Potential role of microRNAs in the regulation of pyroptosis (Review)

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Abstract. MicroRNAs (miRNAs) perform a variety of important cellular functions, including regulating the cell cycle, apoptosis and differentiation, amongst others. Recent research has demonstrated an essential function performed by miRNAs in regulating pyroptosis, which is a type of programmed cell death associated with inflammatory responses that plays a critical role in numerous diseases. Through direct or indirect action on proteins associated with the pyroptosis signaling pathway, miRNAs are involved in the pathological processes of cardiovascular, kidney and immune diseases, among others. The present review discusses the maturation process of miRNAs and the process of pyroptosis, with a specific focus on the transport of miRNAs to damaged cells via exosomes, shedding vesicles and protein stabilized complexes, as well as the role of different miRNAs in the regulation of pyroptosis through different gene and protein targets. The aim of the present review was to provide a novel insight into the regulatory role of miRNAs in pyroptosis and new treatment options for pyroptosis-associated diseases.

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Abbreviations: ASC, apoptosis-associated speck-like protein containing a CARD; DAMPs, danger-associated molecular patterns; DCM, diabetic cardiomyopathy; FOXO3a, forkhead box O3; GSDMD, gasdermin D; IL-1β, interleukin-1β; IL-18, interleukin-18; lncRNAs, long non-coding RNAs; LPS, lipopolysaccharide; LRR, leucine-rich repeats; MI, myocardial infarction; miRNAs, microRNAs; ncRNAs, non-coding RNAs; NLRP3, NOD-like receptor protein 3; NLRs, Nod-like receptors; PAMPs, pathogen-associated molecular patterns; PD, Parkinson's disease; SIRT1, silencing information regulator 2-related enzyme 1; TET2, tet methylcytosine dioxygenase 2

Key words: miRNAs, pyroptosis, inflammatory responses, programmed cell death, diseases

Contents

1. Introduction

The transcription of genetic information from DNA to RNA and the subsequent translation into proteins constitutes the core of molecular biology. It has been long established that the key factor in gene regulatory networks is the protein-coding gene. Non-coding RNAs (ncRNAs) were first identified in the early 1990s with the advent of RNA interference technology. However, it took ~10 years until the fundamental roles of ncRNAs in gene silencing and biological functions were recognized (1). MicroRNAs (miRNAs/miRs) are a major family of ncRNAs, and numerous studies have demonstrated that most miRNAs play key roles in biological processes and cellular metabolism, which are tightly regulated at multiple levels. Aberrant miRNA expression is involved in various pathophysiological processes, such as spinal cord injury, neurodegenerative and cardiovascular diseases, and aging (2-5). However, to the best of our knowledge, the potential mechanisms have not yet been fully elucidated.

Pyroptosis is a form of programmed cell removal as a result of various factors. Firstly, it is through a CARD-containing inflammasome that a directly-activated inflammatory caspase triggers the removal of cells (6). Secondly, the pores, 1-2 nm in diameter, develop in the plasma membrane of cells due to the activation of the inflammatory caspase, resulting in cell swelling due to water uptake and subsequent cell lysis through rapid disruption of the plasma membrane. Thirdly, the local or systemic inflammatory effects are amplified by membrane

rupture and various cytosolic contents entering the extracellular environment, for example, interleukin (IL)-1β and IL-18 (7,8). Pyroptosis processes function as a double-edged sword through both rapidly eliminating intracellular pathogens by coordinating antimicrobial host defenses, and deleteriously amplifying local destructive pathways (9,10). The regulatory mechanisms of pyroptosis involve a variety of molecular mechanisms and signaling pathways, but there has been little research investigating the effects of miRNAs on the regulatory mechanisms of pyroptosis. In the present review, the expression of miRNAs and the association between miRNAs and pyroptosis are summarized in order to provide a novel insight into the prevention and treatment of diseases associated with pyroptosis.

2. Overview of ncRNAs

ncRNAs fall into the category of functional RNA molecules responsible for the coding of substances other than protein (11). In 1970, most scholars widely accepted that humans have >10,000 genes, the majority of which possess protein-coding functions (12). By the 1990s, the existence of numerous more genes had been revealed in the Human Genome Project and Encyclopedia of DNA Elements. Genomic transcription is common, but >80% of genes are transcribed into ncRNAs, which lack the ability to encode proteins (13,14). Nevertheless, a number of recent studies have demonstrated that numerous ncRNAs not only regulate DNA expression, but are also involved in several complex biological processes (4,15,16).

