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REVIEWS

# Infarction or reperfusion-induced cardiac autophagy: role of microRNAs

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**[Abstract]** The process of cardiomyocyte death is triggered by prolonged ischemia in the heart during myocardial infarction (MI). And the role of non-coding RNAs in the pathophysiology of cardiovascular diseases has become increasingly important in recent years. RNA molecules known as microRNAs (miRNAs) are small non-coding RNAs whose expression varies across organs. microRNAs play an important role in processes associated with autophagy, which contribute to the development of heart failure. These processes include mitochondrial integrity and function, antioxidant defense, oxidative stress, iron overload, ferroptosis, and survival pathways. microRNAs may serve as promising biomarkers and useful targets in the treatment of cardiovascular disease. For the development of new targeted drugs, it is vital to uncover how microRNA expression changes and how they regulate autophagy. In order to comprehend the mechanisms of myocardial infarction and ischemic reperfusion injury, it is crucial to understand how these two processes relate to each other. In this review, we will provide a brief introduction to microRNAs, autophagy, and associated medicine to microRNAs.

**[Key words]** Myocardial infarction/reperfusion injury; Autophagy; MicroRNA

## 1 Introduction

Coronary heart disease patients with myocardial infarction and patients with ischemic heart failure can experience a range of quality of life problems. Managing stable coronary artery disease requires the management of myocardial ischemia. Despite great progress in the treatment of myocardial ischemia includes oxidative stress, mitochondrial $Ca^{2+}$ overload, pH change, inflammatory and metabolizing. Further clinical trials and translational studies are needed.

A conserved process in evolution is autophagy and increasing heart function by modulating myocardiocyte autophagy has been extensively studied. Numerous noncoding RNAs have been shown to regulate myocardial ischemia and post-ischemic injury, but the interaction between autophagy and non-coding RNAs in myocardial ischemia remains unclear. And, it is vital for the clinical translation of cardiac diseases to understand precisely how non-coding RNAs are regulated in the heart. An overview of recent research on the interactions and signaling pathways between non-coding RNAs and autophagy is presented in this article.

## 2 Upregulated autophagy through manipulating microRNA

Autophagy flux is a determinant factor of

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cardiomyocyte survival following ischemia-reperfusion injury. Autophagy regulation is a novel therapeutic target for cardiovascular disease. Some research shows that the reduction in autophagy levels is consistent with a decrease in cardiac function. Autophagy is primarily cytoprotective, tissue-protective, and anti-inflammatory, protecting the heart from insult. However, multiple studies have demonstrated that an increased stress response results in excessive autophagy and is detrimental to cell survival. microRNA can stimulate autophagy to protect or deteriorate cardiac function following ischemia, depending on the type, stage, or genetic context type, according to some research.

Upregulation of miR-145 boosted autophagy levels in infarcted myocardium via increasing phosphorylated (p)-RAC-$\gamma$ serine/threonine-protein kinase (Akt3) and p-mechanistic target of rapamycin (mTOR)[1]. Another group confirmed the same microRNA in a rabbit model of myocardial infarction, albeit with a different target. miR-99a suppressed the mammalian target of rapamycin (mTOR)/P70/S6K signaling pathway in the border zones of hearts, resulting in less cardiac remodeling[2]. Also, miR-18a target to Akt/mTOR axis could promote brain-derived neurotrophic factor BDNF expression, which offers protection against AMI[3]. Tail vein injection is a safe and effective mode of drug delivery or gene therapy. miR-144 injection increases its endogenous expression. Alleviates the decline in autophagy and reduces LV dilation and heart failure marker MMP2 and MMP9 activity[4]. Autophagy was determined in most studies by assay p-mTOR, mTOR, LC3II/I, and p62 protein expression in the border zone post-MI. In these studies, the extent of microRNA was down-regulated in the injury condition, but whether it directly regulates autophagy remains confirmed.

