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2021-04

Ajoolabady , A , Tuomilehto , J , Lip , G Y H , Klionsky , D J & Ren , J 2021 , ' Deciphering the Role of Autophagy in Heart Failure ' , Cardiology Plus , vol. 6 , no. 2 , pp. 92-101 . https://doi.org/10.4103/2470-7

http://hdl.handle.net/10138/352962
https://doi.org/10.4103/2470-7511.320324

publishedVersion

Review Article

Deciphering the Role of Autophagy in Heart Failure

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Submitted: 07-May-2021
Accepted: 07-Jun-2021
Published online: 30-Jun-2021

Abstract

Heart failure (HF) refers to a progressive pathological condition when cardiac muscles fail to pump adequate blood supply (cardiac output) to meet the metabolic demand of the body. Among various cellular and molecular mechanisms identified for the onset and progression of HF, autophagy dysregulation is increasingly getting recognized. Autophagy is a natural cellular process that is observed in almost all eukaryotic cells. Autophagy removes damaged/long-lived organelles, protein aggregates, and unwanted cellular compomemts via forming autophagosomes then fusing with lysosomes. Although mild-to-moderate induction of autophagy is deemed cytoprotective and adaptive, excessive or unchecked induction of autophagy can be detrimental and maladaptive. Both adaptive and maladaptive autophagy play a vital role in the pathophysiology of HF. In the current review, we provide an overview of autophagy regulation in HF and possible strategies targeting autophagy for the management of HF.

Keywords: *Autophagy; Cardiac myocytes; Heart failure; Stress; Therapeutics*

Introduction

Macroautophagy is the major type of autophagy present in almost all eukaryotic cells. Macroautophagy (from now on referred to as autophagy) denotes a process that recognizes, sequesters and degrades intracellular components including damaged/long-lived organelles, pathogens, and protein/lipid aggregates.[1-4] In mammalian cells, autophagy is activated in response to multiple stress conditions, including metabolic stress and energy crisis, oxidative stress, invasion of pathogens, ischemia and reperfusion, physical trauma, and inflammation.[5-8] Indeed, autophagy helps maintain cellular homeostasis by removing superfluous materials

Access this article online

Quick Response Code:

Website: www.cardiologyplus.org

DOI: 10.4103/2470-7511.320324

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How to cite this article: Ajoolabady A, Tuomilehto J, H. Lip GY, Klionsky DJ, Ren J. Deciphering the role of autophagy in heart failure. Cardiol Plus 2021;6:92-101.

and recycling energy-generating elements such as amino acids and glucose.[9-12] In this context, autophagy is a cytoprotective mechanism and is termed "adaptive/mild/cytoprotective" autophagy. However, ample evidence has shown that hyperactivation of autophagy can be detrimental and may lead to autophagy-dependent cell death (autosis) independent of other forms of cell death such as apoptosis, ferroptosis, and necroptosis. Therefore, hyperactivated autophagy is termed "maladaptive/excessive/unchecked autophagy."[13-16]

Mechanistically, the autophagy process is initiated with the formation of a temporary double-membrane compartment known as a phagophore. The phagophore is nucleated and surrounds the targeted cellular components, namely autophagy cargos. Subsequently, phagophores mature into another temporary double-membraned structures, namely autophagosomes, which transport the sequestered autophagy cargos before the fusion with lysosomes for ultimate degradation of the cargos content into new building blocks and ATP regeneration.[8,15,17,18] Construction of autophagosomes is a rather complicated and highly regulated process that entails a protein family of autophagy-targeted genes (*ATG*). These ATGs are hierarchically recruited to phagophore formation site to mediate the formation of phagophores, and autophagosomes, and also participate in fusion with the lysosomes.[17,18] While ATG proteins are primary constituents of the autophagy machinery, other proteins and complexes such as 5' AMP-activated protein kinase (AMPK) and mechanistic target of rapamycin kinase complex 1 (MTORC1) also participate in the signaling regulation of autophagy process.[18] Among various environmental factors, oxidative stress, abiotic stress, pathogens, ischemia, starvation, and nutrient deprivation are well-known inducers for autophagy in the mammalian cells.[15] To delineate the role of signaling pathways in the regulation of autophagy, we put cardiomyocytes under the perspective of consistent energy crisis such as glucose deprivation (GD) and amino acid deprivation (AAD) [Figure 1]. GD significantly reduces adenosine monophosphate (AMP) level in the cytosol and thereby activates AMPK. Being a master upstream regulator of autophagy, AMPK phosphorylates/activates other autophagy regulators including mitogen-activated protein kinase 8, forkhead box O transcription factor family, sirtuin 1, and tumor protein p53, all of which translocate to the nucleus and regulate *ATG* and autophagy-associated genes.[1,2,19-21] AMPK also activates other proteins such as regulatory-associated protein of MTOR complex 1 and TSC complex subunit 1/2 which regulate/inhibit MTORC1 and activate unc-51 like autophagy activating kinase 1 (ULK1). Subsequently, ULK1 initiates autophagy by forming the ULK1-autophagy-related 13 (ATG13)-ATG101-RB1-inducible coiled-coil 1 complex (also known as the autophagy initiation complex). In the next step, Class III phosphatidylinositol 3-kinase complex that contains phosphatidylinositol 3-kinase catalytic subunit type 3, phosphoinositide-3-kinase regulatory subunit 4, ATG14, and beclin 1 (BECN1) mediates the formation of phagophores. Ultimately, two conjugation systems similar to ubiquitin build protein complexes ATG5-ATG12-autophagy-related 16-like 1 and autophagy related 8-phosphatidylethanolamine that orchestrate the size and construction of autophagosomes around autophagy cargo that is supposed to be encapsulated within autophagosomes. Fusion between autophagosome and lysosome confers degradation of autophagy cargo into its building blocks[1,2,19-21] [Figure 1]. Due to the cardinal and indispensable role of autophagy in the maintenance of cellular homeostasis and alleviation of cellular stress, autophagy process is implicated in a variety of human diseases such as cancer,[22-24] neurodegenerative, cardiovascular, and metabolic diseases, as well as heart failure (HF).[1-3] In the current review, we provide an overview on the role of autophagy in the etiology of HF and explain the rationale for targeting autophagy as a new therapeutic strategy in the management of HF.

