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Sophisticate Mechanisms and Unsolved Problems in the Resolution of Acute Gouty Arthritis

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Abstract

Only primates suffer from hyperuricemia and gout. Acute gouty attack with fulminate inflammation may recover within 7-10 days. The pathogenesis of monosodium urate monohydrate (MSU) crystal-induced acute gouty inflammation has been gradually elucidated. It is conceivable that MSU crystals possess both danger-associated pathological pattern (DAMP) and physical microcrystal properties that may activate innate immune cells IL-1 production and subsequent IL-6, IL-8 and TNF-α release from neighborhood cells. By contrast, the molecular basis of acute gouty inflammation resolution mostly remains unclear. Previous studiesdemonstrated that intracellular negative cytokine regulators CIS and SOCS-3 involved in the resolution of acute gouty inflammation in synergism with anti-inflammatory cytokine molecules (TGF-β1, IL-10 and soluble TNF-α receptors type 1 and 2). This commentary aims to dissect the potential mechanisms of induction and resolution of acute gouty attack. Besides, the unsolved problems in these issues are discussed.

Characteristics of monosodium urate crystal (MSU) induced gouty arthritis (GA)

Different from allantoin in avian species, the end-product of purine metabolism in human being is uric acid due to 2 non-sense mutations at codons 33 and 187 of urate oxidase during hominoid evolution [1,2]. The solubility of uric acid in the fluid milieu reaches a maximum of 6.8 mg/dl and becomes hyper-saturation status in plasma when over its solubility capacity. Many factors including [Na^+], pH, temperature, oncostatic pressure, and in presence of nucleating factors/growth promoting factors may accelerate crystal formation in the joints, peri-articular soft tissues, renal tubules or subcutaneous locations [3,4]. Thus, acute inflammation elicited by monosodium urate monohydrate (MSU) crystal deposition occurs usually in the low-temperature joints especially in the lower limbs. Usually, the acute inflammation in the joint of patients with acute attack may last a few days from 7-10 days. Then, spontaneous remission of the inflamed joint ensues after acute attack. Although gouty arthritis has been recognized since ancient age, the actual molecular basis of the acute attack and the subsequent spontaneous remission remain elucidation. In addition to the acute attack, part of the patients result in chronic tophaceous gout in the long-term course of hyperuricemia [5,6]. The etiopathogenesis of chronic gouty tophus formation also remain unclear. In 2011, Chen et al. [7] reported that not only intercellular anti-inflammatory cytokines TGF-β1 and IL-10, and soluble cytokine receptors TNF-α receptor type 1 (sTNF-R1) and type 2 (sTNF-R2), but intracellular cytokine negative regulators may involve in the spontaneous remission of acute gouty inflammation. The intracellular cytokine signaling inhibitors such as CIS and SOCS3 were considered the potent negative regulatory molecules for suppressing inflammatory cytokine-mediated acute gouty inflammation [8-12]. These findings are consistent with Martin et al. [13] that mononuclear phagocytes play a central role in both initiation and resolution of acute gouty inflammation. They showed that interplay between monocytes/macrophages and other elements of innate immune system including neutrophils and complement proteins are important. Despite a number of anti-inflammatory cytokines and endogenous cytokine signaling inhibitors have been found in the literatures, the connection between these cytokine inhibitors and resolution of acute gouty inflammation has never been reported. Figure 1 demonstrates a list of these potential cytokine inhibitors for controlling cytokine signaling.

Interplay among complements, phagocytes, pro-inflammatory cytokines and inflammatory mediators contribute to the initiation of MSU crystal-induced acute inflammation

As illustrated in Figure1, MSU crystals act dual roles in both danger-associated molecular pattern (DAMP) molecules and physical microcrystals in stimulating both mononuclear- and polymorphnuclear phagocytes. It is demonstrated that innate immune cells express Toll-like receptor (TLRs) on the cell surface and contain inflammasomes in the cytoplasm. As DAMP molecules, MSU crystals bind to TLR2/4-CD_{14} complex and are phagocytosed by macrophages in the synovial membrane and neutrophils in the synovial joints [14]. The MSU-engulfed phagocytes transduce signals to activate NF-kB via adaptor protein MyD88 and finally mature IL-1β release [15]. The released IL-1β then binds to IL-1 receptor on the neighborhood phagocytes to induce a bunch of potent pro-inflammatory cytokines (TNF-α, IL-6, IL-8) release. As physical microcrystals, direct phagocytosis of complements (C1q, C3 and C5)- and immunoglobulins-opsonized MSU crystals activates NLRP-3 inflammasome in macrophages. The produced IL-1β can further stimulate neighborhood innate immune cells via binding to IL-1 receptors to produce more and more proinflammatory cytokines [16]. Furthermore, IL-1β would stimulate COX-2 and 5-LOX pathways of

the inflammatory cells to amplify acute inflammation with PMN recruitment and activation [17]. In conclusion, a rapid and vigorous inflammation is triggered by MSU crystals with orchestration of florid inflammatory cytokines, inflammatory mediators, and acute inflammatory cells accumulation in the joint.

