

# *Research progress in the treatment of heart failure with Chinese medicine intervening mitochondrial autophagy*

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**Abstract:** Heart failure, as the final stage of the development of cardiovascular events, has a high incidence rate and a poor prognosis. How to improve its prognosis and prolong the survival of patients is the difficulty of current treatment. Mitochondrial autophagy, as a process of selective elimination of dysfunctional mitochondria, is particularly important for maintaining energy metabolism homeostasis. Many studies have shown that the occurrence and development of heart failure are closely related to the degree of mitochondrial autophagy, and appropriate mitochondrial autophagy is conducive to improving the function of myocardial cells. This article summarized the related mechanism of mitochondrial autophagy and the current research progress in the treatment of heart failure by intervention of mitochondrial autophagy with monomer or compound Chinese medicine, in order to provide more accurate and targeted guidance for the treatment of heart failure by Chinese medicine.

## 1. Introduction

Heart failure, as a group of terminal clinical syndromes caused by various acute and chronic cardiovascular diseases, is characterized by high incidence rate and high mortality. Although considerable efforts have been made in prevention and treatment, which can effectively control the clinical symptoms at all stages, there is still a lack of effective treatment methods, which still needs further exploration. In recent years, with the further study of the internal molecular mechanism of heart failure, it has been found that energy metabolism disorders are closely related to cardiovascular diseases, in which mitochondrial dysfunction plays an important role. It is generally believed that mitochondria are "sentinel" organelles, which can detect cell damage and integrate multiple stress signals, and maintain the stability of the internal environment and quality of mitochondria, which plays a crucial role in myocardial energy metabolism<sup>[1]</sup>. During heart failure, insufficient or excessive degradation of damaged mitochondria caused by various reasons can affect the function of myocardial cells, and this phenomenon is called insufficient or excessive mitochondrial autophagy. Proper drug activation or inhibition of mitochondrial autophagy can play a role in protecting myocardium, which is expected to become one of the potential therapeutic targets for treating heart failure in the future. As an indispensable part of traditional Chinese

medicine, traditional Chinese medicine has the characteristics of multi target and integrated expression. It has unique insights in the treatment of heart failure, and has significant clinical effects. With the continuous improvement of network pharmacology and molecular docking technology, clarifying the mechanism of internal molecular functions is conducive to the greater value of traditional Chinese medicine. At present, many studies have confirmed that some monomers or extracts of traditional Chinese medicine and traditional Chinese medicine compound can improve the function of myocardial cells in heart failure by interfering with mitochondrial autophagy, which has broad prospects for development. Now, it is described as follows, in order to better guide clinical practice.

## 2. Overview of mitochondrial autophagy

Mitochondria, as the main site of energy conversion and biological oxidation in eukaryotic cells, participate in ATP generation, involving calcium homeostasis, oxidative stress and apoptosis<sup>[2]</sup>. The oxidative phosphorylation of mitochondria is accompanied by the generation of some active substances (including  $\cdot O_2^-$ ,  $H_2O_2$ ,  $HO_2 \cdot$ ,  $\cdot OH$ ), which can be metabolized and degraded under normal metabolic conditions. However, when cells suffer from hypoxia, the accumulation of a large amount of active oxygen will damage mitochondria, thus affecting the energy supply of cells. In this case, mitochondrial autophagy plays an important role in protecting myocardial cells. Mitochondrial autophagy refers to the process in which mitochondria selectively degrade damaged mitochondria, maintain the balance of the number of mitochondria in cells by selectively removing dysfunctional mitochondria, and ensure the integrity of mitochondrial structure and function. Mitochondrial phagocytosis is crucial to ensure energy supply<sup>[3]</sup>. The occurrence of mitochondrial autophagy is affected by many factors, including cell energy and oxygen metabolism disorder, mitochondrial membrane potential decrease, intracellular reactive oxygen species increase,  $Ca^{2+}$  overload, mitochondrial DNA damage and mitochondrial protein quality control system disorder.

