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# Complement factor C5 and gene region encoding Fc?RIIb in CIA

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## Keywords

collagen-induced arthritis, diabetes, complement, FcR

# Context

Collagen-induced arthrtis (CIA) is a mouse model of inflammatory synovial disease. T cells, B cells and anti-collagen type II antibodies are all involved in the pathogenesis of disease. The I-A locus is critical for susceptibility to CIA, and H-2q and H-2r are susceptibility haplotypes. However, several other loci have also been implicated. In this study, the arthritis-susceptible strain, B10.Q, is used, which exhibits disease incidence ~50%. An H-2q congenic is made on the insulin-dependent diabetes mellitus (IDDM)-suceptible NOD mouse background (NOD.Q). NOD.Q x B10.Q F1 and F2 intercrosses are used to determine whether insulin-dependent diabetes and CIA share susceptibility genes.

# Significant findings

The NOD.Q congenic and the NOD.Q x B10.Q F1 generation were resistant to CIA. Although NOD mice spontaneously develop insulin-dependent diabetes, it is important to note that NOD.Q and the intercrossed mice did not.

Approximately 25% of the F2 generation was susceptible to CIA and displayed disease onset and severity comparable with B10.Q.

The absence of measurable serum C5 in the F2 generation generally corresponded with resistance to disease, which could thus be attributed partly to the NOD-derived nonfunctional C5 gene.

A second susceptibility region, Cia9, was identified. This contains a number of candidate genes, including Fc?RIIb. An interaction between the Cia2 and Cia9 loci was apparent; in mice heterozygous for Cia2 (C5), inheritance of the B10-derived Cia9 locus was associated with a lower incidence of CIA.

The IDDM susceptibility loci identified in the NOD mouse do not appear to confer susceptibility to CIA. This implies distinct pathogenetic pathways for IDDM and CIA.

# Comments

Previous studies have indicated that mice deficient for complement C5 and the Fc? common chain, which is a component of the multimeric stimulatory Fc?RI and Fc?RIII, are resistant to CIA. In contrast deficiency of the inhibitory single-chain receptor, Fc?RII, has been associated with faster onset and more severe arthritis. The Fc?RIIb locus lies within Cia9. It is notable that it is the NOD- rather than the B10-derived Cia9 segment which confers the susceptibility gene. NOD mice exhibit reduced expression of Fc?RIIb on macrophages and B cells. The interaction between Cia2 (C5) and Cia9 (possibly Fc?RIIb) needs to be confirmed but reinforces the notion that immune complex-mediated inflammation is critical to arthritis induction. The parallel roles of pathogenic antibodies and immune complex formation in the CIA model, the Mathis/Benoist K/B x N model and various lupus models are striking. Further functional studies of Fc?RIIb and other candidate genes in the Cia9 region (e.g. Fc?r3, Fcer1 and lupus susceptibility loci) are required in these models.

# Methods

Generation of congenic mouse strains, induction of collagen-induced arthritis, linkage study

# Additional information

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