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EDITORIAL

How to regulate neutrophils in gout

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Abstract

Most research in gout has concentrated on the proinflammatory mechanisms to explain the inflammation that is generated when leucocytes are in contact with monosodium urate crystals. However, the episodic nature of gout and the absence of inflammation even when crystals are present suggest that there are natural counter-regulatory mechanisms to limit the inflammatory response. Gagné and colleagues showed that myeloid inhibitory C-type lectin, a C-type lectin inhibitory receptor expressed on neutrophils, modulates monosodium urate-induced neutrophil responses *in vitro*.

Neutrophil recruitment and activation play a key role in the acute inflammatory response to monosodium urate (MSU) crystals. In acute gout, our current treatments such as nonsteroidal anti-inflammatory drugs, colchicine or corticosteroids all act on different steps of neutrophil activation. These drugs form part of the first treatment objective in gout – to relieve the painful symptoms of the acute attack – but do not address the second objective, which is to treat the underlying metabolic disorder hyperuricemia. Can neutrophil activation be manipulated or regulated? Are there signals that can be modulated and can this be of clinical relevance?

The article by Gagné and colleagues provides evidence for an inhibitory pathway of neutrophil activation that acts through a recently described C-type lectin receptor called the myeloid inhibitory C-type lectin (MICL) [1]. This membrane receptor, also known as CLEC12A, inhibits neutrophil activation when it is engaged. C-type lectin receptors form a large family of proteins that have a common type of carbohydrate-binding domain that mediate cell adhesion and ligand binding in a calcium-dependent manner. Members of the C-type lectin receptors are known to participate in immune regulation, with well-known examples including Dectin-1 (CLE7A), DC-sign (CD209 or CLEC4L) and natural killer cell receptors (Ly49 or KLRA1). The MICL protein is encoded on chromosome 12p13, closely linked to the natural killer gene complex. MICL contains a cytoplasmic immunoreceptor tyrosine-based inhibitory motif and is expressed mainly on neutrophils and monocytes. Previous work has shown that the receptor could inhibit cellular activation [2]. The ligands that lead to MICL activation are currently unknown, as there is only a small body of data to show that the receptor interacts with ligands expressed in the bone marrow, thymus and kidney [3].

In their studies, Gagné and colleagues showed that MSU crystals as well as a MICL-specific antibody downmodulated MICL expression on neutrophils. Reducing the expression of MICL by transfecting small interfering RNA or by antibody modulation of the receptor led to enhanced production of IL-8 when MSU was added to neutrophils, but no changes in IL-1β secretion were observed. The mechanisms of MICL signaling probably involve tyrosine phosphorylation as well as calcium flux, differing from previous results that showed MICL associated with the phosphatases SHP-1 and SHP-2 [2]. Finally, the addition of colchicine to neutrophils abrogated the negative effect of MSU on MICL expression.

These results showed that reduced MICL expression is associated with augmented inflammatory responses from neutrophils, and a higher level of neutrophil MICL expression is associated with a reduced IL-8 production *in vitro*. As IL-8 is a major neutrophil chemoattractant, this can have important effects on neutrophil recruitment to an inflammatory site in gout. By extrapolation, if MICL expression or signaling could be enhanced or maintained during inflammation, the inhibitory signal may be reinforced and thereby downregulate inflammation. The effect of colchicine in this system is to elevate the expression of MICL, thereby increasing the

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inhibitory signaling mechanisms that counteract the inflammatory process.

A number of caveats need to be mentioned in the interpretation of these results. The data presented were based on *in vitro* models of inflammation using MSU, and we need to see how this works *in vivo* before coming to any conclusions, as we have had examples where the *in vivo* results did not recapitulate the *in vitro* findings. They convincingly showed that reducing MICL expression on the surface of neutrophils enhanced the proinflammatory signature, but they did not show the converse – that enhanced MICL signaling can further downmodulate inflammation. Furthermore, the ligands that bind and activate MICL are unknown, so we have no idea what is the signal or how to reinforce or manipulate this signaling system. The results presented show that MSU had dual effects on neutrophils – the first is to downregulate MICL expression, and the second is to activate IL-8 production. How are these two mechanisms linked? If MSU acts mainly on the cell membrane internalization of MICL, what is the trigger for the IL-8 secretion? Notwithstanding these uncertainties, the finding that MICL modulates neutrophil activation in gout suggests that there are a number of counter-regulatory mechanisms in operation during an inflammatory process. Identifying these mechanisms may help us to understand the nature of gout as well as open up new therapeutic perspectives.

Abbreviations

IL: Interleukin; MICL: Myeloid inhibitory C-type lectin; MSU: Monosodium urate.

Competing interests

The author declares that he has no competing interests.

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References

1. Gagne V, Marois L, Levesque JM, Galarneau H, Lahoud MH, Caminschi I, Naccache PH, Tessier P, Fernandes MJG: **Modulation of monosodium urate crystal-induced responses in neutrophils by the myeloid inhibitory C-type lectin-like receptor: potential therapeutic implications.** *Arthritis Res Ther* 2013, **15:**R73.
2. Marshall AS, Willment JA, Lin HH, Williams DL, Gordon S, Brown GD: **Identification and characterization of a novel human myeloid inhibitory C-type lectin-like receptor (MICL) that is predominantly expressed on granulocytes and monocytes.** *J Biol Chem* 2004, **279:**14792–14802.
3. Pyz E, Huysamen C, Marshall AS, Gordon S, Taylor PR, Brown GD: **Characterisation of murine MICL (CLEC12A) and evidence for an endogenous ligand.** *Eur J Immunol* 2008, **38:**1157–1163.

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