Role of microRNA alternation in the pathogenesis of gouty arthritis

Zhipan Luo1,2,3,4†, Fan Yang1†, Shaocheng Hong1†, Jianpeng Wang3, Bangjie Chen1, Liangyun Li2,3,4, Junfa Yang5, Yan Yao2,3,4, Chenchen Yang2,3,4, Ying Hu2,3,4, Shuxian Wang2,3,4, Tao Xu2,3,4 and Jun Wu6*

1The First Affiliated Hospital, Anhui Medical University, Hefei, China, 2Inflammation and Immune Mediated Diseases Laboratory of Anhui Province, Hefei, China, 3Anhui Institute of Innovative Drugs, Hefei, China, 4School of Pharmacy, Anhui Medical University, Hefei, China, 5Institute of clinical pharmacology, Anhui Medical University, Hefei, China, 6Geriatric Department, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, China

Gouty arthritis is a common inflammatory disease. The condition is triggered by a disorder of uric acid metabolism, which causes urate deposition and gout flares. MicroRNAs are a class of conserved small non-coding RNAs that bind to the 3’ untranslated region (UTR) of mRNA and regulate the expression of a variety of proteins at the post-transcriptional level. In recent years, attention has been focused on the role of miRNAs in various inflammatory diseases, including gouty arthritis. It is thought that miRNAs may regulate immune function and inflammatory responses, thereby influencing the onset and progression of the disease. This article mainly reviewed the roles of miRNAs in the pathogenesis of gouty arthritis and prospected their potential as diagnostic and prognostic relevant biomarkers and as possible therapeutic targets.

1 Introduction

Gouty arthritis (GA) is an inflammatory joint disease with a prevalence of 3.9% of all adults in the United States, 5.2% for men, and 2.7% for women (1). As a disorder of uric acid metabolism, this disease is mainly caused by the deposition of monosodium urate crystals (MSU) in the joint capsule, bursa, bone, and cartilage, ultimately causing joint damage and even deformity (2). With gout flares, the pain increases and seriously affects the patient’s quality of life. In addition, gout is closely associated with metabolic comorbidities that can lead to myocardial infarction, type 2 diabetes, chronic kidney...
disease, and premature death (3, 4). The treatment of gouty arthritis attacks is mainly to control pain and suppress joint inflammation, such as the use of non-steroidal anti-inflammatory drugs, glucocorticoids, etc. The long-term management of patients with gouty arthritis focuses on uric acid-lowering therapy to reverse hyperuricemia and thus prevent gout attacks (5, 6). Despite new treatment strategies and a good understanding of the pathogenesis of gouty arthritis, recurrent attacks continue to occur after treatment (7).

MiRNA is a conserved short-stranded non-coding RNA of approximately 23nt in length, and they were first identified in Caenorhabditis elegans in 1993 (8). miRNAs are first transcribed in the nucleus as longer primary miRNAs (primary miRNA, pri-miRNA), then processed in the nucleus by Drosha into hairpin RNAs of 60-70 nucleotides, i.e. precursor miRNAs (miRNA precursor, pre-miRNA), which are transported out of the nucleus with the help of the Exprotin-5 complex and sheared in the cytoplasm by Dicer to become mature miRNAs (9, 10). Current studies have shown that miRNAs are highly conserved evolutionarily (11). A miRNA can regulate the activity or stability of multiple target genes by recognizing and inducing the assembly of the RNA silencing complex (RISC) with the miRNA response element (MRE) in the mRNA 3’ untranslated region (UTR) region of the target gene, and multiple microRNAs can also synergistically regulate the same target gene (12, 13). More than 1,000 miRNAs have been identified in human cells, while more than 500 microRNAs in the human body (14). Although the functions of miRNAs are not fully understood, relevant studies have shown that miRNAs are involved in various processes, including cell differentiation, metabolism, and inflammation (15).

Recent research has demonstrated that miRNA plays an essential role in the pathogenesis of common nonautoimmune inflammatory diseases, including gouty arthritis (16). Although some studies have attempted to elucidate the crucial role of miRNAs in the pathogenesis of gouty arthritis, their analyses have always been conducted in a single direction. They have not diversified to integrate multiple fields of study. Therefore, this paper reviews the various regulatory mechanisms of miRNAs in developing gout, including its relationship with uric acid metabolism, classical inflammatory signaling pathways, and bone erosion. On this foundation, we considered the promise of miRNA as a potential diagnostic and prognostic marker for gout and as a therapeutic target.

2 Overview of gouty arthritis

Gouty arthritis (GA) is characterized by swelling and heat pain in one side of the joint, causing joint dysfunction, deformity, and even disability (17). Epidemiology reports the current range of gout incidence at 0.6-2.8 per 1000 people per year. The prevalence of gout has continued to increase worldwide in recent decades, probably due to the aging of society’s population and changes in dietary patterns (18–20). The development of gout is based on four pathophysiological stages, the first two of which are hyperuricemia and the formation and deposition of sodium urate crystals, the leading causes of which are disorders of purine metabolism and dysregulation uric acid secretion (Figure 1). The latter two components are mainly gout flares triggered by acute inflammatory reactions and irreversible bone erosion caused by the deposition of tophi in advanced gout (21).

Usually, the intake of purines is converted by xanthine oxidase in the liver to uric acid, which is excreted mainly through the kidneys (22). The renal tubular transporters such as OAT4 and GLUT9 are responsible for the reabsorption of uric acid (23, 24), while ABCG2 and ABCC4 are responsible for the secretion of uric acid (25, 26). And once a high purine diet such as alcohol, seafood, and meat is accompanied by impaired renal excretion function, it will lead to hyperuricemia. Once a high purine diet is accompanied by inadequate excretion by the kidneys, it can lead to hyperuricemia (27, 28).

Due to the high concentration of urate, along with other physical and chemical environments, MSU is generated and deposited in the joint cavity, which in turn acts as foreign bodies to recruit neutrophils and macrophages and initiate toll-like receptor (TLR) and NLRP3 inflammasome signaling pathways to activate innate immunity (29–31). Current studies suggest
that the acute flares of gout depend on two switches, one of which is the activation of the TLR2/4-NF-κB signaling pathway within macrophages or monocytes, which promotes the synthesis of pro-IL1-β and significant components of the inflamasome, and that this activation is associated with the influence of large amounts of free fatty acids, intestinal flora or other microorganisms (32, 33). Stimulating sodium urate crystals is another critical point of activation of gout inflammation, which activates the NLRP3 inflammatory pathway by promoting the assembly of inflammatory vesicles, thereby promoting the conversion of pro-caspase-1 to caspase-1 and the release of large amounts of pro-inflammatory factors such as IL-1β (34–36).

