Autoantibodies: What’s in Their Teeth?

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Serologic identification of circulating autoantibodies has proven useful in the diagnosis of patients with autoimmune disorders. In vitro and in vivo observations suggest that some autoantibodies are more than just serologic markers; they also participate in the pathogenesis of disease. Shining examples of pathogenic autoantibodies are anti-glomerular basement membrane (anti-GBM) autoantibodies found in anti-GBM disease and the Goodpasture syndrome. In 1967, Lerner and colleagues transferred autoantibodies purified from sera of a patient with anti-GBM disease to recipient monkeys and induced glomerulonephritis. Nearly half a century of investigation has served to refine our understanding of these autoantibodies and the havoc they cause. Detection of anti-GBM autoantibodies in patients with glomerulonephritis prompts emergent therapy, and frequently patients on dialysis with persistent anti-GBM antibodies are not eligible for kidney transplantation until their autoantibody titers are reduced to near normal levels.

In this issue of JASN, Olson and colleagues present an intriguing observation of serologic detection of anti-GBM autoantibodies in ostensibly healthy individuals for months if not years before the onset of their anti-GBM disease. This observation is surprising, yet it should not be so, as circulating autoantibodies have been found in healthy individuals who eventually develop other autoimmune diseases. For example, 88% of SLE patients have autoantibodies to at least one autoantigen while clinically asymptomatic. These autoantibodies are detectable in multiple samplings for years before diagnosis. It appears that what tips the balance into the clinical presentation of lupus is accumulation of multiple diverse autoantibodies.

The question that arises with the finding of Olson and colleagues is what triggers the crucial hit that pushes individuals into anti-GBM disease, when they have had years of health with circulating anti-GBM autoantibodies. Explanations to consider include that the reactive sites of these autoantibodies found before the onset of disease are restricted to regions of the α3(IV)NC1 domain of type IV collagen that are nonpathogenic, that is, they do not recognize crucial pathogenic epitopes; that the crucial pathogenic autoantibody is readily available but the target epitope on the autoantigen is hidden; or that these autoantibodies have nothing to do with the pathogenesis of disease. In the case of anti-GBM disease, this last possibility appears remote.

The presence of serologically detectable anti-GBM autoantibodies over years before disease onset compels one to consider what predisposed these individuals to develop disease. Were they naturally occurring autoantibodies, which are known to exist in a number of autoimmune diseases including anti-GBM antibody disease and ANCA vasculitis? Characteristically, these antibodies have low affinity and avidity for their target antigens and thus are less likely to be pathogenic.

The benign nature of naturally occurring autoantibodies makes it more likely that the anti-GBM autoantibodies observed by Olsen and colleagues represent either pathogenic or nonpathogenic autoantibodies, considering that all of the patients in the study eventually developed clinical disease. If these were nonpathogenic, it is possible these autoantibodies were present in the absence of a clinical phenotype because none reacted with a critical epitope required for disease. The pre-existing autoantibodies were lying-in-wait for that final trigger: a response to a molecular mimic or exposure to a complementary protein structure that triggers production of the crucial pathogenic autoantibodies or an alteration in the collagen microenvironment. Fine mapping of epitope specificity would help clarify whether this is the case, but to date, anti-α3(IV)NC1 autoantibodies identified in healthy humans have not been studied in this detail.

A second and more probable possibility is that pathogenic autoantibodies are available for months to years before disease but their target epitope is concealed. Pedchenko and colleagues have demonstrated the conformational nature of collagen molecules in the glomerular basement membrane during active anti-GBM disease. Somehow, a conformation-dependent disease-related epitope is exposed by disassociation of the endogenous hexamer structure of the α3 chain of type IV collagen. The cause of disruption in the hexamer structure is unknown. Do naturally occurring autoantibodies contribute to disruption, or is it due to posttranslational changes, proteolytic cleavage by exogenous environmental factors, or is it a combination of events? Conceivably, asymptomatic autoantibodies reactive to one part of a target antigen could reveal or disrupt autoantigen conformation to expose a cryptic epitope.

Recently, a mechanism underpinning display of critical autoantigens was described that brought into play alterations in epigenetic regulation of the ANCA antigen proteinase 3 (PR3) and myeloperoxidase (MPO) genes. The loss of epigenetic control of these potential antigens results in transcription, likely leading to production of excessive and perhaps aberrant protein. This begs the question of whether changes in these antigens provide a path for production of naturally occurring antibodies that sets the stage for later onset of disease and
moreover, whether this is a direct path for generation of the crucial pathogenic antibodies. To take this one step further, is the relapse and remission phenotype of many autoimmune diseases a consequence of changes in antigen integrity or antigen availability?

The relative rarity of the autoimmune disease most assuredly requires more than a one-hit and probably more than a two-hit phenomena to incite disease. Multiple hits must be required, including a susceptible genetic background (especially HLA genes)\textsuperscript{15} and disregulated T and B cells.\textsuperscript{16–18} Yet the present study, as well as those akin to it, provides critical insights into patient management and eventual novel approaches to treatment. Modern immunosuppressive therapy is aimed at damping down the immune system with drugs including glucocorticoids and alkylating agents or at targeting B cells (rituximab). Perhaps future directions should target understanding the factors that open or close conformational antigens or activate or silence genes that transcribe them. Are the real culprits environmental factors including microbes or toxins that alter antigens and the antibody response to them? In autoantibody diseases, we must consider not only the autoantibody but also the autoantigen to which they are binding.

DISCLOSURES

None.

REFERENCES
