CLINICAL IMPLICATIONS OF BASIC RESEARCH

Basophils and Nephritis in Lupus

Srini V. Kaveri, D.V.M., Ph.D., Luc Mouthon, M.D., Ph.D., and Jagadeesh Bayry, D.V.M., Ph.D.

Systemic lupus erythematosus (SLE) is a complex systemic autoimmune disease that predominantly affects the kidneys in the form of lupus nephritis, although multiple organs can be involved. Lupus nephritis is characterized by the deposition in glomeruli of immune complexes formed by IgG, IgM, and IgA autoantibodies (which collectively are called antinuclear antibodies). These autoantibodies are directed toward ubiquitous nuclear antigens, particularly double-stranded DNA.[1] Deposition of these complexes can result in renal failure and even death.

Several mechanisms are known to contribute to the pathogenesis of lupus nephritis, including those mediated by type 1 helper T (Th1) and type 17 helper T (Th17) cells.[2] Although humoral responses in the form of autoreactive antibodies (also known as immunoglobulins) are effector mediators of lupus nephritis, and the presence of IgE autoantibodies has been reported in some patients, the way in which type 2 helper T (Th2) cells and B cells are activated in the pathogenesis of lupus nephritis has not been clear.

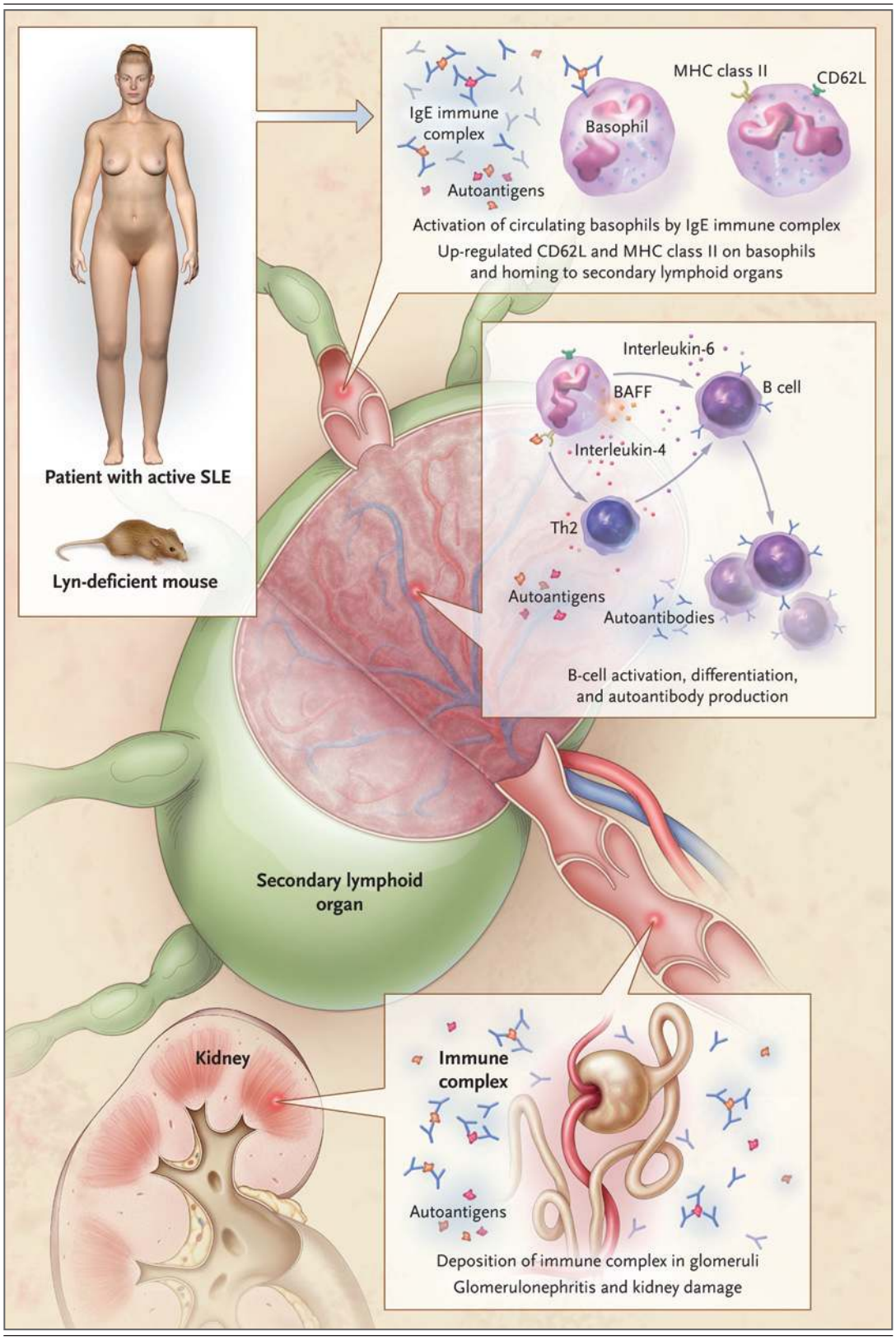
Charles and colleagues[3] shed some light on the question through experiments involving mice with "hyperactive" B cells. Specifically, Lyn, a protein tyrosine kinase that negatively regulates B-cell activation, was absent in these mice. Autoimmune disease developed spontaneously in the mice fairly late in life (at 32 to 40 weeks). This disease shared features with SLE: the mice had anti–double-stranded DNA antibodies, deposition of immune complexes in glomeruli, and kidney damage. In additional experiments with other types of knockout mice, Charles et al. concluded that lupuslike nephritis and the production of antinuclear antibodies and anti–double-stranded DNA immunoglobulins in the Lyn-deficient mice were dependent on both interleukin-4 and IgE (Fig. 1), thus suggesting a role for the Th2 environment. This conclusion shone the spotlight on basophils and mast cells, the two major cell types implicated in Th2-dependent pathogenesis. The authors observed that the induced deficiency of mast cells in the Lyn-deficient mice did not modify the autoimmune process, whereas a depletion of basophils led to markedly reduced numbers of circulating autoreactive IgGs, splenic plasma cells, and levels of proinflammatory mediators (such as interleukin-4) in the kidneys.

