PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

Autoimmunity in IgM-deficient mice

ArticleInfo		
ArticleID	:	185
ArticleDOI	:	10.1186/ar-2000-66806
ArticleCitationID	:	66806
ArticleSequenceNumber	:	142
ArticleCategory	:	Paper Report
ArticleFirstPage	:	1
ArticleLastPage	:	3
ArticleHistory	:	RegistrationDate : 2000–5–8 OnlineDate : 2000–5–8
ArticleCopyright	:	Current Science Ltd2000
ArticleGrants	:	
ArticleContext	:	130753311

Chaim Putterman,[Aff1]

Aff1 Albert Einstein College of Medicine, New York, USA

Keywords

Anti-DNA antibodies, autoimmunity, IgM knockout mice, serum IgM

Context

Mice deficient in serum IgM display an enhanced susceptibility to bacterial infection. In a model of acute bacterial peritonitis, 20% of wild-type mice died within 32 h versus 70% of sIgM-deficient mice. sIgM-deficient mice were also found to have an impaired response to T-cell-dependent antigens, with delayed affinity maturation of IgG responses to foreign antigens. It would seem, therefore, that not only does IgM serve as the first line of defense in the immune response (as natural antibodies, and in the primary immune response), this isotype also plays a role in shaping subsequent immune reactions. Complexes of IgM and antigen may enhance delivery of antigen to those locations important in progression of secondary immune responses, or may act to augment B cell activation. To establish whether sIgM plays a role in the immune response to self-antigens.

Significant findings

Serum antibodies to double-stranded DNA were measured by ELISA, and by Crithidia immunofluorescence. Of the 30 homozygous sIgM knockout mice, 9 developed significant IgG anti-dsDNA antibody titers by ELISA at 12-18 months of age, as compared to none of the 21 controls. Five of the homozygous knockout mice with the highest ELISA titers had IgG anti-dsDNA antibodies as evaluated by Crithidia. The presence of a mixed population of high- and low-affinity anti-DNA antibodies in mice deficient for sIgM was confirmed by surface plasmon resonance.

While none of the control mice had detectable antibodies against cardiolipin or myeloperxidase, these were present in the knockout group (anti-cardiolipin, two mice; anti-myeloperoxidase, one mouse). Kidneys of 13 mice (five Crithidia positive knockout mice and eight controls) were evaluated by light microscopy and immunofluorescence. Six mice had significant glomerular deposition of IgG and/or C3; five of these mice were homozygous for sIgM deficiency. Only one homozygous knockout mouse had significant histopathology. Are sIgM-deficient mice more susceptible to experimental induction of autoantibodies? Treatment with lipopolysaccharide led to a similar degree of hypergammaglobulinemia

in both control and knockout groups of mice however, the IgG anti-dsDNA antibody titer was greatly enhanced in knockout mice compared to the wild type.

Comments

In previous studies, Ehrenstein *et al* describe significant impairment of T cell-dependent responses to foreign antigens in mice deficient for secretory IgM (sIgM). This current paper describes an abnormal immune response to self antigen in this model, manifested by anti-dsDNA antibodies and glomerular deposition of IgG and/or C3. The results by Ehrenstein *et al* are consistent with those recently reported by Boes *et al* for the spontaneous lpr autoimmune model (*Proc Natl Acad Sci USA* 2000 **97**:1184-1189). IgM deficiency in lpr mice led to acceleration of the autoimmune process, with increased titers of IgG anti-DNA and anti-histone antibodies, more severe glomerulonephritis, and premature mortality. In normal mice, autoantibody production was also enhanced. It seems clear that serum IgM deficiency in mice is an important predisposing factor for the development of autoimmunity. Can serum IgM deficiency be demonstrated before onset of disease in humans who go on to develop lupus or related systemic autoimmune disorders? Ehrenstein *et al*propose several reasonable hypotheses to explain the link between serum IgM deficiency and the development of autoimmunity, but this preliminary paper is mostly descriptive and does not provide experimental support for any one mechanism. The augmented type 2 TI (T-cell independent) responses and increased sensitivity to infection seen in sIgM-deficient mice would fit in well with a hypothesized cause and effect relationship between the response to infection and autoimmunity. Finally, the suggestion that polyclonal IgM antibodies might be useful in the treatment of autoimmune disease is intriguing and deserves further study.

Methods

Mice deficient for sIgM were generated by standard 'knockout' methods and analyzed for the presence of a variety of autoantibodies. Kidney histology and immunofluorescence studies were also undertaken.

References

1. Ehrenstein MR, Cook HT, Neuberger MS: Deficiency in serum immunoglobulin (Ig)M predisposes to development of IgG. J Exp Med. 2000, 191: 1253-1257.