Editorial
Gout in the spotlight

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Abstract

Understanding how uric acid crystals provoke inflammation is crucial to improving our management of acute gout. It is well known that urate crystals stimulate monocytes and macrophages to elaborate inflammatory cytokines, but the tissue response of the synovium is less well understood. Microarray analysis of mRNA expression by these lining cells may help to delineate the genes that are modulated. Employing a murine air-pouch model, a number of genes expressed by innate immune cells were found to be rapidly upregulated by monosodium urate crystals. These findings provide new research avenues to investigate the physiopathology of gouty inflammation, and may eventually lead to new therapeutic targets in acute gout.

In this issue of *Arthritis Research & Therapy*, Pessler and colleagues [1] report on mRNA microarray analyses on the equivalent of the synovial lining cells after monosodium urate (MSU) crystals were injected into a murine air-pouch; their study addresses the early phase (9 hours) of the tissue response to gouty inflammation.

Research on gout and how MSU crystals induce inflammation has recently taken a step forward, emerging from the comparative shadows of rheumatoid arthritis research into the spotlight. In particular, two key publications have challenged our previous ideas about the role of MSU in inflammation. Rock and colleagues [2] showed that urate crystals behaved like an adjuvant, stimulating the immune system's response to dying cells, and more recently, Tschopp and colleagues [3] showed that MSU crystals interact directly with the inflammasome, a multicomponent cytoplasmic complex that activates IL-1β. These two reports show that MSU crystals have potent phlogistic properties and outline some of the mechanisms. However, there is still a lot to learn about how MSU crystals trigger an acute attack of gout. The precise mechanisms of how MSU crystals gain entry into the leukocyte and how leukocytes then respond to these crystals still need to be elucidated. There are at least two phases of the early acute inflammatory response that can be studied, the first being the effect of MSU crystals on leukocytes and the second the response of the surrounding tissues. These tissues, which include vascular endothelium, respond to inflammation to modulate cell migration, proliferation and metabolic activities that may all contribute to the clinical physiopathology of acute gouty arthritis.

The murine air-pouch model utilised by Pessler and colleagues [1], together with peritoneal injection of MSU crystals, are both validated models to study the acute inflammatory effects of MSU. The results of their study highlight a set of acute inflammatory genes that were dramatically upregulated early on in the lining tissue, in particular a number of genes known to be expressed by macrophages (*PUMA-g*, *TREM-1* and *Irg-1*). As expected, the expression of pro-inflammatory cytokines (IL-1b, tumour necrosis factor-α, and IL-6) was increased. In addition, some unexpected genes were also upregulated, such as *Hdc* and *PROK-2*. *Hdc* encodes histamine decarboxylase and *PROK-2* encodes prokineticin-2.

Their results raise a number of interesting questions and suggest possible new directions for research that may improve our understanding of acute gout. Firstly, based on their findings, it would appear that the main early cellular response within the pouch lining, and by inference the synovial lining, is from cells of the macrophage lineage or type A cells. Are these cells recruited there? Are they present and ready to respond *in situ* or do they need priming? The demonstration that *Hdc* is upregulated, both in the membrane and in MSU-stimulated macrophages *in vitro*, suggests that histamine is also a key player, though the source is probably not mast cells but the macrophage. Whether these genes are relevant in gouty inflammation can now be investigated, as knockouts for some of these genes are available and pharmaceutical inhibition is possible for some of the up-

IL = interleukin; MSU = monosodium urate.

regulated molecules. A major question, in light of the findings reported by Martinon and colleagues [3], is whether these events take place downstream of the MSU-inflammasome interaction or whether they take place concurrently. This too can be addressed experimentally as the tools are currently available.

The current data show how genomic analysis can reveal new insights into a common clinical problem. As clinicians are all too aware, NSAIDs (non-steroidal anti-inflammatory drugs) and colchicine are not always without their drawbacks in clinical practice, particularly in the elderly population with multiple co-morbidities. Any new therapies that target the new inflammatory processes set off by MSU crystals will potentially have a major impact and this will come about only with a clearer understanding of the underlying mechanisms.

Competing interests

The author declares that they have no competing interests.

References

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