

Review Article

Research progress of autophagy in heart failure

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Abstract: Heart failure poses a significant threat to global public health within the realm of cardiovascular diseases. Its pathological progression involves various alterations in cardiomyocytes, among which autophagy, a crucial intracellular degradation mechanism, plays a pivotal role. Autophagy facilitates the breakdown of damaged organelles and proteins, thereby maintaining cellular homeostasis. In the context of heart failure, autophagy coexists with apoptosis and necrosis, influencing myocardial hypertrophy and ventricular remodeling. However, its impact on heart failure manifests a dual nature: moderate autophagy aids in cardiac repair, whereas excessive autophagy may exacerbate ventricular remodeling and cell demise. This review delves into the fundamental biology of autophagy, elucidating its involvement in the pathological cascade of heart failure and its correlation with cardiac hypertrophy and ventricular remodeling. Furthermore, an analysis of the interplay between autophagy regulatory factors and heart failure sheds light on the potential therapeutic implications of autophagy in the prevention and management of heart failure. This exploration provides a theoretical foundation for novel treatment strategies in combating heart failure.

Keywords: Heart failure, autophagy, cardiomyocyte

Introduction

Heart failure (HF) is a prevalent cardiovascular disease characterized by the heart's inability to adequately maintain blood circulation to meet the body's metabolic demands or sustain it under increased workload [1]. It represents a significant public health challenge globally, with persistently high mortality rates despite advancements in treatment, necessitating the exploration of novel therapeutic avenues. The pathogenesis of HF is multifaceted, involving various cellular and molecular mechanisms such as apoptosis, necrosis, and autophagy in cardiomyocytes, with a particular focus on autophagy in current research [2].

Autophagy constitutes a classical intracellular degradation process that facilitates the breakdown and recycling of cellular components by

transporting them to lysosomes. Under normal physiological conditions, autophagy plays a role in regulating energy balance and facilitating the renewal of intracellular components. However, in pathological states, dysregulated autophagy, either excessive or insufficient, can lead to cellular dysfunction [3]. Optimal autophagic activity serves to eliminate damaged organelles, mitigate free radical generation, and uphold intracellular stability, thereby promoting cardiac repair following injury [4]. Conversely, excessive autophagy may precipitate cardiomyocyte death through autophagy-related pathways, exacerbating the progression of HF [5]. This review aims to delineate the research advancements regarding the role of autophagy in HF, elucidating its association with the condition and exploring the interplay between autophagy regulatory factors and HF.

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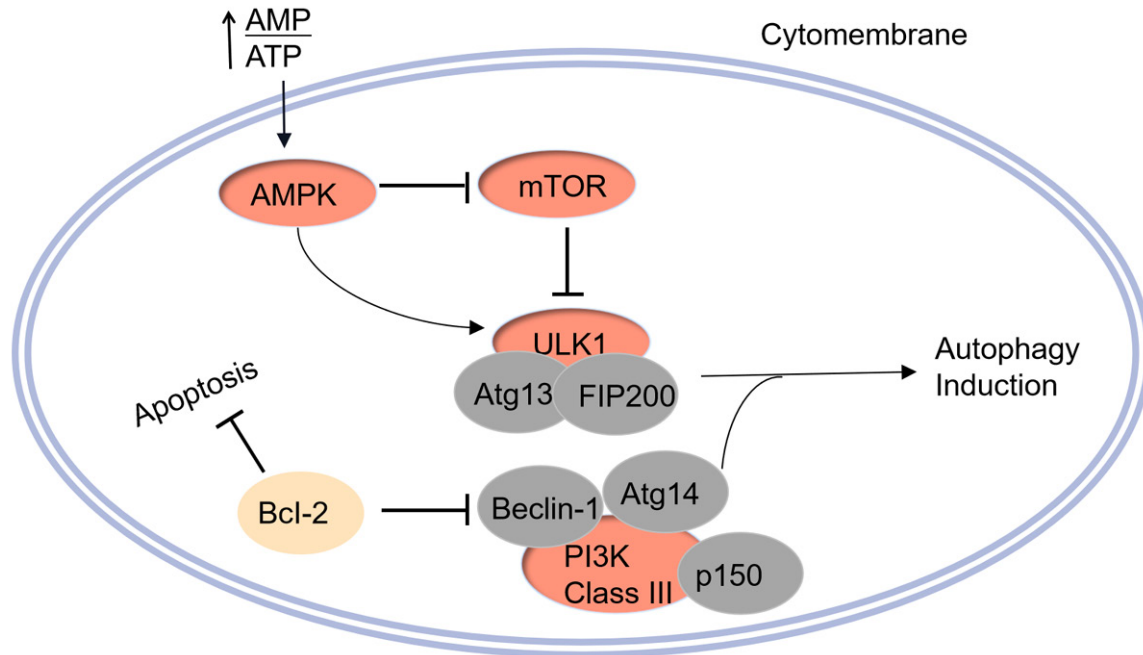


