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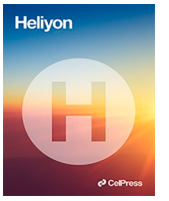

Review article

Mechanism of macrophages in gout: Recent progress and perspective

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ABSTRACT

Gout represents an autoinflammatory disorder instigated by monosodium urate crystals. Its primary manifestation involves the recruitment of diverse immune cell populations, including neutrophils and macrophages. Macrophages assume a pivotal role in the initiation of acute gouty inflammation and subsequent inflammatory cascades. However, recent investigations have revealed that the impact of macrophages on gout is nuanced, extending beyond a solely detrimental influence. Macrophages, characterized by different subtypes, exhibit distinct functionalities that either contribute to the progression or regression of gout. A strategy aimed at modulating macrophage polarization, rather than merely inhibiting inflammation, holds promise for enhancing the efficacy of acute gout treatment. This review centres on elucidating potential mechanisms underlying macrophage polarization in the onset and resolution of gouty inflammation, offering novel insights into the immune equilibrium of macrophages in the context of gout.

1. Introduction

Gout represents a prevalent metabolic condition, and recent reports indicate a global rise in both its prevalence and incidence, affecting approximately 1–6.8 % of the population and contributing to an increased healthcare burden [1]. This condition is typified by self-limiting inflammation triggered by the deposition of monosodium urate (MSU) crystals in joints or kidneys [2]. The inflammatory response in gout is chiefly characterised by the infiltration of various immune cells, including neutrophils and macrophages [3]. Macrophages, sourced from resident tissue macrophages and monocyte-derived macrophages originating from bone marrow

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hematopoietic stem cells, play a pivotal role in the onset of acute gouty inflammation and subsequent inflammatory cascades [4]. Upon MSU stimulation, macrophages exhibit not only a singular set of functions but a succession of functional changes as the microenvironment evolves [5,6].

Notably, despite the sustained presence of MSU crystals, a gout flare typically resolves within 7–10 days [7]. The mechanism underpinning this rapid inflammation subsidence remains unknown. Reports suggest that this process may be regulated by the proinflammatory and anti-inflammatory phenotypes of macrophages [5]. The polarization appears to be a spontaneous process and could represent one of the mechanisms contributing to the spontaneous resolution of gouty inflammation. This review introduces and discusses potential mechanisms involving macrophages in the onset and resolution of gouty inflammation, offering potential therapeutic targets for gout treatment.

2. Macrophage polarization in gout

Macrophages undergo phenotypic transitions contingent upon microenvironmental cues. In a general classification, polarized macrophages are broadly categorised into two primary groups: proinflammatory macrophages (referred to as M1-like macrophages) and anti-inflammatory macrophages (referred to as M2-like macrophages) [8]. M2 macrophages can be further subdivided into M2a, M2b, M2c, and M2d. In the initial stages of gout, the quantity of M1 macrophages is comparable to that of M2. As acute gout ensues, the number of M1 cells increases, reaching a peak concomitant with the zenith of inflammation [9]. Subsequently, the number of M1 macrophages diminishes, while the population of M2 macrophages undergoes augmentation. This dynamic shift contributes to the spontaneous remission of gout or progression to chronic gout until the M2 population surpasses that of M1 [5]. In summary, macrophage polarization during acute gout is predominantly characterised by M1, whereas during acute gout remission or chronic gout, M2 predominates [5,9]. This underscores the close association between macrophage polarization and the development or regression of gout. Regrettably, M2 subtypes remain largely unexplored in the context of gout research. Importantly, this process occurs independent of external intervention or reduction in monosodium urate (MSU) crystals. While the causal relationship between macrophage polarization and gout evolution remains unclear, comprehending the mechanisms of macrophages in gouty inflammation assumes paramount significance.

3. Mechanism of proinflammatory macrophage polarization in gout

The differentiation of macrophages into proinflammatory macrophages in response to MSU crystals has long been acknowledged [10]. Various targets from macrophages in gouty inflammation have been documented.

3.1. LTB4

Leukotriene B4 (LTB4), originating from the enzymatic action of 5-lipoxygenase (LOX), stands as a prominent end-product of arachidonic acid metabolism [11]. It plays a crucial role in macrophage facilitation, initiation of inflammation, and immune response regulation [12]. Macrophages produce LTB4, C-X-C motif chemokine ligand (CXCL)1/2, and interleukin (IL)-1β upon stimulation by MSU crystals. Significantly, LTB4 levels peak earlier than the production of CXCL1/2, IL-1β, and the accumulation of neutrophils in the articular cavity. In *vitro*, LTB4 stimulation induces reactive oxygen species (ROS)-dependent caspase-1 cleavage, MSU-induced NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome assembly, and production of IL-1β in macrophages [13]. Deficiency or blockade of 5-LOX mitigates MSU-induced joint inflammation, preventing IL-1β production and neutrophil migration [13,14]. LTB4 serves as a pivotal signalling mediator activated by MSU crystals in macrophages, triggering the release of essential cytokines and chemokines for inflammation.

3.2. IL-1β

IL-1β, a member of the IL-1 family, is deemed a crucial cytokine in inflammatory diseases [15]. Elevated expression of IL-1β has been identified in the serum of gout patients, affecting multiple cell types [16]. Two primary pathways govern MSU-induced IL-1β production by macrophages [17]. The first pathway involves increased ROS generation by xanthine oxidase (XOD), subsequently inducing inflammasome activation and caspase-1-mediated cleavage of precursor IL-1β [18]. The Toll-like receptor 4/Nuclear factor-κB (TLR4/NF-κB) pathway represents an alternate major route for MSU-induced IL-1β release. TLR4 blockade in peripheral blood from gouty arthritis patients reduces NF-κB levels and IL-1β production [19,20]. Other non-classical mechanisms in MSU-induced IL-1β secretion in gout include cell damage and death, proteases released by neutrophils at the inflammation site, and spleen tyrosine kinase activation in neutrophils [17]. Moreover, IL-1R knockout in a model of MSU-induced peritonitis reduces neutrophil influx [21]. Torres et al. reported pain relief and reduced ankle joint inflammation in IL-1R−/− MSU-induced mice [22]. Conversely, significant ankle swelling was observed in IL-1R−/− mice stimulated with MSU crystals [23]. MSU-induced inflammation in gout is not solely dependent on IL-1β signalling. IL-1β blockers are recommended for treating acute gout flares in patients with frequent flares and contraindications to colchicine, nonsteroidal anti-inflammatory drugs, and corticosteroids [24]. Most IL-1β blockers are not approved for gout by the U.S. Food & Drug Administration (FDA) due to the elevated risk of infections [17].

