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ABSTRACT

Aging is accompanied by a time-dependent progressive deterioration of multiple factors of the cellular system. The past several decades have witnessed major leaps in our understanding of the biological mechanism of aging using dietary, genetic, pharmacological, and physical interventions. Metabolic processes, including nutrient sensing pathways and mitochondrial function, have emerged as prominent regulators of aging. Mitochondria have been considered to play a key role largely due to their production of reactive oxygen species (ROS), resulting in DNA damage that accumulates over time and ultimately causes cellular failure. This theory, known as the mitochondrial free radical theory of aging (MFRTA), was favored by the aging field, but increasing inconsistent evidence has led to criticism and rejection of this idea. However, MFRTA should not be hastily rejected in its entirety because we now understand that ROS is not simply an undesired toxic metabolic byproduct, but also an important signaling molecule that is vital to cellular fitness. Notably, mitochondrial function, a term traditionally referred to bioenergetics and apoptosis, has since expanded considerably. It encompasses numerous other key biological processes, including the following: (i) complex metabolic processes, (ii) intracellular and endocrine signaling/communication, and (iii) immunity/inflammation. Here, we will discuss shortcomings of previous concepts regarding mitochondria in aging and their emerging roles based on recent advances. We will also discuss how the mitochondrial genome integrates with major theories on the evolution of aging.

INTRODUCTION

Mitochondria are unique cellular organelles in that they inherently possess their own genome in the form of a circular DNA (mitochondrial DNA; mtDNA) which presumably derived from endosymbiotic alpha-proteobacteria. Traditionally, the main function of mitochondria has been considered to be ATP production by oxidative phosphorylation. However, recently, mitochondria have been increasingly appreciated as a major hub that transmits adaptive regulatory signals to control a wide range of cellular functions, including immunity, survival, and homeostasis, with strong implications in aging. Mitochondria regulate many age-related pathways including senescence, unfolded protein response, autophagy, and inflammation. Some prominent pathways include the following: (i) reactive oxygen species (ROS) signaling that have a broad cellular impact including nuclear gene regulation, (ii) metabolite signaling, (iii) mitochondrial damage-associated molecular patterns (mtDAMPs) that consist of molecules released from injured mitochondria, (iv) mitochondrial unfolded response (UPR_{mt}) whereby mitochondrial perturbations activate stress-responsive transcriptional responses in the nucleus via factors such as activating transcription factor associated with stress-1 (ATFS-1) in *C. elegans* and ATFS-5 in mammals, and (v) mitochondrial-derived peptides (MDPs) that are factors encoded in the mtDNA. Notably, mitochondrial communication is an emerging biology with increasing evidence for a key role in normal aging and age-related disease, but the mechanistic details are largely unclear. In this review, we will discuss mitochondrial communication, with an emphasis on how this communication influences cellular function, homeostasis, and aging.

MITOCHONDRIAL GENOMIC INSTABILITY AND AGING

Several theories have been proposed to unravel the biological basis of aging. The mitochondrial free radical theory of aging (MFRTA) has been a prominent concept that describes mitochondria as a major driving force of aging. Proposed by Denham Harman first in the 1950s, the theory posits that the progressive accumulation of cellular damages inflicted by free radicals generated during mitochondrial metabolism leads to aging [1,2]. However, MFRTA has been increasingly unfavored because of inconsistent data that suggest alternative mitochondrial contributions to aging. Here, we will discuss the past, present, and future of the role of mitochondria in lifespan and healthspan.

Free radicals are molecules with at least one unpaired electron. During mitochondrial oxidative phosphorylation, electrons can 'leak' to form free radicals that react with surrounding oxygen to generate reactive oxygen species (ROS), which in turn can damage cellular macromolecules such as lipids, protein, and DNA. Mitochondrial DNA (mtDNA), due to its proximity to the site of ROS production, was thought to be highly vulnerable [3]. In addition, Further at the contemporary notion that the mitochondrial DNA repair system was inferior to the nuclear counterpart provided added support to MRFTA [4]. However, mtDNA integrity is maintained at multiple levels, including a repair system that is more versatile than previously thought [5], physical shielding by nucleoids [6,7], mitochondrial fission and fusion [8,9], and mitophagy [10]. Nonetheless, mtDNA mutation frequency increases with age in various animal models and humans [11,13,14], although their role as the driver of aging has been unclear [15,16]. A mutation load greater than 60%-90%, which is beyond what is

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incurred by aging, has been suggested to be necessary for age-related phenotypes to manifest [17-19].

