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Mice deficient in secreted IgM develop autoimmune disease

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Keywords

Autoantibody, autoimmunity, IgG, IgM, lupus, MRL-lpr

Context

Elevated levels of IgG and IgM autoantibodies are often associated with autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Several lines of evidence suggest that increased levels of IgG are pathogenic, whereas an increased level of IgM is not. Previous studies have shown that mice deficient in secreted IgM (sIgM), or deficient in various components of the complement system, have an impaired IgG response to a T cell-dependent antigen. This indicates that sIgM and complement are involved in mediating the IgG antibody responses to foreign antigens. In order to elucidate the role of sIgM in the pathogenesis of autoimmune disease, a mutation was introduced into the lupus-prone lymphoproliferative (lpr) mouse, in which B cells are incapable of secreting IgM, while still capable of expressing surface IgM and IgD and secreting IgG antibodies. To investigate the role of secreted IgM autoantibodies in the pathogenesis of autoimmune disease.

Significant findings

As observed in lpr mice, sIgM-/- mice spontaneously developed IgG autoantibodies. At 3 months of age, levels of IgG2a increased threefold in lpr/sIgM-/- mice compared to lpr/sIgM+/+ (lpr) controls, while IgG1, IgG2? and IgG3 isotypes did not change. Increased levels of all IgG isotypes specific for dsDNA were observed in 6 month old lpr/sIgM-/- mice and levels of IgG2a specific for histones were higher than in lpr controls. Levels of ANA were higher in lpr mice and higher still in lpr/sIgM-/- mice compared to both wild-type and sIgM-/- controls. Thus, development of IgG autoantibodies is accelerated in lpr mice in the absence of sIgM.

Increased levels of IgG observed in lpr/sIgM-/- mice were associated with more abundant deposits of immune complexes in glomeruli. Examination of kidney sections from lpr/sIgM-/- mice, and to a lesser extent lpr mice, showed characteristics of a diffuse proliferative glomerulonephritis. IgM deficiency increased the severity of glomerulonephritis and gave rise to higher levels of morbidity in lpr mice compared to controls.

In order to determine whether the elevated levels of IgG autoantibodies are caused by the absence of autoreactive IgM, lpr/sIgM-/- mice were reconstituted with monoclonal IgM specific to dsDNA, and the IgG response to dsDNA was assayed. Despite 150 ?g injections of IgM three times a week, serum levels of anti-dsDNA IgM were not detectable 3 days after injection. Following 10 weeks of IgM reconstitution there were higher levels of IgG1, but not other IgG isotypes, specific for dsDNA in the IgM treated mice compared to saline treated controls. In addition IgM-treated mice had larger glomeruli and more deposits of immune complexes therein.

Comments

The data presented clearly demonstrate that, in the mouse lupus model, the absence of IgM results in accelerated autoimmune disease. Although potential mechanisms by which this occurs are discussed, further experiments are now needed to fully elucidate this pathway. It is perhaps not surprising that in the final experiment injected monoclonal autoreactive IgM failed to reconstitute the immune response in the IgM-deficient mice, since injected IgM tends to aggregate, as the authors point out, and the injected IgM was specific for double-stranded (ds) DNA, therefore not targeted against the autoreactive B cells that would be anergized in the presence of endogenous IgM. Overall, however, this study is an informative contribution to the autoimmunity field.

Methods

Mice deficient in secreted IgM on a mixed 129 x C57BL/6 background were bred with MRL-lpr/lpr mice. These mice were not backcrossed onto a homogeneous background, which potentially could affect the expression of the autoimmune phenotype. However, no significant differences in autoimmune responses were observed among mice of identical genotype but from different litters. Levels of serum IgG isotypes and autoantibodies specific for dsDNA and histones were measured by ELISA. Antinuclear antibody (ANA) staining was measured by immunofluorescent staining of HEp2 cells. The degree of glomerulonephritis was quantified using computer image analysis of formalin fixed, paraffin embedded kidney sections. Frozen sections of the second kidney were assayed for the deposition of immune complexes using a fluorescein isothiocyanate (FITC)-labelled anti-mouse IgG. IgM antibodies specific for dsDNA and histones were isolated from hybridomas and purified by affinity chromatography.

References

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