However, several microRNAs raised and repressed the expression of survival factors, favoring pathological autophagy. MAPK regulates cell growth, differentiation, stress, inflammation, and other physiological/pathological effects. The MAPK pathway has three levels of signal transmission: MAPK, MAPK kinase (MEK or MKK), and MAP kinase kinase kinase (MEKK or MKKK). miR-539 is a critical negative regulator of the MEK pathway that promotes maladaptive autophagy by raising the expression of ATG5[5]. Hypoxia significantly elevated the levels of phosphatase and tensin homolog (PTEN) but decreased p-PI3K and p-AKT, and knockdown of miR-122 protects H9c2 cardiomyocytes from hypoxia-induced injury and increases autophagy[6]. There may be inconsistencies between *in vivo* and ex vivo delivery of autophagy. In the starved neonatal rat cardiomyocytes (NRCMs) model, p38 activates mTOR and inhibits autophagy, and miR-22 overexpression may be a promising therapeutic target[7]. It may be possible to properly characterize microRNA inhibition's role in autophagy by considering its effect on different cell types.

The complex role of autophagy in multiple cell types may be one reason for the elusiveness of *in vivo* animal experiments. miR-30e and miR-30e-3p both belong to the miR-30 family[8]. Both microRNAs were down-regulated in coronary microvascular injury and ischemia-reperfusion injury, respectively. miR-30e silencing significantly inhibited cell apoptosis and increased the expression of microtubule-associated proteins 1A/1B light chain 3B, p62. They believe that decreases in autophagy in this pathological mode impair cardiac function, which is puzzling since autophagy increases and then decreases in the microvascular injury model. We should therefore think about whether microRNAs are changing dynamically. Monitoring microRNA expression can regulate autophagy to improve cardiac function by responding to autophagy. Different microRNAs are upregulated or downregulated following myocardial injury. microRNAs can be associated with multiple targets or multiple targets can be associated with one microRNA. A study found that post-ischemic

postconditioning simultaneously upregulated miR-139-3p and miR-181a-1. The expression of these two microRNAs can target different molecules to alleviate apoptosis and improve autophagy levels, which may be a better strategy for coping with injury. Silencing miR-497 has also proven reduced cell apoptosis and increased autophagic flux[9]. Aiming at the role of microRNA in regulating autophagy in different cell types, Eva-Maria Rogg found that depleted miR-92a-3p expression in endothelial autophagy regulation of autophagy-related genes 4a expression improves myocardial metabolism[10]. This study provides a new method to investigate the complex relationship between autophagy and microRNA *in vivo*. An overview of the relationship between microRNA and increased autophagy can be found in Fig.1. Nevertheless, autophagy appears to be an intrinsic protective mechanism during ischemia-reperfusion injury in the small intestine. To understand autophagy more rationally, we should not judge it based solely on its substrate p62 or autophagy-lysosomal key protein LC3.

## 3 Downregulated autophagy through manipulating microRNA

Under severe stress conditions, autophagy induced by ischemia or ischemia-reperfusion injury in the heart often aggravates organ damage. miR-101, a famous cancer suppressor targeting various pathways and genes, is frequently downregulated in patients after MI[11]. DDIT4 interferes with mTORC1 activity and promotes cell growth, making it a potential target for miR-101. DDIT4 and Tp53inp are also targets of miR-221[12]. miR-101, miR-221, and miR-126 all inhibit autophagy and improve cardiac function[13]. Researchers hypothesized that macrophage accumulation in the marginal zone was associated with the elevation of miR-221 in the infarction. M Su has demonstrated that miR-221 targets cyclin-dependent kinase (CDK) inhibitor p27, releasing its inhibition of CDK2, activating mTOR, and inhibiting autophagy[14]. The overexpression of miR-30d inhibits cardiomyocyte autophagy, stimulates ferroptosis, and inhibits ferritin degradation and lipid peroxidation[15]. This paper clarifies the relationship between autophagy and ferroptosis from another perspective. Some studies have shown that miR-22 is a potent cardiac autophagy inhibitor[16]. In contrast, Li et al. found that miR-22 overexpression increased autophagy[7]. The contradictory results may also be explained by different experimental designs and by different autophagy-related proteins. Pharmacological inhibition (Locked Nucleic Acid-modified miR-

