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REVIEW

Future Perspectives on Pathogenesis of Lupus Nephritis

Facts, Problems, and Potential Causal Therapy Modalities

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Divergent incommensurable models have been developed to explain the pathogenesis of lupus nephritis. Most contemporary models favor a central role for anti-chromatin antibodies. How they exert their pathogenic effect has, however, endorsed conflicts that at least for now preclude insight into definitive pathogenic pathways. The following paradigms are contemporarily in conflict with each other: i) the impact of anti—double-stranded DNA (dsDNA) antibodies that cross-react with inherent renal antigens, ii) the impact of anti-dsDNA antibodies targeting exposed chromatin in glomeruli, and iii) the impact of relative antibody avidity for dsDNA, chromatin fragments, or cross-reacting antigens. Aside from these three themes, the pathogenic role of T cells in lupus nephritis is not clear. These different models should be tested through a collaboration between scientists belonging to the different paradigms. If it turns out that there are different pathogenic pathways in lupus nephritis, the emerging pathogenic mechanism(s) may be encountered with new individual causal therapy modalities. Today, therapy is still unspecific and far from interfering with the cause(s) of the disorder. This review attempts to describe what we know about processes that may cause lupus nephritis and how such basic processes may be affected if we can specifically interrupt them. Secondary inflammatory mechanisms, cytokine signatures, activation of complement, and other contributors to inflammation will not be discussed herein; rather, the events that trigger these factors will be discussed. *(Am J Pathol 2016, ■: 1—11; http://dx.doi.org/10.1016/j.ajpath.2016.06.026)*

Pathogenesis—Background and Present Status

Q7 Lupus nephritis represents the arrowhead among pathogenic manifestations in systemic lupus erythematosus (SLE),[1—4] because it is dangerous, but also because it is scientifically challenging to comprehend its nature.[1,5—7] This situation prevents us from developing therapy strategies that attack the basic pathogenic processes beyond today's therapy regimens.[8—10] In the upcoming sections, contemporary status of the pathogenesis of SLE and lupus nephritis will be reviewed and discussed, and new causal therapy modalities will be suggested.

Pathogenesis of the Autoimmune Syndrome SLE—A Central Role for Anti-dsDNA Antibodies?

One central element when we discuss pathogenic processes in SLE is antibodies to double-stranded DNA (dsDNA) and chromatin structures. Anti-DNA antibodies were, however, first described in 1938 to 1939 in patients with

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infections,[11–14] as reviewed by Rekvig.[15] Approximately two decades later, they were described in the autoimmune syndrome SLE.[16–19] Since then, their role in SLE, rather than in infections and malignancies,[15] has been extensively studied in two contexts: diagnostics and pathogenicity.[15] However, the pathogenesis of SLE is still poorly understood,[20,21] and may even remain unclear because SLE, as classified today, is not linked to any unifying origin or pathogenic process. In fact, if we use the 1982 American College of Rheumatology classification criteria,[22] and classify SLE by randomly selecting 4 of these 11 defined American College of Rheumatology criteria (a minimum requirement to classify a disease as SLE, according to Tan et al[22]), theoretically 330 different clinical phenotypes embrace the term SLE. Does this mean that we, in fact, are dealing with a pile of unrelated disorders and manifestations that today is called SLE—and can we define biomarkers for SLE on this basis?

Recently, Pisetsky[23] characterized anti-dsDNA antibodies as quintessential biomarkers for SLE. In light of the heterogenic image of SLE, and also because anti-dsDNA antibodies occur at various frequencies in different forms of cancers[24,25] and infections,[15] the statement that anti-dsDNA antibodies serve as a quintessential biomarker for SLE is difficult to comprehend. In fact, the first successful experiments that resulted in induction of anti-mammalian B helical (dsDNA) were performed by immunizing mice with dsDNA/chromatin fragments in complex with a peptide from *Trypanosoma cruzii* (Fus 1[26]), or with a complex of polyomavirus T antigen and dsDNA/chromatin fragments (Figure 1A). The [F1] experimental details for this model have been described previously.[27,28] In this experimental context, it is worthwhile to remember that the first discovery of anti-dsDNA antibodies in a natural context was achieved in sera from patients with bacterial infections six decades before the successful immunization experiments with complexes of mammalian chromatin and infectious-derived peptides,[11–14] and also two decades before their discovery in SLE.[15] Later, data demonstrating that pure chromatin fragments by themselves have the potential to induce diverse antibodies to chromatin have been demonstrated. These may represent antibodies to dsDNA, histones, non-histones, and complex determinants. The cellular processes responsible for these responses are, however, still poorly understood,[15] although they are