3.3. NLRP3 inflammasome

The NLRP3 inflammasome is composed of NLRP3, pro-caspase-1, and the adaptor protein ASC facilitating the connection between NLRP3 and caspase-1 upon activation [21]. This complex is predominantly expressed by myeloid cells, such as monocytes and macrophages [25–27]. Notably, the NLRP3 inflammasome stands as the principal pathway through which MSU crystals induce cellular inflammatory responses [28]. In the context of acute gout flares, macrophages initially internalize MSU crystals, triggering the assembly and activation of the NLRP3 inflammasome, resulting in the production and release of IL-1β. This process marks the initial step in neutrophil recruitment to target organs and tissues, culminating in the release of inflammatory mediators like ROS, tumour necrosis factor (TNF)-α, IL-1β, and prostaglandin E2 (PGE2) [29]. An early study demonstrated that macrophages lacking various components of the inflammasome (caspase-1, ASC, and NLRP3) were deficient in MSU-induced IL-1β production and release, accompanied by impaired neutrophil influx in a model of MSU-induced peritonitis with deficiencies in caspase-1, ASC, or IL-1R [21].

Multiple targets play roles in regulating NLRP3 inflammasome activation in macrophages. The mechanosensitive transient receptor potential channel V4 (TRPV4) in macrophages can be selectively activated by MSU crystal-induced cell volume changes, leading to NLRP3 inflammasome activation, cytokine production, and suppression of TRPV4 reduces robust inflammasome activation induced by MSU [30]. In human U937-derived macrophages, caspase-1 enzymatic activity within the NLRP3 inflammasome regulates high-mobility group box 1 (HMGB1), a crucial mediator in uric acid-induced inflammation [31]. Epidermal growth factor receptor pathway substrate 8 (Eps8) plays a significant role in mediating caspase-1 autocleavage and IL-1β maturation; Eps8 silencing abolishes the expression of NLRP3, caspase-1, and the maturation of IL-1β in MSU-treated RAW264.7 macrophages [32]. The active complement fragment C5a and its receptor C5aR2 are closely associated with NLRP3-associated diseases; C5aR2 deficiency dampens caspase-1 cleavage and reduces IL-1β production [33]. NLRP3, ASC, and caspase-1 protein expression and IL-1β production decrease in MSU-induced P2Y14R knockout macrophages differentiated from human myeloid leukemia mononuclear cells (THP-1) [34]. Additionally, cathepsin B (CTSB) is also essential for NLRP3 inflammasome activation in macrophages [35,36].

Remarkably, NLRP3 gene polymorphisms serve as a susceptibility factor for gout, with individuals carrying the single nucleotide polymorphisms NLRP3 rs3806268 or rs10754558 having a higher risk of developing gout [37,38]. Moreover, the NLRP3 transcript variant in peripheral blood mononuclear cells (PBMCs) is closely linked to the occurrence of primary gout [39]. Interestingly, the expression of NLRP3 in PBMCs of gout patients within 48 h is not significantly different from that in patients with asymptomatic hyperuricemia [40]. Even more intriguingly, it is found that the serum NLRP3 level in gout patients is negatively correlated with the serum uric acid level [41]. This suggests that NLRP3 activation does not occur in circulating blood but is confined to the site of MSU crystal deposition, providing evidence for localised treatment of gout.

3.4. TAK1

Transforming growth factor-β (TGF-β)-activated kinase 1 (TAK1) belongs to the mitogen-activated protein kinase kinase kinase family and plays a crucial role in regulating immune responses and inflammatory processes [42,43]. Various studies have identified TAK1 as a therapeutic target for rheumatic diseases, including gout, rheumatoid arthritis, osteoarthritis, and systemic scleroderma [44]. Activation of THP-1 macrophages with MSU crystals results in sustained phosphorylation of TAK1. Silencing TAK1 or using a TAK1 inhibitor (5*Z*-7-oxozeaenol) can inhibit MSU-induced production of IL-1β and TNF-α in THP-1 macrophages [45]. TAK1 appears to play a crucial role in the stability of IL-1β, and TAK1 inhibitors limit the maturation or release of IL-1β by reducing its pre-expression [45]. In *vivo*, a TAK1 inhibitor alleviates features of acute and chronic paw inflammation induced by MSU crystals in mice, including synovitis, fibrous ankylosis, loss of subchondral bone, pannus formation, and erosion of articular cartilage [45]. Thus, TAK1 is suggested to play a key role in the development and progression of gouty inflammation, highlighting the potential application of TAK1 inhibitors in clinical settings [46].

