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REVIEW ARTICLE

Advances in MicroRNA-Mediated Regulation of Cardiomyocyte Injury After Coronary Microembolization

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Abstract

Coronary microembolization (CME) occurs in patients with acute coronary syndrome and is caused primarily by atherosclerotic plaque rupture associated with surgery. CME can lead to arrhythmias, decreased coronary blood flow reserve, and cardiac systolic dysfunction. The clinical efficacy of conventional coronary artery dilation, antiplatelet agents, and direct thrombus aspiration after CME is not satisfactory. Studies have indicated that microRNAs (miRNAs) specifically bind the 3′ untranslated regions (UTRs) of inflammatory response-, apoptosis-, and autophagy-related mRNAs, and ultimately affect CME prognosis. In-depth studies of the roles of miRNAs in CME occurrence and development would not only advance understanding of the mechanisms underlying poor prognosis after CME but also aid in identifying new targets for drug treatment. Here, we review the regulatory effects of miRNAs on myocardial cell injury after CME in terms of the inflammatory response, apoptosis, and autophagy. Overall, changes in miRNA levels after CME decrease myocardial autophagy and worsen cardiac prognosis. Current evidence suggests a potential strategic pathway for therapeutic intervention in CME management.

Keywords: miRNA; CME; myocardial injury

Introduction

The coronary microcirculation comprises anterior small arteries and smaller arteries with diameters less than 500 μm. When an epicardial atherosclerotic plaque spontaneously ruptures or occurs during percutaneous coronary intervention, the emboli fall off and cause distal microcirculation embolism and myocardial microinfarction, a condition known as CME. The incidence of CME during the percutaneous coronary intervention perioperative period has been found to vary from 5% to 70%, depending on the evaluation methods, parameters, and times [1]. The "no-reflow" or "slow-reflow" phenomenon caused by CME is an independent predictor of progressive myocardial dysfunction and poor prognosis in patients with acute coronary

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syndrome (ACS) [2]. However, the effects of routine clinical treatment are limited. With advances in biological techniques, studies have confirmed that CME induces myocardial injury through physical obstruction and vasoconstriction [3], and that CME prognosis is associated with miRNAs. This review describes the regulatory effects of miRNAs on myocardial cell injury after CME in terms of the inflammatory response, apoptosis, and autophagy, and highlights potential new research directions in exploring treatments to improve cardiac dysfunction after CME.

Overview of miRNAs and Their Expression After CME

MicroRNAs are a class of single-stranded, non-coding RNAs with a length of approximately 21–23 nt. Their primary functions are to negatively regulate gene expression by affecting mRNA translation through complete or partial base pairing with the 3′-UTRs of target genes [4]. The process of miRNA formation in animals is highly conserved (Figure 1) [5]: 1) RNA polymerase II transcribes a primary miRNA transcript (pri-miRNA) with a stem-loop structure. 2) The RNase III endonuclease Drosha cleaves the stem-loop structure of pri-miRNA and generates pre-miRNA. 3) The exportin 5 protein transports the pre-miRNA into the cytoplasm. 4) The pre-miRNA is cleaved by the RNase III endonuclease Dicer, thereby forming double-stranded miRNA, which is incorporated into the Argonaute (Ago) protein under the action of a helper protein. Subsequently, one of the single strands is degraded. The mature miRNA and Ago form an RNA-induced silencing complex (RISC) that degrades the target mRNA [5]. Each miRNA can have multiple target genes, and a single gene can be regulated by multiple miRNAs, thereby forming a complex regulatory network [6]. MicroRNAs with the same mRNA binding site can competitively bind mRNA response elements (MREs) and regulate the transcriptional expression of target genes. Such competitive miRNAs are called competitive endogenous RNAs (ceRNAs). When ceRNAs are silenced, miRNAs degrade their target mRNAs through RISC binding to the target RNA. In contrast, when ceRNAs are upregulated, they bind the MREs of miRNAs, and target mRNA levels are increased. ceRNAs also include other transcripts with the same MREs, such as long non-coding RNAs, pseudogene transcripts, and circular RNAs [7]. Li et al. have reported that endogenous miRNAs can exist stably in the blood circulation. Under normal conditions, specific miRNAs are highly expressed in the myocardium [8]. After myocardial infarction, the expression of miRNAs released due to myocardial damage decreases, whereas the level of peripherally circulating miRNAs increases [8]. Dysregulation of miRNAs plays important roles in many cardiovascular diseases, such as cardiac systolic dysfunction, myocardial infarction, myocardial hypertrophy, hereditary cardiomyopathy, and particularly ACS [9]. C-miRNA

