The mechanisms of inflammation in gout and pseudogout (CPP-induced arthritis)

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SUMMARY

Recent advances have stimulated new interest in the area of crystal arthritis, as microcrystals can be considered to be endogenous "danger signals" and are potent stimulators of immune as well as non-immune cells. The best known microcrystals include urate (MSU), and calcium pyrophosphate (CPP) crystals, associated with gout and pseudogout, respectively.

Acute inflammation is the hallmark of the acute tissue reaction to crystals in both gout and pseudogout. The mechanisms leading to joint inflammation in these diseases involve first crystal formation and subsequent coating with serum proteins. Crystals can then interact with plasma cell membrane, either directly or via membrane receptors, leading to NLRP3 activation, proteolytic cleavage and maturation of pro-interleukin-1β (pro-IL1β) and secretion of mature IL1β. Once released, this cytokine orchestrates a series of events leading to endothelial cell activation and neutrophil recruitment. Ultimately, gout resolution involves several mechanisms including monocyte differentiation into macrophage, clearance of apoptotic neutrophils by macrophages, production of Transforming Growth Factor (TGF-β) and modification of protein coating on the crystal surface. This review will examine these different steps.

***Key words**: urate, calcium pyrophosphate crystals, gout, pseudogout, inflammasome, IL1, danger signals, syk kinase.*

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INTRODUCTION

Hyperuricemia is the metabolic abnormality underlying gout, an inflammation of the joints that was already recognized by the ancient Greeks (e.g. Hippocrates and his aphorisms on gout, 5th century BC). Gout has continued to fascinate physicians and scientists over the centuries. The link with hyperuricemia as the underlying metabolic abnormality started with the identification of uric acid in 1776, and progressed through to the famous "thread test" that Garrod used in 1848 to demonstrate that blood in gouty patients contained significant quantities of urate. In 1961, McCarty and Hollander published their observations that crystals obtained from the joints of gout patients were composed of monosodium urate (1). For many, the clinical problem of gout and its treatment would appear to be solved. However, to our surprise, the subject is still proving to be a rewarding topic for clinical investigation, and recent research has led to a renewal of interest in the mechanisms underlying the metabolic abnormality, as well as possible links between hyperuricemia and cardiovascular and metabolic disorders.

Calcium pyrophosphate (CPP) deposition occurs mainly in joint cartilage and intervertebral disc, specifically in hyaline and fibro-cartilage. In order to clarify and to provide a uniform definition of CPP deposition (CPPD) disease, the European League Against Rheumatism (EULAR) task force has recently compiled two sets of recommendations concerning first the diagnosis and terminology, and second the management of the disease (2, 3). Thus, CPPD is the umbrella term for all instances of CPP crystal occurrence, and chondrocalcinosis (CC) means cartilage calcification,

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identified by imaging or histological examination. CC is not always due to CPPD and may occur as an isolated finding in an apparently otherwise normal joint, or coexist with structural changes resembling osteoarthritis. Several types and dimensions of CPP crystals have been identified in synovial fluid (SF) including monoclinic and triclinic dihydrated CPP crystals (m-CPP and t-CPP: $Ca_2P_2O_7$, $2H_2O$) (4). Although often asymptomatic, CPP crystal deposition can be associated with osteoarthritis, acute mono- or oligo-articular arthritis and, more rarely, chronic polyarthritis and destructive arthropathy (2). Acute mono-or oligo-articular arthritis secondary to CPP crystal deposition can mimic gout attacks and has, therefore, been initially referred to as pseudogout. Interestingly, both MSU and CPP crystal-induced inflammation resolve themselves spontaneously.

Last but not least, based on the discovery of the inflammasome and of its activation by MSU and CPP crystals, research has produced new treatments that may be of great relevance to patients suffering from gout, and eventually also pseudogout.

MSU AND CPP CRYSTAL FORMATION

MSU crystallizes when its plasma concentration exceeds its solubility (around 7 mg/dL, or 420 μmol/L). Concentration may not be the only determinant, since we know from clinical observation that patients with hyperuricemia can be asymptomatic, sometimes for long periods before the first presentation of gout, so there must be modifying factors present in biological fluids that affect urate solubility. *In vitro*, several factors have been described as influencing urate solubility, including pH, temperature, ionic strength and the binding of urate to plasma macromolecules (5). Not only is the solubility of urate influenced by its binding to plasma proteins, but also its inflammatory potential (see below).