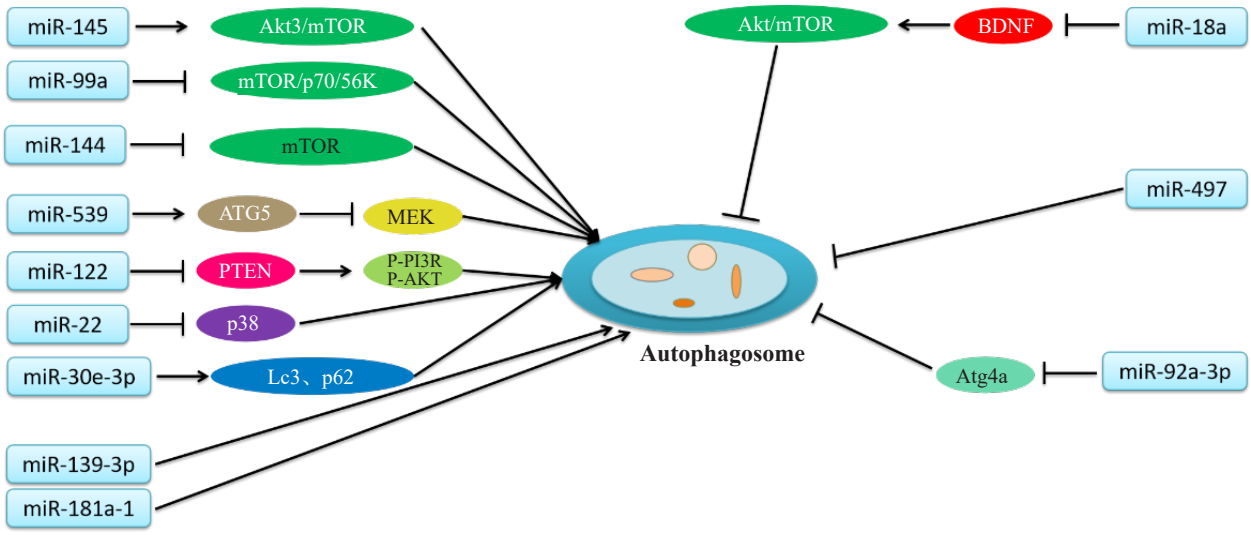


**Fig. 1 The role of microRNAs in the formation of autophagosomes and their associated targets.**

22 inhibitor (LNA-miR-22)) of miR-22 increased autophagy and prevented heart remodeling, indicating that autophagy may be beneficial in chronic diseases such as infarcted hearts[17].

ATG family members play a critical role in autophagy regulation. The expression of miR-431-mimic reduced cell viability and induced apoptosis when ATG3 expression was increased[18]. Additionally, miR-27a-5p inhibits hypoxia-induced cardiomyocyte injury[19]. Moreover, knockdown of miR-143 in Cardiac Progenitor Cells alleviates oxidative stress after MI by enhancing ATG7-mediated autophagy[20]. miR-638 reduced cell death by inhibiting autophagy-related 5 (ATG5) expression, increasing cardiomyocyte viability, and reducing autophagy[21]. Therefore, it appears that microRNAs regulate autophagy by directly interacting with ATGs, but whether a microRNA corresponds to only one or several autophagy-related genes needs to be further elucidated. TNF elevation reduces autophagy[22], but overexpression of miR-34a in the heart suppresses autophagic activity[23].

Under stress conditions, energy changes control the occurrence and development of autophagy, poly (ADP-ribose) polymerase 1 (PARP-1) activate and induce autophagy in low-energy states, transfected NRCMs, and H9c2 cells with miR-223 mimic inhibited hypoxia-induced apoptosis and excessive autophagy by targeting PARP-1 through Akt/mTOR pathway[24]. Similarly, miR-122 up-regulation activates the PI3K/Akt pathway and inhibits PTEN[6]. The PI3K/AKT/mTOR signaling pathway has received plenty of attention for its role in autophagy regulation, especially in energy-depleted conditions. Additionally, miR-494 is also known to target SIRT1, protecting myocardial cells from apoptosis and autophagy[25]. AMPK activated SIRT1 to activate autophagy, while miR-204 downregulates SIRT1 expression to restore viability and mitigate hyperoxia-reperfusion injury[26]. Overexpression of microRNA-384-5p activates the PI3K/Akt pathway by targeting Beclin-1[27]. HSPA5, an ER stress chaperone synchronously expressed with LC3-II, was also associated with autophagy, whereas miR-199a suppresses starvation-induced HSPA5 in CMs[28]. They demonstrated miR-199a impaired CMs autophagy by targeting GSK3β/mTOR complex signaling[29]. An overview of the relationship between microRNA and decline autophagy can be found in Fig. 2. Therefore, dysregulation of autophagy may occur in tandem with microRNA alterations, and regulation of microRNAs is sufficient to affect autophagy and improve disease progression.