The regulation of mitochondrial autophagy can be broadly divided into two types: ubiquitin dependent and non ubiquitin dependent. Ubiquitin dependent mitochondrial autophagy includes PINK1 (PTEN induced kinase 1, PINK1)/E3 ubiquitin ligase parkin dependent and non PINK1/Parkin dependent. In normal mitochondria, PINK1 is transported to the inner membrane of mitochondria and is sheared and degraded by the ubiquitin protease system. When mitochondria are damaged, PINK1 transport is blocked, accumulates in the outer membrane of mitochondria, and is activated by self phosphorylation. The activated PINK1 recruits parkin to the surface of mitochondria and phosphorylates it, The phosphorylated parkin polymerizes the substrate proteins on the mitochondrial membrane [such as VDAC1 (voltage dependent anion channel-1), MFN-1 (mitofusin 1), MFN-2 (mitofusin 2) and Miro (mitochondrial Rho GTPase)] into ubiquitin, and the polyubiquitinated substrate is LC3 (microtubule associated protein 1 light chain 3) The aptamer protein recognizes, combines with LC3 to form autophagosome, and then combines with lysosome to form autophagy lysosome, and finally degrades the damaged mitochondria. The non ubiquitin dependent mitochondrial autophagy means that it does not need PINK1/Parkin to mediate, but directly combines the mitochondrial autophagy receptor with LC3 to mediate the entry of damaged mitochondria into autophagy. At present, mitochondrial autophagy receptors found include Nip3 like protein X (NIX), BCL2/adenovirus E1B19kD interacting protein 3 (BNIP3), FUN14 domain containing protein 1 (FUNDC1), BCL2 like protein 13 (BCL2L13), FK506 binding protein 8 (FK506 binding protein 8, FKBP8) Inhibin 2 (PHB2) and cardiolipin. NIX, BNIP3, FUNDC1, BCL2L13 and FKBP8 are located in the outer membrane of mitochondria, while PHB2 and cardiolipin are located in the inner membrane of mitochondria. Among them, the autophagic receptors related to heart failure are FUNDC1, BNIP3 and Nix/BNIP3L<sup>[4, 5, 6]</sup>. At present, studies

have found that mitochondrial autophagy is involved in the development of multiple organ diseases such as heart and brain, and it is expected to become a potential therapeutic target for the treatment and prognosis of multiple diseases by regulating mitochondrial autophagy.

### **3. Mitochondrial autophagy and heart failure**

#### **3.1. The role of mitochondrial autophagy in heart failure**

Mitochondria account for about 30-40% of the volume of myocardial cells, and their status is closely related to the function of myocardial cells<sup>[7]</sup>. Mitochondrial dysfunction is an important pathophysiological feature in the pathogenesis of heart failure. Under normal circumstances, mitochondrial autophagy can timely remove damaged and dysfunctional mitochondria, maintain mitochondrial quality, avoid the production of a large amount of reactive oxygen species, prevent the initiation of apoptosis, and ultimately reduce oxidative damage in heart failure. Kassiotis et al.<sup>[8,9]</sup> found for the first time from the cardiac biopsy of patients with heart failure that the expression of autophagy specific genes beclin-1 and LC3II increased. When the left ventricular assist device was used to relieve the cardiac load, they found that both decreased. This finding suggests that mitochondrial autophagy may be related to heart failure; Wang B et al.<sup>[10]</sup> found that the mitochondrial autophagy of myocardial cells in patients with heart failure was significantly reduced, and the production of reactive oxygen species and apoptosis of myocardial cells could be reduced by enhancing the level of mitochondrial autophagy; Gvmani et al.<sup>[11]</sup> In the model of heart failure induced by ascending aorta ligation, sustained overload stress can lead to excessive mitochondrial autophagy and cause abnormal apoptosis. After treatment with mitochondrial inhibitor (Mdivi), cardiac function is improved. The beneficial effect of mitochondrial autophagy on cells does not run through the whole process of disease; Insufficient or excessive autophagy will lead to autophagy stress, induce cell structure damage, and instead cause or aggravate heart failure. Therefore, proper induction or inhibition of mitochondrial autophagy is essential for the treatment of heart failure.