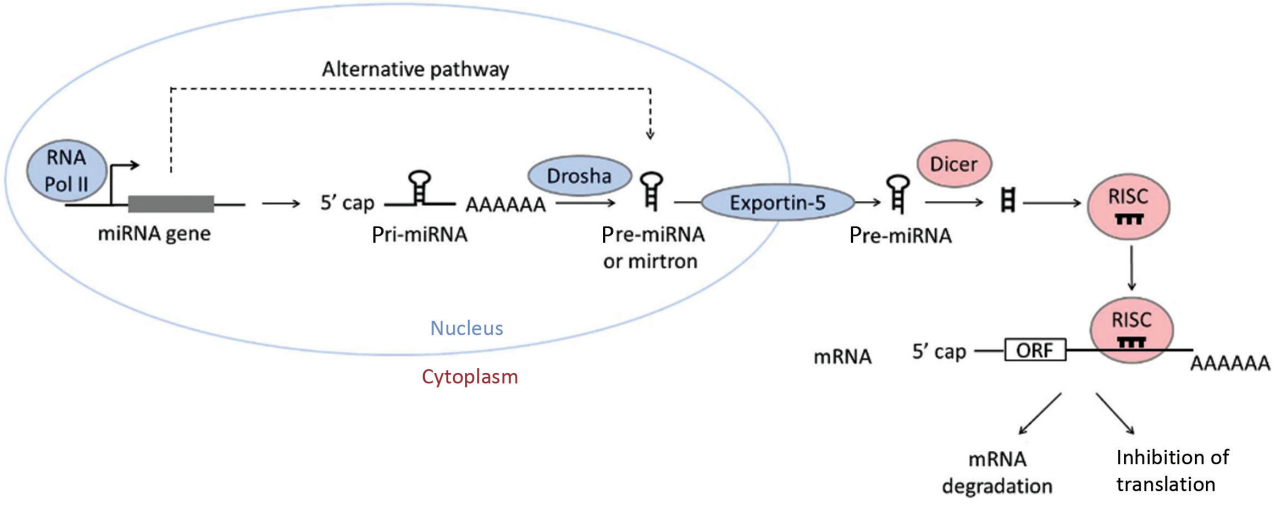

Figure 1 Biogenesis of MicroRNAs and their Modes of Action [5].

protects against RNA enzyme degradation through exosomes, apoptotic bodies, miRNA-binding proteins, or lipoproteins [10]. These findings suggest that miRNAs may be used as potential targets for the diagnosis and treatment of ACS.

MicroRNAs have been widely studied as important factors in the physiological and pathological development of the cardiovascular system. Recent studies have confirmed that miRNAs also play important roles in myocardial injury after CME. In 2017, Su et al. identified 11 miRNAs differentially expressed in myocardial tissue in a pig CME model. Among them, the expression of ssc-miR-136 and ssc-miR-142-3p decreased, and that of ssc-miR-874, ssc-miR-370, and ssc-miR-425-3p increased [11]. In further research, additional miRNAs with altered expression have been found in the CME model (Table 1). The target genes of these miRNAs are associated primarily with apoptosis, inflammation, autophagy, and fibrosis, and play important roles in CME (Table 1). In addition, Xue et al. have shown that miRNA may be a direction for EPC intervention in CME research, and a target for therapeutic detection [28], and miR-132 inhibitors improving myocardial remodeling have entered phase I clinical trials [29]. Thus, miRNAs may serve as potential therapeutic targets for CME.

Regulatory Mechanism Underlying the Effects of miRNAs on CME-Induced Myocardial Injury

