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PAPER

Pathogenic autoantibodies in lupus nephritis

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Lupus nephritis is a major complication of systemic lupus erythematosus (SLE) and is associated with a high rate of morbidity and mortality. While many different immunologic and nonimmunologic factors contribute to disease expression in lupus nephritis, a large body of evidence suggests that the production of anti-DNA antibodies and the formation of glomerular immune deposits are important initial events in the pathogenesis of the disease. This review will summarize our current understanding of the differences between pathogenic and nonpathogenic autoantibodies, the mechanisms by which these autoantibodies induce renal injury and the effector mechanisms which are subsequently activated by the deposited autoantibodies that ultimately lead to the expression of the different lupus lesions. *Lupus* (2005) **14,** 19–24.

Key words: autoantibodies; lupus; nephritis

Introduction

Autoantibody production is one of the hallmarks of systemic lupus erythematosus. Factors leading to their production include breakdown of B- and T-cell tolerance, increased concentrations and abnormal presentation of autoantigens (e.g., nucleosomes) and defects in clearance of apoptotic cells. Variability in these events influences the nature and severity of organ involvement in lupus. In most situations, autoantibodies participate in the initiation of disease activity. The purpose of this review is to summarize current understanding of the role of autoantibodies in the pathogenesis of lupus nephritis with particular focus on the mechanisms that govern antibody pathogenicity. For purposes of this discussion, pathogenic or nephritogenic, is defined as the capacity to cause glomerular or tubular injury as judged by clinical and histologic evaluation of the kidney.

Properties of nephritogenic lupus autoantibodies

After decades of studying antibody profiles, the role of anti-dsDNA antibodies in the pathogenesis of lupus nephritis has been well established.[1–3] A direct pathogenic role for anti-dsDNA is suggested by the correlation of serum antibody levels with nephritis, the temporal association of the rising titers with increased disease activity and the presence of anti-DNA antibodies in glomerular immune deposits in humans and mice with active nephritis. Furthermore, their concentration in glomerular eluates exceeds their concentration in serum in both mice and humans with lupus nephritis.[4] In addition, nephritis can be induced by administration of anti-DNA antibodies to normal mice.[5,6] Nevertheless, the relationship of these autoantibodies to disease is not straightforward since serum levels do not always correlate with disease activity.[7,8] Analysis of murine models provide insights. After transfer to normal mice not all monoclonal anti-DNA antibodies induced glomerulonephritis.[9] Some did not form deposits, some formed deposits, others deposited but did not induce inflammation.[10] Notably, amongst the pathogenic Ig, there were subsets of autoantibodies that produced distinguishable histologic and clinical patterns of disease. For example, some consistently localized to subendothelial regions while others deposited in the mesangium.[11] Collectively, these clinical and experimental observations indicate that not all autoantibodies are nephritogenic; rather, there are qualititative differences among the subsets of lupus autoantibodies that determine their capacity for immune deposition and inflammation and hence make them 'nephritogenic'.[10,12] Consistent with this notion, antibodies eluted from both human and murine lupus

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kidneys can be distinguished from serum autoantibodies by properties of their antigen binding region and isotype. The kidney eluates are predominantly of the IgG isotype[13] and fix complement.[14] Some investigators have demonstrated that the deposited antibodies are more cationic in charge than their serum counterparts[15] however, this has not been a consistent finding. In comparison with serum nonpathogenic autoantibodies, the nephritogenic antibodies are highly crossreactive and react with more than one antigen. This property accounts for their capacity to bind to extracellular antigens (e.g., cell surface, basement membrane). Initial results suggested that affinity for DNA defined pathogenicity, although not all somatically mutated high affinity anti-DNA antibodies are pathogenic.[16–19] Taken together, these observations indicate that pathogenicity is largely governed by properties unique to the antigen binding region and the Ig isotype. The former facilitates deposition, whereas the latter is responsible for recruitment and activation of inflammatory cells.