3.5. IL-33/ST2

IL-33, a member of the IL-1 superfamily, serves as the specific agonist for receptor ST2 (IL-33R) [47,48]. Reports indicate an increased expression of IL-33 in the serum of gout patients compared to healthy controls [49]. Neutralization or knockout of IL-33 alleviates pain hypersensitivities and inflammation in a mouse model of gouty arthritis [50]. Similarly, in ST2−/− mice with MSU stimulation, knee joint edema, ankle edema, mechanical allodynia, neutrophil recruitment, and production of proinflammatory and chemotactic factors such as IL-1β, IL-6, IL-13, C-C motif ligand (CCL)2/3/11, and CXCL1 are reduced [50,51]. In *vitro* studies using bone marrow-derived macrophages from ST2−/− mice show lower levels of MSU-induced IL-1β and TNF-α [51]. Exogenous IL-33 treatment decreases neutrophil recruitment in MSU-induced acute inflammation [52]. However, direct inhibition of IL-33/ST2 signaling is not entirely satisfactory; in one study, the administration of anti-ST2 antibodies, which block IL-33 signaling, did not alleviate MSU-induced inflammation [52]. Moreover, serum IL-33 levels are lower in gout patients with kidney injury compared to those without, and IL-33 might relieve kidney damage by regulating lipid metabolism in gout patients [49]. Metabolic reprogramming induced by IL-33 regulates macrophage differentiation and inflammation resolution [53]. It appears that IL-33 has a paradoxical role in gout.

3.6. Glycolysis

The interplay between inflammatory diseases and glycolysis has garnered increasing attention [54]. Genome-wide association

studies on serum urate have highlighted the major genetic influences on serum urate, focusing on uric acid excretion and glycolysis [55–57]. Additionally, increased glucose uptake has been identified in the joints or soft tissues of individuals afflicted with gout [58,59]. Glucose stands as a pivotal nutrient for inflammatory macrophages, rapidly fuelling inflammation through glycolysis and heightened glucose uptake [60]. In *vitro* observations reveal elevated glucose consumption by macrophages upon MSU stimulation [61]. MSU crystals augment macrophage basal glycolysis, glycolytic rate, and glycolytic activity while upregulating glycolytic genes [61,62].

There is compelling evidence supporting the pivotal regulatory role of glycolysis in the activation of the NLRP3 inflammasome in macrophages. Accumulation of pyruvate-induced glycolysis contributes to the hyperactivation of the NLRP3 inflammasome in macrophages, exacerbating gout development [63]. Moreover, the downregulation of glycolytic enzymes (HK1 or PKM2) can suppress both pro-IL-1β maturation and caspase-1 activation in macrophages [64,65]. The glucose transporter (GLUT)-1, a key player in glycolysis, emerges as the most abundant glucose transporter in macrophages [66]. MSU stimulation upregulates GLUT-1 expression in mouse bone marrow-derived macrophages (BMDMs) and THP-1 cells. Glucose deprivation or glycolysis inhibition through GLUT1 silencing prevents NLRP3 inflammasome activation and IL-1β production induced by MSU crystals [61]. The glycolysis inhibitor 2-Deoxy-D-glucose (2-DG), targeting hexokinase (HK), mirrors the effects of GLUT1 silencing [61]. In *vivo*, intraperitoneal injection of a GLUT-1 inhibitor suppresses all signs of local inflammation, IL-1β production, and neutrophil recruitment in the air pouch of an MSU-induced mouse model [61]. Similarly, GLUT-6 is implicated in regulating glycolysis in inflammatory macrophages [67,68]. Additionally, a recent study has demonstrated that MSU crystals modulate glycolysis and the inflammatory response, depending on c-Jun N-terminal kinase (JNK), and JNK deficiency downregulates several inflammatory and metabolic genes (CCL2/3/4/7/9, CXCL1/2, TNF-α, GLUT-1, AP-1) [62]. In summary, the pathogenesis of gout is intricately linked to glycolysis. Inhibiting the proinflammatory activity of macrophages through metabolic reprogramming may present a novel therapeutic strategy for gout.

3.7. T-bet

The transcription factor T-bet, an immune cell-specific member of the T-box family of transcription factors, serves as a master regulator for Th1 differentiation [69]. A recent study demonstrates T-bet overexpression in $CD4^+$ T lymphocytes from individuals with chronic hyperuricemia, with subsequent reductions following allopurinol therapy [70]. Notably, T-bet is also expressed in macrophages and dendritic cells. Protein levels of T-bet are found to decrease in PBMCs of acute gout patients compared to healthy controls