Genetic manipulations of the antioxidant system intended to test MFRTA (*i.e.*, the role of ROS in aging) more directly has been inconsistent and inconclusive [20]. Only some of the cellular antioxidant systems that were inactivated shortened lifespan in yeast [*i.e.* copper-zinc superoxide dismutase (CuZnSOD; *sod1*), manganese superoxide dismutase (MnSOD; *sod2*), and copper chaperone (*ccs1*)] [21,22], worms (*sod* isoforms) [23], flies (*sod1* and *sod2*) [24-27], and mice (*i.e.* *sod1*) [28]. Notably, many antioxidant genes did not significantly affect lifespan in these model organisms. On the contrary, it has been shown that overexpression of antioxidant components including *sod1* and *sod2* can increase lifespan in yeast [29], worms [30,31], and flies [32-34]. In mice, it has been shown that overexpression of human catalase localized to mitochondria (mCAT) can decrease oxidative stress and extend lifespan [35]. It can also improve age-dependent insulin resistance [36]. One caveat of the report by Schriener *et al.* [35] was that lifespan extension was significant in mCAT mice that were two to four generations backcrossed to the C57BL/6J strain. However, the longevity effect diminished after > 9 generations. This could be a secondary effect derived from epistasis and/or CMV element methylation [37].

Perhaps the most direct challenge to MFRTA comes from the failure to detect age-dependent increase in ROS-induced mtDNA damage. DNA mutations that arise from ROS can cause an 8-oxo-2'-deoxyguanosine (8-oxodG)-mediated G-to-T transversion [38]. However, mtDNA mutations in brain and heart of old mice (< 24 mo. vs < 10 months) were transitions whereas G-to-T transversions were modest [39]. Notably, transitions are mostly caused by replicative

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infidelity (*i.e.*, DNA polymerase errors), indicating that replicative errors, not ROS, are the main culprit of age-dependent mtDNA mutations. In addition, ultra-deep hepatic mtDNA sequencing showed increased age-dependent replicative errors, not ROS-dependent damage [40]. Similarly, highly sensitive duplex sequencing of aged human pre-frontal cortex mtDNA (> 75 yrs vs. < 1 yr) revealed higher proportions of replication errors rather than oxidative damage [41].

Inactivating the proofreading activity of mitochondrial-specific DNA polymerase γ (mtDNA mutator in mice) by targeted mutagenesis at amino acid position 257 (D257A) increased mtDNA mutation frequency to supraphysiological levels in mice: ~2,500-fold and ~500-fold higher in homozygous ($polg^{mut/mut}$) and heterozygous ($polg^{+/mut}$) mutant mice, respectively [39]. Although homozygous ($polg^{mut/mut}$) mice exhibited accelerated aging phenotypes and significantly reduced lifespan, heterozygous ($polg^{+/mut}$) mice did not show early signs of aging. They had a normal lifespan [39,42]. Furthermore, mtDNA mutator mice exhibited OXPHOS dysfunction without significant increase of oxidative damage [43-45]. Notably, ROS levels in young mtDNA mutator mice were not increased despite high levels of mtDNA mutations [46]. Nonetheless, these mutations have been implicated in more than 300 diseases that are linked to aging and age-related diseases listed in the Human DNA Polymerase Gamma Mutation Database (<http://tools.niehs.nih.gov/polg>) [47]. Lastly, mtDNA deletions that become prevalent with aging [48-50] are significantly increased in short-lived homozygous ($polg^{mut/mut}$) mice, but not in heterozygous ($polg^{+/mut}$) mice that had a normal lifespan [51]. These results suggest a more complicated connection between mtDNA mutation frequency and aging.

