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# Mitochondrial dysfunction in cellular senescence

Cellular senescence is a complex biological process characterized by cell cycle arrest and the loss of a cell's ability to divide. Despite the involvement of numerous molecular mechanisms, mitochondria play a central role in this process. Mitochondrial dysfunction, indicated by impaired respiratory capacity and a diminished energy status of the cell, is frequently accompanied by an augmented production of free oxygen radicals, resulting in oxidative stress. This condition not only accelerates cellular aging, but also its progression. A substantial body of research has substantiated the association between mitochondrial dysfunction and cellular senescence, underscoring the significance of mitochondria as a target for anti-aging therapies and interventions. The process of aging is associated with the onset of various age-related diseases, including cancer, cardiovascular diseases, and neurodegenerative diseases. A comprehensive understanding of these mechanisms offers novel opportunities to develop effective strategies that can mitigate the effects of senescence. This article summarizes the mechanisms contributing to the development of mitochondrial dysfunction during aging and discusses the main consequences of this impairment, particularly in the context of its impact on cellular senescence.

*Keywords:* cellular senescence, mitochondria, oxidative stress, mitophagy, microRNAs, age-associated diseases, cancer, Alzheimer's disease, cardiovascular diseases.



## *Introduction*

Cellular senescence is an inevitable state of cells caused by various stress effects and physiological processes, which is characterized by irreversible cell cycle arrest. The process of senescence is influenced by numerous factors, including the accumulation of DNA damage, the shortening of telomeres, and the deterioration of mitochondria [1]. Senescence cells are known to accumulate in the body, which has been associated with an increased risk of developing multiple chronic diseases, decreased physical stability, and mortality [2]. The precise etiology of aging remains to be elucidated, rendering it a fundamental subject in contemporary scientific inquiry.

Mitochondria are membrane-bound organelles that play a central role in the energy metabolism of cells. They are responsible for a significant part of the production of adenosine triphosphate (ATP) molecules required for various cellular processes. In recent years, mounting evidence has indicated a causal relationship between mitochondrial dysfunction and the major mechanisms of senescence. The process of senescence itself has been demonstrated to be a significant factor in the development of various age-related diseases, including cancer, neurodegenerative diseases, and cardiovascular disease [3]. The exploration of these mechanisms may yield novel strategies for decelerating the aging process and addressing age-related diseases. This review aims to explore the intricate relationship between mitochondria and the senescence process, emphasizing the pivotal role of mitochondria in the development of age-related diseases.

### Mitochondria and their role in senescence processes

The efficient operation of mitochondria is vital for the normal functioning of the organism. Mitochondria can be regarded as highly dynamic structures, capable of rapid and substantial adjustment to conditions that reflect the needs of cells. However, it is important to note that various environmental factors, including radiation exposure, as well as endogenous agents, have the capacity to exert influence on mitochondrial function [4, 5]. For example, the synthesis of antioxidants is augmented under conditions of elevated oxidative stress, as well as during periods of enhanced physical exertion, resulting in an escalation of the main mitochondrial enzymes present within skeletal muscle tissues [6]. However, exposure to these factors can lead to mutations in mitochondrial DNA, which in turn contributes to impaired mitochondrial function. Disruption of mitochondrial integrity, both structurally and functionally, is a primary factor contributing to accelerated cellular senescence [4, 7–9].

A plethora of theories has been postulated regarding the etiology of aging. Presently, the free-radical theory of aging, initially proposed by Denham Harman in the mid-1950s [10], occupies a central position among these theories. This theory posits that the accumulation of mitochondrial damage leads to the formation of free radicals, which, when present in excess, can damage cellular components such as proteins, lipids, and nucleic acids.

Mitochondrial DNA (mtDNA) has been shown to be more prone to damage in comparison to nuclear DNA. Its mutagenesis rate has been observed to be 10–20 times higher [11]. This heightened susceptibility can be attributed to the absence of histones and introns within the mtDNA genome, the inefficacy of repair mechanisms, and the proximity to sites of reactive oxygen species formation [12, 13]. It has been established that the frequency of mitochondrial DNA mutations increases with age, and excessive amounts of these mutations can disrupt the normal operation of mitochondria, leading to their dysfunction [14, 15].

Mitochondria are responsible for synthesizing approximately 90 % of the cell's energy, thus acting as the cell's multifunctional energy source. They synthesize ATP in a process known as oxidative phosphorylation via five electron-transport chain complexes. Mutations in mtDNA, which affect genes involved in oxidative phosphorylation, have been shown to have deleterious consequences for cellular energy metabolism, including increased free radical production and decreased antioxidant defenses in the body [16, 17]. Oxidative stress, characterized by an imbalance between the generation and elimination of free radicals, leading to their excessive formation, is considered a contributing factor to cellular senescence. Indeed, research has demonstrated that senescent cells exhibit reduced ATP production efficiency and a diminished energy status [18–20].

Mitochondria, being semi-autonomous organelles, possess a variety of mechanisms that enable them to maintain their integrity under stress. Mitophagy, a term derived from the Greek for "cell death", is a critical process involved in maintaining a healthy mitochondrial population through the constant destruction of dysfunctional mitochondria [21].

The degradation process is mediated by the autophagosome and was first demonstrated in mammalian cells by electron microscopy [22]. The most studied mitophagy pathway is the Parkin/PINK1-mediated pathway [23]. For example, overexpression of PTEN-induced kinase 1 (PINK-1) in dopaminergic neurons extends lifespan in drosophilia, whereas loss of Parkin shortens lifespan [24]. By scavenging dysfunctional mitochondria, mitophagy prevents excessive release of damage-associated molecular patterns (DAMPs), which are based on free-circulating mtDNA [25]. If the damaged mitochondrion cannot be neutralized, mitochondrial membrane rupture and cytosolic release of DAMPs occur, leading to strong inflammatory responses.

Proper control of mitochondrial function can limit inflammation and preserve cell function during senescence, which is supported by numerous experiments [26–28]. In one study, mitophagy also positively affected skeletal muscle cells in mice and humans, preventing senescence [28]. In contrast, disruption of mitophagy contributed to accelerated senescence and the development of several human diseases, including age-related diseases such as Parkinson's disease, Alzheimer's disease [29], cardiovascular disease, and cancer [30, 31].

Mitochondria were originally thought to be isolated organelles, but there is now increasing evidence that they are constantly undergoing fusion and fission. Together, these processes form the basis of mitochondrial dynamics and may also be involved in the control and elimination of dysfunctional mitochondria [32]. The major proteins that enable these processes are mitofusin 1 and mitofusin 2 (Mfn1 and Mfn2) [33]. Mitochondrial fusion can facilitate the exchange of mitochondrial components, including the exchange of mtDNA, which allows the replacement of missing or damaged components in the mitochondrial network [34]. In another case, the mitochondrial proteins Mfn1 and Mfn2 can be degraded, depending on the Parkin-dependent mitophagy pathway, to prevent the fusion of damaged mitochondria with the healthy mitochondrial network [35].

Fission is also a key process in maintaining a healthy mitochondrial population, separating damaged mitochondria from the overall network. Mitochondrial dysfunction disrupts these processes, which can result in a fragmented network dominated by small round or elongated mitochondria [36]. In senescent cells, mitochondria tend to be in a hyper-split state, and deficits in their integrity may contribute to the initiation of various diseases [37, 38], as well as accelerated cellular senescence [39, 40].

In addition to reduced energy status, mitochondrial dysfunction is associated with the development of chronic inflammation [41]. Inflammation is a hallmark of senescence and a risk factor for the development of several diseases, negatively affects the immune system, and accelerates cellular senescence [42, 43]. DAMPs

are the major triggers of inflammation. They are recognized by specialized receptors of the innate immune system, such as toll-like receptors (TLRs) [44, 45]. Activation of this receptor initiates signal transduction pathways that normally trigger inflammation, resulting in the production of pro-inflammatory cytokines, particularly tumor necrosis factor TNF-α and interleukins (IL-6, 8, 12) [46].

Several studies have confirmed a correlation between levels of free circulating mtDNA in cells and proinflammatory cytokines, suggesting a link between mitochondrial dysfunction and inflammatory status [47, 48]. It is now well established that chronic inflammation underlies several age-related diseases such as atherosclerosis, Alzheimer's disease, Parkinson's disease, and type 2 diabetes [49–51].

After reviewing the major functions of mitochondria, we can conclude that they are important regulators of both energy and inflammatory processes, making them key players in the mechanisms of senescence and the pathogenesis of various diseases. As we have seen, genetics plays an important role in controlling and modulating mitochondrial functions. However, in addition to genetics, there is another important aspect that deserves attention — mitochondrial microRNAs.