Figure 1. Induction stage of autophagy. During the induction phase of macroautophagy, starvation triggers the activation of AMPK and inactivation of mTOR. Activated AMPK then catalyzes the phosphorylation of the ULK1 complex, which leads to the promotion of autophagy. Integral to this process is the class III PI3K complex, composed of essential components such as hVps34, Beclin-1 (the mammalian homologue of yeast Atg6), p150 (the mammalian homologue of yeast Vps15), and ATG14-like proteins (Atg14L or Barkor). These proteins are all required for the successful induction of autophagy.

The basic biology of autophagy

Autophagy is a ubiquitous molecular process in eukaryotes aimed at degrading organelles and other intracellular components via the autophagy pathway to maintain cellular homeostasis and function. This mechanism becomes particularly crucial during periods of nutritional deficiencies, metabolic disorders, or other stressful conditions. Autophagy manifests in three primary forms: macro-autophagy, micro-autophagy, and chaperon-mediated autophagy, distinguished by the substrates and pathways they target [6]. In the context of HF and other serious diseases, autophagy not only sustains essential nutrient supply for cell survival but also facilitates the clearance of damaged organelles and proteins, thereby alleviating cellular stress [7]. Moderate autophagic activation serves as a protective strategy under certain conditions. However, dysregulated autophagy, whether excessive or insufficient, may result in protein and organelle accumulation, exacerbating or triggering disease states.

The molecular mechanism of autophagy revolves around a series of proteins known as

autophagy-associated genes (Atgs). Over 30 such genes have been identified in yeast cells, with many homologues present in mammals [8]. Researchers have elucidated the functions of these proteins and their interactions to unravel the intricacies of the autophagy process, which can be delineated into four sequential stages: induction, autophagosome formation, autophagosome-lysosome fusion, degradation, and recovery [9].

During the induction phase (see **Figure 1**), crucial regulatory protein complexes come into play, including the Atg1 kinase complex, the rapamycin target protein (mTOR), and the phosphatidylinositol 3 kinase complex. mTOR, functioning as a sensor for amino acids, ATP, and hormones, acts as a negative regulator of autophagy activity, with ongoing studies investigating its inhibitory effects and underlying mechanisms. In instances of cellular energy deficiency, activation of adenylate-activated protein kinase (AMPK) inhibits mTOR, thereby promoting autophagy initiation [10].

The assembly and maturation of autophagosomes, which constitute the second critical