Roles of miRNAs in the Inflammatory Response After CME

The inflammatory response is an important mechanism underlying myocardial injury after CME. The typical morphological change in microinfarction caused by CME is necrosis, which is often accompanied by inflammatory cell infiltration and even pyroptosis. The diameters of the emboli determine the location of the vascular obstruction as well as the degree of infarction. The degree of systolic dysfunction often exceeds the area of acute ischemia, which is associated with myocardial systolic dysfunction caused by myocardial inflammation. After CME, macrophages and neutrophils that infiltrate around infarct foci release inflammatory mediators such as tumor necrosis factor (TNF) and interleukins (ILs). Subsequently, the induction of reactive oxygen species signal transduction results in the oxidation of myofibrils and ultimately damages the contractile function of adjacent surviving cardiomyocytes. The inflammatory signaling pathway involves primarily TNF as well as nitric oxide and sphingosine, which play important roles in the progression of myocardial injury after CME (Figure 2). NOD-like receptor protein 3 (NLRP3) is activated by the NLRP3 sensor protein and then aggregates with apoptosis-associated speck-like (ASC) protein, which contains a caspase-recruitment domain (CARD), and cysteine aspartic acid specific protease (caspases), thereby forming the classic NLRP3 inflammasome. The NLRP3 sensor protein consists of three domains: an amino-terminal pyrin domain (PYD) that binds ASC; a central nucleotide binding and oligomerization domain (NACHT), with adenosine triphosphate (ATP) activation activity and polymerization function; and a carboxyl-terminal leucine-rich repeat (LRR) domain that inhibits NACHT function. In general, inflammasomes are inhibited by the action of LRR. During inflammatory or traumatic stimulation, active caspases in the NLRP3 inflammasome cleave interleukins and generate active IL-1β and IL-18, thereby causing inflammation. Simultaneously, the N-terminus of Gasdermin-D (GSDMD) is cleaved and inserted into the cell membrane, and subsequently causes pyroptosis.

Recent studies have shown that miRNAs ameliorate myocardial injury after CME by regulating inflammatory signaling pathways (Figure 2). In recent years, several studies have used the CME rat model. Cai et al. have further constructed LPS models. Through qPCR, ELISA, collagen staining, and other methods, miR-136-5P has been observed to be downregulated in the myocardial tissue in CME and LPS mice, whereas TNF, IL-6, and TnI are upregulated. Overexpression of miR-136-5P decreases myocardial cell inflammation and pyroptosis [13]. Immunofluorescence reporter gene detection analysis has confirmed that miR-136-5p inhibits the ATXN1L/Capicua axis, thereby upregulating pyrin domain containing 1 (PYDC1) by targeting ATXN1L, and competitively inhibits the binding of NLRP3 to ASC, thereby inhibiting inflammation and pyroptosis, and decreasing CME-induced cardiac injury [13]. Chen et al. have

Table 1 Expression and Functions of miRNAs after CME.

Animal model	miRNA	Expression (tissue)	Target gene	Effects on cardiomyocytes	Refs
Rat	miR-30e-3p	Downregulation	HDAC2	Overexpression of miR-30e-3p decreases CME-induced cardiomyocyte pyroptosis and inflammation.	[12]
Rat	miR-136-5p	Downregulation	ATXN1L	miR-136-5p protects cardiomyocytes against CME-induced injuries by suppressing pyroptosis.	[13]
Rat	miR-34a-5p	Upregulation	Sirt1	miR-34a-5p contributes to CMD by inhibiting Sirt1 expression. Ligustrazine exerts anti-inflammatory effects that prevent CMD by suppressing miR-34a-5p.	[14]
Rat	miR-142-3p	-	ATXN1L	miR-142-3p overexpression attenuates apoptosis and pyroptosis in cardiomyocytes.	[15]
Rat	miR-29b-3p	Downregulation	GSK-3β BMF	miR-29b-3p upregulation prevents myocardial apoptosis.	[16]
Rat	miR-26a-5p	Downregulation	HMGA1	Cardiac function and myocardial inflammation induced by CME are alleviated by miR-26a-5p overexpression.	[17]
Rat	miR-486-5p	Downregulation	PTEN	Overexpression of miR-486-5p protects against CME-induced cardiomyocyte apoptosis.	[18]
Rat	miR-200a-3p	Downregulation	TXNIP	miR-200a-3p overexpression inhibits cardiomyocyte pyroptosis.	[19]
Pig	miR-142-3p	Downregulation	IRAK-1	Overexpression of miR-142-3p attenuates the CME-induced myocardial inflammatory response.	[20]
hiPSC-CMs	miR-30e-5p	Downregulation	Bim	miR-30e-5p mitigates apoptosis and active autophagy.	[21]
Rat	miR-30e-3p	Downregulation	Egr-1	Overexpression of miR-30e-3p increases autophagy and inhibits apoptosis.	[22]
Rat	miR-186-5p	Upregulation	XIAP	Inhibition of miR-186-5p decreases hypoxia-initiated cardiomyocyte injury and pyroptosis.	[23]
Rat	miR-181a-5p	Upregulation	XIAP	Downregulation of miR-181a-5p alleviates CME-induced myocardial damage by suppressing myocardial oxidative stress and inflammation.	[24]
Rat	miR-30e-3p	Downregulation	-	miR-30e-3p is downregulated in the myocardium after a CME event, and this is accompanied by inhibited autophagy and a decrease in cardiac function.	[25]
Pig	miR-21	-	PDCD4	UTMD-mediated microRNA-21 transfection ameliorates myocardial inflammation.	[26]
Pig	miR-19a	Downregulation	Bim	miR-19a stimulates autophagy, inhibits apoptosis, and ameliorates cardiomyocyte injury.	[27]

