INFLAMMATION

Gouty inflammation crystal clear?

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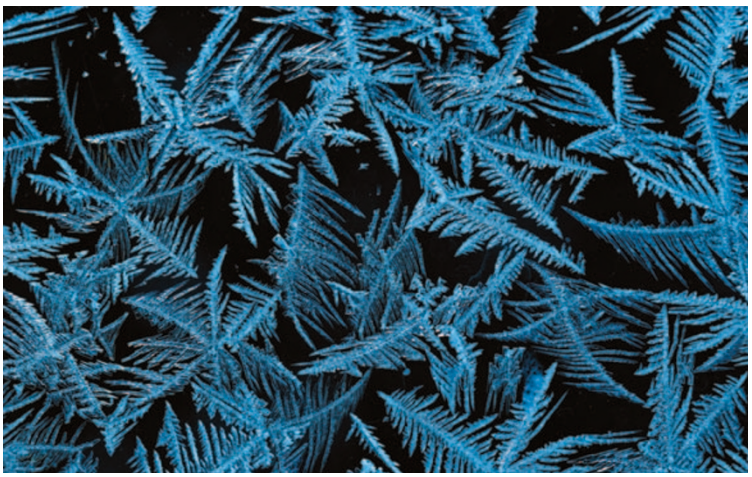

The excruciatingly painful inflammatory condition gout is one of the oldest-recorded human afflictions. It is now well known that acute gouty inflammation results from the deposition of monosodium urate (MSU) crystals in the joints of individuals with hyperuricaemia. But exactly how MSU crystals are linked to the inflammatory response has puzzled scientists for centuries. Kenneth Rock and colleagues now reveal that interleukin-1 (IL-1) and signalling through the IL-1 receptor are crucial components of the inflammatory cascade that is triggered by MSU crystals.

A previous observation by these authors led them to propose that MSU crystals might function as danger signals and trigger an innate immune response in a manner similar to microbial molecules — that is, through Toll-like receptors (TLRs). To test this hypothesis, Chen *et al.* injected MSU crystals into the peritoneal cavity of either wild-type mice or mice deficient in various TLRs and then monitored the inflammatory response by quantifying the influx of neutrophils. Surprisingly, none of the eight TLR-deficient mouse strains analysed showed a defect in neutrophil influx. They confirmed these results, and excluded a role for TLR5 and TLR8 (for which gene-knockout mice are unavailable) in the inflammatory response, by showing that cells transfected with genes that encode these TLRs also did not respond to MSU crystals.

Although these studies rendered improbable the hypothesis that MSU crystals exert their function directly through TLRs, the authors examined the role of the Toll/IL-1 receptor (TIR)-domain-containing adaptor proteins that are involved in TLR signalling: MyD88 (myeloid differentiation primary-response protein 88), TIRAP (TIR-domain-containing adaptor protein), TRIF (TIR-domain-containing adaptor protein inducing interferon-β) and TRAM (TRIF-related adaptor molecule). Although a deficiency in TIRAP, TRIF or TRAM had no effect on neutrophil influx, mice deficient in MyD88 showed marked defects in the inflammatory response, including in neutrophil influx and pro-inflammatory cytokine production. So MSU crystals seem to stimulate inflammation through a MyD88-dependent pathway that does not involve TLRs.

In addition to mediating TLR signalling, MyD88 is downstream of the IL-1 and IL-18 receptors. Consistent with a role for the IL-1 receptor, mice lacking this receptor but not the IL-18 receptor showed defective inflammatory responses to MSU crystals (similar to MyD88-deficient mice). In addition, treatment of mice with neutralizing antibody specific for IL-1 also markedly reduced the inflammatory response.

Further studies led the authors to propose that MSU crystals induce cells to produce IL-1. IL-1 then binds non-bone-marrow-derived cells that express the IL-1 receptor, resulting in MyD88-dependent amplification of the pro-inflammatory response — that is, further IL-1 production and neutrophil recruitment.

Although several steps in the inflammatory cascade remain to be defined, elucidation of a central role for IL-1 in gouty inflammation provides a potential new target for the treatment of gout.

Lucy Bird

ORIGINAL RESEARCH PAPER Chen, C.-J. *et al.* MyD88-dependent IL-1 receptor signaling is essential for gouty inflammation stimulated by monosodium urate crystals. *J. Clin. Invest.* **116**, 2262–2271 (2006)
FURTHER READING Martinon, F. & Glimcher, L. H. Gout: new insights into an old disease. *J. Clin. Invest.* **116**, 2073–2075 (2006)