
Treatment of the SpA-like disease in HLA B27 transgenic animals

M. Breban¹, E. May²

¹INSERM U567 and Service de Rhumatologie B, Hôpital Cochin, Université René Descartes, Paris, France; ²Dept. Biologie II, Institut für Anthropologie und Human-genetik, Ludwig-Maximilians-Universität München, Munich, Germany.

Maxime Breban, MD, PhD; Ekkehard May, PhD.

Please address correspondence to: Maxime Breban, MD, PhD, INSERM U567 and Service de Rhumatologie B, Hôpital Cochin, 27 rue du Faubourg Saint-Jacques, 75014 Paris, France. E-mail: maxime.breban@cch.ap-hop-paris.fr

Clin Exp Rheumatol 2002; 20 (Suppl. 28): S50-S51.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2002.

Key words: HLA-B27, animal models, spondylarthropathy, cytokines, nitric oxide synthase.

ABSTRACT

A major involvement of the immune system and of microbial flora in the HLA-B27 transgenic rat model of spondylarthropathy was demonstrated. The role of inflammatory pathways, such as cytokines and inducible nitric oxide synthase (iNOS) was investigated. Treatment with IL-10 failed to improve established disease, whereas such improvement was achieved with IL-11. In contrast, aggravation was observed after treatment with selective inhibitor of iNOS.

Introduction

The strong association of ankylosing spondylitis (AS) with HLA-B27 still remains enigmatic. Other closely related inflammatory rheumatic diseases that are characterized by extraarticular manifestations, such as psoriasis, and inflammatory bowel disease (IBD), or by the triggering upon bacterial infection (i.e. "reactive arthritis"), also share association with HLA-B27. Altogether, these disorders have been grouped as the spondyloarthropathies (SpA). HLA-B27 transgenic rodent models have provided new opportunities to investigate the pathogenesis of SpA.

Several lines of rats transgenic for HLA-B27 and human β_2 microglobulin, develop a spontaneous multisystemic inflammatory disorder that reproduces the characteristic features of SpA. This SpA in rat combines gut inflammation resembling ulcerative colitis with peripheral sterile arthritis in the hind limbs, and with inflammatory lesions of intervertebral disks, reminiscent of AS. Lesions of the skin and nails, histologically resembling psoriasis, are also present (1).

Rats transgenic for the HLA-B7 gene have remained healthy (2). This confirms the specificity of the inflammatory disease, here referred to as rat-SpA, for the HLA-B27 allele. However, only some HLA-B27 transgenic rat lines are affected. In fact, a correlation has been

established between the susceptibility to disease and the level of expression of HLA-B27 which is itself directly determined by the number of copies of the B27 transgene integrated in the rat genome (2).

Inbred rats from disease-prone B27 transgenic lines uniformly develop rat-SpA, whereas in humans, only a small proportion of HLA-B27 carriers ever suffer from this disease. Additional genes and environmental factors are likely to be involved in the human SpA. This assumption holds true also in rats, as shown by breeding experiments. Several of the rat backgrounds tested (Lewis, Fisher, PVG) are permissive to disease expression, whereas one of them (Dark Agouti) confers disease resistance by a mechanism that is independent from MHC (2).

The role of the immune system

The immunological basis of the rat SpA has been established. All major features of the spontaneous rat-SpA (gut inflammation, arthritis, psoriasis) could be transferred to B27 transgenic rats of a healthy line as well as to non-transgenic recipients by bone marrow engraftment of immature hematopoietic stem cells from disease-prone lines but not by mature lymphocytes. Therefore, expression of B27 in epithelial cells of target organs is not important for disease induction, whereas bone marrow-derived cell, such as a monocyte or dendritic cell, expressing a high level of B27 is critical for disease induction. Depletion of CD8⁺ T cells through thymectomy and short-term treatment with an antibody against CD8 did not reduce arthritis (3). However, depletion of all CD8⁺ cells, including a population of CD8⁺ cells, different of thymus-derived conventional CD8⁺ T cells significantly attenuated arthritis (4). T lymphocytes are also necessary however, the principal effector T cells belonging to the CD4⁺ population. Hence, it has been proposed that a mechanism of periph-

eral interaction between T cells and HLA-B27+ antigen presenting cells leads to the rat SpA (5).

The role of microbial flora

Gut and joint inflammation are suppressed in B27 transgenic rats raised in germfree isolators, whereas exposure of these germfree rats to a normal flora is sufficient to induce gut inflammation and arthritis. Anaerobic bacteria, especially *B. vulgatus*, play a prominent role in the triggering of colitis in the germfree B27 transgenic rats. Accordingly, metronidazole administration prevented colitis during exposure of germfree B27 transgenic rats to a conventional flora (6, 7).

