A NEW MURINE MODEL FOR PROGRESSIVE POLYARTHRITIS AND ANKYLOSING SPONDYLITIS

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Introduction Proteoglycan (aggrecan) is one of the major components of articular cartilage. Systemic immunization with human cartilage proteoglycan (PG) induces progressive polyarthritis in genetically susceptible BALB/c mice. The histopathology of diarthrodial joints in proteoglycan-induced arthritis (PGIA) shows many similarities to rheumatoid arthritis and some BALB/c mice also develop spondylitis with partial or complete resorption of the intervertebral disc. Recently we found an additional PGIA-susceptible mouse strain (C3H/HeJCr) which showed high incidence for (ankylosing) spondylitis. In this study we focused on the spine involvement and the spondylarthropathy in both BALB/c and C3H mouse strains immunized with cartilage proteoglycan aggrecan.

Materials and Methods Female BALB/c and C3H mice, aged 8-12 weeks, were injected intraperitoneally with 100 g of cartilage PG in Freund's adjuvant at three-week intervals. After the 3rd injection arthritis was assessed daily and abnormalities (paw swelling and redness) were recorded as an arthritis score on a scale of 0-4 for each paw. The appearance of joint swelling and redness was considered as the day of the onset of arthritis. Arthritic and non-arthritic mice (n=120) were sacrificed (a) weekly after the 3rd antigen boost, (b) at the time of the onset of arthritis in peripheral joints or (c) weekly up to 8 weeks after the onset of the arthritis. Inflamed and non-inflamed paws and spine were fixed, decalcified and conventional histological sections were prepared. In corresponding studies all animals were tested for antigen-specific T and B cell response and cytokine production.

Results In a genome-wide screening study approximately 15-20% of the F2 (n=949) of genetically susceptible BALB/c mice intercrossed with any other strains developed PGIA. However, when BALB/c and C3H/HeJCr (National Cancer Institute: NCI) were intercrossed, an unexpected high incidence (54%) of F2 hybrids developed arthritis. Therefore, the parent C3H/HeJCr mouse strain was retrospectively tested for PGIA, and the incidence was 95-100% (four independent experiments). Finally a total of ten C3H colonies (sublines) were tested and a wide range of arthritis susceptibility was identified. The most significant difference was found when NCI's C3H/HeJCr (95-100% incidence) were compared, even though these two substrains have the same genetic origin. Jackson's C3H/HeJ colony is hyporesponsive to lipopolysaccharide (LPS) due to the mutation in Tol-4 gene (LPS-receptor), but this was proved to be independent of arthritis susceptibility. Additionally, a new observation was the spine deformities in C3H mice from NCI. In a retrospective study testing the spine of PG immunized mice, only C3H/HeJCr and BALB/c colonies were susceptible to spondylitis. There were large individual variations in spine involvement, and intervertebral discs of the same animal showed various stages of inflammation, cartilage and bone resorption, with or without osteophyte formation. Typically 3-5 weeks after the onset of arthritis in the peripheral joints, one or two intervertebral discs of the low cervical- upper thoracic, and frequently in the lumbar, region showed resorption of the annulus fibrosus and nucleus pulposus due to massive inflammation around the disc. Resorption of intervertebral disc was frequently associated with osteophyte formation leading to complete ankylosis of the neighboring vertebra bodies.

Discussion/Conclusion In this study, we have identified a new arthritis-susceptible mouse strain. More importantly, this is the first study, which describes different levels of susceptibility of an autoimmune disease in a murine strain with identical origin and largely identical genetic background. The two C3H substrains (NCI's and Jackson's) should differ only in a few genes, most likely in a dominant suppressive gene (according to corresponding genetic studies), which controls autoimmune/inflammatory processes in joints and spine. The specific immune response against the mouse-PG (major component of the extracellular matrix in articular cartilage and the intervertebral disc) was evident in all mice with arthritis and spondylitis. The leukocyte infiltration (including lymphocytes in high percentage) followed by the resorption of the intervertebral disc and the ankyllosing osteophyte formation clearly demonstrates the progressive spondylarthropathy. To date this autoimmune murine model represents the only experimental model system, which involves spine (intervertebral disc) components.

Fig. 1. Histopathology of the spine in arthritic C3H/HeJCr mice. The intervertebral discs with the neighboring vertebra bodies are shown. Panel A shows a morphologically intact segment from the lower cervical region. In contrast a complete resorption of the intervertebral disc and marginal vertebral body fusion can be observed in the upper thoracic segment of the same animal (Panel B).

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