Therapeutic potentials of modulating autophagy in pathological cardiac hypertrophy.

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Abstract

Cardiac hypertrophy is an adaptive response to increased overload, which is induced by various physiological or pathological stimuli. It is a common pathological process of a variety of cardiovascular diseases, which eventually leads to heart failure. Several lines of evidence suggested that autophagy as a double-edged sword was involved in cardiac hypertrophy. Autophagy, with a typical feature of double-membrane vesicle called the autophagosome, is a highly conserved lysosomal degradation process and plays an important role in the regulation of diverse physiologic and pathologic processes. However, the exact mechanism underlying the role of autophagy in regulating cardiac hypertrophy remains largely unknown. Here, we comprehensively characterize the dual effects of autophagy in promoting or inhibiting cardiac hypertrophy under different conditions. Moreover, we summarize the potential therapeutic effects of autophagy modulators on pathological cardiac hypertrophy. Finally, we discuss the advantages and challenges of autophagic modulators for the therapy of pathological cardiac hypertrophy.

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Abstract :

Cardiac hypertrophy is an adaptive response to increased overload, which is induced by various physiological or pathological stimuli. It is a common pathological process of a variety of cardiovascular diseases, which

eventually leads to heart failure. Several lines of evidence suggested that autophagy as a double-edged sword was involved in cardiac hypertrophy. Autophagy, with a typical feature of double-membrane vesicle called the autophagosome, is a highly conserved lysosomal degradation process and plays an important role in the regulation of diverse physiologic and pathologic processes. However, the exact mechanism underlying the role of autophagy in regulating cardiac hypertrophy remains largely unknown. Here, we comprehensively characterize the dual effects of autophagy in promoting or inhibiting cardiac hypertrophy under different conditions. Moreover, we summarize the potential therapeutic effects of autophagy modulators on pathological cardiac hypertrophy. Finally, we discuss the advantages and challenges of autophagic modulators for the therapy of pathological cardiac hypertrophy.

Keywords: Autophagy; Cardiac hypertrophy; Autophagy modulator; Therapeutic target

1. Introduction

Cardiac hypertrophy, defined as increased heart mass and the ratio of heart weight to body weight, is a primary adaptive response in essence [1, 2]. An increase in ventricular wall thickness, the growth of cardiomyocytes in size, and the over-synthesis of ubiquitinated proteins are major hallmarks of cardiac hypertrophy [3-6]. Cardiac hypertrophy involves two dominant types: physiological cardiac hypertrophy and pathological cardiac hypertrophy, which can be affected by many signaling molecules in different phases (Fig. 1).

Physiological cardiac hypertrophy is an adaptive response in cardiac morphology and function, which is associated with normal heart function and usually occurs in physical exercise or pregnancy [7]. Conversely, pathological cardiac hypertrophy is a decompensatory process, which is tightly linked with cardiac insufficiency under stress stimuli or diseases (such as coronary artery disease, hypertension and myocardial infarction) [7-10]. Pathological cardiac hypertrophy continues to increase the pre-and post-load of the heart to develop compensatory hypertrophy into a decompensated process, eventually leading to cardiac arrhythmia, dysfunction, failure, or sudden death [11-13]. Many pathological stimuli, such as activated neurohumoral regulators, hypertension and myocardial damage, can lead to dilate cardiac chambers and promote the progression of heart failure (HF). It has been proposed that about 26 million population suffer from heart failure around the world, and nearly half of the cases have heart failure with reduced ejection fraction (HFrEF) [14, 15]. According to the National Health and Nutrition Examination Survey from 2013 to 2016, approximately 6.2 million adults in the US suffered from heart failure per year [14, 16]. Recently, there is growing evidence that autophagy may specifically regulate cardiac hypertrophy through regulating autophagy-related genes expression and some signaling pathways [3].