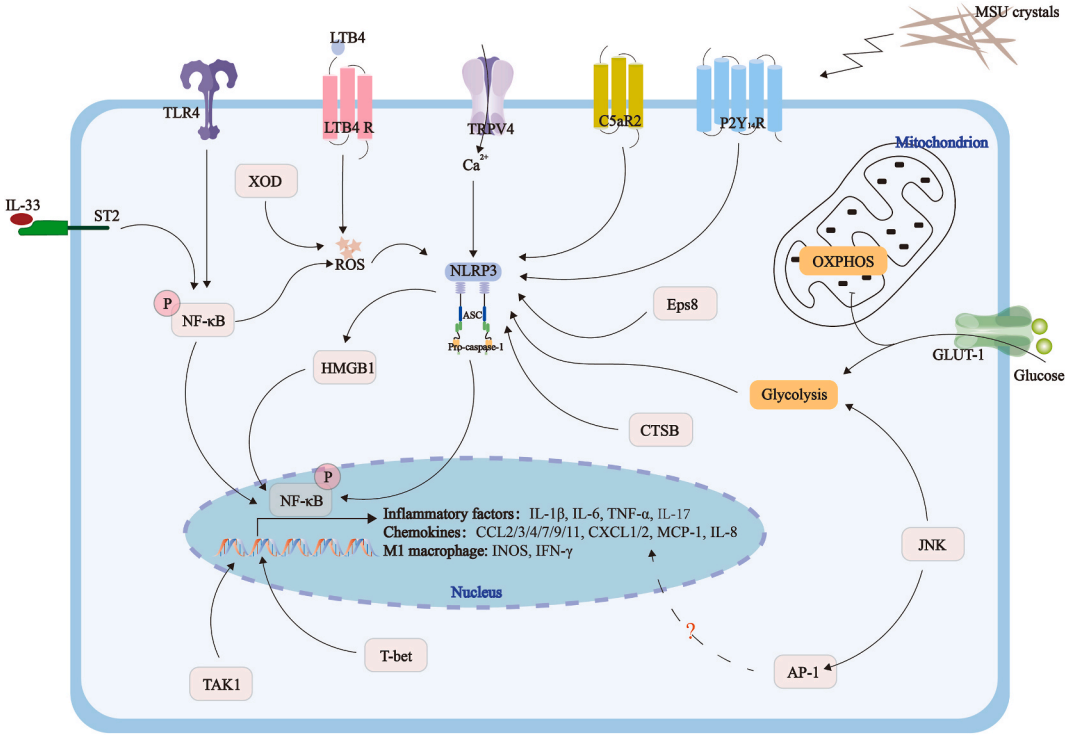

Fig. 1. Mechanism of proinflammatory macrophage polarization in gout. Upon stimulation with MSU crystals, various specific receptors on M1 macrophages are activated, such as TLR4, GLUT-1, $P2Y_{14}R$, and C5aR2. Macrophages also trigger the activation of receptors LTB4R and ST2 through autocrine LTB4 and IL-33, respectively. Subsequently, multiple pathways and biological processes that promote inflammation are initiated, including NF-κB, NLRP3 inflammasome, HMGB1, TAK1, T-bet, JNK, CTSB, Eps8, and glycolysis. The expression levels of proinflammatory factors and chemokines are elevated, ultimately leading to gouty inflammation and tissue damage.

[71]. Importantly, in BMDMs with T-bet knockout, IL-17, IL-23, and interferon-γ (IFN-γ) levels, as well as MSU phagocytosis, decrease after MSU crystal stimulation in *vitro*, while TNF-α levels remain unaffected [71]. The deficiency of T-bet suggests a potential role in alleviating inflammation in gout, though this appears inconsistent with decreased T-bet expression in PBMCs of acute gout patients. Further investigations are warranted, and it would be more convincing if T-bet expression were examined specifically in macrophages at the site of gout, rather than in peripheral blood.

In summary, following MSU crystal stimulation, macrophages can induce the expression of proinflammatory factors and chemokines, leading to gouty inflammation through the regulation of specific receptors (TLR4, GLUT-1, $P2Y_{14}R$, C5aR2, LTB4R, and ST2) and inflammatory pathways (NF-κB, NLRP3 inflammasome, HMGB1, TAK1, T-bet, JNK, CTSB, and Eps8) (Fig. 1).

4. Mechanism of anti-inflammatory macrophage polarization in gout

Macrophages are generally considered key immune cells in proinflammation, but mechanisms to maintain the balance between pro- and anti-inflammatory responses have been identified in macrophages. The gout flare subsides without administration despite the sustained presence of MSU crystals. This process might be controlled by the balance of pro- and anti-inflammatory factors in macrophages.

4.1. IL-37

IL-37, a member of the IL-1 family, has recently been acknowledged as a new anti-inflammatory cytokine in inflammatory diseases [72]. In *vitro*, silencing IL-37 increases the production of IL-6, IL-1β, and TNF-α induced by MSU crystals in PBMCs [73]. Conversely, recombinant human IL-37 or overexpression of IL-37 decreases MSU-induced proinflammatory cytokines in THP-1 macrophages, including IL-6, IL-8, IL-1β, TNF-α, and CCL2, without affecting anti-inflammatory IL-10 and TGF-β [73,74]. In *vivo*, IL-37 administration diminishes neutrophil and monocyte recruitment and decreases the production of neutrophil chemoattractants (CXCL1/5/10 and CCL3/20) and monocyte chemoattractants (CCL2/4/5/22) in MSU-induced murine peritonitis [74]. These results underscore the crucial role of IL-37 in limiting the proinflammatory effects of macrophages under MSU stimulation. Mechanistically, IL-37 promotes non-inflammatory phagocytosis of MSU in macrophages, reduces pyroptosis-related protein transcription and inflammatory cytokine release, protects mitochondrial function, and mediates metabolic reprogramming dependent on the regulation of glycogen synthase kinase 3β (GSK-3β) [75]. Moreover, IL-37 mediates inflammation resolution and promotes M2 macrophage polarization via ST2 inhibition [76].

The aforementioned studies demonstrate the inhibitory effect of IL-37 on MSU-induced inflammation. However, the expression of IL-37 in gout patients does not decrease as anticipated. There is an observed higher expression of IL-37 in PBMCs from gout patients compared to healthy controls [73,74]. Serum levels of IL-37 are elevated in active gout patients, particularly those with tophus, while no significant difference exists between hyperuricemia patients and healthy controls. This suggests that IL-37 expression may originate from the deposition of MSU crystals rather than serum uric acid [77,78]. Notably, IL-37 does not exert anti-inflammatory effects on every cell type in gout. In tubule epithelial cells, IL-37 contributes to the pathogenesis of gout by regulating uric acid metabolism and the NF-κB pathway [79]. Moreover, it is observed that patients with rare IL-37 variants suffer from gout at a younger age or exhibit a more severe disease phenotype with multiple inflammatory comorbidities, implying that rare genetic variants in IL-37 contribute to the loss of anti-inflammatory effects and confer a predisposition to gout [80,81]. IL-37 might act as a negative feedback regulation to inhibit excessive inflammation induced by MSU crystals and serve as a potential marker for predicting tophus formation.