#### **3.2. Mitochondrial autophagy signal pathway related to heart failure**

##### **3.2.1. PINK1/parkin ubiquitination pathway**

PINK1/parkin mediated mitochondrial autophagy is the most common mitochondrial autophagy in mammalian cells, and also an important cause of mitochondrial dysfunction and heart failure. Guan et al.<sup>[12]</sup> observed cardiac dysfunction, severe cardiac remodeling, elevated oxidative stress level, decreased ATP level and PINK1/Parkin mediated mitotic inhibition in mice with chronic heart failure induced by myocardial ischemia. Abudureyimu M and Mu J et al.<sup>[13,14]</sup> found in the heart failure induced by pressure overload that, in addition to the down-regulation of PINK1 and Parkin expression, the Parkin mediated mitochondrial ubiquitination was significantly inhibited by gene knockout of PINK1. The loss of PINK1 inhibited mitosis, led to the accumulation of damaged mitochondria, and aggravated cardiomyopathy. In addition, Qiu et al.<sup>[15]</sup> found in the rat model of heart failure induced by myocardial infarction that the cardiac function of late heart failure was significantly reduced, the structure of myocardial mitochondria was damaged, and the levels of proteins related to mitochondrial autophagy, such as pink1, parkin, p62 and LC3, were significantly increased, and there was excessive mitochondrial autophagy. The experimental results of Wang et al.<sup>[16,17]</sup> show that AMPK $\alpha$ 2 is an important regulator of PINK1/Parkin mediated mitosis in the heart, AMPK $\alpha$ 2 Defects lead to decreased phagocytosis and impaired mitochondrial function of the heart, and accelerate the progress of TAC induced heart failure AMPK $\alpha$ 2 Enhancement of PINK1/parkin

mediated mitochondrial autophagy can slow down the progression of heart failure. In conclusion, PINK1/Parkin dependent mitochondrial autophagy runs through the whole process of heart failure. The occurrence of heart failure is mostly related to the inhibition of PINK1/Parkin. Some studies show that late heart failure is mainly related to excessive mitochondrial clearance caused by excessive activation of this pathway. Proper regulation of PINK1/Parkin pathway is conducive to reducing myocardial damage and inhibiting ventricular remodeling.

### 3.2.2. FUNDC1 channel

FUNDC1 is a mitochondrial autophagic receptor that can directly bind to LC3 and mediate the entry of damaged mitochondria into autophagy. In the process of differentiation, the disappearance of BNIP3L and FUNDC1 mediated mitosis led to the continuous division of mitochondria and the formation of ring damaged mitochondria. It also leads to increased susceptibility to cell death, and the infarcted heart cannot survive. Huang Haijun<sup>[18]</sup> found that in the mouse model of heart failure induced by myocardial infarction, the mRNA expression of FUNDC1 was decreased, and the mRNA expression of BNIP3L was increased. Li Yaling<sup>[19]</sup> found that homocysteine can induce FUNDC1 mediated mitochondrial autophagy in cardiomyocytes. As a newly synthesized mitochondrial target H<sub>2</sub>S donor, AP39 can reverse its down-regulation and improve myocardial remodeling. Mitochondrial dysfunction is the main cause of heart failure after acute myocardial infarction (AMI). Hypoxia adaptation (HA) can effectively reduce the area of AMI caused by ischemia and/or reperfusion and delay heart failure. Hypoxia adaptation increased the expression of Fundc1 protein and its related mitotic protein LC3 in myocardial tissue after infarction. The knockout of FUNDC1 weakened the protective effect of HA on mitochondria of myocardial cells and increased apoptosis of myocardial cells. In a word, the protective effect of HA on HF after AMI is realized by regulating Fundc1 mediated mitosis in myocardial tissue<sup>[20]</sup>. In addition,  $\alpha$ -Lipoic acid ( $\alpha$ -LA) is a famous antioxidant  $\alpha$ -LA-ALDH2 mediates FUNDC1 dependent mitochondrial autophagy and plays a positive role in protecting the heart from the adverse effects of chronic pressure overload<sup>[21]</sup>. In conclusion, FUNDC1 mediated mitosis may be a promising strategy for the treatment of cardiovascular diseases, including heart failure.

### 3.2.3. Other access roads

The direct target forkhead box protein subfamily O3 (FOXO3a) is directly involved in the regulation of autophagy, and has a positive regulatory effect on autophagy. Overexpression of FOXO3a can activate antioxidant genes to alleviate the outbreak of ROS, and can act on the downstream target FUNDC1 to promote the occurrence of autophagy<sup>[22]</sup>. In addition, Omentin1 is a new type of fat factor, which can improve myocardial ischemia induced heart failure and myocardial injury by up regulating SIRT3/FOXO3a signal to activate mitosis<sup>[23]</sup>. In addition, autophagy can be induced by activating AMPK/mammalian rapamycin target protein (mTOR) pathway<sup>[24,25]</sup>. As a key molecule to inhibit autophagy, mTOR produces a large amount of reactive oxygen species in myocardial cells under oxidative stress. The significant decrease of ATP level activates AMPK, thereby inhibiting the activity of mTORC1 to induce autophagy<sup>[26]</sup>.