The ncRNAs are classified into three major subclasses according to their sequence length and structure: Short ncRNAs (<200 nucleotides in length), long ncRNAs (lncRNAs; >200 nucleotides in length) and circular RNAs (17). Based on their localization and function, ncRNAs can also be divided into lncRNAs, miRNAs, ribosomal RNAs (17), transfer RNAs (18), piwi-interacting RNAs (19), exosomal RNAs (20), small interfering RNAs (21), small nucleolar RNAs (22) and small nuclear RNAs (23). Due to the limited number of protein-coding genes, miRNAs, of which there are several in the non-coding transcriptome, are attracting much attention as potential therapeutic targets for human diseases. However, the functions, target specificity and molecular mechanisms of numerous miRNAs remain to be determined. Therefore, the ways in which miRNAs can be utilized in the clinical setting remain to be further studied (24).

3. Overview of miRNAs

Discovery and origin of miRNAs and communication of miRNAs between cells. As small ncRNA molecules (19-25 nucleotides in length), miRNAs can regulate the way in which protein-coding genes are negatively expressed (25). Since miRNAs were first identified in *Caenorhabditis elegans* in 1993 (26), with the continuous maturity of sequencing technologies, scholars have discovered >1,000 types of miRNA genes within the human body (27,28). As much as ~30% of the human genome is suspected to be subject to regulation by miRNAs, thus implying their significance in regulating gene expression. Biological activities such as growth, cell multiplication, apoptosis, the immune response and pyroptosis are all associated with miRNAs (29).

The biogenesis of miRNAs and various other small-size RNAs are different. miRNAs are obtained by creating distinctive hairpin structures after folding back transcripts (30). A two-step cleavage process is required for miRNA biogenesis. The first step is miRNA cleavage by the ribonucleases Drosha and DiGeorge syndrome critical region gene 8 (DGCR8). A miRNA duplex is obtained from the second cleavage event performed by Dicer and argonaute protein (31). The processes are shown in Fig. 1. However, there are some endogenous small RNAs stemming from the hairpins with a far greater length, thus making small RNAs, bimolecular RNA duplexes or the precursors lacking double-stranded character even more diversified (25).

There are three major miRNA communication pathways between cells that inhibit pyroptosis, including exosomes, shedding vesicles and RNA-binding proteins (Fig. 1). In exosome pathways, studies have identified that miR-148a derived from the M2 exosome, which is secreted by macrophages, can inhibit thioredoxin interacting protein and the toll-like receptor 4/NF-κB/NLR family pyrin domain-containing 3 (NLRP3) inflammasome signaling pathway (32,33). Wang *et al* (34) also reported that macrophages secrete exosomes that release miR-155 into the cytosol, which can directly target forkhead box O3 (FOXO3a) to inhibit pyroptosis in uremic cardiomyopathy. Regarding the shedding of vesicles, it was revealed that extracellular vesicles carrying miR-21-5p affect podocyte pyroptosis in diabetic nephropathy (35). Another communication pathway is associated with RNA-binding proteins (36), such as RNA-Binding Protein Dnd1. It has been reported that Dnd1 can stabilize miR-221, which can further suppress activation of the NLRP3/apoptosis-associated speck-like protein containing a CARD (ASC)/pro-caspase-1 inflammasome pathway (37,38).

miRNA maturation pathways and regulatory mechanisms of miRNAs. The maturation of miRNA is a tightly regulated multistep procedure. In most cases, the respective facilitators are what the transcription of intergenic miRNAs with gene regulatory regions is reliant on. In addition, the expression of host mRNAs determines the transcription of intronic miRNAs. Following transcription, primary miRNAs undergo two processes that form mature miRNAs of 21-22 nucleotides in length (39,40). When liberating a 60-70 nucleotide-length stem loop intermediate, the first process is the nuclear cleavage of the primary miRNA in the nucleus, which is then referred to as the precursor miRNA. The cleavage occurs through the use of the Drosha RNase III endonuclease (41). As performed by the enzyme Dicer, which is also an RNase III endonuclease, the second step occurs in the cytoplasm, whereby the protein Dicer acts with argonaute protein to cleave the pre-miRNA into ~22 nucleotide miRNA duplexes (double-stranded RNA) (42,43). The mechanism by which miRNAs regulate gene expression is relatively simple. It requires an ideal base pairing between the seed and target sequences. The direct interaction between miRNA and mRNA can silence the majority of mRNAs targeted by miRNAs, thus inducing mRNA degradation and/or inhibiting mRNA translation (44,45). It is common

