Pleiotropic effects of inflammasome modulation in chronic gout and associated comorbidities: potential therapeutic implications

Gout and hyperuricemia are among the most common inflammatory–metabolic disorders of mankind. Evidence gathered in recent years clearly identifies monosodium urate crystals as exerting a powerful inflammatory stimulus through activation of the inflammasome. Dysregulation of inflammasome function has been implicated in the pathogenesis of a variety of autoinflammatory disorders – so-called inflammasomopathies, including gout, Type 2 diabetes and cancer. Activation of the inflammasome results in the release of proinflammatory cytokines, particularly IL-1, which has been shown to significantly contribute to human disease, and its inhibition has proven of benefit for certain autoinflammatory disorders. The potential therapeutic benefit of inflammasome inhibition with the use of biologic agents used alone or in combination for the therapy of gout is discussed.

KEYWORDS: atherosclerosis ▪ gout ▪ hypertension ▪ hyperuricemia ▪ IL-1 inhibitors ▪ inflammasome ▪ inflammasomopathies ▪ metabolic syndrome ▪ obesity ▪ renal insufficiency

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An association of gout with hypertension, diabetes, kidney disease and cardiovascular disease has been observed since the late 19th century. This association is not only observed with frank hyperuricemia defined as more than 6 mg/dl (360 µm/l) in women and more than 6.5–7 mg/dl (420 µm/l) in men but also with uric acid levels considered to be in the normal to high range of >5.2–5.5 mg/dl (310–330 µm/l). Furthermore, a 1 mg/dl increase in serum uric acid level is associated with a 26% increase in mortality, which is comparable in magnitude to the 20–25% increase in myocardial infarction associated with a 10- to 12-mmHg increase in systolic blood pressure [1–9].

Uric acid is an acute soluble mediator, which has anti-inflammatory properties such as being a neurostimulant (protective in acute stroke, multiple sclerosis and Parkinson's disease) and acts as an antioxidant in hydrophilic environments of biologic fluids such as plasma. By contrast, in chronic inflammatory states it can act as a pro-oxidant becoming a danger signal released by infected cells or injured tissues, and is able to induce immune-mediated cell injury, lipid peroxidation, smooth muscle cell proliferation, increased oxygen free-radical (reactive oxygen species) production, platelet adhesiveness and aggregation, endothelin-1 expression and activate NADPH oxidase in adipocytes. The latter favors hypertension and prehypertension, cardiovascular disease (carotid, coronary artery, peripheral vascular disease), vascular dementia, pre-eclampsia, sleep apnea, pulmonary arterial hypertension, renal disease (reduced glomerular filtration rate and microalbuminuria), kidney stones, metabolic syndrome (for which prevalence is 19% for serum urate levels <6 mg/dl and increases to 71% for levels of 10 mg/dl or greater) and Type 2 diabetes. It is also associated with alcoholism, obesity, malignancies, polycythemia vera, hemolytic anemia, HIV and certain drugs such as cyclosporine, low-dose aspirin, diuretics and β-blockers [5,10–15].

Monosodium urate (MSU) crystals (the most proinflammatory form as compared with soluble uric acid) stimulate monocytes–macrophages, dendritic cells and synoviocytes to release IL-1β, through its interaction with a cytosolic structure known as the 'inflammasome'. The inflammasome is a high-molecular-weight complex, composed of a protein of the nucleotide oligomerization domain-like receptor (NLR; also known as nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing [NLRP or NALP]) family, an adapter of the apoptotic speck protein containing a caspase recruitment domain as well as an inflammatory caspase. It displays enzymatic activity that processes and secretes IL-1β, through caspase-1 activation, which further regulates the secretion of additional cytokines and stress signals. Binding of IL-1β to its target cells activates inflammatory transcription factors such as NF-κB that promotes the production and release of inflammatory mediators such as neutrophil-recruiting chemokines [16–20].