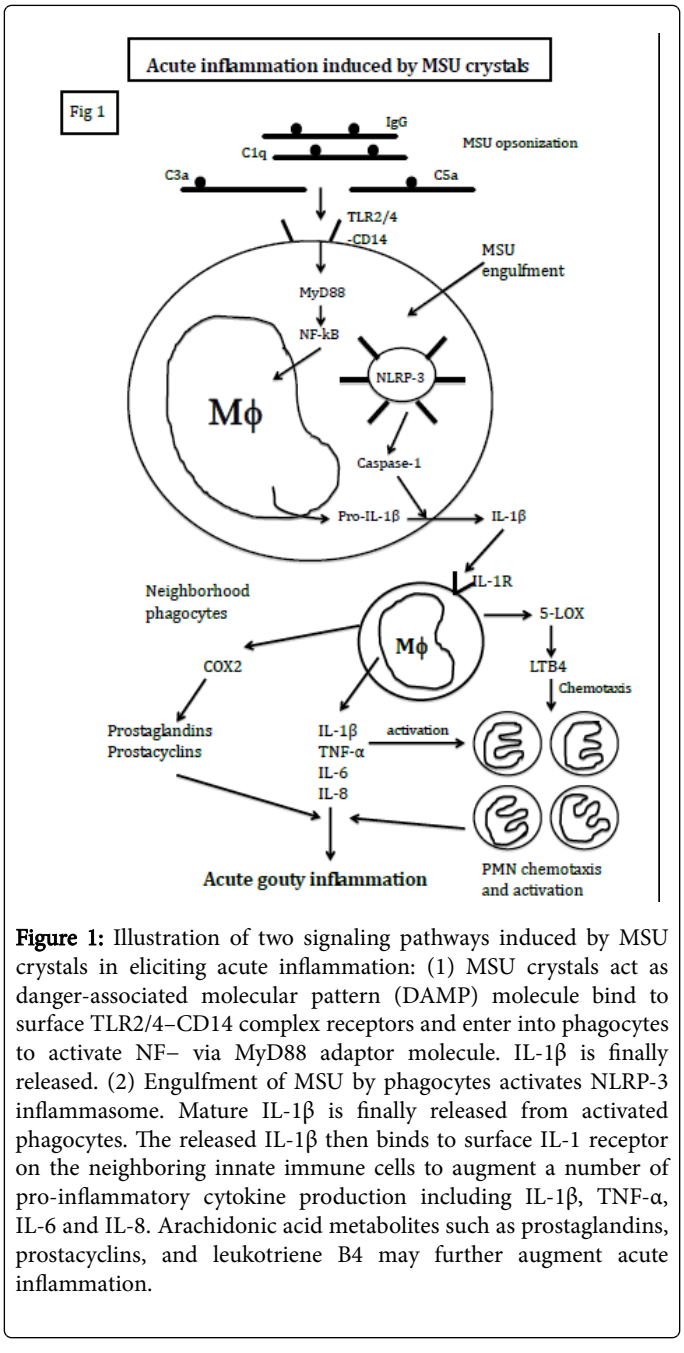

Figure 1: Illustration of two signaling pathways induced by MSU crystals in eliciting acute inflammation: (1) MSU crystals act as danger-associated molecular pattern (DAMP) molecule bind to surface TLR2/4–CD14 complex receptors and enter into phagocytes to activate NF– via MyD88 adaptor molecule. IL-1β is finally released. (2) Engulfment of MSU by phagocytes activates NLRP-3 inflammasome. Mature IL-1β is finally released from activated phagocytes. The released IL-1β then binds to surface IL-1 receptor on the neighboring innate immune cells to augment a number of pro-inflammatory cytokine production including IL-1β, TNF-α, IL-6 and IL-8. Arachidonic acid metabolites such as prostaglandins, prostacyclins, and leukotriene B4 may further augment acute inflammation.

