

# Pathogenesis of Lupus

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This review highlights advances made over the past 2 years in understanding the pathogenesis of systemic lupus erythematosus (lupus). The criteria used in selecting the articles include: 1) the study was performed using human subjects as opposed to animal models; 2) the quality of methods, data, and interpretation were acceptable; and 3) a current body of literature exists supporting causality for the mechanisms studied. Because lupus is a complex disorder, difficulties arise in distinguishing causal mechanisms from secondary effects. The rationale for selecting these reports rests in our present understanding of the pathogenesis of this disease.

Current paradigms maintain that lupus develops in people with a genetic predisposition, but also requires an initiating event usually assumed to be environmental. Many researchers are involved in identifying genes predisposing the patient to develop lupus (1,2), and a representative article characterizing potentially pathogenic Fc $\gamma$  receptor (Fc $\gamma$ R) alleles is discussed. Although the initiating event for most lupus cases is unknown, studies in both human and murine systems indicate that T cells recognizing antigenic determinants in nucleosomes maintain and possibly initiate the hallmark anti-DNA antibody response (3), therefore a recent article examining this response in lupus patients is discussed. Finally, a growing body of literature indicates that the abnormal cell driving lupus is the T lymphocyte, with numerous signaling and other biochemical abnormalities reported in this profoundly disturbed cell (4). One recent paper demonstrating a signaling defect common to the majority of lupus patients is reviewed. Abnormalities in T cell DNA methylation have also been identified in lupus patients and shown to cause a lupus-like disease in animal models (5,6). Therefore a report examining the mechanisms causing DNA hypomethylation in human lupus T cells is discussed.

## The Fc $\gamma$ receptor IIIA-158F allele is a major risk factor for the development of lupus nephritis among Caucasians but not non-Caucasians (*Arthritis Rheum*, 2001) (7)

This retrospective study compares the frequency of 2 low affinity Fc $\gamma$ R alleles, Fc $\gamma$ RIIA-131R and Fc $\gamma$ RIIIA-158F, between 235 multiethnic lupus patients with biopsy proven nephritis, and 352 multiethnic SLE patients without evidence of renal involvement. The significant observation is that the presence of the Fc $\gamma$ RIIIA-158F allele, but not the Fc $\gamma$ RIIA-131R allele, confers an increased risk of nephritis among Caucasians. This study also implicates additional genes beyond Fc $\gamma$ R alleles in disease susceptibility, because an increased risk was not seen in other ethnic populations, although small numbers may limit this conclusion. The observation that the Fc $\gamma$ RIIIA-158F allele confers susceptibility to lupus nephritis alone may provide useful prognostic information for Caucasian lupus patients. However, the etiologic importance of this study is that it identifies a candidate gene conferring an increased risk for developing lupus nephritis.

Familial studies have established that genetic composition influences lupus susceptibility, although incomplete concordance in identical twins implies the need for additional and presumably environmental factors. Previous work has established that certain major histocompatibility complex and complement alleles confer lupus susceptibility, and gender clearly plays a role. However, familial studies demonstrate other multiple predisposing loci, and the identity of these genes is unknown (1, 2). The present study suggests that Fc $\gamma$ RIIIA-158F could be one of these genes, although it is also possible that the risk comes from a gene in close proximity to this allele, or an interacting gene that differs in frequency between ethnic groups. Nonetheless, there is theoretical rationale for proposing low affinity Fc $\gamma$ R alleles as candidate genes. Fc $\gamma$ R are involved in the clearance of IgG-containing immune complexes, and the Fc $\gamma$ RIIIA-158F allele (with phenylalanine at position 158) binds IgG1 and IgG3 less avidly than the 158V isoform (with valine at position 158). The decreased binding affinity of the Fc $\gamma$ RIIIA-158F allele may result in ineffective clearance of antigen-antibody complexes, resulting in an increased susceptibility to immune complex-mediated nephritis.

Supported by PHS grants AG014783, AR42525, and AI42753, a Merit grant from the Department of Veterans Affairs, and a grant from the Arthritis Foundation.

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Submitted for publication September 14, 2001; accepted in revised form January 7, 2002.

**Nucleosomes are major T and B cell autoantigens in systemic lupus erythematosus**  
(*Arthritis Rheum*, 2000) (8)

This article examines the sensitivity and specificity of immune responses to nucleosomes in lupus patients and controls. A unique feature of this study is that T cell responses as well as antibody reactivity are examined. The authors reported that 54% of 26 patients with lupus had proliferative T cell responses to nucleosomes, and none of the 7 healthy controls or 10 patients with other autoimmune rheumatic diseases mounted a response. Using enzyme-linked immunosorbent assay, the authors found that 56% of 136 lupus sera reacted with nucleosomes, while comparison with sera from 309 subjects with other inflammatory autoimmune and infectious conditions gave a specificity of 97%. The specificity was significantly greater than that of the anti-double-stranded DNA (dsDNA) response (97% versus 79%), although the sensitivity was lower (56% versus 70%), and others have reported a higher specificity for the anti-dsDNA response in lupus (9). The relatively low sensitivity of the T lymphocyte and antibody responses may be due in part to the use of chicken rather than human nucleosomes, because autoreactive T and B cells may not recognize chicken proteins in the antigen preparation. Furthermore, T cells from patients with active lupus are relatively anergic, and no specific information is shown relating disease activity and the proliferative response, so it is possible that disease activity confounded the assays. However, this article does support the concept that the autoimmune response in lupus involves T and B cell reactivity to nucleosomal components.