Pathogenesis of Heart Failure

HF is a persistent and progressive condition, in which the cardiac muscle fails to pump adequate blood supply to the body to meet the metabolic demand for oxygen and nutrients. Ample evidence to date has indicated that HF pathogenesis is an array of complex cellular and molecular alterations that ultimately culminate in cardiomyocyte death.[25-29] HF is derived from health conditions that impair the heart or dampen its normal function. A myriad of lifestyle factors such as cigarette smoking, consumption of a high fat diet, being overweight, and a sedentary life style can all predispose to the etiology of HF.[30,31] Coronary artery disease is a condition that can contribute to HF. Ensuring the formation of fatty and cholesterol deposits in myocardial vessles, cardiac blood perfusion is gradually diminished due to inadequate blood flow and increased vascular resistance, en route to HF over time.[32] Myocardial infarction is an another contributing factor of HF and occurs when an artery gets obstructed and fails to carry blood to cardiac muscles. As a result, part of myocardium suffers from cell death and is unable to contract sufficiently and pump blood adequately.[33] Further, uncorrected high blood pressure is another serious factor which promotes HF. With the higher blood pressure (afterload), cardiac muscle is forced to pump

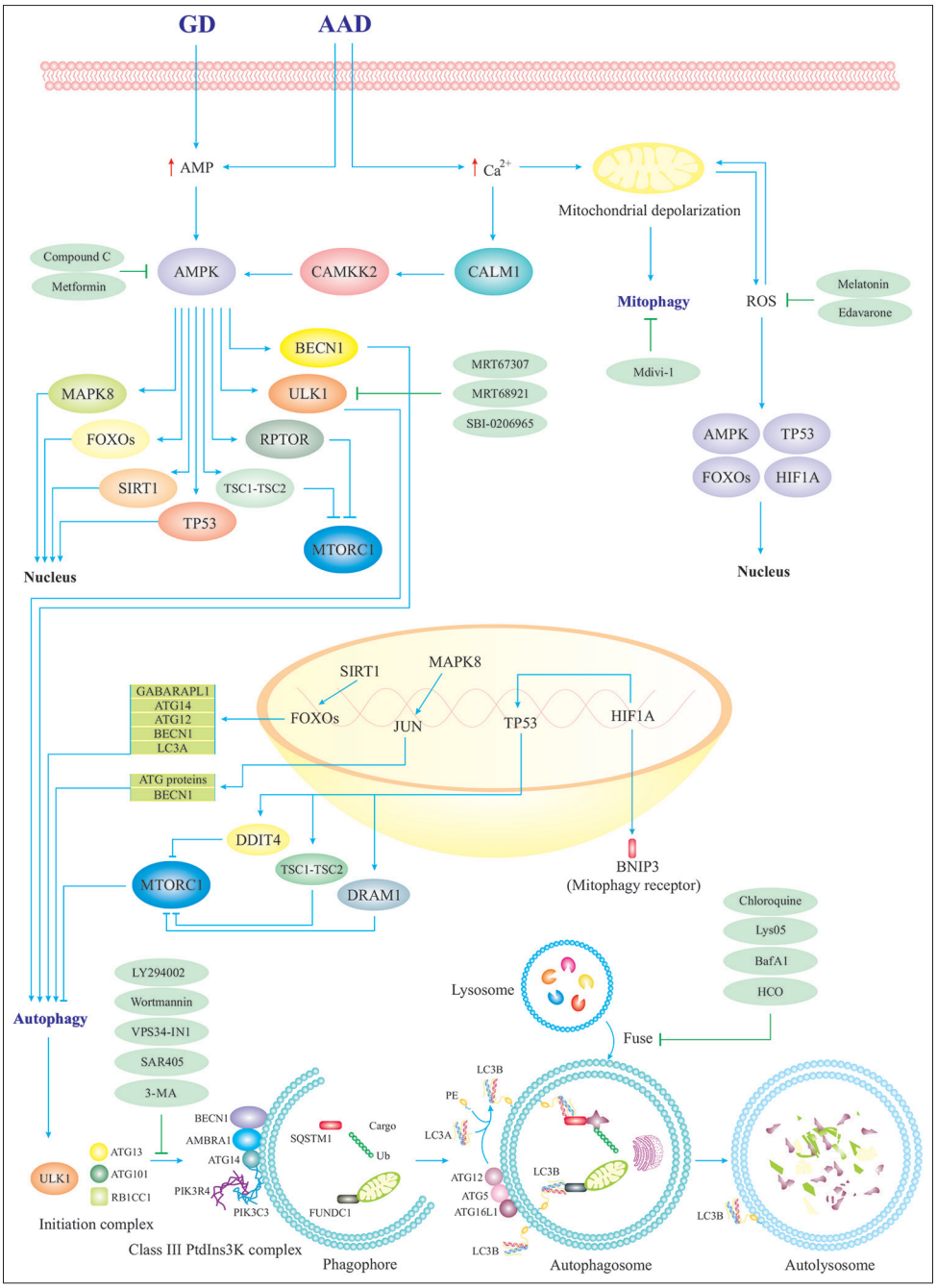

Figure 1: Autophagy machinery and its potential regulators.

Energy crises such as GD and AAD can activate upstream signaling pathways of autophagy. GD culminates in AMP reduction in the cytosol, which subsequently activates AMPK. AMPK is a master regulator of autophagy and phosphorylates/activates other autophagy regulator proteins such as MAPK8, FOXOs, SIRT1, and TP53, all of which, translocate to the nucleus and regulate autophagy-associated genes. Besides, AMPK mediates MTORC1 inhibition, which results in ULK1 activation. The ULK1 complex initiates autophagy in association with ATG proteins that result in the formation of the phagophore, the autophagosome, and ultimately the autolysosome. If this process continues excessively it can lead to maladaptive autophagy, however, its basal induction is an adaptive response to GD and AAD and other stress types.[1,2,19-21] GD: Glucose deprivation, AAD: Amino acid deprivation, AMPK: AMP-activated protein kinase,CAMKK2: Calcium/calmodulin dependent protein kinase kinase 2,CALM1: Calmodulin 1, MAPK8: Mitogen-activated protein kinase 8, ULK1: Unc-51 like autophagy activating kinase 1, FOXO: Forkhead box O transcription factor family, BCL2: BCL2 apoptosis regulator, DAPK1: Death associated protein kinase 1, DDIT4: DNA damage-inducible transcript 4, GABARAPL1: GABA type A receptor-associated protein like 1, JUN: Jun proto-oncogene, AP-1 transcription factor subunit, SIRT1: Sirtuin 1, TP53: Tumor protein p53, MTORC1: Mechanistic target of rapamycin kinase complex 1, ATG: autophagy-targeted genes, DRAM1: DNA damage-regulated autophagy modulator 1, BNIP3: BCL2 interacting protein 3, AMBRA1: Autophagy and beclin 1 regulator 1, FUNDC1: FUN14 domain containing 1

harder, resulting in weaker and larger ventricular chambers over time.[34] Heart valve derangements may also contribute to the malfunction of cardiac pump. When valves fail to open and close properly, cardiac

