



EDITORIAL

Should we be using organ-specific antigens to understand organ-specific autoimmune disease?

Shen et al. in their article "Novel Autoantibodies in Sjogren's Syndrome (SS)" have identified autoantibodies to several salivary gland antigens. Autoantibodies to salivary gland protein-1 (SP-1) and carbonic anhydrase-6 (CA6) were found initially in a mouse model, and were later found in SS (and idiopathic sicca) patients. Their hypothesis is that these novel salivary gland antigens may appear before SS-A/SS-B and thus, identify a patient population more responsive to treatment.

Among 13 patients who had Sjogren's syndrome (SS) as classified by the American–European Classification Criteria (AECG) [1], 62% had antibodies to SS-A (Ro) or SS-B (La) detected by ELISA assay and confirmed by a line blot assay. Antibodies among the SS patients included anti-SP1 (54%), anti-CA6 (54%), and antibodies to either SP1 or CA6 (69%). Among the SS patients, all patients lacking anti-SS A/SS-B, the anti CA6 or anti-SP1 were present.

They also examined a cohort of 29 patients with "idiopathic" xerostomia and xerophthalmia (i.e., fulfilling only 3 criteria for SS). Antibodies to CA6 or SP-1 were found in patients with negative lip biopsies including several patients who subsequently developed positive minor salivary gland biopsies.

They found that 76% of this "idiopathic" cohort had antibodies to CA6 or SP-1, and propose that the salivary gland-associated antibodies identify a subset of "pre-Sjogren's" antibodies, and thus, may identify a subset for early treatment.

The study is a preliminary report, and the authors note that many more patients' sera are required to determine the predictive value of these antibodies to SP-1 or CA6. However, the paper does point out several interesting issues.

First, our definition of SS depends on the presence of an autoantibody that reacts with an antigen found in Hep-2 cells (i.e., SS-A/SS-B proteins) rather than a salivary gland specific protein. The reactive antigens in Hep 2 cells were cloned by phage display library methods, leading to our current use of SS-A/SS-B [2] in the diagnostic tests in SS and in our diagnostic criteria for SS. Although this sounds like circular logic, diagnostic criteria often serve to "confirm" their own methodology.

Indeed, initial studies by Arnett [3] showed that antibody to SS-A/SS-B correlated more closely with HLA-D associations

than with clinical symptoms. Thus, we need to remember that SS-A and SS-B are produced in all nucleated cells, and so the salivary gland preference exhibited in SS patients cannot be due to these antigens. It is possible that their strong association is due to their HLA-association and their unusual processing in apoptotic blebs in a manner that leads to Toll receptor stimulation. Thus, the paper by Shen et al. returns our attention to a salivary gland-associated antigen.

Over 50 years ago, Bertram and Halberg detected an autoantibody to ductal salivary cells [4]. However, the failure of McSween et al. to reliably detect characteristic antibodies to salivary gland antigens in SS patients led to the early demise of the field [5]. Other antigens were also detected in phage display libraries of Hep-2 or Hela cells [6], but never really gained a trial as diagnostic markers.

Similarly, tear lipocalins made a brief appearance on the diagnostic stage of , but never made the final act [7,8]. The use of antigens first detected in a murine model (and later detected in SS patients) in this paper is reminiscent of the initial detection of antibody to fodrin in a mouse model [9]. The antigen was later detected in a human salivary gland cell line and in the sera of SS patients [10]. Fodrin is also found in other tissues and antibodies may be detected in other conditions.

However, this paper by Shen et al. concentrates on salivary gland specific antigens. In this regard, the diagnostic assay is analogous to anti-thyroid antibodies in thyroid disease, anti-body to acetylcholine receptors in myasthenia gravis, or anti-adrenal specific antibodies in certain types of Addison's disease. Our concepts of pathogenesis of SS would change rather dramatically if the "characteristic" target antigen were salivary gland restricted.

Second, the need for early diagnosis is important in any autoimmune disease. The presence of a characteristic marker before irreversible damage is critical. However, the time required for validation of such markers is difficult. Even in conditions with well recognized diagnostic criteria such as systemic lupus, it was very difficult to identify markers that reliably predicted eventual diagnosis or prognosis of SLE patients [11–13].

The diagnosis for SS is currently at a crossroad with the American College of Rheumatology providing "provisional" acceptance of the SICCA criteria, which requires characteristic autoantibodies (SS-A/SS-B) or minor salivary gland biopsy. Since lip biopsies are not frequently performed in clinical practice, there is increased emphasis placed on autoantibodies in diagnosis.

In parallel, the only clear success in use of the biologic *rituximab* was found in patients with early-stage SS, and the potential importance of a characteristic organ-specific autoantibody is the identification of cohort that reliably identifies disease within that critical early juncture.

References

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