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Review

Microcrystals as DAMPs and their role in joint inflammation

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Abstract

Microcrystals associated with joint diseases, namely monosodium urate, calcium pyrophosphate and basic calcium phosphate, can be considered as 'danger signals' to the innate immune system and provoke inflammation through inflammasome-dependent as well as inflammasome-independent pathways. Direct crystal membrane interactions can also lead to cell activation. The result is the generation of IL-1β and other pro-inflammatory cytokines. The primacy of IL-1β in the case of gouty inflammation has been demonstrated by the efficacy of IL-1 inhibitors in clinical studies. These findings may be relevant to other diseases where crystal formation is found, such as OA and atherosclerosis.

Key words: crystal arthropathies, inflammation, cytokines, animal models, physiology.

REVIEW

Introduction

Crystal arthritis is a topic that does not attract enough attention within rheumatology, probably due to the erroneous notion that all is understood in terms of pathophysiology. The first convincing demonstration of crystals in the joint fluid of certain forms of arthritis by McCarty and Hollander [1] led to the widespread use of polarizing microscopy in rheumatology clinics as a diagnostic technique, but the performance of such a simple diagnostic test is not always taught during medical training and crystals are not searched for systematically when joint fluids are examined. Recent advances have stimulated new interest in the subject, as microcrystals can be considered as endogenous 'danger signals' and are potent stimulators of immune as well as non-immune cells. The best known microcrystals include monosodium urate (MSU), calcium pyrophosphate (CPP) and basic calcium phosphate (BCP). Rarer causes of crystal arthritis are oxalate and cholesterol. Principally, crystal formation takes place due to high local concentrations of the solutes, but as yet poorly understood physico-chemical and biochemical factors also play a part in either promoting or preventing crystallization. Once formed, they elicit reactions from leucocytes as well as tissues where they are deposited, such as skin, cartilage and ligaments. Acute inflammation is the hallmark of the acute tissue reaction to crystals, but a major enigma in the field is why crystal deposits are often asymptomatic. This observation suggests that besides crystal formation, other factors are necessary in order for inflammation to develop fully. Alternatively, there may be natural counter-regulatory mechanisms that dampen down crystal-induced inflammation. Indeed, it has been recently found that increased production of TGF-β1, IL-1ra, IL-10 and soluble TNF receptor I/II (sTNFR-I/II) and up-regulation of the intracellular cytokine negative regulators CIS and SOCS3 were associated with spontaneous resolution of acute gout [2]. Currently our understanding of these pathways is still very rudimentary.

Hyperuricaemia is the underlying cause of MSU crystal formation and deposition, and persistent hyperuricaemia predisposes to clinical gout in an incremental fashion [3]. The epidemiology of gout and hyperuricaemia has been reviewed recently and the importance of dietary factors as well as associations with the metabolic syndrome highlighted [4]. Local factors that may influence crystallization of urate include connective tissue components such as hyaluronan [5] and previous injury or OA [6]. Crystal diagnosis by polarizing light microscopy remains the gold standard for the diagnosis of gout, and joint aspiration should be performed to ascertain the diagnosis whenever possible. The formation of CPP and BCP crystals is determined principally by local factors that influence the concentrations of the principal substrates: Ca^{2+}, PPi and phosphate in connective tissues, such as cartilage (leading to chondrocalcinosis) and around ligaments and tendons (calcific periarthritis). Several mechanisms

