

toid arthritis–specific autoantibodies.” Thus, ACPAs are just ACPAs.

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Reply

To the Editor:

We thank Dr. Konig and colleagues for their interest in our work and their insightful comments. In our report, we provide evidence that PAD4 augments autoantibody production, total IgG levels, T cell activation, and arthritis in mice with chronic inflammatory arthritis due to overexpression of TNF α . As part of our studies, we investigated autoantibody production by these TNF α -overexpressing mice. Konig et al comment that our data do not support the conclusion that TNF α -overexpressing mice produce ACPAs, and they stress the need for stringency in defining murine ACPAs.

We agree that our report does not provide data showing that TNF α -overexpressing mice generate ACPAs, which specifically target citrulline (1). However, the main goal of our study was to understand how PAD4 and TNF α might synergize to exacerbate autoantibody production and arthritis, not specifically to focus on ACPAs. In the introduction we hypothesized that PAD4 could contribute to arthritis via antigen citrullination given the development of ACPAs in human RA, and/or could contribute to inflammation given the presence of PAD4 in immune cells. We examined the auto-

antibody repertoire in TNF α -overexpressing mice to determine whether ACPAs could be part of a role of PAD4 in this model of arthritis. In the assays depicted in Figure 1 of our article, sera from TNF α -overexpressing mice exhibited increased reactivity against native and citrullinated antigens compared to sera from wild-type mice. Therefore, we state that TNF α -overexpressing mice have increased autoantibodies reactive against native and citrullinated antigens, which is, in our opinion, the most precise way to describe our results. Since the autoantibodies bind to both native and citrullinated antigens, we conclude that chronic overexpression of TNF α in mice amplifies autoantibody production but does not lead to a classic ACPA response, which exclusively targets citrullinated antigens. We also found that TNF α -overexpressing mice have reduced levels of total IgG compared to TNF α -deficient mice (Figure 3), which could be the cause of the reduced autoantibody levels in TNF α -deficient mice compared to TNF α -overexpressing mice (Figure 2). Thus, determining if citrulline is targeted by a subset of the autoantibodies in TNF α -overexpressing mice was not a central part of this study.

One theory on the development of RA is that disease can be triggered by antigen citrullination followed by the production of ACPAs, which leads to increased TNF α levels and ultimately inflammation and arthritis (2). Our data suggest that PAD4 may act downstream of TNF α to augment overall antibody levels and inflammation. Given its role in neutrophil extracellular trap formation (3,4) and hypercitrullination (5), PAD4 might also contribute to the production of citrullinated antigens and ACPAs in genetically susceptible humans as part of a feedback network. However, at this time we can only speculate about a definitive, unique role of PAD4 in ACPA production.

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The systemic-onset variant of juvenile idiopathic arthritis needs to be recorded as an autoinflammatory syndrome: comment on the review by Nigrovic

To the Editor:

We read with interest the recent review article by Nigrovic (1) describing the uniqueness of systemic juvenile idiopathic arthritis (JIA) among the different subtypes of JIA, because it is characterized by systemic features during the initial phase and severe articular signs during the later phase of disease. As discussed by Nigrovic, there is increasing evidence that initiating cytokine blockade early during the systemic phase might alter disease pathophysiology to avoid chronic inflammation and even the arthritic manifestations of systemic JIA.

The umbrella-term “JIA” still identifies a heterogeneous group of inflammatory joint diseases. In particular, according to the International League of Associations for Rheumatology classification (2), JIA refers to all forms of arthritides of unknown etiology beginning before age 16 years and persisting for at least 6 weeks, supposing that all other known causes of arthritis have been ruled out. The results of previous studies have indicated that systemic JIA is associated with abnormalities of the innate immune system rather than the classic autoimmune system, because neither autoantibodies nor strong HLA genetic associations can be demonstrated (3). Indeed, systemic JIA does not behave as an articular disease, and many investigators have shown how its manifestations closely mimic those of autoinflammatory syndromes, with an exaggerated innate immune response leading to recurrent sterile inflammation, phagocyte activation, and oversecretion of proinflammatory cytokines such as interleukin-1 β (IL-1 β), in synergy with endogenous Toll-like receptor ligands, resulting in significant long-term morbidity (4).

Although many investigators agree that the systemic inflammation in systemic JIA is driven mostly by up-regulated innate immune pathways, including IL-1, it remains unestablished whether this is attributable to intrinsic abnormalities in caspase 1 activation or environmental triggers. Pascual et al (5) showed that different innate immunity genes were overworking in patients with active systemic JIA. Moreover, different studies have also revealed the dramatic impact of IL-1 blockade, in the form of either the IL-1 receptor antagonist anakinra or the anti-IL-1 β blocker canakinumab, in the induction of clinical remission in a substantial subset of patients with systemic JIA.

Although we believe that reconsidering the nomenclature of JIA should be approached with caution and global consensus, the newer insights into the pathogenesis and treatment of systemic JIA suggest that this disorder should be

drawn away from the group of juvenile arthritides and definitely included in the group of acquired autoinflammatory syndromes, which day after day continues to enlarge and includes nonhereditary periodic fever syndromes, vascular diseases, and metabolic diseases.

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Reply

To the Editor:

I am grateful for the interest of Drs. Rigante and Cantarini in my recent review of the role of IL-1 in systemic JIA. They highlight, very correctly, the abundant evidence for innate immune dysfunction in this condition and suggest that systemic JIA should be recognized as part of the growing family of autoinflammatory diseases.

This is clearly a very legitimate position and places Drs. Rigante and Cantarini in the company of other authorities who share this view. JIA is an umbrella term that includes a diverse range of clinical phenotypes, and systemic JIA is without doubt the most distinctive of these. As a form of idiopathic childhood arthritis, systemic JIA seems to me to fit comfortably enough under the umbrella, but other ways of grouping these diseases are certainly reasonable.

However, it seems to me that we should not—yet—become too comfortable with the conclusion that systemic JIA is an autoinflammatory disease. In its most precise use, this term encompasses inflammatory diseases that arise through aberrant antigen-independent activation of the immune system. Paradigmatic examples include familial Mediterranean fever (FMF) and the cryopyrinopathies. Like these conditions, systemic JIA is characterized by fever and responds briskly to IL-1 antagonism, although there are also differences. Garden-variety systemic JIA is almost never familial, and monozygotic