4.2. MTA1/TG2

Transglutaminase 2 (TG2), a crosslinking enzyme abundantly expressed in macrophages [82,83], is a significant player in the regulation of inflammation from M2 macrophages. TG2 knockdown reduces MSU crystal-induced TGF-β1 production while enhancing the production of proinflammatory cytokines, including IL-1β and TNF-α, in macrophages [84,85]. Conversely, MSU crystal-induced TGF-β1 levels are elevated in TG2-overexpressing macrophages, leading to reduced IL-1β and TNF-α production [85]. Additionally, defective phagocytosis of apoptotic neutrophils by TG2−/− macrophages is corrected by soluble extracellular TG2, highlighting TG2's role in engulfing apoptotic cells [84]. Metastatic tumor antigen 1 (MTA1), a master chromatin modifier, is essential for the regulation of TG2 expression [86]. Silencing MTA1 compromises the ability of MSU crystals to induce TG2 and TGF-β1 expression while increasing IL-1β and TNF-α production. Recombinant TG2 corrects the defect in TGF-β1 production and decreases MSU-induced IL-1β and TNF-α production in MTA1-silenced cells suggesting that TG2 in macrophages is regulated by MTA1 [85].

4.3. Sirt1

The silent information regulator sirtuin 1 (Sirt1) protein, a highly conserved NAD-dependent deacetylase, plays a crucial role in inflammation [87]. Compared to healthy controls, both Sirt1 mRNA and protein levels are reduced in PBMCs of gout patients [88]. In *vitro*, with MSU crystal stimulation, a Sirt1 agonist suppresses the gene expression of proinflammatory cytokines including monocyte chemoattractant protein-1 (MCP-1), IL-1β, IFN-γ, IL-6, and TNF-α, and reduces inducible nitric oxide synthase (iNOS) expression, a vital transcription factor indicative of M1 polarization in macrophages [89,90]. This reveals the inhibition of Sirt1 on M1 macrophages. The phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), peroxisome proliferator-activated receptor (PPAR)γ, and signal transducer and activator of transcription (STAT)6 pathways are involved in the program of M2 macrophage activation [91–93].

Inhibiting PI3K/AKT, PPARγ, or STAT6 diminishes the Sirt1-mediated inhibition of gouty inflammation, suggesting that they are downstream pathways of Sirt1 [89,90].

4.4. Epigenetic regulation and microRNAs

Epigenetic mechanisms are typically mediated by post-translational modifications and noncoding RNA, such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) [94]. Recently, epigenetic regulation has been found to play potential roles in subtype-specific signaling pathways and downstream transcription factors in macrophages, including interferon regulatory factor (IRF), NF-κB, PPARs, and STATs which are essential for macrophage polarization, activation, and inhibition [95]. It is involved in multiple autoimmune and chronic inflammatory diseases, including diabetes mellitus, obesity, gout, cardiovascular diseases, and so on. Interestingly, food components and their metabolites are emerging as regulators of the human epigenome in metabolic disease. Excessive intake of fructose, a monosaccharide abundant in fruits and sugary drinks, increases the risk of developing gout and hyperlipidemia, which may be related to miRNA [96]. Additionally, as a meat- and seafood-derived metabolite, urate triggers an epigenetic anti-/pro-inflammatory response [97].

MiRNA, a short noncoding RNA highly conserved during evolution, plays a key role in immune and inflammatory diseases [98]. The expression of miRNA is closely related to macrophage polarization and activation [99,100]. Recent studies have shown the anti-inflammatory effect of miRNA in gout [101,102]. Epiregulin (EREG), a member of the epidermal growth factor (EGF) family, promotes the secretion of pro-inflammatory factors in macrophages. MiR-192-5p overexpression reduces EREG expression, attenuates ankle joint swelling, and synovial inflammatory cell infiltration, and improves bone erosion in MSU-induced mice [103]. In *vitro*, miR-192-5p reduces the release of inflammatory cytokines TNF-α and IL-1β and decreases iNOS expression in RAW264.7 macrophages, and these changes are partially reversed by EREG overexpression [103].

MiR-449a deficiency upregulates the expression of NLRP3, ASC, and caspase-1 in BMDMs treated with MSU crystals [104]. Moreover, overexpression of miR-302b in THP-1 macrophages inhibits NF-κB and caspase-1-mediated proinflammatory factors by directly targeting IRAK4 and EphA2 [105]. It dramatically upregulates the protein level of TRAF6 and IRAK1, the gene expression of NLRP3, ASC, and caspase-1, and enhances IL-1β and TNF-α secretion in MSU-induced miR-146a deficiency BMDMs [106]. The level of TNF-α and IL-1β secretion was markedly elevated, and expression of NLRP3 was increased in MSU-induced MiR-223 knockout BMDMs [107]. In contrast, it is shown a proinflammatory effect of miRNA in gout, such as miR-155. Overexpression of miR-155 decreases the promoted production of MSU-induced proinflammatory cytokines in THP-1 macrophages, while there is no difference in another study [108,109]. It may support that miR-155 does not directly affect MSU-induced gouty inflammation.

