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LETTERS

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Serum levels of tryptase suggest that mast cells might have an antiinflammatory role in rheumatoid arthritis: comment on the article by Rivellese et al

To the Editor:

In their recent report (1), Rivellese et al describe newly identified mast cell–mediated inhibitory pathways that might have functional relevance in the pathogenesis of rheumatoid arthritis (RA). They observed that when human mast cells are activated an immunomodulatory phenotype develops, with human mast cells gaining the ability to suppress monocyte activation via the release of interleukin-10 and histamine. They also describe the presence of interactions between mast cells and monocytes in the synovium, and an inverse association between expression of mast cell genes at the synovial level and disease activity.

Human tryptase is a tetrameric serine protease that is concentrated and stored selectively in the secretory granules of human mast cells; during mast cell activation, it is secreted into the circulation (2). Given that tryptase is expressed in the synovial tissue of patients with RA (3), we tested whether tryptase levels are also elevated in the sera of RA patients and investigated for a possible correlation with markers of disease activity.

We measured serum tryptase levels by fluoro–enzyme immunoassay (ImmunoCAP Tryptase; Phadia) in 45 healthy individuals and in 23 age- and sex-matched patients with early RA who had not been treated with disease-modifying antirheumatic drugs or glucocorticoids. We found that serum levels of tryptase in RA patients were not significantly higher than those in healthy controls (mean ± SD 3.4 ± 1.2 μg/liter and 3.2 ± 1.4 μg/liter, respectively). However, there was a negative correlation between C-reactive protein and serum tryptase levels ($r = -0.426$, $P = 0.043$) (Figure 1).

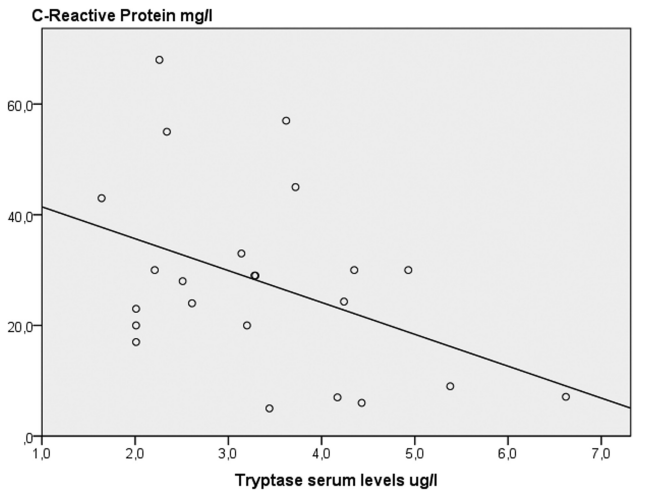

Figure 1. Negative correlation between levels of C-reactive protein and levels of tryptase in the serum of patients with early rheumatoid arthritis.

Our data on circulating levels of tryptase, a systemic marker of mast cell activation, are consistent with the synovial-level findings reported by Rivellese et al. Our results provide further evidence that mast cells might exert antiinflammatory action in RA.

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Reply

To the Editor:

We would like to thank Dr. Rossini and colleagues for their interest in our article on the immunomodulatory role of mast cells in RA. Rossini et al show a negative correlation between C-reactive protein and serum tryptase levels in patients with early RA, consistent with the notion that mast cells might have an antiinflammatory role in this disease.

As tryptase was among the mast cell–related markers we used to infer the presence of mast cells in synovial tissue, we have now performed an additional analysis of our data. In accordance with the results presented by Rossini et al, we found an inverse correlation between synovial tryptase messenger RNA levels and serum C-reactive protein levels in patients with RA (Figure 1).

In addition to being a validated marker of mast cell activation in conditions such as anaphylaxis (1), tryptase has been used to study mast cell presence and activation in RA (2–4). However, those studies were conducted in patients with longstanding disease and often during treatment with steroids and immunosuppressive drugs, conditions that can clearly influence mast cell numbers and their activation.

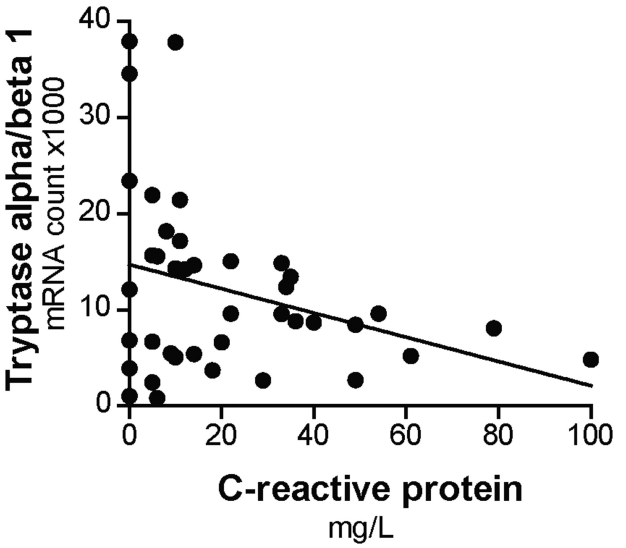

Figure 1. Negative correlation between serum levels of C-reactive protein and synovial levels of tryptase mRNA in patients with early RA.

As highlighted in our report, we assessed the presence of mast cells in synovium obtained by ultrasound-guided biopsy (5) from patients with early RA, who had not begun treatment. Our findings, now supported by the data presented by Rossini and colleagues (also from RA patients with early disease), suggest that mast cells are able to modulate the inflammatory responses in the early phases of RA.

Mast cells have been described as tunable immunomodulatory cells (6,7), which could explain the contrasting data obtained to date in the context of RA and other autoimmune diseases (8), with experimental models not taking into account the fine-tuning of mast cell functions and the clinical and biologic disease heterogeneity. To further elucidate the contribution of mast cells to RA, we are currently analyzing the presence of synovial mast cells in relation to disease subsets and outcomes, within broader investigations on the use of synovial histopathology as a potential prognostic biomarker for patient stratification in RA (9). We believe such studies will finally help to identify the complex and perhaps multifaceted roles of mast cells in the development of RA and, potentially, their contribution to disease progression and response to therapy.

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Bcl-3 in CD4+ T cell–mediated rheumatoid arthritis pathogenesis: comment on the article by Meguro et al

To the Editor:

We read with interest the report by Meguro et al, in which they concluded that Bcl-3 is involved in the pathogenesis of rheumatoid arthritis (RA) by enhancing follicular helper T (Tfh) cell development (1). We agree that there is accumulating evidence implicating this atypical IκB protein as a mediator of RA pathogenesis in CD4+ T cells. Based on the murine experiments presented, we find the mechanistic insights offered by Meguro and colleagues intriguing, but we conclude that much has yet to be learned before Bcl-3 may be confirmed as a potential therapeutic target in RA.

The authors' data from humans provide welcome independent validation of our own published observations indicating that interleukin-6 (IL-6)–induced STAT-3 phosphorylation