Further investigations are needed to identify other aspects of mtDNA mutator mice such as mitochondrial communication.

CELL-AUTONOMOUS MITOCHONDRIAL COMMUNICATION AND AGING

Eukaryotic cells are functionally compartmentalized into organelles with assigned distinct tasks that work in concert. Such subcellular coordination is mediated by inter-organellar communication to maintain cellular homeostasis. The mechanism underlying inter-organellar communication is an emerging topic in biology that has much implications for aging. On that line, the connection between mitochondria and the nucleus is of special interest considering that they uniquely possess independent genomes (**Figure 1A**).

Mitonuclear communication

Mitochondria presumably originate from α -proteobacteria that have sustained an endosymbiotic relationship with our ancestral cells ~1.5 billion years ago. Notably, mitochondrial retained a portion of the original bacterial genomes that co-evolved with nuclear genome. However, -mitochondria import over a thousand proteins ~~that are~~ encoded in the nuclear genome to maintain their diverse functions, reflecting their close relationship. Therefore, it is critical that mitochondria and the nucleus dynamically communicate (*i.e.*, mitonuclear communication) with each other to coordinate adaptive responses to the constantly changing intrinsic and extrinsic cellular milieu and maintain homeostasis. In fact, impaired mitonuclear communication is strongly implicated in aging and age-dependent

diseases. Mitonuclear communication is bi-directional. It is mediated by several factors transmitted from each organelle. In this review, we will focus on signals transmitted from mitochondria to the nucleus (*i.e.*, retrograde signals), including reactive oxygen species (ROS), metabolites, mitochondrial damage-associated molecular patterns (mtDAMP), mitochondrial unfolded response (UPR^{mt}), and mitochondrial derived peptides (MDPs).

Reactive Oxygen Species (ROS) signaling

ROS is often considered as a toxic metabolic byproduct that causes detrimental damage to multiple cellular components, thereby contributing to the aging process [52,53]. However, as discussed above, mitochondrial ROS is not the major cause of mtDNA mutations, indicating a more complex cellular role. Actions of ROS are pleiotropic. They cause oxidative stress at higher concentrations (pathological) while they act as signaling molecules at lower levels (physiological). In fact, physiological ROS response has been suggested as eustress [54] that increases mitohormesis as an adaptive response to promote health and extend lifespan [55]. Increasing interest in ROS as signaling molecules that regulate normal physiological processes has provided insight into its role in regulating lifespan and/or healthspan [54,56,57]. **Many-In fact, lifespan extension ~~in~~ using in various model organisms such as worm, fly, and mice is mediated by retrograde ROS. (53)** In worms, RNAi screens **have have** identified long-lived animals that **have-harbor** mutations in mitochondrial respiration [58,59]. On that line, retrograde ROS signaling can mediate lifespan extension in worms with impaired insulin/IGF-1 signaling while inhibition of ROS signals using antioxidants can reduce such longevity by up to 60% [60]. Furthermore, a mild increase in ROS levels by inhibiting respiration can

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activate transcription factor hypoxia-inducible factor 1 (HIF-1) and consequent nuclear gene expression to promote longevity in worms [61]. In addition to modulating factors, ROS can also lead to epigenetic alternations [62,63]. For instance, ROS can regulate the chromatin binding capacity of histone demethylase Rph1p, thereby extending chronological lifespan in yeast [64]. Moreover, ROS can promote mitochondrial unfolded protein response (UPR^{mt}). This will be further discussed in the following section.

