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Editorial

Neutrophil Activation by Gout-Causing Monosodium Urate Crystals

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EDITORIAL

Gout is a leading cause of joint inflammation that has been crippling mankind for centuries. Notwithstanding the tremendous progress made in the medical sciences in the recent past, the conventional treatments are suboptimal for gout to this day. So far, we know the inflammation is caused by monosodium urate (MSU) crystals aggravating immune cells, specifically neutrophils and macrophages. It is predominantly neutrophil-driven and neutrophil extracellular traps (NETs) play a major role in regulating inflammation. Auto-inflammatory disorders such as gout are notorious for generating an overt immune response [1-7]. Gout is characterized by joint inflammation in the synovium accompanied by frequent flares, which progressively become more aggressive over time (Figure 1a) [6-8]. Gout has been documented since 2000 B.C. but an effective cure has not yet been found [1,2]. However, the diagnosis and staging of gout is well-established in the medical profession [9].

GOUT

In 2007-2008 there were 8.3 million gout cases and each year 3 million cases are being added [10]. A frequent target for gout attack is the first metatarsophalangeal joint [1-3,7,11]. Currently available gout medications are only able to treat the symptoms of the disease [4,11]. Patients manage their gout with the help of therapeutics and by making lifestyle alterations such as regular exercise and diet changes [11]. Men above the age of 40 and menopausal women are at the greatest risk to be afflicted by gout [12-14]. Gout is less common in younger women, since female hormones are known to inhibit uric acid accumulation [14].

Gout can also occur at other locations within the body, such as the knees, metatarsophalanges, and proximal interphalangeal joints (PIPs) and distal interphalangeal joints (DIPs) [15-17]. Gout manifests itself as mono-arthritis or bilateral asymmetric polyarthritis [11,17,18]. Gout has emerged as a risk factor for cardiovascular disorder [19,20]. The hyperuricemic condition is linked to multiple comorbidities (diabetes, hypertension, and congestive heart failure), which are vital for disease establishment [21]. When it is left untreated, the disease progresses through the following four stages, as is also shown in Figure 1b [22,23].

Stage I. Asymptomatic hyperuricemia

Stage II. Acute gout

Stage III. Intercritical gout

Stage IV. Chronic tophaceous gout

In advanced stages of gout, painful inflammation becomes chronic and leads to 'tophus' formation [23-26]. A tophus is a conglomeration of dead synovial tissue, MSU crystals and activated or dead leukocytes (like neutrophils) [23-26]. It appears chalky and gritty due to the presence of MSU crystals [16,23-26]. Prolonged bone destruction in gout causes osteoblast retraction due to the elastase and osteoclasts resorbing cell-free areas of the matrix [22]. Tophi are very dynamic structures, which constantly undergo remodeling during gouty flares and are associated with the resolution of gouty inflammation [23-26]. This is due to the production of anti-inflammatory cytokines such as transforming growth factor β_1 (TGF-β_1), IL-10 and other nuclear receptor factors, like peroxisome proliferator activated receptor-γ (PPAR-γ), and the clearance of apoptotic cells by monocyte-macrophages [4,7,11,27,28]. Recent studies suggest that the tophus can resolve inflammation by releasing proteases that can cleave the proinflammatory cytokines [23,25,26,29]. However, the jury is still out on whether tophi are beneficial or unfavorable towards the mitigation of gouty inflammation [23,25,26,29].

Monosodium urate (MSU) crystals

MSU crystal accumulation in the joints powers the overt immune response, driven primarily by innate immune cells such as macrophages and neutrophils [7,26]. Primates (including humans) are unable to excrete or decompose uric acid (UA) from the body due to the evolutionary loss of the enzyme uricase [11,23]. The uricase gene is disrupted by two mutations that introduce a premature stop codon [11]. In most cases, renal urate transporters such as uric acid transporters (URAT 1) and organic anion transporters (OAT4) malfunction, and cause accumulation of uric acid in the body [11].

