Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 8
MMTCS 2025

Role of Mitochondrial Autophagy in Cell Aging and Its Molecular Mechanism

Xinyi Yang

University of Illinois Urbana-Champaign, USA

23130002466@qq.com

Abstract. Cell aging is the basis of organism aging, which is closely related to many aging-related diseases. Mitochondria, as the energy factory of cells, its function decline and damage play a key role in the process of cell aging. Mitochondrial autophagy is an intracellular quality control mechanism to selectively remove damaged mitochondria, which can delay cell aging by maintaining mitochondrial function and intracellular homeostasis. This paper reviews the role of mitochondrial autophagy in cell aging and its molecular mechanism. Mitochondrial autophagy is closely related to the occurrence of aging-related diseases such as Parkinson's disease (PD), Alzheimer's disease (AD) and heart failure, and activating mitochondrial autophagy can prolong the life of model organisms. The molecular mechanisms of mitochondrial autophagy mainly include ubiquitin-dependent pathway (PINK1/Parkin pathway) and non-ubiquitin-dependent pathway (NIX, BNIP3, FUNDC1-mediated autophagy), and are regulated by AMPK/mTOR, Sirtuin and other signal pathways. In addition, metabolic state and nutritional signals finely regulate the dynamic process of mitochondrial autophagy through energy perception mechanism. Although mitochondrial autophagy shows great potential in delaying aging and treating diseases, its clinical application still faces many challenges. Future research needs to further explore the molecular mechanism of mitochondrial autophagy, develop more accurate intervention methods, and verify its safety and effectiveness through clinical trials, so as to promote the development of anti-aging and disease treatment strategies.

Keywords: mitochondrial autophagy; cell senescence; molecular mechanism; PINK1/Parkin.

1. Introduction

Cell senescence is a common phenomenon in the life process of organisms, which is accompanied by the gradual decline of cell morphology, structure and function, and eventually leads to the loss of cell proliferation ability and the decline of physiological function. Cell aging is not only the basis of the whole aging of organisms, but also closely related to the occurrence and development of many aging-related diseases. Therefore, it is of great significance to deeply explore the mechanism of cell aging for understanding the process of biological aging and preventing and treating aging-related diseases [1].

Mitochondria are "energy factories" in cells, which are responsible for producing energy molecules such as ATP and maintaining normal physiological functions of cells. However, with the aging of cells, mitochondria will also be damaged and function will decline, and a large number of reactive oxygen radicals will be produced, which will aggravate the oxidative stress of cells and further promote cell aging and apoptosis [2]. Mitochondrial autophagy, as an intracellular quality control mechanism, can selectively remove damaged or redundant mitochondria and maintain the overall quality of mitochondria, thus delaying the process of cell aging [3].

Although some progress has been made in the research on the relationship between mitochondrial autophagy and cell aging, there are still many unsolved mysteries. For example, what is the specific molecular mechanism of mitochondrial autophagy? How to regulate mitochondrial autophagy to delay cell aging? What aging-related diseases are related to mitochondrial autophagy? These problems need to be further studied. This paper reviews the role and molecular mechanism of mitochondrial autophagy in cell aging, reviews the relevant research progress at home and abroad,

summarizes the existing research results, and points out the hot spots and blank spots of current research.

2. Role of mitochondrial autophagy in cell senescence

2.1. Prevention of aging-related diseases: mitochondrial autophagy defect is related to diseases

Mitochondrial autophagy is one of the core pathological mechanisms of many aging-related diseases. In patients with Parkinson's disease (PD), the mutation of PINK1/Parkin pathway leads to mitochondrial autophagy disorder, abnormal mitochondrial accumulation in dopamine neurons, and the surge of reactive oxygen species (ROS), which eventually leads to neuronal death [4]. In Alzheimer's disease (AD), β -amyloid (Aβ) induces mitochondrial damage, while insufficient autophagy clearance accelerates the pathological and cognitive decline of tau protein [5-6].

Mitochondrial autophagy has dual functions [7-8]: on the one hand, its defects lead to genomic instability and ROS accumulation, which promotes tumor occurrence; On the other hand, cancer cells may hijack autophagy mechanism to cope with hypoxia or nutritional deficiency and enhance their viability. Lack of mitochondrial autophagy in myocardial cells leads to heart failure, such as ischemia-reperfusion injury. Autophagy activation mediated by PINK1 can reduce cell apoptosis.