HDAC2, Histone Deacetylase 2; ATXN1L, Ataxin-1-like; Sirt1, Sirtuin 1; GSK-3β, Glycogen Synthase Kinase-3β; BMF, Bcl-2 modifying factor; HMGA1, High Mobility Group AT-hook 1; PTEN, Phosphatase and Tensin Homolog; TXNIP, Thioredoxin-interacting protein; IRAK-1, Interleukin-1 Receptor-associated Kinase 1; Bim, Bcl-2 Interacting Mediator of Cell Death; Egr-1, Early Growth Response 1; XIAP, X-linked Inhibitor of Apoptosis; PDCD4, Programmed Cell Death 4.

found that miR-200a-3p decreases after CME; consequently, myocardial injury induced by CME is ameliorated through inhibition of the TXNIP/NLRP3 axis, the inflammatory response, and oxidative stress [19]. Xu et al. have found that overexpression of miR-142-3p targets ATXN1L, thus decreasing myocardial injury after CME, and that ATXN1L binds HDAC3, thus promoting histone 3 deacetylation and consequently inhibiting NOL3 expression, promoting caspase-1/IL-1β/IL-18 signaling, and inducing myocardial injury [15]. Kong et al. have found that miR-26a-5p is downregulated after CME; this miRNA binds HMGA1 mRNA and regulates the HMGA1/nuclear factor kappa-B (NF-κB)/TNF-α pathway, thus ameliorating myocardial inflammation and injury after CME