Uric acid (UA) reacts with free sodium in the plasma, forming MSU, which crystalizes in the synovial space [6,30-32]. UA is a product of purine metabolism and it scavenges singlet oxygen regulates oxidative stress in humans [11,30]. UA is also an anti-

oxidant that plays an interchanging role between a pro-oxidant and proinflammatory agent [11,30,33]. UA forms MSU and causes ROS-dependent NET formation [30,33]. In low concentrations, UA acts as an anti-oxidant and inhibits nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-dependent NET formation [30,33]. It has been shown that at a high concentration of non-crystalline UA (8 mg/dl) crystals induce NADPH oxidase/ROS-independent NETosis (Figure 1c) by utilizing the NFκB signaling pathway in neutrophils from Chronic Granulomatous Disease (CGD) patients [30]. Unlike UA, MSU crystals induce NETs in a ROS-dependent manner [30,33]. Analyses of gout synovial fluid and tissue samples, including those in our study, have shown the presence of NETs with MSU crystals [34-36] (Sil & Rada., JI., under revision). During the resolution phase of inflammation, the crystals isolated from SF lose IgG coating [6,7,28,37]. These isolated MSU crystals are reported to bind to the lipoproteins ApoE and ApoB, which suppress MSU crystal-induced neutrophil activation [1-3,7,28].

Risk factors

Consumption of purine-rich foods, high fructose corn syrup, and alcohol (beer) causes the liver to produce more uric acid [11]. Human beings as a species lack uricase, and therefore, are unable to breakdown uric acid to a more soluble excretory product known as allantoin [11,23]. Although the urate acts as an anti-oxidant in the human body, the evolutionary advantage gained by uricase elimination is still not apparent [11,23].

Individuals that have a defect in uric acid transporters such as URAT1 and OAT4 tend to accumulate uric acid [11]. Asymptomatic hyperuricemic condition is an indicator for gout [11,21,38]. Genome-wide association study (GWAS) scans suggest that SLC2A9 and ABCG2 are the major genes responsible for the hyperuricemic condition [11,21,38]. SLC2A9 is involved in renal and gut excretion of uric acid [11,21,38]. ABCG2 gene Q141K polymorphism (A allele or AA genotype) has an increased risk of gout and is involved in only renal excretion of uric acid [11,21,38].

Mechanism of action

MSU crystals are damage-associated molecular pattern molecules (DAMPs), which trigger inflammasome activation in macrophages [1,2,7,28,35,39-42]. Activated macrophages produce IL-1β and IL-18, which are strong neutrophil chemoattractants [1-3,7,34,35,40,41,43,44]. Neutrophils gather at the site of inflammation and exaggerate the joint inflammation [1-3,7,11,17,28,39]. MSU crystals are coated with immunoglobulin, which drives the immune response [7,28]. Gouty inflammation can self-resolve in 7-10 days in most situations [6,11,23,35].

Clinical significance

To ease the pain caused by joint damage in gout, patients typically rely on pain relieving drugs, as well as on urate lowering therapeutics [4]. The most commonly prescribed gout drugs are colchicine and xanthine oxidase inhibitors (such as febuxostat, allopurinol) [4,17]. Colchicine blocks microtubules, inflammasome assembly, and inducible nitric oxide (iNOS) production in neutrophils and macrophages [1-3,28,45,46]. More recently, angiotensin receptor blocker drugs have been shown to increase uric acid excretion [47]. These drugs only provide temporary symptomatic relief, and are accompanied with multiple side effects [6,7,47].

Gout has been called the 'disease of the kings' [48,49]. Gout is often confused with other joint related arthritis such as pseudogout and rheumatoid arthritis (RA) [19]. Therefore, there exists a significant risk of misdiagnosis by clinicians. NETs have been implicated in both RA and pseudogout [15,50,51]. A hyperuricemic condition is a prerequisite for the genesis of gout and therefore, it is used as an indicator for gout diagnoses [11,52]. However, not everyone with hyperuricemia is afflicted by gout [9,11]. Factors such as genetic pre-disposition to hyperuricemia, obesity, diuretic medication, and kidney stones usually cause a build-up of uric acid in the body [11,19,53]. The auto-inflammation experienced in gout is mainly driven by neutrophils [1-3,7,28]. Blocking the influx of neutrophils may help in coping with recurrent attacks [11,20]. Dietary and lifestyle interventions are often incorporated into gout patients' regimens as preventive measures [9,11,19,20]. However, there is a gap in the understanding of the mechanism(s) of neutrophil

