Review Article

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Mitophagy stimulation as a novel strategy for the treatment of mitochondrial diseases

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Mitophagy, the selective degradation of damaged or surplus mitochondria using core autophagy machinery, plays an essential role in maintaining cellular mitochondrial function. Impaired mitophagy is closely linked to various human diseases, including neurodegenerative diseases, cardiovascular diseases, cancers and kidney disease. Defective mitophagy induces the accumulation of damaged mitochondria and thereby results in a decline in cellular survival and tissue function. Accordingly, enhancement of mitophagy has been proposed as a novel strategy for the treatment of human diseases closely linked to mitochondrial dysfunction. Recent studies showing that the stimulation of mitophagy has a therapeutic effect on several disease models highlight the possibility of disease treatment using mitophagy. The development of mitophagy inducers with toxicity and the identification of molecular mechanisms will enable the clinical application of mitophagy-based treatments.

Key words: Mitophagy, Mitochondrial disease, Drug development.

Introduction

Mitochondrial dysfunction is a common hallmark of various human diseases, including neurodegenerative diseases, cardiovascular disease, and cancer [1]. Moreover, extensive studies have revealed that mitochondrial dysfunction plays a fundamental role in the development of many human diseases. In particular, an increasing number of previous studies have demonstrated that mitochondrial dysfunction is one of the primary causes of many neurodegenerative diseases [2]. Accordingly, many attempts have been made to improve mitochondrial dysfunction. In addition to relatively conventional attempts, such as stimulation of biogenesis and mitochondria-specific antioxidants, new strategies have recently been attempted. These include direct transplantation of healthy mitochondria and editing of mutated mitochondrial DNA. The stimulation of mitophagy is also considered a new strategy.

Among the various quality control methods, mitophagy is the most efficient way to remove damaged mitochondria [1]. Mitophagy promotion induces new mitochondrial biosynthesis as well as the removal of damaged mitochondria [3]. Recent studies showing the therapeutic effect of mitophagy stimulation in several disease models raise positive expectations for mitophagy-based treatment strategies for human diseases.

Recent extensive studies have demonstrated that there are multiple molecular pathways and regulators mediating cellular mitophagy in addition to the PINK1-Parkin pathway, the most well characterized mitophagy pathway. These include various mitochondria receptor-mediated pathways and the alternative mitophagy pathway [4]. As the molecular mechanisms of mi-

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tophagy have been discussed in other reviews [5-7], this review will focus on impaired mitophagy in human diseases and introduce recent studies showing the beneficial effect of mitophagy stimulation in disease models.

Mitophagy Defects in Human Diseases

Previous studies have shown that defects in mitophagy are mainly related to diseases that occur in tissues with high energy consumption and high mitochondrial dependence, such as nerves and muscles.

1. Neurodegenerative diseases

Given that neurons are highly dependent on mitochondria, improper removal of dysfunctional mitochondria could be harmful to neuronal function and survival [8]. Indeed, mounting recent studies indicate impaired mitophagy in major neurodegenerative diseases, such as Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) [9]. Because mitochondrial dysfunction is not only a common hallmark in neurodegenerative diseases but also plays a critical role in pathogenesis, impaired mitophagy could contribute to the development of neurodegenerative diseases by inducing mitochondrial dysfunction.

1) PD

Impaired mitophagy is closely linked to the development of PD. Defective mitophagy has been reported in PD tissues and various PD disease models [10-12]. In addition, mitochondrial dysfunction and a PD phenotype have been observed in a loss-of-function model of PD genes, such as PINK1, Parkin, and DJ-1 [12,13]. Interestingly, a recent study showing that dopaminergic neurons are not efficient against 6-hydroxydopamine-induced mitophagy provides an explanation for why dopaminergic neurons are highly sensitive to the development of mitochondrial dysfunction upon neurotoxic stresses [14].

2) AD

Previous studies have also shown a strong link between impaired mitophagy and AD, the most prevalent neurodegenerative disease. Fang et al. [15] recently revealed decreased mitophagy in the hippocampus of AD patients, AD-induced pluripotent stem cell-derived neurons and AD mouse models. In addition to impaired mitophagy in AD models, amyloid beta (Aβ) and pathological tau can induce mitochondrial dysfunction and mitophagy impairment [16,17]. These studies suggest that defective mitophagy acts as a driver of AD pathogenesis through a vicious cycle with AD pathological factors such as Aβ and tau [18].

3) ALS

ALS, also known as "Lou Gehrig's disease", is a progressive neurodegenerative disease accompanying motor neuron degeneration. Although the precise role of mitophagy in the pathogenesis of ALS is not yet completely understood, most ALS-linked genes, including superoxide dismutase 1 (SOD1), TAR DNA binding protein 43 (TDP-43), optineurin (OPTN), and TANK-binding kinase 1 (TBK1), play critical roles in mitophagy [19-21], suggesting that mitophagy impairment is closely linked to ALS development.

4) HD

HD is a neurodegenerative disease caused by a mutation within the huntingtin (HTT) gene. Our group previously revealed decreased mitophagy in the hippocampus of HD model mice [22]. Recent studies suggest that the mutant HTT protein could impair mitophagy and mitochondrial dysfunction [23,24].