Mitochondrial unfolded protein response (UPR^{mt})

Mitochondrial unfolded protein response (UPR^{mt}) is a mitochondria-to-nuclear communication mechanism that promotes adaptive regulation of nuclear genes related to mitochondrial chaperones, proteases, antioxidants, xenobiotic response, and metabolism, ultimately rewiring the cell to survive. UPR^{mt} was initially thought to be triggered by mtDNA depletion or by protein misfolding in the mitochondrial matrix [65]. However, it now encompasses various mitochondrial stress conditions, including dysfunctional metabolism, defective iron sulfur cluster assembly, and immune response [65,66]. The activating transcription factor associated with stress 1 (ATFS-1) in worms is a major mediator of UPR^{mt}. Normally, ATFS-1 is imported into mitochondria for proteolytic degradation. However, mitochondrial stress will trigger ATFS-1 to translocate from mitochondria to the nucleus where it regulates the expression of a considerable portion of mitochondrial stress-responsive genes [66,67]. Such bi-organellar trafficking to coordinate mitonuclear communication is possible because ATFS-1 possesses both a mitochondrial-targeting sequence (MTS) and a nuclear localization signal (NLS) [66,67]. ATFS-1 also plays a role in chromatin remodeling which is required for full

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activation of UPR^{mt} via the histone methyltransferase met-2 and a nuclear co-factor lin-65 to promote longevity [68]. CLOCK-1 (CLK-1; human homolog COQ7) acts as a ROS barometer that mediates mitochondria to nuclear signaling by activating UPR^{mt} . *clk-1* null worms have extended lifespans [69]. Such effect appears to be mediated by UPR^{mt} [67]. In mice, the loss of *clk1* also increases cellular fitness and lifespan [70].

Metabolite signaling

Mitochondria are metabolic hubs that perform a wide range of catabolic and anabolic processes, thereby generating a variety of metabolites. Mitochondrial metabolites can also act as secondary messengers for genetic or epigenetic regulation [71,72]. Of these metabolites, many are products of the tricarboxylic acid (TCA) cycle, such as acetyl-coenzyme A (acetyl-CoA), succinyl-CoA, and nicotinamide adenine dinucleotide (NAD^+). The pyruvate dehydrogenase (PDH) complex that normally resides in mitochondria and generates acetyl-coenzyme A (acetyl-CoA) can translocate from mitochondria to the nucleus where it is involved in producing acetyl-CoA in the nucleus and modulate histone acetylation which requires acetyl-CoA as a substrate for lysine acetylation [73,74]. Under growth conditions, acetyl-CoA levels are higher in the nucleus and cytosol for lipid synthesis and histone acetylation. However, under starvation conditions, acetyl-CoA predominantly resides in mitochondria for ATP and ketone body production [75]. Succinyl-CoA is another TCA cycle intermediate that can post-translationally modify proteins by succinylating lysine residues of proteins [76] such as histones, thereby affecting chromatin dynamics and consequently the epigenome [77]. In a similar way, other TCA intermediates, including oxaloacetate, malate,

fumarate and α -ketoglutarate, can also induce genetic and epigenetic reprogramming and extend worm lifespan [78]. NAD^+ is also a crucial mitochondrial gero-metabolite that declines with age [79,80]. Reduced age-dependent NAD^+ availability is linked to decreased deacetylase sirtuin activities, ultimately affecting the communication between mitochondria and nucleus [81,82]. It also affects longevity [83,84]. Retrograde Ca^{2+} is another important inorganic gero-metabolite [85]. Nuclear skeletal muscle gene expression is regulated by mitochondrial Ca^{2+} which mediates mitochondria to nucleus route [86].

Mitochondrial damage-associated molecular patterns (mtDAMP)

Our immune system becomes progressively impaired with age, leading to the loss of immune function (*i.e.*, immunosenescence) and elevated chronic low-grade inflammation (*i.e.*, inflammaging) [87]. Immune responses can be triggered not only by foreign materials/organisms, but also by endogenous factors. Pathogen-associated molecular patterns (PAMPs) derived from bacteria, fungi, and viruses can induce innate immune responses via inflammasomes that are intracellular complexes capable of promoting pro-inflammatory cytokines such as interleukin- 1β (IL- 1β) and IL-18 [88]. Damage-associated molecular patterns (DAMPs) derived from endogenous intracellular components that are released during cellular stress and/or damage can also mount an immune response [89]. Especially, injured mitochondria can release their contents known as mitochondrial damage-associated molecular patterns (mtDAMP) recognized as PAMPs owing to their bacterial ancestry. Some well described mtDAMPs include mtDNA, *N*-formyl peptides (specific to mitochondrially-translated proteins), and fragments of mitochondrial proteins [90,91]. The innate immune