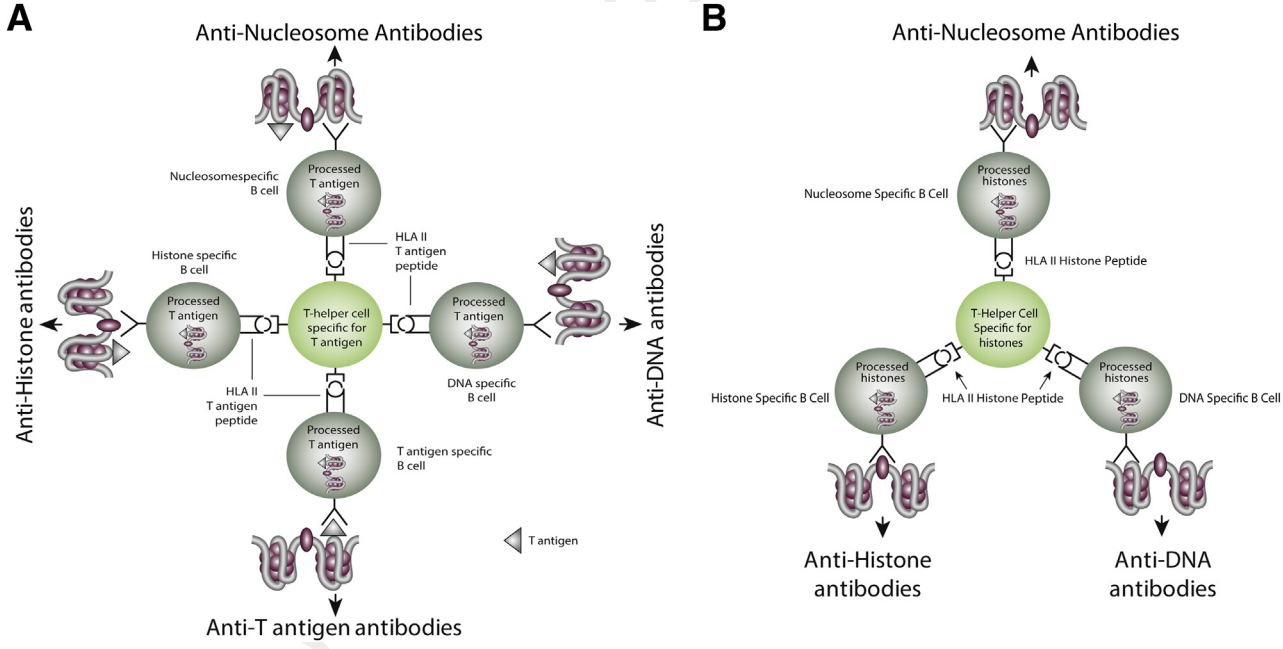

Figure 1 Cognate interaction of nucleosome-specific B cells and infectious-derived (**A**) or autoimmune-derived (**B**) peptide-specific T cells. The figure presents classic hapten-carrier–like models to explain linked production of chromatin-reactive antibodies. **A:** In this model, chromatin plays the role as a hapten, whereas heterologous (infectious-derived DNA-binding proteins like polyomavirus large T antigen) peptides play the role as carrier protein. In this model, primed T cells recognize T-antigen–derived peptides presented by B cells specific for different nucleosome structures. This model describes two features typical for systemic lupus erythematosus (SLE), production of affinity-maturated anti-dsDNA antibodies and linked production of antibodies to dsDNA, histones, and nonhistone chromatin-associated proteins. However, in this context, the individual may not at all experience SLE—rather the individual may experience infection. The principal paradigm for the hapten-carrier models presented in this figure is based on strong experimental evidence (see text for details). **B:** A hapten-carrier–like model is presented where chromatin represent the hapten, whereas chromatin-derived peptides represent the [Q10] carrier protein. At difference from the model in **A**, T-cell tolerance to nucleosomes is terminated. As in **A**, this model also describes linked production of antibodies reactive with chromatin constituents. In this situation, T-cell tolerance to nucleosomal proteins is terminated, and the immune response is truly autoimmune. The cognate interaction of chromatin-specific B cells and immune (**A**) or autoimmune (**B**) peptide-specific T cells may explain the origin of the comprehensive repertoire of chromatin-reactive IgG antibodies in human patients. Used with permission from Springer Science and Business Media.[21] HLA, human leukocyte antigen.

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