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Naturally occurring V region connected antibodies inhibit anti-dsDNA antibody reactivity with dsDNA

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ABSTRACT

The production of autoantibodies against a vast array of self antigens, most notably double stranded (ds) DNA, characterized systemic lupus erythematosus (SLE). The purpose of this work is to study specific Ig fractions isolated from normal human serum (NHS) and their effect on the binding of anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies (Abs) to dsDNA. A fraction named immunoglobulin G (IgG)-reactive IgG was purified from total NHS IgG by absorption onto (CNBr)-activated Sepharose 4B linked to intact IgG molecules (IgG-Sepharose column). IgG-reactive IgG was co-incubated with systemic lupus erythematosus (SLE) patient's serum and binding of the anti-dsDNA Abs to dsDNA was measured by enzyme-linked immunosorbent assay (ELISA). Co-incubation of SLE patient's serum with IgG-reactive IgG resulted in a dose-dependent reduction in binding of anti-dsDNA Abs to dsDNA. A reduction greater than 70% was observed at a concentration of 300 μg of IgG-reactive IgG per mL of a 400-fold diluted SLE patient's serum whereas total NHS IgG, at the same concentration, resulted in a 10% reduction in binding. The purification process used to isolate IgG-reactive IgG was based on interactions between intact Ig rather than on interactions between $F(ab')_2$ portions. IgG_2 is the predominant immunoglobulin (Ig) subclass in IgG-reactive IgG. Thus, IgG_2 might have an important role in the connectivity characteristics of NHS IgG. The capacity of IgG-reactive IgG to inhibit anti-DNA Ab binding to dsDNA may have potential application in the treatment of SLE. This targeted biological approach may provide an alternative strategy to immunosuppressants.

Introduction

Despite a rigorous selection process during B cell development in the bone marrow a where B lymphocytes with potentially dangerous self-reactivity are eliminated a significant number of self-reactive B cell survives to enter the peripheral compartment (Monroe and Dorshkind 2007). In healthy individuals, a major point at which reduction in the number of self-reactive B cells takes place is during transition from IgM naive, to IgM memory B cells before the onset of somatic hypermutation. In patients with SLE, this progressive decline in self-reactive cells does not occur, suggesting that SLE is associated with a failure to establish self-tolerance during early B cell development which leads to increased numbers of autoreactive mature naive B cells (Yurasov et al. 2005).

SLE, the most serious of the lupus disorders, is characterized by the production of a number of autoantibodies which involves any B cell subset including B1 cells, marginal zone (MZ) B cells, short-lived plasma cells or germinal centre-matured long-lived plasma cells (Jacobi and Diamond 2005). The most common autoantibody seen in lupus is the antinuclear antibody (ANA). The type of ANA pattern helps to determine if SLE or a related connective tissue disease is present and anti-dsDNA antibodies are the most frequently detected antibodies in SLE. Current diagnostic criteria for

Abbreviations: Abs, antibodies; Ag, antigen; BF, binding buffer; CDR, complementary determining regions; CNBr, cyanogen bromide; CRI, cross-reactive idiotypes; dsDNA, double-stranded deoxyribonucleic acid; ELISA, enzyme-linked immunosorbent assay; FR, framework; GB, GammaBind G Sepharose; GBF, GammaBind G Sepharose flowthrough; Id, idiotype; Ig, immunoglobulins; MZ, marginal zone; NHS, normal human serum; ORG, ORGENTEC; PBS, phosphate buffered saline; PS, polysaccharides; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; RF, rheumatoid factor.

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