The mechanisms of CPP crystal deposition in human cartilage are still not clear and involve chondrocyte alterations and extracellular matrix (ECM) modifications. Recognized risk factors of cartilage mineralization are aging, osteoarthritis, previous joint trauma or injury, metabolic disease and familial predisposition (6). Cartilage calcification depends on cartilage cells (chondrocytes), ECM proteins and ECM concentration of Ca^{2+}, inorganic phosphate (Pi), and inorganic pyrophosphate (PPi). Extracellular PPi is produced either *de novo* through the extracellular metabolism of nucleotides or originates from the release of intracellular PPi (7). The concentration of extracellular PPi depends chiefly on four proteins: membrane glycoprotein-1 or PC-1, tissue non-specific alkaline phosphatase (ALP), the PPi transmembrane transporter ANK and CD73 protein (7, 8). Extracellular PPi concentration is increased by PC-1, ANK and CD73 and decreased by ALP, which hydrolyzes PPi. PC-1, ANK and ALP expression is modulated by cytokines and growth factors, as well as by Pi and PPi ions. Thus, TGF-β increases *ANK* expression and CPP crystal formation (9), whereas insulin growth factor-1 has the opposite effect (10). Similarly, intracellular PPi decreases the transcription of both ANK and PC-1 mRNAs, whereas Pi has the opposite effect (6).

CELLULAR RECOGNITION OF CRYSTALS

The cells interacting and responding to crystals are leukocytes, in particular neutrophils and macrophages, but also endothelial cells, synoviocytes and mast cells (11, 12). Resident macrophages are of particular interest, as they have been reported to play a role in initiating the tissue response to MSU in a mouse peritonitis model (13). Mast cells also deserve a mention, as in the peritonitis model of gout, depletion of peritoneal mast cells attenuated the neutrophil inflammatory response (14). Finally, resident macrophages and mast cells are able to release IL-1β upon crystal activation of the NALP3 inflammasome (see below). These results suggest that these cells par-

ticipate in the acute response of tissue to MSU and CPPD crystals and contribute to neutrophil recruitment. Thus, inflammation initiation would depend on resident cells, which have been partly identified, whereas the amplification of the inflammatory reaction includes mast cells, macrophages, monocytes, endothelial cells and PNN. The essential questions are: how are crystals recognized by cells and what cellular signaling is involved in their response? The first mechanism in the interaction between crystals and cells involves phagocytosis which was shown to be essential for the activation of neutrophils and macrophages, and in the case of macrophages, Toll-like receptors (TLRs) may play a role. TLRs are pivotal sensors of danger signals and infection on leukocytes, and are an integral part of the innate immune system (15). In this context, MSU crystals may be a danger signal released from injured cells that trigger innate immune responses via TLRs. Experimental evidence is available which shows a role for TLR2 and TLR4 in MSU recognition by monocyte/macrophages, as the presence of TLR2 and TLR4 exacerbated MSU crystal-induced IL-1β production and PMN recruitment in the murine air pouch model (16). Similarly, CPP and MSU crystals trigger nitric oxide production through TLR-2 activation in articular chondrocytes (17). However, these results should be viewed with caution since another group found that none of the known TLRs were essential in the murine peritonitis model (18).

A second mechanism may involve a direct interaction between crystals and cell membrane leading to intracellular signaling cascades. Indeed, atomic force microscopy has shown that specific interaction of MSU crystals with dendritic cell membrane occurs (19). This interaction led to activation of the tyrosine kinase *Syk* that might mediate either internalization of the crystal or a cellular response to the binding of the crystal (20, 21). However, there is still no evidence for direct binding of MSU crystals to other cell membranes apart from dendritic cell membranes. Finally, there are no reports to date of direct interactions between CPP crystals and cell membranes and *Syk* activation.

A third mechanism involves proteins coated at the crystal surface. Indeed, several proteins have been identified on both MSU and CPP crystal surfaces, including complement fractions such as C1q, C5 and C6, IgG and IgM immunoglogulins, Fc fragment of Ig, apolipoproteins E (ApoE), high density lipoproteins and low density lipoproteins (22-25).

These coating proteins play an important role in the inflammatory reaction and its resolution. Thus, the complement fraction stimulates PNN recruitment, whereas ApoE protein promotes inflammation resolution (26). For instance, knee joint inflammation induced by MSU crystal injection was inhibited in C6 deficient rabbits which displayed less IL-8 production and PNN influx in the knee (27). Finally, opsonization of IgG and/or complement fractions also favor crystal phagocytosis and cell activation.