system can express pro-inflammatory cytokines upon sensing circulating mtDNA and *N*-formyl peptides using pattern recognition receptors (PRR) such as toll-like receptors (TLRs) and NOD-like receptors (NLRs) [91]. Notably, circulating mtDNA levels are increased with age. Their increase is associated with elevated levels of cytokines and inflammatory markers, indicating a role of mtDNA in inflammaging [92] and may ~~These events appears to be increased in the elderly. They might individuals and~~ contribute to ~~the development of the~~ age-related diseases ~~development and inflammaging~~ [93,94].

Mitochondrial-derived peptides (MDPs)

The human mtDNA encodes only 13 protein-coding genes that are all structural components of the electron transport chain (ETC) without known signaling roles. Thus, active gene-encoded mitonuclear communication pathways were known to be exclusively mediated by factors encoded in the nuclear genome. More recently, short open reading frames (sORFs) encoded in the mitochondrial genome that yield bioactive peptides, collectively referred to as mitochondrial-derived peptides (MDPs), have been identified [95]. There are now eight published MDPs, including humanin, MOTS-c (~~mitochondrial~~ open reading frame of the ~~twelve S rRNA type-c~~), and small humanin-like peptide (SHLP)~~1-to SHLP6~~. They regulate various cellular functions. Humanin is encoded within the mitochondrial 16S rRNA. It was identified from a surviving brain fraction of an Alzheimer's disease (AD) patient as a protective factor against AD-related toxins such as β -amyloid [96]. It is also a binding partner of insulin-like growth factor binding protein 3 (IGFBP-3) [97] and an anti-apoptotic factor that inhibits Bax [98]. SHLP1~~-to SHLP6~~ were also identified within the 16S rRNA [99]. MOTS-c

is encoded within the mitochondrial 12S rRNA. It acts as a regulator of metabolic homeostasis that can prevent diet-induced obesity and insulin resistance, and age-dependent insulin resistance in mice [100-102]. Notably, MOTS-c can translocate to the nucleus upon cellular stress to regulate adaptive nuclear gene expression by interacting with other stress-responsive transcription factors including nuclear factor erythroid 2-related factor 2 (NFE2L2/NRF2) and binding to chromatin [103-105]. HEK293 cells that over-express MOTS-c were significantly protected against metabolic stress (*i.e.*, glucose and serum deprivation) [103]. This indicates that our co-evolved mitonuclear genomes have established a genetically integrated bi-directional communication system.

Humanin, SHLP2, and MOTS-c levels decline with age and their actions are positively correlated with longevity [95,99,101,106]. Humanin levels are negatively regulated by the GH/IGF axis in both mice and humans [107]. Circulating humanin levels are elevated in long-lived GH-deficient Ames mice, but decreased in short-lived GH-transgenic mice [107]. MOTS-c can reversed age-dependent insulin resistance. A ~~and a~~ functional MOTS-c polymorphism is related to exceptional longevity in a Japanese population [108,109]. Furthermore, ~~the~~ MOTS-c actions are, in part, dependent on sirtuin 1 (SIRT1) and AMPK [101,103], two prominent related factors shown to regulate longevity in various model organisms [110,111].

Because of the unique bi-genomic cellular setup, it is important to consider mitonuclear epistasis. mtDNA is maternally transmitted, which forces a cell to coordinate gene expression with a foreign (*i.e.*, paternal) genome upon fertilization. The compatibility between maternal mtDNA and paternal nuclear DNA is thea major ground for intergenomic epistasis [112-114].