These pro-inflammatory factors recruit more neutrophils to exacerbate the inflammatory response; however, along with the inflammatory death of large numbers of neutrophils, activated neutrophils release extracellularly depolymerized chromatin and intracellular granule proteins, called neutrophil extracellular traps (NETs), to trap and break down inflammatory factors to relieve gout flares (37, 38). This chronic inflammatory response develops into the advanced disease characterized by tophi (Figure 1), a microenvironment of adaptive and innate immune cells, MSU, and fibroblasts, promoting bone resorption by osteoclasts and reducing bone formation osteoblasts, and ultimately causes bone erosion (39, 40).

3 The function and mechanism of miRNAs in GA

Extensive studies illustrate that abnormal expression in miRNAs occurs during the pathophysiology of gouty arthritis (15, 41, 42). Only 10% of the population with high uric acid has positive signs of gouty arthritis, which may be associated with different genetic backgrounds, and miRNA sequence alterations affect the genetic susceptibility background (43). In addition to this, human genome-wide association studies (GWAS) have identified many loci associated with hyperuricemia and gout, and these single nucleotide polymorphism (SNP) loci are mainly associated with the coding of uric acid transporter genes (44, 45). Further studies have illustrated the ability of miRNAs to regulate inflammatory immune-related processes in gouty arthritis (46, 47).

Over the past years, attempts have been made to identify aberrantly expressed MiRNAs in gout to explore the role of these molecules in the pathogenesis of gout. In 2014 Tae-Jong Kim et al. first investigated the role of Mir-155 in acute gouty arthritis (48). So far, studies on gouty arthritis have been divided into omics-based high-throughput studies and in vitro cellular models stimulated with MSU or in vivo animal models. A large number of meaningful results have now been identified. Therefore, we will summarize the relationship between miRNAs and gout pathogenesis in terms of hyperuricemia, inflammatory immunity, and bone erosion and look at their diagnostic and therapeutic value based on the last five years of publication and older but more classic literature.

3.1 Involvement of miRNAs in the hyperuricemia

Hyperuricemia (HUA) is the prodromal stage of gout attack and a common clinical feature in the course of gouty arthritis. The inability to excrete uric acid from purines promptly leads to a series of disturbances in the metabolic environment and can even cause damage to liver and kidney function (49). As the body’s primary urate handling organ, the kidney generally relies on renal tubular urate transport proteins, such as URAT1, GLUT9, and ABCG2, to regulate uric acid excretion (26, 44).

It was reported that C421A polymorphism enhanced the degradation of ABCG2 in a miRNA-dependent manner and that the use of inhibitors of miR-519c and miR-328 reversed this translational repression (50). Sun, W. et al. reported that Xie-Zhuo-Chu-Bi-Fang could upregulate miR-34a and downregulate URAT1 to treat hyperuricemia (51). In addition, miR-143-3p can directly target the 3’UTR of GLUT9 in renal tubular epithelial cells to reduce uric acid reabsorption and inflammatory response (52).

In a clinical study, miR-155 was elevated in the serum of HUA patients, and subjects with urate deposition had higher miR-155 than those without deposition findings (53). In vitro experiments also revealed that miR-155 was elevated in high-uric acid-stimulated venous endothelial cells (HUVEC) and inhibited eNOS expression causing endothelial cell dysfunction (54).

Similarly, hyperuricemic stimulation led to the downregulation of miR-92a, thereby inhibiting vascular neogenesis through the KLF2-VEGFA axis (55). Hong Q et al. also found that miR-663 could act on the transcript of TGF-β1 to regulate PTEN to inhibit endothelial cell migration (56). These studies also suggest that high uric acid causes cardiovascular damage and explains the correlation between gout and cardiovascular disease such as myocardial infarction. And miRNAs also play a precise regulatory role in liver and kidney function damage caused by excessive uric acid. Uric acid damages renal interstitial fibroblasts by downregulating miR-9 and causing activation of NF-κB and JAK-STAT pathways (57). Besides, Chen, S et al. also reported that overexpression of miR149-5p inhibited FGF21 expression and attenuated uric acid-induced lipid deposition in hepatocytes (58).

Chi, K et al. found that HOTAIR competitively binds miR-22 in hyperuricemia to regulate NLRP3 inflammasome activation to promote endothelial cell pyroptosis and exacerbate renal injury (59). Recent studies have also reported a decrease in miR-30b and an increase in IL-6R in serum urine and kidney tissue in a mouse model of HUA (60). The above study we summarized in the Table 1. In summary, miRNAs are involved in the development of
hyperuricemia and play an important role, and targeting miRNA processing may provide new insights for the future treatment of hyperuricemia.

### 3.2 Role of miRNAs in the regulation of immune-inflammatory responses

#### 3.2.1 miRNAs and TLR2/4/MyD88/NF-KB pathway in GA

The onset of gouty arthritis results from an inflammatory immune response triggered by MSU deposition. Two pathways mediate the main molecular mechanisms: activation of the TLR-related NF/KB signaling pathway and activation of the inflammatory vesicle NLRP3, respectively. The former is mainly microbial or free fatty acids activating Toll-like pattern recognition receptors, mainly TLR2/4, recognizing the downstream signaling molecule myeloid differentiation factor 88 (MyD88) for intracellular signaling and finally leading to the activation of NF-KB (31, 35, 61). Numerous studies have illustrated the significant correlation between miR-192 and NF-KB pathway. For example, miR-192-5p effectively alleviated tumor progression by inhibiting the IRAK1/NF-κB pathway in endometrial cancer (62, 63). Recently, Lian, C et al. found that miR-192-5p in MSU-treated synovial fluid mononuclear cells (SMFCs) and THP-1 could target TLR4 to inhibit NF-KB pathway activation reducing TNF-a and IL-1β release (Figure 2)(64). MiR-146a is the first regulator that is involved in innate immunity. It has been reported that miR-146a can regulate key downstream adaptor molecules of TLR in sepsis by complementary pairing with the 3’UTR base sequence of TNF receptor-associated

| miRNA     | Result                                                                 | model          | reference |
|-----------|------------------------------------------------------------------------|----------------|-----------|
| miR-22-3p | ↓ NLRP3 inflamasome†, pyroptosis†                                     | In vivo and in vitro | (59)     |
| miR-30b   | ↑ IL-6R†                                                               | In vivo        | (60)     |
| miR-34a   | ↓ URAT1†                                                               | In vivo        | (51)     |
| miR-149-5p| ↑ FGF21∥, hepatocytes lipid accumulation†                              | In vitro       | (58)     |
| miR-143-3p| ↑ GLUT9†                                                               | In vitro       | (52)     |
| miR-9†    | ↑ NF-KB†, JAK-STAT†, injury in NRK-49F†                                | In vitro       | (57)     |
| miR-92a   | ↑ KLF2†, VEGFA †, Angiogenesis†                                       | In vitro       | (55)     |
| miR-663†  | ↑ TGF-β1†, PTEN†, migration†                                          | In vitro       | (56)     |
| miR-155†  | ↑ eNOS†, endothelial dysfunction                                       | In vitro       | (54)     |

a "↑" indicates elevated expression or facilitation.
b "↓" indicates reduced expression or inhibitory effect.