muscle is forced to pump harder, again resulting in HF.[35] The association of HF with other organs is also complex with more and more physicians and researchers perceiving HF as a multiorgan disease.[36] For instance, some evidence suggests that a damaged bowel wall allows the escape of bacterial endotoxins, which may provoke activation of proinflammatory cytokines in the setting of chronic HF.[36] Hypertension also contributes to the emergence of HF syndrome. Hypertrophy evoked by pressure overloaded in left ventricle (LV) results in ventricular diastolic impairment, myocardial infarction, and LV systolic dysfunction.[37,38] Examining T-cell recruitment to LV demonstrates that T-cell activation along with endothelial activation culminates in T-cell infiltration that contributes to HF. Mechanistically, T-cell infiltration activates cytokine release and triggers fibrotic cell death and hypertrophy.[39] Given that cardiomyocytes are prone to infection, inflammatory responses are mounted in these cells following infection via the generation of pro-inflammatory cytokines and the function of natural killer cells and monocytes, which provoke apoptosis.[40,41] Therefore, inflammation also plays a role in the pathogenesis of HF.

Besides, genome-wide association studies reveal 12 variants at 11 genomic loci associated with LV dysfunction, atrial fibrillation, and HF, suggesting that HF can be categorized as a rather complex genetic disease.[42] Moreover, Qishenkeli, a traditional Chinese medicine, attenuates reactive oxygen species generation, improves mitochondrial integrity, and inhibits apoptosis, and with specific regard to the cardiovascular system reduces infarct size and fibrosis and improves cardiac function.[43] Thus, apoptosis and fibrosis are two common culprit cellular processes, contributing to HF. In line with this, there is a plethora of evidence that autophagy also takes part in the pathology of HF, and modulation of autophagy could be a potential area for the management of HF.[27] Baseline autophagy induction acts as a protective and housekeeping mechanism that sustains ventricular mass and cardiomyocyte function.[44,45] Upregulation of autophagy has been reported in failing heart in animal models with a protective function; however, in load-induced HF, excessive autophagy may contribute to cell death of cardiomyocytes and further exacerbation of HF.[45,46] Thus, dysfunction of basic autophagy may predispose to the onset of HF, while excessive or maladaptive autophagy may contribute to the worsening of HF, in a manner reminiscent of apoptosis and fibrosis. In the section below, we briefly describe both protective and detrimental role of autophagy in HF.

Autophagy in Heart Failure

Various experimental findings have favored a protective role for adaptive autophagy in the pathogenesis of HF, whereas maladaptive autophagy may provoke HF.[45] Adaptive autophagy is often reported to be defective upon HF, whereas maladaptive autophagy is commonly observed during disease progression. For example, Oka *et al.* determined that failure of autophagy in capturing mitochondrial DNA and its subsequent degradation in deoxyribonuclease 2, lysosomal-deficient hearts can result in Toll-like receptor (TLR) 9-mediated inflammation in cardiomyocytes, resulting in dilated cardiomyopathy and myocarditis.[47] These findings favor a notion of defective autophagy in HF etiology. In a murine model of postinfarction HF, induction of mild autophagy using either chemical inducers or caloric restriction attenuates infarct size and alleviates cardiac dysfunction during chronic postinfarct stages, suggesting a protective role for adaptive autophagy in HF-induced myocardial damage.[48] Besides, LV tissue samples from dilated cardiomyopathy patients displayed changes in the levels of autophagy-associated genes including calcium-binding and coiled-coil domain 2 and nuclear receptor-binding protein 2 in close association with cardiac remodeling and dysfunction.[49] This study suggests that adaptive autophagy becomes defective to evoke LV dysfunction, possibly due to changes in genetic modulation of autophagy under HF. Moreover, autophagy genes along with endoplasmic reticulum (ER) stress-associated genes are upregulated in a mouse model of HF with arrhythmias.[10,50] Indeed, adaptive autophagy tends to reverse ER stress, a maladaptive process in HF.

Mitophagy is a selective type of autophagy that removes damaged/long-lived mitochondria and plays a crucial role in mitochondrial quality and integrity in cardiomyocytes.[1,51] Shirakabe *et al*. subjected mice to transverse aortic constriction as a model of cardiac hypertrophy and found transiently upregulated mitophagy followed by subsequent downregulation of mitophagy. In addition, these investigators showed that mitophagy downregulation culminates in mitochondrial impairment and HF. However, reactivation of mitophagy alleviates HF upon pressure overload challenge.[52] Hence, strategies to reinvigorate adaptive mitophagy may be of promise in diseased cardiomyocytes upon HF challenge.

Ferritinophagy is a form of selective autophagy that degrades ferritin to release Fe^{2+} into the cytosol and may lead to ferroptotic cell death via cytosolic accumulation of Fe^{2+}.[53,54] In line with this, the activation of ferritinophagy can lead to HF development, whereas its inhibition prevents HF in a pressure overload-induced

mouse model of dilated cardiomyopathy.[55] Therefore, certain types of autophagy such as ferritinophagy and mitophagy are adaptive responses that undergo mild induction during HF.

Although basal autophagy is generally cytoprotective, excessive autophagy can exacerbate HF pathology. For example, lymphocyte antigen 86 (*Ly86*) deletion hyperactivates autophagy by triggering ROS-MAPK signaling cascade, en route to the progression of murine HF with preserved ejection fraction (HFpEF).[56] Thus, modulation of LY86 may be a potential strategy to maintain basal autophagy in the face of HF. Moreover, activation of AMPK attenuates excessive autophagy via the modulation of MTORC2 and its downstream signaling, which prevents HF and alleviates cardiac dysfunction, suggesting a dual role of AMPK in autophagy regulation.[57] In addition, excessive autophagy culminates in necroptotic cell death in end-stage HF, but the receptor interacting serine/threonine kinase 1-nuclear factor kappa B subunit 1 axis counters cell death and is correlated with cell survival.[58] Further, TLR3 upregulation induces Toll-like receptor adaptor molecule 1 signaling, which culminates in excessive autophagy in murine chronic myocardial infarction models.[59] However, *Tlr3* knockout effectively interrupts autophagy, diminishes infarct size, and alleviates HF severity. Therefore, TLR3 upregulation contributes to excessive autophagy ensuing in myocardial infarction, which favors HF.

Of note, vagus nerve stimulation (VNS) is a newly identified therapy for chronic systolic HF. Upon VNS challenge, microRNA *MIR183-3p* significantly downregulates BCL2-interacting protein 3 like (BNIP3L) and inhibits BNIP3L-mediated autophagy. Therefore, the upregulation of *MIR183-3p*, which occurs during VNS, is a potential strategy to reduce excessive autophagy and confer cardioprotection.[60] Along these lines, angiotensin converting enzyme 2 administration inhibits the damaging role of doxorubicin and remarkably alleviates LV contractility dysfunction, which is attributed to the upregulation of microRNA *Mir30e* that targets the three prime untranslated region of *BECN1* and inhibits its expression.[61] Thus, microRNA *Mir30e* confers cardioprotection via the inhibition of excessive autophagy.