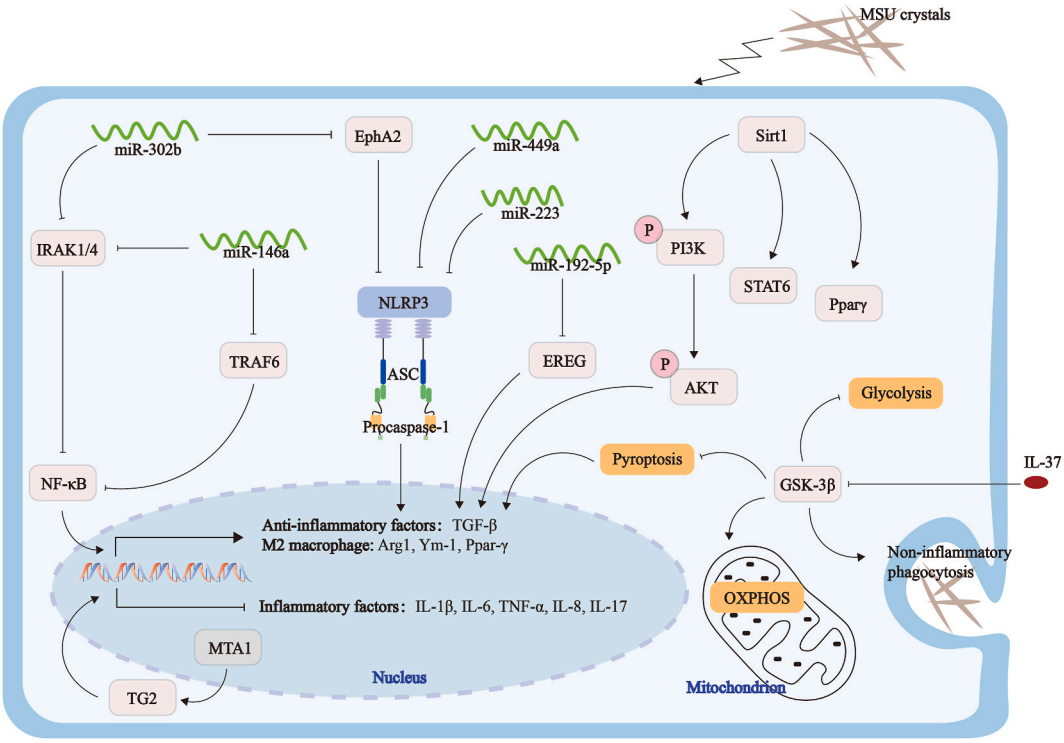

Fig. 2. Mechanism of anti-inflammatory macrophage polarization in gout. Anti-inflammatory macrophages suppress the activation of inflammatory pathways and the expression of proinflammatory factors and chemokines. This process is possibly related to miR-302b, miR-449a, miR-223, miR-192-5p, Sirt1, IL-37, and the MTA1/TG2 signaling pathway, ultimately leading to the resolution of gout.

In clinical observations, a significant reduction in miR-192-5p and an increase in EREG are noted in the serum of gout patients [103, 110]. Similarly, the level of miR-223 is downregulated in PBMCs from gout patients [107]. Interestingly, after stimulation with MSU, MiR-223 is upregulated in the early phase in macrophages and decreases rapidly [101,107]. However, not all anti-inflammatory miRNAs are downregulated in gout patients, and a higher level of miR-302b and miR-146a is found in gout patients when compared to healthy controls [105,111]. Direct evidence of a link between these anti-inflammatory miRNAs and anti-inflammatory macrophages is still pending and the molecular mechanisms of miRNA in M2 macrophages remain to be confirmed.

Overall, anti-inflammatory macrophages suppress the activation of inflammatory pathways, and the expression of proinflammatory factors and chemokines may be related to miR-302b, miR-449a, miR-223, miR-192-5p, Sirt1, IL-33, and MTA1/TG2 signaling pathway (Fig. 2). Induction of anti-inflammatory macrophages might cause spontaneous regression of gout. However, the expression of these pathways has yet to be demonstrated in inactive gout patients. Further studies should focus on the role of macrophages in the gout interval.

5. Clinical applications of the targets from macrophages

As mentioned earlier, multiple targets influence macrophage polarization and gout progression. These targets may become therapeutic targets for inhibiting gouty inflammation in the clinic. Currently, only drugs targeting IL-1/IL-1β have entered clinical practice (Table 1). An early pilot, open-labeled study reveals that IL-1 blockade appears to be an effective treatment for acute gouty arthritis [112]. Subsequently, several randomized controlled trials have found that IL-1/IL-1β inhibitors (anakinra and canakinumab) could alleviate gouty inflammation and reduce the risk of gout development [113–116]. Strikingly, fatal infections are more common after using canakinumab [117]. Indeed, gout is not just a purely inflammatory disease; it is a combination of inflammation and immune and metabolic disorders. Inhibition of inflammation as the dominant may contribute to a disappointing treatment.

6. Conclusions and future perspectives

Over the past decade, the initiation and driving force of MSU-induced inflammation by macrophages have been increasingly appreciated and gradually accepted [118]. Various therapeutic targets focusing on macrophages have been constantly discovered in experimental gout (Tables 2 and 3), with their expression levels being explored in human gout (Table 4). Strikingly, most of the targets are related to the proinflammatory and anti-inflammatory activities of macrophages, but it has not been directly deciphered whether they license macrophage polarization. Furthermore, the intermediate link between them is easily overlooked. MSU crystals promote the secretion of multiple factors and structures in gout, such as inflammatory factors and neutrophil extracellular traps, which also influence the function of macrophages.

Despite extensive studies on human and experimental gout, the in *vivo* dynamics of gout macrophages have not been thoroughly investigated. Table 3 shows that most in *vivo* studies on targets related to macrophage polarization, activation, and inhibition are focused on the whole organism rather than single cells. Indeed, these targets can also be found in other immune cells, such as neutrophils and lymphocytes, which are important in gout. Immune cell activation and crosstalk induced by MSU crystals increase the difficulty of in *vivo* studies. Moreover, macrophages located in various tissues perform different functions. For instance, microglia are tissue-resident macrophages of the central nervous system. MSU crystals induce microglia activation and neuronal damage through the NF-κB and NLRP3 pathways, resulting in learning and memory impairment in mice [119]. However, research on the nervous system in gout remains insufficient. Studying macrophages in gout in *vivo* with precision is a challenge.

Macrophages play an instrumental role in the occurrence and resolution of gout. It is feasible to envisage therapeutic strategies for targeting the immune activation of macrophages in gout. A strategy to improve the immune balance of macrophages rather than simply inhibiting pro-inflammatory macrophages may be more beneficial for the treatment of gouty inflammation. More in-depth studies are urgently needed to determine the mechanism and balance point for macrophage activation in different stages of gout.

Table 1
Clinical trial study of IL-1/IL-1β for gout.

