A pathophysiology-based approach to the diagnosis and treatment of lupus nephritis

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Lupus is no longer an unknown chameleon of medicine. Significant progress has been made on unraveling the pathogenesis of lupus and lupus nephritis, and how to treat the disease. Here we provide an update on the pathophysiology of lupus and its related kidney disease, consider areas of controversy in disease management, and discuss the unmet needs of lupus nephritis and how to address these needs. We focus on rethinking how innovative therapies for lupus nephritis should be evaluated and evolving strategies to more efficiently mitigate irreversible nephron loss in patients with lupus nephritis.

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The diagnosis of lupus nephritis (LN) implies significant morbidity and mortality, especially if LN cannot be controlled and ongoing loss of nephrons occurs. This is illustrated by a recent outcomes analysis of an inception cohort of 1827 new systemic lupus erythematosus (SLE) patients followed up from 1999 to 2012.[1] The cohort was 89% women, of which were 49% white, 17% black, 15% Asian, and 15% Hispanic. The overall incidence of LN in this population was 38%. After adjusting for sex, enrollment age, and race/ethnicity, the hazard ratio for death (vs. no LN) was 3.2-fold, and the 10-year cumulative incidence of end-stage renal disease (ESRD) and death among the LN patients was 10.1% and 5.9%, respectively. Although significant progress has been made in understanding the pathogenesis of SLE, management of LN remains unsatisfactory. In this review we focus on recent advances in the pathophysiology of LN and how to further improve LN management and outcomes using these advances.

Central avenues in the pathophysiology of SLE and SLE-related kidney diseases

Autovaccination against nuclear antigens. The central paradigm of SLE is the loss of immune tolerance to nuclear autoantigens, based on bypassing checkpoint mechanisms that normally assure self-tolerance.[2] Checkpoint mechanisms include, for example, avoidance of nuclear material exposure to immune recognition receptors via strict compartmentalization to the intracellular space, apoptotic rather than necrotic cell death, rapid phagocytosis of dead cells, and masking of any potential autoadjuvant activity of self-nucleic acids, for example by the methylation of immunostimulatory RNA and DNA sequences.[3] The genetic heterogeneity of the global population implies that everyone maintains immune tolerance a bit differently,[4] which is also supported by a variable prevalence of SLE in different populations. Patients with SLE carry an unfortunate combination of genetic variants that compromises immune tolerance to nuclear material at many of the aforementioned checkpoints, often at the same time. Importantly, each patient has his or her own combination of genetic susceptibilities, and therefore SLE is usually not monogenic but is a polygenic disorder inherited as a Mendelian trait.[4] Familial SLE or sporadic monogenic SLE does occur but is rare and only seen when a single (mutation-like) gene variant elicits a very prominent effect on tolerance, such as complement C4 or TREX1 deficiency.[5,6] Therefore, SLE is a clinically defined syndrome with several causes rather