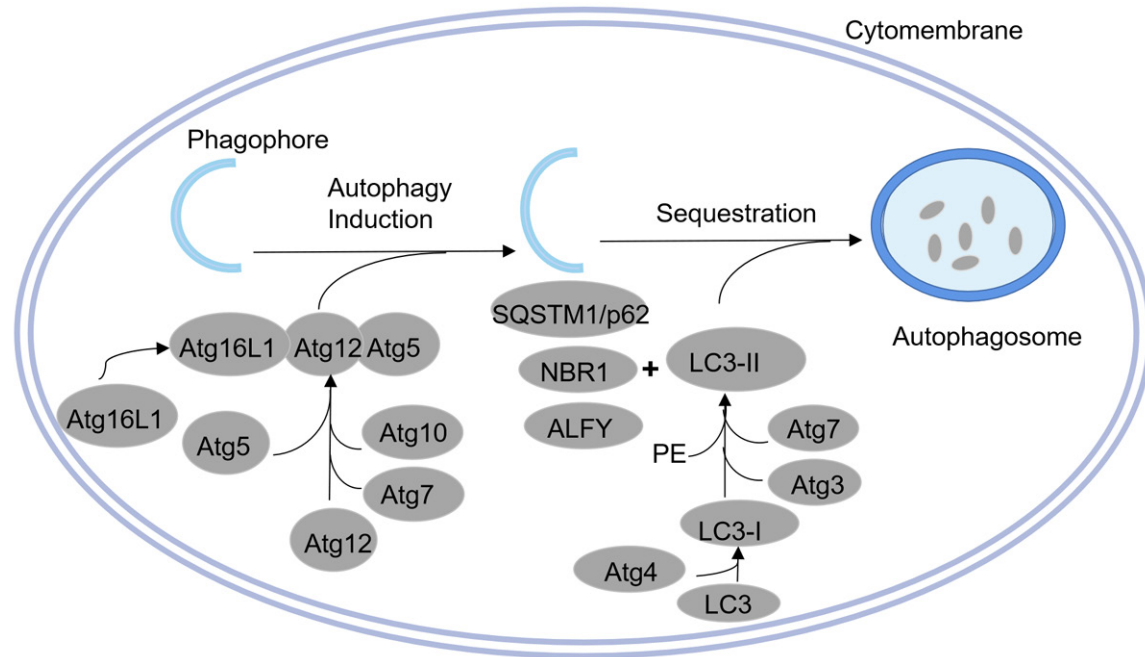


Figure 2. Assembly stages of autophagosomes. In the assembly phase of macroautophagy, upstream signaling induces the formation of the ATG12-ATG5 complex. Specifically, ATG12 and ATG5 are catalyzed by ATG7 and ATG10, respectively, to form this complex. The ATG12-ATG5 complex subsequently associates with ATG16L1 to participate in the assembly of autophagy vesicles. Concurrently, the C-terminal of LC3/Atg8 is proteolytically cleaved by Atg4 to generate cytoplasmic LC3-I. This LC3-I then covalently attaches to phosphatidylethanolamine via the action of ATG7 and ATG3, forming membrane-bound LC3-II. LC3-II subsequently binds to the autophagosome membrane, facilitating its assembly and maturation.

stage in autophagy (**Figure 2**), rely on the coordinated action of two ubiquitin-like protein systems: the LC3-phosphatidylethanolamine complex (LC3-PE) and Atg12-Atg5. These systems facilitate the gradual elongation of the membrane structure (termed the phagophore) and the sequestration of cytoplasmic components, ultimately forming the characteristic double-membrane structure of the autophagosome. LC3, a protein associated with microtubules, undergoes post-translational modifications to convert into LC3-II and covalently binds to phosphatidylethanolamine (PE), a pivotal step in autophagy maturation [11]. Moreover, Atg5 conjugates with Atg12 and interacts with the Atg16 complex, facilitating autophagosome membrane expansion and completion of autophagosome maturation. Subsequent to autophagosome formation, the Atg12-Atg5-Atg16 complex dissociates from the autophagosome membrane, while LC3-II remains, rendering LC3 a vital biological marker for monitoring autophagosome formation. Through techniques like immunofluorescence, researchers can

visually discern and quantify autophagosome numbers and activity within cells [12].

In the final two stages of autophagy (**Figure 3**), the autophagosome fuses with the lysosome to form the autophagolysosome, initiating the degradation process wherein intracellular materials are broken down into small, recyclable molecules such as amino acids, facilitating cellular recycling. This degradation process is pivotal to autophagic recycling, ensuring efficient reuse of cellular components.

Mechanism of HF

The mechanism underlying HF encompasses multiple facets, and as modern medicine advances, our understanding of this disease process continues to deepen. Initially, HF was simplistically viewed as a hemodynamic abnormality stemming from the heart's pump dysfunction. However, research in the 1980s shifted focus towards structural and functional remodeling of the heart, alongside alterations

