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Genetic susceptibility to antibody-mediated arthritis

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Keywords

Arthritis, complement, quantitative trait locus

Context

The K/BxN model of murine inflammatory arthritis has provided exciting insights into this rheumatoid-like disease. The model emerged serendipitously from the intercross of T-cell receptor (TCR) transgenic mice x nonobese diabetic (NOD) mice (See Additional information [1]). Erosive arthritis occurred spontaneously in all the offspring. Arthritis was found to be intiated following recognition by the transgenic TCR of a glucose-6-phosphate isomerase (GPI) peptide, presented by the NOD class II molecule, I-Ag7. Transfer of serum from arthritic mice, containing anti-GPI antibodies was shown to induce arthritis in recipients, even if they were devoid of T and B cells. This paper explores the genetic basis for the variable susceptibility of different strains of inbred mice to serum-mediated arthritis.

Significant findings

Transfer of serum from arthritic K/BxN mice produced four categories of response in different inbred mouse strains: rapid and severe joint inflammation (Balb/c), slower and less severe (B6, DBA/1, CBA), slow and low-grade (SJL, 129/Sv), resistant (NOD, NZB, DBA/2). The crossing of strains with different susceptibilities indicated that the interaction of several genes was responsible for this effect.

In (B6 x NOD)F2 mice, homozygosity for the NOD-derived C5 allele (n/n) conferred resistance to arthritis transfer. Homozygotes for the B6-derived C5 allele (b/b) showed more severe disease than heterozyogotes (b/n). A genome screen was applied to 132 susceptible F2 mice with either b/b or b/n C5 genotypes. Two major qualitative trait loci were identified, one corresponding to the C5 locus on chromosome 2 and the second, on chromosome 1, close to the locus encoding the Fc?RII. Further studies using *fcgr2* deficient mice and B6 mice congenic for the NOD *fcgr2* allele failed to substantiate a role for this locus in conferring susceptibility to arthritis transfer.

Comments

Inflammatory arthritis is the culmination of several steps in the immune cascade. This study facilitates the identification of genetic influences on this process by utilising inbred mouse strains and by isolating a late step in the development of arthrits, distal to the influence T- and B-cell function. Two major quantitative trait loci are identified and strong evidence implicating the complement C5 locus is presented. The similarity between evidence accruing for the role of immune complexes in arthritis in this model and collagen-induced arthritis is striking (see Additional information [2]).

Further work is required to map the allele(s) responsible for the second quantitative trait locus defined and to determine whether the weaker linkages identified are real. These data will prompt functional studies concerning the role of C5 in early synovial inflammatory events and will restimulate interest in complement components as therapeutic targets in rheumatoid arthritis.

Methods

Arthritis induction by serum transfer from arthritic K/BxN mice to a panel of inbred strains, PCR - based genotyping of loci, Genetic mapping of quantitative trait loci

Additional information

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