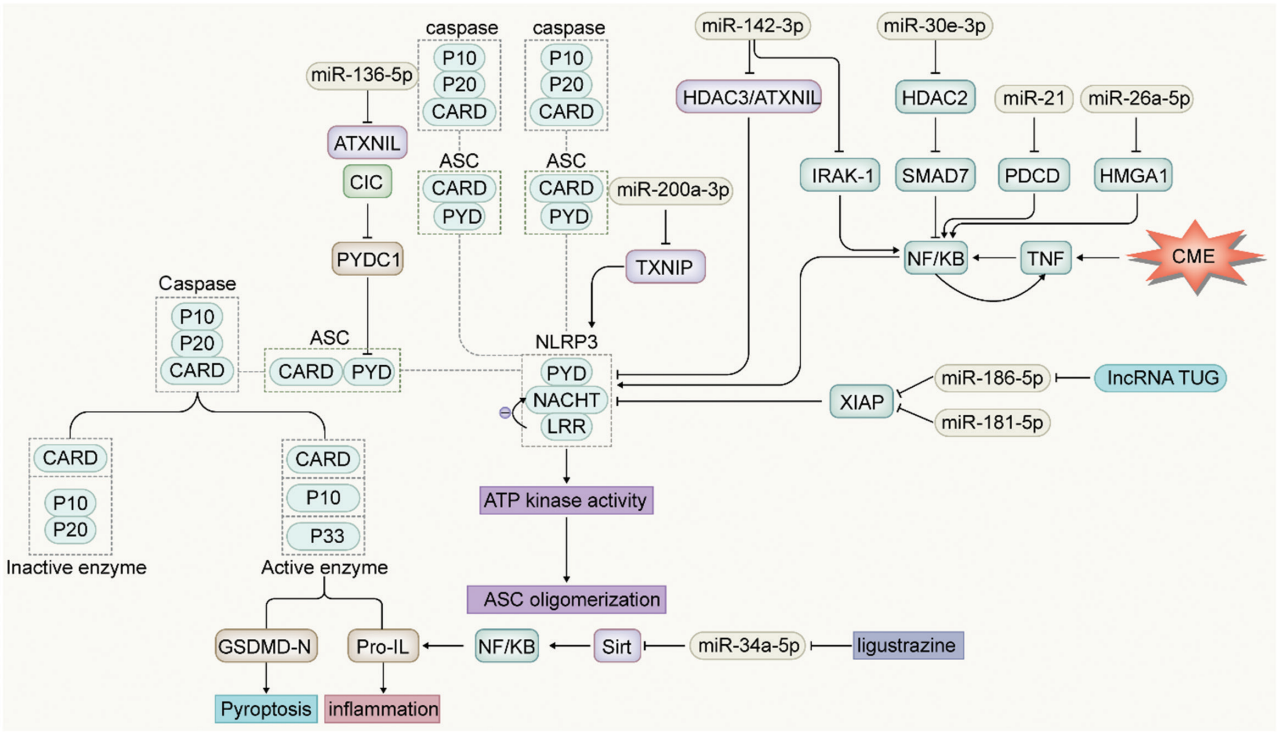

Figure 2 Regulation of Inflammation by miRNAs after Coronary Microembolization (CME).
Inflammasome formation is critical in mediating the inflammatory response. After CME, NLRP3 is activated by the sensor, then aggregates with ASC and caspase, thereby forming the classic NLRP3 inflammasome. The NLRP3 sensor protein consists of three domains: an amino-terminal PYD that binds ASC; a central nucleotide domain (NACHT) with ATP activation activity and polymerization function; and a carboxyl-terminal LRR domain that inhibits NACHT function. In general, inflammasomes are inhibited by the action of LRR. During inflammatory or traumatic stimulation, active caspases in the NLRP3 inflammasome cleave interleukins and generate active IL-1β and IL-18, which in turn lead to inflammation. Simultaneously, the N-terminus of GSDMD is cleaved and inserted into the cell membrane, thus causing pyroptosis. Inflammation is regulated by the inflammatory signaling pathway, and miRNAs regulate CME by regulating the inflammatory signaling pathway.

[17]. Gao et al. have found that ligustrazine pretreatment inhibits the expression of miR-34a-5p in CME rats, thereby inhibiting the inflammatory response and alleviating coronary microvascular dysfunction through the Sirt1/Endothelin Nitric Oxide Synthase and Sirt1/NF-KB pathways [14]. Zhou et al. have found that miR-181a-5p and miR-186-5p are upregulated after CME; these miRNAs promote pyroptosis and aggravate myocardial injury by targeting XIPA [23, 24]. Dai et al. have found that miR-30e-3p is downregulated after CME; this miRNA inhibits the inflammatory response by inhibiting the HDAC2/SMAD7 pathway [12]. In a porcine CME model, Su et al. have found that miR-142-3p inhibits the IRAK-1/NF-κB signaling pathway by targeting IRAK-1, thus decreasing myocardial inflammation and myocardial injury after CME [20]. Ultrasound microbubble-mediated miR-21 transfection inhibits the PDCD4/NF-κB/TNF-α pathway by targeting PDCD4 mRNA, and decreases inflammation and myocardial injury after CME [26].

Roles of miRNAs in CME-Induced Apoptosis

Classical apoptosis is an active programmed death process characterized by nuclear condensation, chromatin condensation, and apoptotic body formation, as viewed through microscopy. Cardiomyocyte apoptosis, a cause of poor prognosis after CME, is regulated by the apoptotic signaling pathway. The mitochondrial pathway, endoplasmic reticulum pathway, and death receptor pathway initiate apoptosis at different stages and finally activate caspase for completion of apoptosis. The balance between pro-apoptotic factors and anti-apoptotic factors in the B-cell lymphoma-2 (Bcl-2) family is key to apoptosis regulation. Anti-apoptotic factors, such

as Bcl-2, B-cell lymphoma-extra-large (Bcl-xl), and Bcl-2-like protein 2 (Bcl-w), inhibit the activity of pro-apoptotic factors by binding Bcl-2 homology motif (BH3)-only and Bak proteins. When stimulated, the pro-apoptotic factor Bak accumulates on the mitochondrial membrane, separates from the anti-apoptotic factor, and binds Bcl-2 antagonist killer 1 (Bak1) and Bcl-2-associated X protein (Bax), thus forming a porin complex, which in turn increases mitochondrial membrane permeability and releases cytochrome C (Cyt c). Cyt c in the cytoplasm binds apoptosis-associated factor 1 (Aprf-1) and recruits caspase to the cytoplasm, thus inducing apoptosis.