Year	Target	Registration number	Disease	Drug	Recruitment numbers	Effectiveness	Reference
2007	IL-1	ISRCTN10862635	Acute gout	Anakinra	10	The pain in all the patients was relieved within 48 h.	[112]
2010	IL-1β	NCT00798369	Acute Flares in difficult-to-treat gouty arthritis	Canakinumab	191	It rapid and sustained relieved pain and significantly reduced the risk of recurrent flares.	[114]
2011	IL-1β	NCT00819585	Acute gouty arthritis flares	Canakinumab	432	It reduced the risk of acute gouty arthritis flares during initiation of allopurinol treatment.	[115]
2018	IL-1β	NCT01327846	Gout	Canakinumab	10061	It reduced the risk of the incidence of gout attacks by approximately 50 % in patients with a myocardial infarction.	[116]
2021	IL-1	NCT03002974	Gout flare	Anakinra	165	Anakinra can be considered an effective option in the treatment of gout flares when conventional therapy is unsuitable.	[113]

Table 2
Macrophage-associated targets influence gout in *vitro*.

Cell type	Treatment	Genotype	Phenotypic changes	Reference
Mouse macrophage	MSU	Caspase-1 knockout/ASC knockout/NLRP3 knockout	It was defective in crystal-induced IL-1β activation.	[21]
THP-1/Human PBMC	MSU + TRPV4 inhibitor	/	It significantly reduced MSU-induced robust inflammasome activation.	[30]
RAW 264.7 macrophage	MSU	Eps8 silencing	It dramatically abolished the MSU crystal-induced expression of NLRP3 and caspase-1 and the maturation of IL-1β.	[32]
Mouse peritoneal macrophage	MSU + LPS	C5aR2 knockout	It dampened the cleavage of caspase-1 and reduced IL-1β production and HMGB1 expression, but the expression of NLRP3 and TNF-α was not affected.	[33]
THP-1 macrophage	MSU	$P2Y_{14}R$ silencing	The protein expression of NLRP3, ASC, and caspase-1 and production of IL-1β were decreased.	[34]
	MSU	TAK-1 silencing	It successfully inhibited MSU-induced IL-1β and TNF-α production.	[45]
Mouse BMDM	MSU + LPS + IL-33	/	It showed lower levels of IL-1β and TNF-α from the medium.	[51]
	MSU + LPS	ST2 knockout	It potentiated IL-1β and TNF-α released in supernatant.	
	MSU	GLUT-1 silencing	It led to a reduced glucose uptake in the medium, an inhibition of the NLRP3 inflammasome activation, and an inhibition of IL-1β production.	[61]
	MSU	T-bet knockout	The levels of IL-17, IL-23, and IFN-γ were reduced, as well as MSU phagocytosis, but TNF-α was not.	[71]
	MSU	JUN silencing	Several inflammatory genes, metabolic genes, and AP-1 were upregulated.	[62]
Human PBMC	MSU	IL-37 silencing	The production of IL-6, IL-1β, and TNF-α were increased.	[73]
THP-1 macrophage	MSU + IL-37	/	It reduced the production of mature IL-1β, IL-8, and CCL2.	[74]
	MSU + IL-37	/	It promoted non-inflammatory phagocytosis of MSU, reduced pyroptosis-related protein transcription and inflammatory cytokines release, and mediated metabolic reprogramming which depends on the mediation of GSK-3β.	[75]
RAW 264.7	MSU	MTA1 silencing/TG2 silencing	Enhanced levels of IL-1β and TNF-α, but reduced levels of TGF-β1.	[85]
Mouse BMDM	MSU	TG2 knockout	Severe impairment in phagocytosis of apoptotic thymocytes.	[84]
Mouse peritoneal macrophage	MSU + Sirt1 agonist	/	It suppressed the gene expression of proinflammatory cytokines (MCP-1, IL-1β, IFN-γ, IL-6, and TNF-α).	[89]
RAW 264.7	MSU	miR-192-5p overexpression	It reduced the release of inflammatory cytokines TNF-α and IL-1β and decreased iNOS expression	[103]
Mouse BMDM	MSU	miR-223 knockout	The level of TNF-α and IL-1β secretion was markedly elevated and protein expression of NLRP3 was increased.	[107]
THP-1 macrophage	MSU	miR-302b overexpression	It inhibited the protein expression of IRAK4, p-NF-κB, EphA2, and caspase-1, as well as IL-1β and TNF-α production.	[105]
Mouse BMDM	MSU	miR-449a silencing	The protein expression of NLRP3, ASC, and caspase-1 were increased.	[104]
	MSU	miR-155 knock in	There was no difference in the production of TNF-α.	[109]
THP-1 macrophage	MSU	miR-155 transfection	The TNF-α and IL-1β levels were dramatically increased.	[108]
Mouse BMDM	MSU	miR-146a knockout	It dramatically upregulated the protein levels of TRAF6 and IRAK1, the gene expression of NLRP3, ASC, and caspase-1, and enhanced IL-1β and TNF-α secretion.	[106]

*/, no mention.
Abbreviations: BMDM, Bone marrow-derived macrophage; THP-1, Human myeloid leukemia mononuclear cell; PBMC, Peripheral blood mononuclear cell; RAW264.7, Leukemia cells of mouse mononuclear macrophage.

There remain major gaps in the knowledge of the time, molecular mechanisms, and physiological significance of macrophage polarization in gout. These problems are an important reason that prevented targets from macrophages from being used in clinics.

Publication ethics

The authors declare the manuscript and actions are ethically sound.

Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Haibo Tan: Writing – review & editing, Writing – original draft. **Shan Zhang:** Writing – review & editing. **Junlan Liao:** Writing – review & editing. **Xia Qiu:** Writing – review & editing. **Zhihao Zhang:** Writing – review & editing. **Ziyu Wang:** Writing – review & editing. **Hongling Geng:** Writing – review & editing. **Jianyong Zhang:** Conceptualization. **Ertao Jia:** Conceptualization.

Table 3
Macrophage-associated targets influence gouty inflammation in *vivo*.