How then would basophils promote lupus nephritis? Basophils express FcεRI (a high-affinity receptor for IgE antibodies), the binding of which (by the IgE immune complex) leads to activation of basophils. Charles et al. found that Lyn-deficient mice indeed contained autoreactive IgE and IgE immune complex in the circulation that both mediated the activation of basophils and their homing to secondary lymphoid organs. Through their secretion of interleukin-4 in these organs, the basophils promote Th2 differentiation (Fig. 1). Th2 cells, in cooperation with interleukin-6 and B-cell–activating factor (bound to the basophil

Figure 1 (facing page). The Basophil and Lupus Nephritis.

Charles et al.[3] recently described a study providing support for a model of pathogenesis of nephritis in systemic lupus erythematosus (SLE). IgE-containing immune complexes in both mice with "hyperactive" B cells (Lyn-deficient mice) and persons with SLE trigger circulating basophils to express a secondary lymphoid organ–homing receptor (CD62L, also known as L-selectin) and the antigen-presenting molecule, major-histocompatibility-complex (MHC) class II. In secondary lymphoid organs, these activated basophils secrete interleukin-4 and thus promote type 2 helper T (Th2) cell differentiation. Th2 cells — in cooperation with basophil-derived interleukin-6 and basophil membrane-bound B-cell–activating factor (BAFF) — enhance B-cell differentiation and survival and production of autoreactive antibodies. The immune complexes of which these autoreactive antibodies are part are deposited in glomeruli and cause lupus nephritis.

The New England Journal of Medicine
Downloaded from nejm.org at MICHIGAN STATE UNIV LIB on February 7, 2015. For personal use only. No other uses without permission.
Copyright © 2010 Massachusetts Medical Society. All rights reserved.



