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Bcl-2 and anti-DNA antibodies

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Keywords

Anti-DNA, apoptosis, Bcl-2, nephritis, systemic lupus erythematosus, transgenic mice

Context

Anti-double stranded (ds) DNA antibodies are a characteristic serological hallmark of

systemic lupus erythematosus (SLE). Moreover, anti-dsDNA antibodies have

also been shown to be important in the pathogenesis of nephritis in SLE. The mechanisms underlying the generation of pathogenic anti-dsDNA antibodies in lupus are not fully understood. The authors have previously studied the regulation of anti-dsDNA antibodies in autoimmune and non-autoimmune murine genetic backgrounds, using mice transgenic for the heavy chain of R4A. R4A is a murine immunoglobulin (Ig)G2b anti-dsDNA antibody, which deposits in the glomeruli of non-autoimmune mice. Non-autoimmune BALB/c mice expressing the R4A heavy chain transgene do not exhibit significant titers of anti-DNA antibodies in their serum (indicating regulation of this specificity). Following lipopolysaccharide (LPS) stimulation, anergic anti-DNA B cells can be recovered from these mice,

which for the most part express the Vk1 light chain together with the transgenic heavy chain. When the R4A heavy chain transgene is bred onto the NZB x NZW F1 autoimmune background, anti-dsDNA-specific B cells can be immortalized by fusion without LPS stimulation. These B cells utilize non-Vk1 light chains, indicating that in the autoimmune background there is a population of B cells being rescued that is deleted in the nonautoimmune background (and therefore in BALB/c mice these B cells are not recoverable). Bcl-2 is an anti-apoptotic protein that has been shown to rescue lymphocytes from apoptosis induced by several different stimuli. On the SJL background, mice transgenic for *bcl*-2 express high titers of anti-dsDNA antibodies in their serum. Furthermore, previous work has indicated that bcl-2 may play a role in regulation of autoreactive B cells in germinal centers. To investigate the role of bcl-2 in regulation of anti-dsDNA antibodies in the nonautoimmune BALB/c background.

Significant findings

Double transgenic mice had high titers of high affinity anti-dsDNA antibodies, but without histological evidence of immunoglobulin deposition in glomeruli or renal damage. High affinity and low affinity IgG2? (transgene encoded) anti-dsDNA B cells could be rescued by fusion, without

LPS stimulation. Low affinity anti-DNA B cells utilized a variety of light chain genes, with some over-representation of ? light chains. Non-Vk1 light chains predominated among the high affinity anti-DNA antibodies, suggesting that the *bcl*-2 transgene rescued a B cell population that was deleted in the BALB/c R4A single transgenic mouse. Finally, some of the

high affinity anti-dsDNA antibodies had pathogenic potential, as demonstrated by the ability to deposit in glomeruli of SCID mice when given as purified antibody by intraperitoneal injection.

Comments

This is a very interesting and innovative paper, which adds to the growing literature supporting a potentially important role for disturbed apoptosis in the genesis of tolerance breakdown to DNA in SLE. The presence of mutated fas in the MRL background in the mouse reproduces many of the features of human SLE, and represents an important animal model for this disease. Interestingly, patients with defects in fas displaying autoimmune features have also been recently described. As for bcl-2, previous studies in the mouse have shown that overexpression of bcl-2 can lead to autoimmunity, but

the exact phenotype is dependent on the genetic background in which the transgene is expressed. As the authors point out, initial studies have not demonstrated a consistent defect in bcl-2 expression in patients with SLE, but perhaps specific B cell subsets should be further studied. Dysregulated B cell survival is shown here to induce autoimmunity (anti-DNA antibodies); which additional factors are necessary for full expression of lupus-like disease (tissue damage) remain to be determined.

Methods

The authors crossed *bcl*-2 transgenic mice with the R4A heavy chain transgenic mice, creating double transgenic mice (R4A/bcl-2) on the BALB/c background. Serum studies, histology, and B cell immortalization by fusion were carried out using conventional methods.

References

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