2. Heart/cardiovascular diseases

The heart is a highly energy-consuming organ; therefore, cardiac function is mitochondria dependent. Mitochondrial dysfunction is closely associated with various heart diseases, including heart failure, cardiomyopathy, and ischemia–reperfusion injury, and mitophagy regulates cardiac health through mitochondrial quality control [25]. Studies showing cardiac dysfunction as well as the accumulation of damaged mitochondria in mice deficient in mitophagy regulators such as ATG5, ATG7, PINK1, and Parkin highlight the significance of mitophagy in the heart [26-30]. Recent intensive studies have revealed the essential role of mitophagy in cardiac function and the pathogenesis of various cardiovascular diseases [31-33]. Notably, Saito et al. [34] and Tong et al. [35], Tong et al. [36] recently revealed that alternative mitophagy plays a critical protective role in pathophysiological conditions such as myocardial ischemia and diabetic cardiomyopathy, highlighting the complexity of mitophagy regulatory networks for the maintenance of cardiac mitochondrial homeostasis.

3. Cancer

The link between cancer and mitophagy was first indicated by changes in the level of important regulators of mitophagy in tumors. Downregulation of mitophagy regulators such as Parkin, PINK1 and BNIP3 has been reported in various tumors [37-

42]. A decrease in these genes accompanying the accumulation of damaged mitochondria, increased reactive oxygen species (ROS) levels, genomic instability, and their activation inhibits cancer cell growth or tumor growth [43,44]. The protective role of mitophagy in tumorigenesis is further supported by defective mitophagy in cancer predisposition syndromes such as xeroderma pigmentosum (XP), ataxia telangiectasia (AT), and Fanconi anemia (FA) [45-49]. It should be noted that although a tumor suppressive role of mitophagy has been shown, protumorigenic results have also been reported. For example, the expression of BNIP3 and BNIP3L is induced and required for cancer cell survival by stimulating mitophagy, suggesting a prometastatic function of these genes [50,51]. In addition, mitophagy may play a role in nutrient recycling and promote cancer growth by influencing the host stromal microenvironment [52]. These results suggest that mitophagy plays a tumor-suppressive or tumor-promoting role depending on the tumor type and stage of progression, so further investigation using more precise preclinical cancer models is needed [53].

4. Other diseases

In addition to the diseases mentioned above, there are an increasing number of studies confirming impaired mitophagy in various other diseases. For example, mitophagy plays an important protective role in liver diseases, including alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD), drug-induced liver injury, and hepatic ischemia–reperfusion injury (IR) [54]. Impaired mitophagy has been observed in ALD and NAFLD *in vivo* and *in vitro* models [55-58]. While mitophagy was enhanced at the early stages in the IR model, impaired mitophagy at the late stage of reperfusion caused the accumulation of dysfunctional mitochondria and eventually cell death [59-61].

Recent studies have also shown that mitophagy plays a protective role in kidney diseases, including acute kidney injury (AKI) and chronic kidney disease (CKD) [62]. Impaired mitophagy is observed in models of diabetic kidney disease (DKD), the most common cause of end-stage kidney disease [63]. Recent studies on different renal cell types, tubular epithelial cells, podocytes, glomerular mesangial cells, and endothelial cells have shown diminished mitophagy levels upon high glucose treatment in *in vitro/in vivo* models or in DKD patient tissues [64-66]. These studies suggest that specific stimulation of mitophagy could be beneficial for protecting and restoring mitochondrial function in the kidney and treating kidney diseases.

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is a genetic mitochondrial disease caused by mutations in mitochondrial DNA. While only a few studies have been conducted on the role of mitophagy in primary mitochondrial diseases (PMDs), a recent study reported impaired mitophagy in MELAS patient-derived RPE cells [67].

Therapeutic Effect of Mitophagy Stimulation

Although pharmacological agents that selectively induce mitophagy are currently lacking, recent experimental studies have shown the therapeutic effect of synthetic and natural compounds in several disease models (Table 1).

Metformin, a general autophagy inducer, has been shown to induce Parkin-mediated mitophagy in an obese mouse model through the downregulation of cytosolic p53 [68]. Another well-known autophagy inducer, rapamycin, also showed a suppressive effect on neurological symptoms and metabolic defects in a mouse model of Leigh syndrome, a mitochondrial disease, although the mitophagy-dependent effect has not been verified [69]. Several natural compounds, such as resveratrol, spermidine, and urolithin A, also showed beneficial effects

Table 1. Therapeutic effect of mitophagy stimulation in human diseases

Disease	Mitophagy inducer	Therapeutic effect	Reference
Obesity/diabetes	Meformin	Induced mitophagy in ob/ob mouse model	Song et al. [68]
	Resveratrol	Improved mitochondrial function and metabolic phenotype	Lagouge et al. [70]
	Wolberries	Induced mitophagy and prevent hepatic steatosis	Lin et al. [75]
	Akebia saponin D	Inhibited hepatis steatosis through BNIP3 induced mitophagy	Gong et al. [74]
Leigh syndrome	Rapamycin	Inhibited neurological symptoms and metabolic defects	Johnson et al. [69]
Heart failure	Spermidine	Enhanced cardiac function and protect form salt-induced heart failure	Eisenberg et al. [71]
AD	NAD+, Urolithin A, Actinonin	Reversed memory impairment of *C. elegans* and APP/PS1 mouse model	Fang et al. [15]
	UMI-77	Reversed cognitive decline of APP/PS1 mouse model	Cen et al. [83]
	Kaempferol, Rhapntigenin	Inhibited memory loss in *C. elegans*, 3XTg AD animals	Xie et al. [84]