Mechanisms of immune deposit formation

The precise mechanisms by which autoantibodies form immune deposits have been an area of much debate. Three theories have been proposed: 1) deposition of circulating immune complexes; 2) direct binding to endogenous renal antigens; and 3) direct binding to endogenous antigens localized within the kidney ('planted antigen'). These are not mutually exclusive and all likely contribute to some extent at various times during disease.

The circulating immune complex theory, in which preformed immune complexes are passively trapped within glomeruli, has lost steam as a primary event since transfer of preformed immune complexes has never been recapitulated in lupus or other experimental forms of nephritis. In addition, DNA/anti-DNA complexes are rapidly cleared by the liver, and administration of DNA/anti-DNA complexes to lupus prone mice suppress disease by reducing autoantibody production.[20] Nevertheless, immune complexes have been shown to transiently localize in the glomerulus, typically in the mesangium. Although the deposits are subsequently phagocytosed by endogenous cells, their transient localization may not be inconsequential. In culture, immune complexes stimulate mesangial cells, and in lupus patients this may lower their threshold for activation, accentuation of cytokine release and/or increase in matrix production.[21,22] This situation may be amplified in lupus patients since clearance of immune complexes by phagocytic cells may be impaired, due in part to either reduced numbers of CR1 receptors for complement or functional defects of the receptors on cell surfaces with low binding allelic variants of the Fc gamma receptors.[23,24] So, although they may not initiate inflammation, they likely contribute to amplify inflammation.

Most evidence supports the initiation of immune deposition by *in situ* mechanisms with either antibody binding to intrinsic glomerular antigens including cell surface and basement membrane antigens (cross reactive theory) or circulating autoantigens that localize within the glomeruli (planted antigen theory).

In support of the former, early experiments revealed that pathologic antibodies eluted from both human and murine lupus kidneys bound directly to glomerular extracts.[5,25] Subsequently, many autoantibody-glomerular cell surface and matrix antigen interactions have been described. For example, anti-DNA antibodies have been shown to cross react with laminin,[26] heparan sulfate,[27] and α-actinin 4,[28–30] a protein involved in cross linking the actin cytoskeleton within the podocyte foot process with components of the slit diaphragm.

Other reports have highlighted the planted antigen theory as a major operative mechanism in lupus nephritis. Intracellular antigens released into the circulation after cell death may deposit in various sites within the glomerulus where they can then serve as a nidus for binding by circulating autoantibodies. Most of the recent evidence suggests that nucleosomes are the major autoantigens involved in the *in situ* interactions with autoantibodies.[31] However, both low molecular weight DNA[32,33] and histones have been shown to localize in kidney and serve the same purpose. Furthermore, anti-Ig (i.e., rheumatoid factors) may amplify disease by this mechanism. In support of the central role of nucleosomes, anti-DNA, anti-histone and anti-nucleosome antibodies all have been shown to bind nucleosomes previously localized within glomeruli.[34–36] In this case, the nucleosome–glomerular interaction is facilitated by the relatively cationic charge of the histones and the negative charge of the GBM. Studies with murine and human lupus sera have identified heparan-sulfated glycosaminoglycan as the candidate ligands for this initial nucleosome binding. The binding then presumably exposes the DNA from the nucleosome that can then serve as a planted antigen for anti-DNA antibodies.

Regardless of which mechanism predominates in an individual, both the antigen binding region and the isotype contribute to variations in disease expression among individual patients with lupus nephritis. As previously alluded to, the antigen binding region through specific interactions with different cell surface and basement membrane constituents, (e.g., heparan sulfate, laminin, α-actinin 4) can alter physiology. The ensuing inflammation may also lead to further exposure

of relevant epitopes leading to more immune deposition, inflammation and disruption of the glomerular architecture.