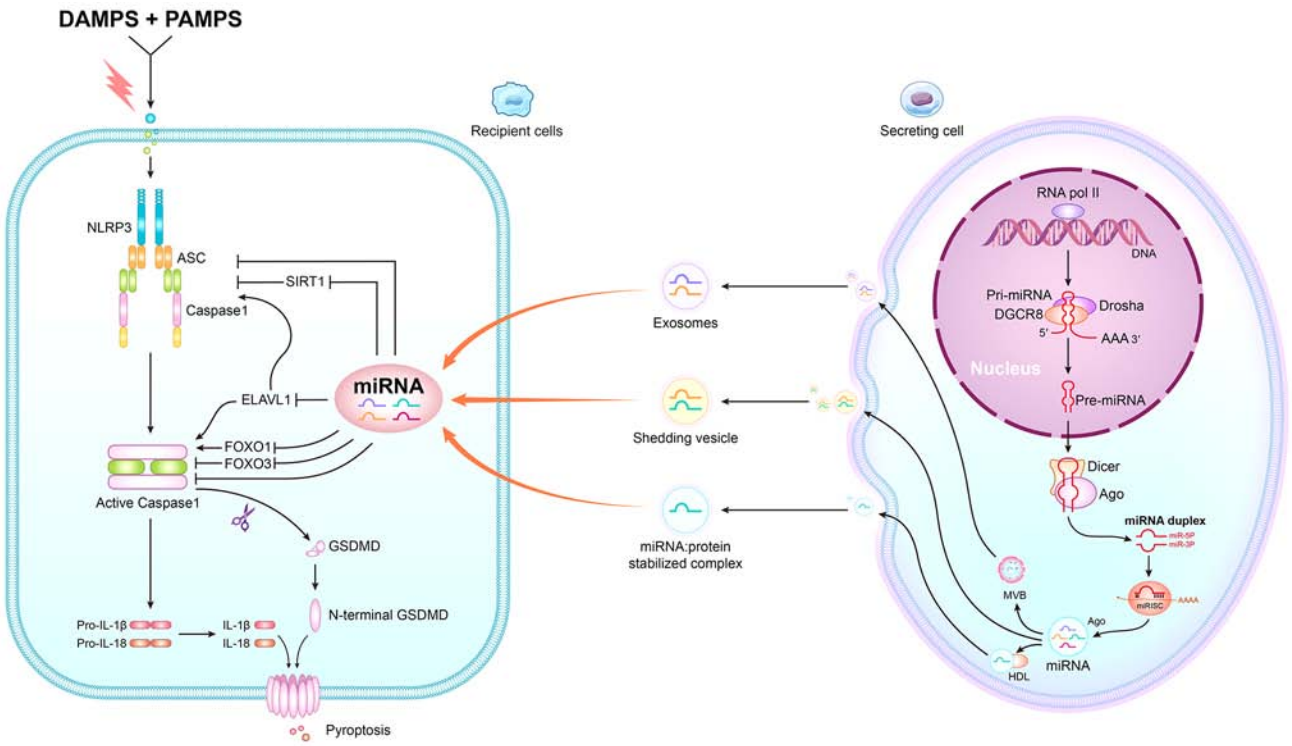

Figure 1. Graphical depiction of the process of miRNA regulating pyroptosis. On secreting cells, miRNAs are first transcribed as pri-miRNAs, typically by RNA polymerase II. Pri-miRNAs are processed by the Drosha-DGCR8 complex in the nucleus to generate pre-miRNAs, which are then exported to the cytoplasm to be cleaved by Dicer, producing duplexes containing both Ago and guide miRNA strands. The passenger strand is degraded and the guide strand is loaded onto an Ago to form the miRISC. On recipient cells, DAMPs and PAMPs can activate the NLRP3 inflammasome, which includes NLRP3, ASC and pro-caspase-1 and cleavage of the caspase-1 precursor, which activates caspase-1. Caspase-1 then regulates the production of the inflammatory cytokines IL-1β and IL-18. Horizontal transfer of miRNAs from secreting cell to receiving cell includes three pathways: i) First pathway, active secretion via MVBs, such as exosomes; ii) second pathway, shedding vesicles are another active secretion pathway; and iii) third pathway, uses RNA-binding protein to secrete miRNA. For instance, HDL can associate with exogenous miRNAs and deliver them to recipient cells. The received miRNAs regulate the activity of NLRP3 by targeting SIRT1. In addition, the expression of ELAVL1, which is a target of miRNAs, can affect the activity of caspase-1 and NLRP3 to regulate pyroptosis. In addition, miRNAs also can regulate the activity of caspase-1 by affecting FOXO3 and FOXO1 expression. miRNA, microRNAs; pri-miRNA, primary miRNA; pre-miRNA, precursor miRNAs; miRISC, miRNA-induced silencing complex; DAMPs; danger-associated molecular patterns; PAMPS pathogen-associated molecular patterns; NLRP3, NLR family pyrin domain containing 3; ASC, apoptosis-associated speck-like protein; SIRT1, silencing information regulator 2-related enzyme 1; GSDMD, gasdermin D; ELAVL, ELAV-like RNA binding protein 1; FOXO, forkhead box O; IL, interleukin; HDL, high density lipoprotein; MVBs, multivesicular bodies.

that miRNAs are able to bind to multiple mRNA species and inhibit the expression of several different transcripts simultaneously (46). Individual miRNAs target mRNAs, which frequently encode the proteins performing relevant functions (47). However, miRNA inhibitory effects on individual mRNAs are generally modest when it comes to regulating critical biological events, and the combined effects of several miRNAs on multiple mRNAs can induce strong biological responses (48,49).