2.2. Influence on life span: mitochondrial autophagy and aging regulation

Mitochondrial autophagy is directly related to life extension by maintaining cell energy metabolism and redox balance. In nematode and mouse models, activating mitochondrial autophagy, such as overexpressing PINK1 or Parkin, can prolong life span, while knocking out autophagy-related genes, such as Atg5 and Atg7, can accelerate aging phenotype [9]. Autophagy can eliminate dysfunctional mitochondria, reduce ROS release and DNA damage, and delay cell aging. AMPK/mTOR and Sirtuin pathways affect life span by regulating autophagy activity. For example, rapamycin (mTOR inhibitor) and resveratrol (SIRT1 activator) can enhance autophagy and prolong the life span of model organisms [10]. Small molecules targeting mitochondrial autophagy, such as uridine, NAD+ precursors, or gene therapy, such as CRISPR, activate autophagy genes, showing the potential to delay aging.

2.3. Metabolism and nutrition regulation: energy perception and autophagy dynamics

Mitochondrial autophagy is precisely regulated by metabolic and nutritional signals and interacts with the aging process [11]. The low-energy state activates AMPK, inhibits mTORC1 and promotes PINK1/Parkin-mediated autophagy. On the contrary, overnutrition inhibits autophagy through insulin /IGF-1 pathway and accelerates mitochondrial dysfunction. Fasting or low-carbohydrate diet can enhance mitochondrial autophagy, remove mitochondrial debris related to aging and improve metabolic flexibility of elderly individuals. For example, intermittent fasting enhances mitochondrial autophagy and delays muscle atrophy by activating SIRT3 deacetylase [12]. Metabolic intermediates, such as α-ketoglutarate and NAD+, regulate the expression of autophagy-related genes through epigenetic modification and affect the aging process.

3. Molecular mechanism of mitochondrial autophagy

Mitochondrial autophagy is a form of autophagy that selectively removes damaged mitochondria. Its molecular mechanism can be divided into three categories: ubiquitin-dependent pathway, non-ubiquitin-dependent pathway and regulatory factor network.

3.1. Ubiquitin-dependent pathway

Damaged mitochondria are eliminated by a precisely regulated autophagy process, which relies on the orderly cooperation of a series of key molecules (Figure 1). Firstly, PINK1 protein stably exists in the outer membrane of damaged mitochondria and activates Parkin, an E3 ubiquitin ligase.

Activated Parkin catalyzes ubiquitination of various substrates (such as Miro and MFN1/2), and forms ubiquitin chains in cooperation with phosphorylated ubiquitin, which serves as the anchor point of autophagy receptors [13]. Subsequently, receptors such as OPTN, NDP52 and TAX1BP1 recognize these ubiquitination markers and bind to autophagy membrane through their LC3 interaction region (LIR) to recruit autophagy. Finally, Rab7 and HOPS complexes promote the fusion of autophagy and lysosome, thus completing the degradation of damaged mitochondria.