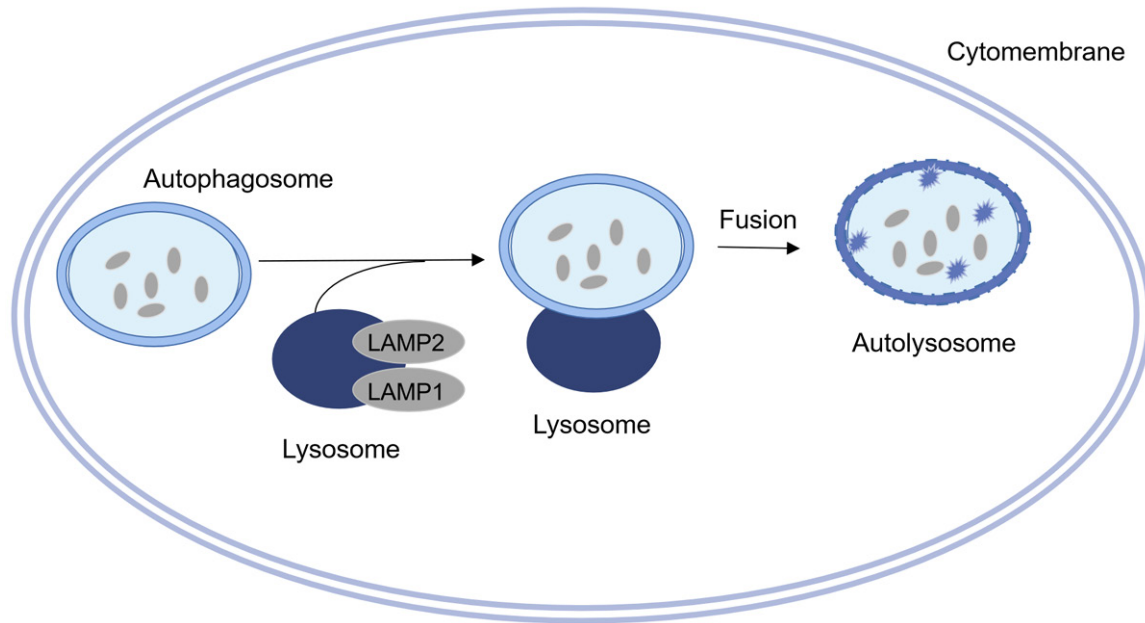


Figure 3. Fusion stage of autophagosome. In the fusion stage of macroautophagy, the autophagosome and lysosome fuse via the interaction between STX17 on the autophagosome membrane and VAMP8 on the lysosome membrane. This fusion process ultimately results in the formation of the autophagolysosome. Following fusion, the contents of the autophagolysosome are degraded, contributing to cellular homeostasis and self-renewal.

in the neuroendocrine system, as fundamental to HF development [13].

In the progression of HF, a cascade of intricate molecular and cellular mechanisms precipitates changes in myocardial structure, function, and phenotype [14]. Pathological cardiomyocyte hypertrophy ensues, leading to diminished contractility and reduced cardiomyocyte lifespan. Cardiomyocyte apoptosis serves as a crucial juncture, marking the transition from compensatory to decompensated HF, as it diminishes cardiomyocyte numbers, further compromising the heart's pumping capacity. Excessive fibrosis or heightened degradation of the myocardial extracellular matrix can impair the heart's elasticity and contractile function. Concurrently, heightened activity in the renin-angiotensin-aldosterone system and sympathetic nervous system occurs in HF, alongside activation of various endogenous neuroendocrine pathways and cytokines. Prolonged and chronic activation of the renin-angiotensin-aldosterone system fosters myocardial remodeling, exacerbating myocardial injury and cardiac function decline, while further stimulating neuroendocrine pathways and cytokine release, thus perpetuating a detrimental cycle that exacerbates HF progression [15].

Autophagy has also been observed in cardiomyocytes associated with HF, encompassing conditions such as dilated cardiomyopathy, valvular heart disease, and ischemic heart disease. Cytoplasmic ubiquitin protein aggregates have been identified in 0.3% of cardiomyocytes in end-stage HF patients with ischemic heart disease and dilated cardiomyopathy [16]. Additionally, autophagy, apoptosis, and necrosis can be detected in cardiomyocytes affected by dilated cardiomyopathy.

