INVESTIGATION OF THE GENETIC BACKGROUND OF SPONDYLARTHROPATHY IN MURINE MODEL OF SPONDYLITIS

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Summary

The HLA-B27 antigen has been accounted for 20-50% of the total genetic risk for ankylosing spondylitis (AS). However, susceptibility to AS cannot be fully explained by associations with the major histocompatibility complex (MHC). Recent studies including linkage analyses as well as candidate gene and, most recently, genome-wide association studies indicate significant associations of the interleukin-1 gene cluster, interleukin-23 receptor and ARTS1 genes, as well as other possible loci with AS.

In our experimental model autoimmune spondylitis was induced in BALB/c mice and their MHC-matched (BALB/c x DBA/2) F1 and F2 hybrids by systemic immunization with cartilage/intervertebral disk proteoglycan (PG). As in human ankylosing spondylitis, the MHC was the major permissive genetic locus in murine PG-induced spondylitis (PGIS). Two major non-MHC chromosome loci with highly significant linkage were found on chromosomes 2 (*Pgis2*) and 18 (*Pgis1*) accounting for 40% of the entire F2 trait variance. The dominant spondylitis-susceptibility allele for *Pgis2* locus is derived from the BALB/c strain, whereas the *Pgis1* recessive allele was present in the disease-resistant DBA/2 strain. The *Pgis1* locus significantly affected the disease-controlling *Pgis2* locus, inducing as high incidence of spondylitis in F2 hybrids as was found in the spondylitis-susceptible parent BALB/c strain. Additional disease-controlling loci with suggestive linkage were mapped to the chromosomes 12, 15, and 19. Severity of spondylitis in F2 mice positively correlated with serum levels of amyloid A, IL-6, and Pg-specific Abs, and showed negative correlation with Ag-induced T cell proliferation, IFN-_, IL-4, and TNF-_ production. A major locus controlling serum IL-6 was found on chromosome 14 near osteoclast differentiation factor *Tnfsf11*. Locus on chromosome 11 near the *Stat3* and *Stat5* genes controlled serum level of the Ig IgG2a isotype. The two major genetic loci *Pgis1* and *Pgis2* of murine spondylitis were homologous to chromosome regions in human genome, which control ankylosing spondylitis in human patients. Thus, this animal model of experimentally induced spondylitis might facilitate the identification of spondylitis-susceptibility genes in humans.

Keywords: ankylosing spondylitis; proteoglycan induced spondylitis; susceptibility genes; linkage analysis; HLA-B27 association; genome scan

Kulcsszavak: spondylitis ankylopoetica; proteoglikán indukálta spondylitis; fogékonysági gének; kapcsoltság analízis; HLA-B27 kapcsoltság; genomszűrés