## 4. TCM treatment

### 4.1. Single traditional Chinese medicine and its extract

Icariin can inhibit mitochondrial autophagy through PINK1/parkin pathway, that is, down regulate PINK1, parkin and LC3II/LC3I, and increase p62 and ATP. Icariin can significantly improve the cardiac function and myocardial energy metabolism of rats with heart failure after

myocardial infarction. In addition, icariin can inhibit myocardial oxidative stress, lower the lipid oxidation rate of main autophagy promoting markers Beclin-1 and LC3, and restore the physiological activation level of protective autophagy process, Thus, it has beneficial cardiac protective effect in reducing cardiac toxicity<sup>[27,28]</sup>. Astragaloside A can also improve mitochondrial function and alleviate oxidative stress by inhibiting PINK1/parkin mediated mitochondrial autophagy; In addition, astragalosides can also interfere with the expression of BNIP3LNIX and FUNDC1, increase mitochondrial membrane potential, regulate the positive balance of mitochondrial fission and fusion, and inhibit the occurrence of myocardial remodeling caused by adverse factors<sup>[18,29]</sup>. Luteolin<sup>[30]</sup> can improve LPS induced damage to H9c2 cells, and its mechanism may be related to inhibition of receptor mediated FUNDC1/BNIP3/BNIP3L mitochondrial autophagy pathway.

Proper enhancement of mitochondrial autophagy also has a protective effect on myocardium. Resveratrol (RES)<sup>[31]</sup> preconditioning can increase the expression of DJ-1 protein in hypoxic cardiomyocytes, promote DJ-1 binding and stabilize PINK1 protein, and then activate mitochondrial protective autophagy through PINK1/Parkin pathway, alleviate mitochondrial dysfunction, and fight against hypoxic injury of cardiomyocytes. Berberine<sup>[13]</sup> plays a key role in reducing myocardial hypertrophy and protecting cardiac function in stress induced heart failure. Its potential mechanism may be realized through PINK1/Parkin/ubiquitination pathway to activate mitochondrial autophagy. Baicalein<sup>[29]</sup> can directly act on FOXO3a, activate FUNDC1, promote autophagy and alleviate isoproterenol induced cardiac hypertrophy.

## 4.2. Compound Chinese medicine

Cao Chenghao et al.<sup>[32]</sup> found that Wenyang Yiqi Formula can improve the myocardial function of rats with heart failure after myocardial infarction, and its internal mechanism may be related to the inhibition of AMPK mediated mitochondrial autophagy. On the contrary, Bie Mingke et al.<sup>[33]</sup> found in the study of heart failure mediated by mitochondrial autophagy that Zhenwu decoction may play a role in treating CHF by up regulating the expression level of extracellular signal regulated kinase 5 (ERK5) in cardiac myocytes and down regulating the expression level of mitochondrial autophagy related key proteins (PINK1, Parkin, Prohibitin2, LC3 - II/LC3 - I). Wang Qiang et al.<sup>[34]</sup> found in vitro that Yiqi Wenyang Huoxue Lishui Recipe can reduce the ROS level in H9C2 myocardial cells induced by pentobarbital sodium, reduce the number of autophagosomes, alleviate mitochondrial swelling, and inhibit mitochondrial autophagy, which may be one of the important mechanisms of this recipe in treating heart failure. Li Chao et al.<sup>[35]</sup> found that the expression of ROS, malondialdehyde (MDA) and mitochondrial autophagy related proteins (LC3I/LC3II, p62) in the myocardial tissue of rats with chronic heart failure decreased, but increased after the treatment of Xiefei Lishui Mixture, which confirmed that Xiefei Lishui Mixture may play a myocardial protective role by inhibiting oxidative stress and mitochondrial autophagy. Xinfukang Oral Liquid can inhibit PINK1/Parkin mediated mitochondrial autophagy over activation in the myocardium of rats with advanced heart failure, promote myocardial energy metabolism, and improve cardiac function<sup>[15]</sup>. Qiangxin Fang<sup>[36]</sup> may inhibit p38MAPK activation and promote PPAR-  $\gamma$  The protein expression can enhance the energy metabolism of myocardial mitochondria, reduce the autophagy of myocardial cells, and thus play the role of anti chronic heart failure.