**Mitochondrial microRNAs and their involvement in cellular senescence processes**

MicroRNAs (miRNAs) are a group of small non-coding RNAs that play an important role in the regulation of gene expression. The fact that microRNAs are located in mitochondria was discovered only recently, with the first discovery made by Barray and colleagues in 2011 [52]. These molecules have been collectively named "MitomiR", and each mitochondrion has its own unique set of microRNAs specific to a particular cell type [53]. The origin of these elements may be either the nuclear or mitochondrial genome, and their function is of paramount importance in ensuring proper mitochondrial functionality. They fulfill this role by regulating mitochondrial genes themselves or by modulating the expression of nuclear genes that play a role in mitochondrial processes [54, 55]. In addition, mitochondrial microRNAs can influence mitochondrial dysfunction, making them one of the major catalysts for accelerated cellular senescence [56–58].

Recent studies show that MitomiR serves as crucial sensors of cellular senescence, exerting control over mitochondrial homeostasis and influencing metabolic state, redox balance, apoptosis, mitophagy, all processes closely related to senescence. Some mitochondrial microRNAs, associated with cellular senescence are summarized in the Table.

Table

**The role of mitochondrial microRNAs in senescence**

| Name | Level | Role in senescence | Reference |
|---|---|---|---|
| miR-15b: | ↓ | Promotes formation of mitochondrial ROS, decreases mitochondrial membrane potential. Causes ATP deficiency, impairing cellular metabolism. Causes the development of a senescence-associated secretory phenotype (SASP), accelerating cellular senescence. | [59] |
| miR-181c: | ↓ | Disrupts respiratory complex IV, causing mitochondrial dysfunction. Enhances cellular damage through excessive production of ROS. | [60] |
| miR-4485: | ↑ | Negatively modulates respiratory complex I activity, ATP production, increases ROS levels. Inhibits caspase-3/7 activation and apoptosis, slows down mitophagy. | [61] |
| miR-181a, miR- 34a: | ↑ | Activate Bcl-2, affecting sensitivity to apoptosis, leading to impaired mitophagy, accumulation of old cells. Contribute to mitochondrial dysfunction. | [56] |
| miR-146a-5p: | ↑ | Promotes activation of NF-κB pathway, initiates transcription of pro-inflammatory cytokines. Accelerates senescence through SASPs. | [62] |
| miR-1, miR-133a, let-7b: | ↓ | Negatively modulates the function of key proteins involved in oxidative phosphorylation, reduce ETC functionality. Decrease the energy status of the cell. | [62] |
| miR-378-3p: | ↑ | Decrease the functionality of ATP synthase. Decrease oxidative capacity. | [62] |

Continuation of Table

| Name | Level | Role in senescence | Reference |
|---|---|---|---|
| miR-20b, miR-214, miR-200a-3p: | ↑ | Negatively affect the expression of MFN1 and MFN2 genes, Disrupt the mitochondrial fusion-release balance, leading to impaired fusion and increased fragmentation. | [63–65] |
| miR-17: | ↓ | Promotes ROS formation. | [66] |
| miR-574-5p: | ↑ | Regulates protein expression of mitochondrial electron transport chain (ETC) genes, supporting normal mitochondrial function. | [67] |
| miR-762: | ↑ | May contribute to inhibition of ATP production and induction of ROS formation and apoptotic cell death. | [68] |
| miR-106a: | ↑ | Negatively regulates the expression of some critical cell cycle and apoptosis factors. Inhibits mitophagy. | [66, 69] |

Thus, it is easy to speculate that miRNAs can regulate mitochondrial function, and this phenomenon has important implications for the aging process, as mitochondrial dysfunction has devastating consequences for cell fate.

**Mitochondrial Dysfunction and Age-Related Diseases**

*Neurodegenerative diseases*

To date, the pathogenesis of neurodegenerative diseases remains in the center of scientific attention as it represents one of the most important problems facing modern society [70]. The factors underlying cognitive impairment in both natural aging and neurodegenerative diseases are not fully understood. There is considerable evidence that mutations in mitochondrial DNA and oxidative stress contribute to accelerated cellular senescence, which is a major risk factor for neurodegenerative diseases.

Alzheimer's disease (AD) is the most common neurodegenerative disease characterized by impairment of memory, language, and other thinking skills, with dementia at its core [70, 71]. A number of mitochondrial abnormalities have been identified in AD: changes in mitochondrial structure, mutations in mtDNA, changes in mitochondrial membrane potential, formation of ROS, decreased ATP, and impaired mitochondrial fusion. There is a wealth of evidence linking mtDNA mutations to the pathogenesis of AD [72–78].

The brain is particularly susceptible to oxidative damage due to its high oxygen consumption. One of the most common defects in the mitochondrial ETC in AD is cytochrome-c-oxidase deficiency, which leads to increased production of ROS and impaired energy metabolism [79]. Several studies have shown impairments of all five ETC complexes in different brain regions in AD [80]. Numerous studies have documented that mitochondrial dysfunction due to abnormal ROS processing is an important factor in the pathogenesis of Alzheimer's disease [81]. It is known that brain cells must constantly produce ATP to maintain neuronal function. For example, oxidative damage to the promoter of the gene encoding a subunit of mitochondrial ATP synthase can lead to a decrease in its level, resulting in decreased ATP production, increased oxidative stress, and cell death [82, 83].

Oxidative stress may also contribute to the pathogenesis of AD by disrupting calcium homeostasis [84, 85]. Glutamate is a neurotransmitter in the mammalian central nervous system that often mediates the synaptic transmission of nerve impulses. However, high levels of glutamate can be toxic, promoting neuronal death [86], and dendritic degeneration [87, 88]. Increased extracellular glutamate leads to its binding to NMDA calcium receptors. NMDA activation causes a massive influx of sodium and calcium into neurons and an outflow of potassium. Elevated Ca2+ levels cause irreversible damage to neurons, which promotes neuronal death [89].

Mitochondrial dysfunction and glutamate toxicity are linked. It has been shown that neurons have the ability to "burn" glutamate in the mitochondria, thereby preventing its toxicity [90]. In one of the studies, it was observed that when pyruvate is inhibited in neurons, glutamate consumption by the neurons increases, which leads to a decrease in extracellular glutamate levels, resulting in a decrease in cell death [91]. It is logical to assume that mitochondrial dysfunction will inhibit this process, resulting in an opposite increase in extracellular glutamate levels. Thus, neuroinflammation caused by mitochondrial dysfunction leads to neuronal loss and impaired neuronal plasticity, ultimately leading to Alzheimer's disease Mitophagy is a critical pathway for mitochondrial quality control. The accumulation of beta-amyloid (Aβ) and phosphorylated tau-protein (pTau) in the brain is a pathological hallmark of Alzheimer's disease. Aβ and pTau impair mitochondrial integrity and exacerbate mitochondrial dysfunction. Oxidative damage caused by Aβ and pTau leads to

decreased levels of PINK1 and Parkin protein, which inhibits mitochondrial autophagy and thereby increases Aβ and pTau [92]. Disruption of fission or fusion processes, namely mutations in the MFN1, MFN2, and OPA1 genes, are also found in several neurodegenerative diseases, including AD [93–96]. In addition, abnormal mitochondrial fission and decreased expression of proteins related to their biogenesis (PGC-1α, TFAM, and NRF2) have been observed in AD patients, indicating impaired mitochondrial dynamics and biogenesis [97].

Parkinson's disease (PD) is a common neurodegenerative disorder associated with motor dysfunction. A loss-of-function mutation in PARK2 is the most common cause of early-onset PD [98–100]. Loss of function of the PINK1 gene, which encodes a mitochondrial serine/threonine kinase, is the second most common cause of PD [101,102].

*Cancer*

As early as 1924, Heinrich Warburg discovered that tumor cells are characterized by high glucose consumption and use "aerobic glycolysis" to produce ATP even when oxygen is available. Based on these observations, it has been suggested that altered respiratory capacity caused by mitochondrial abnormalities may be one of the causes of cancer development. Indeed, increased glucose uptake and decreased OXPHOS activity have been observed in many tumor types, and it is believed that high glycolytic capacity is an important hallmark of cancer. For example, glycolysis is common in rapidly growing tumors and oxidative phosphorylation is slowed in these tumors [103].

Oxidative stress due to mitochondrial dysfunction, which is characterized by the production of reactive oxygen species in cells, plays a critical role in cancer development by affecting genome stability and signaling pathways in the cellular microenvironment. Large amounts of ROS, which are by-products of mitochondrial dysfunction, are known to irreversibly damage cellular components, including nucleic acids. Such damage can cause genetic or epigenetic alterations by upregulating oncogenes and tumor suppressor genes. For example, impaired expression of the gene encoding NADH dehydrogenase can stimulate aerobic glycolysis, ROS production, and tumor growth [104].

In addition, ROS can activate various signaling pathways that may contribute to oncogenesis. Examples include the epidermal growth factor receptor EGFR signaling pathway or the Akt/NF-κB-dependent signaling pathway, which correlate with cancer development [105, 106].