In recent years, a small number of studies have suggested that miRNAs induce myocardial injury after CME by regulating apoptosis-associated signaling pathways. In a study of rat cardiomyocytes isolated in vitro, Su et al. have found that miR-30e-3p expression decreases, whereas apoptosis levels and caspase expression increase, after myocardial cells are exposed to ischemia and hypoxia; in contrast, Egr-1 and caspase expression and apoptosis decrease when miR-30e-3p is overexpressed, thus indicating that miR-30e-3p ameliorates myocardial injury by targeting Egr-1 and decreasing apoptosis [22]. In a human-induced pluripotent stem cell-derived cardiomyocyte (hiPSC-CM) model, Mo et al. have found that the expression of miR-30e-5p decreases, and apoptosis increases, after exposure to hypoxia for 24 h. Luciferase reporter gene testing has confirmed that miR-30e-5p directly targets Bim, thus decreasing apoptosis [21]. Qin et al. have found that miR-29b-3p expression decreases in a rat CME model, and its upregulation inhibits the expression of Bax, caspase 3, and caspase 9, but increases the expression of Bcl-2; double fluorescence gene assays further confirmed that this process is achieved by miR-29b-3p targeting Bcl-2 modifying factor (BMF) [16]. When the damage to signal persists, the secretion of BMF increases. BMF, through binding and degrading the antiapoptotic protein Bcl-2, induces cells apoptosis [16]. The expression of miR-486-5p decreases after CME. Through WB detection and TUNEL staining, overexpression of miR-486-5p has been found to decrease the expression of PTEN and the number of apoptotic cardiomyocytes. Moreover, miR-486-5p inhibits apoptosis by targeting PTEN, thus activating the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway [18].

Roles of miRNAs in CME-Induced Autophagy

In autophagy, dysfunctional cellular components are transported to lysosomes for degradation under the regulation of autophagy-related genes (ATG), to meet cellular metabolic needs and renew organelles [30]. Autophagy can be categorized into macroautophagy, microautophagy, or chaperone-mediated autophagy, according to how cellular substances are transported to lysosomes [31]. Macroautophagy refers to the encapsulation of the cytoplasm by a double-layer membrane structure, thus forming an "autophagosome," which fuses with lysosomes for degradation [32]. In microautophagy, lysosomes directly invaginate into vesicles, encapsulating part of the cytoplasm in lysosomes [32]. Chaperone-mediated autophagy is independent of the vesicle structure and directly uses the chaperone protein heat shock protein 70 to recognize lysosomes and guide the target protein to lysosomes for degradation through a highly selective process [32].

Macroautophagy, the most common process in mammalian cardiomyocytes, can be divided into three stages: formation of autophagosomes, extension of autophagosome membranes, and fusion of autophagosome and lysosome membranes (Figure 3). The mitochondria and other organelles in the cytoplasm shed part of their bimolecular membrane, which encloses parts of organelles, cytoplasm, proteins, and other components, and forms a phagocytic vesicle assembly site. ATG proteins mediate phagosome membrane elongation and the formation of autophagosomes, which in turn bind lysosomes and form autolysosomes. There are several products of autophagic lysosome degradation, some of which include amino acids, ATP, and other substances for cellular reuse.

Under normal conditions, cardiomyocytes have basal levels of autophagy. However, the level of autophagy fluctuates when cells are exposed to external factors, such as elevated AMP/ATP and amino acid deficiency, which increase cellular autophagy. Autophagy is involved in several

