

The role of monosodium urate crystals in gout

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The Mortellaro group at SIGN. Credit: A*STAR Singapore Immunology Network

An attack of gout is said to be like your joint catching fire, and someone slamming it with a hammer to put out the flames. Now A*STAR researchers have identified how the build-up of monosodium urate (MSU) crystals in the joints triggers such excruciating pain, raising the prospect of new treatments.

Gout has been dubbed the disease of kings, because it is sometimes—but crucially, not always—associated with the overconsumption of alcohol, fatty or protein-rich foods. These boost levels of blood uric acid, which crystallizes in the joints: but it was unclear how these crystals caused severe [inflammation](#).

One clue came with the discovery of inflammasomes, complexes of molecules within [cells](#) that respond to environmental "danger signals" by mediating the release of active message molecules called cytokines. These rally immune cells, which release further substances, resulting in excessive inflammation and pain.

Inflammasomes can become activated in response to bacterial or viral invaders, but they also respond to particulate structures such as MSU crystals. To investigate how MSU activates inflammasomes, a team led by Alessandra Mortellaro of the A*STAR Singapore Immunology Network turned to the complement system, a group of more than 20 proteins circulating in blood and tissue fluids which act as first line of immune defense.

One way of mimicking what happens in [gout](#) is to inject MSU crystals into the peritoneal cavity of mice; this usually triggers an influx of immune cells and inflammation. It also raises levels of two [complement proteins](#), C3a and C5a, the team found.

Experiments revealed that incubating immune cells in the presence of C5a, but not C3a, increased levels of the cytokines, IL-1 β and IL-1 α . "This is a hallmark of [inflammasome](#) activation," says Hanif Khameneh, one of the lead investigators.

Next, the team used mice engineered without receptors for either complement protein. Those lacking C5a receptors, but not C3a receptors, failed to show the usual infiltration of [immune cells](#), and inflammation in response to MSU crystals. Treating mice with a drug that blocks C5a receptors produced a similar result. C5a most likely triggers inflammasome activation by boosting cellular levels of [reactive oxygen species](#), which are toxic at high levels.

The discovery could have consequences for gout treatment. Current

drugs merely dampen pain and inflammation, rather than addressing its root cause. "At least in our mouse model, we've shown that complement is involved in initiating inflammation," says Khameneh. "Targeting complement may therefore benefit gout sufferers."

More information: Hanif J. Khameneh et al. C5a Regulates IL-1 β Production and Leukocyte Recruitment in a Murine Model of Monosodium Urate Crystal-Induced Peritonitis, *Frontiers in Pharmacology* (2017). [DOI: 10.3389/fphar.2017.00010](https://doi.org/10.3389/fphar.2017.00010)

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