Autophagy, also known as "self-eating" in Greek, widely exists in eukaryotic cells [17]. Autophagy is a lysosome-dependent degradation pathway mediated by *Atgs* , which essentially degrades and recovers cytoplasmic components to maintain cellular homeostasis and provide energy [18, 19]. There are at least three major types of autophagy: macro-autophagy, micro-autophagy, and chaperone-mediated autophagy (CMA) [20]. Macro-autophagy (hereafter referred to as autophagy) characterized by the formation of a distinctive double-membrane structure called the autophagosome is the uppermost type of autophagy [21]. Micro-autophagy is an inward invagination process of the lysosomal membrane and CMA does not contain membrane reorganization process, but mediated by the chaperone hsc70 (heat shock cognate 70), cochaperones, and LAMP-2A (lysosomal-associated membrane protein type 2A) [20]. Notably, autophagy bidirectionally regulates cell survival and death. Basal autophagy degrades damaged organelles and regulates apoptotic proteases to maintain normal cell growth [22]. However, under continuous stress stimuli, the excessive activation of autophagy may lead to cell death [23]. Due to the complicated and bidirectional characteristics of autophagy, the effect (beneficial or harmful) of autophagy in cardiac hypertrophy remains controversial [24, 25].

In this review, we discuss the underlying mechanism of autophagy-related influencing factors for cardiac hypertrophy in existing reports. Subsequently, we analyze the potential effects of current autophagy modulators for pathological cardiac hypertrophy and focus on the advantages and challenges faced by autophagy

modulators for the therapy of pathological cardiac hypertrophy.

2. Roles of autophagy in cardiac hypertrophy

Pathological cardiac hypertrophy is one of the pathological manifestations of cardiovascular disease remains the world's leading cause of death. Cardiomyocyte autophagy plays complicated but indispensable roles in helping preserve normal metabolism and function of the heart. Importantly, pieces of evidence have revealed that autophagy plays a critical role in cardiac hypertrophy (Fig. 2). On the one hand, autophagy can act as a pro-survival factor in cardiac hypertrophy. Firstly, autophagy can promote the degradation of aging and damaged organelles, long-lived proteins and misfolded proteins to supply part of the energy needed by the heart. Secondly, some growth hormones such as insulin and IGF-1 (insulin-like growth factor 1), which are the upstream regulator of autophagy, can promote physiological cardiac hypertrophy development [26]. For example, Mcmullen *et al.*have reported that growth hormones (e.g., insulin) and activated several signaling pathways such as PI3K (phosphoinositide 3-kinase), Akt (protein kinase B), AMPK (AMP-activated protein kinase), and mTOR (mechanistic target of rapamycin), also participate in autophagy pathway [26-28]. Thirdly, autophagy eliminates the ill effects of ROS on cardiomyocytes by removing damaged mitochondria from hypertrophic hearts. On the other hand, autophagy can act as a pro-death factor in cardiac hypertrophy. For instance, Nakai and Taneike *et al.* found that conditional inactivation of either the *Atg5* or *Atg7*genes in the adult heart, which led to abrogation of autophagy pathways, resulted in rapid onset of cardiac hypertrophy, left ventricular dilation, and diminished cardiac output [25, 29]. Therefore, under physiological conditions, basal autophagy maintains cell metabolic balance by transforming damaged organelles into energy substances (e.g., amino acids) and controlling protein quality, and promotes myocardial survival [30]. However, Qi *et al.* reported that autophagy flux is markedly induced in a swimming- induced and IGF-1-induced physiological cardiac hypertrophy rat model, which indicated that excessive autophagy was also occurred during cardiac hypertrophy and might be harmful [28, 30, 31].