One may ask what is the difference between adaptive and maladaptive autophagy in terms of mechanism, inducing factors, and regulatory proteins. The current literature suggests that adaptive and maladaptive autophagy are favored with the same regulatory proteins, pathways, and mechanisms, as well as inducing factors, except the extent and duration of their induction. Mild induction of autophagy confers adaptive function in cardiomyocytes, while persistent induction of autophagy confers maladaptive functions and activates cell death domains.[62] Nonetheless, the fine-line separately adapative and maladaptive autophagy remains essentially unclear. Besides, the threshold at which mild induction converts to excessive or persistent induction differs in different cell types and organs. Further, determination of this threshold is still a challenge, and we propose the application of mathematical and statistical analysis to determine the persistance and endurance of induction at which adaptive autophagy ultimately turns to maladaptive autophagy. Taken together, both adaptive and maladaptive autophagy are reported in HF. Thus, it can be perceived that the application of strategies to maintain adaptive autophagy, while suppressing maladaptive autophagy should be practiced for clinical management of HF.

Autophagy Modulation for the Management of Heart Failure

A number of maneuvers have been considered for the manipulation of autophagy in HF. The very first step in targeting autophagy is perhaps to recognize molecules governing autophagy alteration in HF. For example, eva-1 homolog A, regulator of programmed cell death (EVA1A) is an ER- and lysosome-associated protein that maintains cardiac homeostasis. Interestingly, cardiac-specific knockout of *Eva1a* results in autophagy inhibition and apoptosis activation in mice. The underlying mechanism is that *eva1a*-knockout induces MTORC1 activation, which suppresses autophagy, leading to sarcomere disorganization, mitochondrial damage, reduced ATP production, and development of HF.[63] This study further indicates a promising role of autophagy in the prevention of HF. Besides, EVA1A can be a potential therapeutic target to sustain cytoprotective autophagy in cardiomyocytes in the realm of HF. Subjecting FYVE and coiled-coil domain autophagy adaptor 1 (FYCO1)-deficient mice to pressure overload and starvation impairs autophagy and cardiac function. However, FYCO1 overexpression reactivates autophagy to boost cardiomyocyte resistance against pathological biomechanical stress.[64] This observation shows that FYCO1 is also a potential therapeutic target for autophagy modulation upon HF challenge. Moreover, mitochondrial calcium uniporter (FYCO1) inhibition upregulates parkin RBR E3 ubiquitin protein ligase and PTEN-induced kinase 1, sustains mitochondrial integrity, downregulates SQSTM1, and promotes microtubule-associated protein 1 light chain 3 beta, to evoke protection in both early and end stage of pressure

overload-induced HF. Therefore, MCU inhibition activates mitophagy and autophagy and may be considered a new therapeutic target for the manipulation of autophagy upon HF.[65]

Besides specific therapeutic targets for the manipulation of autophagy, there are general strategies to modulate autophagy in the mammalian cells.[22-24,66-68] These strategies are based on using therapeutic compounds to

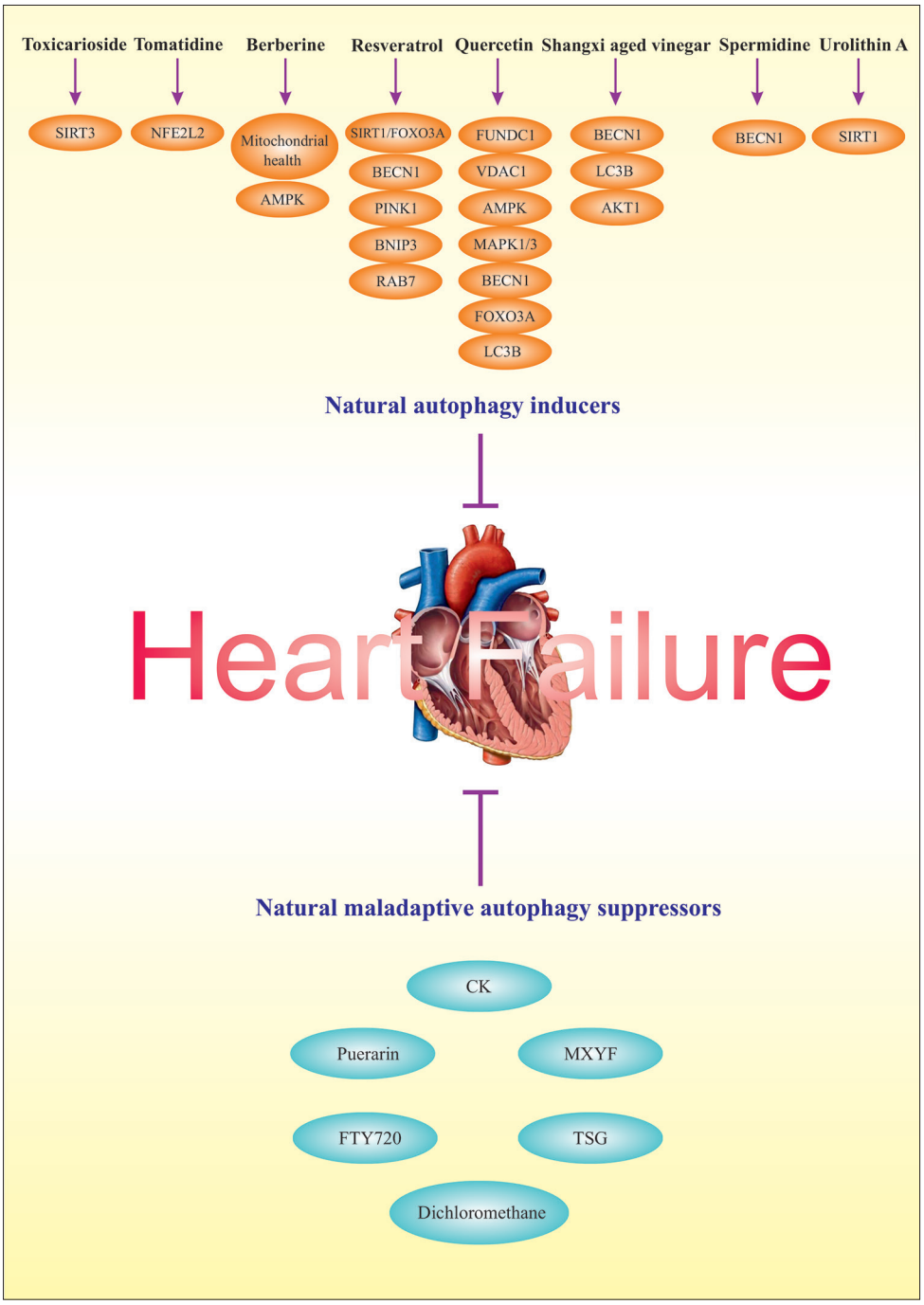

Figure 2: Autophagy modulators for the management of heart failure.