Autophagy and HF

Autophagy in cardiomyocytes: moderate autophagy delays HF progression

Cardiomyocyte hypertrophy, myocardial fibrosis, and cardiomyocyte apoptosis constitute the primary pathological features of myocardial remodeling, intricately involved in the onset and progression of HF [17, 18]. Among these, cardiomyocyte hypertrophy marks the initial phase of HF and, if left unchecked, accelerates cardiac function deterioration. Hypertrophic cardiomyocytes accumulate misfolded proteins and damaged organelles [19], which autophagy can effectively clear to mitigate their detrimental effects on cardiomyocytes. Myocardial fibro-

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Table 1. Studies on autophagy of cardiomyocytes

Research type	Method	Research object	Key finding
Preclinical study	In vitro cell assay	Rat myoblast	Inhibition of the autophagy fusion process, resulting in increased oxidative stress and cardiomyocyte death [25]
Preclinical study	In vitro cell assay	AC16 cell	Promoting apoptosis and autophagy of cardiomyocytes can slow the progression of heart failure [26]
Preclinical study	In vitro animal experiment	HF mouse	Enhanced autophagy of cardiomyocytes can reduce apoptosis and oxidative stress and improve heart failure [24]

Table 2. Studies on mitochondrial autophagy

Research type	Method	Research object	Key finding
Preclinical study	In vivo animal experiment	HF mouse	Activation of mitochondrial autophagy can improve heart failure and myocardial injury induced by myocardial infarction [31]
Preclinical study	In vitro experiment	Mouse	Yiqi Huoxue (YQHx) formula alleviates myocardial ischemia/reperfusion injury by targeting mitochondrial autophagy [32]
Preclinical study	In vitro cell assay	Peripheral Blood mononuclear cells	Mitochondrial autophagy can reduce the generation of mitochondrial oxidative stress in PBMC of chronic HF patients [33]

PBMC, Peripheral Blood mononuclear cells; HF, Heart Failure.

sis, impacting myocardial systolic and diastolic function, exhibits improvement with rapamycin administration, an autophagy agonist, in HF rat models. Conversely, chloroquine-induced autophagy inhibition exacerbates myocardial fibrosis and cardiac function decline in rats [20]. Additionally, activation of AMPK/ULK1-mediated autophagy has shown promise in reducing collagen deposition and alleviating myocardial fibrosis [21]. In the early stages of HF, oxidative stress and inflammation induce cardiomyocyte apoptosis [22, 23], subsequently triggering autophagy. Moderate autophagy clears reactive oxygen species (ROS) and inflammatory factors, thus reducing cardiomyocyte apoptosis and forestalling cardiac function deterioration. These findings underscore the role of cardiomyocyte-autophagy activation in eliminating deleterious factors and retarding HF progression. However, in advanced HF stages, autophagy inhibition may occur, likely attributable to cellular metabolic exhaustion, impairing autophagy pathway function. Insufficient autophagy levels hinder the clearance of harmful factors, hastening ventricular remodeling and worsening cardiac function (**Table 1**).

Excessive autophagy accelerates cardiac deterioration

Contrary to the notion that autophagy universally safeguards a failing heart, in the terminal

stages of HF, the myocardium enters a decompensated state. This condition fosters the accumulation of detrimental factors such as misfolded proteins, damaged organelles, and ROS within cardiomyocytes, triggering an excessive autophagic response. However, this overactivation of autophagy not only eliminates harmful factors but also impairs essential organelles and proteins, prompting apoptosis and cardiomyocyte loss [24]. Consequently, this process accelerates the decline in cardiac function. Under such circumstances, downregulating autophagy levels may serve a cardioprotective role.

Mitochondrial autophagy and HF

The heart, one of the body's most energy-demanding organs, relies heavily on mitochondria, the principal functional cellular unit. Aberrant mitochondrial function is closely linked to HF onset. Mitochondrial autophagy assumes a crucial role in timely eliminating damaged mitochondria and preserving their normal functionality (**Table 2**). This selective form of autophagy entails the removal of dysfunctional mitochondria within cells, preventing the toxic impact of ROS and contributing significantly to cardiomyocyte homeostasis maintenance.

Recent research by Wang [27] revealed a significant decrease in myocardial mitochondrial

autophagy among HF patients. Durga [28] observed that disrupted mitochondrial autophagy hastened HF onset post-myocardial infarction in type 2 diabetes-afflicted mice. These findings underscore the pivotal role of mitochondrial autophagy in HF etiology. Dysfunctional mitochondrial autophagy markedly elevates ROS levels, damages mitochondrial DNA, induces myocardial calcium overload, inflammation, necrosis, apoptosis, and fibrosis, thereby promoting HF progression.