4. Pyroptosis

Origin and characteristics of pyroptosis. Cell death is not only the end of life, it is also necessary to sustain life. There are three different types of cell removal that have been widely studied: Apoptosis (50), autophagic cell death (51) and necrosis (52). Among the most classical types of cell death, apoptosis features a number of morphological changes: Cell shrinkage, cytoplasm condensation, chromatin condensation and apoptotic body formation. In contrast to necrotic cells, apoptotic cells do not release intracellular contents into the extracellular environment upon death (53). Cytoplasmic vacuolization, phagocytic uptake and consequent lysosomal degradation are the manifestations of autophagic cell removal (54). Pyroptosis, as the other form of programmed cell death, has been widely investigated. Pyroptosis was first observed in *Shigella flexneri*-infected macrophages in 1992 by Zychlinsky *et al* (55). In 2001, caspase-1-dependent cell removal was termed pyroptosis, combining the Greek roots 'pyro', associated with fire or fever, and 'ptosis', signifying decline (56). The characteristics of pyroptosis include pore formation in plasma membranes, cell swelling and discharge of pro-inflammatory cytokines (IL-1β and IL-18) (57,58). The process is mediated by Nod-like receptors with C-terminal leucine-rich repeats (LRRs) that can detect the pathogen-associated molecular patterns (PAMPs) or the damage-associated molecular patterns (DAMPs). Next, through the homotypic interaction of NACHT domains, NLR monomers oligomerize before attaching to an adapter protein known as ASC/PYCARD, by means of PYD-PYD interaction. Subsequently, procaspase-1 is recruited by adaptor proteins and cleaved into caspase-1. Caspase-1-mediated pyroptosis requires pores to develop in the cell membrane, thus causing water influx and the discharge of pro-inflammatory factors, such as IL-18 and IL-1β (59,60).

Canonical and non-canonical pathways of pyroptosis. Signaling pathways for pyroptosis mainly include a canonical pathway that depends on caspase-1 activation, and a non-canonical pathway that relies on caspase-4/5 (human) or caspase-11 (mouse) activation.