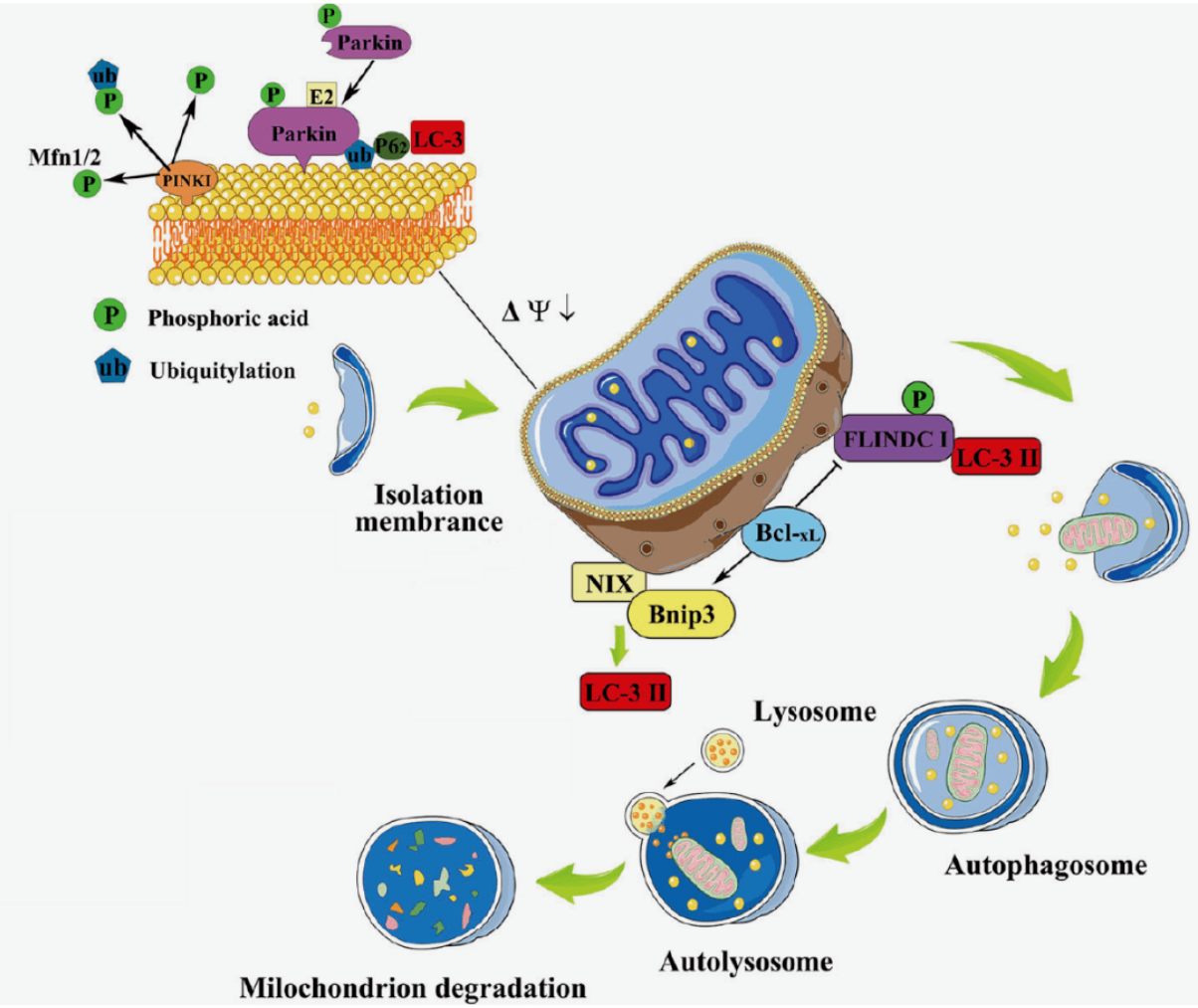

Figure 1 Molecular mechanism of mitochondrial autophagy (Chen, J., Wang, D, et al. 2021)

3.2. Nonubiquitin-dependent pathway

This kind of pathway directly binds to LC3 through the receptor protein on the mitochondrial membrane, and starts autophagy. The main receptors and functions are shown in Table 1 below:

Table 1 Main receptors and functions

receptor	architectural feature	Activation condition	function
NIX	Transmembrane protein, containing LIR domain	Hypoxia and erythrocyte maturation	Mediate mitochondrial clearance in red blood cell maturation period
BNIP3	Homodimer, containing LIR and TM domains	Hypoxia and myocardial ischemia	Promote mitochondrial autophagy in ischemic myocardium and inhibit ROS production.
FUNDC1	Mitochondrial outer membrane protein, containing LIR	Hypoxia and cold stress	Through the activation of phosphorylation of ULK1, the quality control of mitochondria is regulated.

In the process of autophagy, the receptor protein directly binds to LC3 through its LIR motif, anchoring the autophagy membrane to the surface of mitochondria, and realizing the recognition and encapsulation of damaged mitochondria [14]. Under certain stress conditions, such as anoxic environment, BNIP3 expression will be induced and mTORC1 activity will be inhibited, thus releasing mTORC1' inhibition on autophagy process, promoting autophagy activity to remove damaged organelles and maintaining intracellular homeostasis.