The natural compounds shown in the figure are potential activators of adaptive autophagy and suppressors of maladaptive autophagy that have been examined in animal studies of human diseases. Natural autophagy inducers manipulate different regulatory proteins that culminate in autophagy initiation and activation. However, natural maladaptive autophagy suppressors have been reported to block excessive induction of autophagy in mammalian cells. Even though the endurance and severity of the induction that convert adaptive autophagy to maladaptive autophagy are still unmeasurable, maladaptive autophagy suppressors might be useful to suppress maladaptive autophagy upon advanced stages of HF.[1,69] SIRT3: Sirtuin 3, MAPK1/3: Mitogen-activated protein kinase 1/3, BNIP3: BCL2-interacting protein 3, RAB7: Member RAS oncogene family, VDAC1: Voltage-dependent anion channel 1, FOXO3A: Forkhead box O3a, AKT1: AKT serine/threonine kinase 1, MXYF: Mu-Xiang-You-Fang [Chinese herbal compound], TSG: Tetrahydroxystilbene glucoside derived from Fallopia multiflora

Table 1: Autophagy-modulating compounds in the cardiovascular system.

Compounds	Full name/source	Role in autophagy
Danqi pill		Improves myocardial injury and cardiac function regulated autophagy mainly by enhancing autophagosome formation, upregulation of AMPK and TSC2, and downregulation of MTORC1 in HF rats[69]
Grb1	Ginsenoside Rb1	Prevents HF via blocking excessive autophagy in cardiomyocytes through manipulation of RHO-ROCK1 and PI3K-MTORC1 signaling in a murine model of pressure-overload HF[70]
Hyperoside	Natural drug	Alleviates HF by inhibiting apoptosis and activating autophagy[71]
Moxibustion	Traditional Chinese medicine	Inhibits excessive autophagy by downregulating *ATG* genes; thus, attenuates myocardial inflammation[72]; Acts as an autophagy inhibitor and blocks the overexpression of autophagy-related proteins upon chronic HF [73]
PNS	*Panax notoginseng* saponins	Enhances GD-induced autophagy through AMPK and CAMK2A phosphorylation[74]
QD	Qi Dan Li Xin pill	Improves LV remodeling and cardiac function, promotes autophagy via MTORC1-RPS6KB2 axis modulation; thus, blocks inflammation and apoptosis [75]
Tanshinone IIA	Traditional Chinese medicine	Improves cardiac function, induces autophagy, upregulates autophagy-associated genes such as *MAP1LC3A, BECN1*, and *SQSTM1* [76]

AMPK: Activated protein kinase, TSC2: Tuberous sclerosis complex subunit 2, MTORC1: Mechanistic target of rapamycin kinase comple×1, HF: Heart failure, RHO: Rhodopsin, ROCK1: Rho associated coiled-coil containing protein kinase 1, PI3K: Phosphoinositide 3-kinase, ER: Endoplasmic reticulum, ATG: Autophagy-targeted gene, GD: Glucose deprivation, CAMK2A: Calcium/calmodulin dependent protein kinase II alpha, LV: Left ventricular, RPS6KB2: ribosomal protein S6 kinase B2, MAP1LC3A/LC3A: Microtubule associated protein 1 light chain 3 alpha, BECN1: Beclin 1, SQSTM1: Sequestosome 1, MI: Myocardial infarction

overload-induced HF. Therefore, MCU inhibition activates mitophagy and autophagy and may be considered a new therapeutic target for the manipulation of autophagy upon HF.[65]

Besides specific therapeutic targets for the manipulation of autophagy, there are general strategies to modulate autophagy in the mammalian cells.[22-24,66-68] These strategies are based on using therapeutic compounds to target core autophagy proteins or their upstream signaling pathways. Figure 2 summarizes these compounds and their targets.[69] In addition, Table 1 lists newly identified compounds that are under preclinical and clinical research that can be used for autophagy modulation upon HF.[70-77]

Concluding Remarks

In sum, autophagy functions as a double-edged sword in the pathology of HF. On the one hand, adaptive autophagy prevents HF or alleviates HF symptoms. On the other hand, maladaptive autophagy is one of the underlying causes of HF pathology. Therefore, it is plausible to conclude that intervention which halts excessive induction of autophagy or maintains adaptive autophagy should be engaged in the clinical management of HF. Further studies are required to identify new therapeutic targets capable of manipulating autophagy or selective autophagy such as mitophagy in the management of HF. In particular, application of common pharmaceutical and natural compounds to manipulate autophagy may be recommended in the prevention or treatment of HF.

Financial support and sponsorship

This study is supported by the funds from the Science and Technology Commission of Shanghai Municipality (No. 18411950200).

Conflicts of interest

Jun Ren is an Editorial Board member of *Cardiology Plus*. The article was subject to the journal's standard procedures, with peer review handled independently of these Editorial Board members and their research groups.

References

1. Ajoolabady A, Aslkhodapasandhokmabad H, Aghanejad A, Zhang Y, Ren J. Mitophagy receptors and mediators: Therapeutic targets in the management of cardiovascular ageing. Ageing Res Rev 2020;62:101129. doi: 10.1016/j.arr.2020.101129.
2. Ajoolabady A, Aghanejad A, Bi Y, Zhang Y, Aslkhodapasandhukmabad H, Abhari A, *et al.* Enzyme-based autophagy in anti-neoplastic management: From molecular mechanisms to clinical therapeutics. Biochim Biophys Acta Rev Cancer 2020;1874:188366. doi: 10.1016/j.bbcan.2020.188366.
3. Ajoolabady A, Aslkhodapasandhokmabad H, Henninger N, Demillard LJ, Nikanfar M, Nourazarian A, *et al.* Targeting autophagy in neurodegenerative diseases: From molecular mechanisms to clinical therapeutics. Clin Exp Pharmacol Physiol 2021;48:943-53. doi: 10.1111/1440-1681.13500.
4. Zhang Y, Ren J. Epigenetics and obesity cardiomyopathy: From pathophysiology to prevention and management. Pharmacol Ther 2016;161:52-66. doi: 10.1016/j.pharmthera.2016.03.005.
5. Corti O, Blomgren K, Poletti A, Beart PM. Autophagy in neurodegeneration: New insights underpinning therapy for neurological diseases. J Neurochem 2020;154:354-71. doi: 10.1111/jnc.15002.
6. Giorgi C, Bouhamida E, Danese A, Previati M, Pinton P, Patergnani S. Relevance of autophagy and mitophagy dynamics

and markers in neurodegenerative diseases. Biomedicines 2021;9:149. doi: 10.3390/biomedicines9020149.