IDH is a family of enzymes involved in oxidative phosphorylation. It includes three isoforms located in the cytoplasm, peroxisomes (IDH1) and mitochondria (IDH2 and IDH3). Some studies show that many tumors, including gliomas and leukemias, have mutations in the genes encoding IDH1 or IDH2 [107, 108].

*Cardiovascular Diseases*

One of the leading causes of death worldwide is cardiovascular disease (CVD). CVDs are a group of multifactorial diseases that affect the heart or blood vessels. Heart cells have a high energy demand, requiring a constant supply of ATP to maintain cardiac activity. In cardiomyocytes, mitochondria make up about one-third of the cell volume. Not surprisingly, proper mitochondrial function and dynamics are critical for these cells, and their dysfunction is a key factor in cardiovascular disease.

Oxidative stress is central to the development of CVD. Reduced mitochondrial function leads to the production of reactive oxygen species, depletion of cellular ATP, cellular damage and cardiomyocyte apoptosis. Unregulated production of ROS is responsible for a variety of cardiovascular diseases, including cardiac hypertrophy, heart failure, and cardiac ischemia-reperfusion injury [109].

Alterations in mtDNA genes, including NADH dehydrogenase, cytochrome b, and ATP synthase genes, are observed in cardiomyopathies and heart failure [110]. In heart failure, mitochondria are damaged by membrane rupture and depletion of their matrix, resulting in decreased ATP synthesis [111]. It has been shown that patients with heart failure have decreased activity of respiratory complexes I and IV [112]. A study has also shown that the process of mtDNA replication is impaired in cardiomyocytes from people with heart failure, resulting in depletion of mitochondrial DNA, reduction of mitochondrial proteins, and impaired mitochondrial biogenesis [113].

A study has also shown that the process of mtDNA replication is impaired in cardiomyocytes from people with heart failure, resulting in depletion of mitochondrial DNA, reduction of mitochondrial proteins, and impaired mitochondrial biogenesis [114]. Cardiac ischemia due to oxygen deprivation leads to mitochondrial fragmentation due to dysregulation of the Mfn2 protein [115]. The role of mitophagy in the development of CVDs cannot be overlooked. Atherosclerosis is an inflammatory disease of the arteries associated with im-

paired lipid metabolism. The pathogenesis of this disease is associated with the accumulation of macrophages, lipids, cholesterol, migration and proliferation of vascular smooth muscle cells. Mitophagy plays a key role in the removal of these accumulated substances, and disruption of this process will have devastating consequences, increasing vascular plaque formation due to the increase in ROS from damaged mitochondria [116].

**Prospects for using mitochondria to fight senescence**

Given the close association of mitochondria with senescence, several approaches have been developed and used as strategies to treat mitochondrial dysfunction and age-related diseases. Mitochondrial transplantation is one of the new therapeutic methods used to treat age-related diseases, especially cardiovascular diseases. The essence of the method is the transfer of "healthy" donor mitochondria into cells to replace dysfunctional or damaged mitochondria.

The concept of transferring mitochondria between cells is similar to installing new batteries in malfunctioning devices. By providing healthy mitochondria to cells with impaired energy metabolism, their ability to produce ATP and maintain cell survival can be restored.

One study showed that mesenchymal stem cells could gradually transfer their mitochondria to lung epithelial cells through structures called tunneled nanotubes (TNTs). This transfer helped reduce ATP loss in BEAS-2B cells exposed to cigarette smoke [117]. In another study, umbilical cord mesenchymal stem cells successfully transferred their mitochondria into mtDNA-deficient cells. This restored the expression of genes encoding mitochondrial proteins and improved the function of the ETC [118].

The energy produced by transplanted mitochondria can improve the function of recipient cells. For example, transplantation of isolated mitochondria into ischemic hearts helps to reduce infarct size and improve senolytic function [119]. Mitochondrial transfer opens new doors by providing additional options for the treatment of age-related diseases.

In recent years, hay therapy targeting mitochondria and antioxidants has gained particular popularity. Senotherapy is divided into two groups: senolytics, which kill senescent cells, and senomorphics, which inhibit inflammation. Senolytics have been shown to be highly effective in treating a wide range of age-related diseases, and clinical trials are currently underway for many of these modalities.

Examples of senolytic drugs include BH3 mimetics such as ABT-263 (navitoclax). These drugs are used in certain types of senescent cells based on increased expression of anti-apoptotic proteins of the BCL-2 family [120]. By inhibiting anti-apoptotic proteins, these drugs stabilize mitophagy and thereby remove old cells. In a study, procyanidin, a component of grape seed extract, was shown to have senotherapeutic activity and to extend the lifespan of mice by inhibiting SASP expression [121].

Thus, the use of mitochondria in the fight against aging represents a promising direction that opens new opportunities for improving health and quality of life. The development of various therapeutic approaches aimed at restoring mitochondrial function and overcoming age-related changes may have a significant impact on the treatment of age-related diseases. These strategies highlight the importance of mitochondria as key players in the aging process and their potential role in the future medical approach to longevity.

## *Conclusion*

This article has reviewed the multifunctional role of mitochondria in senescence processes and their impact on cellular physiology. As the major source of cellular energy, mitochondria act as key regulators of oxidative stress in cells. Various environmental factors affect mitochondrial function on a daily basis, leading to an increased frequency of mitochondrial DNA mutations. All of this leads to mitochondrial dysfunction, which in turn causes a decrease in ATP synthesis, production of reactive oxygen species, and promotes chronic inflammation. The vicious cycle between oxidative stress and mitochondrial dysfunction leads to the development of cellular senescence. Furthermore, microRNAs have been demonstrated to play a pivotal role in the regulation of mitochondrial function, which is a critical aspect in comprehending the mechanisms of cellular senescence. A variety of age-related pathologies are marked by distinct mitochondrial mutations, which may contribute to the development and progression of these diseases. Consequently, mitochondria emerge as pivotal subjects for research in the biology of aging and the development of novel therapeutic strategies. A comprehensive understanding of these mechanisms could lead to the development of interventions that enhance health in older individuals and decelerate the senescence process at the cellular level.

*Author Contributions*

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## References


1 Annesley, S. J., & Fisher, P. R. (2019). Mitochondria in Health and Disease. *Cells*, *8*(7), 680. doi: 10.3390/cells8070680

2 Arbustini, E., Diegoli, M., Fasani, R., Grasso, M., Morbini, P., Banchieri, N., Bellini, O., Dal Bello, B., Pilotto, A., Magrini, G., Campana, C., Fortina, P., Gavazzi, A., Narula, J., & Viganò, M. (1998). Mitochondrial DNA Mutations and Mitochondrial Abnormalities in Dilated Cardiomyopathy. *The American Journal of Pathology*, *153*(5), 1501–1510. doi: 10.1016/S0002-9440(10)65738-0

3 Balaban, R. S., Nemoto, S., & Finkel, T. (2005). Mitochondria, Oxidants, and Aging. *Cell*, *120*(4), 483–495. doi: 10.1016/j.cell.2005.02.001

4 Barrey, E., Saint-Auret, G., Bonnamy, B., Damas, D., Boyer, O., & Gidrol, X. (2011). Pre-microRNA and Mature microRNA in Human Mitochondria. *PLoS ONE*, *6*(5), e20220. doi: 10.1371/journal.pone.0020220

5 Bernardini, J. P., Lazarou, M., & Dewson, G. (2017). Parkin and mitophagy in cancer. *Oncogene*, *36*(10), 1315–1327. doi: 10.1038/onc.2016.302

6 Bertholet, A. M., Delerue, T., Millet, A. M., Moulis, M. F., David, C., Daloyau, M., Arnauné-Pelloquin, L., Davezac, N., Mils, V., Miquel, M. C., Rojo, M., & Belenguer, P. (2016). Mitochondrial fusion/fission dynamics in neurodegeneration and neuronal plasticity. *Neurobiology of Disease*, *90*, 3–19. doi: 10.1016/j.nbd.2015.10.011

7 Bishop, D. J., Botella, J., Genders, A. J., Lee, M. J. -C., Saner, N. J., Kuang, J., Yan, X., & Granata, C. (2019). High-Intensity Exercise and Mitochondrial Biogenesis: Current Controversies and Future Research Directions. *Physiology*, *34*(1), 56–70. doi: 10.1152/physiol.00038.2018

8 Boutant, M., Kulkarni, S. S., Joffraud, M., Ratajczak, J., Valera-Alberni, M., Combe, R., Zorzano, A., & Cantó, C. (2017). Mfn2 is critical for brown adipose tissue thermogenic function. *The EMBO Journal*, *36*(11), 1543–1558. doi: 10.15252/embj.201694914