Induction of phenotype transformation, intracellular negative cytokine signaling regulators, and probably apoptosis in macrophages by MSU crystals involve in the resolution of acute gouty inflammation

Acute gouty arthritis is generally self-limited and underlies spontaneous remission without 7-10 days. It has been demonstrated that low density lipoprotein (more specifically apolipoprotein B in the LDL) is elevated with acute inflammation [13,18]. This particular lipoprotein coats MSU crystals and renders the crystals non-inflammatory to prevent further engulfment by phagocytes (Figure 2). In the mean time, the MSU-engulfed inflammatory macrophages (M1) transform to M2 phenotype that conversely produces anti-inflammatory cytokines TGF-β_1, IL-1ra or IL-10 [19]. On the other hand, the MSU-engulfed PMNs in synovial joints transform to apoptotic and NETotic cells are phagocytosed by M1 macrophages that eventually transform to M2 phenotype [20]. The highlight findings of Chen et al. [7] suggest that MSU-engulfed macrophages not only produced proinflammatory cytokines but spontaneously transcribed CIS/SOCS3 gene expression immediately to enhance TGF-β_1 as well as sTNF-α receptors release by innate immune cells. It is also possible that MSU crystals-engulfed macrophages proceed to apoptosis. These sophisticate and potential mechanisms involving in acute gouty inflammation resolution are schemmed in Figure 2.

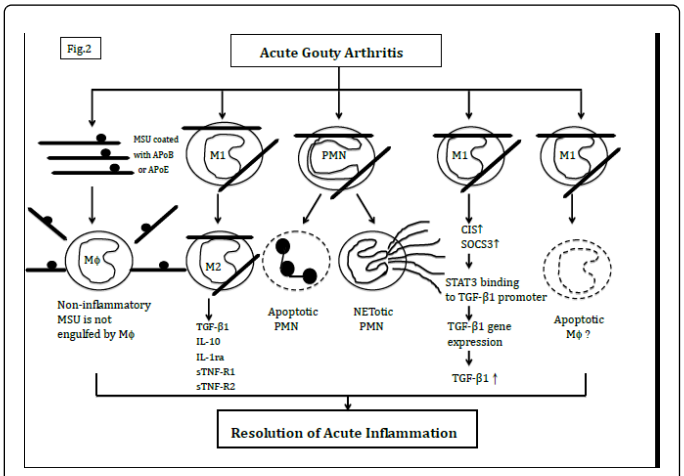

Figure 2: Illustration of sophisticate molecular basis for terminating acute gouty inflammation by at least 4 different mechanisms: (1) MSU crystals are coated by ApoB or ApoE and become non-inflammatory crystals that suppress engulfment by phagocytes. (2) MSU-engulfed macrophages transform from M1 to M2 phenotype that produce anti-inflammatory cytokines, TGF-β1 and IL-10. (3) MSU-engulfed neutrophils transform to apoptotic and NETotic cells are phagocytosed by macrophages that eventually become M2 cells. (4) Intracellular negative cytokine regulators CIS and SOCS3 are activated in MSU-engulfed macrophages to transcribe TGF-β1 gene expression (5) MSU-engulfed macrophages may probably lead to cell apoptosis.

Unsolved problems in spontaneous remission of acute gouty inflammation

Almost of the studies suggest that IL-1β production is the milestone and initiator for MSU-induced acute inflammation. However, Martin et al. [21] have demonstrated that the production of IL-6 by MSU-stimulated peritoneal exudate macrophages is much higher than IL-1β or TNF-α. Chen et al. [7] also found that IL-1β production by MSU-stimulated mouse macrophage cell line was less than TNF-α after 24h incubation. It is deduced that the levels and activities of IL-1β and TNF-α in gout synovial fluid can be counteracted by large amount of IL-1ra and soluble TNF-α receptor 1. Undoubtedly, the comparative

roles of IL-1β, IL-6 and TNF-α in acute gouty inflammation need further investigations.

It is conceivable that CIS/SOCSs family is a potent intracellular cytokine negative regulator to suppress cytokine signaling by preventing STATs phosphorylation [22]. However, both CIS and SOCS3 are not endogenous inhibitors for terminating IL-1β- or TNF-α-induced signaling pathway. In contrast, IL-6 signaling can be inhibited by SOCS3. Thus, the anti-inflammatory roles of TGF-β1 and IL-10 in the remission of acute gouty inflammation seem more realistic than CIS/SOCS family but more investigations are required to solve the problem [23]. Furthermore, the molecular basis of MSU-induced NETosis in the resolution of acute gouty inflammation as suggested by Mitroulis et al. [24] and MSU-induced macrophage apoptosis warrants intensive investigation.

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