Cellular Physiology and Biochemistry

Cell Physiol Biochem 2015;36:2085-2092
DOI: 10.1159/000430176
Published online: July 21, 2015
Accepted: April 08, 2015

1421-9778/15/0366-2085$39.50/0

Review

Could MicroRNAs be Regulators of Gout Pathogenesis?

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Key Words
MicroRNAs • Gout • Pathogenesis

Abstract
MicroRNAs (miRNAs) are a class of noncoding RNAs that mainly negatively regulate gene expression. miRNAs have important roles in many diseases, including inflammatory diseases. Gout is a common arthritis caused by deposition of monosodium urate crystals within joints. Recent studies suggested that miRNAs may be involved in the development of inflammatory arthritis, including acute gouty arthritis. In the present review, we systemically discuss relevant publications in order to provide a better understanding on the possible role of miRNAs in gout. miRNAs may act as regulators of gout pathogenesis via several pathways. Targeting miRNAs may be a promisingstrategy in the treatment of gout.

Introduction

Gout is a common arthritis caused by deposition of monosodium urate (MSU) crystals within joints and periarticular tissues after chronic hyperuricaemia [1]. It affects 1-2% of adults in the world, and there is a consistent rise in the prevalence of gout in recent years, especially in developing countries [2]. Hyperuricemia is not a sufficient risk factor for the development of acute gouty arthritis, and there are several other important risk factors for

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gout, such as obesity, hyperlipidaemia, and dietary factors [3]. MicroRNAs (miRNAs) are a class of noncoding RNAs that mainly negatively regulate gene expression [4]. miRNAs play an important role in human diseases, including some inflammatory diseases. Recent studies suggested that miRNAs may be involved in the development of inflammatory arthritis, including acute gouty arthritis [5, 6]. In resent review, we will systemically review relevant literatures to get a better understanding on the possible roles of miRNAs in gout.