Intracellular penetration of anti-DNA antibodies

Another potential mechanism by which antibodies may inflict injury is via intracellular penetration. Only a small subset of autoantibodies enter cells, and some of these have been shown to alter cell function.[37] One subset of anti-DNA antibodies we identified entered cells and localized in the nucleus. In animals this was associated with glomerular hypercellularity and proteinuria. In cell culture, the autoantibodies inhibited features of apoptosis. Other autoantibodies have been found to have cytopathic effects that vary with their intracellular antigen targets.[38] Extrapolating from studies of artificial introduction of antibodies into cells, it appears that once internalized, antibodies can move to and bind to their target antigen, and in some situations this causes cellular perturbations associated with the function of the ligand. With the aforementioned autoantibodies that inhibit apoptosis, it is tempting to speculate that this could result in either further activation of the autoantibody response or additional organ impairment (i.e., with impairment of apoptosis).

Activation of effector mechanisms

In most instances, deposition of antibody alone is insufficient for the severe and diverse renal pathology characteristic of lupus nephritis. For the pathogenicity, activation of effector mechanisms is required. This is largely influenced by the Fc region of the complexed antibody as well as the location of the deposits. Recent work has contributed significantly to current concepts. For many years, the accepted model of immune mediated injury, based on studies done in the 1950s–1960s involving the Arthus reaction, held that complement activation was responsible for all the effector responses and consequences of immune complex deposition. The advent of contemporary molecular biology tools in the past decade, such as targeted gene disruption and generation of recombinant forms of proteins and antibody inhibitors, has provided novel insights and changed concepts.

The contributions of complement independent mechanisms were derived from observations in mice with targeted disruptions of complement components C3 or C4; they still mounted an Arthus reaction and had normal inflammatory responses.[39] Furthermore, they developed autoimmunity spontaneously despite a lack of these components. This led to consideration of FcR dependent events as primary effectors of antibody-based inflammation.[40]

Fc receptors (FcR), widely expressed on lymphoid and myeloid cells, can both trigger and regulate a diverse array of biological responses after cross linking by the Fc regions of antibodies, and as such, link the antigen specificity to the innate immune response.[41] FcRs exert their function through paired expression of activator (FcγRI, FcγRIII) and inhibitor (FcγRII) receptors. The sum of the activation and inhibitory signals determines the cellular response. For example, cross-linking of activating FcRs can trigger degranulation, phagocytosis, antibody dependent cellular cytoxicity (ADCC), oxidative burst, release of cytokines and other inflammatory cell mediators depending on the cell that is involved. However, signals favoring activation of the inhibitor FcR inhibit these effector responses.

A critical role for Fc receptor engagement in lupus nephritis was demonstrated by Ravetch *et al*. using the spontaneous murine model of lupus (NZB/NZW F1) bearing a deletion of the common FcRγ chain.[42] The generated homozygous FcR$\gamma-/-$ mice are unable to produce the activator IgG Fc receptors, FcγRI and FcγRIII (and the IgE receptor), as the γ chain is essential for the surface expression and cellular signaling. These Fc$\gamma-/-$ mice (with intact inhibitory receptor, FcγRIIb) produced anti-DNA antibodies and circulating immune complexes, and they developed IgG and C3 deposits in glomeruli. However, they did not have proteinuria or histologic evidence of nephritis. The 'uncoupling' of the pathogenic potential of immune complexes from inflammatory consequences by removing FcR engagement supports the conclusions that: 1) deposited immune complexes and C3 are insufficient to trigger effector cell activation; and 2) functional activator FcRs play a pivotal role in mediating immune complex injury in autoimmune disease. These findings were corroborated and extended by several investigators using other murine models. For example, Park *et al*. demonstrated that anti-GBM nephritis was abrogated in FcRγ chain deficient mice despite antibody and complement deposition.[43]

The role of FcRs in autoimmunity is not limited to its triggering of effector cells. The inhibitory FcγRIIB suppresses B cell activation and proliferation by opposing activation through the B cell receptor (BCR).[44] By contrast, activation of B-cells and exaggerated antibody responses occur if either FcγRIIB expression is decreased or signaling is impaired. This can result in loss of tolerance and the development of autoimmunity. In this regard, inactivation of FcγRIIb

in normal mice (C57BL/6) leads to a spontaneous lupus like disease with anti-dsDNA autoantibodies, glomerular immune complexes and severe glomerulonephritis.[45] Interestingly, some autoimmune prone mice such as NZB and MRL show reduced surface expression of FcγRIIB, which has been attributed to polymorphisms in the promoter region of this receptor gene.[46] In this regard, genetic polymorphisms of Fc receptors have also been described in humans. Some of the allelic variants alter the binding of the FcR to the immunoglobulin Fc region, thereby affecting immune complex clearance. In some populations, the low affinity binding polymorphisms confer a higher risk for development of lupus nephritis in comparison to the higher binding variants.