In the canonical pathway, LRR recognition of DAMPs and PAMPs can activate the NLRP3 inflammasome, which includes NLRP3, ASC and pro-caspase-1 and cleavage of the caspase-1 precursor, which activates caspase-1. Caspase-1 then regulates the production of the inflammatory cytokines IL-1β and IL-18 (61). Following the activation of caspase-1 acting on gasdermin-D (GSDMD), GSDMD is cleaved to generate a reactive amino (N) end and a carboxyl (C) end. The formation of 10 to 15-nm pore-like structures inside the membrane lipid bilayer is preceded by the oligomerization of an N-terminal domain (62). These pores are assumed to play the role as conduits in the discharge of small molecules, such as IL-1β and IL-18. These mechanisms are shown in Fig. 1. Furthermore, a local inflammatory response is prompted by stimulating various target cells, such as monocytes, macrophages and dendritic cells. In the meantime, systemic inflammatory functions, such as neutrophil recruitment, are initiated (63).

The non-canonical pathway of inflammasome activation is dependent on human caspase-4/-5 and murine caspase-11. Caspase-4 is linked to pyroptotic cell removal in monomyelocytic cell lines (THP1 and U937) as a result of delivering lipopolysaccharide (LPS) within cells (64). In addition, the activated stimuli and function of caspase-5 have been revealed. Both caspase-4 and -5 were verified by Viganò *et al* (65) as critical downstream targets for activating LPS in human monocytes. Furthermore, intracellular LPS can be sensed by caspases-4 and -5, both of which contribute to self-activation (64). Caspase-11 has two different effects. Not only does caspase-11 activation directly lead to macrophage pyroptosis, but it also acts as a binding partner in regulating how caspase-1 is activated, leading to the production of IL-1β and IL-18, and subsequent pyroptosis (66-68).

5. Association between miRNAs and pyroptosis

miRNA pathways regulating cell pyroptosis

Post-transcriptional modifications negatively regulate inflammasome activation. Generally involved in the pathological processes of various diseases, miRNAs can bind to complementary target mRNAs, thus regulating gene expression in a negative way (25,69). Thus, numerous mRNAs that encode proteins with shared biological processes are regulated by one miRNA. In addition, one mRNA can also be regulated by a number of other miRNAs. It was indicated that miRNAs perform regulation in two ways. One way is inhibiting mRNA translation. Another way is decreasing target mRNA amounts (70,71). As revealed by some previous studies, NLRP3 is a direct target for miR-223, which negatively regulates the development of inflammasomes (69,72). Bauernfeind *et al* (69) identified miR-223 as playing a vital role in regulating the activity performed by NLRP3 inflammasomes in macrophages. For suppressed expression, miR-233 gets attached to a preserved binding site within the 3'-untrnaslated region (UTR) of NLRP3 (69). Thus, miR-223 plays a crucial role in NLRP3 inflammasome activity for rheostat control considering the strict transcriptional regulation of NLRP3 mRNA. Furthermore, a previous study revealed that the same site in the NLRP3 mRNA 3'-UTR was targeted by EBV miR-BART15 for hindering the inflammasome from being activated (72).

Transcription factors negatively regulating inflammasome activation. Silencing information regulator 2-related enzyme 1 (SIRT1) and FOXO3a expression levels were silenced by the transcription factors negatively regulating pyroptosis (73). SIRT1 is essential for suppressing apoptosis, decreasing inflammatory reactions, preserving mitochondrial function and oxidative stress. STAT1 hinders pyroptosis by making the NLRP1 and NLRP3 inflammasomes less active (74). In a bioinformatics analysis, Wang *et al* (75) revealed that miR-9-5p could bind to the 3'-UTR of SIRT1 for the negative regulation of SIRT1 expression. In addition, Ding *et al* (76) revealed that SIRT1 was targeted by miR-29a in H9c2 cardiomyocytes using a dual luciferase assay. The inhibition of SIRT1 resulted from miR-29a binding to SIRT1, which promoted pyroptosis.