Animal	Sex	Gout model	Genotype	Knockout position	Treatment	Inflammation	Reference
C57BL/6J mice	♂	Arthritis	NLRP3−/−	Global	/	↑	[13]
	♂	Arthritis	5-LOX−/−	Global	/	↑	
	♂	Arthritis	IL-1β−/−	Global	/	↑	
	♂	Arthritis/Peritonitis	ASC−/−	Global	/	↑	[13,21]
	♂	Arthritis/Peritonitis	Caspase 1−/−	Global	/	↑	
	♂	Arthritis/Peritonitis/Air pouch	IL-1R−/−	Global	/	↑	[13,21,22]
	/	Arthritis	TRPV4−/−	Macrophage	/	↑	[30]
	/	Peritonitis	C5aR2−/−	Global	/	↑	[33]
SD rat	♂	Arthritis	$P2Y_{14}R$−/−	Global	/	↑	[34]
C57BL/6J mice	♂	Arthritis	/	/	5Z-7-Oxozeaenol (TAK1 inhibitor)	↑	[45]
BALB/C mice	♂	Arthritis	ST2−/−	Global	/	↑	[51]
/	/	Air pouch	/	/	STF-31 (GLUT-1 inhibitor)	↑	[61]
C57BL/6J mice	♂	Arthritis/Peritonitis/Air pouch	T-bet−/−	Global	/	↑	[71]
	♂	Arthritis/Air pouch	/	/	SP600125 (JUK inhibitor)	↑	[62]
	♂	Arthritis/Air pouch	/	/	Recombinant IL-37	↑	[74]
	♂	Arthritis	IL-37 $^{KI/+}$	Global	/	↑	[75]
	/	Peritonitis	TG2−/−	Global	/	↓	[84]
	/	Arthritis	/	/	Resveratrol (Sirt1 agonist)	↑	[89]
	♂	Arthritis	/	/	MiR-192-5p agomir	↑	[103]
	/	Arthritis/Air pouch	MiR-223−/−	Global	/	↓	[107]
BALB/C mice	♂	Air pouch	/	/	MiR-302b agomir	↑	[105]
C57BL/6J mice	♂	Arthritis/Air pouch	MiR-155−/−	Global	/	↔	[109]
/	/	Peritonitis	MiR-146a	Global	/	↓	[106]

*, compared to the control group; ↑, improve; ↓, worsens; ↔, no difference;/, no mention.

Table 4
The expression of targets in macrophage from human gout.

Disease	Target	Compared to normouricemia		Compared to hyperuricemia		Reference
		From serum or plasma	From PBMC	From serum or plasma	From PBMC	
Gout	NLRP3	/	/	/	↔	[40]
Gouty arthritis	NLRP3	↑	/	/	/	[41]
Gout nephropathy	NLRP3	/	↑	/	↔	[120]
Gout nephropathy	ASC	/	↑	/	↑	
Gout nephropathy	Caspase-1	/	↑	/	↑	
Gouty arthritis	TLR4	↑	↑	/	/	[19]
Gouty arthritis	NF-κB	↑	↑	/	/	
Gout/Gout nephropathy	IL-1β	↑	/	↑	/	[40,120]
Acute gout	TRPV4	/	↑	/	/	[30]
Gout	HMGB1	/	↑	/	/	[31]
Gout	IL-33	↑	/	/	/	[49]
Gout nephropathy	IL-33	↓	/	/	/	
Acute gout	T-bet	/	↓	/	/	[71]
Gouty arthritis	EREG	↑	/	/	/	[103]
Gouty arthritis	miR-192-5p	↓	/	/	/	
Gout	IL-37	↑	↑	/	/	[73,78]
Gout	Sirt1	/	↓	/	/	[88]
Gout	miR-223	/	↓	/	/	[107]
Gout	miR-223	↔	/	↔	/	[121]
Gouty arthritis	miR-302b	↑	/	/	/	[105]
Gout	miR-155	↑	/	↔	/	[121]
Gout	miR-146a	↔	/	↔	/	
Intercritical gout	miR-146a	/	↑	/	↑	[111]

* ↑, increase; ↓, decrease; ↔, no difference;/, no mention.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

AKT	Protein kinase B
ASC	Apoptosis-associated speck-like protein containing card
AP-1	Activator protein-1
BMDM	Bone marrow-derived macrophage
CCL	C-C motif ligand
CTSB	Cathepsin B
CXCL	C-X-C motif chemokine ligand
EREG	Epiregulin
EphA2	EPH receptor A2
ENO1	Enolase-1
GLUT	Glucose transporter
GSK-3β	Glycogen synthase kinase 3β
HMGB1	High-mobility group box 1
HK	Hexokinase
IFN	Interferon
IL	Interleukin
IL-1R	IL-1 receptor
iNOS	Inducible nitric oxide synthase
IRAK	IL-1 receptor-associated kinase
IRF	Interferon regulatory factor
JNK	c-Jun N-terminal kinase
LncRNAs	Long non-coding RNAs
LOX	Lipoxygenase
LTB4	Leukotriene B4
MCP	Monocyte chemoattractant protein
miRNA	MicroRNA
MSU	Monosodium urate
MTA1	Metastatic tumor antigen 1
NET	Neutrophil extracellular trap
NF-κB	Nuclear factor-κB
NLRP3	NOD-like receptor family pyrin domain containing 3
PBMCs	Peripheral blood mononuclear cells
ROS	Reactive oxygen species
Sirt1	Sirtuin 1
STAT	Signal transducer and activator of transcription
TAK1	TGF-β-activated kinase 1
TG2	Transglutaminase 2
TGF-β	Transforming growth factor-β
THP-1	Human myeloid leukemia mononuclear cell
TLR4	Toll-like receptor 4
TNF	Tumor necrosis factor
TRPV4	Transient receptor potential channel V4
PGE2	Prostaglandin E2. PI3K, Phosphoinositide 3-kinase
PKM2	Pyruvate kinase isozymes M2
PPAR	Peroxisome proliferator-activated receptor

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