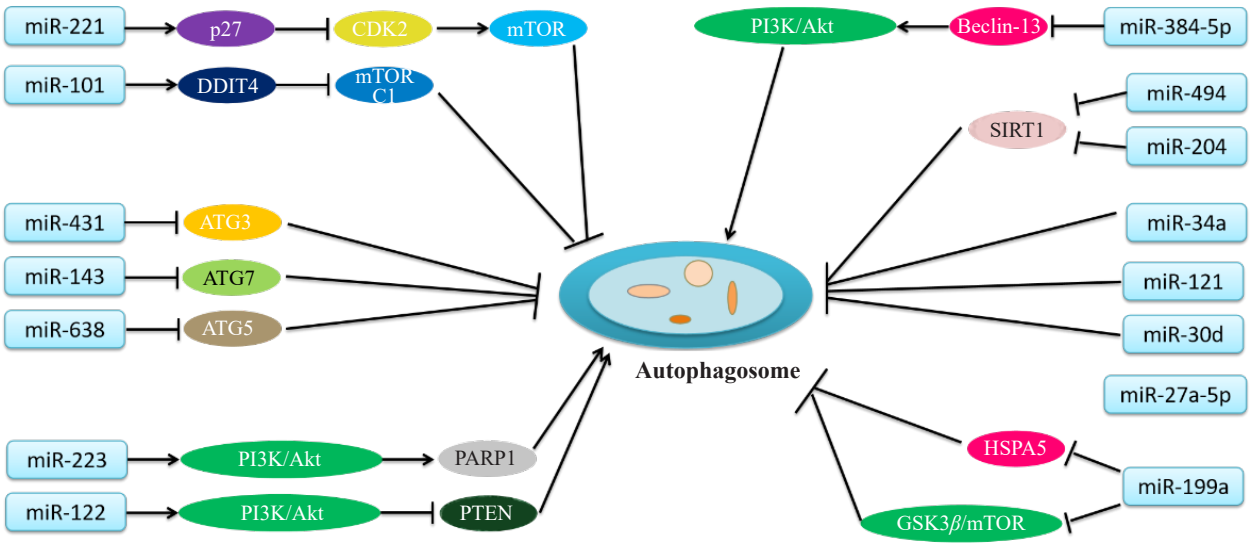


**Fig. 2 Autophagosome formation is inhibited by microRNAs and their associated targets.**

## 4 LncRNA sponge microRNA to regulate cardiac autophagy

Long noncoding RNAs (lncRNAs) are emerging as new factors in cardiovascular disease, but how lncRNAs regulate autophagy in the heart is unclear. Noncoding RNAs, such as lncRNA and microRNA, play a role in multiple heart diseases and regulating autophagy after myocardial infarction requires their intrinsic link. Fig. 3 summarizes how lncRNAs and microRNAs influence cardiac autophagy. miR-188-3p inhibits autophagy by targeting the autophagy mediator ATG7, and lncRNA APF suppresses autophagy by inhibiting miR-188-3p[30]. Another study showed autophagy promotes fibrosis after myocardial infarction, and inhibition of lncRNA XIST may exert an antifibrotic role through sponging miR-133a and inhibit SOCS2-activated autophagy[31]. Li also demonstrated that lncRNA xist targeting miR-133a alleviates IRI via similar mechanisms[32]. Knockdown of lncRNA PVT1 regulates miR-186/Beclin-1 axis and protects against hypoxia/reoxygenation-induced apoptosis and autophagy[33]. Another study showed that lncRNA AK088388 competitively binds to miR-30a, promoting the expression of Beclin-1 and autophagy cell damage[34]. Even though lncRNA MRAK088388 possessed the same miRNA response elements (MREs) as miR-200, miR-429, and miR-29, not all microRNAs are cardioprotective.