**TABLE 1** The miRNAs involved in Hyperuricemia.
factor 6 (TRAF6) and IL-1 receptor-associated kinase 1 (IRAK1) genes, thereby inhibiting the activity of TLR signaling pathway and thus inhibiting NF-κB signaling pathway to exert inflammatory suppressive effects (65). Another study indicates miR-146a alleviates inflammation in acute gouty arthritis in rats via TLR4/MyD88/NF-κB signaling pathway. And further study demonstrated that miR-146a knockout mice promoted the development of gouty arthritis by upregulating TRAF6 and IRAK-1 expression compared to wild type (Figure 2) (66, 67). Ma, T et al. illustrated that MicroRNA-302b could directly bind to the 3’ UTR of IRAK4 and EphA2 in an in vivo and in vitro model of gout to inhibit activation of the NF-κB pathway to reduce IL-1β (Figure 2) (68). Therefore, targeting the TLR-mediated NF-κB pathway via miRNA can be a promising approach for GA treatment.

### 3.2.2 miRNAs and NLRP3 inflammasome pathway in GA

NLRP3 is the most comprehensive subfamily studied in the nucleotide-binding oligomerization domain-like receptor (69). NLRP3 inflammasome comprises NLRP3, recruitment domain, an adaptor protein, apoptosis-associated spot like protein (ASC), and caspase-1, expressed in many immune cells. In gouty arthritis, MSU crystal acts as a ligand to bind and activate NLRP3 inflammasome. After the conformational change of NLRP3 protein, it polymerizes with ATP to form a protein oligomer. It then recruits pro-caspase-1 and ASC through its effector domain PYD. The caspase-1 precursor was automatically catalyzed into the active form, and pro-IL-1β was enzymolysis into IL-1β (70, 71). Current studies have confirmed that miRNAs are critical regulators of the NLRP3 inflammasome pathway (72). In recent years, it has been reported that circHIPK3 can act as a molecular sponge to adsorb miR-561 to competitively bind NLRP3 mRNA to reduce inflammation in GA (64). Upregulation of miR-20b expression and downregulation of NLRP3 protein was also found in macrophages with HOTAIR knockdown (73). Wang, X et al. reported that miR-223-3p and miR-22-3p could reduce inflammatory effects in monocytes and mouse models of gout by interacting with the 3’ untranslated region segment of NLRP3 mRNA (74). And Tian, J et al. also found that miR-223 could target NLRP3 mRNA in MSU-induced rat models and fibroblast-like synoviocytes to inhibit inflammation and cellular pyroptosis. Further studies confirmed that miR-223 deficiency exacerbated the swelling index of MSU-induced joint inflammation and intensified inflammatory cell infiltration and cytokine release, including IL-1β and MCP-1, compared to WT mice (75, 76). Similarly, the expression of NLRP3 was dramatically upregulated in Bone marrow-derived macrophages (BMDMs) from miR-146a KO mice (67). Besides, the active ingredients of some Chinese traditional medicines also exert anti-inflammatory effects in GA by regulating the miRNA/NLRP3 axis. Total glucosides of paeony alleviate in vitro MSU-induced inflammation in macrophage THP-1 via the MALAT1/miR-876-5p/NLRP3 cascade pathway. Wang Y et al. also reported that Tripterine alleviates GA by modulating miR-449a to act directly on NLRP3 mRNA and inhibit its expression (Figure 2) (77, 78).

### 3.2.3 miRNAs and other mechanisms of inflammation in GA

In GA, when inflammatory pathways in macrophages are activated, they are polarized toward the M1 phenotype and release large amounts of pro-inflammatory factors such as TNF-α, IL-1β, and MCP-1. miRNAs also play a regulatory role in this process. MiR-449a and miR-192-5p can target NLRP3 and epiregulin (EREG) to inhibit macrophage M1 polarization in gout (77, 79). Apart from this, miRNA-488-3p and -920 both can interact with the 3’UTR of IL1-β to exert anti-inflammatory effects (80). Li, G. et al. also reported that miR-221-5p represses IL1-β expression in acute gouty arthritis to regulate the inflammatory response (81). Although Jin, H. M et al. reported that overexpression of miR-155 in vitro reduced SHIP-1 levels and promoted MSU-induced TNF-α and IL-1β production (Figure 2), it was later indicated that there was no remission of GA in miR-155 knockout mice compared to wild type (48, 82). Inflammatory factors tend to infiltrating immune cells, such as neutrophils, which on the one hand, worsen inflammation.

On the other hand, large numbers of neutrophils accumulate inflammatory death, chromatin remodeling, and ejection outside the cells to form NETs, called NETosis. These aggregated NETs can trap pro-inflammatory factors such as TNF-α, IL-1β, and MCP-1. miRNAs also play a regulatory role in the development of NETs in gout. Recently, it has been shown that MSU stimulation can significantly increase miR-3146 expression in neutrophils, accompanied by the formation of many NETs. In contrast, treating rats with antagonim-3146 reduced NETs formation and relief of joint swelling and inflammation, suggesting that early NETs formation exacerbates GA and that miR-3146 plays a role vital role before NETs formation (83). However, the current research on NETs is still inadequate, and how miRNAs regulate the development of NETs in gout is still unclear. Further studies are needed to reveal the potential mechanisms to help people understand gout and identify potential therapeutic targets. We conclude with a summary of miRNAs involved in inflammatory immunity. (Table 2)

### 3.3 The regulatory role of miRNAs in bone erosion

There is irreversible joint damage and deformity in advanced gout, mainly due to local cartilage damage and bone erosion caused by tophi (40). The primary mechanism is that MSU...
TABLE 2 The miRNAs involved in inflammatory immunity.

| miRNA          | target gene/pathway | Role in GA | model                  | reference |
|----------------|---------------------|------------|------------------------|-----------|
| miR-223-3p     | NLRP3/NF-KB         | –          | In vivo and in vitro    | (74–76)   |
| miR-449a       | NLRP3               | –          | In vivo and in vitro    | (77)      |
| miR-22-3p      | NLRP3               | –          | In vivo and in vitro    | (74)      |
| miR-3146       | SIRT1               | +          | In vivo and in vitro    | (83)      |
| miR-876-5p     | NLRP3               | –          | In vitro               | (78)      |
| miR-20b        | NLRP3               | –          | In vitro               | (73)      |
| miR-561        | NLRP3               | –          | In vitro               | (64)      |
| miR-192-5p     | TLR4                | –          | In vivo and in vitro    | (64, 79)  |
| miR-221-5p     | IL1-β               | –          | In vitro               | (81)      |
| miR-146a       | TRAF6/IRAK1/NLRP3   | –          | In vivo                | (66, 67)  |
| miR-155        | SHIP-1              | +          | In vivo and in vitro    | (48, 82)  |
| miR-302b       | IRAK4               | –          | In vivo and in vitro    | (68)      |
| miR-488-3p     | IL1-β               | –          | In vitro               | (80)      |
| miR-920        | IL1-β               | –          | In vitro               | (80)      |

a “−” indicates an inhibitory role during disease progression.