Nuclear gene expression is dependent on the mtDNA background. Nuclear mutations can manifest very differently under varying mtDNA context. For instance, patients with a mutation in the adenine nucleotide translocator 1 gene (*SLC25A4*, *ANT1*) exhibit a wide range of cardiomyopathies that are correlated with their mtDNA lineage [115]. In 2015, the United Kingdom approved mtDNA replacement therapy to allow a woman to transfer her nuclear genome to an egg with healthy mitochondria to prevent transmission of mtDNA disease. Such forced mtDNA-nDNA combinations may be incompatible. It can cause dysregulated mitonuclear communication (Hamilton 2015). In fact, alloantigenicity and immune rejection have been documented in nuclear-transfer-derived embryonic stem cells (NT-ESCs) [116]. In addition, Mitochondrial-Nuclear eXchange (MNX) mice with interchanged nuclear and mitochondrial genomes from different mice (similar to three-parent baby) have differential oxidative stress, resistance to heart failure, lipid concentration, and bioenergetics [117,118]. Aging is a complex process with strong genetic components. It is likely to be dependent on both of our genomes. Thus, the interaction between factors encoded in each genome may further our understanding of aging genetics.

Other mito-organellar communication

Cellular functions are compartmentalized into various organelles with unique roles. Their orchestrated processes together support survival. Therefore, inter-organellar communication is key to cellular homeostasis and ultimately organismal fitness. On that line, mitochondria not only communicate with the nucleus, but also dynamically interact with other organelles [119] (**Figure 1B**). Although the field of inter-organellar communication is still in its early stages, it

is undoubtedly of great interest. Further investigation of mito-organellar communication with high spatial and temporal resolution and identification of key signaling mediators are necessary to understand the complex coordination of subcellular processes and their roles in aging. Here, we will focus on mitochondrial communication with the ER, peroxisomes, and lysosomes in the context of aging.

Mitochondria and Endoplasmic Reticulum (ER) Communication

The ER physically interacts with mitochondria to regulate organelle morphology and various metabolic signaling [120]. The contact sites that ER forms with mitochondria are called mitochondria-associated membranes (MAM), which have numerous roles in controlling lipid and calcium homeostasis, mitochondrial metabolism, insulin and glucose signaling, and ultimately aging [121]. Proteome analysis of MAM has revealed its connection to various age-related diseases, such as Alzheimer's disease and type 2 diabetes [121]. Cisd2 knockout mice also provide evidence that MAM may play a role in aging. {Editor's Note: Please cite reference for the highlighted area. This is discussed in the following sentences and referenced}. Cisd2 is a regulator of intracellular Ca^{2+} and glucose homeostasis that localizes to the ER, mitochondrial membranes, and MAM [122]. Mice that lacked Cisd2 showed mitochondrial degeneration and functional decline in skeletal muscle and neurons, glucose intolerance, premature aging phenotypes (e.g. ocular degeneration, dermal deterioration, sarcopenia, etc.), and shortened lifespan [123], implying that disruption of mitochondria and ER communication could affect the aging process.

Mitochondria and Peroxisome Communication

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Increasing evidence points to the mitochondrial-peroxisomal connection as an important aspect of aging and age-related disease [124,125]. Restoring the import of peroxisomal catalase which decomposes hydrogen peroxide can restore mitochondrial integrity and reverse the senescent phenotype of human fibroblasts [126]. Another study demonstrated that peroxisome proliferation and higher peroxisomal antioxidant activity can regulate the aging of hippocampal neurons [127,128]. Furthermore, the three-way communication among mitochondria, peroxisome, and ER may contribute to the aging process by fine-tuning redox and ion signaling pathways [129]. Redox-regulatory enzymes can assemble at the “redox triangle” created by these three organelles to sense ROS accumulations and redox imbalances. The redox triangle may become dysfunctional with age [129]. However, further investigations on the mechanistic details regarding the multidirectional communication among mitochondria, ER, and peroxisome and their roles in aging are needed.

