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EDITORIAL

A complicated liaison: IL-33 and IL-33R in arthritis pathogenesis

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Abstract

Interruption of cytokine signaling, by targeting either the cytokine itself or its cellular receptor, is a mainstay in the therapy for patients with rheumatic diseases. Interleukin (IL)-33, a member of the IL-1 cytokine family, has emerged as an important mediator of inflammatory responses. In a side-by-side examination of IL-33-deficient and IL-33 receptor (IL-33R)-deficient mice in the K/BxN serum transfer model, arthritis was ameliorated in the IL-33R knockout (KO) mice but not in the IL-33 KO mice. These findings complement previous knowledge on IL-33R signaling, demonstrating that the IL-33R cross-activates other signaling pathways in addition to IL-33-mediated signals. The results reported by Martin and colleagues in a previous issue of *Arthritis Research & Therapy* underline the clinical relevance of IL-33R cross-signaling and further illustrate that targeting a cytokine receptor (IL-33R) can have completely different clinical outcomes than targeting the respective cytokine.

In a previous issue of *Arthritis Research & Therapy*, Martin and colleagues [1] reported a puzzling finding: in a side-by-side comparison of interleukin-33 (IL-33)-deficient mice and mice that lacked the receptor for IL-33 (IL-33R), K/BxN serum transfer arthritis was ameliorated only in the IL-33R-deficient but not the IL-33-deficient mice. IL-33 is an IL-1 family member that has emerged as a key regulator of protective and pathogenic immune responses [2,3]. It is also a chromatin-associated nuclear protein acting as a transcriptional regulator [2,3]. IL-33 is expressed by fibroblasts and epithelial, endothelial, mast, and innate immune cells. Similar to other IL-1 family members IL-33 signals through a heterodimeric complex consisting of the binding receptor (T1/ST2) and the IL-1R accessory protein (IL-1RAcP) [2,3]. T1/ST2 occurs in membrane-bound or soluble (sIL-33R) isoforms. Expression of membrane-bound IL-33R is restricted to hematopoietic cells, most prominently in T helper 2 (Th2) lymphocytes, mast cells, eosinophils, basophils, and innate lymphoid cells. Signaling via IL-33R is relevant in type 2 immune responses as it induces the expression of IL-4, IL-5, and IL-13 in Th 2 lymphocytes, independently of T-cell receptor triggering [4]. Soluble T1/ST2 functions as a decoy receptor that can block IL-33/IL-33R interaction [2,3].

IL-33 is expressed in the synovium of patients with rheumatoid arthritis (RA), and IL-33 serum concentrations are elevated in patients with RA [3]. These findings suggest that IL-33 is involved in RA pathogenesis. This concept is supported by data obtained in collagen-induced arthritis (CIA). Treatment with a monoclonal antibody against T1/ST2 or genetic ablation of T1/ST2 ameliorated arthritis [5,6]. In contrast, injection of IL-33 exacerbated CIA [6].

IL-33 and IL-33R have also been studied in the human tumor necrosis factor-alpha transgenic [7] and the K/BxN serum transfer models of arthritis. It was reported, in line with the conclusions from the CIA model, that K/BxN serum transfer arthritis was ameliorated in IL-33R (T1/ST2) knockout (KO) mice [8]. As expected from this finding, injection of IL-33 exacerbated K/BxN serum transfer arthritis [8]. Another study, however, yielded contradicting findings. There, the injection of IL-33 ameliorated K/BxN serum transfer arthritis and this was dependent on IL-4 signaling [9].

It is against this background that Martin and colleagues [1] aimed to compare the contributions of IL-33 and its receptor directly within the same model (K/BxN serum transfer) in the same laboratory. The authors found both the incidence and severity of arthritis to be reduced in ST2 KO mice in comparison with wild-type (WT) controls. In striking contrast, arthritis incidence and severity did not differ in IL-33 KO mice and WT mice. Moreover, the authors found that sT1/ST2, the decoy receptor for IL-33, had no effect on arthritis [1].