2.1 Factors associated with autophagy promote cardiac hypertrophy

2.1.1 Abnormal expression of autophagy-related genes

Autophagy-related genes play a crucial role in the initiation and elongation of the autophagosome and also participate in the fusion of autophagosome and lysosome to form autolysosome. Accordingly, abnormal expression of *Atgs* may be an important factor affecting pathological cardiac hypertrophy. Recently, Ljubojević-Holzer *et al* . found that loss of cardiac Atg5 can reduce mitochondrial abundance and disrupt Ca^{2+} cycling and eventually lead to energetic exhaustion and myocardial damage [32]. Nakai *et al* . found that cardiac-specific autophagy-related 5 (*Atg5*)-deficient mice developed left ventricular dilation, contractile disorders, and a significant increase in a myocardial cross-sectional area [25]. Another animal model autophagy-related 7 (*Atg7*)-knockdown rat phenocopied the effects of Atg5 deficiency [25]. Results also showed that protein levels of microtubule-associated protein 1 light chain 3-II (LC3-II) were significantly decreased with cardiomyocyte hypertrophy. Cao *et al* . found that overexpression of beclin 1, which is indispensable for autophagosome formation, promoted autophagy induction and hypertrophic, maladaptive growth of cardiac muscle [33]. These studies provided direct evidence that the abnormal expression of core autophagy factors is indeed a contributing factor to promote cardiac hypertrophy.

2.1.2 Chemical stimuli

A recent study by Ceylan-Isik *et al.* showed that autophagy-related protein levels of beclin 1, Atg5, Atg7, and LC3-II were observably decreased and hypertrophic markers such as aminopeptidase N (ANP), transcription factor GATA4 and phosphorylated nuclear factor of activated T cells 3 (NFATc3), was activated in H9c2 myoblasts induced by endothelin-1 (ET-1), which is a polypeptide of 21 amino acids [34]. Chen *et al.* revealed that decreasing of connexin 43, a key protein involved in information transmission among organizations, can attenuate the expression of LC3-II and increase cell death and apoptosis in Ang II-treated H9c2 cells [35]. Another report showed that High-fat diet (HFD) decreased autophagy activity and increased cardiac hypertrophy, fibrosis, and apoptosis [36]. Similar to HFD, Guo *et al.* found that ethanol can induce the accumulation of acetaldehyde and autophagosomes, then promote cardiac hypertrophy. However, ethanol

can also reduce compensatory wall thickening in the hearts of pressure-overloaded (PO) mice [37-39]. These chemical stimuli share a common feature that deteriorates cardiac hypertrophy by altering autophagic levels. Therefore, myocardial hypertrophy can be prevented by targeting these chemical stimuli.

2.1.3 Mitochondrial dysfunction

Since the heart constantly needs a large number of energy, mitochondria, as a central energy supply source, play a vital role in maintaining optimal cardiac performance [40]. Mitophagy which functions in regulating energy homeostasis for cells by producing energy in the form of ATP is one of the specialized forms of autophagy that regulates the turnover of damaged and dysfunctional mitochondria [41]. Xu *et al* . found that SAMM50 sorting and assembly machinery component (Samm50), a key positive regulator of cardiac hypertrophy, promoted cardiac hypertrophy through regulating Pink1-Parkin-mediated mitophagy [42]. Shirakabe *et al* . found that in transverse aortic constriction (TAC)-treated mouse hearts models, mitophagy and general autophagy were briefly activated and then down-regulated respectively, which ultimately promoted mitochondrial dysfunction and heart failure [43]. Trincado *et al.* found that in a *Parkin* -KO*Drosophila* model, disruption of mitophagy lead to mitochondrial dysfunction and accumulation of enlarged mitochondria in heart tubes and dilated cardiomyopathy [44]. Nakayama *et al.* reported that cardiomyocyte Ca^{2+} overload as one of the typical characteristics of mitochondrial dysfunction, induced cardiomyocyte cell death via a mitochondrial-dependent necrotic process [45]. These findings suggest that mitophagy induced by mitochondrial dysfunction may play a critical role in the pathogenesis of cardiac hypertrophy.