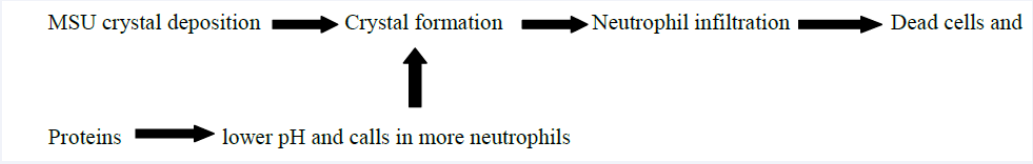

Figure 1a The vicious cycle of Gout progression.

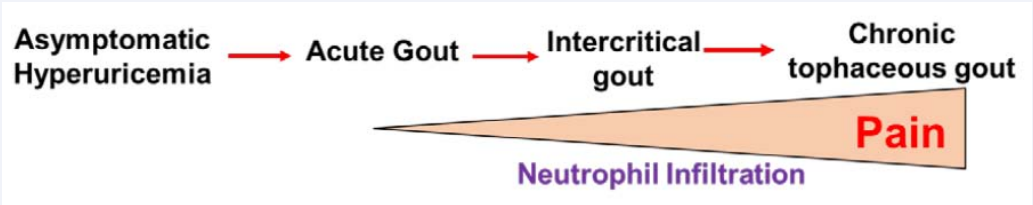

Figure 1b Different stages of gout and the associated symptoms.

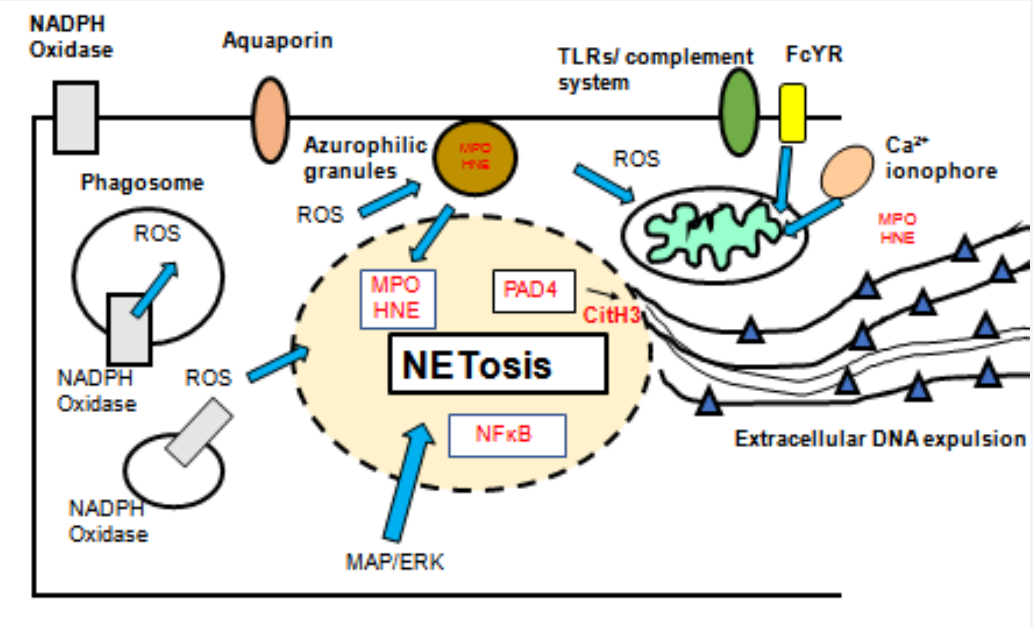

Figure 1c Pathways involved in NETosis.

activation as well as macrophage and neutrophil interactions, which contribute towards exaggeration of the inflammation [54,55]. Our study will investigate the factors contributing to neutrophil activation and will strive to shed light on the underlying mechanism(s). The ultimate goal is to effectively block this interaction and thereby, intercept the progression of gout.

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