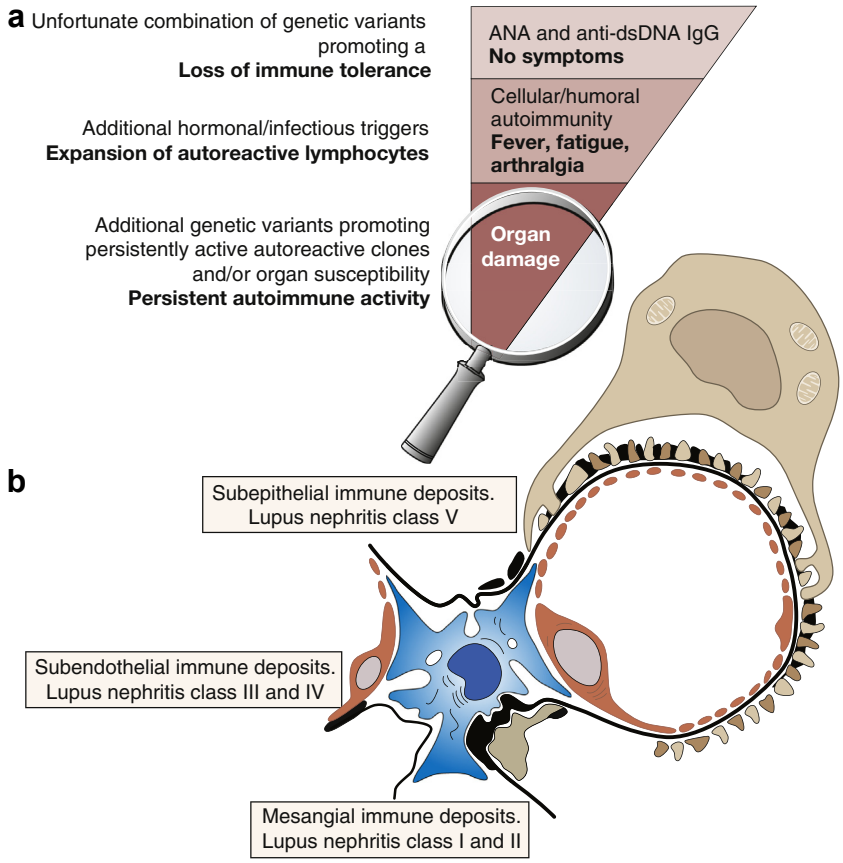

Figure 1 | Pathogenesis of lupus nephritis. Lupus nephritis develops in individuals with an unfortunate combination of genetic variants that compromise the maintenance of immune tolerance to endogenous nuclear material (**a**). The consequence of tolerance loss is autovaccination and lifelong persistence of antinuclear antibodies (ANA), indicating persistently active autoreactive T- and B-cell clones. Only a subset of patients develops clinical symptoms, often upon (viral) infections or hormonal influences that provide an unspecific stimulus for the expansion of these autoreactive lymphocyte clones. The symptoms depend on interferon-alpha release, hence they are unspecific just as in any viral infection. A further subset of patients develops organ manifestations such as lupus nephritis, which depends on the presence of additional susceptibility genes, some of which affect the kidney itself, whereas others drive persistent systemic inflammation and autoimmunity. The inverted triangle indicates the prevalence of the respective stage of the syndrome. Inside the kidney, lupus nephritis is an immune complex glomerulonephritis (**b**). Other types of renal injury may occur in patients with lupus either alone or with lupus nephritis, including thrombotic microangiopathy and renal vasculitis (not shown). Immune complexes can deposit in the subendothelial, mesangial, or subepithelial compartments of the glomerulus. The location of immune complex accumulation defines the different histopathological classes of lupus nephritis according to the current International Society of Nephrology/Renal Pathology Society classification. Because these classes differ in terms of prognosis and management, a kidney biopsy is usually required. dsDNA, double-stranded DNA.

than a disease with a single cause.[7] Hormonal or X-chromosomal factors certainly play an important role as the male-female ratio of SLE is 1:9. A unifying pathway present in every SLE patient is the overt autovaccination/immunization to nuclear material exemplified by the presence of antinuclear antibodies.[7] This implies, potentially, that lifelong immune memory is established in the memory T cells of lymphoid organs and in long-lived plasma cells in the bone marrow.[8] The concept of autovaccination is useful because patients can understand that after autovaccination has occurred their immune systems will remain primed like after other vaccine shots, and so there is no cure for SLE but lifelong monitoring and suppression of autoimmune disease activity are necessary.[8] The diagnostic hallmark of circulating antinuclear antibodies consists of various specificities depending on the dominant antigens during the autovaccination process.[7] This humoral autoimmunity is accompanied by less clinically evident expansion of autoreactive T cells and T cell–mediated autoimmunity. Epitope spreading can cause additional autoimmune manifestations such as secondary Sjogren's syndrome or antiphospholipid antibody syndrome in patients with lupus.[9]

Lupus autoantigens trigger immune responses and symptoms similar to viral infection. Loss of immune tolerance and antinuclear antibodies production does not necessarily produce any clinical symptoms (Figure 1a). Often, however, immune recognition of endogenous nucleic acids via Toll-like receptors 7 and 9 induces interferon-α–dependent antiviral immunity, which manifests clinically as fatigue, fever, arthralgia, and myalgia, as may be seen in any viral infection.[10–12] This central role of antiviral immunity in the pathogenesis of SLE has been referred to as "pseudoantiviral immunity."[13] SLE activity can be influenced by environmental factors that contribute to DNA unmasking (certain drugs)