2.1.4 microRNAs

microRNAs (miRNAs) are small non-coding RNAs with a length of approximately 20 to 22 nucleotides, which are widely regarded as important post-transcriptional regulators [46]. miRNAs are involved in regulating cell differentiation, growth, proliferation, and apoptosis. According to the different function or interaction of mRNA-3' untranslated region (UTR), mature miRNAs can regulate cardiac autophagy through mediated the expression of *Atg* s and hypertrophy-related signaling pathways, which are eventually involved in the pathogenesis of cardiac hypertrophy [47, 48].

miR-29 family is often regarded as an important regulator of cardiac fibrosis [49]. Overexpressed miR-29a decreased autophagy activity and promoted pathological cardiac hypertrophy via inhibiting the expression of phosphatase and tension homolog (PTEN) and activating the protein kinase B (Akt)/mechanistic target of rapamycin (mTOR) pathway [50]. Similar to miR-29a, PTEN is also the shared target of pro-hypertrophic miR-302 and miR-367. In Ang II-induced H9c2 cell models, miR302-367 impaired autophagy to aggravate cardiac hypertrophy by silencing PTEN and thus activating PI3K/Akt/mTOR pathway [51]. Hence, it is indicated that miRNAs can promote the hypertrophic growth of cardiomyocytes by inhibiting autophagy through targeting PETN and PI3K/Akt/mTORC1 pathways.

miR-199a is specifically expressed in cardiomyocytes and promotes the size of cardiomyocytes [52]. In cardiomyocyte-specific miR-199a transgenic mice, overexpressed miR-199a activated glycogen synthase kinase 3β (GSK3β)/mTOR signaling pathway to inhibit autophagy, then induce pathological cardiac hypertrophy [4, 53]. It has been pointed out that knockdown of miR-199 in sponge transgenic mouse hearts developed physiological cardiac hypertrophy with up-regulation of peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC1-α) [54]. Wu *et al* . showed that miR-365 can attenuate the LC3-II and beclin 1 expression and suppress autophagy by directly down-regulating S-phase kinase-associated protein 2 (Skp2), thus releasing the Skp2-mediated inhibition of mTORC1 and accelerating the hypertrophic growth of cardiomyocytes [55, 56]. Shao *et al.*reported that miR-377 reduced autophagy and promoted cardiac hypertrophy via targeting peroxisome proliferator-activated receptors γ (PPARγ) in a TAC-mice model [57]. The miR-212/132 cluster displayed an important function in the development of promoting pathological cardiac hypertrophy into HF [58]. Ucar *et al.* reported that overexpression of miR-212/132 down-regulated anti-hypertrophy and pro-autophagic factor FoxO3 and over-activated hypertrophic calcineurin/nuclear factor of activated T-cells (NFAT) signaling pathway which significantly impaired autophagic response upon starvation in a transgenic mice model and cardiomyocytes overexpressing miR-212/132 cell models [59].

These miRNAs can promote the progression of cardiac hypertrophy through regulating hypertrophy-related signaling pathways, which also regulate autophagy.

2.2 Factors associated with autophagy inhibit cardiac hypertrophy

2.2.1 microRNAs

miRNAs can not only promote cardiac hypertrophy but also inhibit physiological and pathological cardiac hypertrophy through inhibiting autophagy. The reason is probably that different lengths of miRNAs have a different effect on cardiomyocytes, resulting in seemingly contradictory situations that miRNAs can both promote or inhibit myocardial hypertrophy. A recent study by Huang *et al.* showed that in an Ang II-induced rat model of cardiomyocytes, miR-34a attenuates cardiomyocytes hypertrophy through inhibiting the expression of Atg9A, which is the only transmembrane Atg proteins involved in forming autophagosomes [60, 61]. Accordingly, the above inhibitory effect of miR-34a on cardiac hypertrophy through inhibiting Atg9A expression suggested that miR-34a-targeted Atg9A may be a new target for treating cardiac hypertrophy [62]. Qi *et al.* found that in pressure-overloaded induced rat hearts, miR-103, which is often regarded as a negative regulator for HF specifically through inhibiting target transient receptor potential vanilloid 3 (TRPV3) to decrease cardiac autophagic flux and the protein levels of hypertrophic markers (BNP and β-MHC), could partially alleviate cardiac hypertrophy [63, 64]. Similar result has been reported by Qi *et al.* used in vivo and in vitro models of cardiac hypertrophy induced by swimming and IGF-1, respectively [31]. The research showed that overexpressed miR-26b-5p, miR-204-5p and miR-497-3p attenuated the expression of hypertrophic mRNA levels (ANP and BNP), and significantly reduced the autophagy related protein levels of Atgs (ULK1, LC3B and beclin 1) [31].