7. Ghislat G, Knecht E. Regulation of autophagy by amino acid starvation involving Ca2+. In: Autophagy: Cancer, Other Pathologies, Inflammation, Immunity, Infection, and Aging. United States.: Elsevier; 2015. p. 69-79. doi: 10.1016/B978-0-12-801032-7.00003-4.
8. Ren J, Sowers JR, Zhang Y. Metabolic stress, autophagy, and cardiovascular aging: From pathophysiology to therapeutics. Trends Endocrinol Metab 2018;29:699-711. doi: 10.1016/j.tem.2018.08.001.
9. Peker N, Gozuacik D. Autophagy as a cellular stress response mechanism in the nervous system. J Mol Biol 2020;432:2560-88. doi: 10.1016/j.jmb.2020.01.017.
10. Ajoolabady A, Wang S, Kroemer G, Klionsky DJ, Uversky VN, Sowers JR, *et al*. ER stress in Cardiometabolic Diseases: from Molecular Mechanisms to Therapeutics. Endocr Rev 2021. doi: 10.1210/endrev/bnab006.
11. Ren J, Bi Y, Sowers JR, Hetz C, Zhang Y. Endoplasmic reticulum stress and unfolded protein response in cardiovascular diseases. Nat Rev Cardiol 2021;18:499-521. Epub 2021/02/24. doi: 10.1038/s41569-021-00511-w.
12. Ren J, Anversa P. The insulin-like growth factor I system: Physiological and pathophysiological implication in cardiovascular diseases associated with metabolic syndrome. Biochem Pharmacol 2015;93:409-17. doi: 10.1016/j.bcp.2014.12.006.
13. Shi R, Weng J, Zhao L, Li XM, Gao TM, Kong J. Excessive autophagy contributes to neuron death in cerebral ischemia. CNS Neurosci Ther 2012;18:250-60. doi: 10.1111/j.1755-5949.2012.00295.x.
14. Galluzzi L, Vitale I, Abrams JM, Alnemri ES, Baehrecke EH, Blagosklonny MV, *et al.* Molecular definitions of cell death subroutines: Recommendations of the Nomenclature Committee on Cell Death 2012. Cell Death Differ 2012;19:107-20. doi: 10.1038/cdd.2011.96.
15. Zhang Y, Whaley-Connell AT, Sowers JR, Ren J. Autophagy as an emerging target in cardiorenal metabolic disease: From pathophysiology to management. Pharmacol Ther 2018;191:1-22. doi: 10.1016/j.pharmthera.2018.06.004.
16. Ren J, Taegtmeyer H. Too much or not enough of a good thing – The Janus faces of autophagy in cardiac fuel and protein homeostasis. J Mol Cell Cardiol 2015;84:223-6. doi: 10.1016/j.yjmcc.2015.03.001.
17. Zhang Y, Sowers JR, Ren J. Targeting autophagy in obesity: From pathophysiology to management. Nat Rev Endocrinol 2018;14:356-76. doi: 10.1038/s41574-018-0009-1.
18. Ren J, Zhang Y. Targeting autophagy in aging and aging-related cardiovascular diseases. Trends Pharmacol Sci 2018;39:1064-76. doi: 10.1016/j.tips.2018.10.005.
19. Tang Y, Wang Y, Wang C, Yu M, Li L, Chen S, *et al.* Isoliquiritigenin attenuates LPS-induced acute kidney injury through suppression of HMGB1 pathway in renal tubular against ferritinophagy. 21 February 2020, PREPRINT (Version 1) available at Research Square. doi: 10.21203/rs.2.24196/v1.
20. Gatica D, Chiong M, Lavandero S, Klionsky DJ. Molecular mechanisms of autophagy in the cardiovascular system. Circ Res 2015;116:456-67. doi: 10.1161/CIRCRESAHA.114.303788.
21. He C, Klionsky DJ. Regulation mechanisms and signaling pathways of autophagy. Annu Rev Genet 2009;43:67-93. doi: 10.1146/annurev-genet-102808-114910.
22. Rostami N, Nikkhoo A, Ajjoolabady A, Azizi G, Hojjat-Farsangi M, Ghalamfarsa G, *et al.* S1PR1 as a novel promising therapeutic target in cancer therapy. Mol Diagn Ther 2019;23:467-87. doi: 10.1007/s40291-019-00401-5.
23. Alizadeh L, Zarebkohan A, Salehi R, Ajjoolabady A, Rahmati-Yamchi M. Chitosan-based nanotherapeutics for ovarian cancer treatment. J Drug Target 2019;27:839-52. doi: 10.1080/1061186X.2018.1564923.
24. Hashemi V, Farhadi S, Ghasemi Chaleshtari M, Seashore-Ludlow B, Masjedi A, Hojjat-Farsangi M, *et al.* Nanomedicine for improvement of dendritic cell-based cancer immunotherapy. Int Immunopharmacol 2020;83:106446. doi: 10.1016/j.intimp.2020.106446.
25. Bogaard HJ, Abe K, Vonk Noordegraaf A, Voelkel NF. The right ventricle under pressure: Cellular and molecular mechanisms of right-heart failure in pulmonary hypertension. Chest 2009;135:794-804. doi: 10.1378/chest.08-0492.
26. Gajarsa JJ, Kloner RA. Left ventricular remodeling in the post-infarction heart: A review of cellular, molecular mechanisms, and therapeutic modalities. Heart Fail Rev 2011;16:13-21. doi: 10.1007/s10741-010-9181-7.
27. Xu HX, Cui SM, Zhang YM, Ren J. Mitochondrial Ca^{2+} regulation in the etiology of heart failure: Physiological and pathophysiological implications. Acta Pharmacol Sin 2020;41:1301-9. doi: 10.1038/s41401-020-0476-5.
28. Wang S, Ren J. Obesity paradox in aging: From prevalence to pathophysiology. Prog Cardiovasc Dis 2018;61:182-9. doi: 10.1016/j.pcad.2018.07.011.
29. Yin Z, Ren J, Guo W. Sarcomeric protein isoform transitions in cardiac muscle: A journey to heart failure. Biochim Biophys Acta 2015;1852:47-52. doi: 10.1016/j.bbadis.2014.11.003.
30. Djoussé L, Driver JA, Gaziano JM. Relation between modifiable lifestyle factors and lifetime risk of heart failure. JAMA 2009;302:394-400. doi: 10.1001/jama.2009.1062.
31. Steiner JB, Wu Z, Ren J. Ticagrelor: Positive, negative and misunderstood properties as a new antiplatelet agent. Clin Exp Pharmacol Physiol 2013;40:398-403. doi: 10.1111/1440-1681.12097.
32. Lala A, Desai AS. The role of coronary artery disease in heart failure. Heart Fail Clin 2014;10:353-65. doi: 10.1016/j.hfc.2013.10.002.
33. Gabriel-Costa D. The pathophysiology of myocardial infarction-induced heart failure. Pathophysiology 2018;25:277-84. doi: 10.1016/j.pathophys.2018.04.003.
34. Diamond JA, Phillips RA. Hypertensive heart disease. Hypertension research 2005;28:191-202. doi: 10.1291/hypres.28.191.
35. DeFrancesco T. POCUS: Heart-Abnormalities of Valves, Myocardium, and Great Vessels. Point-of-Care Ultrasound Techniques for the Small Animal Practitioner. 2021:403-16.
36. Krack A, Sharma R, Figulla HR, Anker SD. The importance of the gastrointestinal system in the pathogenesis of heart failure. Eur Heart J 2005;26:2368-74. doi: 10.1093/eurheartj/ehi389.
37. Vasan RS, Levy D. The role of hypertension in the pathogenesis of heart failure. A clinical mechanistic overview. Arch Intern Med 1996;156:1789-96.
38. Ren J, Wu NN, Wang S, Sowers JR, Zhang Y. Obesity cardiomyopathy: Evidence, mechanisms and therapeutic implications. Physiol Rev 2021;May 5. doi: 10.1152/physrev.00030.2020.
39. Nevers T, Salvador AM, Grodecki-Pena A, Knapp A, Velázquez F, Aronovitz M, *et al.* Left ventricular T-cell recruitment contributes to the pathogenesis of heart failure. Circ Heart Fail 2015;8:776-87. doi: 10.1161/CIRCHEARTFAILURE.115.002225.

