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Fc?RIIB knockout develops B lymphocytes loss of self tolerance

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Keywords

Animal model, autoantibodies, epistasis, Fc?RIIB, knockout, SLE

Context

Fc?Rs can activate or inhibit the cellular responses by sending opposing signals upon activation by immune complexes. Fc?RIIB belongs to the inhibitory group; it can inhibit and limit the threshold of immune complex activation of both B lymphocytes and macrophages, possibly by recruiting the inhibitory phosphatase SHP-1. It may also contribute to the maintenance of tolerance during affinity maturation by deleting the low affinity, self-reactive lymphocytes from the germinal centres. Both activating and inhibitory Fc?Rs can modify the development and progression of autoimmune diseases by influencing B lymphocytes and/or macrophages. This study aimed to investigate the role of Fc?RIIB in the development of spontaneous autoimmune disease in the mouse.

Significant findings

The original RIIB$^{-/-}$ 129Sv/B6 mouse was healthy, but after seven generations of backcrossing the RIIB$^{-/-}$ B6 mice were losing weight, and showed dehydration and reduced viability. RIIB$^{-/-}$ BALB/c mice on the other hand were healthy and had a life span comparable to that of the wild type. Proteinurea had developed in 90% of the RIIB$^{-/-}$ B6 mice by 9 months, as well as very high antinuclear antibody (ANA) titres (>1:1000) with homogenous nuclear staining, and both anti-DNA and anti-chromatin antibodies. Interestingly, these mice did not develop any of the common autoantibodies such as anti-Sm, cardiolipin or myeloperoxidase antibodies. None of the BALB/c RIIB$^{-/-}$ animals developed proteinurea or autoantibodies. Pathologically, the RIIB$^{-/-}$ B6 mice suffered from a severe multi-organ inflammatory disease. The lungs and kidneys revealed systemic vasculitis with inflammatory cell infiltration. The kidneys showed evidence of glomerulonephritis (extensive glomerular sclerosis, hypercellularity and mesangial thickening) suggesting an ongoing chronic inflammatory disease. Bone marrow transfer experiments suggested that the autoimmune phenotype of the RIIB$^{-/-}$ B6 mouse was dependent upon the deficiency of the RIIB in the B lymphocytes but not in macrophages.

Comments

Fc?RIIB is an inhibitory receptor that seems to play an important role in the maintenance of self-tolerance. Results from this work suggest that lack of expression of the Fc?RIIB on B cells is the driving force behind the autoimmune responses developed in the knockout mouse. Fc?RIIB occurs within the systemic lupus erythematosus (SLE) linkage area on chromosome 1 identified in the NZB/NZW and NZM2410 strains. results from this work suggest that polymorphisms in this gene may influence disease expression only in the susceptible genetic background. Interpretation of these results should take into consideration interaction with other genes, and the function of any such polymorphisms should be investigated in a cell-specific manner. Recent published data demonstrated that, in the mouse, naturally occurring polymorphisms within this gene are associated with the development of autoimmune responses (see Additional information).

Methods

The original Fc?RIIB knockout ($RIIB^{-/-}$) was generated on the 129SV/B6-hybrid background and was subsequently backcrossed on BALB/c and C57BL/6 (B6) background for 12 generations. Deposition of immune complexes was detected by fluorescein-conjugated anti-mouse IgG antibodies. Anti-DNA was determined by ELISAand ANAs were detected on Hep-2 cells with fluorescein-conjugated anti-mouse IgG antibodies.

Additional information

Jiang Y, Hirose S, Abe M, Sanokawa-Akakura R, Ohtsuji M, Mi X, Li N, Xiu Y, Zhang D, Shirai J, Hamano Y, Fujii H, Shirai T: **Polymorphisms in IgG Fc receptor IIB regulatory regions associated with autoimmune susceptibility**. *Immunogenetics* 2000, **51**:429-435 (PubMed abstract).

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