MSU AND CPP ACTIVATION OF NLRP3 INFLAMMASOME AND SECRETION OF IL-1β

Proinflammatory cytokines undoubtedly play a critical role in orchestrating the inflammatory reaction to MSU crystals. Recent attention has focused in particular on the role of IL-1β. IL-1β is the prototypic inflammatory cytokine and exerts different types of action on cells and tissues. The cytokine is produced as an inactive promolecule by immune cells such as macrophages, monocytes and dendritic cells, and is then cleaved into the active p17 form of IL-1β to be secreted out of the cell. Cleavage of pro-IL-1β is catalyzed by caspase-1 (also known as IL-1- converting enzyme, ICE). Caspase-1 is a member of the family of inflammatory caspases that include caspase-4, caspase-5, caspase-11 and caspase-12; in the context of IL-1β processing, caspase-1 accounts for the main activity that requires the formation of a molecular platform known as the inflammasome

(28). Other pathways of IL-1β processing independent of caspase-1 have been described, implicating neutrophil-derived and mast cell-derived proteases (29, 30).
The NLRP3 inflammasome is a cytoplasmic protein complex composed of NLRP3, a protein of the NLRP (or NALP) family, an adapter ASC protein as well as the inflammatory caspase-1. The ASC adapter contains a PYD domain that mediates interaction with a homologous domain on NLRP, as well as a CARD domain that interacts with caspase-1 (Figure 1). The group of Tschopp discovered that many inorganic particles, including MSU and CPP crystals, are capable of activating the NLRP3 inflammasome to process and secrete active IL-1β as well as IL-18 (31). The list of NRLP3 triggers is still growing, and includes alum, hemozoin and DNA. Macrophages deficient for components of the NLRP3 inflammasome were unable to secrete active IL-1β following stimulation with MSU and CPP crystals. Moreover, MSU-induced peritonitis was decreased in ASC-deficient or caspase-1-deficient mice. Colchicine, a drug commonly used in the treatment of acute gout, was found to block