2.2.2 Inhibition or activation of specific proteins

As the complicated mechanism of cardiac hypertrophy, the changes of many enzymes, proteins, and proteasomes may inhibit the pathogenesis of cardiac hypertrophy. Ba *et al* . reported that nucleotide-binding oligomerization domain (NOD)-like receptor family CARD domain containing 5 (NLRC5), as a nuclear receptor, ameliorated cardiac hypertrophy through enhancing autophagy via inactivation of Akt/mTOR pathway [65]. Cao *et al.* found that the inhibition of histone deacetylases (HDACs) by trichostatin A (TSA), a broad-spectrum HDAC deacetylase family inhibitor, repressed cardiac autophagy and decreased cardiomyocyte hypertrophy in C57BL/6 mice subjected by TAC [33]. Qi*et al.* showed that in response to pathological stimuli, the anti-hypertrophic and anti-autophagic effects of myostatin (MSTN), a protein for inhibiting the growth of skeletal muscle, were associated with the direct inhibition of AMPK/mTOR and activation of the peroxisome proliferator-activated receptor-gamma (PPARγ)/nuclear factor-κB (NF-κB) signaling pathway [66]. Another report showed that immunoproteasome catalytic subunit b5i interacted with Atg5 and promoted its degradation, then inhibited autophagy and cardiac hypertrophy [67].

2.2.3 Endogenous molecules

A recent study by Shi *et al* . showed that targeting of midkine alleviated cardiac hypertrophy by inhibiting autophagy indicating that midkine may be a novel target for treating cardiac hypertrophy [68]. Another report showed that 9-PAHSA, a recently discovered endogenous lipid, can alleviate cardiac hypertrophy by improving autophagy through down-regulating Akt/mTOR and activating PI3K/BECN1 complex [69].

3. Therapeutic application of autophagy modulators for treating pathological cardiac hypertrophy

There are a lot of therapeutic approaches for HF, in which cardiac pacemaker is one of the conventional treatments. However, for some partial HF patients, cardiac pacemaker implantation is expensive and patients' compliance with routine physical exercise is poor [70, 71]. Drug therapy is widely available, mainly because of its lower cost [2, 72]. However, due to a series of factors (e.g., adverse drug reactions), there are few drugs with excellent efficiency and good safety in treatment of pathological cardiac hypertrophy. For example, angiotensin-converting enzyme (ACE) inhibitors often lead to side effects in partial patients, such as coughing and kidney damage, which significantly limits the use of ACE inhibitors [72]. A lot of studies

have shown that autophagy may be a potential target for cardiac hypertrophy and autophagy modulators may be a promising strategy for the treatment of cardiac hypertrophy (Table 1) [11, 53, 73].

