RHEUMATOID ARTHRITIS

New role for mast cells as IL-17-expressing effector cells in established RA

When searching for the cellular source of interleukin (IL)-17A in the inflamed synovium of patients with rheumatoid arthritis (RA), CD4⁺ type 17 T helper (T_H17) cells are obvious possible culprits. However, research from the University of Glasgow, UK, published in the *Journal of Immunology*, identifies mast cells, not T cells, as the primary source of this proinflammatory cytokine in individuals with established disease.

“Since IL-17 is proposed as a key proinflammatory cytokine in the pathogenesis of RA and anti-IL-17 clinical trials are ongoing for RA and other rheumatic diseases, we wanted to identify the tissue sources of IL-17 in the inflamed synovium from patients with established RA,” explains Iain McInnes, the lead researcher on this paper. To achieve this goal, the investigators studied synovial tissue samples obtained from patients with RA by immunohistochemistry and fluorescent microscopy. By co-localization studies, the researchers showed that only a few of the IL-17A-positive cells in the inflamed synovium were T cells, as most of them were negative for the T cell markers CD3, CD4 and CCR6; they were, however, positive for mast cell tryptase (MCT), a specific marker of mast cells.

Having identified mast cells as the principal cellular source of IL-17A in the inflamed synovium of individuals with established disease, the authors then investigated what signals might be involved in triggering these cells to express IL-17A. “We go on to show that *in vitro*, human mast cells secrete IL-17A in response to various stimuli which have been suggested to play a role in RA,” says McInnes. These stimuli included tumor necrosis factor, IgG complexes, the complement component C5a and lipopolysaccharide. Other T_H17-associated cytokines, including IL-21 and IL-22, were not detected in these experiments.

IL-17A⁺MCT⁺ cells in the RA synovium, identified by co-localization fluorescent microscopy studies. Image courtesy of A. J. Hueber, A. J. Melendez and I. B. McInnes.

Next, the authors discovered that mast cells express *RORC*, the gene encoding the transcription factor retinoic acid receptor-related orphan receptor C. They also showed that the expression of *RORC* is increased by the factors that induce IL-17A production, and that silencing of *RORC* expression using *RORC* small interfering RNA blocked the expression of IL-17A, but not IL-5 or IL-6, by these cells. IL-17A production was not influenced when other genes, such as those encoding RORA and signal transducer and activator of transcription 3, were silenced in this way. So, in human mast cells the production of IL-17A appears specifically to be *RORC*-dependent.

This work focuses on the source of IL-17A in established synovitis, where mast cells are important, but are T_H17 cells perhaps more central in this regard in early arthritis? Further research is needed to answer this question.

McInnes and his team are now investigating the pathways that lead to the recruitment of mast cells, or their precursors, to sites of inflammation, as well as the molecular mechanisms that lead to mast cell activation. Through this work they hope to “identify potential novel targets for therapeutic intervention and potential novel targets and biomarkers derived from mast cells to understand disease progression from early to established, or more active, disease”.

What are the clinical implications of this research? According to McInnes, “We

have opened a new field of investigation in which mast cells assume new importance in RA and other human ‘T_H17’ driven disorders, thereby expanding the cellular targets that already exist and contributing to a better understanding of a very complex disease, RA.”

David Lee, Associate Professor of Medicine at Brigham and Women’s Hospital and Harvard Medical School, USA, whose research has focused on the role of mast cells in inflammatory arthritis since 2001, agrees that this work is clinically interesting. “Of significant importance, these studies identify mast cells, a tissue-resident innate immune cell population, as the predominant cellular source of IL-17 in this disease. These findings contrast with expectations regarding the cellular source of IL-17 in the inflamed joint.”

Lee goes on to say that “Further examination of mast cell IL-17A production in human tissues before and after treatment with therapeutics used in RA will also provide valuable information about this pathway. Understanding the triggers and the cellular sources of IL-17 could lead to more effective targeting of this proinflammatory pathway in disease.”

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Original article Hueber, A. J. *et al.* Cutting edge: Mast cells express IL-17A in rheumatoid arthritis synovium. *J. Immunol.* **184**, 3336–3340 (2010)

Further reading Lee, D. M. *et al.* Mast cells: a cellular link between autoantibodies and inflammatory arthritis. *Science* **297**, 1689–1692 (2002)