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An interferon-inducible gene in lupus susceptibility

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Keywords

genetics, inbred mice, lupus, microarray

Contex

Crossing New Zealand Black (NZB) and New Zealand White (NZW) mice generates one of the most studied animal models of human systemic lupus erythematosus (SLE). Genetic analyses have revealed that this model shares with human lupus a complex genetic basis. One locus that is consistently linked with lupus traits is the distal chromosome 1 locus known as the *Nba2* locus (New Zealand black autoimmunity 2). In this paper the *Nba2* locus was investigated for the presence of susceptibility genes. Nonautoimmune C57BL/1 (B6) mice were made congenic for *Nba2*. Subsequently, the congenic mice were crossed with NZW mice. Spleen cells from the B6.Nba2 animals were used to screen for candidate genes using oligonucleotide microarrays.

Significant finding

The B6.Nba2 congenic mice developed high levels of autoantibodies but only a small number developed lupus nephritis. However, offspring of the B6.Nba2 congenic mice crossed with NZW mice developed high levels of antibodies and severe lupus nephritis similar to NZB x NZW mice. Expression profiling of spleen cells of the B6.Nba2 mice showed only two differentially expressed genes, interferon-inducible genes *Ifi202* and *Ifi203*. In B6.Nba2 mice, *Ifi202* levels were higher whereas *Ifi203* levels were lower than in controls. More importantly, both genes are located in the Nba2 interval. Quantitative PCR showed that *Ifi202* transcripts are specifically increased in B cells and non T/non B cells of B6.Nba2 spleen cells.

Comment

Ifi202 and *Ifi203* belong to the *Ifi200* gene cluster. This family of genes encodes structurally related proteins that may be induced by interferons. These cytokines have been shown to enhance murine lupus and SLE. Increased *Ifi202* expression inhibits cell proliferation. The authors suggest that inhibition of apoptosis of B cells, which showed increased levels of *Ifi202*, may be the underlying mechanism by which *Ifi202* contributes to lupus susceptibility.

Taken together these results implicate *Ifi202* as a candidate gene in murine lupus susceptibility. This offers potential insight to disease pathogenesis, in particular suggesting a potential pathway to disease expression through dysregulation of B-cell survival. An important proviso however is the necessity to now demonstrate similar involvement of this gene family in human SLE itself.

Method

Mouse models - generation of congenic strains, microroarray, PCR

Additional informatio

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