b “+” indicates a promoting role during disease progression.

disrupts the balance between osteoblasts for bone formation and osteoclasts for bone resorption, decreases the activity of osteoblasts, promotes the aggregation and differentiation of osteoclasts, and promotes the development of inflammation and bone damage (84–86). Extensive studies have confirmed the involvement of miRNAs in the development of bone erosion. For instance, miR-20a targets RANKL through the TLR4/p38 pathway, hindering osteoclast proliferation and differentiation (87). Sujitha, S et al. found that miR-23a altered the expression level of LRPS through RNA interference and contributed to a decrease in bone loss and an increase in calcium retention (88). In addition, Najm, A. et al. also demonstrated that miR-17 inhibits the autocrine effects of the IL-6 family in vivo by directly targeting JAK1 and STAT3 to exert anti-inflammatory and anti-bone erosion effects (89). There are few studies on miRNAs affecting bone erosion in gouty arthritis. Only An L et al. reported that miR-192-5p could inhibit MSU-induced EREG expression in GA mice to alleviate bone erosion (79). This case suggests that the underlying molecular mechanisms of miRNAs affecting bone erosion in GA remain to be explored.

4 Application of miRNAs in clinical diagnosis and treatment of GA

First of all, miRNA widely exists in a variety of body fluids, such as whole human blood (90), urine (91) saliva (92). Secondly, miRNA is stable in body fluid in a specific secretion mode, and it is easy to extract tissue samples without invasion. Even under changing environmental conditions, miRNA can stably exist. Because of its specificity, sensitivity, and stable expression in a wide range of diseases, MiRNA has early diagnostic capabilities and is rapid and accurate (92). In studies of gouty arthritis, several miRNAs are up-or down-regulated, and some of these miRNAs also vary with the extent of the disease. BohataJ et al. found elevated levels of five circulating miRNAs, miR-17, miR-18a, miR-30c, miR-142, and miR-223, in the plasma of patients with GA and HUA (93). In addition, it has been reported that miR-221 is lowly expressed in the serum of AGA patients and the receiver operating curve (ROC) applied to the diagnostic value analysis showed an area under the curve of 0.884 (81). Therefore miRNAs have the potential to become markers for gout diagnosis.

The treatment of GA is mainly divided into anti-inflammatory and analgesic, and uric acid lowering. The primary treatment for gout attacks is cortisol, non-steroidal anti-inflammatory drugs (including selective and non-selective COX2 inhibitors), and low-dose colchicine to control pain and lessen inflammation (94–97). Although IL-1 inhibitors can effectively control gout attacks, they are usually reserved for patients with intolerable side effects or contraindications to first-line anti-inflammatory therapy (98, 99). The first-line uric acid-lowering therapy drug is allopurinol, a xanthine oxidase inhibitor. Still, patients who do not respond to or are intolerant of allopurinol are treated with febuxostat (6, 100). Probencid, sulfinpyrazone, and benzbramorone can be used as monotherapy or combined with xanthine oxidase inhibitors by promoting uric acid excretion (101, 102). Liu, P et al. found that colchicine upregulated mir-223-3p and downregulated IL-1β, and etoricoxib treated AGA by upregulating miR-451a and downregulating COX-2 (103). A recent study reported that
two novel hexapeptides (GPAGPR and GPSGRP) found in Apostichopus japonicus hydrolysates inhibit uric acid biosynthesis and reabsorption. The expression profiles of GPSGRP-treated HUA model mice were analyzed, and 21 differentially expressed miRNAs were identified (104).

Chinese medicine or natural products have been developed to treat gout arthritis in recent years. The drugs for acute gout arthritis have severe adverse reactions such as bone marrow suppression, liver cell damage, and gastrointestinal bleeding (105). Traditional Chinese medicine has some advantages in terms of low toxicity and adverse reactions. Wang Y et al. indicated that both Chuan Hu Tong Feng Compound and Allopurinol upregulated miR-486-5p, miR-339-5p, and miR-361-5p expression and decreased CCL2 and CXCL8 protein levels in patients with chronic gouty arthritis (106). Another research proved that benz bromarone and Xiezhuo Chub Decoction reduced uric acid levels by increasing the expression levels of miR-34a and miR-146a (107). In addition, like Tripterine (77), Total glucosides of paony (78) and Epigallocatechin (57) were also reported to regulate the suppression, liver cell damage, and gastrointestinal bleeding (106). Therefore, miRNAs related to gout treatment need further exploration and development.

5 Future expectation

Since the discovery of miRNAs, their wide range of biological effects have been gradually revealed, also indicating that they play an important regulatory role in various cellular activities. Based on recent research results in related fields, in this section, we will look at the future directions of miRNA research and the prospects of clinical applications.

Exosomes, a cellular vesicle structure widely found in body fluids, have been identified for the presence of miRNAs. In recent years, several studies have demonstrated that miRNAs regulate inflammatory immunity and tumor progression through exosomes as vectors. Jiang, K et al. found that peripheral-derived exosome-mediated miR-155 promoted the polarization and proliferation of macrophage M1 and activated the NF-KB pathway to promote the release of inflammatory factors TNF-α and IL-6 in an acute lung injury model in mice (109). Similarly, Yingying Cao et al. reported that Enterotoxigenic Bacteroides fragilis (ETBF) promotes intestinal inflammation and malignancy by inhibiting exosome-encapsulated miR-149 (110). Naive bone marrow-derived macrophages produce exosomes with anti-inflammatory miRNAs that target receptor macrophages to promote their M2 polarization and alleviate inflammation (111). Therefore, it is natural to speculate that circulating exosomes contain miRNAs that may influence the development of GA by regulating macrophage polarization or other key molecules of inflammation. Furthermore, such exosome-derived miRNAs have great application in both the diagnosis and treatment of GA.