Mitochondria and Lysosome Communication

Lysosomes are subcellular sites of protein turnover and metabolite storage. Its dysfunction is linked to aging and age-associated diseases [130]. Mito-lysosomal communication is mediated by physical contact, lipids, and metabolite exchange [131]. In yeast, lysosome-like vacuoles are functionally linked to mitochondria. Increased vacuolar pH gives rise to age-dependent mitochondrial dysfunction [132], indicating that mito-lysosomal communication is important for organismal homeostasis and lifespan. In addition, the contact site between mitochondria and yeast lysosome-like vacuoles known as vCALMP (*vacuole and mitochondria patch*) is enriched with ion and amino acid transporters. It is important for lipid exchange between the two organelles [133]. Furthermore, the inter-organellar lipid homeostasis coordinated

among mitochondria, lysosomes, and ER [ER-mitochondria encounter structure (ERMES)) may be important in aging [133,134]. This is also supported by Ltc1 (lipid transfer at contact site 1), a sterol-dependent regulator of organelle and cellular homeostasis via its dual localization to ER-mitochondria and ER-vacuole contact sites [135]. It is especially important in nutrient sensing and signaling [136] as well as replicative aging in yeast [132].

NON-CELL AUTONOMOUS MITOCHONDRIAL COMMUNICATION AND AGING

Mitochondrial communication is not confined to intracellular coordination. Recent studies have shown that mitochondria can also transmit signals to distal cells of different tissues as described in this section(95, 137, 138). {Editor's Note: Please cite reference for the highlighted area – Described in this section – this is intro.} Such non-cell autonomous mitochondrial signals are often referred as mitochondrial cytokines (mitokines) or mitochondrial hormones. The evolutionary aspect of intra-organ mitochondrial communication is interesting in that they may represent an archaic endocrine system. Non-cell autonomous mitochondrial signals provide another layer of endocrine regulation of longevity (Figure 1A).

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Mitokines

The connection between UPR^{mt} and longevity has been investigated in mutant worms with perturbed mitochondrial ETC (e.g., *cco-1* knockdown) that exhibited extended lifespan [137]. Interestingly, *cco-1* knockdown in neurons activated UPR^{mt} in the intestine, indicating a

soluble factor that could relay signals between distal tissues, dubbed mitokine [138]. In addition, Wnt signaling may be a mitokine in worms [139]. Neuronal expression of the Wnt ligand/EGL-20 in worms activated cell-non-autonomous UPR^{mt} that required the orchestrated actions of a retromer complex, Wnt signaling, and serotonin [139]. In flies, mild ETC disruption in muscles prolonged lifespan through UPR^{mt} and insulin signaling [140]. In mice, fibroblast growth factor 21 (Fgf21) has also been proposed as a mitokine because its production by muscle cells can trigger mitochondrial biogenesis, browning of white adipose tissue (WAT), and increase lipid oxidation [141]. These results support the existence of systemic mitochondrial communication factors that can regulate longevity, including neurotransmitters and neuropeptides [142,143]. The scope of factors that can act as mitokines is likely to be broad.

Mitochondrial derived peptides (MDPs)

MDPs are found in circulation. They can act on certain tissues. Thus, they have been dubbed mitochondrial hormones [85,144] [145]. Circulating humanin levels are decreased with age in mice and humans [106,107,146]. Humanin is integrated with the GH/IGF-1 axis which is the most prominent endocrine regulator of aging. Long-lived GH-deficient Ames mice showed higher circulating humanin levels whereas short-lived GH-transgenic mice had lower humanin levels compared to their wild type counterparts [107]. Notably, an Ecuadorian cohort with GH receptor deficiency (GHRD) that have very low levels of IGF-I are exceptionally protected against cancer and diabetes [147]. However, they showed 80% increase in circulating humanin levels compared to their unaffected relatives. These studies indicate a role for humanin as an

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endocrine regulator of aging that is tethered with the GH/IGF-1 axis. Similar to humanin, levels of circulating SHLP2 are also decreased with age, indicating its relevance to aging as a mitochondrial hormone [148]. Plasma levels of MOTS-c are also decreased ~30% in old mice. Systemic injection of MOTS-c reversed age-dependent skeletal muscle insulin resistance in mice [101].

