Murine and Human Lupus Nephritis: Pathogenic Mechanisms and Theoretical Strategies for Therapy

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Summary: Lupus nephritis is one of the most serious manifestations of systemic lupus erythematosus, and represents one of the criteria implemented to classify systemic lupus erythematosus. Although studied for decades, no consensus has been reached related to the basic cellular, molecular, and immunologic mechanism(s) responsible for lupus nephritis. No causal treatments have been developed; therapy is approached mainly with nonspecific immunosuppressive medications. More detailed insight into disease mechanisms therefore is indispensable to develop new therapeutic strategies. In this review, contemporary knowledge on the pathogenic mechanisms of lupus nephritis is discussed based on recent data in murine and human lupus nephritis. Specific focus is given to the effect of anti–double-stranded DNA/antinucleosome antibodies in the kidneys and whether they bind exposed chromatin fragments in glomeruli or whether they bind inherent glomerular structures by cross-recognition. Overall, the data presented here favor the exposed chromatin model because we did not find any indication to substantiate the anti–double-stranded DNA antibody cross-reacting model. At the end of this review we present data on why chromatin fragments are expressed in the glomeruli of patients with lupus nephritis, and discuss how this knowledge can be used to direct the development of future therapies.

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Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by various aberrant clinical and biological parameters.[1–4] A characteristic phenomenon in SLE is the presence of autoantibodies against double-stranded DNA (dsDNA), histones, nucleosomes, and chromatin.[1,5,6] Renal accumulation of antinuclear antibodies by direct binding to intrinsic renal antigens, or in complex with chromatin antigens, induces severe kidney inflammation analogous to a type II or type III immune-mediated hypersensitivity reaction.[7,8] To understand the nature of the processes that account for lupus nephritis and to develop new specific treatment modalities, we need to determine the nature of the renal target structures for anti-dsDNA antibodies and the processes that account for their exposure.

Since 1957, the year anti-dsDNA antibodies were discovered in an autoimmune context,[9–12] they have been linked to SLE[3,4,13,14] and to lupus nephritis.[7,15] International consensus has concluded that this autoantibody family is central to the pathogenesis of lupus nephritis.[16,17] However, how these antibodies participate in the pathogenesis of lupus nephritis has been and remains controversial.[7] The reason for this is simple. Many patients produce anti-dsDNA antibodies, however, of these patients, many do not develop lupus nephritis. Therefore, a unique property must exist among the antibodies that make them nephritogenic,[16] or, as an alternative, all anti-dsDNA antibodies have nephritogenic potential, but this is manifest only in individuals in whom the chromatin fragments, the target for anti-dsDNA antibodies, are exposed and accessible in glomeruli.[18]

These alternatives have resulted in two main directions in the study of the pathogenesis of lupus nephritis. One is dominated by evidence that the anti-dsDNA antibodies cross-react with intrinsic renal antigens, such as phospholipids,[19–21] laminin or the extracellular matrix,[22–25] entactin,[26] α-actinin,[27] annexin II,[28] ribosomal P protein,[29] vimentin,[30] or others. Whether the antilaminin antibodies detected in the urine of lupus nephritis patients[22] really cross-reacts with DNA was not investigated, however, in other studies, such cross-reactions have been suggested.[23,25] Lupus nephritis may develop only in patients with such cross-reacting anti-dsDNA antibodies.

In the alternative model, antibodies comprising the whole spectrum of specificities of dsDNA, as found in chromatin fragments, such as elongated or highly bent DNA,[31,32] may initiate lupus nephritis, but only when

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chromatin fragments are exposed in the glomeruli. This is not considered in the Witebsky criteria that classify a disease as autoimmune in nature.[33] These criteria require three types of evidence of the pathogenicity of an autoimmune factor: direct evidence from the transfer of a pathogenic antibody and/or a T cell, indirect evidence based on replication of the autoimmune disease in experimental animals, and circumstantial evidence from clinical parameters. If the alternative chromatin model is correct then an additional Witebsky criterion may include showing that chromatin fragments are exposed in affected organs.

