

EDITORIAL

Do we need new autoantibodies in lupus?

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Abstract

Systemic lupus erythematosus (SLE) is a clinically and serologically complex disease that demonstrates clinical, epidemiological and genetic differences among racial and ethnic groups. Some autoantibodies are useful for diagnosis of the illness. Others are clinically important because of associations with a particular manifestation of SLE. Antibodies to RNA helicase A (anti-RHA) comprise a newly described class of SLE autoantibodies. These antibodies have so far been found only in SLE patients and differ substantially in prevalence and nature between Mexican and white American SLE patients. Study of anti-RHA may provide insights into the origin of population differences in SLE.

Systemic lupus erythematosus (SLE) is a complex disease, including serological differences between patients from different ethnicities [1]. Clinically, the range of illness is great - patients may have life-threatening manifestations, or the disease may not be much more than a nuisance. An SLE patient of ours once noted she was sitting next to someone else with SLE in the waiting area, but that they seemed to have nothing in common but the diagnosis. The patient was, understandably, suspicious that two people could share the diagnosis but otherwise not have any shared feature. That one must meet only 4 of 11 criteria to be classified as SLE demonstrates that this is indeed the case [2].

Historically, and perhaps still, the major evidence that SLE is autoimmune is the presence of antibodies in the serum of SLE patients that bind self-structures. Here, too, the disease is extremely complex. Antinuclear antibody is a near-universal finding. Antibodies binding

double-stranded DNA (dsDNA) are not nearly as common but are specific for the disease, and are strongly associated with kidney disease [3]. Antibodies to extractable nuclear antigens (anti-ENA) include anti-nRNP, anti-Sm, anti-Ro (or SSA) and anti-La (or SSB). Numerous other antibodies are found in the sera of patients with SLE, almost too numerous to keep up with.

What, then, might be useful properties of autoantibodies in SLE? First, we should not forget that these antibodies have been useful in biology unrelated to clinical SLE. Anti-nRNP and anti-Sm played a critical part in defining the cellular role of the spliceosome [4]. In fact, without these naturally occurring antibodies to the spliceosome ribonucleoprotein components, we might still be working on how mature mRNA is produced.

How are autoantibodies of use in regards to SLE itself [5]? One area is diagnosis. Clearly this is the case for some specificities. If a patient is not antinuclear antibody positive, then she (occasionally he) has almost no chance of having SLE. On the other hand, some autoantibodies are highly specific for SLE, but not very sensitive. Anti-dsDNA, anti-P and anti-Sm fall into this category in that they are exclusively, or virtually exclusively, found in the sera of persons with SLE, but only among a fraction of these patients (reviewed in [5]). Antibodies might give information about clinical manifestations or prognosis. Anti-dsDNA is associated with kidney disease [3]. In addition, a rising titer of anti-dsDNA can, when partnered with complement measurements, predict exacerbations of the disease [6]. The combination of anti-Ro and anti-La is associated with protection from kidney disease [7]. SLE autoantibodies also may inform us as to, and be involved in, pathogenesis of the illness. Such information might range from molecular mimicry [8] to toll-like receptor binding [9] to autoantibody immune complexes stimulating interferon, a key cytokine in the pathogenesis of SLE [10]. Thus, autoantibodies are especially useful if they are helpful in eliminating or establishing the diagnosis, parsing patients in terms of prognosis or risk, or elucidating the underlying mechanisms of the disease.

In a recent issue of *Arthritis Research and Therapy*, Monica Vázquez-Del Mercado and her colleagues extend their studies of a new autoantigen-autoantibody system,

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namely, antibodies binding RNA helicase A (anti-RHA) [1]. These antibodies were found in the sera of 14 (23%) of 62 Mexican SLE patients using immunoprecipitation of ³⁵S-methionine-labeled cells. Of particular interest, this is much higher than reported previously by this same group, using the same technique, among American SLE patients, where only 6% had the anti-RHA [11]. Other anti-ENA and anti-dsDNA antibodies had about the same frequency in this Mexican cohort as the previously studied white American group. Another difference was the tendency of anti-RHA to be stable in the Mexican SLE patients, but to disappear with time in the white Americans. There were not any important relationships between anti-RHA and disease activity or manifestations, including other autoantibodies.

Thus, this new antibody is of interest because, at least so far, it is found only among patients with SLE. But there are caveats. First, perhaps anti-RHA will be found in patients with other illnesses once testing has taken place in large numbers. There is certainly precedent for this [12]. Second, the investigators used immunoprecipitation techniques that are not easily applied to clinical care. For several serologies, including anti-Sm and anti-dsDNA, development of high-throughput ELISA has led to a loss of disease specificity. That is, ELISA-based determination of anti-Sm or anti-dsDNA gives positive results in patients without SLE; therefore, one of the most important clinical implications of these antibodies is lost.

Anti-RHA is also remarkable because the results of the present work [1] show an ethnic difference. SLE exhibits clinical, epidemiological and genetic differences in patients from disparate ethnicities; however, the etiology of these differences is unknown. If study of anti-RHA can give insights into the origin of such differences, be they genetic or environmental, then these antibodies will be important indeed.

So, do we need more autoantibodies in lupus? The answer is a resounding yes, especially if a new autoantibody-autoantigen system can provide diagnostic or prognostic information, or help us understand the etiology and pathogenesis of the disease in general, or in a particular ethnic or racial group. Thus far, anti-RHA meets these standards.

Abbreviations

dsDNA = double-stranded DNA; ELISA = enzyme-linked immunosorbent assay; ENA = extractable nuclear antigen; RHA = RNA helicase A; SLE = systemic lupus erythematosus.

Competing interests

The author declares that they have no competing interests.

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