In addition, nanomaterials as carriers of drug-targeted delivery systems have become a hot research topic due to the development of the interdisciplinary intersection of materials science and medicine in recent years. Since miRNA mimics are not resistant to nucleic acid endonucleases and are prone to degradation in circulation, nanomaterials can be used to wrap miRNAs for targeted therapy. Wang, F et al. reported that microRNA-31 bound to adriamycin-loaded mesoporous silica nanoparticles would be used to target tumor cells high in MTEF4 expression to promote mitochondrial apoptosis (112). Moreover, Ahir, M. et al. also reported that the use of mesoporous silica nanoparticles as co-delivery carriers of miR-34a-Mimic and antisense-miR-10b on tumor cells effectively inhibited tumor growth and metastasis in triple-negative breast cancer (113). Although nanomaterials are being studied as potential therapies for tumors and inflammatory diseases, they may still cause an immune response in the body and exacerbate inflammation. Therefore the development of low inflammatory response nanomaterials for the treatment of inflammatory diseases remains a great challenge. With the development of basic science and technology, gene-editing technology is becoming more and more mature and is expected to be used for the treatment of many diseases. CRISPR/Cas9 technology, which won the Nobel Prize, has brought a revolution to the life science field. Recently, Zhou, W et al. reported that CRISPR/Cas9-mediated knockdown of miRNA-363 effectively promoted apoptosis in diffuse large B-cell lymphoma cell lines in response to adriamycin-induced apoptosis (114). And, Yu Toyoda et al. also utilized CRISPR/cas9 to construct knockout mice to identify the role of GLUT12 in regulating blood urate levels (115). Therefore, the use of CRISPR/cas9-mediated miRNA knockdown to suppress inflammation in gouty arthritis still holds great promise for research.

6 Conclusion

In recent years, miRNAs have become a hot topic in biomedical research. Current studies have shown that miRNAs are closely associated with the development and progression of gouty arthritis, and miRNAs play an essential role in the post-transcriptional regulation process of genes. Despite the large number of studies reporting miRNA regulation of the gouty inflammatory process, there is still a significant gap in gouty arthritis, especially in bone erosion.
The underlying mechanisms of self-remission of gout as a recurrent chronic disease and the formation of gouty stones remain unclear. What is neutrophil-associated NETosis in the inflammatory process, and is it the culprit that exacerbates inflammation or relieves it leading to recurrent gout attacks?

Although gout is already a treatable rheumatic disease, the side effects of drugs are still evident, and targeting miRNAs may provide a new idea and insight for gout treatment. In the future, miRNA is expected to be a marker for diagnosing gouty arthritis or a target for drug therapy. However, further studies are still needed. Therefore, the search for relevant miRNAs and further study of their mechanisms are essential for diagnosing and treating gouty arthritis.

Author contributions

TX and JWu conceived and designed the article, ZL and FY wrote the manuscript, SH and JW reviewed the literature, BC, LL and JY revised the article, and YY, CY, YH, and SW proofread the language. All authors contributed to the article and approved the submitted version.

References

1. Chen-Xu M, Yokose C, Rai SK, Pillinger MH, Choi HK. Contemporary prevalence of gout and hyperuricaemia in the united states and decadal trends: the national health and nutrition examination survey, 2007–2016. Arthritis Rheumatol (2019) 71:991–9. doi: 10.1002/art.40807

2. Perez-Ruiz F, Marimon E, Chinchilla SP. Hyperuricaemia with deposition: latest evidence and therapeutic approach. Ther Adv Musculoskelet Dis (2015) 7:225–33. doi: 10.1177/1759720815559974

3. Fisher MC, Rai SK, Lu N, Zhang Y, Choi HK. The unclosing premature mortality gap in gout: a general population-based study. Ann Rheum Dis (2017) 76:1289–94. doi: 10.1136/annrheumdis-2016-210588

4. Roughley MJ, Belcher J, Mallen CD, Roddy E. Gout and risk of chronic kidney disease and nephroliathiasis: meta-analysis of observational studies. Arthritis Res Ther (2015) 17:90. doi: 10.1186/s13075-015-0610-9

5. Richette P, Doherty M, Pascual E, Barskova V, Castaneda-Sanabria J, et al. Updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis (2017) 76:29–42. doi: 10.1136/annrheumdis-2016-209707

6. FizGerald JD, Dalbeth N, Mókás T, Brignardello-Petersen R, Gayatt G, Abdes AM, et al. 2020 American College of Rheumatology guideline for the management of gout. Arthritis Rheumatol (2020) 72:879–95. doi: 10.1002/art.41247

7. Tin A, Li Y, Brody JA, Nutile T, Chu AY, Huffman JE, et al. Large-Scale exome sequencing association studies identify rare functional variants influencing serum urate levels. Nat Commun (2018) 9:4228. doi: 10.1038/s41467-018-06620-4

8. Cai Y, Yu X, Hu S, Yu J. A brief review on the mechanisms of miRNA regulation. Genomics Proteomics Bioinformatics (2009) 7:147–54. doi: 10.1016/S1672-0229(08)60044-5

9. Cheng J, Roden CA, Pan W, Zhu S, Bacci A, Pan X, et al. A molecular chipping technology for CRISPR sgRNA library generation and functional mapping of noncoding regions. Nat Commun (2016) 7:11178. doi: 10.1038/ncomms11178

10. Suzuki HI, Katsura A, Miyazato K. A role of uridylation pathway for blockade of let-7 microRNA biogenesis by Lin28B. Cancer Sci (2015) 106:1174–81. doi: 10.1111/cas.12721

11. Chen GR, Sive H, Bartel DP. A seed mismatch enhances Argonaute2-catalyzed cleavage and partially rescues severely impaired cleavage found in fish. Mol Cell (2017) 68:1095–107 e5. doi: 10.1016/j.molcel.2017.11.032

12. Bronisz A, Rooij AK, Kravczynski K, Peruzzi P, Salinska E, Nakano I, et al. The nuclear DICER-circular RNA complex drives the deregulation of the globlastoma cell microRNANome. Sci Adv (2020) 6(51):eabc0221. doi: 10.1126/sciadv.abcd0221

13. Grasso G, Higuchi T, Mac V, Barbier J, Helsenmoettl M, Lorenzi C, et al. NF90 modulates processing of a subset of human pri-miRNAs. Nucleic Acids Res (2020) 48:8674–88. doi: 10.1093/nar/gkaa386

14. London E, Lobor P, Tolosn AG, Quann K, Clark P, Jing Y, et al. Analysis of 13 cell types reveals evidence for the expression of numerous novel primate- and tissue-specific microRNAs. Proc Natl Acad Sci U S A. (2015) 112:E1106–15. doi: 10.1073/pnas.1420955112

15. Papangagou P, Stivarou T, Tsironi M. The role of mirnas in common inflammatory arthropathies: osteoarthritis and gouty arthritis. Biomolecules. (2016) 6(4):44. doi: 10.3390/biom6040044

16. Alevizos I, Illei GG. MicroRNAs as biomarkers in rheumatic diseases. Nat Rev Rheumatol (2016) 10:391–8. doi: 10.1038/nrrheum.2010.81