AD, Alzheimer's disease.

on disease models. Resveratrol supplementation improved mitochondrial function and metabolic phenotype in a high-fat diet mouse model through Sirt1 and PGC-1α [70]. Natural polyamine spermidine feeding in mice enhanced cardiac function and protected against heart failure through induction of autophagy and mitophagy [71]. Urolithin A extended the lifespan of *Caenorhabditis elegans* and improved age-associated muscle function in mice [72]. Several other natural compounds also showed mitophagy induction and preventive effects in a hepatic steatosis model [73-75]. However, the molecular mechanism for mitophagy induction and the requirement of mitophagy in their therapeutic effect need further investigation.

Supplementation with NAD+ or NAD+ intermediates also showed therapeutic effects in a mouse model of diabetes and AD [15,76]. In addition to NAD+, Fang et al. [15] showed that mitophagy induction using urolithin A and the antibiotic actinonin reversed memory impairment in *C. elegans* and APP/PS1 mouse models in their finely designed study.

For cancer treatment, combined treatment with the general autophagy inhibitor chloroquine with other anticancer drugs increased patient survival times [77,78], although the importance of the mitophagy inhibition effect in these studies was not clear. In contrast, some studies revealed that mitophagy stimulation could be beneficial. Meyer et al. [79] showed that mitophagy induction by treatment with the cotton seed-derived compound AT-101 resulted in the death of apoptosis-resistant cancer cells, highlighting the complexity of the role of mitophagy in cancer development and progression.

Despite the lack of proper mitophagy inducers, mitophagy stimulation is now considered a potent treatment strategy for many mitochondrial diseases because mitophagy can selectively eliminate damaged mitochondria. The severity of mitochondrial disease directly correlated with the percentage of mutant mitochondria versus wild-type mitochondria [80]. Thus, mitophagy stimulation would be a potential strategy to decrease the percentage of heteroplasmy [81]. Suen et al. [82] showed that overexpression of Parkin in MELAS cybrid cells led to increased mitophagy and lowered the mutation burden by approximately 30%.

Moreover, new attempts to develop mitophagy inducers have led to meaningful outcomes. Cen et al. [83] recently identified UMI-77 as a mitophagy inducer by screening FDA-approved drugs using the mt-Keima system, a fluorescent mitophagy reporter [22] and showed that UMI-77 reversed cognitive decline in the APP/PS1 mouse model. Xie et al. [84] also recently identified kaempferol and apigenin as novel mitophagy inducers using machine learning-based screening and demonstrated therapeutic effects on *C. elegans* and 3xTg AD mouse models.

Concluding remarks/prospective

Recent studies have shown that pharmacological induction of mitophagy has therapeutic effects in various disease models. However, clinically applicable mitophagy-based drugs have not yet been developed due to several limitations. First, the mitophagy inducers used in these studies are highly toxic and cannot be used in clinical treatment [6]. In addition, the ability of most previously reported compounds to induce mitophagy at the tissue level and their underlying molecular mechanisms have not been properly studied [7]. Therefore, the development of mitophagy-specific inducers with low toxicity and defined molecular mechanisms is essential for the clinical application of mitophagy-based therapy. Previous studies for mitophagy inducer screening used indirect mitophagy indicators such as GFP-LC3 puncta formation and Parkin translocation. Because recent studies revealed that there are various mitophagy pathways in mammalian cells, including LC3- and Parkin-independent mitophagy pathways [6], a more direct marker to monitor mitophagy activity should be used to identify suitable mitophagy inducers.

In addition, several issues should be considered for mitophagy-based treatment. Mitophagy stimulation over a certain threshold could induce harmful side effects, so it is important to identify a tolerable mitophagy induction range. In this respect, organ-specific induction of mitophagy would be desirable to avoid off-target side effects. Moreover, due to multiple mitophagy pathways in mammalian cells, it is essential to identify which pathway is the optimal target to induce therapeutic effects but minimize side effects. Because upstream regulators usually regulate multiple pathways simultaneously, the identification of specific downstream targets is critical.

Although there are still many problems to be solved, modulation of mitophagy is a promising strategy for the treatment of various human diseases as a fundamental way to improve mitochondrial dysfunction. Recent technological advances in mitophagy research and mitophagy inducer screening have provided a positive outlook on the development of clinically applicable mitophagy inducers in the near future.

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Authors' Contributions

Conception and design: JY. Acquisition of data: KML, JY. Analysis and interpretation of data: none. Drafting the article: KML, JY. Critical revision of the article: JH. Final approval of the version to be published: all authors.

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