Another transcription factor is FOXO3a, which was reportedly associated with the negative regulation of pyroptosis. As revealed in a previous study, miRNAs enhanced the downregulation of FOXO3a before the decreased suppression of apoptosis, as regulated by FOXO3a (77). This led to the upregulation of caspase-1 and the induction of pyroptosis (78).

miRNA suppresses pyroptosis by inhibiting caspase-1. As a major enzyme involved in regulating pyroptosis, caspase-1 processes pro-IL-1β and pro-IL-18 into mature inflammatory cytokines (57,79). The activation of caspase-1 and subsequent cleavage of GSDMD contributes to the formation of pores on the cell membrane, thus causing pyroptosis. Jin *et al* (80) demonstrated caspase-1 to be a functional downstream target of miR-214, revealing that partial sequences of miR-214 could bind to sites in the caspase-1 3'-UTR (80). This may be evidence to support that caspase-1 is targeted by miRNA to regulate pyroptosis. These regulating pathways are presented in Fig. 1.

Association between miRNAs and pyroptosis in disease. Cardiovascular disease. i) Myocardial infarction (MI). The various types of miRNAs that target pyroptosis following MI have been extensively studied. Mezzaroma *et al* (81) demonstrated the presence of the NLRP3 inflammasome in the heart in an experimental mouse model of MI. However, whether miRNAs inhibit pyroptosis in such cases should be further investigated and validated. Thus, Li *et al* (82) revealed that miR-135b targeted and regulated caspase-1, as assessed by a luciferase assay. By detecting the expression of mRNA, the study further discovered that miR-135b downregulated the mRNA expression of caspase-1, suggesting that miR-135b is associated with MI and that its expression can assist with the diagnosis and treatment of MI (82).

ii) Diabetic cardiomyopathy (DCM). Some studies have shown that miRNAs regulate pyroptosis over the course of DCM. A study by Yang *et al* (83) reported that miR-214-3p targets caspase-1 to regulate the expression of NLRP3, IL-1β and IL-18 in DCM. Cell dysfunction *in vitro* was triggered, and the pathological process of DCM *in vivo* was facilitated as a result

of inflammatory cytokine enhancement (83). Furthermore, Li *et al* (84) revealed that miR-30d increased the downregulation of FOXO3a in a diabetic rat model. Thus, miR-30d directly represses FOXO3a expression, which leads to the inhibition of its downstream proteins. Subsequently, the upregulation of caspase-1 occurred, which contributed to pyroptosis. These findings provide another potential mechanism of cardiomyocyte pyroptosis: The upregulation of miR-30d promotes pyroptosis via the downregulation of FOXO3a, which may increase apoptosis repressor with caspase recruitment domain, thus promoting caspase-1 expression and subsequently increasing IL-1β and IL-18 levels, ultimately increasing the levels of pyroptosis (84). In addition, Jeyabal *et al* (85) revealed that in human cardiomyocytes, hyperglycemic conditions enhance the expression of ELAV-like RNA binding protein 1 (ELAVL1), and the expression levels of caspase-1 and IL-1β are increased. Furthermore, ELAVL1-knockdown inhibited pyroptosis through NLRP3, caspase-1 and inflammatory cytokine inhibition. In addition, direct targeting of ELAVL1 by miR-9 was confirmed via bioinformatics analysis and target validation assays (85). Thus, the application of miR-9 can inhibit not only the ELAVL1 overexpression caused by hyperglycemia but also cardiomyocyte pyroptosis. Overall, these studies show that miRNA can inhibit caspase-1-induced pyroptosis, and their results may identify novel therapeutic targets in the pyroptosis signaling pathway in DCM.

iii) Atherosclerosis. Atherosclerotic plaques result in inflammatory processes and lipid metabolism abnormalities (86). Furthermore, several studies have revealed that cholesterol crystals and oxidized low-density lipoproteins (ox-LDLs) can cause inflammasome activation, and have also demonstrated the role of pyroptosis in atherosclerosis (87,88). In addition, miRNAs play a crucial role in treating endothelial dysfunction and have potential for treating atherosclerosis (89). Thus, miRNAs may contribute to the progression of atherosclerosis via pyroptosis. In human aortic endothelial cells, ox-LDL-activated pyroptosis was indicated by Li *et al* (90) as capable of suppressing miR-30c-5p. Furthermore, FOXO3 is considered to be a target gene of miR-30c-5p; however, whether it promotes or inhibits FOXO3 expression remains controversial. These findings provide an alternative method for treating atherosclerosis (90). Furthermore, the impact of lncRNA metastasis-associated lung adenocarcinoma transcript 1 on high glucose-induced cell pyroptosis can be offset by the overexpression of miR-22 (91). Functioning as a DNA demethylase, tet methylcytosine dioxygenase 2 (TET2) is effective in decreasing atherosclerosis (92). In a study by Zhaolin *et al* (93), a bioinformatics analysis was performed to determine whether miR-125a-5p can bind to the 3'-UTR of TET2 mRNA. As revealed by a luciferase reporter gene assay, the expression of TET2 could be suppressed by an miR-125a-5p mimic and enhanced by an miR-125a-5p inhibitor, implying that targeting the TET2 3'-UTR may result in abnormal mitochondrial DNA methylation levels and mitochondrial dysfunction, which induces the production of reactive oxygen species and activates NF-κB, and subsequently, induces the formation of the NLRP3 inflammasome (93). Thus, miR-125a-5p may regulate TET2 expression from the perspective of post-transcription.