9 Bravo-San Pedro, J. M., Kroemer, G., & Galluzzi, L. (2017). Autophagy and Mitophagy in Cardiovascular Disease. *Circulation Research*, *120*(11), 1812–1824. doi: 10.1161/CIRCRESAHA.117.311082

10 Bucha, S., Mukhopadhyay, D., & Bhattacharyya, N. P. (2015). Regulation of mitochondrial morphology and cell cycle by microRNA-214 targeting Mitofusin2. *Biochemical and Biophysical Research Communications*, *465*(4), 797–802. doi: 10.1016/j.bbrc.2015.08.090

11 Calió, M. L., Henriques, E., Siena, A., Bertoncini, C. R. A., Gil-Mohapel, J., & Rosenstock, T. R. (2020). Mitochondrial Dysfunction, Neurogenesis, and Epigenetics: Putative Implications for Amyotrophic Lateral Sclerosis Neurodegeneration and Treatment. *Frontiers in Neuroscience*, *14*. doi: 10.3389/fnins.2020.00679

12 Canugovi, C., Stevenson, M. D., Vendrov, A. E., Lozhkin, A., Britton, S. L., Koch, L. G., Runge, M. S., & Madamanchi, N. R. (2022). Mitochondrial DAMPs-dependent inflammasome activation during aging induces vascular smooth muscle cell dysfunction and aortic stiffness in low aerobic capacity rats. *The Journal of Cardiovascular Aging*, *2*(4), 47. doi: 10.20517/jca.2022.35

13 Chan, D. C. (2012). Fusion and Fission: Interlinked Processes Critical for Mitochondrial Health. *Annual Review of Genetics*, *46*(1), 265–287. doi: 10.1146/annurev-genet-110410-132529

14 Chistiakov, D. A., Shkurat, T. P., Melnichenko, A. A., Grechko, A. V., & Orekhov, A. N. (2018). The role of mitochondrial dysfunction in cardiovascular disease: a brief review. *Annals of Medicine*, *50*(2), 121–127. doi: 10.1080/07853890.2017.1417631

15 Choi, D. W. (2020). Excitotoxicity: Still Hammering the Ischemic Brain in 2020. *Frontiers in Neuroscience*, *14*. doi: 10.3389/fnins.2020.579953

16 Chung, H. Y., Cesari, M., Anton, S., Marzetti, E., Giovannini, S., Seo, A. Y., Carter, C., Yu, B. P., & Leeuwenburgh, C. (2009). Molecular inflammation: Underpinnings of aging and age-related diseases. *Ageing Research Reviews*, *8*(1), 18–30. doi: 10.1016/j.arr.2008.07.002

17 Clark, I. E., Dodson, M. W., Jiang, C., Cao, J. H., Huh, J. R., Seol, J. H., Yoo, S. J., Hay, B. A., & Guo, M. (2006). Drosophila pink1 is required for mitochondrial function and interacts genetically with parkin. *Nature*, *441*(7097), 1162–1166. doi: 10.1038/nature04779

18 Cortopassi, G. A., & Arnheim, N. (1990). Detection of a specific mitochondrial DNA deletion in tissues of older humans. *Nucleic Acids Research*, *18*(23), 6927–6933. doi: 10.1093/nar/18.23.6927

19 Daneshpour, M., & Ghadimi-Daresajini, A. (2023). Overview of miR-106a Regulatory Roles: from Cancer to Aging. *Bioengineering*, *10*(8), 892. doi: 10.3390/bioengineering10080892

20 Das, S., Kohr, M., Dunkerly-Eyring, B., Lee, D. I., Bedja, D., Kent, O. A., Leung, A. K. L., Henao-Mejia, J., Flavell, R. A., & Steenbergen, C. (2017). Divergent Effects of miR-181 Family Members on Myocardial Function Through Protective Cytosolic and Detrimental Mitochondrial microRNA Targets. *Journal of the American Heart Association*, *6*(3). doi: 10.1161/JAHA.116.004694

21 de Duve, C., & Wattiaux, R. (1966). Functions of Lysosomes. *Annual Review of Physiology*, *28*(1), 435–492. doi: 10.1146/annurev.ph.28.030166.002251

22 DeBalsi, K. L., Hoff, K. E., & Copeland, W. C. (2017). Role of the mitochondrial DNA replication machinery in mitochondrial DNA mutagenesis, aging and age-related diseases. *Ageing Research Reviews*, *33*, 89–104. doi: 10.1016/j.arr.2016.04.006

23 Delfarah, A., Parrish, S., Junge, J. A., Yang, J., Seo, F., Li, S., Mac, J., Wang, P., Fraser, S. E., & Graham, N. A. (2019). Inhibition of nucleotide synthesis promotes replicative senescence of human mammary epithelial cells. *Journal of Biological Chemistry*, *294*(27), 10564–10578. doi: 10.1074/jbc.RA118.005806

24 Divakaruni, A. S., Wallace, M., Buren, C., Martyniuk, K., Andreyev, A. Y., Li, E., Fields, J. A., Cordes, T., Reynolds, I. J., Bloodgood, B. L., Raymond, L. A., Metallo, C. M., & Murphy, A. N. (2017). Inhibition of the mitochondrial pyruvate carrier protects from excitotoxic neuronal death. *Journal of Cell Biology*, *216*(4), 1091–1105. doi: 10.1083/jcb.201612067

25 Dodig, S., Čepelak, I., & Pavić, I. (2019). Hallmarks of senescence and aging. *Biochemia Medica*, *29*(3), 483–497. doi: 10.11613/BM.2019.030501

26 Drummond, M. J., Addison, O., Brunker, L., Hopkins, P. N., McClain, D. A., LaStayo, P. C., & Marcus, R. L. (2014). Downregulation of E3 Ubiquitin Ligases and Mitophagy-Related Genes in Skeletal Muscle of Physically Inactive, Frail Older Women: A Cross-Sectional Comparison. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *69*(8), 1040–1048. doi: 10.1093/gerona/glu004

27 Du, H., Guo, L., & Yan, S. S. (2012). Synaptic Mitochondrial Pathology in Alzheimer's Disease. *Antioxidants & Redox Signaling*, *16*(12), 1467–1475. doi: 10.1089/ars.2011.4277

28 Erkkinen, M. G., Kim, M. -O., & Geschwind, M. D. (2018). Clinical Neurology and Epidemiology of the Major Neurodegenerative Diseases. *Cold Spring Harbor Perspectives in Biology*, *10*(4), a033118. doi: 10.1101/cshperspect.a033118

29 Fan, S., Tian, T., Chen, W., Lv, X., Lei, X., Zhang, H., Sun, S., Cai, L., Pan, G., He, L., Ou, Z., Lin, X., Wang, X., Perez, M. F., Tu, Z., Ferrone, S., Tannous, B. A., & Li, J. (2019). Mitochondrial miRNA Determines Chemoresistance by Reprogramming Metabolism and Regulating Mitochondrial Transcription. *Cancer Research*, *79*(6), 1069–1084. doi: 10.1158/0008-5472.CAN-18-2505

30 Fivenson, E. M., Lautrup, S., Sun, N., Scheibye-Knudsen, M., Stevnsner, T., Nilsen, H., Bohr, V. A., & Fang, E. F. (2017). Mitophagy in neurodegeneration and aging. *Neurochemistry International*, *109*, 202–209. doi: 10.1016/j.neuint.2017.02.007

31 Fulop, T., Witkowski, J. M., Olivieri, F., & Larbi, A. (2018). The integration of inflammaging in age-related diseases. *Seminars in Immunology*, *40*, 17–35. doi: 10.1016/j.smim.2018.09.003

32 García-Prat, L., Martínez-Vicente, M., Perdiguero, E., Ortet, L., Rodríguez-Ubreva, J., Rebollo, E., Ruiz-Bonilla, V., Gutarra, S., Ballestar, E., Serrano, A. L., Sandri, M., & Muñoz-Cánoves, P. (2016). Autophagy maintains stemness by preventing senescence. *Nature*, *529*(7584), 37–42. doi: 10.1038/nature16187

33 Gauba, E., Chen, H., Guo, L., & Du, H. (2019). Cyclophilin D deficiency attenuates mitochondrial F1Fo ATP synthase dysfunction via OSCP in Alzheimer's disease. *Neurobiology of Disease*, *121*, 138–147. doi: 10.1016/j.nbd.2018.09.020

34 Gegg, M. E., Cooper, J. M., Chau, K. -Y., Rojo, M., Schapira, A. H. V., & Taanman, J. -W. (2010). Mitofusin 1 and mitofusin 2 are ubiquitinated in a PINK1/parkin-dependent manner upon induction of mitophagy. *Human Molecular Genetics*, *19*(24), 4861–4870. doi: 10.1093/hmg/ddq419

35 Geiger, J., & Dalgaard, L. T. (2017). Interplay of mitochondrial metabolism and microRNAs. *Cellular and Molecular Life Sciences*, *74*(4), 631–646. doi: 10.1007/s00018-016-2342-7