The degree of mitochondrial autophagy is closely related to heart failure. When autophagy is insufficient, damaged mitochondria cannot be cleared in time, but myocardial cell damage is aggravated. Therefore, appropriately enhancing mitochondrial autophagy is conducive to identifying and clearing redundant or damaged mitochondria, and is conducive to reducing myocardial damage. Cao Yaxuan et al.<sup>[37]</sup> found that Shenfu Yixin Granule can reduce ROS in

myocardial tissue of rats with heart failure, increase the expression level of PINK1, Parkin, P62 proteins, reduce the level of oxidative stress, alleviate heart failure after acute myocardial infarction, which may be related to activating Parkin dependent pathway, enhancing mitochondrial autophagy, and reducing mitochondrial dysfunction. Zhou Junyang<sup>[38]</sup> found that Qiliqiangxin can enhance mitochondrial autophagy through Pink1/Parkin pathway, reduce myocardial cell apoptosis and fibrosis, reduce mitochondrial damage, and improve ventricular remodeling after myocardial infarction. Similarly, Guan et al.<sup>[13]</sup> found that Nunxinkang could increase PINK1/Parkin mediated mitosis in myocardial cells in the model of heart failure induced by myocardial infarction. Danqi Pill can improve FUNDC1 mediated mitosis through synergetic regulation of ULK1 and PGAM5, thus reversing energy metabolism, thus protecting heart failure<sup>[39]</sup>. Long K et al.<sup>[40]</sup> found that the Yangxinxue Granule drug serum can clear the active oxygen in the doxorubicin (DOX) induced H9C2 myocardial cells, maintain the mitochondrial membrane potential, and promote the mitochondrial function, including ATP synthesis, mitochondrial DNA quality, and transcriptional activity. In addition, it also inhibits DOX induced mitochondrial autophagy or mitosis by clearing the active oxygen, It is speculated that Yangxinxue Granule may be related to the regulation of mitochondria in the treatment of oxidative stress related heart failure. Peng LQ et al.<sup>[41]</sup> found that Wenyang Zhenshuai Granules can down regulate the expression of key mitochondrial autophagic proteins in DOX injured cells, so as to regulate ventricular remodeling and cardiomyocyte apoptosis to play a role in myocardial protection.

### 4.3. Other treatments

The study found that<sup>[42]</sup>, moxibustion (MOX) has a protective effect on DOX induced chronic heart failure in rats, promotes mitochondrial fusion, and inhibits mitochondrial autophagy, such as the decrease of the number of autophagosomes, the decrease of LC3II/LC3I ratio, and the increase of p62 expression. The potential mechanism may be related to the inhibition of FUNDC1 signal pathway.

## 5. Conclusion

With the increase of incidence rate of metabolic diseases such as hypertension and diabetes, various cardiovascular events are also on the rise. As the end stage of various cardiovascular diseases, heart failure is progressing, which seriously affects human life and health. In recent years, autophagy, as a new emerging discipline, has played a key role in the occurrence and development of heart failure through the research on autophagy and heart failure. Under normal conditions, autophagy exists in the heart muscle of the human body. Under the condition of myocardial hypertrophy and ischemia, autophagy protects myocardial cells by increasing the number of itself and clearing damaged mitochondria. However, when autophagy is excessive, it accelerates cell death. Traditional Chinese medicine believes that mitochondrial autophagy is the micro basis of the balance between yin and yang, while "insufficient autophagy" and "excessive autophagy" are the micro manifestations of the imbalance between yin and yang. In terms of treatment, we can start with the transformation of yin and yang and the restriction of yin and yang opposites to harmonize yin and yang. Moreover, many studies on heart failure and autophagy by traditional Chinese medicine and its compounds have also confirmed that autophagy participates in the progress of heart failure, can inhibit oxidative stress, reduce myocardial damage, and has a significant protective effect on myocardial cells. However, how to properly control the degree of mitochondrial autophagy is a hot and difficult topic in current research. In conclusion, the clarification of the role of mitochondrial autophagy in the occurrence of heart failure will help better understand the pathogenesis of heart failure, and also provide more potential targets for the treatment of heart

failure with traditional Chinese medicine, which has broad application prospects.

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