Nevertheless, several studies [29, 30] have identified the downregulation of the PINK1/parkin signaling pathway as a significant contributor to mitochondrial autophagy dysfunction and subsequent HF. Enhancing myocardial mitochondrial autophagy via PINK1/parkin signaling pathway upregulation holds promise as a novel therapeutic avenue for HF treatment.

Autophagy and cardiac hypertrophy

The relationship between autophagy and cardiac hypertrophy, characterized by increased cell size to maintain cardiac function, is multifaceted. Autophagy may rise in response to accelerated protein turnover during myocardial hypertrophy. However, earlier investigations have revealed that in cardiac hypertrophy induced by aortic coarctation, autophagy activity not only fails to increase but decreases. This suggests that autophagy might not be activated during compensatory cardiac hypertrophy. Atg5, crucial for autophagy, is indispensable, and its deficiency results in near complete autophagy cessation. Studies have indicated myocardial hypertrophy in ATG5-deficient mice [34]. These findings suggest reduced autophagy activity during myocardial hypertrophy occurrence. However, morphological characteristics of myocardial hypertrophy remain similar in the absence of Atg5 and in aortic coarctation cases, implying that autophagy may not be pivotal in myocardial volume increase, or it might exert its influence through alternate signaling pathways [35].

Autophagy and ventricular remodeling

Ventricular remodeling constitutes another crucial aspect of HF, involving oxidative stress, endoplasmic reticulum (ER) stress, and the ubiquitin-proteasome system. Autophagy participates in these processes, responding to

both physiological and pathological stress by degrading and recycling intracellular materials. However, under prolonged stress, the role of autophagy as a survival mechanism may become ambiguous, potentially leading to the release of proapoptotic factors from damaged organelles, thereby inducing apoptosis. Indeed, heightened ER stress levels are often accompanied by the aggregation of polyubiquitinated proteins, which can trigger apoptosis. In adult rats subjected to myocardial ischemia/reperfusion conditions, numerous autophagosomes containing normal mitochondria were observed, suggesting that autophagy may entail the degradation of cellular contents and organelles, ultimately culminating in apoptosis [36].

Furthermore, autophagy not only regulates the metabolic dynamics of cardiomyocytes but also influences changes in cardiac structure and function through epigenetic mechanisms. Epigenetic regulation encompasses DNA methylation, histone modification, and non-coding RNAs, such as microRNAs, which modulate gene expression without altering the DNA sequence. In cardiac remodeling, autophagy interacts with these epigenetic regulatory mechanisms, collectively influencing the fate of cardiac cells. For instance, autophagy can impact cardiac remodeling by modulating microRNA expression [37]. Several microRNAs have been identified to regulate autophagy levels by targeting specific signaling pathways, such as mTOR and Akt/GSK-3 β , thereby influencing cardiomyocyte proliferation and apoptosis [38]. DNA methylation, another critical form of epigenetic regulation, suppresses gene expression by methylating DNA molecules. Autophagy may regulate DNA methylation by modulating the activity or localization of DNA methyltransferases, consequently influencing gene expression during cardiac remodeling.

Sex differences in autophagy mediated HF

Gender disparities significantly influence the manifestation and prognosis of HF, a phenomenon also evident in the autophagy pathway. Studies [39] indicate that female HF patients are more prone to experiencing HF with preserved ejection fraction, whereas male patients are more predisposed to HF with reduced ejection fraction. In female HF patients, the autophagic process may correlate with coronary

microvascular dysfunction, endothelial inflammatory responses, and vascular endothelial dysfunction [40], leading to heightened oxidative stress in cardiomyocytes, consequently impacting autophagy activation and regulation. Moreover, autophagy regulation in women with HF may be linked to sex hormone levels. Estrogen modulates the expression of autophagy-related genes by binding to estrogen receptors, thereby influencing cardiomyocyte autophagic activity and exerting a protective effect on cardiomyocyte autophagy processes.