40. Lindner D, Li J, Savvatis K, Klingel K, Blankenberg S, Tschöpe C, *et al.* Cardiac fibroblasts aggravate viral myocarditis: Cell specific coxsackievirus B3 replication. Mediators Inflamm 2014;2014:519528. doi: 10.1155/2014/519528.
41. Raulet DH. Missing self recognition and self tolerance of natural killer (NK) cells. Semin Immunol 2006;18:145-50. doi: 10.1016/j.smim.2006.03.003.
42. Shah S, Henry A, Roselli C, Lin H, Sveinbjörnsson G, Fatemifar G, *et al.* Genome-wide association and Mendelian randomisation analysis provide insights into the pathogenesis of heart failure. Nat Commun 2020;11:163. doi: 10.1038/s41467-019-13690-5.
43. Chang H, Li C, Wang Q, Lu L, Zhang Q, Zhang Y, *et al.* QSKL protects against myocardial apoptosis on heart failure via PI3K/Akt-p53 signaling pathway. Sci Rep 2017;7:16986. doi: 10.1038/s41598-017-17163-x.
44. Wang S, Ren J. Role of autophagy and regulatory mechanisms in alcoholic cardiomyopathy. Biochim Biophys Acta Mol Basis Dis 2018;1864:2003-9. doi: 10.1016/j.bbadis.2018.03.016.
45. Yang M, Wang S, Fu S, Wu NN, Xu X, Sun S, *et al.* Deletion of the E3 ubiquitin ligase, Parkin, exacerbates chronic alcohol intake-induced cardiomyopathy through an Ambra1-dependent mechanism. Br J Pharmacol 2021;178:964-82. doi: 10.1111/bph.15340.
46. De Meyer GR, De Keulenaer GW, Martinet W. Role of autophagy in heart failure associated with aging. Heart Fail Rev 2010;15:423-30. doi: 10.1007/s10741-010-9166-6.
47. Oka T, Hikoso S, Yamaguchi O, Taneike M, Takeda T, Tamai T, *et al.* Mitochondrial DNA that escapes from autophagy causes inflammation and heart failure. Nature 2012;485:251-5. doi: 10.1038/nature10992.
48. Takemura G, Kanamori H, Okada H, Miyazaki N, Watanabe T, Tsujimoto A, *et al.* Anti-apoptosis in nonmyocytes and pro-autophagy in cardiomyocytes: Two strategies against postinfarction heart failure through regulation of cell death/degeneration. Heart Fail Rev 2018;23:759-72. doi: 10.1007/s10741-018-9708-x.
49. Gil-Cayuela C, López A, Martínez-Dolz L, González-Juanatey JR, Lago F, Roselló-Lletí E, *et al.* The altered expression of autophagy-related genes participates in heart failure: NRBP2 and CALCOCO2 are associated with left ventricular dysfunction parameters in human dilated cardiomyopathy. PLoS One 2019;14:e0215818. doi: 10.1371/journal.pone.0215818.
50. Jensen BC, Bultman SJ, Holley D, Tang W, de Ridder G, Pizzo S*, et al*. Upregulation of autophagy genes and the unfolded protein response in human heart failure. Int J Clin Exp Med 2017;10:1051-8.
51. Ren J, Sun M, Zhou H, Ajoolabady A, Zhou Y, Tao J, *et al.* FUNDC1 interacts with FBXL2 to govern mitochondrial integrity and cardiac function through an IP3R3-dependent manner in obesity. Sci Adv 2020;6:eabc8561. doi: 10.1126/sciadv.abc8561.
52. Shirakabe A, Zhai P, Ikeda Y, Saito T, Maejima Y, Hsu CP, *et al.* Response by Shirakabe *et al*. to letter regarding article, "Drp1-dependent mitochondrial autophagy plays a protective role against pressure overload-induced mitochondrial dysfunction and heart failure". Circulation 2016;134:e75-6. doi: 10.1161/CIRCULATIONAHA.116.023667.
53. Li N, Wang W, Zhou H, Wu Q, Duan M, Liu C, *et al.* Ferritinophagy-mediated ferroptosis is involved in sepsis-induced cardiac injury. Free Radic Biol Med 2020;160:303-18. doi: 10.1016/j.freeradbiomed.2020.08.009.
54. Ajoolabady A, Aslkhodapasandhokmabad H, Libby P, Tuomilehto J, Lip G, Penninger J M, *et al.* Ferritinophagy and ferroptosis in the management of metabolic diseases. Trends Endocrinol Metab 2021;32:444-62. doi: 10.1016/j.tem.2021.04.010.
55. Ito J, Omiya S, Rusu MC, Ueda H, Murakawa T, Tanada Y, *et al.* Iron derived from autophagy-mediated ferritin degradation induces cardiomyocyte death and heart failure in mice. Elife 2021;10:e62174. doi: 10.7554/eLife.62174.
56. Yang HJ, Kong B, Shuai W, Zhang JJ, Huang H. MD1 deletion exaggerates cardiomyocyte autophagy induced by heart failure with preserved ejection fraction through ROS/MAPK signalling pathway. J Cell Mol Med 2020;24:9300-12. doi: 10.1111/jcmm.15579.
57. Li Y, Wang Y, Zou M, Chen C, Chen Y, Xue R, *et al.* AMPK blunts chronic heart failure by inhibiting autophagy. Biosci Rep 2018;38:BSR20170982. doi: 10.1042/BSR20170982.
58. Corsetti G, Chen-Scarabelli C, Romano C, Pasini E, Dioguardi FS, Onorati F, *et al.* Autophagy and oncosis/necroptosis are enhanced in cardiomyocytes from heart failure patients. Med Sci Monit Basic Res 2019;25:33-44. doi: 10.12659/MSMBR.913436.
59. Gao T, Zhang SP, Wang JF, Liu L, Wang Y, Cao ZY, *et al.* TLR3 contributes to persistent autophagy and heart failure in mice after myocardial infarction. J Cell Mol Med 2018;22:395-408. doi: 10.1111/jcmm.13328.
60. Ouyang S, Chen W, Zeng G, Lei C, Tian G, Zhu M, *et al.* MicroRNA-183-3p up-regulated by vagus nerve stimulation mitigates chronic systolic heart failure via the reduction of BNIP3L-mediated autophagy. Gene 2020;726:144136. doi: 10.1016/j.gene.2019.144136.
61. Lai L, Chen J, Wang N, Zhu G, Duan X, Ling F. MiRNA-30e mediated cardioprotection of ACE2 in rats with Doxorubicin-induced heart failure through inhibiting cardiomyocytes autophagy. Life Sci 2017;169:69-75. doi: 10.1016/j.lfs.2016.09.006.
62. Denton D, Kumar S. Autophagy-dependent cell death. Cell Death Differ 2019;26:605-16. doi: 10.1038/s41418-018-0252-y.
63. Zhang S, Lin X, Li G, Shen X, Niu D, Lu G, *et al.* Knockout of Eva1a leads to rapid development of heart failure by impairing autophagy. Cell Death Dis 2017;8:e2586. doi: 10.1038/cddis.2017.17.
64. Kuhn C, Menke M, Senger F, Mack C, Dierck F, Hille S, *et al.* FYCO1 regulates cardiomyocyte autophagy and prevents heart failure due to pressure overload *in vivo*. JACC Basic Transl Sci 2021;6:365-80. doi: 10.1016/j.jacbts.2021.01.001.
65. Yu Z, Chen R, Li M, Yu Y, Liang Y, Han F, *et al.* Mitochondrial calcium uniporter inhibition provides cardioprotection in pressure overload-induced heart failure through autophagy enhancement. Int J Cardiol 2018;271:161-8. doi: 10.1016/j.ijcard.2018.05.054.
66. Akbarzadeh Khiavi M, Safary A, Barar J, Ajoolabady A, Somi MH, Omidi Y. Multifunctional nanomedicines for targeting epidermal growth factor receptor in colorectal cancer. Cell Mol Life Sci 2020;77:997-1019. doi: 10.1007/s00018-019-03305-z.
67. Vakifahmetoglu-Norberg H, Xia HG, Yuan J. Pharmacologic agents targeting autophagy. J Clin Invest 2015;125:5-13. doi: 10.1172/JCI73937.
68. Condello M, Pellegrini E, Caraglia M, Meschini S. Targeting autophagy to overcome human diseases. Int J Mol Sci 2019;20:725. doi: 10.3390/ijms20030725.
69. Ajoolabady A, Wang S, Kroemer G, Penninger JM, Uversky VN, Pratico D, *et al.* Targeting autophagy in ischemic stroke: From molecular mechanisms to clinical therapeutics. Pharmacol Ther 2021;225:107848. doi: 10.1016/j.pharmthera.2021.107848.
70. Wang X, Jiang Y, Zhang Q, Tian X, Sun Q, Guo D, *et al.* Autophagy as a novel insight into mechanism of Danqi pill against