According to one study, hypoxic environments increased Beclin-1 expression, while targeting LncRNA-MALAT1 affected miR-30a/beclin-1 signaling[35]. Propofol acts as an anesthetic to protect cardiomyocytes from hypoxia/reoxygenation injury via regulating MALAT1/miR-206/ATG3 axis[36]. However, Hao Hu studies demonstrated that MALAT1 overexpression recruited EZH2 to TSC2 promoter regions and reduced TSC2 transcription, and activated mTOR signaling, which activated autophagy[37]. Study results suggest that suppression of the lncRNA NEAT1 stimulates cell proliferation and migration by promoting miR-378a-3p and ATGA12-dependent autophagy[38]. LncRNA KCNQ1OT1 acts as a miR-26a-5p sponge and promotes cardiomyocyte autophagy and exacerbates myocardial infarction and ischemia-reperfusion injury[39]. Inhibition of lncRNA TUG1 upregulates miR-142-3p to ameliorate autophagy-induced apoptosis[40]. And overexpression of lncRNA Dancr inhibits apoptosis and enhances autophagy via sponging microRNA-632[41]. LncRNA MIRF seems to function to inhibit autophagy and promote apoptosis through miR-26a[42]. Further investigation is needed to determine whether autophagy induces

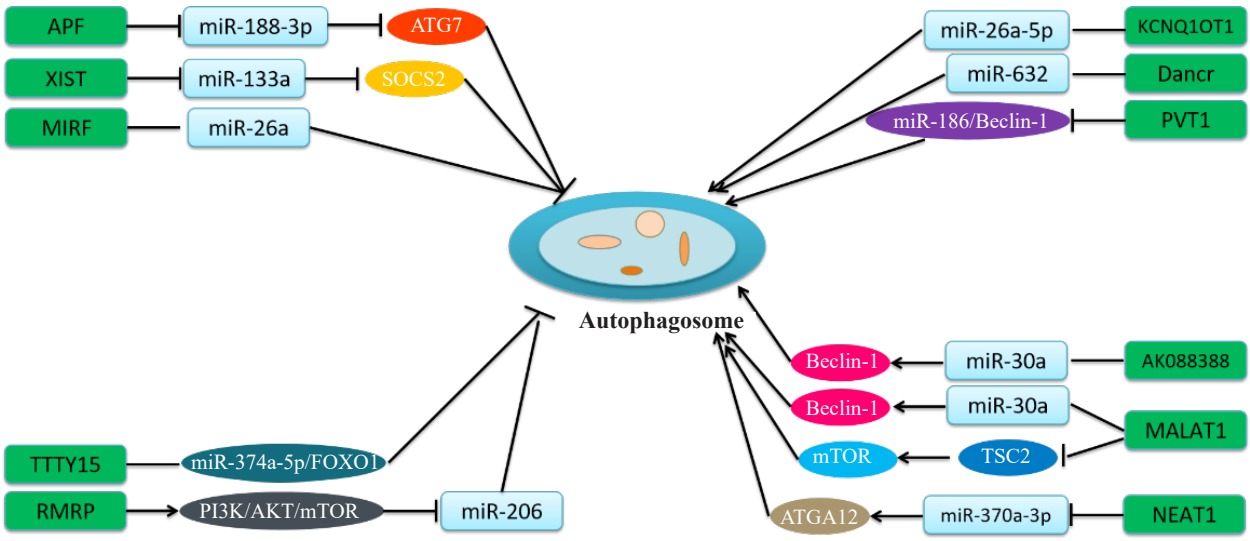


**Fig. 3 Autophagosome is modulated differently by lncRNA and microRNA.**

or inhibits apoptosis. Substantial evidence indicates that FOXO1 modulation of downstream targets and activating autophagy in MI[43], silencing of lncRNA TTTY15 inhibiting autophagy via regulation of the miR-374a-5p/FOXO1 axis[44]. Overexpression of RMRP activated PI3K/AKT/mTOR pathway then downregulation of miR-206, and this effect could inverse by knockdown ATG3[45].

## 5 CircRNA sponge microRNA to regulate cardiac autophagy

CircRNA, as a type of non-coding RNA, plays a significant role in heart disease. However, how it regulates microRNA and autophagy is not fully understood. The interaction between autophagy and circRNA can be seen in Fig. 4. circPAN3 was significantly upregulated in MI, especially in the infarction region. circPAN3 sponging miR-221 through FoxO3/ATG7-activated autophagy further worsened cardiac function[46]. It has also shown that circPAN3 suppresses autophagy and ameliorates myocardial ischemia/reperfusion injury by targeting miR-421/Pink1 axis[47]. In addition to regulating autophagy, HMGB1 plays a role in limiting apoptosis and maintaining the survival of cancer cells, such as pancreatic and colon. HMGB1 can directly activate autophagy through the PI3KC3-MEK-ERK signaling pathway and regulate autophagosome formation.

