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T-antigen and anti-DNA antibody production

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Context

IgG anti-double-stranded (ds) DNA antibodies are a distinctive serologic hallmark of systemic lupus erythematosus (SLE). The anti-dsDNA antibodies present in human SLE and in murine models of the disease have the characteristics of antibodies arising as an antigen driven response. Lupus-associated anti-DNA antibodies are class-switched to IgG, and somatic mutations are present in both heavy and light chains. Several studies have demonstrated an important role for T cells, particularly T cells specific for self-nucleosomal antigens, in providing help for the anti-DNA antibody response in lupus.

While immunization with mammalian DNA does not induce anti-dsDNA antibodies in non-autoimmune mice, it has been demonstrated in various experimental models that immunization with complexes of DNA and DNA-binding proteins can break tolerance to nuclear antigens. It has been postulated that peptides derived from the associated DNA binding proteins may be the antigen recognized by T cells providing help for anti-DNA antibody production.

In two previous studies, (paper%201) (paper%202) Rekvig *et al* have shown that expression of polyomavirus T antigen, a DNA binding protein important in viral replication, can induce the production of anti-dsDNA antibodies. Furthermore, they demonstrated that reactivation of polyomavirus in lupus patients is associated with anti-DNA antibody production. This led to the hypothesis that T antigen-specific T cells may provide help for anti-DNA antibody producing B cells. To investigate whether T antigen specific T cells are present *in vivo*, and if T antigen (T-Ag) complexed with nucleosomes is stimulatory for such T cells.

Significant findings

After demonstrating that T-Ag can bind nucleosomes, Rekvig *et al*show that T-Ag (and to a lesser degree SV-T2) stimulated PBMCs as demonstrated by proliferation assays. Proliferation was inhibited by anti-CD4 monoclonal antibodies. T-Ag specific T cell lines were generated from both normal and SLE patients. These T cell lines responded to T-Ag, as well as to T-Ag complexed to nucleosomes. Finally, in coculture experiments, T-Ag specific T cells provided help for anti-T-Ag and anti-DNA antibody production from B cells of both normal and lupus patients.

Comments

With progression of disease in SLE, anti-DNA antibodies display somatic mutations that increase the affinity of these antibodies to DNA. Yet mammalian DNA has not been shown to be immunogenic. This study helps to elucidate the mechanism by which DNA binding proteins in complex with nuclear material can trigger anti-DNA antibody production. However, in this paper T-Ag specific T cells were also demonstrated in normal donors. The differences between DNA-tolerant normal individuals, and lupus patients with loss of tolerance to DNA in the disease state, remain to be elucidated.

Methods

Peripheral blood mononuclear cells (PBMCs) were obtained from four patients with SLE, and from ten normal controls. SV40 T-Ag was purified from recombinant baculovirus. Nucleosomes were prepared from cells with constitutive expression (SV-T2) or without expression (A31) of SV40 large T-Ag. T cell proliferation assays, generation of T cell lines, FACS analysis, and T and B cell co-culture were performed using standard methodologies.

References

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