The source of antigen initiating the lupus anti-DNA response has long been a mystery, and nucleic acids from exogenous agents such as viruses or bacteria are traditionally invoked. However, DNA rarely if ever exists free of bound proteins *in vivo*. Rather, it can be detected in the form of nucleosomes in the peripheral blood of patients with lupus presumably reflecting increased apoptosis, decreased clearance of apoptotic debris, or both (3). Interestingly, injecting sufficient numbers of apoptotic cells into mice will directly induce an anti-DNA response (10). Further, kinetic evidence and specificity studies support the concept that the nucleosome is the primary target of lupus anti-histone and anti-DNA antibodies (3). Finally, nucleosome-reactive T cells that promote anti-DNA antibody synthesis can be isolated from the peripheral blood of lupus patients (11). Although these observations do not exclude the possibility that infectious agents initiate the autoimmune response, nucleosomes appear to play an important role in sustaining it and may provide the initiating antigen as well. Together these reports support the important role of the nucleosome as a stimulating antigen in human lupus.

**High prevalence of T cell type I protein kinase A deficiency in systemic lupus erythematosus**  
(*Arthritis Rheum*, 1999) (12)

Lupus T lymphocytes demonstrate numerous biochemical abnormalities, and one of the better characterized is a deficiency of protein kinase A type I (PKA-I). PKA-I is a signaling molecule activated by cyclic AMP, and is re-

sponsible for the phosphorylation of several membrane proteins. This article examines the prevalence of PKA-I deficiency in lupus T cells and determines the relationship between the enzyme deficiency and disease activity. The authors report that T cells from 80% of 35 lupus patients had decreased PKA-I enzyme activity, compared with 35 age-, sex-, and race-matched controls; that the defect was stable over a period of 4 years in the 15 patients studied; and that the decrease in enzyme activity was independent of disease activity or treatment. Overall, PKA-I activity in lupus T cells was approximately one-third the activity of the controls. In other studies by the same group, the mechanism for the decreased activity has been explored and appears to be multifactorial. Decreased transcription of messenger RNA (mRNA) encoding subunits of this enzyme, transcript mutations resulting in abnormal mRNA, and decreased translation of the mRNA into protein all appear to be involved (13,14). It is also possible that allelic differences contribute to the decreased expression, although this remains to be established.

This report is significant because it identifies a T cell signaling defect common to a majority of lupus patients that is present independent of disease activity. This molecular defect thus provides a candidate mechanism for some of the T cell abnormalities associated with lupus and possibly contributes to its development. The role that PKA-I plays in the T cell signaling cascade is not completely characterized, so the full impact of this enzyme defect is not well understood. However, restoration of this enzyme by transfection into lupus T cells has restored interleukin-2 production, known to be decreased in lupus, so the PKA-I signaling defect appears to have functional significance (14). Given the evidence from other groups (discussed below), altered expression of T cell genes involved in signaling may well contribute to the pathogenesis of human lupus.

**Decreased ras-mitogen-activated protein kinase signaling may cause DNA hypomethylation in T lymphocytes from lupus patients**  
(*Arthritis Rheum*, 2001) (15)

Studies involving patients with drug-induced lupus have shown that hydralazine and procainamide are T cell DNA methylation inhibitors, and adoptive transfer of T cells made autoreactive by treatment with these or other DNA methylation inhibitors causes a lupus-like disease in murine models. T cells from patients with active lupus have decreased levels of DNA methylating enzymes and hypomethylated DNA (5), suggesting that the same process may contribute to human lupus, but the mechanism causing the DNA hypomethylation in lupus is unknown. This article by Deng et al examines mechanisms that may contribute to T cell DNA hypomethylation in lupus. DNA methyltransferase enzyme levels are regulated by signals transmitted through the ras-mitogen-activated protein kinase (MAPK) pathway; therefore, ras-MAPK signaling was examined in lupus patients and controls. Signaling was decreased only in lupus T cells, and the magnitude of the decrease was directly proportional to disease activity. Inhibiting T cell ras-MAPK signaling with a pharmacologic inhibitor de-

creased DNA methyltransferase to the levels seen in lupus T cells, and resulted in hypomethylated DNA. Although the reason for the decreased signaling is unknown, this study does demonstrate a specific pathway defect that may account for the DNA hypomethylation seen in lupus T cells. Because lupus T cells have multiple signaling defects (discussed previously), a common pathway may link abnormalities in the expression of a signaling molecule such as PKA-I to decreased signaling through the ras-MAPK pathway. Alternatively, a generalized defect in other cellular functions such as protein synthesis or mRNA editing may be responsible for a number of otherwise unrelated signaling abnormalities.

How does DNA hypomethylation relate to lupus? The DNA hypomethylation model assumes that the same genes are affected by DNA hypomethylation induced by DNA methylation inhibitors *in vitro* and in human lupus. In support of this, the autoreactivity observed in T cells treated with DNA methylation inhibitors is due in part to overexpression of the adhesion molecule leukocyte function-associated antigen 1 (LFA-1), and LFA-1 is overexpressed on an autoreactive T cell subset in patients with active lupus (16,17). Thus, the LFA-1 overexpression and DNA hypomethylation may be linked to defective T cell signaling, and contribute to disease pathogenesis. Furthermore, cells made autoreactive by DNA hypomethylation or LFA-1 overexpression will spontaneously kill macrophages, releasing nucleosomal material (16). These processes, together with a genetic predisposition from genes like FcγRIIIA-158F, may initiate an autoimmune response that is then maintained by nucleosome-reactive T and B lymphocytes, consistent with the conclusions of the other articles discussed above.

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