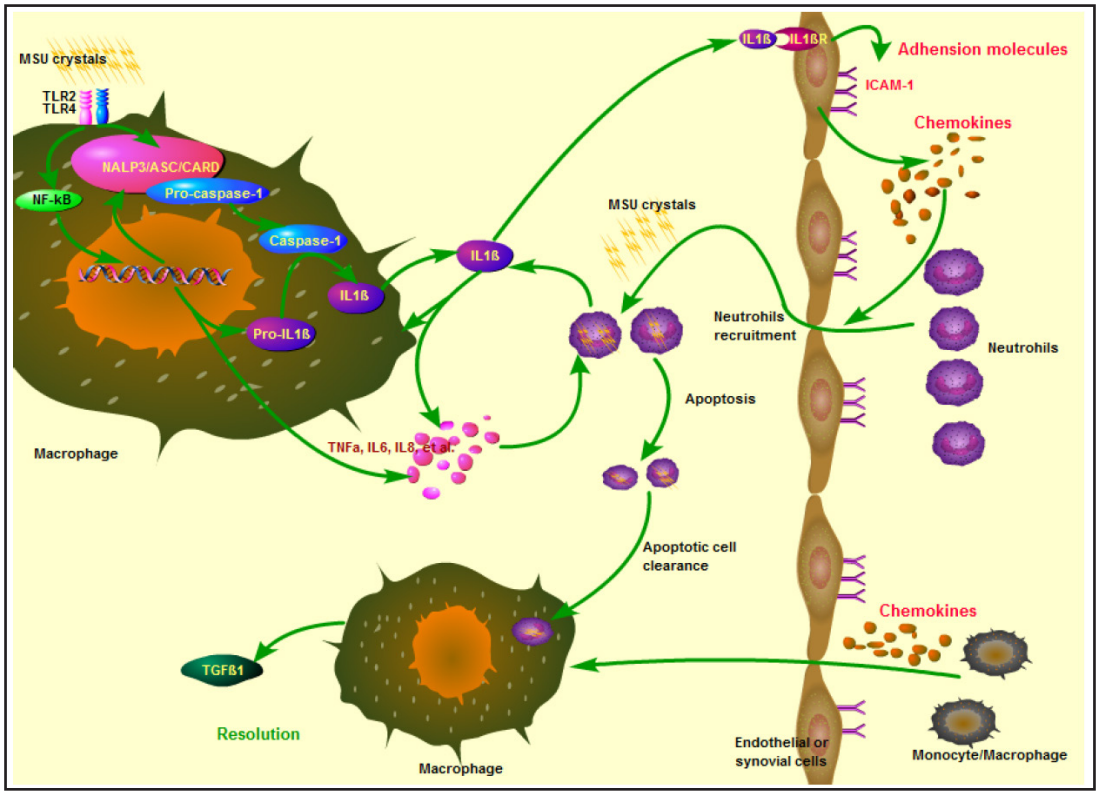
Overview of gout pathogenesis

The pathogenesis of gout is still not well understood, and there is still lack of effective treatment for acute gouty arthritis [1, 2, 7]. MSU crystals can powerfully stimulate toll-like receptors and NLRP3 inflammasome, and further lead to complex inflammatory reaction (Fig. 1) [8]. In acute gouty arthritis, phagocytosis of MSU crystals in macrophages leads to the generation of reactive oxygen species (ROS) through activation of NADPH oxidases [8, 9]. Toll-like receptor 2 (TLR2) and toll-like receptor 4 (TLR4) on the macrophages are an integral part of the innate immune system and MSU crystals rigger innate immune responses via TLR2/TLR4, which further leads to inflammatory reaction [8, 9]. The initiating step in nucleotide-binding oligomerization domain (NOD)-like receptor containing pyrin domain 3 (NLRP3) activation is a priming signal by toll-like receptors that activate transcription of NLRP3 and pro-interleukin-1β (IL-1β) through NF-κB (Fig. 1). Phagocytosis of monosodium urate (MSU) crystals will further activate the NLRP3 inflammasome, which consists of NLRP3, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and procaspase-1 (Fig. 1). The activation of NLRP3 inflammasome will lead to activation of caspase-1, which in turn cleaves pro-IL-1β to produce biologically active IL-1β. Thus, MSU crystals finally lead to the production of and secretion of IL-1β. IL-1β secretion can induce further production of IL-1β and other proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-8 (IL-8) and interleukin-6 (IL-6), which further lead to expanded inflammation (Fig. 1). IL-1β can bind to the IL-1 receptor on endothelial or synovial cells and result in signal transduction, which further leads to the production and secretion of adhesion molecules and chemokines (Fig. 1). Adhesion molecules and chemokines together result in subsequent inflammatory events including neutrophil recruitment and a series of intense inflammation.

Overview of miRNAs

miRNAs are evolutionarily-conserved endogenous non-coding RNAs that have been identified as post-transcriptional regulators of gene expression [10]. miRNAs are approximately 19-22 nucleotide single-stranded RNAs that regulate the stability of target messenger RNA by selective binding to specific sites [4]. Over 5000 miRNAs have now been identified, and miRNAs play an important role in a wide range of human diseases, including cancer, metabolic diseases, and inflammatory diseases. Recent studies suggested that miRNAs may be involved in the development of inflammatory arthritis, including acute gouty arthritis [5, 6]. The miRNAs mainly bind to the 3′-untranslated regions (3'UTR) of target mRNAs, resulting in mRNA degradation or the inhibition of mRNA translation [10]. Recent studies further show that miRNAs can bind to other regions of target mRNAs, resulting in translational repression or activation [10]. Previous studies have estimated that approximately 60% of protein-coding genes are modulated by miRNAs in either a single or multiple cellular pathways. miRNAs existing in a stable form in human body fluid, such as plasma, saliva, and urine, and thus are potential to be a biomarker of relevant diseases [4, 11]. It's no doubt that the clarification of miRNAs involved in the pathogenesis of gout might lead to a novel effective treatment.