17. Richette P, Doherty M, Pascual E, Barakova V, Becce F, Castaneda-Sanabria J, et al. 2018 Updated European league against rheumatism evidence-based recommendations for the diagnosis of gout. Ann Rheum Dis (2020) 79:31–8. doi: 10.1136/annrheumdis-2019-213515

18. Ragab G, Elshahaly M, Bardin T. Gout: An old disease in new perspective - a review. J Adv Res (2017) 8:495–511. doi: 10.1016/j.jare.2017.04.008

19. Kim JW, Kwak SG, Lee H, Kim SK, Choe YJ, Park SH. Prevalence and incidence of gout in Korea: data from the national health claims database 2007–2015. Rheumatol Int (2017) 37:1499–506. doi: 10.1007/s00296-017-3768-4

20. Dehnin M, Drivelegka P, Sigurdardottir V, Svard A, Jacobsson LT. Incidence and prevalence of gout in Western Sweden. Arthritis Res Ther (2016) 18:164. doi: 10.1186/s13075-016-0982-6

21. Dalbeth N, Stamp L. Hyperuricaemia and gout: time for a new staging system? Ann Rheum Dis (2014) 73:1598–600. doi: 10.1136/annrheumdis-2014-203504

22. Han M, Park HC, Kim H, Jo HA, Huh H, Jang JY, et al. Hyperuricaemia and deterioration of renal function in autosomal dominant polycystic kidney disease. BMC Nephrol (2014) 15:63. doi: 10.1186/1471-2369-15-63

Funding

This study was supported by the youth scientific research fund of Anhui Medical University (2021xkj275, chaired by zhipan Luo) and the school level quality project of Anhui Medical University (2021xjyxm24, chaired by zhipan Luo).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.
advances in renal urate transport: characterization of candidate transporters and risk of incident gout in men: a prospective study. *J Natl Acad Sci U S A.* (2009) 106:10338–42. doi: 10.1073/pnas.0901249106

Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Purine-rich foods, dairy and protein intake, and the risk of gout in men. *N Engl J Med* (2004) 350:1093–10. doi: 10.1056/NEJMoa035700

Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Alcohol intake and risk of incident gout in men: a prospective study. *Lancet.* (2004) 363:1277–81. doi: 10.1016/S0140-6736(04)16000-5

Cronsten BN, Sunkureddi P. Mechanistic aspects of inflammation and clinical management of inflammation in acute gouty arthritis. *J Clin Rheumatol* (2013) 19:19–29. doi: 10.1097/RHU.0b013e3283622790

Martinson F, Petrelli V, Mayer A, Tzardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature* (2006) 440:237–41. doi: 10.1038/nature4516

Liu-Bryan R, Scott P, Sydäske A, Rose DM, Terkeltaub R. Innate immunity responses license NLRP3 in macrophages: a molecular platform for the purine end metabolite urate pump for the purine end metabolite. *Am J Physiol Renal Physiol* (2009) 304. doi: 10.1152/ajprenal.00133.2004

Zhong X, Chen Y, Yao C, Xu L, Peng Y, Yang Q, et al. MicroRNA-30b participates in the pathological process of hyperuricemia as a proinflammatory response to monosodium urate crystals. *Ann Rheum Dis* (2014) 73:1646–52. doi: 10.1136/annrheumdis-2013-205409

Wang Y, Xu D, Wang B, Hou X. Could MicroRNAs be regulators of gout pathogenesis? *Am J Clin Pathol* (2012) 138:831–3. doi: 10.1093/ajcp/qxs059

Yu S, Hong Q, Wang Y, Hou K, Wang L, Zhang Y, et al. High concentrations of uric acid inhibit angiogenesis via regulation of the kruppel-like factor 2 vascular endothelial growth factor-a axis by miR-92a. *Circ J* (2015) 79:1814–21. doi: 10.1253/circj.CJ150011

Hsieh CM, Hsieh CM, Zhang YY, Hsu CC, Wang Y, et al. Urinary loss of uric acid via the ASC/caspase 1 pathway in monosodium urate monohydrate-induced gouty arthritis. *Arthritis Rheumatol* (2016) 67:1646–53. doi: 10.1002/art.35549

Zhang X, Hong Q, Hou K, Wang Y, Wu D, Chen X. [High concentration uric acid regulates endothelial function via miR-155.] *Nan Fang Yi Ke Da Xue Xue Bao* (2013) 33:1141–5.

Sun WF, Zhu MM, Li J, Zhang XX, Liu YW, Wu XR, et al. Effects of sie-Xiao-Chu-Bi-Fang on miR-34a and URI1 and their relationship in hyperuricemic mice. *J Ethnopharmacol* (2015) 161:163–9. doi: 10.1016/j.jep.2014.12.001

Zhou Z, Dong Y, Zhou H, Liu J, Zhao W. MiR-143-3p directly targets GLUT9 to reduce uric acid reabsorption and inflammatory response of renal tubular epithelial cells. *Biochem Biophys Res Commun* (2015) 457:413–20. doi: 10.1016/j.bbrc.2015.07.114

Estevez-Garcia IO, Gallegos-Nava S, Vera-Pérez E, Silvera LH, Ventura-Rios L, Vancini G, et al. Levels of cytokines and micrornas in individuals with asymptomatic hyperuricemia and ultrasonographic findings of gout: a bench-to-bedside approach. *Arthritis Care Res (Hoboken)* (2018) 70:1814–21. doi: 10.1002/acr.23549

Zhang X, Hong Q, Hou K, Wang Y, Wu D, Chen X. [High concentration uric acid regulates endothelial function via miR-155.] *Nan Fang Yi Ke Da Xue Xue Bao* (2013) 33:1141–5.

60. Zhong X, Chen Y, Yao C, Xu L, Peng Y, Yang Q, et al. MicroRNA-30b participates in the pathological process of hyperuricemia by regulating interleukin-6 receptor. *Nucleic Acids Research* (2020) 49:11672–8. doi: 10.1093/nar/ggaa195

58. Estevez-Garcia IO, Gallegos-Nava S, Vera-Pérez E, Silvera LH, Ventura-Rios L, Vancini G, et al. Levels of cytokines and micrornas in individuals with asymptomatic hyperuricemia and ultrasonographic findings of gout: a bench-to-bedside approach. *Arthritis Care Res (Hoboken)* (2018) 70:1814–21. doi: 10.1002/acr.23549

Zhang X, Hong Q, Hou K, Wang Y, Wu D, Chen X. [High concentration uric acid regulates endothelial function via miR-155.] *Nan Fang Yi Ke Da Xue Xue Bao* (2013) 33:1141–5.