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Four major prototypes of inflammasomes are recognized, NALP1/NLRP1, NALP3/NLRP3, IPAF/NLRC4 and AIM2, which activate caspase-1 in the absence of an NLR protein. AIM2 has been shown to detect DNA and may therefore be involved in sensing pathogenic nucleic acids that reach the cytosol of host cells [21–25].

NALP3/NLRP3 on monocytes and macrophages senses danger and stress signals, such as uric acid and/or calcium-containing crystals, bacteria-producing α-toxins [19,26–29] and extracellular ATP. The mechanisms by which crystal-bound proteins and other particulate elements modify the cellular response-inducing activation of the NALP3/NLRP3 inflammasome is not fully understood, but it seems that the activation may require direct plasma membrane binding and crystal phagocytosis [30,31], which leads to toxic effects on cells.

Activation of inflammasomes

Inflammasome activation is a multistep process. Four mechanisms have been proposed:

- The role of synergisms between Toll-like receptors (TLRs) and NLRs *in vivo* is still not well defined; however, it is tempting to speculate that such regulatory mechanisms may participate in the initiation phase of inflammation episodes in gout as well as in periodic fevers. TLR stimulation primes macrophages to induce the production of NALP3/NLRP3 and pro-IL-1β. Costimulation (free fatty acids, CD14) with TLR2/TLR4 has also been shown to synergize with uric acid crystals and enhance inflammasome activation and IL-1β maturation in human mononuclear cells [32]. It has been shown that TLRs quantitatively contribute to the production of cytokines by MSU, but TLRs do not detect uric acid crystals directly and are not essential for uric acid-mediated response in mice. Recently, it has been suggested that CD14 could also bind to MSU crystals leading to the production and release of IL-1β, IL-18 and CXCL1 [7,33–37].
- The inflammasome senses ionic perturbations, such as uric acid crystals that can trigger potassium efflux, dropping potassium levels and promoting oxidative stress [18,19,37–39].
- It senses lysosomal damage and the release of cathepsin B, which triggers the release of reactive oxygen species [31,40–42].
- Deficient phagocytosis induced by large particles and crystals leads to the so-called frustrated phagocytosis, which results in the formation of cytoskeletal filaments [14,31,43–47]. In agreement with this hypothesis, certain pharmacological agents such as cytochalasin D or colchicine, which inhibit cytoskeletal filaments, disrupt the ability of particles to trigger IL-1β maturation, probably by influencing and/or presenting of crystals to the inflammasome. Hornung *et al.* reported that phagolysosomes formed in macrophages upon uptaking of MSU are unstable, which leads to intracellular release of phagocytosed crystals and cathepsin B, which itself can lead to NALP3 activation [14,16,17,48].

Chronic inflammation is an established instigator of several diseases such as obesity, Type 2 diabetes, defective immunity, atherosclerosis, autoimmune diseases and certain cancers, among others. The activation of M1 macrophages at the expense of anti-inflammatory M2 macrophages has been linked to the development of adipose tissue inflammation and metabolic syndrome. It is recognized that several proinflammatory cytokines including IL-1β, TNF-α and IL-6 are implicated in disrupting insulin signaling and induce insulin resistance and metabolic syndrome; in addition, obesity-induced elevation in specific saturated free fatty acids is known to activate the TLR4-mediated signaling pathway in macrophages and participate in inducing insulin resistance. NLRP3 inflammasome activation in obesity promotes macrophage-mediated T-cell activation in adipose tissue and impairs insulin sensitivity, therefore regulating the development and the magnitude of inflammation and its downstream effects on insulin signaling. It has been shown that mice deficient in either NLRP3, caspase-1 or IL-1β and fed a normal-chow diet have improved insulin sensitivity, suggesting a role of the NLRP3 inflammasome in regulating glucose homeostasis [40,49–55].

Oxidized low-density lipoprotein, cholesterol crystals, cell necrosis, adipocyte death and hypoxia leading to activation and secretion of IL-1β and IL-18 can activate the NLRP3 inflammasome. Furthermore, visceral adiposity and obesity are associated with an increase in MSU levels and increased risk of diabetes and atherosclerosis [56–59]. Given that MSU is sensed by the NLRP3 inflammasome and causes an increase of the inflammatory reaction, it is possible that MSU may be one of the danger signals sensed by the NLRP3 inflammasome, contributing to obesity-induced disease.