CONCLUSION

Mitochondria are versatile organelles that play roles in multiple cellular functions that ultimately affect organismal fitness and lifespan/healthspan. The multifaceted nature of mitochondria indicates its complex roles in aging and age-related diseases. Thus, it is imperative to investigate how mitochondria contribute, and even drive, aging with a comprehensive and holistic approach. The silver lining of the downfall of MFRTA is that dynamic expansion of concepts and experimental data have continued to reveal the complexity and breadth of mitochondria in aging and age-related diseases.

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CONFLICTS OF INTEREST

C.L. is a consultant for and a shareholder of CohBar, Inc. The remaining authors declare no competing interests.

FIGURE LEGENDS

Figure 1. Mitochondrial Communication Modes. (A) Mitochondria communicate to the nucleus and other cells (*i.e.*, mitochondrial endocrine signaling) using various mediators such as ROS, UPR^{mt}, DAMPs, and mitochondrial-encoded MDPs. (B) Mitochondria also communicate with other organelles (*e.g.*, endoplasmic reticulum, lysosomes, and peroxisomes) to coordinate complex cellular processes.

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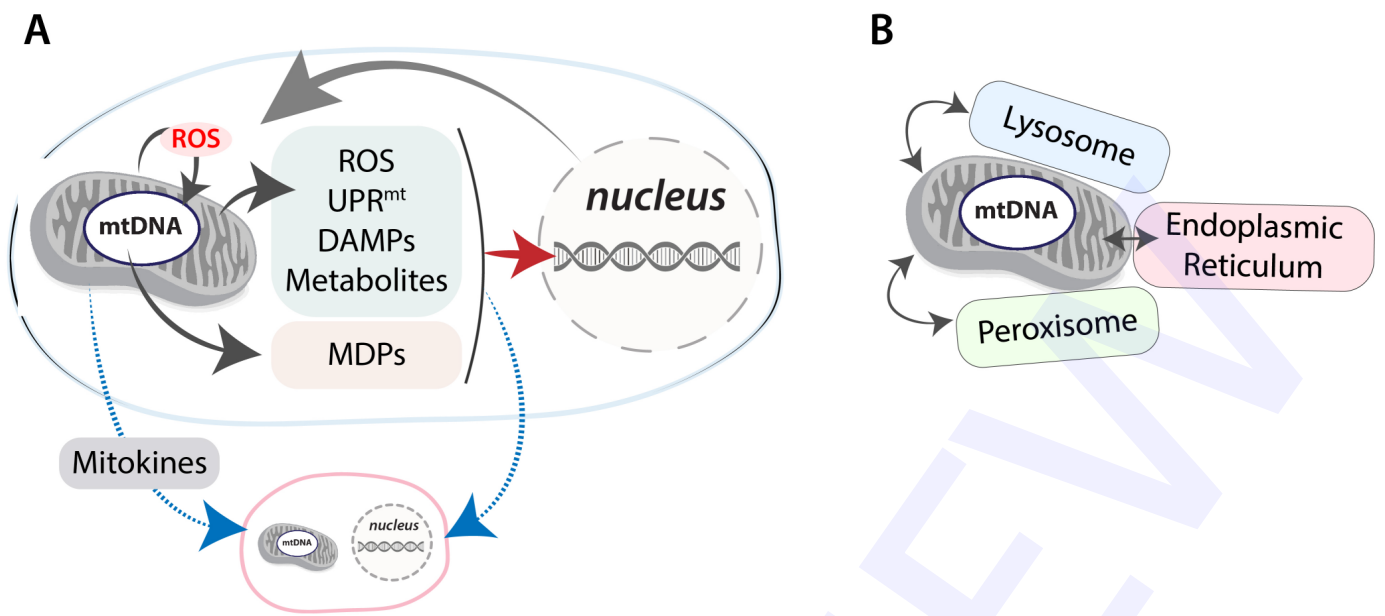


Fig. 1.