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Development of collagen-induced arthritis in H-2b mice

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Keywords

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Context

Various studies have shown that the incidence of CIA is linked to the H-2 haplotype of the mouse strain, with H-2q mice being the most sensitive and H-2b mice being amongst the least sensitive strains. These observations are validated by the linkage of human RA with various MHC class II alleles. Various approaches using gene-knockout (KO) strategies have been tested in order to elucidate the precise mechanisms of CIA progression. However, the genetic background of most KO mice (B6 or 129 strains) carry H-2b, a putative CIA-resistant haplotype, thereby hampering any substantial progress using this model. Normally, CIA is induced by two injections of CII, the first injection via the intradermal route (id) with complete Freund's adjuvant (CFA) and the second one 21 days later via the intraperitoneal (ip) route without any adjuvant. However, this approach has several limitations, and the severity and frequency of arthritis are variable even in H-2q mice.

To re-examine the protocol of CIA induction and to develop CIA responsiveness in H-2b mice derived from mice with a B6 genetic background.

Significant findings

CIA was induced in D1 mice with a success rate of 90-100%, 30-35 days after immunisation. Mice with an H-2b background developed CIA with an incidence of 60-70% by day 60 after immunization. In B6 mice, CIA reached a maximum incidence 10 days later than in to D1 mice, but the clinical score was maintained up to 100 days after immunization. The CIA histopathology was similar in B6 and D1 mice and anti-CII antibodies were detectable in both strains. However, some differences were observed in the isotype of the anti-CII antibodies and the levels of anti-CII antibodies in B6 mice were generally lower than those in D1 mice. These results suggest that B cells are less important for CIA in B6 mice. However, B cell deficient mice with a B6 genetic background were resistant to CIA induction showing the importance of B cells. Finally, T cell proliferation to CII was similar in B6 and D1 mice. Moreover, depletion of $CD4^+$ T-cells inhibited CIA induction in both strains, thus confirming the importance of T

cells in this autoimmune disease. It is important to note that 129/Sv mice, which also carry H-2b were resistant to CIA induction, whereas B10 mice (H-2b) were sensitive to CIA.

Comments

Previous studies in mice have demonstrated that the development of autoimmune disease is restricted to different H-2 haplotypes. These observations have helped to develop models for understanding the linkage of human disease with certain MHC alleles. This is also true for collagen-induced arthritis (CIA), a mouse model of human rheumatoid arthritis (RA). Here, the authors demonstrate that changing the protocol of type II collagen (CII) injection is sufficient to induce CIA in mouse strains previously reported as carrying a resistant haplotype. The data showing the similarities between CIA development in sensitive and resistant mice are not entirely convincing and further work will be needed to confirm this suggestion. However, these results highlight once again that the cause of autoimmune diseases is multifactorial, with both MHC and non-MHC genes, as well as environmental factors implicated. Nevertheless, this model provides an experimental framework for analysing additional genes implicated in the pathogenesis of CIA.

Methods

Mice of five different strains were used in this study: D1 (H-2q), B6 (H-2b), B10 (H-2b), 129/sv (H-2b) and a B-deficient mouse backcrossed on to B6 mice (?MT/?MTB6). CIA was induced by two id injections of 100 ?g CII with CFA containing 250 ?g of *Mycobacterium tuberculosis*, with 21 days interval between injections. To study progression, clinical and histological analyses were performed, anti-CII antibodies were measured by ELISA and *in vitro* T cell proliferative responses to CII were determined by 3[H] thymidine incorporation. In some experiments, $CD4^+$ T-cells were depleted, using the anti-CD4 mAb GK1.5 1 day before the induction of CIA and at 7-day intervals thereafter.

References

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