With regard to other cardiovascular diseases, such as viral myocarditis, Tong *et al* (94) revealed that the downregulation of NLRP3 and caspase-1 expression could decrease pyroptosis following the inhibition of miR-15 (94).

iv) Ischemia-reperfusion (I/R) injury. According to previous studies, small miRNAs are associated with I/R injury (95,96). In addition, pyroptosis plays a crucial role in the tissue impairments caused by I/R injury (97). Thus, there may be an association between miRNAs and pyroptosis in I/R injury. As revealed by Wu *et al* (98), the direct binding of FOXO3a with miR-155 could enable the induction of pyroptosis in renal tubular cells, which plays a vital role in the regulation of various cellular activities. Capable of inhibiting apoptosis, the proteins downstream of FOXO3a cause both the intrinsic and extrinsic pathways of cell death to be antagonized, thus producing an inhibitory effect (98). Thus, miR-155 has a significant role in renal tubular cell pyroptosis. Furthermore, in a study on blood perfusion following myocardial ischemia, Lin *et al* (99) revealed that miR-149 can bind to the 3'-UTR to negatively regulate FOXO3 expression, whereas silencing of FOXO3 promoted pyroptosis in I/R-treated cells.

A previous study demonstrated that the suppression of pyroptosis and alleviation of inflammatory reactions were largely affected by SIRT1 (100). In addition, Ding *et al* (76) revealed that myocardial I/R injury can be alleviated by inhibiting miR-29a, targeting SIRT1 and decreasing NLRP3-mediated pyroptosis.

Neurodegenerative disease. Individuals aged >90 years have a high risk of developing Parkinson's disease (PD) (101). An increasing number of studies have shown that the pathophysiological process of PD is closely associated with miRNAs (102). In a recent study, Zeng *et al* (103) demonstrated that FOXO1 expression in patients with PD can be enhanced by downregulating miR-135b, which can also affect the activation of the NLRP3 inflammasome and pyroptosis. With respect to PD, one of the complicated mechanisms of its progression is miR-135b-mediated cell death (103). Fan *et al* (104) confirmed that the expression of *Renilla* luciferase can be decreased by miR-7 via the NLRP3 3'-UTR as analyzed using a luciferase assay, which enabled the assessment of NLRP3 protein translation levels (104). In addition, miR-7 overexpression significantly downregulated NLRP3 protein expression levels. By contrast, miR-7 silencing upregulated the expression of NLRP3. The protein levels of caspase-1 or IL-1β production were unaffected by miR-7 overexpression or silencing, suggesting that miR-7 targets NLRP3 (104,105). This may represent a novel therapeutic avenue for neurodegenerative diseases, including PD.

Cancer. As revealed by a previous study, both glioma tissues and cell lines had significantly upregulated caspase-1 expression levels, but significantly downregulated miR-214 expression levels (106). This same studied demonstrated via a luciferase reporter assay that caspase-1 was a target gene of miR-214, and intervention with pyroptosis was found to render miR-214 effective in restricting cell migration and multiplication (106). In addition, miR-181a could enhance the growth and invasiveness of osteosarcoma cells by blocking

Table I. Association between miRNAs and pyroptosis.