36 Geng, X., Geng, Z., Li, H., Zhang, Y., Li, J., & Chang, H. (2020). Over-expression of TFB2M facilitates cell growth and metastasis via activating ROS-Akt-NF-κB signalling in hepatocellular carcinoma. *Liver International*, *40*(7), 1756–1769. doi: 10.1111/liv.14440

37 Gerasymchuk, M., Cherkasova, V., Kovalchuk, O., & Kovalchuk, I. (2020). The Role of microRNAs in Organismal and Skin Aging. *International Journal of Molecular Sciences*, *21*(15), 5281. doi: 10.3390/ijms21155281

38 Giuliani, A., Cirilli, I., Prattichizzo, F., Mensà, E., Fulgenzi, G., Sabbatinelli, J., Graciotti, L., Olivieri, F., Procopio, A. D., Tiano, L., & Rippo, M. R. (2018). The mitomiR/Bcl-2 axis affects mitochondrial function and autophagic vacuole formation in senescent endothelial cells. *Aging*, *10*(10), 2855–2873. doi: 10.18632/aging.101591

39 Giuliani, A., Prattichizzo, F., Micolucci, L., Ceriello, A., Procopio, A. D., & Rippo, M. R. (2017). Mitochondrial (Dys) Function in Inflammaging: Do MitomiRs Influence the Energetic, Oxidative, and Inflammatory Status of Senescent Cells? *Mediators of Inflammation*, *2017*, 1–11. doi: 10.1155/2017/2309034

40 Giuliani, A., Prattichizzo, F., Micolucci, L., Ceriello, A., Procopio, A. D., & Rippo, M. R. (2019). Corrigendum to "Mitochondrial (Dys) Function in Inflammaging: Do MitomiRs Influence the Energetic, Oxidative, and Inflammatory Status of Senescent Cells?" *Mediators of Inflammation*, *2019*, 1–1. doi: 10.1155/2019/8716351

41 Gorgoulis, V., Adams, P. D., Alimonti, A., Bennett, D. C., Bischof, O., Bishop, C., Campisi, J., Collado, M., Evangelou, K., Ferbeyre, G., Gil, J., Hara, E., Krizhanovsky, V., Jurk, D., Maier, A. B., Narita, M., Niedernhofer, L., Passos, J. F., Robbins, P. D., … Demaria, M. (2019). Cellular Senescence: Defining a Path Forward. *Cell*, *179*(4), 813–827. doi: 10.1016/j.cell.2019.10.005

42 Greene, J. C., Whitworth, A. J., Kuo, I., Andrews, L. A., Feany, M. B., & Pallanck, L. J. (2003). Mitochondrial pathology and apoptotic muscle degeneration in *Drosophila parkin* mutants. *Proceedings of the National Academy of Sciences*, *100*(7), 4078–4083. doi: 10.1073/pnas.0737556100

43 Guerriero, R. M., Giza, C. C., & Rotenberg, A. (2015). Glutamate and GABA Imbalance Following Traumatic Brain Injury. *Current Neurology and Neuroscience Reports*, *15*(5), 27. doi: 10.1007/s11910-015-0545-1

44 Guo, Y., Guan, T., Shafiq, K., Yu, Q., Jiao, X., Na, D., Li, M., Zhang, G., & Kong, J. (2023). Mitochondrial dysfunction in aging. *Ageing Research Reviews*, *88*, 101955. doi: 10.1016/j.arr.2023.101955

45 Hackl, M., Brunner, S., Fortschegger, K., Schreiner, C., Micutkova, L., Mück, C., Laschober, G. T., Lepperdinger, G., Sampson, N., Berger, P., Herndler-Brandstetter, D., Wieser, M., Kühnel, H., Strasser, A., Rinnerthaler, M., Breitenbach, M., Mildner, M., Eckhart, L., Tschachler, E., … Grillari, J. (2010). miR-17, miR-19b, miR-20a, and miR-106a are down-regulated in human aging. *Aging Cell*, *9*(2), 291–296. doi: 10.1111/j.1474-9726.2010.00549.x

46 Hassanpour, M., Rahbarghazi, R., Nouri, M., Aghamohammadzadeh, N., Safaei, N., & Ahmadi, M. (2019). Role of autophagy in atherosclerosis: foe or friend? *Journal of Inflammation*, *16*(1), 8. doi: 10.1186/s12950-019-0212-4

47 HUTTER, E., RENNER, K., PFISTER, G., STÖCKL, P., JANSEN-DÜRR, P., & GNAIGER, E. (2004). Senescence-associated changes in respiration and oxidative phosphorylation in primary human fibroblasts. *Biochemical Journal*, *380*(3), 919–928. doi: 10.1042/bj20040095

48 Ibragimova, M., Kussainova, A., Aripova, A., Bersimbaev, R., & Bulgakova, O. (2024). The Molecular Mechanisms in Senescent Cells Induced by Natural Aging and Ionizing Radiation. *Cells*, *13*(6), 550. doi: 10.3390/cells13060550

49 Ikeda, Y., Shirakabe, A., Brady, C., Zablocki, D., Ohishi, M., & Sadoshima, J. (2015). Molecular mechanisms mediating mitochondrial dynamics and mitophagy and their functional roles in the cardiovascular system. *Journal of Molecular and Cellular Cardiology*, *78*, 116–122. doi: 10.1016/j.yjmcc.2014.09.019

50 Jin, H. S., Suh, H. -W., Kim, S. -J., & Jo, E. -K. (2017). Mitochondrial Control of Innate Immunity and Inflammation. *Immune Network*, *17*(2), 77. doi: 10.4110/in.2017.17.2.77

51 Karamanlidis, G., Garcia-Menendez, L., Kolwicz, S. C., Lee, C. F., & Tian, R. (2014). Promoting PGC-1α-driven mitochondrial biogenesis is detrimental in pressure-overloaded mouse hearts. *American Journal of Physiology-Heart and Circulatory Physiology*, *307*(9), H1307–H1316. doi: 10.1152/ajpheart.00280.2014

52 Karamanlidis, G., Nascimben, L., Couper, G. S., Shekar, P. S., del Monte, F., & Tian, R. (2010). Defective DNA Replication Impairs Mitochondrial Biogenesis In Human Failing Hearts. *Circulation Research*, *106*(9), 1541–1548. doi: 10.1161/CIRCRESAHA.109.212753

53 Kerr, J. S., Adriaanse, B. A., Greig, N. H., Mattson, M. P., Cader, M. Z., Bohr, V. A., & Fang, E. F. (2017). Mitophagy and Alzheimer's Disease: Cellular and Molecular Mechanisms. *Trends in Neurosciences*, *40*(3), 151–166. doi: 10.1016/j.tins.2017.01.002

54 Kim, Y., Ji, H., Cho, E., Park, N. -H., Hwang, K., Park, W., Lee, K. -S., Park, D., & Jung, E. (2021). nc886, a Non-Coding RNA, Is a New Biomarker and Epigenetic Mediator of Cellular Senescence in Fibroblasts. *International Journal of Molecular Sciences*, *22*(24), 13673. doi: 10.3390/ijms222413673

55 Kirkland, J. L., & Tchkonia, T. (2020). Senolytic drugs: from discovery to translation. *Journal of Internal Medicine*, *288*(5), 518–536. doi: 10.1111/joim.13141

56 Koyano, F., Yamano, K., Kosako, H., Tanaka, K., & Matsuda, N. (2019). Parkin recruitment to impaired mitochondria for nonselective ubiquitylation is facilitated by MITOL. *Journal of Biological Chemistry*, *294*(26), 10300–10314. doi: 10.1074/jbc.RA118.006302

57 Kroemer, G., & Pouyssegur, J. (2008). Tumor Cell Metabolism: Cancer's Achilles' Heel. *Cancer Cell*, *13*(6), 472–482. doi: 10.1016/j.ccr.2008.05.005

58 Kussainova, A., Bulgakova, O., Aripova, A., Khalid, Z., Bersimbaev, R., & Izzotti, A. (2022). The Role of Mitochondrial miRNAs in the Development of Radon-Induced Lung Cancer. *Biomedicines*, *10*(2), 428. doi: 10.3390/biomedicines10020428

59 Lang, A., Grether-Beck, S., Singh, M., Kuck, F., Jakob, S., Kefalas, A., Altinoluk-Hambüchen, S., Graffmann, N., Schneider, M., Lindecke, A., Brenden, H., Felsner, I., Ezzahoini, H., Marini, A., Weinhold, S., Vierkötter, A., Tigges, J., Schmidt, S., Stühler, K., … Piekorz, R. P. (2016). MicroRNA-15b regulates mitochondrial ROS production and the senescence-associated secretory phenotype through sirtuin 4/SIRT4. *Aging*, *8*(3), 484–505. doi: 10.18632/aging.100905