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How can these contradictory findings be explained? Mouse models of inflammatory diseases, including arthritis, are sometimes affected by environmental factors such as the different microbial colonization of experimental animals in different animal facilities. By performing the experiments in IL-33 and IL-33R KO mice within one group and the same facilities, Martin and colleagues could rule out such explanations for their findings. The il-33$^{-/-}$ and t1/st2$^{-/-}$ mice were made from genetically modified embryonic stem cells of the 129/Sv mouse strain and then back-crossed to C57BL/6 mice, in which the experiments were performed. Martin and colleagues used a 377 SNIP panel to determine that the il-33$^{-/-}$ mice were 100% C57BL/6. In contrast, the t1/st2$^{-/-}$ mice shared only 89% of 55 tested markers with the C57BL/6 mice that were used as WT controls [1]. The possibility, therefore, remains that subtle genetic polymorphisms may form the basis for the observed differences [10]. An obvious solution to this problem is to use littermate controls for each genetically modified strain [10].

Alternative explanations for the opposite findings in il-33$^{-/-}$ and t1/st2$^{-/-}$ mice stem from the IL-1R family signaling pathways. IL-1R family members share the IL-1RAcP. It is, therefore, conceivable that, in the absence of one receptor (for example, T1/ST2), the formation of other receptor complexes (IL-1R1/IL-1RAcP and IL-18Rα/IL-1RAcP) is increased, allowing enhanced IL-1 or IL-18 signaling. In fact, macrophages from T1/ST2-deficient mice were reported to produce more proinflammatory cytokines than cells from WT mice in response to IL-1 or lipopolysaccharide [11]. Both CIA and K/BxN arthritis depend on IL-1 [12]. Increased responsiveness toward IL-1 would be expected to increase incidence and severity of arthritis. Therefore, enhanced formation of other receptor complexes is unlikely to explain why mice lacking T1/ST2$^{-/-}$ are protected from arthritis whereas IL-33$^{-/-}$ mice are susceptible [1].

Earlier findings from other disease models resemble those reported by Martin and colleagues [1] and have been reported for IL-18, another IL-1 family member, and its receptor. IL-18Rα-deficient mice were resistant to experimental autoimmune encephalomyelitis, a mouse model for multiple sclerosis. In contrast, IL-18-deficient mice were susceptible to experimental autoimmune encephalomyelitis [13]. The published data on the role of IL-33 and T1/ST2 in Leishmania infection allow the conclusion that T1/ST2^{+} effector cells, but not IL-33-induced signaling, are relevant for disease pathogenesis [3]. Consequently, T1/ST2 may exert functions in addition to the transduction of IL-33-induced signals.

We found that IL-33-induced signaling via T1/ST2 cross-activates the receptor tyrosine kinase c-Kit, the receptor for stem cell factor in human and murine mast cells. T1/ST2-induced activation of c-Kit is required to elicit optimal effector functions in response to IL-33 [14]. The structural basis for this cross-activation is the ligand-induced complex formation between c-Kit, T1/ST2, and IL-1R accessory protein (IL-1RAcP). The requirement for T1/ST2 for optimal signal transduction from other receptors could provide one mechanistic explanation for the fact that T1/ST2-deficient mice, but not IL-33-deficient mice, are protected from arthritis. Together with the data reported by Martin and colleagues [1], these findings indicate that targeting IL-33 or its receptor might result in fundamentally different outcomes in patients (with arthritis).

To date, the cross-activation of c-Kit by T1/ST2 has been reported [14]. Mast cells are probably involved in arthritis pathogenesis, but most cell lineages relevant for arthritis pathogenesis do not express c-Kit. It remains to be elucidated whether T1/ST2 cooperates with other receptor tyrosine kinases in other effector cells that do not express c-Kit. A detailed understanding of such interactions between T1/ST2 with other signaling pathways seems to be mandatory for rational therapeutic manipulation of this system. More surprises, in addition to the puzzling findings reported by Martin and colleagues [1], regarding T1/ST2 signaling in health and disease are likely to be discovered.

Abbreviations

CIA, collagen-induced arthritis; IL, interleukin; IL-33R, interleukin-33 receptor; IL-1RAcP, interleukin-1 receptor accessory protein; KO, knockout; RA, rheumatoid arthritis; Th2, T helper 2; WT, wild-type.

Competing interests

The authors declare that they have no competing interests.

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