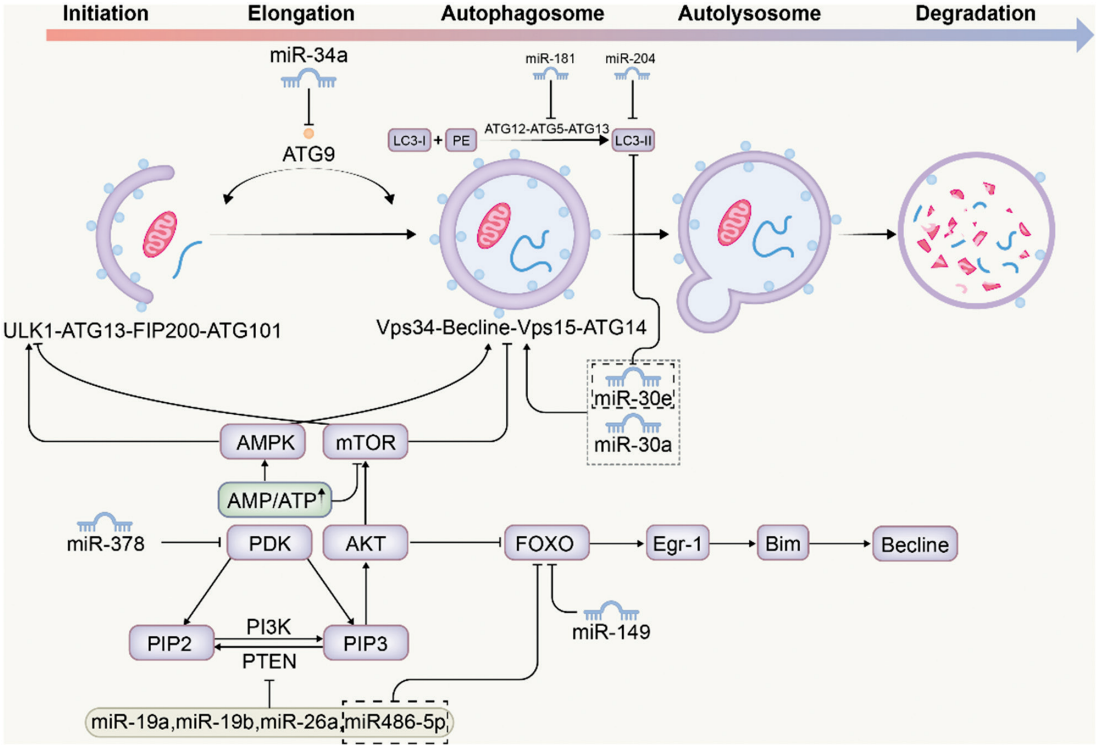

Figure 3 Regulation of Macroautophagy by miRNAs.
The decrease in autophagy flux after CME aggravates myocardial injury. Macroautophagy can be divided into three stages: formation of autophagosomes; extension of autophagosome membranes; and fusion of autophagosome and lysosome membranes. During the autophagy induction phase, the ULK1-ATG13-FIP200-ATG101 and Vps34-Beclin-Vps15-ATG14 complexes, which comprise autophagy proteins in mammalian cells, regulate autophagy initiation and nucleation, respectively. Atg9 promotes autophagosomal membrane extension via the bidirectional movement of membrane lipids between phagosome assembly sites and organelle membranes. The Atg12-Atg5-Atg16L complex aids in the conjugation of LC3-I to PE, thus forming LC3-II, which in turn promotes phagosome closure and maturation. AMPK and mTOR regulate the autophagy induction phase. mTOR is a "gate switch" molecule regulated primarily by the PI3K-AKT pathway. PTEN negatively regulates the PI3K-AKT pathway, and PTEN inactivation can result in constitutive activation of the PI3K-AKT pathway and induction of autophagy. MicroRNAs affect autophagy flux and cardiac function by regulating ATG and autophagy upstream signaling pathways. PIP2: Phosphatidylinositol 3,4-Bisphosphate; PIP3: Phosphatidylinositol 3,4,5-Trisphosphate.

physiological processes, including myocardial cell energy metabolism, heart development, and myocardial protein and organelle catabolism [33]. Fernandez et al. have determined that the Beclin 1 (F121A) mutation disrupts Beclin1-Bcl2 binding, increases basal autophagy, and inhibits cardiac fibrosis in mice [34]. These findings suggest that insufficient autophagy may cause myocardial cell injury and decrease cardiac function. CME stimulates a decrease in autophagy in cardiomyocytes. In a rat CME model [25], electron microscopy and immunofluorescence analyses have revealed a considerable decrease in the number of autophagic vacuoles 6–12 h after CME. Moreover, the intensity of the anti-light chain 3 (LC3)-II band is considerably weakened, levels of MI markers increase, and a reduced ejection fraction is observed. These results have confirmed that autophagy flux and cardiac function decrease after CME, indicating a causal relationship. Yan et al. have speculated that the decrease in autophagy levels after CME causes a decrease in cardiac resistance to ischemic injury and cardiac remodeling [35], thus contributing to the poor prognosis after CME.