Expression of FcRs on glomerular cells (i.e., mesangial cells) may also contribute to nephritis.[47,48] Cultured mesangial cells express Fcγ receptors when stimulated by IFN-γ and LPS, and immune complexes induced cellular proliferation, matrix synthesis and release of several mediators implicated in the initiation and progression of glomerular injury.

Circumstantial evidence for a role of complement in immune complex mediated injury is provided by the identification of complement components in human renal biopsies and the appearance of complement activation products in the sera. Additional support comes from studies of inhibition of complement activation in experimental models, although the results are conflicting. Administration of anti-C5 antibody near the onset of autoimmune disease in NZB/W mice prevented the development of glomerulonephritis and improved survival.[49] Crry 1-Ig, a soluble recombinant complement regulatory protein (inhibits C3 convertase), inhibited nephritis in MRL-lpr/lpr mice.[50] Comparable results occurred in transgenic MRL-lpr/lpr mice when Crry was overexpressed either systemically or within the kidney.[50] Furthermore, chronic Crry expression downregulated inflammatory cytokine production (i.e., TGF β, TNF) and extracellular matrix expression.[51] By contrast, MRL/lpr mice with a targeted deletion of C3 showed earlier and greater albuminuria and glomerular deposits and nephritis was not ameliorated, indicating complement independent pathways.[52,53] Similarly, C4 deficient B6/lpr mice (that normally have low titer anti-DNA antibodies but no renal disease), developed increased autoantibody production and proliferative nephritis.[54]

In man, genetic deficiencies of early components of the classical pathway (C1q, C4 and C2) predispose these individuals to lupus, although nephritis is atypical in this group.[55] This apparent paradox reflects the different roles of complement in the development and manifestations of systemic autoimmune disease. On the one hand, complement components facilitate the clearance of circulating and apoptotic cell derived autoantigens, thereby helping to maintain tolerance and protect against systemic autoimmune disease. On the other hand, complement components contribute to inflammatory and cytolytic injury once autoantibodies deposit within tissues.

In addition to the roles of complement in immune regulation, there is also evidence that complement regulates FcR expression. Shushakova *et al.*, using a murine lung model of immune complex induced inflammation, demonstrated that C5a, acting through C5aR, influenced FcR expression on alveolar macrophages.[56] The suppression of inhibitor FcR and induction of the activator FcR via C5a enhanced alveolar macrophage response to immune complexes, triggering cytokine release and neutrophil chemotaxis, exacerbating disease. Thus, C5a via its interactions with C5aR may mediate complement-dependent inflammatory reactions by modulating FcR expression. This warrants study in other organs.

Location of immune deposits

In lupus nephritis, the anatomic location of the immune deposits most likely influences both the predominant effector mechanism and the ultimate clinical and histologic manifestations of the disease.[57,58] For example, if immune deposits form in the subepithelial area, as in membranous lupus, the presence of the GBM prevents inflammatory cell recruitment to the site, and thus, the resultant pathology is nonexudative. In this setting, the membrane attack complex (C5b-9), generated from complement activation, mediates most of the injury by direct glomerular endothelial cell injury. This is modulated through hydrogen peroxide production and the upregulation of inflammatory cytokines. This leads to altered glomerular barrier function, significant proteinuria, overproduction of extracellular matrix components and renal scarring. By contrast, if the immune deposit is accessible to the vascular space, such as in the subendothelial and mesangial regions, effector cells are recruited and inflammatory lesions dominate. In the latter situation, activation of resident glomerular cells through similar mechanisms also contributes to the lesions.

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