60 Lee, A., Kondapalli, C., Virga, D. M., Lewis, T. L., Koo, S. Y., Ashok, A., Mairet-Coello, G., Herzig, S., Foretz, M., Viollet, B., Shaw, R., Sproul, A., & Polleux, F. (2022). Aβ42 oligomers trigger synaptic loss through CAMKK2-AMPK-dependent effectors coordinating mitochondrial fission and mitophagy. *Nature Communications*, *13*(1), 4444. doi: 10.1038/s41467-022-32130-5

61 Lee, H., Tak, H., Park, S. J., Jo, Y. K., Cho, D. H., & Lee, E. K. (2017). microRNA-200a-3p enhances mitochondrial elongation by targeting mitochondrial fission factor. *BMB Reports*, *50*(4), 214–219. doi: 10.5483/BMBRep.2017.50.4.006

62 Levine, B., & Kroemer, G. (2019). Biological Functions of Autophagy Genes: A Disease Perspective. *Cell*, *176*(1–2), 11–42. doi: 10.1016/j.cell.2018.09.048

63 Li, F., He, X., Ye, D., Lin, Y., Yu, H., Yao, C., Huang, L., Zhang, J., Wang, F., Xu, S., Wu, X., Liu, L., Yang, C., Shi, J., He, X., Liu, J., Qu, Y., Guo, F., Zhao, J., … Zhao, S. (2015). NADP+-IDH Mutations Promote Hypersuccinylation that Impairs Mitochondria Respiration and Induces Apoptosis Resistance. *Molecular Cell*, *60*(4), 661–675. doi: 10.1016/j.molcel.2015.10.017

64 Li, Xia, Li, C., Zhang, W., Wang, Y., Qian, P., & Huang, H. (2023). Inflammation and aging: signaling pathways and intervention therapies. *Signal Transduction and Targeted Therapy*, *8*(1), 239. doi: 10.1038/s41392-023-01502-8

65 Li, Xiang, Zhang, Y., Yeung, S. C., Liang, Y., Liang, X., Ding, Y., Ip, M. S. M., Tse, H. -F., Mak, J. C. W., & Lian, Q. (2014). Mitochondrial Transfer of Induced Pluripotent Stem Cell–Derived Mesenchymal Stem Cells to Airway Epithelial Cells Attenuates Cigarette Smoke–Induced Damage. *American Journal of Respiratory Cell and Molecular Biology*, *51*(3), 455–465. doi: 10.1165/rcmb.2013-0529OC

66 Liang, W. S., Reiman, E. M., Valla, J., Dunckley, T., Beach, T. G., Grover, A., Niedzielko, T. L., Schneider, L. E., Mastroeni, D., Caselli, R., Kukull, W., Morris, J. C., Hulette, C. M., Schmechel, D., Rogers, J., & Stephan, D. A. (2008). Alzheimer's disease is associated with reduced expression of energy metabolism genes in posterior cingulate neurons. *Proceedings of the National Academy of Sciences*, *105*(11), 4441–4446. doi: 10.1073/pnas.0709259105

67 Li-Harms, X., Milasta, S., Lynch, J., Wright, C., Joshi, A., Iyengar, R., Neale, G., Wang, X., Wang, Y. -D., Prolla, T. A., Thompson, J. E., Opferman, J. T., Green, D. R., Schuetz, J., & Kundu, M. (2015). Mito-protective autophagy is impaired in erythroid cells of aged mtDNA-mutator mice. *Blood*, *125*(1), 162–174. doi: 10.1182/blood-2014-07-586396

68 Lin, H. -Y., Liou, C. -W., Chen, S. -D., Hsu, T. -Y., Chuang, J. -H., Wang, P. -W., Huang, S. -T., Tiao, M. -M., Chen, J. -B., Lin, T. -K., & Chuang, Y. -C. (2015). Mitochondrial transfer from Wharton's jelly-derived mesenchymal stem cells to mitochondria-defective cells recaptures impaired mitochondrial function. *Mitochondrion*, *22*, 31–44. doi: 10.1016/j.mito.2015.02.006

69 Liou, G. -Y., Döppler, H., DelGiorno, K. E., Zhang, L., Leitges, M., Crawford, H. C., Murphy, M. P., & Storz, P. (2016). Mutant KRas-Induced Mitochondrial Oxidative Stress in Acinar Cells Upregulates EGFR Signaling to Drive Formation of Pancreatic Precancerous Lesions. *Cell Reports*, *14*(10), 2325–2336. doi: 10.1016/j.celrep.2016.02.029

70 Maldonado, E., Morales-Pison, S., Urbina, F., & Solari, A. (2023a). Aging Hallmarks and the Role of Oxidative Stress. *Antioxidants*, *12*(3), 651. doi: 10.3390/antiox12030651

71 Maldonado, E., Morales-Pison, S., Urbina, F., & Solari, A. (2023b). Aging Hallmarks and the Role of Oxidative Stress. *Antioxidants*, *12*(3), 651. doi: 10.3390/antiox12030651

72 Masuzawa, A., Black, K. M., Pacak, C. A., Ericsson, M., Barnett, R. J., Drumm, C., Seth, P., Bloch, D. B., Levitsky, S., Cowan, D. B., & McCully, J. D. (2013). Transplantation of autologously derived mitochondria protects the heart from ischemia-reperfusion injury. *American Journal of Physiology-Heart and Circulatory Physiology*, *304*(7), H966–H982. doi: 10.1152/ajpheart.00883.2012

73 McLelland, G. -L., Goiran, T., Yi, W., Dorval, G., Chen, C. X., Lauinger, N. D., Krahn, A. I., Valimehr, S., Rakovic, A., Rouiller, I., Durcan, T. M., Trempe, J. -F., & Fon, E. A. (2018). Mfn2 ubiquitination by PINK1/parkin gates the p97-dependent release of ER from mitochondria to drive mitophagy. *ELife*, *7*. doi: 10.7554/eLife.32866

74 Meissner, C., Lorenz, H., Hehn, B., & Lemberg, M. K. (2015). Intramembrane protease PARL defines a negative regulator of PINK1- and PARK2/Parkin-dependent mitophagy. *Autophagy*, *11*(9), 1484–1498. doi: 10.1080/15548627.2015.1063763

75 Monzio Compagnoni, G., Di Fonzo, A., Corti, S., Comi, G. P., Bresolin, N., & Masliah, E. (2020). The Role of Mitochondria in Neurodegenerative Diseases: the Lesson from Alzheimer's Disease and Parkinson's Disease. *Molecular Neurobiology*, *57*(7), 2959–2980. doi: 10.1007/s12035-020-01926-1

76 Morton, H., Kshirsagar, S., Orlov, E., Bunquin, L. E., Sawant, N., Boleng, L., George, M., Basu, T., Ramasubramanian, B., Pradeepkiran, J. A., Kumar, S., Vijayan, M., Reddy, A. P., & Reddy, P. H. (2021). Defective mitophagy and synaptic degeneration in Alzheimer's disease: Focus on aging, mitochondria and synapse. *Free Radical Biology and Medicine*, *172*, 652–667. doi: 10.1016/j.freeradbiomed.2021.07.013

77 Mu, G., Deng, Y., Lu, Z., Li, X., & Chen, Y. (2020). miR-20b suppresses mitochondrial dysfunction-mediated apoptosis to alleviate hyperoxia-induced acute lung injury by directly targeting MFN1 and MFN2. *Acta Biochimica et Biophysica Sinica*, *53*(2), 220–228. doi: 10.1093/abbs/gmaa161

78 Narendra, D., Tanaka, A., Suen, D. -F., & Youle, R. J. (2008). Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. *The Journal of Cell Biology*, *183*(5), 795–803. doi: 10.1083/jcb.200809125

79 Oka, T., Hikoso, S., Yamaguchi, O., Taneike, M., Takeda, T., Tamai, T., Oyabu, J., Murakawa, T., Nakayama, H., Nishida, K., Akira, S., Yamamoto, A., Komuro, I., & Otsu, K. (2012). Mitochondrial DNA that escapes from autophagy causes inflammation and heart failure. *Nature*, *485*(7397), 251–255. doi: 10.1038/nature10992

80 Ong, S. -B., Subrayan, S., Lim, S. Y., Yellon, D. M., Davidson, S. M., & Hausenloy, D. J. (2010). Inhibiting Mitochondrial Fission Protects the Heart Against Ischemia/Reperfusion Injury. *Circulation*, *121*(18), 2012–2022. doi: 10.1161/CIRCULATIONAHA.109.906610