Death and senescence are interdependent processes, and KAT7 knockout prolongs cellular senescence. CircRNA Foxo3 suppresses autophagy via inhibiting HMGB1 by repressing KAT7 to improve cardiac function[48]. In addition, circRNA_101237 targeting the let-7a-5p/IGF2BP3 axis ameliorated apoptosis induced by hypoxia and reoxygenation[49].

## 6 Exosomes regulate microRNA to regulate cardiac autophagy

A membranous vesicle called exosome forms when intracellular multivesicular bodies fuse with the cell membrane[50]. Almost all types of cells can produce and release exosomes. With a diameter of 30−100 nm, the exosome is a nanoscale lipid inclusion structure encapsulated with proteins, mRNAs, and microRNAs. Heart disease can be treated by altering the level of exosomal microRNAs. A summary of the different sources of exsomes that interfere with autophagy is shown in Fig. 5. A mesenchymal stem cell exosome containing miR-125b suppresses autophagy by inhibiting p53/Bnip3 signaling to protect the heart[51]. Exosomal miR-301 derived from mesenchymal stem cells also played a similar role[52]. Bo Wang revealed that the SOX6 and TFEB genes were two direct and functional targets of miR-342-3p and SOX6 and TFEB

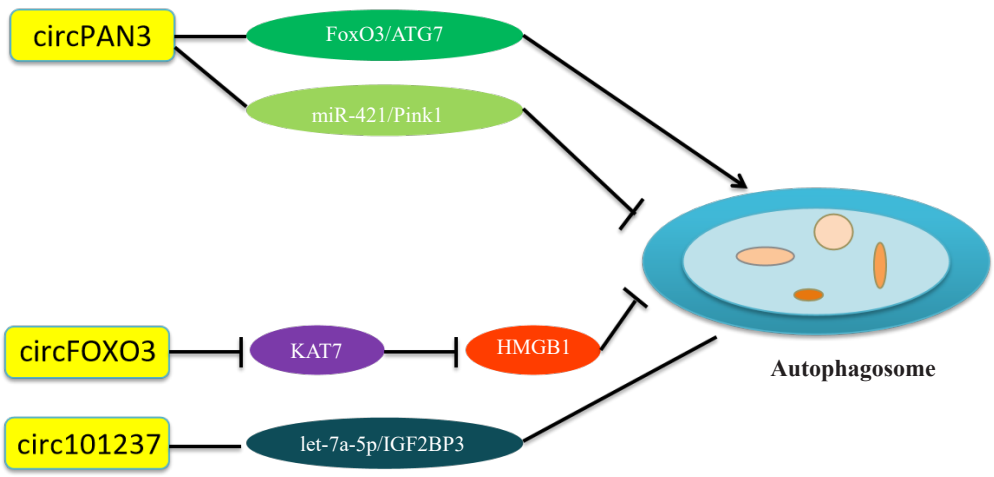


**Fig. 4 CircaRNA modulates autophagosomes in a major way.**

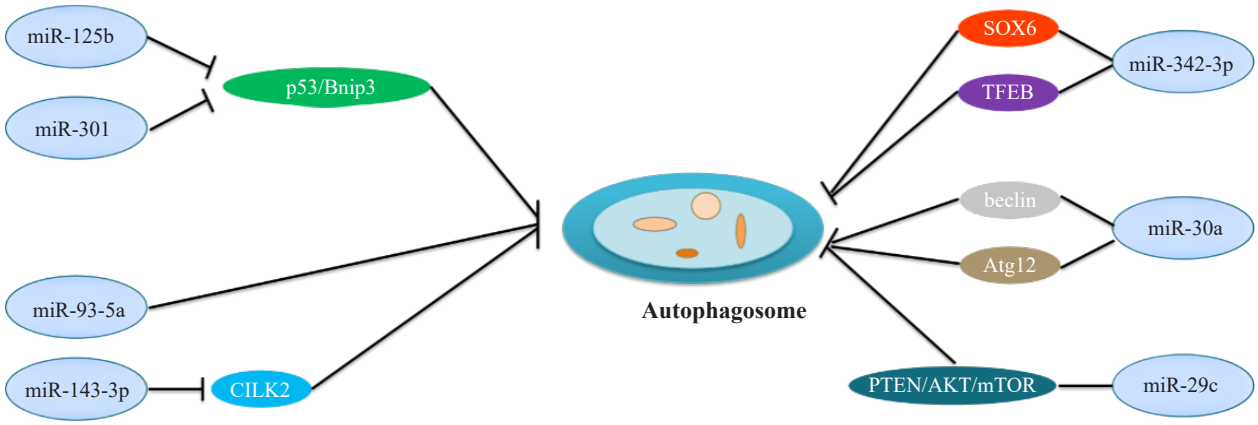


**Fig. 5 Autophagosomes are regulated by microRNAs of different sources of exosomes.**

inhibiting cardiomyocyte apoptosis and autophagy, respectively[53]. Liu et al. reported that exosomes derived from ADSCs are rich in miR-93-5p, which could alleviate infarction-induced myocardial damage by inhibiting autophagy and inflammatory responses[54].

According to previous studies, excessive ROS induces cell apoptosis and autophagy through the ATM/CHK2/Beclin 1 pathway[55]. Mesenchymal stem cell-derived exosomal miR143-3p directly targeted CHK2 and negatively regulated CHK2 expression[56]. AMI showed high levels of miR-30a in exosomes of animals or patients. miR-30a targeting beclin-1 and Atg12 genes inhibit autophagy[57]. Xu YQ found that exosome-carried miR-30a inhibitors can suppress myocardial apoptosis by reducing autophagy[58]. There is evidence that miR-93-5p-containing exosome treatment prevents myocardial damage, and further evidence shows that autophagy inhibits this protective effect[54]. Bone Marrow Mesenchymal Stem Cell-Derived Exosomal miR-29c improves Cardiac Ischemia/ Reperfusion Injury Through Inhibition of Excessive Autophagy via the PTEN/Akt/mTOR Signaling Pathway[59].