3.3. Other regulatory factors

Mitochondrial autophagy is regulated by various signal pathways and post-translational modifications. The key regulatory networks are shown in Tables 2 and 3 below:

Table 2 Protein kinase regulation

kinase	Activation condition	mechanism of action
AMPK	Insufficient energy (low ATP/ADP)	Phosphorylation of ULK1(Ser317) promotes autophagy formation.
mTOR	Adequate nutrition	Inhibit ULK1 complex and block autophagy initiation.
ULK1	AMPK activation /mTOR inhibition	Phosphorylate autophagy receptor (such as FUNDC1) to enhance LC3 binding.

Table 3 Posttranslational modification

Modification type	target spot	effect
Ubiquitination	Mitochondrial outer membrane protein (MFN2)	Parkin mediates ubiquitin chain labeling and recruits autophagic linker proteins.
phosphorylation	FUNDC1 (Ser13/17)	Phosphorylation of ULK1 enhances its affinity with LC3.
acetylization	LC3 (Lys49)	Deacetylation of SIRT1 promotes autophagy maturation.

By developing small molecule activators, such as NMN, to enhance the level of NAD+ and inhibitors, such as mTOR inhibitor rapamycin, various diseases are targeted for treatment. Especially in Parkinson's disease, the mitochondrial autophagy defect caused by PINK1/Parkin mutation reveals the possibility of gene editing therapy. In-depth understanding of the molecular mechanism of mitochondrial autophagy provides a theoretical basis for precise intervention of neurodegenerative diseases, cancer and aging-related diseases.

4. Research prospects and challenges

Future research will continue to explore the specific molecular mechanism of mitochondrial autophagy, including the recognition of new autophagy receptors, protein kinases and the role of post-translation modification, and analyze how they cooperatively regulate this process. At the same time, in order to better understand the aging diseases related to mitochondrial autophagy, the research will be devoted to establishing more accurate disease models and providing new ideas for treatment. In view of the importance of mitochondrial autophagy in delaying aging, researchers will also explore ways to regulate mitochondrial autophagy through drugs, diet and exercise, so as to develop new anti-aging strategies, aiming at prolonging the healthy life span of organisms and improving the quality of life.

At present, the technology of studying mitochondrial autophagy faces limitations, such as the accuracy of real-time monitoring and autophagy flow measurement. In the future, more sensitive and specific methods need to be developed to explore its mechanism in depth. Since aging-related diseases are the result of many factors, such as heredity, environment and lifestyle, it is necessary to comprehensively consider these variables to understand the role of mitochondrial autophagy in order to fully reveal the disease mechanism and formulate effective treatment strategies. Although mitochondrial autophagy shows potential in anti-aging and disease treatment, its clinical application still faces challenges such as drug safety, effectiveness and tolerance. Therefore, more clinical trials and long-term follow-up are needed to verify the safety and effectiveness of relevant intervention measures in the future, so as to provide a solid basis for clinical practice.

5. Conclusion

Mitochondrial autophagy is very important to prolong biological life by selectively removing damaged or redundant mitochondria, maintaining mitochondrial quality, delaying cell aging and preventing related diseases. Its functional defects are closely related to the pathological mechanisms of many aging-related diseases, such as Parkinson's disease and Alzheimer's Harmo's disease, in which the mutation of PINK1/Parkin pathway or the damage induced by β -amyloid protein aggravate the progress of the disease. Mitochondrial autophagy involves ubiquitin-dependent and non-ubiquitin-dependent pathways, and is regulated by AMPK/mTOR and Sirtuin pathways, which affects life span. Metabolic and nutritional status also precisely regulate this process. For example, low-energy state or specific diet (such as fasting) can enhance mitochondrial autophagy and improve metabolic flexibility of elderly individuals. Future research needs to further analyze its specific molecular mechanism, establish a more accurate disease model, develop new regulatory means to cope with the challenges of aging and disease treatment, overcome the limitations of existing technologies, and comprehensively consider the effects of genetic, environmental and lifestyle factors.