81 Paschka, P., Schlenk, R. F., Gaidzik, V. I., Habdank, M., Krönke, J., Bullinger, L., Späth, D., Kayser, S., Zucknick, M., Götze, K., Horst, H. -A., Germing, U., Döhner, H., & Döhner, K. (2010). *IDH1* and *IDH2* Mutations Are Frequent Genetic Alterations in Acute Myeloid Leukemia and Confer Adverse Prognosis in Cytogenetically Normal Acute Myeloid Leukemia With *NPM1* Mutation Without *FLT3* Internal Tandem Duplication. *Journal of Clinical Oncology*, *28*(22), 3636–3643. doi: 10.1200/JCO.2010.28.3762

82 Peoples, J. N., Saraf, A., Ghazal, N., Pham, T. T., & Kwong, J. Q. (2019). Mitochondrial dysfunction and oxidative stress in heart disease. *Experimental & Molecular Medicine*, *51*(12), 1–13. doi: 10.1038/s12276-019-0355-7

83 Pernas, L., & Scorrano, L. (2016). Mito-Morphosis: Mitochondrial Fusion, Fission, and Cristae Remodeling as Key Mediators of Cellular Function. *Annual Review of Physiology*, *78*(1), 505–531. doi: 10.1146/annurev-physiol-021115-105011

84 Pickles, S., Vigié, P., & Youle, R. J. (2018a). Mitophagy and Quality Control Mechanisms in Mitochondrial Maintenance. *Current Biology*, *28*(4), R170–R185. doi: 10.1016/j.cub.2018.01.004

85 Pickles, S., Vigié, P., & Youle, R. J. (2018b). Mitophagy and Quality Control Mechanisms in Mitochondrial Maintenance. *Current Biology*, *28*(4), R170–R185. doi: 10.1016/j.cub.2018.01.004

86 Pinti, M., Cevenini, E., Nasi, M., De Biasi, S., Salvioli, S., Monti, D., Benatti, S., Gibellini, L., Cotichini, R., Stazi, M. A., Trenti, T., Franceschi, C., & Cossarizza, A. (2014). Circulating mitochondrial DNA increases with age and is a familiar trait: Implications for "inflamm-aging". *European Journal of Immunology*, *44*(5), 1552–1562. doi: 10.1002/eji.201343921

87 Plowey, E. D., Johnson, J. W., Steer, E., Zhu, W., Eisenberg, D. A., Valentino, N. M., Liu, Y. -J., & Chu, C. T. (2014). Mutant LRRK2 enhances glutamatergic synapse activity and evokes excitotoxic dendrite degeneration. *Biochimica et Biophysica Acta (BBA) — Molecular Basis of Disease*, *1842*(9), 1596–1603. doi: 10.1016/j.bbadis.2014.05.016

88 Pomatto, L. C. D., & Davies, K. J. A. (2018). Adaptive homeostasis and the free radical theory of ageing. *Free Radical Biology and Medicine*, *124*, 420–430. doi: 10.1016/j.freeradbiomed.2018.06.016

89 Pradeepkiran, J. A., & Reddy, P. H. (2020). Defective mitophagy in Alzheimer's disease. *Ageing Research Reviews*, *64*, 101191. doi: 10.1016/j.arr.2020.101191

90 Proietti, S., Cucina, A., Minini, M., & Bizzarri, M. (2017). Melatonin, mitochondria, and the cancer cell. *Cellular and Molecular Life Sciences*, *74*(21), 4015–4025. doi: 10.1007/s00018-017-2612-z

91 Rak, M., Bénit, P., Chrétien, D., Bouchereau, J., Schiff, M., El-Khoury, R., Tzagoloff, A., & Rustin, P. (2016). Mitochondrial cytochrome c oxidase deficiency. *Clinical Science*, *130*(6), 393–407. doi: 10.1042/CS20150707

92 Rice, A. C., Keeney, P. M., Algarzae, N. K., Ladd, A. C., Thomas, R. R., & Bennett Jr., J. P. (2014). Mitochondrial DNA Copy Numbers in Pyramidal Neurons are Decreased and Mitochondrial Biogenesis Transcriptome Signaling is Disrupted in Alzheimer's Disease Hippocampi. *Journal of Alzheimer's Disease*, *40*(2), 319–330. doi: 10.3233/JAD-131715

93 Ryter, S. W., Rosas, I. O., Owen, C. A., Martinez, F. J., Choi, M. E., Lee, C. G., Elias, J. A., & Choi, A. M. K. (2018). Mitochondrial Dysfunction as a Pathogenic Mediator of Chronic Obstructive Pulmonary Disease and Idiopathic Pulmonary Fibrosis. *Annals of the American Thoracic Society*, *15*(Supplement_4), S266–S272. doi: 10.1513/AnnalsATS.201808-585MG

94 Santos, R. X., Correia, S. C., Zhu, X., Smith, M. A., Moreira, P. I., Castellani, R. J., Nunomura, A., & Perry, G. (2013). Mitochondrial DNA Oxidative Damage and Repair in Aging and Alzheimer's Disease. *Antioxidants & Redox Signaling*, *18*(18), 2444–2457. doi: 10.1089/ars.2012.5039

95 Sebastián, D., Sorianello, E., Segalés, J., Irazoki, A., Ruiz-Bonilla, V., Sala, D., Planet, E., Berenguer-Llergo, A., Muñoz, J. P., Sánchez-Feutrie, M., Plana, N., Hernández-Álvarez, M. I., Serrano, A. L., Palacín, M., & Zorzano, A. (2016). Mfn2 deficiency links age-related sarcopenia and impaired autophagy to activation of an adaptive mitophagy pathway. *The EMBO Journal*, *35*(15), 1677–1693. doi: 10.15252/embj.201593084

96 Sheeran, F. L., & Pepe, S. (2017). *Mitochondrial Bioenergetics and Dysfunction in Failing Heart* (pp. 65–80). doi: 10.1007/978-3-319-55330-6_4

97 Shen, J., Dai, Z., Li, Y., Zhu, H., & Zhao, L. (2022). TLR9 regulates NLRP3 inflammasome activation via the NF-kB signaling pathway in diabetic nephropathy. *Diabetology & Metabolic Syndrome*, *14*(1), 26. doi: 10.1186/s13098-021-00780-y

98 Sripada, L., Tomar, D., Prajapati, P., Singh, R., Singh, A. K., & Singh, R. (2012). Systematic Analysis of Small RNAs Associated with Human Mitochondria by Deep Sequencing: Detailed Analysis of Mitochondrial Associated miRNA. *PLoS ONE*, *7*(9), e44873. doi: 10.1371/journal.pone.0044873

99 Stanga, S., Caretto, A., Boido, M., & Vercelli, A. (2020). Mitochondrial Dysfunctions: A Red Thread across Neurodegenerative Diseases. *International Journal of Molecular Sciences*, *21*(10), 3719. doi: 10.3390/ijms21103719

100 Stöckl, P., Hütter, E., Zwerschke, W., & Jansen-Dürr, P. (2006). Sustained inhibition of oxidative phosphorylation impairs cell proliferation and induces premature senescence in human fibroblasts. *Experimental Gerontology*, *41*(7), 674–682. doi: 10.1016/j.exger.2006.04.009

101 Suomalainen, A., & Nunnari, J. (2024). Mitochondria at the crossroads of health and disease. *Cell*, *187*(11), 2601–2627. doi: 10.1016/j.cell.2024.04.037

102 Swerdlow, R. H. (2018). Mitochondria and Mitochondrial Cascades in Alzheimer's Disease. *Journal of Alzheimer's Disease*, *62*(3), 1403–1416. doi: 10.3233/JAD-170585

103 Thundyil, J., & Lim, K. -L. (2015). DAMPs and neurodegeneration. *Ageing Research Reviews*, *24*, 17–28. doi: 10.1016/j.arr.2014.11.003

104 Tobore, T. O. (2019). On the central role of mitochondria dysfunction and oxidative stress in Alzheimer's disease. *Neurological Sciences*, *40*(8), 1527–1540. doi: 10.1007/s10072-019-03863-x

105 Vaglio-Garro, A., Kozlov, A. V., Smirnova, Y. D., & Weidinger, A. (2024). Pathological Interplay between Inflammation and Mitochondria Aggravates Glutamate Toxicity. *International Journal of Molecular Sciences*, *25*(4), 2276. doi: 10.3390/ijms25042276

106 Valente, E. M., Abou-Sleiman, P. M., Caputo, V., Muqit, M. M. K., Harvey, K., Gispert, S., Ali, Z., Del Turco, D., Bentivoglio, A. R., Healy, D. G., Albanese, A., Nussbaum, R., González-Maldonado, R., Deller, T., Salvi, S., Cortelli, P., Gilks, W. P., Latchman, D. S., Harvey, R. J., … Wood, N. W. (2004). Hereditary Early-Onset Parkinson's Disease Caused by Mutations in *PINK1*. *Science*, *304*(5674), 1158–1160. doi: 10.1126/science.1096284