Central to understanding these two models is identifying the characteristics of a pathogenic anti-dsDNA antibody, and determining the origin and characteristics of cross-reacting renal antigens and/or chromatin fragments retained in the glomeruli and targeted by anti-dsDNA antibodies. Linked to this is defining the exact role of the silencing of renal DNase I in progressive lupus nephritis.[34–36] This is potentially important because silencing *DNASE1* gene expression is central to chromatin exposure in kidneys.[37,38] Both the cross-reacting and the chromatin models are attractive, and provide a basis to explain how anti-dsDNA antibodies may initiate and maintain lupus nephritis.

In this review, we present data that favor the exposed chromatin model. Experimental and observational data developed in the autoimmune, lupus-prone (NZB × NZW)F1 mouse strain will be compared with analyses of renal biopsy specimens from patients with lupus nephritis. The data are discussed in the context of new causal therapy modalities that are expected to eventually confirm the chromatin model.

SYSTEMIC LUPUS ERYTHEMATOSUS: ONE OR SEVERAL DISEASES?

The etiology of SLE is unknown. Moreover, one may raise the provocative question as to whether human SLE is one disease entity, or a mixture of individual, etiologically unrelated organ manifestations as defined by the American college of Rheumatology[3] or the Systemic Lupus International Collaborating Clinics classification criteria[4] for SLE. The classification criteria do not appear to reflect a common pathogenic process, so it is not clear how genetic aberrancies and biomarkers can be associated with SLE when SLE represents such a divergent mixture of phenotypes. For example, evidence of autoimmunity to nucleosomes, particularly to the individual components of nucleosomes, such as native (ds)DNA and histones, is an important diagnostic criteria for SLE.[3,4,39] In addition, autoantibodies to dsDNA have the potential to induce nephritis.[40,41] However, although anti-dsDNA antibodies have a strong pathogenic potential in SLE, this potential appears to be related only to lupus nephritis (see studies by Seredkina et al,[7] Krishnan et al,[26] Van Bruggen et al,[42] and Berden et al[43]), lupus dermatitis,[44–46] and possibly certain forms of cerebral lupus.[47–49]

MURINE AND HUMAN LUPUS NEPHRITIS: NEW INSIGHTS

We studied the evolution of lupus nephritis by serial examination of kidneys of lupus-prone (NZB × NZW) F1 and observed a two-step process in the pathogenesis of murine lupus nephritis. First, a mild mesangial nephritis developed simultaneously with the appearance of anti-dsDNA antibodies. Later, the disease progressed to a membranoproliferative nephritis with chromatin-IgG immune-complex deposition in the glomerular basement membrane (GBM). As the disease progressed, the *DNASE1* gene was silenced, followed by a profound increase of proteinuria.[34]

In human lupus nephritis, it is not clear whether classes II through IV represent different directions of lupus nephritis, or if the natural course of lupus nephritis is to progress from one class to another, similar to the steady progression seen in the (NZB × NZW)F1 mouse. Mesangial proliferative nephritis (class II) generally has been considered a mild form without progression, and with a 10-year renal survival rate of 100%.[50] However, two recent studies assessing the course of class II lupus nephritis showed progression from class II to class III or IV despite treatment. Lee et al[51] found progression from class II to class III or IV in 5 of 15 patients over a mean of 5 years, and, earlier, Tam et al[52] described poor prognosis, reported as progression in 9 of 19 patients originally diagnosed with class II nephritis. Although these were small studies, and the exact progression rate of class II lupus nephritis has yet to be determined, these data support the continuous progressive model in at least some patients with lupus nephritis.

Murine Lupus Nephritis

Given the fact that nephritis is a serious manifestation of SLE,[7,40,41,53] it is important to determine by which pathways anti-dsDNA antibodies act as pathogenic factors. Parameters that historically have been regarded as important in determining the nephrogenicity of anti-dsDNA antibody subpopulations are antibody avidity for DNA, specificity for unique DNA or nucleosomal structures,[31,32,54–57] as well as cross-reactivity with inherent renal or non-nucleosomal DNA molecules.[23,24,27,58–62]

The murine data were reviewed recently.[2,7,63] In one central study, we focused on the pathogenic processes in kidneys taken at time intervals from lupus-prone (NZB × NZW)F1 mice. For these studies we developed high-resolution techniques that provided evidence