Autophagy is highly dependent on cellular energy and nutrient status, and is tightly regulated by ATG proteins, to maintain the stability of the intracellular environment. MicroRNAs play key roles in regulating autophagy in multiple organs and tissues (Figure 3). During the autophagy induction phase, the unc-51-like kinase 1 (ULK1) and phosphatidylinositol 3-kinase (PI3K) class III complexes, which

comprise autophagy proteins in mammalian cells, regulate autophagy initiation and nucleation, respectively [30]. AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR), important kinases that regulate the autophagy induction phase [36], regulate autophagic flux by sensing the intracellular AMP/ATP ratio and amino acid levels, respectively. Various upstream signaling pathways regulate autophagy by affecting autophagy "gate switch" mTOR activity [37]. Among them, the PI3K-AKT pathway is the primary signaling pathway for autophagy regulation. MicroRNAs regulate autophagy by regulating the expression of ATG proteins at different stages. For example, miR-30a directly targets the autophagy initiation and nucleation-associated proteins Beclin1 and PI3K. PTEN is regulated by miR-19a, miR-19b, miR-26a, and miR-486-5p, thus resulting in constitutive activation of the PI3K-AKT pathway and autophagy induction [18, 38–40]. The expression of 3-Phosphoinositide Dependent protein Kinase (PDK)-1 is regulated by miR-378, thereby affecting AKT activation and promoting autophagy [41]. Simultaneously, miR-378 promotes cell survival by targeting caspases and consequently increasing the apoptosis threshold [41, 42]. Recent studies have shown that AKT substantially affects autophagy by regulating mTOR and Forkhead box O (FoxO). miR-378 regulates the PI3K-AKT pathway and influences the mTOR/ULK1 pathway, thereby promoting autophagy initiation while maintaining autophagy through FoxO-mediated transcriptional enhancement [41]. FoxO is regulated by miR-486-5p [43] and miR-149 [44], and plays multiple roles in autophagy regulation. Atg9 is a transmembrane autophagy protein that promotes autophagosomal membrane extension via the bidirectional movement of membrane lipids between phagosome assembly sites and organelle membranes. Yang et al. have found that Atg9 is directly inhibited by miR-34a, thereby affecting autophagosomal membrane extension [45]. The E3-like enzyme Atg12-Atg5-Atg16L promotes the binding of Atg8 (LC3-I) to phosphatidylethanolamine (PE), thus forming LC3-PE (LC3-II) [46], which in turn promotes phagosome closure and maturation. miR-181a and miR-204 directly downregulate the expression of Atg5 and LC3B, respectively [47, 48], and inhibit autophagosome maturation. Animal experiments have demonstrated the effects of autophagy on cardiac function after both CME and myocardial injury after CME. miR-30e induces changes in cardiac function after CME by targeting LC3B and Beclin [25]. Therefore, miRNAs are involved in myocardial injury after CME through targeted regulation of autophagy-related genes.

Conclusion

Inflammation and apoptosis increase after CME, and autophagy and cardiac function decrease. MicroRNAs regulate inflammation, apoptosis, autophagy-related proteins, and their upstream signaling pathways, thereby affecting the number of viable cardiomyocytes and the systolic function of viable cardiomyocytes, and resulting in poor prognosis after CME. MicroRNAs are regulated by ceRNAs, thereby forming a regulatory network. One miRNA can target multiple mRNAs simultaneously. Investigating the regulatory mechanisms underlying the roles of miRNAs in the development of CME is crucial for identifying novel drugs for the treatment of CME. Exploring miRNAs that can simultaneously regulate the levels of apoptosis, inflammation, and autophagy will be important to decrease myocardial injury after CME. This article does not fall within the scope of data availability considerations, because it involved neither the creation nor the analysis of new data.

Research Outlook

After CME, the ischemic and hypoxic signals of cardiomyocytes are translated into biochemical signals. The molecular mechanism underlying the poor prognosis after CME remains to be further explored, to improve understanding of the theoretical basis of CME, and provide strategies for diagnosis and treatment. Recent studies have shown that CME, as an exogenous stimulus, continually decreases myocardial autophagy and plays an important role in myocardial injury and a poor cardiac prognosis after CME; this process is regulated by miRNAs. Moreover, mTOR, an autophagy-gated molecule regulated by miR-144-3P, has attracted substantial attention. The level of miR-144-3P is significantly elevated in the serum in patients with ACS [49]. Therefore, further

exploration of whether miR-144-3P changes after CME, and its significance in the diagnosis and treatment of CME, is warranted.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

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