107 Verma, M., Callio, J., Otero, P. A., Sekler, I., Wills, Z. P., & Chu, C. T. (2017). Mitochondrial Calcium Dysregulation Contributes to Dendrite Degeneration Mediated by PD/LBD-Associated LRRK2 Mutants. *The Journal of Neuroscience*, *37*(46), 11151–11165. doi: 10.1523/JNEUROSCI.3791-16.2017

108 Verma, M., Lizama, B. N., & Chu, C. T. (2022). Excitotoxicity, calcium and mitochondria: a triad in synaptic neurodegeneration. *Translational Neurodegeneration*, *11*(1), 3. doi: 10.1186/s40035-021-00278-7

109 Wu, J., Venkata Subbaiah, K. C., Jiang, F., Hedaya, O., Mohan, A., Yang, T., Welle, K., Ghaemmaghami, S., Tang, W. H. W., Small, E., Yan, C., & Yao, P. (2021). MicroRNA-574 regulates FAM210A expression and influences pathological cardiac remodeling. *EMBO Molecular Medicine*, *13*(2). doi: 10.15252/emmm.202012710

110 Xu, F., Li, Y., Li, S., Ma, Y., Zhao, N., Liu, Y., Qian, N., Zhao, H., & Li, Y. (2014). Complete Freund's adjuvant–induced acute inflammatory pain could be attenuated by triptolide via inhibiting spinal glia activation in rats. *Journal of Surgical Research*, *188*(1), 174–182. doi: 10.1016/j.jss.2013.11.1087

111 Xu, Q., Fu, Q., Li, Z., Liu, H., Wang, Y., Lin, X., He, R., Zhang, X., Ju, Z., Campisi, J., Kirkland, J. L., & Sun, Y. (2021). The flavonoid procyanidin C1 has senotherapeutic activity and increases lifespan in mice. *Nature Metabolism*, *3*(12), 1706–1726. doi: 10.1038/s42255-021-00491-8

112 Yan, C., Duanmu, X., Zeng, L., Liu, B., & Song, Z. (2019). Mitochondrial DNA: Distribution, Mutations, and Elimination. *Cells*, *8*(4), 379. doi: 10.3390/cells8040379

113 Yan, K., An, T., Zhai, M., Huang, Y., Wang, Q., Wang, Y., Zhang, R., Wang, T., Liu, J., Zhang, Y., Zhang, J., & Wang, K. (2019). Mitochondrial miR-762 regulates apoptosis and myocardial infarction by impairing ND2. *Cell Death & Disease*, *10*(7), 500. doi: 10.1038/s41419-019-1734-7

114 Yang, Y., Ouyang, Y., Yang, L., Beal, M. F., McQuibban, A., Vogel, H., & Lu, B. (2008). Pink1 regulates mitochondrial dynamics through interaction with the fission/fusion machinery. *Proceedings of the National Academy of Sciences*, *105*(19), 7070–7075. doi: 10.1073/pnas.0711845105

115 Youle, R. J. (2019). Mitochondria—Striking a balance between host and endosymbiont. *Science*, *365*(6454). doi: 10.1126/science.aaw9855

116 Zemirli, N., Morel, E., & Molino, D. (2018). Mitochondrial Dynamics in Basal and Stressful Conditions. *International Journal of Molecular Sciences*, *19*(2), 564. doi: 10.3390/ijms19020564

117 Zhang, X., Farrell, J. J., Tong, T., Hu, J., Zhu, C., Wang, L., Mayeux, R., Haines, J. L., Pericak-Vance, M. A., Schellenberg, G. D., Lunetta, K. L., & Farrer, L. A. (2022). Association of mitochondrial variants and haplogroups identified by whole exome sequencing with Alzheimer's disease. *Alzheimer's & Dementia*, *18*(2), 294–306. doi: 10.1002/alz.12396

118 Zhang, Y., Chen, L., Hu, G. -Q., Zhang, N., Zhu, X. -D., Yang, K. -Y., Jin, F., Shi, M., Chen, Y. -P., Hu, W. -H., Cheng, Z. -B., Wang, S. -Y., Tian, Y., Wang, X. -C., Sun, Y., Li, J. -G., Li, W. -F., Li, Y. -H., Tang, L. -L., … Ma, J. (2019). Gemcitabine and Cisplatin Induction Chemotherapy in Nasopharyngeal Carcinoma. *New England Journal of Medicine*, *381*(12), 1124–1135. doi: 10.1056/NEJMoa1905287

119 Zhu, X., Perry, G., Smith, M. A., & Wang, X. (2012). Abnormal Mitochondrial Dynamics in the Pathogenesis of Alzheimer's Disease. *Journal of Alzheimer's Disease*, *33*(s1), S253–S262. doi: 10.3233/JAD-2012-129005

120 Zhu, Y., Tchkonia, T., Fuhrmann-Stroissnigg, H., Dai, H. M., Ling, Y. Y., Stout, M. B., Pirtskhalava, T., Giorgadze, N., Johnson, K. O., Giles, C. B., Wren, J. D., Niedernhofer, L. J., Robbins, P. D., & Kirkland, J. L. (2016). Identification of a novel senolytic agent, navitoclax, targeting the Bcl-2 family of anti-apoptotic factors. *Aging Cell*, *15*(3), 428–435. doi: 10.1111/acel.12445

121 Zhunina, O. A., Yabbarov, N. G., Grechko, A. V., Starodubova, A. V., Ivanova, E., Nikiforov, N. G., & Orekhov, A. N. (2021). The Role of Mitochondrial Dysfunction in Vascular Disease, Tumorigenesis, and Diabetes. *Frontiers in Molecular Biosciences*, *8*. doi: 10.3389/fmolb.2021.671908

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## Жасушаның қартаюы кезіндегі митохондриялық дисфункция

Жасушаның қартаюы — жасушалық циклдің тоқтауымен және жасушаның бөліну қабілетінің жоғалуымен сипатталатын күрделі процесс. Қартаю көптеген молекулалық механизмдерден туындаса да, оның дамуында митохондриялар маңызды орын алады. Тыныс алу қабілетінің бұзылуымен және жасушаның энергетикалық статусының төмендеуімен көрінетін митохондриялық дисфункция жиі тотығу стрессіне әкелетін бос оттегі радикалдарының жоғарылауымен бірге жүреді. Бұл жағдай жасушаның қартаюына ықпал етіп қана қоймайды, сонымен қатар оның дамуын тездетеді. Бүгінгі күні митохондриялық дисфункция мен жасушалық қартаю арасындағы байланысты растайтын көптеген зерттеулер бар, бұл митохондриялардың қартаюға қарсы терапия мен араласудың мақсаты ретіндегі маңыздылығын көрсетеді. Қартаю әртүрлі жасқа байланысты аурулар мен жағдайлардың, соның ішінде қатерлі ісік, нейродегенеративті аурулар және жүрек-тамыр ауруларының пайда болуымен байланысты. Бұл механизмдерді түсіну қартаюды бәсеңдетуге бағытталған стратегияларды әзірлеу үшін жаңа көкжиектерді ашады. Мақалада қартаю процесінде митохондриялық дисфункцияның дамуына ықпал ететін механизмдер жинақталған, сонымен қатар бұл бұзылыстың негізгі салдары, әсіресе жасушалық қартаюға әсер ету контексінде қарастырылған.

*Кілт сөздер:* жасушаның қартаюы, митохондрия, тотығу стресі, митофагия, микроРНҚ, жасқа байланысты аурулар, қатерлі ісік, Альцгеймер ауруы, жүрек-қан тамырлары аурулары.

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## Митохондриальная дисфункция при клеточном старении

Клеточное старение — это сложный биологический процесс, который характеризуется остановкой клеточного цикла и утратой способности клеток к делению. Несмотря на участие множества молекулярных механизмов, центральную роль в этом процессе играют митохондрии. Митохондриальная дисфункция, проявляющаяся нарушением дыхательной способности и снижением энергетического статуса клетки, часто сопровождается увеличением продукции свободных радикалов кислорода, что ведет к окислительному стрессу. Это состояние не только способствует клеточному старению, но и ускоряет его прогрессирование. На сегодняшний день существует множество исследований, подтверждающих связь между митохондриальной дисфункцией и клеточным старением, что подчеркивает важность митохондрий как мишени для антивозрастных терапий и вмешательств. Старение связано с возникновением различных возрастных заболеваний и состояний, включая рак, нейродегенеративные и сердечно-сосудистые заболевания. Понимание этих механизмов открывает новые горизонты для разработки стратегий, направленных на замедление старения. В данной статье обобщены механизмы, способствующие развитию митохондриальной дисфункции в процессе старения, а также рассмотрены основные последствия этого нарушения, особенно в контексте влияния на клеточное старение.

*Ключевые слова:* клеточное старение, митохондрии, окислительный стресс, митофагия, микроРНК, возраст-ассоциированные заболевания, рак, Болезнь Альцгеймера, сердечно-сосудистые заболевания.

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