## 7 Drugs targeting microRNA and their relationship to autophagy

Traditional Chinese medicines are found to act as cardioprotective agents through microRNA, and they also indirectly or directly affect autophagy. Luteolin inhibits rat ischemia/reperfusion-induced myocardial injury through miR-208b-3p downregulation[60]. Additionally, research has shown that luteolin inhibits autophagy and inflammation, protecting the brain from ischemia and reperfusion[61]. As a result, luteolin may enhance organ function by controlling the degree of autophagy following injury through microRNA. Melatonin (MT) protects the ovary by inhibiting miR-15a-5p and Stat3, activating the PI3K-Akt-mTOR pathway, and repressing cell autophagy[62]. Numerous heart disease drugs target miR-34a, and multiple transcription factors and autophagy may be united by miR-34a. Resveratrol and Crocin attenuate myocardial ischemia/reperfusion injury through down-regulating miR-34a expression[63-64]. In diabetic rats, trimetazidine improves dyslipidemia, inflammation, and hypotension by increasing the levels of miR-24 and miR-126 in the plasma[65]. Ginsenoside Rb1 protects OGD-damaged cardiomyocytes by lowering intracellular ROS and normally miR-21 and its target gene PDCD4 expression[66]. It is a component of panaxadiol saponins. GS-Rb1 also initiates mTOR signaling, which is linked with the reduction of intracellular ROS[67]. Furthermore, Gs-Rb1 may enhance cell viability in hypoxia cardiomyocytes through AMPK[68]. Similar studies have shown that Panax quinquefolium saponin inhibits hypoxia-

induced cardiomyocyte injury through AMPK-activated metabolic pathways[69]. Berberine can promote angiogenesis and protect the myocardium by up-regulating a variety of microRNAs in cardiac autophagy[70], although its role in cardiac autophagy is controversial. Sacubitril/valsartan (LCZ696, Sacubitril, Valsartan) works by acting on angiotensin receptors in the body to treat hypertension and heart failure. LCZ696 ameliorated collagen deposition, ventricular degeneration, and various ultrastructural abnormalities by normalizing miR-377 expression and increasing autophagy[71]. In contrast to the intricate process of autophagy in the body, regulating microRNAs may be a more effective method of treating heart disease.