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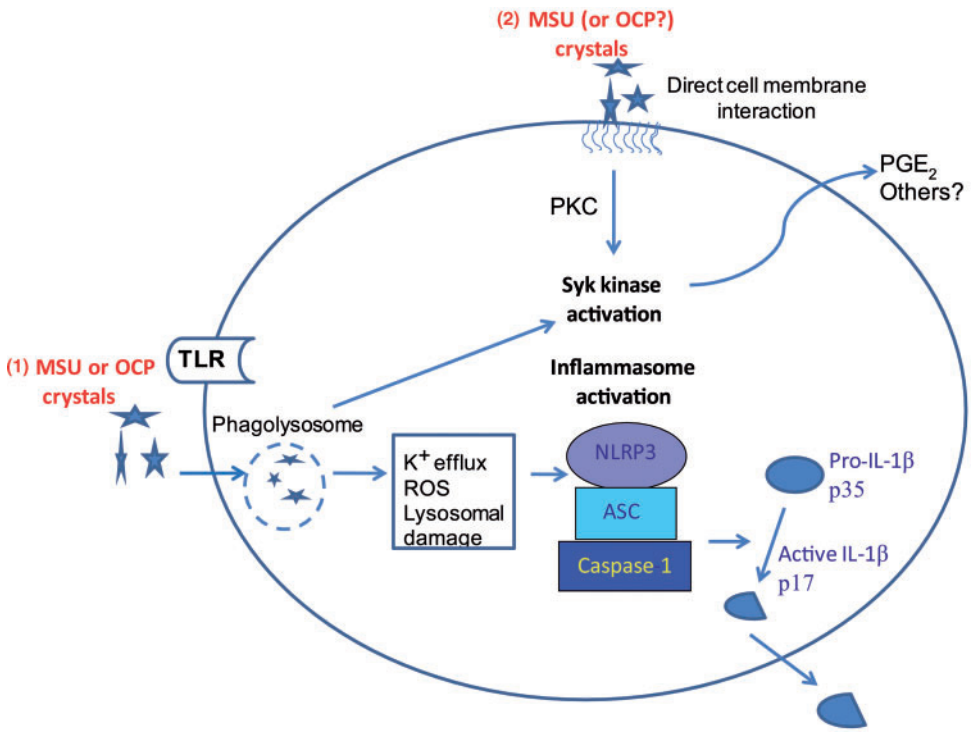
have been elucidated, including the function of cell membrane transporters of PPi and membrane phosphatases (reviewed in [7]). Both BCP and CPP crystals are recognized causes of pseudogout, and their presence in OA cartilage and SF suggests a pathogenic role for calcium-containing crystals in the development and progression of OA [8–11].

MSU and BCP crystals are danger signals that activate the NLRP3 inflammasome

Infectious agents and damaged cells release molecules that are potent stimulators of cells in the immune system, as they contain danger-associated molecular patterns (DAMPs) that are capable of binding to innate immune receptors. In the 'Danger hypothesis' proposed by Matzinger [12], these signals are key to the initiation of an immune response, primarily by interacting with cells of the innate immune system, such as dendritic cells and macrophages, which in turn primes the adaptive immune system. The number of DAMPs is constantly increasing, as endogenous cell components that fulfil the functions described become recognized. In 2003, uric acid released from damaged cells was found to be a powerful adjuvant, and hence was considered to be a DAMP [13]. Recently it was demonstrated that the adjuvant property of alum was accounted for by urate released by dying cells and subsequent crystallization of urate. Immunization of mice with ovalbumin + alum induced an allergic Th2 cell response that could be inhibited by uricase treatment and reproduced by sensitizing mice with ovalbumin + MSU [14]. It is therefore likely that locally released urate from dying cells will crystallize and rapidly phagocytosed, initiating inflammation pathways (Fig. 1).

A property common to many DAMPs is the capacity to activate dendritic cells and macrophages to secrete pro-inflammatory cytokines such as IL-1β. The production of IL-1β is tightly controlled on several levels as it is a potent cytokine that is active in picomolar concentrations. The post-translational regulation involves the cleavage of the inactive 35-kDa IL-1β precursor (pro-IL-1β) into the active 17-kDa IL-1β. This process requires assembly of

Fig. 1 Mechanisms of crystals-induced inflammation. (1) Crystals eventually interact with membrane via Toll-like receptor 2 (TLR2) and/or TLR4 or other receptors of the innate immune system. Upon phagocytosis, crystals induce K^+ efflux via ATP binding to P2X7R, ROS generation and lysosomal damage (probably via cathepsin B release). These events lead to NLRP3 inflammasome activation. The resulting autocatalytic activation of caspase-1 then induces pro-IL1β cleavage into biologically active IL-1β. (2) Alternatively, crystals can directly bind to the membrane, in a receptor-independent manner, leading to Syk kinase activation, which in neutrophils is mediated by PKC. It is not known at the moment what mediators are released upon Syk activation by MSU, apart from prostaglandin E_2 (PGE_2), neutrophils and dendritic cells. Although pathway 2 (Syk kinase activation) is independent of pathway 1 (inflammasome activation), lysosomal damage may be a common step for both pathways. Finally, there is no evidence yet for BCP crystal binding and Syk activation.