post-acute myocardial infarction heart failure. J Ethnopharmacol 2021;266:113404. doi: 10.1016/j.jep.2020.113404.

71. Yang T, Miao Y, Zhang T, Mu N, Ruan L, Duan J, *et al.* Ginsenoside Rb1 inhibits autophagy through regulation of Rho/ROCK and PI3K/mTOR pathways in a pressure-overload heart failure rat model. J Pharm Pharmacol 2018;70:830-8. doi: 10.1111/jphp.12900.
72. Guo X, Zhang Y, Lu C, Qu F, Jiang X. Protective effect of hyperoside on heart failure rats via attenuating myocardial apoptosis and inducing autophagy. Biosci Biotechnol Biochem 2020;84:714-24. doi: 10.1080/09168451.2019.1685369.
73. Li Q, Wang W, Ma Q, Xia R, Gao B, Zhu G, *et al.* Moxibustion improves chronic heart failure by inhibiting autophagy and inflammation via upregulation of mTOR expression. Evid Based Complement Alternat Med 2021;2021:6635876. doi: 10.1155/2021/6635876.
74. Li QL, Ma Q, Li Y, Liu CY, Xin QL, Xu WN, *et al.* Effect of moxibustion on cardiac function and expression of autophagy-related proteins of cardiomyocytes in chronic heart failure rats. Zhen Ci Yan Jiu 2020;45:259-63. doi: 10.13702/j.1000-0607.190138.
75. Wang D, Lv L, Xu Y, Jiang K, Chen F, Qian J, *et al.* Cardioprotection of Panax Notoginseng saponins against acute myocardial infarction and heart failure through inducing autophagy. Biomed Pharmacother 2021;136:111287. doi: 10.1016/j.biopha.2021.111287.
76. Shi B, Huang Y, Ni J, Chen J, Wei J, Gao H, *et al.* Qi Dan Li Xin pill improves chronic heart failure by regulating mTOR/p70S6k-mediated autophagy and inhibiting apoptosis. Sci Rep 2020;10:6105. doi: 10.1038/s41598-020-63090-9.
77. Zhang X, Wang Q, Wang X, Chen X, Shao M, Zhang Q, *et al.* Tanshinone IIA protects against heart failure post-myocardial infarction via AMPKs/mTOR-dependent autophagy pathway. Biomed Pharmacother 2019;112:108599. doi: 10.1016/j.biopha.2019.108599.