## 8 Conclusion

It is still unclear whether autophagy is adaptive or maladaptive *in vivo*, but its increase appears more beneficial for ischemic conditions. Several studies have shown an increase in overall cardiac autophagic flux after ischemia, unchanged in the infarcted area, and tended to decrease in the infarct border area in another 24-hour MI study. A well-designed study found that autophagy increases in the marginal zone for two weeks and then decreases for four weeks. Similarly, autophagy increased in risk zone tissues compared to the blank control group. Our hypothesis is that autophagy is maintained at a certain level *in vivo*, and that ischemia starts the autophagy mechanism, but does not increase autophagy. After a while (when cardiomyocytes reach the time limit for their ability to withstand ischemia or when ubiquitin proteasomes are unable to degrade excess malignant aggregated proteins). Autophagy, like calcium transients, is a metastatic process *in vivo* from the infarcted to the marginal zone and then to the risk zone. The transport of autophagy may be in the opposite direction to inflammation and calcium accumulation. Autophagy and local ubiquitination or deubiquitination may be associated with sarcomere function. After myocardial infarction, electrophysiological changes precede structural changes. This likely explains why the increase in autophagy in myocardial ischemia-reperfusion injury is often a paradoxical outcome for the body. Autophagy is closely related to apoptosis, but the relationship with necrosis is unclear. One possible reason may be that the mode of cell death in the infarcted area is necrosis, while autophagy does not occur or reduce in the necrotic area. Autophagy-induced death is often the second mode of death. Several studies have shown that mitochondrial dysfunction and its associated pathways are severely affected after myocardial infarction. Myocardial infarction increases autophagy in a mechanism that needs further investigation. What factors can induce the occurrence of autophagy? Considering autophagy is involved in a wide range of physiological and pathological processes, new drugs targeting microRNAs to interfere with autophagy may be crucial to drug discovery. A summary of the relationship between changes in representative microRNAs and autophagy is shown in Table 1.

## 9 Conflicts of interest

These authors have no conflict of interest to declare.

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**Table 1 The summary of microRNA in autophagy and their associated messages**

| MicroRNA | Expression | Species | Pathway/Targets | Autophagy expression | PMID |
|---|---|---|---|---|---|
| **miR-145** | ↓ | Rat/Rabbit | PI3K/Akt/mTOR, Angpt2 | ↓ | 29956747/26432843/ 30662618 |
| **miR-144** | ↓ | Mice | mTOR | ↓ | 30084039 |
| **miR-539** | ↑ | Rat | ERK1/2 MEK/ATG5 | ↓ | 27981363 |
| **miR-122** | ↑ | H9c2 | PTEN/PI3K/AKT | ↓ | 28871076 |
| **miR-22** | ↓ | NRCMs | p38*α* | ↓ | 27544030 |
| **miR-497** | ↓ | Mice/NRCMs | Bcl2 and LC3B | ↓ | 26299920 |
| **miR-101** | ↓ | Mice/ H9c2 | DDIT4 | ↑ | 32072912 |
| **miR-126** | ↓ | Rat | Beclin-1 | ↑ | 32633391 |
| **miR-30d** | ↓ | H9c2/Rat | Atg5 | ↑ | 32720797 |
| **miR-143** | ↑ | Mice/NRCMs | Atg7 | ↓ | 29858017 |
| **miR-223** | ↑ | NRCMs/H9c2 | Akt/mTOR, PARP-1 | ↑ | 29608885 |
| **miR-122** | ↑ | H9c2 | PTEN/PI3K/AKT | ↓ | 28871076 |
| **miR-494** | ↓ | H9c2 | PI3K/AKT/mTOR, SIRT1 | ↑ | 33174056 |
| **miR-204** | ↓ | H9C2 | SIRT1 | ↑ | 29421577 |
| **miR-384-5p** | ↓ | H9c2 | PI3K/Akt, Beclin-1 | ↑ | 31802847 |
| **miR-199a** | ↓ | NRCMs/293T | Hspa5 | ↑ | 28969032 |
| **miR-186** | ↓ | AC16 | Beclin-1 | ↑ | 32428696 |
| **miR-221** | ↓ | NRCMs/H9c2 | FoxO3/ATG7 | ↑ | 32629000 |

↑ Represents upward adjustment or promotion. ↓ Represents downward adjustment or suppression.

reduces left ventricular remodeling after myocardial infarction[J]. *Basic Res Cardiol*, 2018, 113(5):36.

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