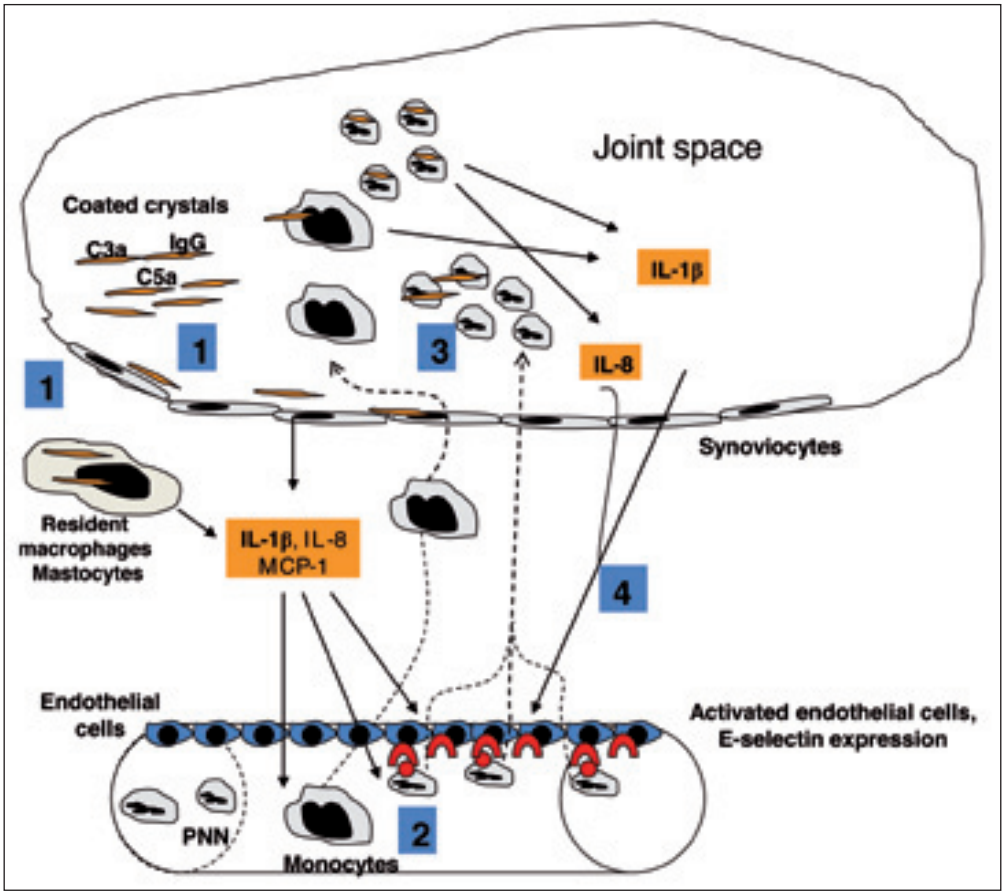

Figure 1 - Initiation and amplification of joint inflammation by crystals. Crystals into the joint cavity are covered by serum proteins (C3a, C5a et C5b-9) and/or immunoglobulin G (IgG) and activate resident cells such as macrophages and mast cells, or eventually also non-hematopoietic cells (such as synoviocytes and endothelial cells) (step 1). These cells will produce inflammatory cytokines and chemokines such as IL1β, IL8 and MCP-1, which in turn will activate endothelial cells (which will then start to express E-selectin) and stimulate monocyte and polymorphonuclear neutrophil cell (PNN) infiltrate (step 2). Infiltrating cells will also contribute to further IL-1β and IL-8 secretion (step 3) thereby amplifying the inflammatory reaction by recruiting additional inflammatory cells (step 4).

IL-1β maturation, probably by influencing crystal endocytosis and/or presentation of crystals to the inflammasome. The results show that MSU crystals initiate an inflammatory cascade, the starting point being the release of active IL-1β from monocytes and macrophages.

These findings, however, also raise questions about the steps that connect cellular contact with crystals with inflammasome activation, processes that are still not completely understood. It may involve general mechanisms shared by other inflammasome activators, such as potassium efflux that is regulated by K^+ channels like P2X7, or by the sensing of reactive oxygen species that are released during cell stress and the release of lysosomal contents such as cathepsin B. The different mechanisms involved in crystal cellular recognition and activation of NLRP3 inflammasome are summarized in Figure 2.

In a study published in 2010, Joosten et al. provide important new insights into the mechanisms underlying gout inflammation (30). It is known that patients can have MSU deposits that are clinically quiescent, indicating that there is further regu-