The New England Journal of Medicine
Downloaded from nejm.org at MICHIGAN STATE UNIV LIB on February 7, 2015. For personal use only. No other uses without permission.
Copyright © 2010 Massachusetts Medical Society. All rights reserved.

plasma membrane), enhance B-cell differentiation and survival and the production of autoreactive antibodies. The immune complexes formed by these autoreactive antibodies are deposited in glomeruli and cause lupus nephritis. Consistent with this model is the observation by Charles et al. that, similar to Lyn-deficient mice, persons with active SLE had elevated serum levels of anti–double-stranded DNA IgE and activated basophils in the circulation, lymph nodes, and spleen.

Collectively, these results suggest that basophils, interleukin-4, and IgE mediate the pathogenesis of glomerulonephritis by promoting the Th2 environment and activating autoreactive B cells. However, the authors did not determine how basophils are activated in the early phase of disease flare in the absence of autoreactive IgE.

How do these findings extend our knowledge of the pathogenesis of lupus nephritis? What are the limitations of these results? IgE autoantibodies are detected in about 30% of patients with SLE[4]; thus, the Lyn-deficient mouse is unlikely to model SLE in the majority of affected persons. The study by Charles et al. raises the question of whether patients should be classified according to their Th subgroups and whether a therapeutic approach should be devised accordingly. Th1 and Th17 cells also have been implicated in the pathogenesis of lupus nephritis in animals and humans. Further, the phenotype of nephritis varies depending on the Th subgroup involved: a Th1 response is associated with diffuse proliferative lupus nephritis, whereas a Th2 response is associated with membranous lupus nephritis.

A study of genes (such as *IL4*) that govern Th2 and basophil functions might further strengthen these observations and possibly elucidate the reasons for the severity of SLE in certain populations, such as blacks. Lacking in the authors' investigations is a test of the role of type I interferon, a cytokine with a key role in the pathogenesis of SLE.

Clinical trials have shown an uncertain efficacy of B-cell–targeted therapies such as anti-CD20 monoclonal antibodies (rituximab) in lupus nephritis — possibly reflecting heterogeneity in pathogenesis.[2] Further, phase 2 and phase 3 studies involving persons with generalized SLE have indicated the clinical efficacy of antibodies (belimumab) against B-cell–activating factor (also known as B-lymphocyte stimulator, or BLyS) in a subgroup of patients. The results reported by Charles et al. suggest that, in addition to affecting B cells, belimumab may affect therapy by depleting basophils (which contain membrane-bound B-cell–activating factor). It is therefore possible that rituximab or belimumab, in combination with therapies that suppress the production of IgE or the activation and homing of basophils to the lymph nodes and spleen, may benefit some persons with lupus nephritis.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Institut National de la Santé et de la Recherche Médicale, Centre de Recherche des Cordeliers, Université Pierre et Marie Curie, and Université Paris Descartes (S.V.K., J.B.), and Université Paris Descartes, Institut National de la Santé et de la Recherche Médicale, Institut Cochin and Pôle de Médecine Interne, Assistance Publique–Hôpitaux de Paris (L.M.) — both in Paris.

1. Rahman A, Isenberg DA. Systemic lupus erythematosus. N Engl J Med 2008;358:929-39.
2. Crispín JC, Liossis SN, Kis-Toth K, et al. Pathogenesis of human systemic lupus erythematosus: recent advances. Trends Mol Med 2010;16:47-57.
3. Charles N, Hardwick D, Daugas E, Illei GG, Rivera J. Basophils and the T helper 2 environment can promote the development of lupus nephritis. Nat Med 2010;16:701-7.
4. Atta AM, Santiago MB, Guerra FG, Pereira MM, Sousa Atta ML. Autoimmune response of IgE antibodies to cellular self-antigens in systemic lupus erythematosus. Int Arch Allergy Immunol 2010;152:401-6.

Copyright © 2010 Massachusetts Medical Society.

The New England Journal of Medicine
Downloaded from nejm.org at MICHIGAN STATE UNIV LIB on February 7, 2015. For personal use only. No other uses without permission.
Copyright © 2010 Massachusetts Medical Society. All rights reserved.