Of note, numerous evidence suggested that modulating autophagy may prevent or cure cardiac hypertrophy, but there were some limitations in detecting and analyzing cardiac autophagy: (i) Firstly, due to variability between cardiomyocytes, animals or clinical samples, there was a discrepancy for detecting autophagic flux, which may not accurately represent the true connection between the heart function and autophagy [74, 75]. (ii) Secondly, the mechanism of autophagy-related drugs in cardiac hypertrophy requires to be further studied, and their effects on cardiac hypertrophy may not be entirely originated from autophagy-related pathways [24, 74]. (iii) Thirdly, at present, there are few clinical examples using autophagy modulators to treat pathological myocardial hypertrophy. Therefore, it is necessary to pay close attention to the physiological indexes of patients after drug treatment, especially the side effects of drug treatment [76]. (iv) Finally, existing autophagy modulators showed a low specificity for diseases. Thus, how to avoid the side effects of excessively high or low autophagic activity in patients with cardiac myocardial hypertrophy after taking autophagic modulators remains to be further investigated.

4. Conclusion

In order to solve the above problems, we may find clues from the following aspects: (i) Excavating high-specific autophagy biomarkers and optimal cardiac hypertrophy animal models: Under ideal conditions, high-specific autophagy biomarkers may be autophagy-related genes and proteins in blood and urine, which can accurately reflect the exact autophagic activity of the myocardia at different stages [77]. Then, reflecting disease progression through changes in autophagic biomarkers can not only reduce the damage to the patient's body and the economic burden, but also effectively reflect the disease process and provide an important reference for the treatment of cardiac hypertrophy. (ii) Ensuring the specificity of autophagy modulators: We can monitor the process of disease through the changes of autophagy biomarkers, and then use autophagy inhibitors/inducers to treat diseases accordingly. Due to the complex metabolic process of drugs in vivo, the mechanism of the drug efficacy must be clear to effectively avoid the side effects of the drugs, so as to improve the safety and effectiveness of the drugs. Therefore, the specificity of autophagy modulators is crucial. (iii) Real-time monitoring: since autophagy is a double-edged sword, real-time monitoring of autophagy status and drug blood concentration in patients taking autophagy modulators is needed to avoid excessive or insufficient regulation which may aggravate the disease [78].

Overall, existing studies have shown that the role of autophagy on cardiac hypertrophy requires specific analysis and autophagy may be a potential therapeutic target for pathological cardiac hypertrophy. However, the current therapeutic mechanism related to autophagy remains to be further studied. Research and development of autophagy modulators represented by miRNAs may be important potential strategies for treating pathological cardiac hypertrophy. Additionally, since the existing autophagy modulators often have low specificity, improving the specific therapeutic efficacy of autophagy modulators may be a very important research hotspot in the future.

Competing Interests' Statement

None.

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Figure and Table legends

Fig. 1. Signaling pathways and molecules related to physiological and pathological cardiac hypertrophy (Modified from[2]).

4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1; Akt1, protein kinase B; AT_1-R, angiotensin II receptor; β-AR, β-adrenergic receptor; C/EBPβ, CCAAT/enhancer-binding protein b; CITED4, CBP/p300-interacting transactivator 4; DAG, diacylglycerol; ET 1 endothelin-1; ET-R, endothelin receptor; IP3, inositol trisphosphate; IP3R, inositol triphosphate receptor; NE, noradrenaline; PKA, protein kinase A; PKC, protein kinase C; PKD, protein kinase D; PKG, protein kinase G; PLC, phospholipase C; PRAS40, proline-rich AKT substrate; S6K1, ribosomal protein s6 kinase 1; SRF, serum response factor; Raf1, RAF proto-oncogene serine/threonine-protein kinase; HDACs, histone deacetylases; IGF-1, Insulin-like growth factor-1; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; AMPK, AMP-activated protein kinase;

