Lupus Nephritis: Toll the Trigger!

Kelly D. Smith

Department of Pathology, University of Washington, Seattle, Washington


Systemic lupus erythematosus (SLE) is an autoimmune disorder that is characterized by the development of autoantibodies against nuclear antigens. These autoantibodies and their cognate antigens form immune complexes that are deposited in the kidneys, lungs, cerebrovasculature, serosal surfaces, and skin, leading to the active and chronic sequelae of this disease. In the past several years, elucidation of the immunologic mechanisms that drive this peculiar autoantibody response has been aided by studies in innate immunity and in particular the Toll-like receptors (TLR). In the current issue of JASN, Pawar et al. (1) provide exciting data that activation of the innate immune system with a specific nucleic acid agonist for TLR-9 induces lupus nephritis in genetically predisposed mice. These data further strengthen the emergence of the innate immune system as a central player in inducing autoimmunity, specifying the nature of the autoantibody response, and regulating the inflammatory activity in the target organs of SLE.

Why Nuclear Autoantigens?

Several recent studies have shed light on the antigen specificity of the SLE autoantibody response that characterizes SLE. The SLE autoantigens, which include double- or single-stranded DNA (ssDNA), histones, chromatin, and ribonucleoproteins such as Smith antigen, are composed of or intimately associated with nucleic acids. Nucleic acid recognition is a prime strategy for the innate immune system’s detection of microbial pathogens, especially viral pathogens (2,3). The Toll-like receptor family of innate immune receptors is the best characterized and has four receptors that are capable of recognizing nucleic acid ligands: TLR-3 recognizes double-stranded RNA (dsRNA); TLR-7 and TLR-8 recognize ssRNA; and TLR-9 recognizes CpG rich, unmethylated DNA (4). All of these receptors require endocytosis of their ligands for proper recognition, and it is thought that microbial pathogen specificity is determined by the combination of requirements for endocytosis and specific nucleic acid motifs or structures (5). However, the ability to differentiate pathogens from self is only relative, and in the right context, self-nucleic acids, in the form of chromatin, RNA, or RNA–protein complexes, also can activate these receptors (6–13). Herein lies the rub. Certain pathologic conditions may lead to an excess of extracellular self-nucleic acids and nucleic acid–protein complexes, which gain access to the endocytic compartment and activate Toll-like receptors. Thus, endogenous nucleic acids may function as adjuvants and promote autoantibody responses to the TLR ligands themselves (ssDNA and dsDNA), associated proteins (histones and Smith antigen), or nucleic acid–protein complexes (chromatin and small nuclear ribonucleoproteins). In effect, the ligand specificity of the innate immune receptors dictates the antigen specificity of the autoantibody response.

A similar mechanism may promote rheumatoid factor production in the setting of autoimmune diseases and infections. Rheumatoid factor production can be elicited by immune complexes that contain IgG and chromatin (14,15). Similarly, in the setting of infection, IgG immune complexes may contain microbial nucleic acids, as has been demonstrated for hepatitis C virus infection (16). Thus, IgG immune complexes that contain either endogenous or exogenous (i.e., viral) nucleic acids may promote rheumatoid factor production and cryoglobulinemia (17). In addition, such immune complexes that contain TLR agonist activity also may promote local inflammation at the site of immune complex deposition (17).

Infectious Triggers to Autoimmunity

Infections commonly are associated with low levels of transient autoantibodies and autoreactive T cells (18–21). This suggests that the vast majority of us experience subclinical and transient loss of self-tolerance during infections, when the innate and adaptive immune responses are highly activated. In this issue of the JASN, Pawar et al. (1) use the MRL<sup>lpr/lpr</sup> mouse model of lupus to demonstrate that activation of the innate immune system in genetically predisposed individuals can trigger disease onset. The studies of Pawar et al. establish that stimulation with CpG DNA, a specific agonist for TLR-9, induces disease in mice with a lupus-prone genetic background. Other TLR agonists tested include poly-I:C, a synthetic dsRNA agonist for TLR-3, and imiquimod, a small molecule agonist for TLR-7; neither of these agonists was capable of inducing lupus in MRL<sup>lpr/lpr</sup> mice.

A major implication of the findings of Pawar et al. is that CpG DNA and TLR-9 have properties that differ from the other agonists and TLR, and that microbes that are capable of activating TLR-9 may be potent inducers of SLE. The ability of CpG DNA to induce lupus was multifactorial and correlated with its superior ability to induce B cell IL-12p40, B cell proliferation, anti-dsDNA antibodies, and type I IFN (1). The selectivity for
CpG is a bit surprising, given the overlap in signaling properties and biologic activities for these TLR. All of these receptors are capable of inducing type I interferons, which have been linked closely to autoimmune disease and lupus in particular (22), suggesting that activation of type I IFN pathway is not sufficient to induce disease. TLR-3 is the most different among these receptors in terms of signaling and cellular distribution, yet TLR-7 and TLR-9 share many similarities in signaling and cellular distribution (4). Both TLR-7 and TLR-9 are expressed on B lymphocytes, a critical feature for the induction of nucleic acid–specific autoantibodies; however, Pawar et al. (1) found that only CpG DNA was capable of potent activation of B lymphocyte proliferation and anti-dsDNA IgG2a.

Other model systems have demonstrated that TLR-9 contributes to the production of specific autoantibodies, but, in contrast to the findings of Pawar et al., TLR-9 has been found to protect against the development of lupus nephritis (6,23–25). One clear difference between these studies and those of Pawar et al. is that the former studies focused on endogenous agonists of TLR-9, whereas Pawar et al. examined the activation of TLR-9 with an exogenous agonist. Therefore, many factors, such as the nature and the dosage of the agonist, timing of exposure, and genetic background, are likely to influence disease.

Testing different agonists, including endogenous or infectious agonists, dosages, and model systems, may unveil roles for other nucleic acid–specific TLR. In fact, recent studies in other model systems support a role for TLR-7 in the generation of autoantibodies and lupus nephritis (24,26). In addition, the γ-linked autoimmune accelerating (yaa) locus has been mapped to a translocation and duplication of the TLR-7 locus, indicating that gene dosage and expression of TLR-7 also can contribute to SLE (27,28).

Conclusion

Pawar et al. (1) make an important contribution to the concept that exogenous stimuli may induce autoimmune diseases and that these function through activating specific innate immune pathways. This study also adds to the authors’ earlier studies that demonstrated that activation of the innate immune system with nucleic acid–specific agonists augments lupus nephritis in mice with established disease (29–32). It will be interesting to see how these findings apply to other autoimmune and acquired diseases, in which self-tolerance, graft tolerance, and inflammation may be modulated by secondary environmental influences.

Acknowledgments

I am supported by National Institutes of Health grants AI062859 and AI052286.

References

17. Smith KD, Alpers CE: Pathogenic mechanisms in mem-
branoproliferative glomerulonephritis. *Curr Opin Nephrol Hypertens* 14: 396, 2005


See the related article, “Ligands to Nucleic Acid–Specific Toll-Like Receptors and the Onset of Lupus Nephritis,” on pages 3365–3373.