More Targeted Treatments for Lupus Nephritis: Is the Future (Nearly) Here?

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The adaptive arm of the immune system confers substantially increased power, specificity, and memory to the arsenal with which we control infection. However, it brings increased complexity and the potential for antigens irrelevant to infectious threats to induce damaging immune responses. The consequences of significant reactivity to innocuous environmental antigens or self-antigens are allergy or autoimmunity. Systemic lupus erythematosus (SLE), the prototypic systemic autoimmune disease, results from losing tolerance to a range of self-antigens, particularly nuclear proteins. The potentially life-threatening and relapsing expression of disease makes more severe forms of SLE a debilitating condition from which to suffer. Standard treatments for severe, diffuse, proliferative lupus nephritis lack specificity and have a significant side-effect profile. Two studies in this issue of JASN may point the way toward more specific therapies for this disease (1,2).

Recent developments in understanding both the biology of an immune response and the pathogenesis of SLE and lupus nephritis may lead to more effective, targeted treatments. Human lupus results from multiple genetic susceptibilities and environmental effects (3). These range from the combined influence of abnormalities in the maintenance of immunological tolerance, to autoantibody formation and the participation of a variety of immune effectors in renal disease. Advances in understanding the immunobiology of links between innate and adaptive immunity (4) are informing our understanding of the maintenance of tolerance and its breakdown in autoimmunity. Dendritic cells (DC) play a central role in the development of adaptive immunity to infectious agents, in maintaining tolerance and conversely in the loss of tolerance leading to autoimmunity (5). Pattern recognition receptors on DC, Toll-like receptors (TLR) bridge innate and adaptive immunity (6). Different TLR recognize different motifs and help trigger responses to different pathogens by activating DC with upregulation of co-stimulatory molecules and cytokine production. Clinical observations suggest that infection often precedes the development or relapse of an autoimmune disease, raising the question whether TLR engagement and signaling may be relevant to lupus and other autoimmune diseases. In SLE, TLR9 may be important in disease pathogenesis (7–9). TLR9 recognizes CpG DNA, a hypomethylated form of DNA found predominantly (although not exclusively) in invertebrates (10). CpG DNA has the capacity to activate potentially autoreactive B cells as well as (in humans) plasmacytoid DC (9). Recent evidence suggests that in susceptible individuals aberrant activation of TLR9 either by hypomethylated self-DNA, found in cells from patients with SLE (11), or by viral CpG DNA may play a role in triggering disease (7,8), inducing T helper 1 (Th1) responses and isotype-switching to more injurious autoantibody production.

Effector responses in lupus nephritis unfortunately involve a range of damaging immune mediators. Abnormal B cell responses and humoral factors are important, including the involvement of circulating immune complexes and antibody responses to planted self-antigens or constitutive components of the kidney. Antibodies may induce injury by their deposition alone, but their links with innate effector activation by Fc-dependent activation of complement and macrophages provide greater injurious power (12,13). Although Th1- and Th2-type responses demonstrate heterogeneous patterns of involvement in SLE (14), in severe lupus nephritis there is growing evidence for the involvement of effector T cells that have the capacity to activate macrophages locally, potentially by IL-12p40– and possibly IL-18–dependent stimulation of IFN-γ (a type II IFN) (15,16).

Careful observations of disease in humans and advances in basic immunobiology suggest hypotheses that can be tested only in relevant experimental models. One commonly employed animal model of lupus is the MRL1pr/lpr mouse, possessing a spontaneous fas mutation that, when linked to the MRL background, develops systemic autoimmunity (17). Although humans with lupus do not have this mutation, the MRL1pr/lpr mouse shares similarities in effector mechanisms of injury with human lupus nephritis, making it a potentially useful tool in defining mechanisms of disease and potential therapies. The two articles in this edition of JASN (1,2) both use the MRL1pr/lpr mouse as a model of lupus nephritis. The first report, by Patole et al. (1), uses synthetic G-rich DNA in an intervention study to block the effects of hypomethylated DNA
on TLR9. Administering G-rich DNA from 11 wk (before clinical renal disease) reduced antibody deposition, cellular proliferation, interstitial infiltrates, and injury in the kidney and lung. In vitro data implied inhibitory effects both on effector macrophages and directly on B cell proliferation. Given our knowledge of TLR9 biology, G-rich DNA is likely to have affected DC as well as macrophages and B cells. Another recent report described TLR9<sup>−/−</sup>MRL<sup>lpr/lpr</sup> mice, finding that whereas endogenous TLR9 promotes anti-dsDNA autoantibody formation and is relevant to disease pathogenesis, TLR9 deficiency did not affect the severity of renal disease (18). Despite these somewhat conflicting results, TLR9 inhibition has potential in the treatment of lupus nephritis. If effective, blocking a single TLR in human SLE is an attractive strategy, as immune responses to most pathogens remain largely intact, lessening the risk of immunosuppression-induced infection.

The second paper in this issue of JASN describes amelioration of lupus nephritis with markedly reduced mortality in MRL<sup>lpr/lpr</sup> mice treated with IFN-β (2). Adapting a therapy already used for another disease (multiple sclerosis) for use with SLE is an attractive proposal. Although functional data in genetically deficient mice are conflicting (19,20), it has been hypothesized that type I IFN promote systemic autoimmunity (21). Nonetheless, Schwarting et al. found that IFN-β had strikingly protective effects that were evident when IFN-β treatment was started relatively early in the disease or later, when renal disease was well established (2). IFN-β reduced renal IgG3 (a complement-fixing and macrophage-recruiting subclass) deposition, reduced local IFN-γ and TNF gene expression, and also possessed local and systemic antiproliferative effects. Evidence from humans and mice suggest severe disease, particularly ISN/RPS Class IV lupus nephritis in humans is associated with a high IFN-γ-producing phenotype (22,23), implying that IFN-β may find a place in treating severe proliferative forms of lupus nephritis. It remains a little difficult to clearly reconcile how two approaches, one involving TLR9 blockade (leading to reduced type I IFN production), the other involving the administration of a type I IFN, can both result in disease protection. There are some differences in both TLR9 and type I IFN biology between mice and humans (24). However, one advantage of murine models of immune disease, compared with other species, is the vast knowledge of the (overall relatively minor) differences between the immune systems of mice and men (24), with the resulting ability to take these differences into account when evaluating advances in knowledge.

There remain several major hurdles before more effective and targeted therapies are delivered to people with lupus nephritis. Different combinations of more targeted agents might need to be employed at different times during the disease. A clearer understanding of disease pathogenesis and its variable manifestations is important, as are well-designed, multicenter, clinical trials enrolling carefully selected subgroups of patients with lupus nephritis (25). Together, these approaches hold promise for the future in the translation of key basic discoveries to better outcomes for patients with lupus nephritis through hypothesis-driven research using relevant models.

References