miRNA	Mechanism	Regulatory effect on pyroptosis	Disease	(Refs.)
miR-223	Inhibiting NLRP3 activation	Negative	Unclear	(69)
miR-7	Inhibiting NLRP3 activation	Negative	PD	(104,105)
miR-495	Inhibiting NLRP3 activation	Negative	Acute lung injury	(109)
miR-9-5p	Activating SIRT1/NLRP3 pathway	Positive	PD	(75)
miR-29a	Activating SIRT1/NLRP3 pathway	Positive	Myocardial I/R injury	(76)
miR-214	Inhibiting caspase-1 activation	Negative	Glioma	(80,83,106)
miR-135b	Inhibiting FOXO1/caspase-1 pathway	Negative	PD	(82,103)
miR-181a	Unclear	Negative	Osteosarcoma	(107)
miR-30d	Activating FOXO3/caspase-1 pathway	Positive	DCM	(84)
miR-155	Activating FOXO3/caspase-1 pathway	Positive	Renal I/R injury	(98)
miR-149	Activating FOXO3/caspase-1 pathway	Positive	Myocardial I/R injury	(99)
miR-30c-5p	Inhibiting FOXO3/caspase-1 pathway	Negative	Atherosclerosis	(90)
miR-22	Unclear	Negative	Atherosclerosis	(92)
miR-125a-5p	Activating tet methylcytosine dioxygenase 2/NLRP3 pathway	Positive	Atherosclerosis	(93)
miR-15	Unclear	Negative	Viral myocarditis	(94)
miR-9	Inhibiting ELAV-like RNA binding protein 1/caspase-1 and NLRP3 pathways	Negative	DCM	(85)
miR-21	Unclear	Negative	Lipopolysaccharide-induced septic shock	(108)

miRNA/miR, microRNA; NLRP3, NLR family pyrin domain containing 3; SIRT1, silencing information regulator 2-related enzyme 1; I/R, ischemia-reperfusion injury; PD, Parkinson's disease; DCM, diabetic cardiomyopathy; FOXO3, forkhead box O3.

the activation of NLRP3-dependent pyroptosis, as proposed by Tian *et al* (107). These findings suggested that miR-181a could serve as a therapeutic target in osteosarcoma progression. In summary, miR-214 and miR-181 are associated with the regulation of pyroptosis in cancer.

Other diseases. In LPS-induced septic shock, Xue *et al* (108) revealed that the knockdown of miR-21 downregulated NLRP3, ASC and caspase-1 protein levels and inflammasome activation in myeloid cells. In acute lung injury, Ying *et al* (109) showed that alveolar macrophage inflammation and pyroptosis can be decreased by the overexpression of miR-495, while negative regulation of the NLRP3 gene rendered the NLRP3 inflammasome less active. The association between miRNAs and pyroptosis is summarized in Table I.

6. Conclusion

Recently, the regulation of pyroptosis in different pathological situations has attracted significant attention. Considering the complex functions of miRNAs in regulating cell proliferation, survival and death, it is sensible to predict that miRNAs are also associated with biological functions, such as pyroptosis. The present review discussed the maturation process of miRNAs and the process of pyroptosis, with a focus on the transport of miRNA to damaged cells through exosomes, shedding vesicles and protein stabilized complexes. Currently, these miRNA communication pathways between cells that regulate pyroptosis are less studied in diseases. This needs to be a focus of attention in future research. The review also determined the different miRNAs that specifically regulate the process of pyroptosis through different genes and protein targets. In addition, the review aimed to summarize the current evidence available to verify the mechanisms underlying miRNA regulation in pyroptosis. Moreover, it provided evidence of the regulatory role of miRNAs on pyroptosis in the cardiovascular system, nervous system and cancer, which indicates that miRNAs may play an important role in the regulation of pyroptosis. Apart from contributing evidence that miRNAs mediate cell death, an attempt was made to provide recommendations for further research into investigating other mechanisms by which miRNAs may regulate cell death. It is expected that the current understanding of miRNA-dependent regulation of pyroptosis can be improved by performing further research. The present review provides a novel insight into potential targets for the development of novel therapeutic strategies to alter miRNAs *in vivo* to treat pyroptosis-associated diseases.

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Availability of data and materials

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Authors' contributions

XH, CW, JL, HM and YX searched and reviewed the literature, and drafted and revised the manuscript; YC, SS, HuaX and XiaW provided important interpretation of content; XinW and HuiX designed the figure. WN and KZ designed and formulated the review theme, and revised and finalized the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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