We found multimolecular antigen mimicry of arthritogenic autoantigens and peptides from several other "self" or foreign antigens sharing amino acid sequence homologies. Many of these new mimotopes induced arthritis and/or uveitis upon immunization in Lewis rats, indicating a role for multiple antigens in the initiation of a certain autoimmune disease.

Uveitis and arthritis are T-cell-mediated diseases in patients as well as in the Lewis rat model. Cross-reactivity of T cells between peptide antigens is the basis for molecular mimicry, a mechanism that is proposed to initiate autoimmunity. We have previously described HLA class I-derived peptides that mimic retinal (B27PD/PDSAg from retinal S-antigen) or synovial (B2702PA/Ker333 from cytokeratin) antigens, cause uveitis (10, 14) or arthritis (11), and may also be used therapeutically as oral tolerogens in uveitis patients (8) and rats (11, 14). Additional uveitogenic peptides that resemble retinal autoantigen peptide PDSAg can be derived from environmental antigens, such as rotavirus- or food-derived peptides (from bovine milk casein). The peptides induce cross-reactive T-cell responses in rats and uveitis patients (10). Here we present the effect of a variety of new arthritogenic peptides that share amino acid homologies with the mimotope pairs B27PD/PDSAg and B2702PA/Ker333 as well as with B27PB, a new pathogenic HLA peptide (Fig. 1). All peptides were identified by National Institutes of Health database searches for sequence homologies with peptides PDSAg, B27PD, B2702PA, Ker333, and B27PB.

To test pathogenicity, we subcutaneously immunized Lewis rats (Janvier, France) with 100 µg of each peptide (Biotrend, Germany) listed in Fig. 1 in complete Freund’s adjuvant as described previously (11) (only PDSAg was used at a dose of 20 µg per rat). Ten days later, the animals underwent daily clinical examination, and arthritis and uveitis were graded as described previously (2, 11). Histological uveitis grading was performed with cryosections of eyes stained for CD4 (14). All animal experiments were approved by the review board of the government of Oberbayern.

Uveitis was induced only after immunization with peptides PDSAg and Rota and, in a very mild form, with B27PD (Fig. 2). No other morbidities or abnormalities were observed by physical and morphological examination of the animals, except for arthritis in the cases shown in Fig. 1. Complete Freund’s adjuvant immunization alone was neither arthritogenic nor uveitogenic (data not shown). Of those peptides, which repre-
tion of RORα (9) was previously described as a potential treatment for arthritis (6).

The HLA-B27-derived peptide B27PB was highly arthritogenic in Lewis rats following subcutaneous immunization. However, testing proliferation of peripheral blood lymphocytes from patients with ankylosing spondylitis or rheumatoid arthritis did not reveal B27PB-specific responses (4). Kleb was derived from *Klebsiella pneumoniae*, which can cause urinary tract infections and pneumonia. This pathogen is described as a potential causative agent for ankylosing spondylitis (3). Peptide Kleb has only three major amino acid differences from B27PB (Y5, A9, Y10) but is significantly (P = 0.045 by the Mann-Whitney test) less arthritogenic.

Peptide CMV differs from B27PB in four amino acids (Y1, Y4, S9, and W10) but completely lacks pathogenicity. The restriction element for B27PB and its potential mimotopes Kleb and CMV is unknown; therefore, we cannot speculate about anchor positions that facilitate or impede MHC binding. The joint-specific mimotope of T cells reactive to B27PA and its derivatives B27PA and B2702PAS is postulated as being cytokeratin, represented by peptide Ker333. The joint-specific autoantigens mimicked by peptides Rota, B27PB, and Kleb finally targeted by the arthritogenic immune responses are unknown.

Experimental autoimmune uveitis and arthritis in the Lewis rat reflect the human situation with respect to immune responses to the uveitogenic peptides PDSAg, B27PD, and Rota (10, 14) as well as to peptide B27PA (4). In vivo we observed pathogenic effects by induction of autoimmune diseases (arthritis and/or uveitis) in rats; in vitro we found cross-reactive
T-cell responses (PDSAg and Rota [10]; B2702PA and Ker333 [11]).

We have shown that cross-reactive immune responses can be highly promiscuous, because certain autoantigen peptides can be mimicked by more than one mimotope of viral, bacterial, or even self origin. This indicates that an autoimmune response must not originate from a single mimotope of a certain infectious agent and is probably not even directed to only a single autoantigen. Multiple cross-reactivities between tissue-specifically expressed autoantigens might explain the effect on multiple tissues or organs by some autoimmune diseases.

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