Obesity is also associated with an increase in the number of IFN-γ T cells in the adipose tissue [48]. It is well known that IFN-γ alone or together

with microbial stimuli can cause induction of M1 macrophages. Purified adipose T cells produce several cytokines that further activate macrophages; elimination of the NLRP3 inflammasome reduces M1-like macrophage gene expression and increases the expression of M2-like cytokines. Together these data suggest that the NLRP3 inflammasome sensing pathway participates in the origin of inflammation in obesity by inducing macrophage and subsequent T-cell activation, impairing insulin sensitivity [58,59].

Inflammasome modulation in inflammasomopathies & their comorbidities

Inflammasome overactivation plays a key role in the pathogenesis of autoinflammatory disorders including gout and its comorbidities. In recent years, it has been shown that inflammasome inhibition is highly effective in the therapy of inflammasomopathies, but it is quite likely that inflammasome modulation may also affect some of the aberrant pathways of the associated comorbidities such as diabetes and cardiovascular complications, obesity and metabolic syndrome.

Activation of IL-1 is a critical step in the inflammatory response observed in gout and other autoinflammatory diseases or 'inflammasomopathies' (Box 1). More recently, it has been shown that its inhibition results in amelioration of the inflammatory response in certain inflammasome-related disorders. IL-1β, originally identified as the endogenous pyrogen, is a strong proinflammatory cytokine that plays an active role in the inflammatory response with the production and release of several inflammatory mediators that lead to the recruitment of neutrophils, macrophages and other immune cells to the site of inflammation. The IL-1β cytokine is produced in an inactive promolecule by macrophages, monocytes and dendritic cells, and is then cleaved by caspase-1 into the active p17 form of IL-1β to be secreted out of the cell [60–69].

Therapeutic inhibition of IL-1 has been shown to be effective in patients with hereditary periodic fever secondary to mutations in *NALP3*/*NLRP3* gene. Several reports have shown that treatment of the disorders with an inhibitor of IL-1 receptor antagonist (IL-1Ra) leads to a significant clinical improvement. *IL-1Ra* is an endogenous gene that blocks the proinflammatory action of IL-1. Anakinra (exogenous recombinant IL-1Ra), when given to patients, prevents both recurrence of episodes and also decreases chronic inflammatory processes that can lead to amyloidosis. More recently, two new drugs have been developed that show more sustained effects. Rilonacept (IL-1 Trap) is a dimeric fusion protein consisting of the ligand-binding domains of the IL-1 receptor complex that inhibits IL-α and IL-1β, and has a half-life of more than 8 days. Rilonacept was approved by the US FDA in 2008 for use in children with autoinflammatory cryopyrin-associated periodic syndrome. Canakinumab (ACZ885) is a fully human monoclonal IL-1β antibody with a half-life of 28 days and was approved by the FDA in 2009 for cryopirin-associated periodic syndromes. Injections every 8 weeks are sufficient to maintain remission in most patients [70–80].

The importance of IL-1 in the pathology of gout is supported by preliminary clinical trials and case studies in patients with acute gout. Patients responded positively to the injection of anakinra, rilonacept and canakinumab. Moreover, anakinra and rilonacept were effective in reducing inflammation and neutrophil influx in mice gout models [81–86].

Treatment strategies that target the patient's primary disease and can also manage risk factors and comorbidities would be very attractive options. It is recognized that several proinflammatory cytokines, including IL-1β, TNF-α and IL-6, are implicated in disrupting insulin signaling and induce insulin resistance and metabolic syndrome. NLRP3 inflammasome-dependent post-translational processing of IL-1β and IL-18

Box 1. Inflammasomopathies NLRP3/caspase-1 activation.