Research progress of targeted intervention of autophagy during HF

Autophagy, a cellular process in which eukaryotic cells engulf their own cytoplasmic proteins or organelles for metabolic needs and organelle renewal through lysosomal degradation, notably includes mitochondrial autophagy as a critical form of selective autophagy. Studies [41] have underscored the close association between mitochondrial autophagy and HF, particularly in mediating the selective removal of damaged mitochondria via the PINK1/Parkin pathway. This pathway holds promise as a potential therapeutic target for HF treatment. Investigations have revealed that knockout of the PINK1 gene significantly inhibits Parkin-mediated mitochondrial ubiquitination, consequently nullifying the beneficial effects of berberine on HF. This suggests that berberine may promote mitochondrial autophagy mediated by the PINK1/Parkin signaling pathway for HF treatment [42].

Furthermore, recent years have witnessed notable progress in understanding the regulatory mechanisms of Chinese medicine on autophagy during heart failure progression. Chinese medicine has shown the potential to delay heart failure progression by either upregulating or inhibiting autophagy. Numerous studies have affirmed the efficacy of traditional Chinese medicine (TCM) monomers and compounds in modulating autophagy. TCM regulates the expression of autophagy-related proteins such as ATG5, Beclin1, LC3, LAMP, and various signaling pathways including PI3K/Akt, AMPK/mTOR/ULK1, and ERK to modulate autophagy levels for improved cardiac function. For instance, hypericin, a flavonoid glycoside compound with anti-inflammatory and antioxi-

dant properties, has been shown to upregulate Beclin1 and LC3II expression while downregulating p62, Bcl-2, and Bnip3 levels, thereby promoting autophagy, reducing cardiomyocyte apoptosis, and enhancing rat cardiac function [43]. Additionally, Wang [44] demonstrated that the Qiliqiangxin capsule can inhibit autophagy by significantly downregulating p53 and LC3 expression, thereby contributing to improved cardiac function.

Expectations

Currently, the consensus in the literature generally acknowledges the protective role of autophagy in HF. Autophagy clears damaged mitochondria and organelles, reduces oxidative stress and inflammatory responses, thus delaying ventricular remodeling and HF progression. However, excessive autophagy has been implicated in cardiomyocyte apoptosis and myocardial damage, hastening HF development. This dual mechanism poses a challenge for HF treatment, emphasizing the importance of regulating autophagy at an appropriate level. Yet, dynamic observation of autophagy levels is lacking, and the timing for upregulation or downregulation of autophagy in HF treatment remains unclear, necessitating further research. Future studies aim to develop drugs and therapeutic strategies precisely modulating autophagy, offering novel treatment options for HF patients.

Most studies propose mitochondrial autophagy dysfunction's association with HF occurrence [45], suggesting increasing mitochondrial autophagy as a therapeutic target. However, excessive autophagy can result in mitochondrial loss and myocardial necrosis. Moreover, mitochondrial autophagy status varies across disease stages. Hence, future endeavors should focus on precisely controlling the degree of mitochondrial autophagy and regulating it at different disease stages, offering potential treatment targets for HF.

Moreover, the crucial role in gender differences in autophagy during HF is analyzed, indicating their potential impact on disease progression and treatment response. Further studies [46] are warranted to elucidate how gender influences autophagy mechanisms in HF, paving the way for personalized treatment strategies for both male and female patients. Additionally,

considering women's underrepresentation in clinical trials, future research should encompass more female participants to ensure gender differences are comprehensively addressed in HF treatment strategies, facilitating personalized and precise treatment approaches.

The discovery of autophagy presents a promising therapeutic target for HF, although its clinical application is not yet fully mature. Firstly, the regulatory mechanism of autophagy may vary across different cardiac disease states, necessitating the specific characterization of autophagy's role in various pathological conditions. Secondly, current research on autophagy heavily relies on animal models and in vitro experiments, which may not fully replicate the complexity of human HF. Moving forward, future research will focus on developing drugs and therapeutic strategies that can precisely modulate autophagy, offering novel treatment options for HF patients based on a deeper understanding of autophagy mechanisms. Additionally, a comprehensive analysis of the interplay between autophagy, apoptosis, and necrosis will be conducted to unveil new therapeutic targets and intervention opportunities in HF. Considering the genetic and physiological differences among individuals, personalized autophagy-related treatment strategies may be necessary, with the application of precision medicine expected to be a crucial direction for future research. It is essential to validate the findings from preclinical studies through clinical trials to establish the practical value of regulating the autophagy process in HF treatment.

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Disclosure of conflict of interest

None.

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