

## Commentary

# Pathogenesis of rheumatoid arthritis: how early is early?

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### Abstract

Studies of cytokine expression in rheumatoid arthritis have provided key insights into the pathogenesis of disease and have offered clues for effective therapy. Patterns of T-cell products in chronic rheumatoid synovitis suggest that T helper type 1 cells contribute to the perpetuation of disease. However, there is no guarantee that the mechanisms of late disease are identical to very early rheumatoid arthritis. Evaluation of the cytokine profile at the earliest time points after onset of symptoms could identify novel targets that prevent progression to chronic arthritis.

Development of hypotheses to explain the pathogenesis of chronic rheumatoid arthritis (RA), including the interesting new study by Raza and colleagues [1], has been a wondrous adventure. Virtually every immune cell type and inflammatory mediator has been implicated in the disease process at one time or another. Older, temporarily discarded hypotheses on B cells and immune complexes have enjoyed renewed energy with the advent of anti-B-cell therapies [2]. Now that T-cell-directed approaches, such as CTLA4-Ig [3], demonstrate efficacy, it appears that therapies targeting this cell lineage also are effective in a subpopulation of patients. Hence, chronic rheumatoid synovitis is marked by a complex interplay between multiple cell types, and individual patients display their own distinct hierarchy for the efficacy of therapeutic interventions [4].

On the other hand, there is much less information on disease mechanisms in the earliest stages of RA. This is, in part, due to the changing definitions of 'early RA', with a cutoff that has gradually migrated from 2 years of symptoms to as little as 6 weeks. Even in the latter case, a prolonged preclinical period of immune hyper-reactivity and asymptomatic synovitis could exist before the disease becomes fully established. Many investigators believe that an appropriate genetic background in combination with stochastic events, such as activation of innate immunity, can serve as the trigger for RA.

Subsequent perpetuation of the disease might involve entirely distinct adaptive immune mechanisms that are independent of the initiating events.

Implicit in this assessment, an adaptive T-cell response might be required for full expression of RA. The nature of this response remains poorly defined, and studies of chronic rheumatoid synovitis have generally demonstrated blunted T-cell function and surprisingly limited cytokine production compared with other T-cell-mediated diseases. The lymphocyte cytokine profile in chronic RA synovium and surface chemokine receptor display is most consistent with a T helper cell type 1 (Th1)-driven disease [5]. This cell type plays a key role in the pathogenesis of many rodent models of arthritis, including collagen-induced arthritis, antigen-induced arthritis, and adjuvant arthritis, where Th1 cytokines generally predominate early and T helper cell type 2 (Th2) factors contribute to the resolution. In this context, the study by Raza and colleagues raises questions about the role of T cells in RA and other forms of inflammatory arthritis.

Many studies have suggested that 'chronic' RA and 'early' RA have more similarities than differences [6]. Histopathologic evaluation of synovial tissue shows chronic changes shortly after the onset of symptoms, and the cytokine profile in early disease as determined by immunohistochemistry is nearly identical to long-standing RA [7-9]. The latter finding was based on patients with up to 1 year of disease, but some patients with synovitis for as little as 2 months were included in the analysis. Asymptomatic joints in patients with RA also have very similar profiles to chronic RA, albeit with fewer synovial macrophages and less immunoreactive IL-8 [10]. These data suggest either that the mechanisms of RA in early disease are the same as in late arthritis or that the window of obvious T-cell activation needs to be pushed even earlier, perhaps to the preclinical phase.

The present study demonstrating T-cell cytokines in the first few months of disease might provide some insights into the time frame of T-cell activation in early RA. The data suggest that T-cell cytokines might be abundant in the first 3 months but that the levels later drift downward and are eventually undetectable. However, there are some discrepancies with many previous reports that remain unexplained. For instance, IL-4 and IL-13 (both classic Th2 cytokines) but not interferon gamma (IFN- $\gamma$ ) were detected early in RA, thereby making it difficult to call RA a 'Th1'-mediated disease. In contrast, seronegative spondyloarthropathies had high IFN- $\gamma$ , which is the opposite of the 'Th2' pattern observed in chronic disease [11]. The absence of IFN- $\gamma$  in synovial effusions of patients with chronic RA contrasts with other studies, including our experiments over 15 years ago when we were impressed by surprisingly low IFN- $\gamma$  concentrations [12]. Although the levels are below the amount required to induce HLA-DR on monocytes, detectable amounts were clearly identified in synovial effusions. Other cytokines previously reported in chronic RA, such as granulocyte-macrophage colony-stimulating factor and IL-17, were not detected with the multiplex system employed by the authors [13,14]. In contrast to previous studies, the levels of IL-15 were similar in chronic RA and osteoarthritis synovial effusions [15].

The authors also comment on a potential role of stromal-derived cytokines and growth factors in early RA and late RA. Compared with the lengthy list of T-cell products and macrophage products, the array of mesenchymal cell products evaluated was more limited. Additional information on key cytokines such as stromal derived factor 1, transforming growth factor beta, and the bone morphogenic proteins would be useful, even if individual immunoassays are required to quantify these data [16,17].

Many of the differences with previous studies are difficult to resolve and could be due to concomitant medications or other confounding technical influences. The use of multiplex assay systems is relatively new, and the correlations with standard single analyte assays of complex body fluids would be helpful to assess precision and accuracy. The authors did perform several careful studies that appeared to rule out interference by rheumatoid factors, although validation to evaluate the effect of other synovial fluid constituents on multiplex analysis and the antibody pairs is very important. Antibody pairs validated for tissue culture supernatants or blood do not always perform to specifications in more complex biological samples or tissue extracts. One also needs to be cautious about the use of synovial fluid as the ultimate arbiter of synovial tissue cytokine levels. Synovial effusion levels could reflect tissue concentrations, but the joint space is a separate compartment with distinct cell populations and kinetics that do not always mirror the synovium.

Despite these concerns, the questions addressed are indeed quite important. Are there divergent mechanisms in early RA

and late RA, and is there a transient window for curing the disease with aggressive therapy? Recent data using infliximab in early synovitis, defined as less than 12 months of symptoms, show that treatment can be withdrawn in some patients without subsequent flares, supporting the authors' contention that early RA has a distinct pathogenesis [18]. 'Early' intervention (<18 months of disease) with anti-CD4 antibody, however, demonstrates little or no benefit even though T cells were depleted from the synovium [19]. Both of these studies were beyond the short window of elevated Th2 cytokine production observed in the present study.

## Conclusions

Although data implicating Th2 cytokines in early arthritis differ from our expectations, this information might influence our concepts of how RA evolves. In light of the possible technical issues related to multiplex analysis, confirmatory studies to evaluate the cytokine profile in early synovitis are essential to resolve the differences with previous work. If validated, a careful reassessment of Th1/Th2 balance in early RA and late RA would be important.

## Competing interests

The author(s) declare that they have no competing interests.

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