'Classic' autoinflammatory diseases
- Gout
- Familial Mediterranean fever
- TNF-receptor-associated periodic syndrome

Cryopirin-associated periodic syndromes
- Familial cold autoinflammatory syndrome
- Muckels–Wells syndrome
- Neonatal-onset multisystem inflammatory disease
- Deficiency of IL-1 receptor antagonist
- Pediatric granulomatous arthritis
- Pyogenic arthritis, pyoderma gangrenosum and acne
- Hyperimmunoglobulinemia D with periodic fever syndrome
- IL-10 receptor deficiency

'Potential' autoinflammatory diseases
- Obesity
- Metabolic syndrome
- Diabetes mellitus
- Dyslipidemia/atherosclerosis
- Ischemia reperfusion injury
- Chronic kidney disease
- Chondrocalcinosis

Autoimmune connective tissue diseases/comorbidities
- Rheumatoid arthritis
- Systemic sclerosis
- Psoriasis/psoriatic arthritis
- Ankylosing spondylitis

in response to obesity-associated danger signals participates in the development of a chronic proinflammatory state that impairs insulin sensitivity. These findings highlight the potential of targeting the molecular pathways regulating caspase-1 activation in obesity for management of insulin resistance and chronic inflammation-induced comorbidities. Consistent with these data, randomized clinical trials have shown that blockade of IL-1β signaling by anakinra leads to a sustained reduction in systemic inflammation and improvement of Type 2 diabetes. Antidiabetic sulfonylurea drugs such as glyburide can also block NLRP3 inflammasome activation and reduce mortality due to septic shock.

Several other pathways involved in the regulation of the inflammasome have been characterized. One of the better-characterized pathways is the proinflammatory transcription factor NF-κB, which plays an important role in the downmodulation of the inflammasome. In murine models, effector and memory $CD4^+$ T cells have been shown to downregulate inflammasome activation by various factors including uric acid crystals. In another murine model of NALP3/NLRP3-dependent peritonitis, $CD4^+$ T cells were shown to be responsible for decreasing neutrophil recruitment. Furthermore, suppression of inflammasome activation by $CD4^+$ T cells can be reproduced by macrophage stimulation with CD40L, supporting the notion that ligands of the TNF family might be involved in the inhibitory activity of $CD4^+$ T cells.

Several cohort studies associated with hydroxychloroquine (HCQ) use have shown that this therapy is associated with a decrease risk of diabetes mellitus (DM) or improved glycemic control. More than 10,000 patients with rheumatoid arthritis or psoriasis have been studied, with a mean follow-up of 23 months and HCQ exposure for about 14 months. The authors found that the adjusted risk of DM is lower (71% reduction) for individuals on or starting HCQ compared with initiation of other disease-modifying antirheumatic drugs. The hypoglycemic effect of HCQ is not well understood; the antimalarials act as lipophilic weak bases, have a lysomotrophic action and participate in multiple cell functions including receptor recycling, intracellular processing, protein secretion, inhibition of cytokine production (TNF, IL-1, IL-6 and IFN-γ), lymphocyte activity and autoantibody production, as well as reducing natural killer cell activity and antigen presentation to CD4 cells [87–92]. A new mechanism of action has also been postulated recently; antimalarials can inhibit the function of intracellular TLRs (TLR9, less so 7 and 8), in line with this hypothesis it is tempting to suggest that, "TLRs in conjunction with costimulatory signals (crystals, oxidized low-density lipoprotein) activate the inflammasome, which in turn induces activation of the innate immune system that leads to insulin resistance, metabolic syndrome, DM, atherosclerosis [and] hypertension," therefore antimalarials could play a role in the treatment of some inflammasomopathies and their comorbidities, as well as in several other chronic inflammatory conditions such as chronic kidney disease, atherosclerosis and ischemia/reperfusion injury [93,94]. The presence of chronic inflammation and hyperuricemia, which characterizes certain disorders associated with an increased cardiovascular risk such as rheumatoid arthritis, psoriasis and spondyloarthropathies, may promote inflammasome activation and lead to the production of proinflammatory cytokines (IL-1β and IL-18). The latter may subsequently lead to abnormal glycemic and lipid metabolism, clinically expressed as metabolic syndrome, DM, dyslipidemia, coronary artery disease, peripheral vascular disease, hypertension and chronic kidney disease. Therefore, it can be suggested that in addition to the use of antimalarials, combination biologic therapy such as a TNF blocker plus IL-1 inhibition may be able to better target the deregulated pathway of the innate (inflammasome) and adaptive immune system, thus preventing or ameliorating the comorbities associated with these autoinflammatory disorders including increased cardiovascular risk.