Yu S, S Hong Q, Wang Y, Hou K, Wang L, Zhang Y, et al. High concentrations of uric acid inhibit angiogenesis via regulation of the kruppel-like factor 2 vascular endothelial growth factor-a axis by miR-92a. *Circ J* (2015) 79:1814–21. doi: 10.1253/circj.CJ150011

Hong Q, Yu S, Geng X, Duan L, Zheng W, Fan M, et al. High concentrations of uric acid inhibit endothelial cell migration via miR-663 which regulates phosphatase and tensin homolog by targeting transforming growth factor-β1. *Microcirculation.* (2015) 22:306–14. doi: 10.1111/mic.12200

Chen LL, Xu Y. Epigallocatechin gallate attenuates uric acid-induced injury in rat renal interstitial fibroblasts NRK-49F by up-regulation of miR-9. *Eur Rev Med Pharmacol Sci* (2018) 22:7548–69. doi: 10.26355/eurrev_201811_16287

Chen S, Chen D, Yang H, Wang X, Wang J, Xu C. Uric acid induced hepatocytes lipid accumulation through regulation of miR-149-5p/FGF21 axis. *BMC Gastroenterol* (2020) 20:39. doi: 10.1186/s12876-020-01189-z

Ebihara M, Hatanaka D, Shiga H, Yoneda K, et al. LncRNA-HOTAIR promotes endothelial cell pyroptosis by regulating the miR-22/NLRP3 axis in hyperuricemia. *J Cell Med* (2021) 25:8504–21. doi: 10.1111/jcc.16812

Zhong X, Chen Y, Yao C, Xu L, Peng Y, Yang Q, et al. MicroRNA-30b participates in the pathological process of hyperuricemia by regulating interleukin-6 receptor. *Nucleic Acids Research* (2020) 49:11672–8. doi: 10.1093/nar/ggaa195

Stöttmeier B, Dick TP. Redox sensitivity of the MyD88 immune signaling pathway. *Free Radic Biol Med* (2016) 101:93–101. doi: 10.1016/j.freeradbiomed.2016.10.004

Wang Y, Ma H, Li Y, Su R. MiR-192-5p-modulated tumor-associated macrophages-derived exosome suppressed endometrial cancer progression through targeting irak2/ndk-kappa signaling. *PloS One* (2022) 29:436–47. doi: 10.1371/journal.pone.0270089

Doukas SG, Vagelis DP, Sasaki CT. NF-kappaB inhibition reverses acidic bile-induced miR-21, -155, miR-192, -miR-34a, -miR-34c and -miR-451a deregulations in human hypopharyngeal cells. *J Cell Med* (2018) 22:2922–34. doi: 10.1111/jcc.13591

Lian C, Sun J, Guan W, Zhang L, Zhang X, Yang L, et al. Circular RNA circRipk3 activates macrophage NLRP3 inflammasome and flt4 pathway in gouty arthritis via sponging mir-561 and mir-192. *Inflammation.* (2021) 44:2065–77. doi: 10.1007/s10753-021-01483-2

Gao M, Wang X, Zhang X, Hu T, Ma H, Liu L, et al. Attenuation of cardiac dysfunction in polymicrobial sepsis by mircoRNA-146a is mediated via targeting of irak1 and irak3 expression. *J Immunol* (2015) 195:672–82. doi: 10.4049/jimmunol.1401551

Luo et al. 10.3389/fendo.2022.976769
A shift in osteocyte function towards a proinflammatory state may have implications for development of bone erosion in gout. Monosodium urate monohydrate crystals inhibit osteoblast viability and function:

1. Studies in osteoclast development through interactions with stromal cells.
2. Monosodium urate crystals inhibit osteoclastogenesis in patients with tophaceous gout: urate crystals promote osteoclast development through interactions with stromal cells.
3. Protein Cell governs NLRP3 and interleukin-1β activation on macrophages.
4. Flknockdown alleviates gouty arthritis through miR-20b upregulation and NLRP3 inflammasome.
5. Knockdown through miR-20b alleviates gouty arthritis through miR-20b upregulation and NLRP3 inflammasome.
6. MiR-20b upregulation and NLRP3 inflammasome.
7. miR-20b upregulation and NLRP3 inflammasome.
8. MiR-20b upregulation and NLRP3 inflammasome.
9. In mice with collagen-induced arthritis and directly targets the IκB/STAT pathway in rheumatoid arthritis fibroblast-like synoviocytes. Arthritis Rheumatol (2020) 72:2300–9. doi:10.1002/art.41444
10. miR-20b upregulation and NLRP3 inflammasome.
11. miR-20b upregulation and NLRP3 inflammasome.
12. miR-20b upregulation and NLRP3 inflammasome.
13. miR-20b upregulation and NLRP3 inflammasome.
14. miR-20b upregulation and NLRP3 inflammasome.
15. miR-20b upregulation and NLRP3 inflammasome.
16. miR-20b upregulation and NLRP3 inflammasome.
17. miR-20b upregulation and NLRP3 inflammasome.
18. miR-20b upregulation and NLRP3 inflammasome.
19. miR-20b upregulation and NLRP3 inflammasome.
20. miR-20b upregulation and NLRP3 inflammasome.
21. miR-20b upregulation and NLRP3 inflammasome.
22. miR-20b upregulation and NLRP3 inflammasome.
23. miR-20b upregulation and NLRP3 inflammasome.
24. miR-20b upregulation and NLRP3 inflammasome.
25. miR-20b upregulation and NLRP3 inflammasome.
26. miR-20b upregulation and NLRP3 inflammasome.
27. miR-20b upregulation and NLRP3 inflammasome.
28. miR-20b upregulation and NLRP3 inflammasome.
29. miR-20b upregulation and NLRP3 inflammasome.
30. miR-20b upregulation and NLRP3 inflammasome.
31. miR-20b upregulation and NLRP3 inflammasome.
32. miR-20b upregulation and NLRP3 inflammasome.
33. miR-20b upregulation and NLRP3 inflammasome.
34. miR-20b upregulation and NLRP3 inflammasome.
35. miR-20b upregulation and NLRP3 inflammasome.
36. miR-20b upregulation and NLRP3 inflammasome.
37. miR-20b upregulation and NLRP3 inflammasome.
38. miR-20b upregulation and NLRP3 inflammasome.
39. miR-20b upregulation and NLRP3 inflammasome.
40. miR-20b upregulation and NLRP3 inflammasome.
41. miR-20b upregulation and NLRP3 inflammasome.
42. miR-20b upregulation and NLRP3 inflammasome.
43. miR-20b upregulation and NLRP3 inflammasome.
44. miR-20b upregulation and NLRP3 inflammasome.
45. miR-20b upregulation and NLRP3 inflammasome.
46. miR-20b upregulation and NLRP3 inflammasome.
47. miR-20b upregulation and NLRP3 inflammasome.
48. miR-20b upregulation and NLRP3 inflammasome.
49. miR-20b upregulation and NLRP3 inflammasome.
50. miR-20b upregulation and NLRP3 inflammasome.
51. miR-20b upregulation and NLRP3 inflammasome.
52. miR-20b upregulation and NLRP3 inflammasome.
53. miR-20b upregulation and NLRP3 inflammasome.
54. miR-20b upregulation and NLRP3 inflammasome.
55. miR-20b upregulation and NLRP3 inflammasome.
56. miR-20b upregulation and NLRP3 inflammasome.
57. miR-20b upregulation and NLRP3 inflammasome.
58. miR-20b upregulation and NLRP3 inflammasome.
59. miR-20b upregulation and NLRP3 inflammasome.
60. miR-20b upregulation and NLRP3 inflammasome.
61. miR-20b upregulation and NLRP3 inflammasome.
62. miR-20b upregulation and NLRP3 inflammasome.
63. miR-20b upregulation and NLRP3 inflammasome.
64. miR-20b upregulation and NLRP3 inflammasome.
65. miR-20b upregulation and NLRP3 inflammasome.
66. miR-20b upregulation and NLRP3 inflammasome.
67. miR-20b upregulation and NLRP3 inflammasome.
68. miR-20b upregulation and NLRP3 inflammasome.
69. miR-20b upregulation and NLRP3 inflammasome.
70. miR-20b upregulation and NLRP3 inflammasome.
71. miR-20b upregulation and NLRP3 inflammasome.
72. miR-20b upregulation and NLRP3 inflammasome.
73. miR-20b upregulation and NLRP3 inflammasome.
74. miR-20b upregulation and NLRP3 inflammasome.
75. miR-20b upregulation and NLRP3 inflammasome.
76. miR-20b upregulation and NLRP3 inflammasome.
77. miR-20b upregulation and NLRP3 inflammasome.
78. miR-20b upregulation and NLRP3 inflammasome.
79. miR-20b upregulation and NLRP3 inflammasome.
80. miR-20b upregulation and NLRP3 inflammasome.
81. miR-20b upregulation and NLRP3 inflammasome.
82. miR-20b upregulation and NLRP3 inflammasome.
83. miR-20b upregulation and NLRP3 inflammasome.
84. miR-20b upregulation and NLRP3 inflammasome.
85. miR-20b upregulation and NLRP3 inflammasome.
86. miR-20b upregulation and NLRP3 inflammasome.
87. miR-20b upregulation and NLRP3 inflammasome.
88. miR-20b upregulation and NLRP3 inflammasome.
89. miR-20b upregulation and NLRP3 inflammasome.
90. miR-20b upregulation and NLRP3 inflammasome.
91. miR-20b upregulation and NLRP3 inflammasome.
92. miR-20b upregulation and NLRP3 inflammasome.
93. miR-20b upregulation and NLRP3 inflammasome.
94. miR-20b upregulation and NLRP3 inflammasome.
95. miR-20b upregulation and NLRP3 inflammasome.
96. miR-20b upregulation and NLRP3 inflammasome.
97. miR-20b upregulation and NLRP3 inflammasome.
98. miR-20b upregulation and NLRP3 inflammasome.
99. miR-20b upregulation and NLRP3 inflammasome.
100. miR-20b upregulation and NLRP3 inflammasome.
101. miR-20b upregulation and NLRP3 inflammasome.
102. miR-20b upregulation and NLRP3 inflammasome.
103. miR-20b upregulation and NLRP3 inflammasome.
104. miR-20b upregulation and NLRP3 inflammasome.
an in vivo model of gouty inflammation. *Free Radic Biol Med* (2009) 47:616–21. doi: 10.1016/j.freeradbiomed.2009.05.035