References

[1] Hui, S. , George, J. , Kapadia, M. , Chau, H. , Bariring, Z. , & Earnshaw, R. , et al. (2024). Mitophagy upregulation occurs early in the neurodegenerative process mediated by α-synuclein. Molecular Neurobiology, 61(11), 9032-9042.

[2] Mubthasima, P. P. , Singh, S. A. , & Kannan, A. (2024). Sesamol-mediated targeting of epha2 sensitises cervical cancer for cisplatin treatment by regulating mitochondrial dynamics, autophagy, and mitophagy. Molecular Biology Reports, 51(1), 1-11.

[3] Kodali, S. , Li, M. , Budai, M. M. , Chen, M. , & Wang, J. (2022). Protection of quiescence and longevity of igg memory b cells by mitochondrial autophagy. Journal of immunology (Baltimore, Md. : 1950), 208(5), 1085-1098.

[4] Ping, K. , Yang, R. , Chen, H. , Xie, S. , Xiang, Y. , & Li, M. , et al. (2025). Gypenoside xlix activates the sirt1/nrf2 signaling pathway to inhibit nlrp3 inflammasome activation to alleviate septic acute lung injury. Inflammation, 48(1), 42-60.

[5] Scaini, G. , Mason, B. L. , Diaz, A. P. , Jha, M. K. , Soares, J. C. , & Trivedi, M. H. , et al. (2022). Dysregulation of mitochondrial dynamics, mitophagy and apoptosis in major depressive disorder: does inflammation play a role?. Molecular psychiatry, 27(2), 1095-1102.

[6] Liu, Z. , Ye, Q. , Wang, F. , Guo, Y. , Cui, R. , & Wang, J. , et al. (2021). Overexpression of thioredoxin reductase 1 can reduce dna damage, mitochondrial autophagy and endoplasmic reticulum stress in parkinson's disease. Experimental Brain Research, 239(2), 475-490.

[7] Luana, N. , Makoto, S. , & Erika,BereczkiXidan,LiJianping,LiuRicheng,JiangRomain,GiraudNuno Santos,LealCatarina Moreira,PinhoErik,BergerVictoria Lim,FalkGiacomo,DentoniMaria,AnkarcronaPer,Nilsson. (2023). Mitochondrial hypermetabolism precedes impaired autophagy and synaptic disorganization in app knock-in alzheimer mouse models. Molecular psychiatry, 28(9), 3966-3981.

[8] Guo, W. , Zhang, B. , Liu, M. , Zhang, J. , & Feng, Y. (2024). Correction: based on virtual screening and simulation exploring the mechanism of plant-derived compounds with pink1 to postherpetic neuralgia. Molecular Neurobiology, 61(11), 9204-9209.

[9] Yang, L. , Ying, J. , Tao, Q. , & Zhang, Q. (2024). Rna n6-methyladenosine modifications in urological cancers: from mechanism to application. Nature Reviews Urology, 21(8), 460-476.

[10] Wang, X. , Li, Y. , Deng, X. , Jia, F. , Cui, X. , & Lu, J. , et al. (2021). Colloidally stabilized dspe-peg-glucose/calcium phosphate hybrid nanocomposites for enhanced photodynamic cancer therapy via complementary mitochondrial ca. ACS applied materials & interfaces, 13(33), 39112-39125.

[11] Su, L. Y. , Liu, Q. , Jiao, L. , & Yao, Y. G. (2021). Molecular mechanism of neuroprotective effect of melatonin on morphine addiction and analgesic tolerance: an update. Molecular neurobiology, 58(9), 4628-4638.

[12] Peng, S. , Ma, S. , Yang, F. , Xu, C. , Li, H. , & Lu, S. , et al. (2022). Prognostic value and underlying mechanism of autophagy-related genes in bladder cancer. Scientific reports, 12(1), 2219.

[13] Chen, J. , Wang, D. , Zong, Y. , & Yang, X. (2021). Dha protects hepatocytes from oxidative injury through gpr120/erk-mediated mitophagy. International Journal of Molecular Sciences, 22(11), 5675.

[14] Zhang, Y. , Yin, S. , Song, R. , Lai, X. , Shen, M. , & Wu, J. , et al. (2024). A novel mechanism of phb2-mediated mitophagy participating in the development of parkinson's disease. Neural Regeneration Research, 19(8), 1828-1834.