Fig. 1. Mechanisms of inflammation in acute gout.



miRNAs and hyperuricaemia

Hyperuricaemia is a major risk factor of gout, and about 10% of patients with hyperuricaemia will suffer from gout [3]. In addition, hyperuricaemia is also an independent risk factor of a series of various diseases, including cardiovascular disease, stroke, and diabetes [11]. Currently, there are limited numbers of studies assessing the roles of miRNAs in hyperuricaemia. miR-34a can inhibit the expression of human urate anion exthanger 1 (URAT1) and reduce the excretion of uric acid [12, 13]. Another study suggested that miR-448 could target the xanthine oxidase (XO), which is a vital enzyme involving the production of uric acid [14]. Hyperuricaemia can down-regulate eNOS expression via miR-155 to induce endothelial dysfunction, and hyperuricaemia can stimulate the expression of miR-155 in endothelial cells [15]. However, there is no other miRNA reported to be involved with hyperuricaemia.

miRNAs and toll-like receptors

TLR2 and TLR4 on the macrophages are an integral part of the innate immune system and MSU crystals rigger innate immune response and inflammatory reaction via TLR2/TLR4 (Fig. 1). Several miRNAs have been shown to directly target components of the TLR signalling system [9]. miR-144 can bound to 3'UTR of TLR2, and miR-144 can enhance TNF-α production by targeting TLR2 in non-alcoholic steatohepatitis (NASH) [16]. miR-154 and miR-143 can target TLR2 and inhibit the expression of TLR2 in colorectal cancer [17, 18]. miR-19a and miR-19b can target TLR2 mRNA, and decrease TLR2 protein expression in rheumatoid fibroblast-like synoviocytes [19]. miR-105 can modulate TLR2 protein expression in human oral keratinocytes [20]. miR-181c can suppress TLR4 by directly binding its 3'UTR in regulating the inflammatory response in oxygen-glucose-deprived

microglia [21]. miR-146b can also modulate the TLR4 expression in inflammatory response [22]. Let-7b can target at TLR4 mRNA, and regulates the expression of the downstream genes related to the inflammation in H.pylori infection [23], while let-7i can down-regulate TLR4 expression in both coronary artery disease and epithelial immune responses to microbial infection [24, 25]. miR-511 also can target TLR4 and is another potent modulator of immune response [26]. miR-146a can target TLR4 and further inhibit the activation of TLR4-dependent inflammatory cytokine secretion [27]. Though there are a large number of studies published to assess the roles of miRNAs in regulating TLR2/TLR4 expression in various diseases, there is no study assessing the relationship between miRNAs and TLR2/TLR4 in gout. Additional studies investigating the roles of those miRNAs targeting TLR2/TLR4 in gout are recommended.

miRNAs and NLRP3 inflammasome

The NLRP3 protein has emerged as a central regulator in the inflammatory process [28, 29]. There is now clear evidence that MSU crystals trigger activation of the NLRP3/ASC/caspase 1 inflammasome, which further lead to the production of IL-1β. miR-223 can suppress NLRP3 expression through a conserved binding site within the 3'-UTR of NLRP3, reducing NLRP3 inflammasome activity [30]. miR-92a can indirectly activate the NLRP3 inflammasome by targeting key molecules in endothelial homeostasis, including Sirtuin 1, Kruppel-like factor 2 (KLF2), and KLF4 during oxidative stress [31]. However, there is no other miRNA identified to targeting NLRP3, and more studies are needed to further identify other possible miRNAs targeting NLRP3 inflammasome in inflammatory action. There is only one miRNA identified to control the ASC expression [32], and no microRNA to target caspase-1. Given the vital role of NLRP3 inflammasome for inflammatory diseases including gout, more researches on its modulation through miRNAs will help us get a better understanding of NLRP3 in gout and find potentially therapeutical target for gout.

miRNAs and inflammatory cytokines

IL-1β is a cytokine protein encoded by the IL1B gene. IL-1β precursor is cleaved by cytosolic caspase 1 to form mature IL-1β. IL-1β has a central role in the regulation of immune and inflammatory responses to infections or sterile insults, and it also has a vital role in gout. However, there is no miRNA identified to target IL-1β from current literature. Previous studies have shown that miRNA-155 is a proinflammatory regulator via SHIP-1 down-regulation in acute gouty arthritis, and overexpression of miR-155 can lead to suppress SHIP-1 levels and enhance proinflammatory cytokines including IL-1β [5]. In other inflammatory diseases, miRNA-155 can also indirectly promote the production of IL-1β [33, 34]. There are also several miRNAs which can indirectly inhibit the production of IL-1β, such as miR-146a miR-223, and miRNA-146b-5p [30, 35-39].