106. Wang Y, Dong L, Liu P, Chen Y, Jia S, Wang Y. A randomized controlled trial of chuanhuutongfeng mixture for the treatment of chronic gouty arthritis by regulating miRNAs. *Evid Based Complement Alternat Med* (2019) 2019:5917269. doi: 10.1155/2019/5917269

107. Sun WF, Zhang XX, Sun FY, Xu W, Liang J, Feng SM, et al. MicroRNA expression patterns of the kidney in hyperuricemia mice treated with xiezhuo chubi decoction. *Chin J Integr Med* (2011) 17:35–42. doi: 10.1007/s11655-011-0605-6

108. Li X, Liu Y, Shan Y, Wang Y, Li Z, Bi Y, et al. MicroRNAs involved in the therapeutic functions of noni (*Moringa citrifolia*) fruit juice in the treatment of acute gouty arthritis in mice induced with monosodium urate. *Foods* (2021) 10 (7):1638. doi: 10.3390/foods10071638

109. Jiang K, Yang J, Guo S, Zhao G, Wu H, Deng G. Peripheral circulating exosome-mediated delivery of mir-155 as a novel mechanism for acute lung inflammation. *Mol Ther* (2019) 27:1758–71. doi: 10.1016/j.ymthe.2019.07.003

110. Cao Y, Wang Z, Yan Y, Li L, He J, Xuan B, et al. Enterotoxigenic bacteroidesfragilis promotes intestinal inflammation and malignancy by inhibiting exosome-packaged mir-149-3p. *Gastroenterology*. (2021) 161:1552–66 e12. doi: 10.1053/j.gastro.2021.08.003

111. Bouchareychas L, Duong P, Covarrubias S, Alop E, Phu TA, Chung A, et al. Macrophage exosomes relieve atherosclerosis by regulating hematopoiesis and inflammation via microRNA cargo. *Cell Rep* (2020) 32:107881. doi: 10.1016/j.celrep.2020.107881

112. Wang F, Zhang L, Bai X, Cao X, Jiao X, Huang Y, et al. Stimuli-responsive nanocarrier for co-delivery of mir-31 and doxorubicin to suppress high mitf4 cancer. *ACS Appl Mater Interfaces* (2018) 10:22767–73. doi: 10.1021/acsami.8b07698

113. Ahir M, Upadhyay P, Ghosh A, Sarker S, Bhattacharya S, Gupta P, et al. Delivery of dual miRNA through CD44-targeted mesoporous silica nanoparticles for enhanced and effective triple-negative breast cancer therapy. *Biomater Sci* (2020) 8:2939–54. doi: 10.1039/D0BS00015A

114. Zhou W, Xu Y, Zhang I, Zhang P, Yao Z, Yan Z, et al. MiRNA-363-3p/DUSP10/JNK axis mediates chemoresistance by enhancing DNA damage repair in diffuse large b-cell lymphoma. *Leukemia* (2022) 36(7):1861–9. doi: 10.1038/s41375-022-01565-6

115. Toyoda Y, Takada T, Miyata H, Matsuo H, Kassai H, Nakao K, et al. Identification of GLUT12/SLC2A12 as a urate transporter that regulates the blood urate level in hyperuricemia model mice. *Proc Natl Acad Sci U S A*. (2020) 117:18175–7. doi: 10.1073/pnas.2006958117