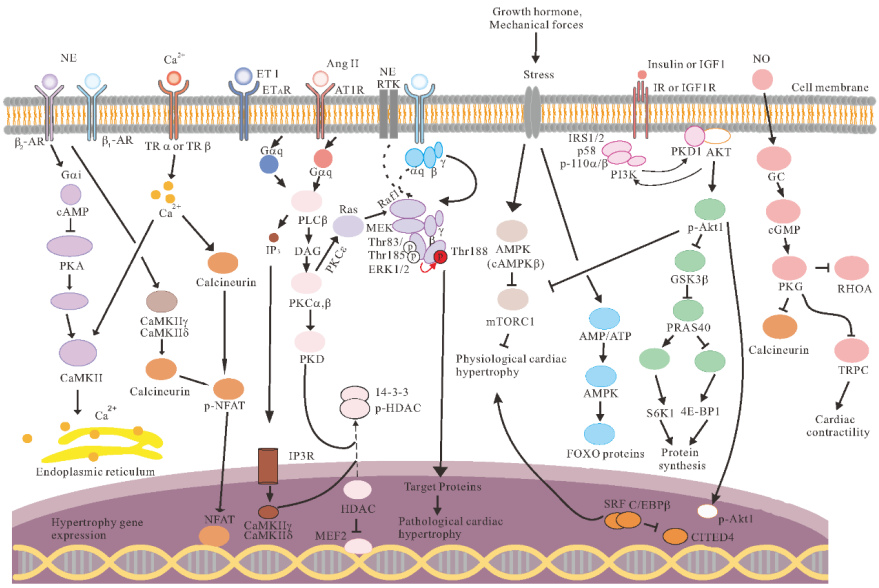
mTOR, mammalian target of rapamycin; MEK, MAP kinase kinase; ERK, extracellular signal-related kinase; NFAT, nuclear factors of activated T cell; CaMKII, Ca^{2+}-regulated calmodulin-dependent kinase II; NO, Nitric oxide; cGMP, 3',5'-Cyclic guanosine monophosphate; GC, guanylate cyclase; RHOA, transforming protein RHOA; TRPC, transient receptor potential channel; IRS1/2, insulin receptor substrate proteins 1 and 2.

Fig. 2. Roles of autophagy in cardiac hypertrophy.

Atg5, autophagy-related 5; Atg7, autophagy-related 7; NLRC5, nucleotide-binding oligomerization domain (NOD)-like receptor family CARD domain containing 5; HDAC, histone deacetylases; MSTN, myostatin.

Table 1 The potential autophagy modulators for treating pathological cardiac hypertrophy.

Figure:



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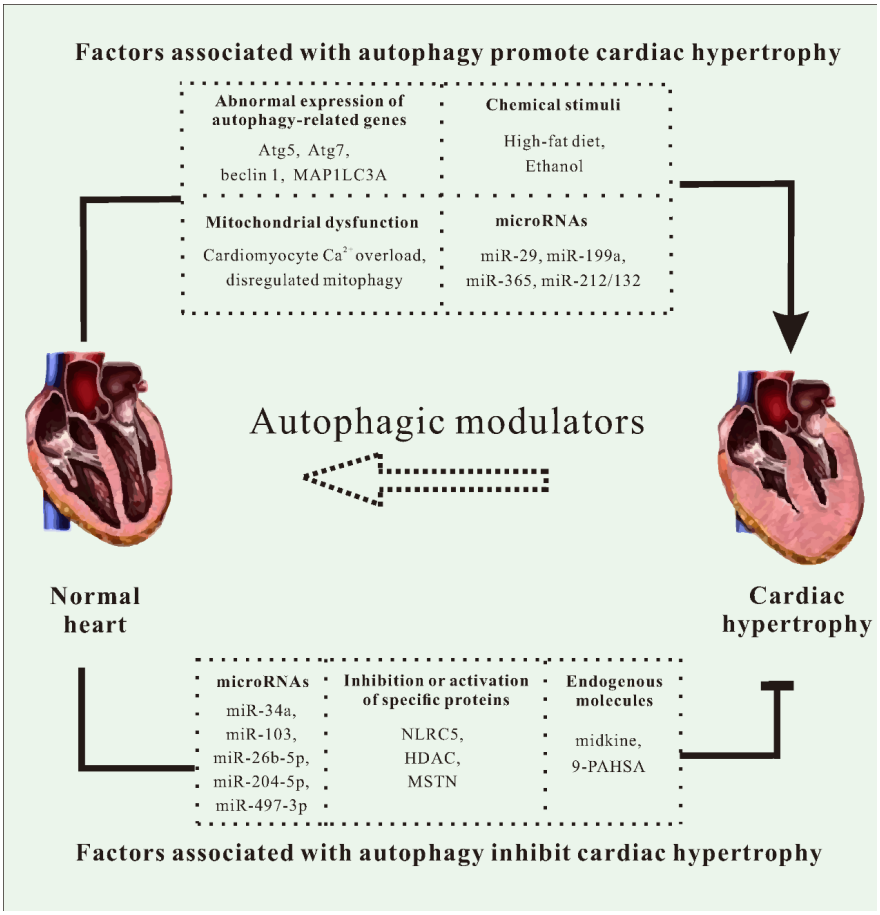

