Editorial

The role of anti-α-actinin antibodies in the pathogenesis and monitoring of lupus nephritis

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Abstract

Antibodies to double-stranded DNA are important in the pathogenesis of nephritis, a major clinical manifestation in lupus patients. Since earlier diagnosis of renal involvement may lead to better outcomes, identification of the nephritogenic specificity of lupus-associated autoantibodies is important in understanding the disease, while monitoring their titer clinically may serve as an improved biomarker. Based upon work in animal models and cross-sectional human studies, kidney α-actinin was thought to be a plausible cross-reactive target for pathogenic lupus antibodies. Manson and colleagues longitudinally evaluated anti-nucleosome, anti-DNA, and anti-α-actinin antibodies in 16 lupus patients with new-onset nephritis. While anti-nucleosome and anti-DNA antibody levels were significantly associated and correlated with measures of kidney disease, these were not found to be significant with anti-α-actinin antibodies. While in lupus patients the diagnostic use of serum anti-α-actinin antibodies, alone or with other novel biomarkers, is still under investigation, such studies are vital in improving our monitoring of systemic lupus erythematosus patients and in developing new treatment paradigms that meet the continuing clinical challenge of lupus nephritis.

In the previous issue of *Arthritis Research & Therapy*, Manson and colleagues [1] report the results of their valuable study in which they longitudinally followed systemic lupus erythematosus (SLE) patients with new onset of lupus nephritis (LN) while measuring the titers of autoantibodies against α-actinin, nucleosomes, and double-stranded DNA (dsDNA). Based on the known link of these specificities to nephritis, the authors set out to measure the correlation between these three autoantibodies and determine how well each reflected the renal outcome.

Indeed, LN remains a major challenge for clinicians treating lupus patients. Despite the use of potent immunosuppressives, many patients fail to enter into remission, while drug regimens used today can be associated with serious side effects or poor patient tolerance or both [2]. Assuming that earlier diagnosis of LN is associated with better outcomes, investigators are undertaking major efforts to identify serologic markers to assist in diagnosis and follow-up and thereby improve prognosis. Since autoantibodies are crucial in LN pathogenesis [3], identifying the specificities of such nephritogenic antibodies is an important objective.

While anti-dsDNA autoantibodies have been closely linked to the pathogenesis of LN, the mechanisms by which they induce nephritis remain unclear [3,4]. Many authorities believe that the pathogenicity of anti-DNA antibodies is mediated by 'indirect' or 'direct' cross-reactivity. In the indirect model, the binding of anti-DNA antibodies to renal antigens is mediated by a bridge of nuclear antigens, specifically nucleosomes [5]. In contrast, the direct model implies that the binding of anti-nuclear antibodies to DNA/nucleosomes is irrelevant to their nephritogenicity. Rather, it is direct binding to cross-reactive kidney antigens which leads to renal immunoglobulin (Ig) deposition. Strong support for the central role of non-nuclear antigen-binding autoantibodies in the pathogenesis of LN can be found in the seminal observation that less than 10% of the total IgG eluted from kidneys of LN patients was accounted for by antibodies binding to dsDNA, C1q, Sm, SSA (Sjögren syndrome antigen A), SSB, histone, and chromatin [6]. Additional impetus to search for kidney antigens bound by non-dsDNA-specific antibodies is found in a study by Waters and colleagues [7], which demonstrated that abrogation of tolerance to nuclear components may not be required for the development of LN in a lupus animal model.

dsDNA = double-stranded DNA; Ig = immunoglobulin; LN = lupus nephritis; SLE = systemic lupus erythematosus.

In our studies to discover the renal target antigen for pathogenic autoantibodies, we had identified α-actinin in mesangial cells as a plausible candidate in murine lupus. Furthermore, high titers of anti-α-actinin antibodies were present in the serum and kidney eluates of LN mice [8]. Our results confirmed and extended those reported by Mostoslavsky and colleagues [9], who had previously found that the renal pathogenicity of murine lupus antibodies was dependent on direct α-actinin binding. Subsequently, we found that there are *ACTN* polymorphisms in MRL-lpr lupus mice and that enhanced expression of α-actinin may determine the extent of antibody deposition [10]. These observations, together with the demonstration that α-actinin immunization generates nephritogenic autoantibodies [11], strongly suggested a possible role of α-actinin as an important kidney target for pathogenic antibodies and encouraged studies in human disease.

Human studies have shown that anti-dsDNA antibodies from lupus patients with active nephritis displayed an increased binding to α-actinin as compared with patients with no nephritis [12] and that pathogenic human anti-dsDNA antibodies bound strongly to α-actinin [12,13]. Moreover, an increase in serum anti-α-actinin antibodies in lupus patients was associated with a 2.5-fold increase in the prevalence of LN [14]. Finally, levels of anti-α-actinin antibodies correlated with those of anti-DNA antibodies and were significantly higher in patients with renal flares [5]. While these results were quite telling, studies looking at serial determinations of anti-α-actinin antibodies over time were necessary for proving more conclusively a pathogenic as well as a diagnostic role for these autoantibodies in human lupus.

In their prospective study, Manson and colleagues [1] directly compared the titers of anti-α-actinin, high-avidity anti-dsDNA, and anti-nucleosome antibodies in 16 patients with new onset of biopsy-proven LN followed for up to 2 years. In addition, at each follow-up visit, urine protein/creatinine ratio, serum albumin, a renal disease composite score, and renal remission status were determined. Only 2 of 16 patients showed high anti-α-actinin antibody titers at baseline. Whereas a significant association was found between anti-nucleosome and anti-dsDNA antibody levels, with each showing a positive correlation with urine protein/creatinine ratio and a negative correlation with serum albumin, these were not found to be significant with anti-α-actinin antibodies.

How can the discrepancies between these disappointing results and the previous studies be explained? No doubt, a longitudinal design is important, although the number of patients who were studied was relatively low, especially considering that only 7 of the 16 patients had pure proliferative disease (in which the association with pathogenic antibodies is the strongest). The low frequency of α-actinin antibodies in this cohort also has to be considered since in previous studies about 20% of SLE patients had increased anti-α-actinin antibodies [5,14]. Moreover, the lack of a difference in α-actinin antibody titers between patients with LN and controls is in contrast to what was reported previously in two independent cohorts [5,14]. Variations between the different studies could also be ascribed to the drug regimens: all of the patients followed by Manson and colleagues [1] were being treated, and anti-α-actinin antibody titers may decrease with therapy. Finally, perhaps anti-dsDNA antibodies not measured by the assay used in this particular study would show a better correlation with anti-α-actinin antibodies.

Although intensive efforts are being invested into developing a more targeted lupus therapy that would be, if not more effective, at least better tolerated and with fewer side effects, several recent trials examining promising new therapies were not able to demonstrate any major benefit over existing modalities. Therefore, the challenge remains to use our existing treatments more effectively by developing ways to anticipate renal flares and their outcome and to profile kidney pathology without resorting to repeat renal biopsy [2]. While the results reported by Manson and colleagues [1] do not provide support for the widespread application of serial monitoring of anti-α-actinin antibodies in lupus patients at the present time, additional studies to confirm these results in a larger number of patients are surely indicated.

Competing interests

The authors declare that they have no competing interests.

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