Currently, there are also no miRNAs identified to target TNF-α, IL-8, or IL-6 in gout. Previous studies have found several miRNAs targeting TNF-α in other diseases, such as miR181s, miR181c, miR-19a, miR-155, miR-125b, and miR-130a [40-45]. Several miRNAs targeting IL-8 have also been identified in non-gout diseases, such as miR-106b, miR-520b, miR-203 and miR-93 [46-49]. In addition, there are also several miRNAs targeting IL-6 in non-gout diseases, such as miR-98, miR-365 and let-7a [50-52]. Future studies may investigate whether the above miRNAs targeting TNF-α, IL-8, or IL-6 in non-gout diseases also have some roles in the pathogenesis of gout.

miRNAs and chemokines

Chemokines are small proteins that play a crucial part in directing the movement of circulating mononuclear cells or leukocytes to sites of inflammation or injury [53]. Chemokines

can regulate immune responses through the activation and recruitment of leukocytes. The approximately 50 human chemokines segregate into four families on the basis of differences in structure and function [53]. The most thoroughly characterized CC chemokine is monocyte chemoattractant protein 1 (MCP-1), termed "chemokine ligand CCL2" in the systematic nomenclature. Other CC chemokines include macrophage inflammatory protein (MIP)-1α (CCL3) and MIP-1β (CCL4). Some CXC chemokines, of which interleukin-8 (CXCL8) is the classic type, attract polymorphonuclear leukocytes to sites of acute inflammation. There are a number of chemokines and their receptors identified to have some roles in acute gouty arthritis, such as CCL2, CCL3, CCL4, CXCL1,CXCL2, CXCL8(IL-8), CXCL10, CXCL16, CCR5, CXCR2, CXCR4, and CXCR6 [54-57].

Currently, there is also no miRNA identified to target chemokines in the development of gout. There are several miRNAs identified to target chemokines in other diseases. miR-125b is a negative regulator of CCL4 and its reduction is partially responsible for the age-related increase of CCL4 [58]. miR-495 could affect the proliferation and apoptosis of human umbilical vein endothelial cells by directly targeting CCL2 [59]. miR141 can regulate the expression of CXCL1 in lung cancer cells [60]. miR181b down-modulates CXCL1 and -2 through a direct binding to their 3'-UTR in breast cancer [61]. miR-141 regulates colonic leukocytic trafficking by targeting CXCL12 during murine colitis and human Crohn's disease [62]. miR-7641 can modulate the expression of CXCL1 during endothelial differentiation derived from human embryonic stem cells [63]. miR-126 bounds directly to the 3'-UTR of CCL2 mRNA, and overexpression of miR-126 in a human monocyte/macrophage cell line can attenuate CCL2 production [64]. miR-124a directly binds to the 3'-UTR of MCP-1 mRNA, and the induction of miR-124a in rheumatoid arthritis synoviocytes can significantly suppress the production of MCP-1 proteins [65]. However, the role of these miRNAs above targeting chemokines in the pathogenesis of gout is still unclear. Targeting chemokines through miRNAs is a promising strategy for the treatment of gout, and it deserves future studies.

Summary

The pathogenesis of gout is still not well understood now, and there is still lack of good and effective treatment for acute gouty arthritis. miRNAs have important roles in inflammatory diseases, and current literatures also show that they may act as important regulators of gout pathogenesis via several pathways. Given the importance of miRNAs for inflammatory diseases including gout, more studies on their roles in gout are needed, which will help us get a better understanding of gout pathogenesis and develop some promising effective treatments for gout [66].

Disclosure Statement

All authors declare that they have no conflicts of interest.

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