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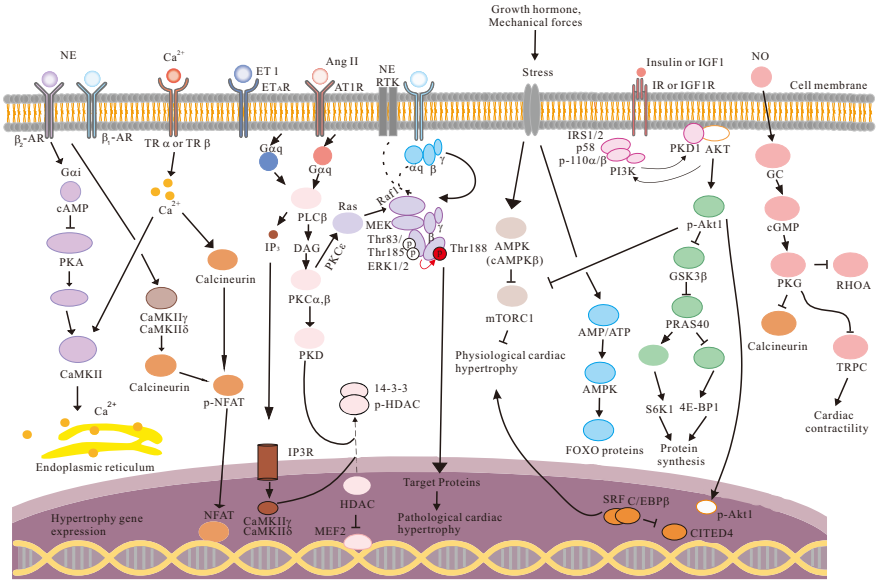
Tables:

Table 1 The potential autophagy modulators for treating pathological cardiac hypertrophy

Autophagy modulators	Targets	Mechanisms
Oridonin	Akt-AMPK	Oridonin expedites autophagic lysosomal degrad
Irisin	AMPK-ULK1	Irisin stimulates autophagic flux to significantly
Cucurbitacin B	Akt	Cucurbitacin B protects against hypertrophy, fib
Aliskiren	Renin	Aliskiren inhibits the regulation of Ang II-PKCβ
SB-216763	GSK-3β	SB-216763 activates autophagy to protect heart
Allicin	mTOR	Allicin suppresses autophagy to preserve cardiac
Rapamycin	mTORC1	Rapamycin inhibits mTORC1 and increases the
Amalaki Rasayana	Unknown	Amalaki Rasayana increases autophagy and sign
Curcumin	AMPK	Curcumin ameliorated CH and fibrosis in a rat r
Metformin	AMPK	Metformin stimulates autophagy to inhibit hype
Corosolic Acid	AMPK	Corosolic Acid can prevent cardiac hypertrophy
Simvastatin	Hydroxymethylg-lutaryl coenzyme A reductase	Simvastatin inhibits overactive autophagy and in

Autophagy modulators	Targets	Mechanisms
Baicalein	FOXO3a	Baicalein increases the expression of catalase and



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