the cytoplasmic multiprotein complex, termed the inflammasome, responsible for the conversion of the zymogen procaspase-1 into the active caspase-1 that mediates IL-1β and IL-18 maturation [15]. As pro-IL-1β cleavage is immediately followed by the release of the mature cytokine, processing and secretion are coupled. Four major inflammasome complexes activating caspase-1 have been described to date: NLRP1, NLRP3, IPAF and AIM2 inflammasomes, among which NLRP3 is best studied [16]. The NLRP3 inflammasome is composed of NLRP3 protein, an adapter ASC protein as well as the inflammatory caspase-1. The ASC adapter contains a pyrin domain (PYD) that mediates interaction with a homologous domain on NLRP, as well as a CARD domain that interacts with caspase-1. A large number of stimuli have been described to activate the NLRP3 inflammasome. These can be from bacterial origin (such as the pathogen-associated molecular patterns muramyl dipeptide, bacterial RNA or double-stranded RNA) or DAMPs. The list of DAMPs triggering NRLP3 activation is currently ever expanding, and includes different crystal structures such as alum, haemozoin, silica and cholesterol crystals, as well as crystals found in microcrystalline arthritis such as MSU, CPP [17] and BCP crystals [18]. The diversity of molecular structures represented by these compounds makes it unlikely that they all interact directly with the NLRP3 inflammasome.

The molecular mechanisms underlying processing and secretion of active IL-1β have been studied mainly *in vitro* in macrophages (Fig. 1). As expected, macrophages deficient for components of the NLRP3 inflammasome were unable to secrete active IL-1β following stimulation with MSU, CPP and BCP crystals [17, 18]. These findings raise questions about the steps that connect cellular contact of crystals and cytoplasmic inflammasome activation, processes that are still not completely understood. These steps may involve general mechanisms shared by other inflammasome activators, such as (i) the phagocytosis of crystals; (ii) K^+ efflux that is regulated by K^+ channels like P2X7R; (iii) sensing of reactive oxygen species (ROS) that are released during cell stress; and (iv) destabilization of the lysosomal membrane and activation of the lysosomal protease cathepsin B (see review in [19]). For both MSU and BCP crystals, secretion of active IL-1β by macrophages was blocked by cytochalasin-D, a phagocytosis inhibitor. In addition, ROS formation and K^+ efflux are also linked to MSU and BCP crystal-induced IL-β secretion, as secretion was completely inhibited by ROS inhibitors and by higher extracellular concentrations of K^+. However, controversial results were obtained about the role of P2X7R. MSU elicited a P2X7R-dependent IL-1β secretion in primary human monocytes [20] and murine macrophages (N. Busso *et al*., unpublished results), in contrast with a previous observation that blocking P2X7R pharmacologically did not affect the MSU-induced release of IL-1β by monocytic THP1 cells [17]. This discrepancy may depend on the different cells analysed and the stimulation protocol used.

MSU and BCP interaction with the cell membrane and Syk kinase signalling

What are the first steps in the interaction between crystals and cells? Phagocytosis was shown to be essential for the activation of neutrophils [21] and macrophages [22], and in the case of macrophages, TLRs may play a role. An interaction of MSU crystals with TLR2 and TLR4 has been demonstrated, but the absolute need for TLRs in MSU crystal-induced inflammation is controversial. On the one hand, the presence of TLR2 and TLR4 exacerbated MSU crystal-induced IL-1β production and PMN recruitment in the murine air pouch model, but another group found that none of the known TLRs were indispensable in the murine peritonitis model [22, 23]. We found that both TLR2 and TLR4 were implicated in MSU and octacalcium phosphate (OCP) crystal-induced IL-1β production by monocytic THP1 cells, after the cells had been primed with CpG or with TNF-α (N. Busso, unpublished results).

A second mechanism is the direct activation of cell membrane signalling cascades. A specific interaction of MSU crystals with dendritic cells has been demonstrated by atomic force microscopy to occur [24]. This interaction appears to involve membrane cholesterol, actin polymerization and activation of the tyrosine kinase Syk that might mediate either internalization of the crystal or a cellular response to the binding of the crystal (Fig. 1). Syk expression and its signalling mechanisms are mainly found in haematopoietic cells, so other cell types that express Syk could bind avidly to MSU crystals and respond to them. Indeed, it was shown that intracellular signalling events initiated by the physical interaction between MSU crystals and neutrophils depended on the activation of Syk kinase [25, 26]. However, there is still no evidence for direct binding of MSU crystals to macrophage cell membranes and for Syk signalling that could contribute to the activation of the inflammasome by these crystals. Finally, there are no reports to date of direct interactions between BCP crystals and cell membranes and Syk activation.

Role of the NLRP3 inflammasome in *in vivo* models of crystal-induced joint inflammation

The effects of MSU crystals have been studied *in vivo* using three different modes of administration (subcutaneously, intraperitoneally or IA). When MSU crystals were applied subcutaneously (air pouches) or intraperitoneally, NLRP3, ASC or caspase-1 deficiency led to diminished influx of inflammatory cells in the particular cavity [27, 28].

