioxidant defenses, and calcium buffering capacity, which in turn can affect neuronal plasticity [198–201].

Considering that a single neuron can have upwards of thousands of mitochondria [202], maintaining mitochondrial fitness would require well-tuned orchestration of multiple processes, including mobility, energetics, dynamics (*i.e.* fission and fusion), mitophagy, and biogenesis. Thus, as described below, the role of mitochondrial communication/signaling for successful coordination of complex processes is likely a key factor. In addition, mitochondrial quality control at the genetic level is important as mtDNA heteroplasmy, which increases with age in the brain and other tissues, impairs memory retention [203].

6. Conclusion

Mitochondria are the chief metabolic organelle that not only serves as production sites for bioenergetic units and a myriad of macromolecules, but also as prominent regulatory entities that have a stake in a wide range of physiological processes from inflammation to nuclear gene regulation. Considering that eukaryotic existence can be largely attributed to the establishment of mitochondria at all stages of evolution [204], their broad involvement in cellular functions is not surprising. The early endosymbiotic relationship can be seen as an infection, which, together with the fact the immunity and metabolism co-evolved [62], conceptually supports the fact that metabolic pathways are key regulators of aging [205,206] and immunity [207–211] and the intricate involvement of mitochondria. Further, the mitochondrial and nuclear genomes have co-evolved for the past ~2 billion years as the ancestral cells became functionally more complex [212,213]. It is likely that the cellular network is indeed synthesized by factors from both genomes that co-regulate each other to coordinate adaptive gene expression to maximize cellular fitness. Indeed, currently unknown force of selection likely opted a dual genomic cellular system over a unified singular genome, which evidently was fully possible as the entire mtDNA sequence, although degenerate, is scattered across the nuclear genome [214,215]. "Mitochondrial function" undoubtedly encompasses a broad range of cellular processes that have key roles in aging. However, the multiple functions appear to be mechanistic moving targets that change with age, in part, due to their dynamically adaptive and extensively interconnected nature; what occurs in youth may not necessarily be applicable in old age. Thus, a holistic and

evolutionary perspective would benefit investigations into how mitochondria contribute to aging and age-related diseases.

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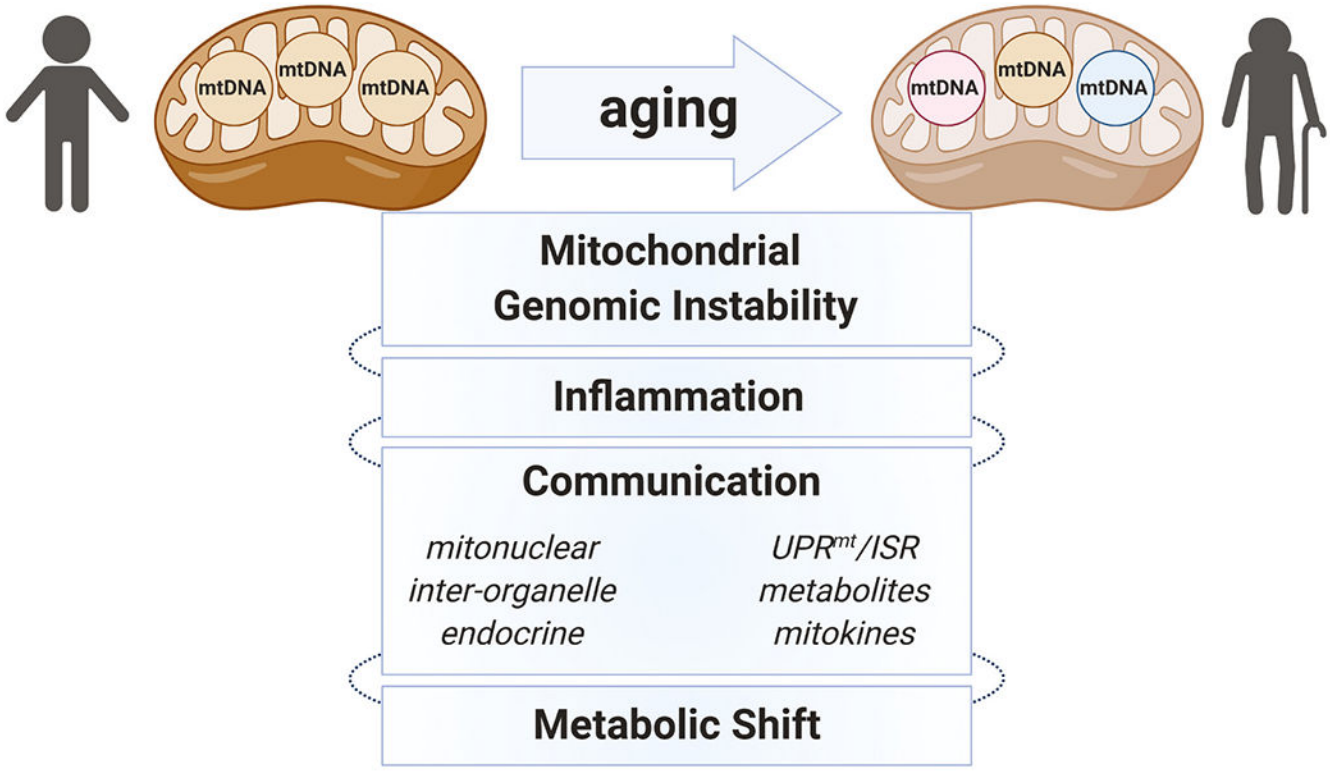

Fig. 1.

Mitochondria are multifunctional organelles that are extensively integrated with many cellular activities. The broad actions of mitochondria that are adaptive to cellular contexts render their role in aging highly complex and a moving target. mtDNA mutations and heteroplasmy increase with age, which are strongly implicated in aging phenotypes and age-related diseases. Mitochondria are also heavily involved in immune responses, including mtDNA-induced stimulation of inflammatory pathways. Further, mitochondria are regulatory hubs that communicate and coordinate many vital physiological processes at the cellular (*i.e.* other subcellular compartments (inter-organelle), including the nucleus(mitonuclear)) and organismal level (*i.e.* endocrine). Several methods of communication are employed, including proteostasis signaling (*i.e.* UPR^{mt} and ISR), mitochondrial metabolites, and mitokines (*e.g.* mitochondrial-derived peptides (MDPs)). Multiple age-dependent mitochondrial dysfunctions are thought to ultimately cause maladaptive metabolic shifts and reduce organismal fitness, contributing to aging phenotypes and age-related disabilities/diseases.