In summary, inhibition of the inflammasome and IL-1 has been shown to be highly effective in the treatment of certain inflammosomopathies, but their long-term safety profile has yet to be determined. The inflammasome is an important component of the innate immune system; therefore, it is possible that these treatments may interfere with the body's immune response to infection [95,96] and other autoimmune diseases due in part to cytokine imbalance and cell modulation.

Future perspective

Gouty arthritis is a chronic and progressive inflammatory disorder that affects joints and is associated with a variety of comorbidities including the metabolic syndrome, obesity, hypertension, renal disease and cardiovascular complications. Most recently, it has been established that MSU crystals can induced the release of IL-1 from inflammatory cells through activation of the inflammasome. In addition, accumulated evidence supports the notion that therapeutic

inhibition of IL-1 with the use of IL-1 inhibitors downregulates inflammasome function, which allows control of the acute inflammatory articular process. Future studies are needed to elucidate whether or not downregulation of inflammasome activity may also ameliorate or suppress associated comorbidities of gout and other autoinflammatory disorders such as rheumatoid arthritis, scleroderma, psoriasis and psoriatic arthritis.

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Executive summary

Gout & hyperuricemia

- The association of gout with hypertension, diabetes, kidney disease and cardiovascular disease has been observed since the 19th century.
- This association is not only observed with frank hyperuricemia but also with uric acid levels considered to be in the normal to high range of >5.2–5.5 mg/dl.

Uric acid as a proinflammatory biomarker

- Uric acid is a soluble mediator that has anti-inflammatory properties and also antioxidant activity in biologic fluids such as plasma.
- Uric acid in chronic inflammatory states stimulates the release of IL-1 from inflammatory cells through activation of the inflammasome.

Inflammasome modulation in inflammasomopathies & their comorbidities

- Overactivation of the inflammasome has been shown to play an important role in the pathogenesis of a variety of autoinflammatory disorders, including gout and its comorbidities, as well as the comorbidities associated with other connective tissue disorders.
- Inhibition of IL-1 has been recognized to be highly effective in the treatment of hereditary periodic fevers associated with mutations in the *NALP3*/*NLRP3* gene.
- The important role of IL-1 in the pathogenesis of gout is supported by clinical trials and case series of patients with acute gouty arthritis. Gout patients exhibited an excellent clinical response to treatment with IL-1 inhibitors such as anakinra, rilonacept and canakinumab. Whether or not the associated comorbidities may also clinically respond to similar treatment requires further investigation.
- Similarly, several cohort studies associated with the use of hydroxychloroquine therapy improved glycemic control. Antimalarials can inhibit the function of intracellular Toll-like receptors, and it is tempting to suggest that Toll-like receptors in conjunction with other costimulatory signals such as monosodium urate crystals may activate the inflammasome, which in turn induces activation of the innate immune system, leading to insulin resistance, metabolic syndrome and other comorbidities.

Conclusion

- The inflammasome is an important component of the innate immune system and its overactivation has been shown to play an important role in the pathogenesis of gout and its associated comorbidities.
- Inhibition of the inflammasome and IL-1 has been shown to be highly effective in the treatment of certain autoinflammatory disorders or inflammasomopathies, but their long-term safety profile has yet to be determined.
- The inflammasome is an important component of the innate immune system; therefore, caution should be taken to not induce an oversuppression.
- Modulation of inflammasome function in the treatment of 'classic/potential' autoinflammatory diseases may be achieved in the future with careful use of combination biological therapy.

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