However, several researchers were unable to reproduce the findings that NLRP3 deficiency resulted in a significant reduction of cell influx after intraperitoneal administration of MSU crystals [29]. Similar results were obtained with two different NLRP3 knockout (KO) strains that showed a lack of effect of NLRP3, suggesting that the genetic

background of the various NLRP3 KO mouse strains used is not the reason for these findings.

It has to be stressed that MSU crystals injected intraperitoneally in mice lacking functional caspase-1 activity only led to a moderate reduction (50%) of cell influx in the peritoneal cavity, indicating that caspase-1-independent mechanisms can also mediate the inflammatory reaction [17, 30]. Since during an acute attack of gout, the main cell type present in the synovial cavity is the neutrophil, it is likely that serine proteases originating from neutrophils (such as cathepsin G, elastase and, in particular, proteinase 3) process pro-IL-1β to bioactive IL-1β in a caspase-1-independent manner [31].

A novel model of murine gouty arthritis induced by IA injection of MSU crystals in combination with long-chain free fatty acids has been recently described, recapitulating some of the clinical features of gouty arthritis [32]. In this model, NLRP3 was found not to be involved in initiating acute joint inflammation. However, ASC and caspase-1 both contributed to acute inflammation, as the influx of neutrophils, as well as local IL-1β production, were strongly decreased in ASC and caspase-1-deficient mice.

Mice peritonitis induced by intraperitoneal injection of OCP crystals was not prevented in NLRP3, ASC or caspase-1 KO mice, whereas IL-1β blockade (with IL-1β monoclonal antibody or IL-1Ra) was effective [33]. In this latter model, OCP crystals induced neutrophil necrosis with subsequent release of pro-IL-1β from intracellular stores. Pro-IL-1β can then be processed extracellular, possibly by neutrophilic proteases such as PR3, without NLRP3 inflammasome involvement. Recently Flavell and colleagues [34] reported on the role of the NLRP3 inflammasome in an animal model of OA, based on progressive ankylosis and hydroxyapatite crystal formation in the ANK-deficient mouse, suggesting that in OA, inflammasome-mediated pathways may play a role.

What have the *in vitro* and *in vivo* studies on crystals taught us? Essentially that one has to be cautious to extrapolate *in vitro* findings (in which MSU and BCP effects are totally NLRP3 inflammasome dependent) to the *in vivo* situation (in which MSU and BCP effects are partially or totally NLRP3 inflammasome independent). These differences are likely to be due to the different mixtures of cell types activated *in vivo*, as well as the involvement of other pathways of inflammation besides the release of IL-1β.

Other crystals and particles

Besides MSU, CPP and BCP crystals, cholesterol crystals have also been shown to trigger the inflammasome to promote IL-1β release from monocyte/macrophages. In an *in vitro* model of atherosclerosis, it has been demonstrated that mice with myeloid cells that carry deletions of ASC, NLRP3 or IL-1α/β were protected from severe atherosclerosis when fed a high-fat diet [35]. These findings suggest that biological crystals are generally pro-inflammatory through their interactions with the NLRP3 inflammasome complex, and that biological crystals can have effects that are not limited only to rheumatological conditions.

Another microparticle that is relevant to the current discussion is that released from prosthetic implants, such as silicone and metallic prosthesis, as they can induce aseptic inflammation that in turn is associated with prosthesis loosening. The NLRP3 inflammasome is again required for the secretion of IL-1β when macrophages are cultured with Co–Cr–Mo alloy particles [36], suggesting that this is a mechanism that should be investigated further in prosthesis failures.

Therapeutic implications

With the increased knowledge of how crystals interact with cells and their effects, treatments that target these pathways have become feasible. Targeting the Syk pathway by small molecule inhibitors has been tested for arthritis [37], and would be one approach to modify the cellular processes that are triggered by crystals, but no data have been presented to date. Another approach is to inhibit the inflammatory cytokines or mediators that are released during inflammation. Targeting IL-1 is an obvious approach in gout, and this approach may also be useful in patients who suffer from CPP- and BCP-induced arthritis. To date, three anti-IL-1 agents have been evaluated in gout, either in treatment of the acute attack or in the prevention of an attack while initiating urate-lowering therapy (Table 1). Overall, IL-1 inhibitors appear to be highly effective in reducing pain and signs of inflammation, and validate the concept that IL-1 is a key cytokine in gouty inflammation. Patients who were given anakinra in open studies were patients who had either failed to respond adequately to treatments such as steroids, colchicine or NSAIDs, or else had contraindications or intolerance to

