Relevance of Interferon-Inducible Protein-16 Rather than Anti-Interferon-Inducible Protein-16 Autoantibodies as a Clinical and Pathogenic Biomarker in Primary Sjögren's Syndrome: Comment on the Article by Baer et al.

Relevance of interferon-inducible protein-16 rather than anti–interferon-inducible protein-16 autoantibodies as a clinical and pathogenic biomarker in primary Sjogren's syndrome: comment on the article by Baer et al

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To the Editor:

We read with interest the article by Baer et al, published recently in Arthritis Care & Research (1), describing high serum levels of autoantibodies against the interferon inducible protein-16 (IFI16) in a subset of patients with primary Sjogren's syndrome (SS). The authors suggested that anti-IFI16 autoantibodies may represent a marker of disease severity, as they were associated with abnormal Schirmer's test results, hypergammaglobulinemia, and antinuclear autoantibodies (ANAs) in the sera, as well as with a higher focus score and presence of germinal center–like structures in salivary gland tissue. In addition, they suggested that IFI16 autoreactivity, essentially directed against an epitope outside the N-terminus, at least in patients with high-titer antiIFI16 autoantibodies, is triggered by elevated IFI16 protein expression in the glands of these patients as detected by immunoblotting in glandular tissue lysates. These results are in agreement with our previously published data showing increased serum levels of both antiIFI16 and IFI16 protein in primary SS patients (2). Our immunohistologic findings also confirmed that IFI16 protein, unlike in normal subjects and those with aspecific sialadenitis, is highly expressed in the salivary gland tissue of these patients with

cytoplasmic mislocalization in acinar and ductal epithelium, peri-/intralesional endothelium, and infiltrating T cells. We believe, however, that the suggested association of anti-IFI16 with disease severity in primary SS deserves some comments. Several clinical, serologic, and histologic elements have been proposed as primary SS disease severity markers in the last years (3 6). However, Schirmer's test is not usually included among these since its positive correlation with glandular infiltration severity is rather poor. Although hypergammaglobulinemia represents a marker of B cell activation and, therefore, can be considered an expression of more active disease, the cutoff employed to identify pathologic values in validated criteria (7) is usually higher (IgG levels 1,600 mg/dl) than that used in the study by Baer et al (1,445 mg/dl), thereby making their data possibly unreliable. Finally, anti-Ro/La autoantibodies, rather than ANAs, are considered highly specific for primary SS, are recognized for their ability to recognize Ro/La autoantigens at the glandular level, and are reliable markers of more severe disease and risk of lymphoma development (6). In this setting, the arbitrarily high cutoff of ANA positivity chosen by Baer and colleagues (1:320, and not the usually employed titer 1:160) may account for their finding of 14 patients with circulating anti-Ro/La autoantibodies without apparent evidence of ANA positivity. The primary SS patient group described by Baer et al is not completely comparable to that recruited in our study. The lower prevalence of anti-Ro/La autoantibodies in the primary SS group described by Baer et al (75.1%) compared to that of our series (83.6%) is easily explainable by the different method of patient recruitment adopted in the study by Baer et al, which considered only sicca syndrome and positive lip biopsy results, but not anti-Ro/La positivity, as unique inclusion criteria. This observation, however, does not account for the slightly higher prevalence of anti-IFI16 in our study (34.3% versus 29%) that confirms, anyway, that only approximately one-third of primary SS patients display circulating anti-IFI16 autoantibodies, the pathogenic and clinical meaning of which remains, however, rather obscure. Some studies, in fact, suggested a protective rather than proinflammatory role of anti-IFI16 autoantibodies (8,9). On the contrary, there is consistent evidence for a pathogenic role of IFI16 protein in triggering and perpetuating inflammation in some chronic inflammatory and autoimmune rheumatic disorders (10).

This fits with the IFI16 overexpression and mislocalization we found in the key cellular players of primary SS, where the main inflammatory process takes place and where the IFI16 protein may act as autoantigen in favoring B cell autoreactivity. In this context, therefore, the association of anti-IFI16 and major glandular infiltration found by Baer and colleagues is not so surprising.

In conclusion, we acknowledge the authors for their interesting results confirming our findings. However, we believe that any definitive conclusion regarding the association between IFI16 autoantibodies and disease severity in primary SS should be drawn with caution. Actually, according to the data described in a number of studies, including those found by Baer et al and us, the IFI16 protein, rather than anti-IFI16 autoantibodies, may represent a relevant target for future investigations focused on pathogenic processes and clinical biomarkers in primary SS.

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