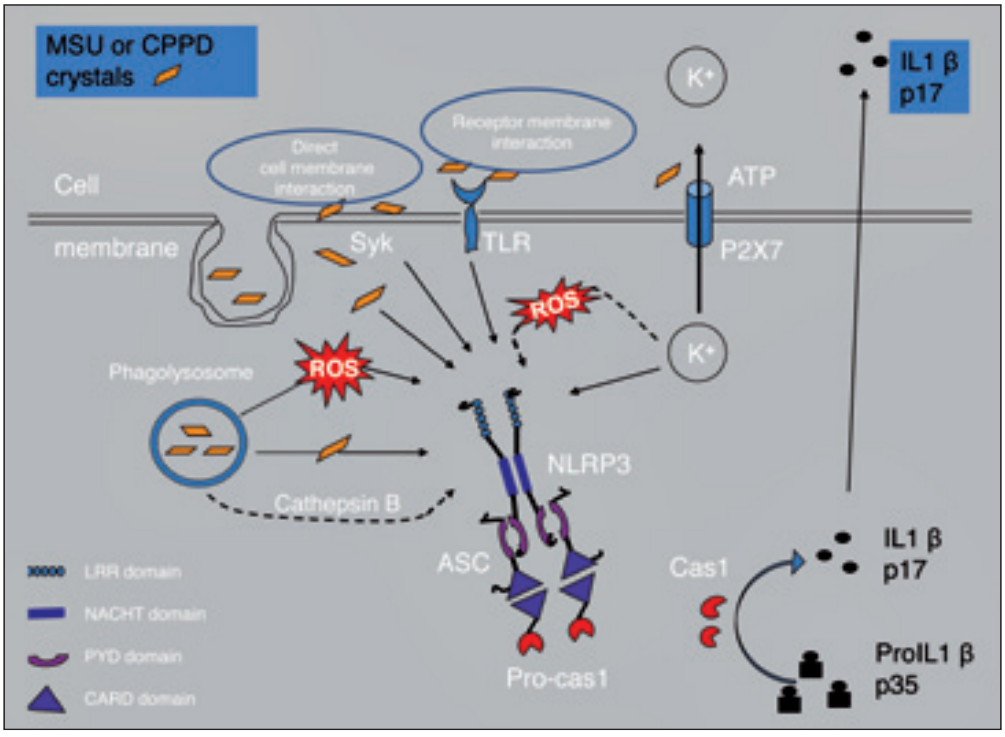

Figure 2 - Crystal activation of the NLRP3 inflammasome. NLRP3 or cryopyrin is composed of three distict domains (NACHT-LRR-PYD domains) and belongs to the NOD-like receptors involved in innate immunity. The inflammasome, formed by NLRP3 (NLRP3 inflammasome), binds to ASC (apoptosis-associated speck-like protein containing a CARD). ASC in turn will bind to caspase-1 (Cas-1), previously known as interleukin-converting enzyme (ICE). Different mechanisms are involved in the inflammasome activation: direct crystal interaction with the cell membrane and subsequent tyrosine kinase Syk activation; crystal interaction with cell membrane receptors such as TLR (Toll-like receptor) and phagocytosis of crystals. Upon phagocytosis, crystals induce K+ efflux via ATP binding to P2X7R, reactive oxygen species (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 (Mw 35 kD) cleavage into biologically active IL-1β (Mw 17 kD). Although Syk kinase activation is independent of inflamamsome activation, lysosomal damage may be a common step for both pathways. Finally, there is as yet no evidence for CPP crystal binding and Syk activation.

lation at the level of the tissue response to urate crystals. It is important to underline here that reports claiming that MSU crystals are potent inducers of IL-1β production have been performed in cell lines that were pre-activated with PMA or LPS. Such pre-activation is necessary for the induction of both IL-1β mRNA and pro IL-1β. In experiments using pure MSU alone, no cytokine was released. It was convincingly demonstrated that free fatty acids C18:0 acting on Toll-like receptor 2 (TLR-2) can synergize with MSU crystals in order to induce inflammasome activation and cytokine release.

This demonstrates that the release of FFAs after food ingestion or alcohol consumption represents the "missing link" between metabolic changes, inflammasome activation, and gout attacks (30).

MECHANISMS SECONDARY TO IL-1β RELEASE

We have seen above that, through a series of steps that are still not well understood, MSU crystals activate the NLRP3 inflammasome of phagocytes, resulting in processing and secretion of IL-1β.

The subsequent recruitment of inflammatory leukocytes to the site, most probably mediated by endothelial activation, can account for the subsequent release of inflammatory mediators and the recognized inflammatory manifestations of acute gout (Figure 1).

Although crystals have been shown to induce multiple cytokines and chemokines that promote gouty inflammation, including tumor necrosis factor-α (TNF-α), IL-6, CXC-chemokine ligand (CXCL) 1 and CXCL8 (also known as IL-8), it has been suggested that these are produced in a hierarchical manner, secondary to IL-1β release. For instance, in experimental MSU-induced inflammation, IL-1β has a more central role than TNF-α (32). Nevertheless, in different experimental settings, a role for CXCL8 has been clearly demonstrated in both CPP and MSU crystal-induced inflammation (33-35).

Mechanisms underlying spontaneous resolution of acute inflammation

Despite the rapid onset and the severity of crystal-associated inflammation, there is a self-limiting factor in the gout crisis and a return *ad integrum* of the affected joint. The first explanation provided for the resolution of inflammation is the nature of the coating of the crystals. Indeed, it was shown that crystals coated with IgG fragments were more inflammatory than naked crystals (36), whereas crystals coated with ApoB and ApoE could contribute in part to the resolution of acute gouty arthritis (37). Another mechanism involved in the resolution of microcrystal-induced arthritis flares involves the physiological transformation of monocyte into macrophage. Indeed, when macrophages were differentiated *in vitro*, they became less proinflammatory in their response to MSU crystals, even though they retained their capacity for phagocytosis (38). The difference in the cellular response seems also to be linked to the state of the macrophage and the phenotypic variations of macrophages (M1 and M2 macrophages) (39). The "switch" monocyte-macrophage has been observed during gout flare resolution and is associated not only with a decrease in the synthesis of proinflammatory cytokines (IL-1, IL-6, TNF-α), but also with an increased production of anti-inflammatory cytokines (IL-10 and TGF-β) (40). Hence macrophages start to produce TGF-β, a key cytokine in this anti-inflammatory process (41). This TGF-β can thus reduce endothelial cell activation, thus limiting PNN and monocyte recruitment and also cytokine expression, such as IL-1 and its receptor. In addition TGF-β secretion is stimulated by macrophagic clearance of apoptotic neutrophils. In this context it should be noted that apoptotic neutrophil clearance can be favored by type 2 transglutaminase (42). In conclusion, the autoregulation of inflammation by phagocytes together with differential coating of MSU crystals may explain the self-limiting nature of acute gout, as well as the fact that the presence of MSU crystals in a joint is not always accompanied by inflammatory response

Abbreviations

ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; IL, interleukin; MSU, monosodium urate; NALP3, NACHT-containing, LRR-containing and PYD-containing protein; NF, nuclear factor; TLR, Toll-like receptor; TNF-α, tumour necrosis factor-α. TGF-β, Transforming Growth Factor-β; ECM, extracellular matrix.

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