Table 1 Studies evaluating IL-1 inhibitors in gout

Agent	Study design	References
Anakinra	Open-label study in acute gout in 10 patients	So *et al*. [38]
	Open-label study in 15 patients	Cho *et al.* [39]
Rilonacept	RCT of rilonacept in 10 patients with chronic gouty arthritis	Terkeltaub *et al*. [40]
	RCT of rilonacept in prevention of gout flares on initiating allopurinol in 241 patients	Terkeltaub *et al*. [41]
Canakinumab	RCT of canakinumab *vs* triamcinolone acetate in acute gout in 200 patients	So *et al*. [42]
	RCT of canakinumab *vs* colchicine in prevention of acute flares on initiating allopurinol in 432 patients	Schlesinger *et al*. [43]

these drugs. In the randomized controlled trials (RCTs) of prevention of gout flares when initiating urate-lowering therapy, both rilonacept and canakinumab markedly reduced the incidence of flares when compared with either placebo or colchicine, respectively.

Extrapolating from the *in vitro* and *in vivo* findings, one would expect that other forms of acute crystal arthropathies would respond to IL-1 inhibition as well. Two reports of difficult cases of CPP responding to anakinra have been published to date [44, 45], but no RCTs have been performed so far. The situation with BCP-associated arthropathies is unknown, as no studies have been reported to date. However, in knee OA, a condition that is frequently associated with Ca^{++} crystal deposition, a controlled trial of anakinra, given as a single IA injection, was not superior to placebo in terms of pain relief at 12 weeks after injection [46]. The lack of efficacy may be due to the short half-life of the compound and the single injection used. Interestingly, in a study of three cases of erosive finger OA that did not respond to conventional NSAIDs, the authors reported a positive effect of anakinra given for more than 3 months on pain and function [47].

Besides efficacy considerations, questions about safety and cost as well as the most appropriate group of patients who should receive this type of treatment have to be raised. To date, short-term treatments with IL-1 antagonists have not shown an adverse safety profile, but there are justified concerns about immunosuppression and risks of infections that longer-term studies will need to address.

Summary

Over the last 5 years there have been major new insights into the pathophysiology of microcrystal-induced diseases, as well as our knowledge of how endogenous and exogenous 'danger signals' lead to cell activation. These include their interactions with the innate immune system and cell signalling cascades to mediate inflammation, particularly the key role of IL-1β. These mechanisms are likely to be relevant in diseases such as crystal-induced arthritis, OA and atherosclerosis. Hopefully this knowledge will lead to improved therapy in these conditions.

Rheumatology key messages

- Microcrystals implicated in joint diseases elicit inflammatory and cellular responses from cells of the innate immune system.
- IL-1β production by activation of the NLRP3 inflammasome is a common feature of microcrystal-induced inflammation.
- Non-NLRP3 inflammasome pathways participate in the generation of active IL-1β.
- Evidence is emerging that Syk kinase signalling plays an important role in the cellular response to microcrystals.

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Clinical vignette

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Sea urchin spine-associated tenosynovitis—recovery with hand therapy

A 55-year-old woman presented with a 6-month history of stiffness and swollen right ring and middle fingers (Fig. 1) following a diving trip to Kenya where she sustained several sea urchin stings. Investigations including white count, CRP, ESR, ENAs, ANAs and RF were negative. Hand radiographs and US showed no bony abnormalities or foreign bodies. MRI revealed florid tenosynovitis affecting right flexor tendons limited to the ring and middle fingers, without evidence of foreign bodies.

A diagnosis of sea urchin spine-associated tenosynovitis was made based on history, clinical signs and symptoms. A plastic surgical opinion was sought; however, surgical intervention was not required as no foreign bodies were identified. She recovered with hand therapy and analgaesia.

Sea urchin sting injuries are relatively common and complications resulting from foreign body reaction or sting toxins include persistent inflammation, arthritis, granulomas and tenosynovitis. Antibiotics and anti-inflammatories are reported to be unhelpful (although early injection of steroids locally may suppress long-term damage). Complete resolution of symptoms often requires surgical removal of the spine or synovectomy [1]. However, there have been no reports of improvement with hand therapy and analgaesia alone, which our patient demonstrated.

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FIG. 1 Dorsal aspect of right hand showing swollen ring finger.