The role of proinflammatory mediators

Colonic mucosa appears as an early site of inflammation in HLA-B27 transgenic rats, where an increase of IFN- and IL-2 is suggestive of a predominantly Th1-mediated response. In established disease, IL-1, IL-1, TNF-, and macrophage inflammatory protein 2, are expressed (2). Elevated plasma levels of nitrite/nitrate are consistent with an increased production of nitric oxide (NO) and the inducible nitric oxide synthase isoform (iNOS) was detected both in the colonic epithelium and in the hip cartilage, where it could play a pathogenic role (8, 9). The ability of IL-10 to inhibit IFN- and IL-2 release by Th1 cells and to down-regulate TNF- and IL-1, produced by activated macrophages was used to examine the role of these cytokines in the HLA-B27 rat model. Administration of recombinant murine

IL-10 to B27 transgenic rats with established disease had no influence on the disease course, albeit the production of IFN-, TNF-, and IL-1 in the gut mucosa was inhibited, arguing for a dispensable role of this set of proinflammatory cytokines in perpetuating the disease process. It is likely that other mediators are critically involved in the sustained colonic inflammation of HLA-B27 (10). By contrast, treatment with recombinant human IL-11, which also down-regulated expression of IFN-, TNF-, and IL-1, presumably by inhibiting NF- κ B, efficiently reduced colitis in B27 transgenic rats (11).

The role played by iNOS in the HLA-B27 transgenic rat model was tested by administering dexamethasone, which may prevent the expression of iNOS, and by administering the iNOS inhibitor L-N6-(1-iminoethyl)lysine (L-NIL) (10). Dexamethasone treatment had no effect on iNOS expression and was not associated with an inhibition of inflammation. L-NIL-treatment was associated with aggravation of arthritis, and colitis. NO from iNOS may contribute to tissue destruction through the generation of peroxynitrite, when produced by macrophages and neutrophils in combination with oxygen free radicals. This consequence is less likely to happen if NO production takes place in epithelial cells, such as in chronic colitis of HLA-B27 transgenic rat. Local production of NO in the epithelium may rather display antibacterial effects that could be beneficial.

References

1. HAMMER RE, MAIKA SD, RICHARDSON JA, TANG J-P, TAUROG JD: Spontaneous inflammatory disease in transgenic rats expressing HLA-B27 and human β_2 m: An animal model of HLA-B27-associated human disorders. *Cell* 1990; 63: 1099-112.
2. TAUROG JD, MAIKA S, SATUMTIRA N *et al.*: Inflammatory disease in HLA-B27 transgenic rats. *Immunol Rev* 1999; 169: 209-23.
3. REHMAN MI, DORRIS ML, KAUSHIK P, SATUMTIRA N, TAUROG JD: Depletion of CD8 T cells does not prevent the development of spondyloarthritis (SPA) in HLA-B27 transgenic rats. *Arthritis Rheum* 2000; 43: S395.
4. MAY E, SATUMIRA N, DORRIS ML, IQBAL I, LIGHTFOOT E, TAUROG JD: Depletion of all CD8a+ cells, but not CD8+ cells alone, attenuates arthritis in HLA-B27 transgenic rats. *Arthritis Rheum* 2001; 44: S160.
5. BREBAN M, FERNANDEZ-SUEIRO JL, RICHARDSON JA *et al.*: T cells, but not thymic exposure to HLA-B27, are required for the inflammatory disease of HLA-B27 transgenic rats. *J Immunol* 1996; 156: 794-803.
6. RATH HC, HERFARTH HH, IKEDA JS *et al.*: Normal luminal bacteria, especially Bacteroides species, mediate chronic colitis, gastritis, and arthritis in HLA-B27/human β_2 microglobulin transgenic rats. *J Clin Invest* 1996; 98: 945-53.
7. RATH HC, BENDER DE, HOLT LC *et al.*: Metronidazole attenuates colitis in HLA-B27/hB2 microglobulin transgenic rats: A pathogenic role for anaerobic bacteria. *Clin Immunol Immunopathol* 1995; 76: S45.
8. AIKO S, GRISHAM MB: Spontaneous intestinal inflammation and nitric oxide metabolism in HLA-B27 transgenic rats. *Gastroenterology* 1995; 109: 142-50.
9. BLANCHARD H S, DERNIS-LABOUS E, LAMARQUE D *et al.*: Inducible nitric oxide synthase attenuates chronic colitis in HLA-B27/human β_2 -microglobulin transgenic rats. *Eur Cytokine Netw* 2001; 12: 111-8.
10. BERTRAND V, QUERE S, GUIMBAUD R *et al.*: Effects of murine recombinant IL-10 on the inflammatory disease of rats transgenic for HLA-B27 and human β_2 -microglobulin. *Eur Cytokine Netw* 1998; 9: 167-70.
11. PETERSON RL, WANG L, ALBERT L, KEITH JCI, DORNER AJ: Molecular effects of recombinant human interleukin-11 in the HLA-B27 rat model of inflammatory bowel disease. *Lab Invest* 1998; 78: 1503-12.