Staphylococcal enterotoxin B increases the severity of type II collagen induced arthritis in mice

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Abstract

Objective—To observe the influence of T cell subset changes on the development of experimental arthritis, by using the bacterial superantigen staphylococcal enterotoxin B (SEB) to modulate the T cell repertoire during the arthritogenic response to type II collagen (CII) in vivo. Methods—DBA/1 mice were injected with SEB before immunisation with CII, and assessed for the development of collagen induced arthritis (CIA) and an immune response to CII. Mice with established arthritis were also treated therapeutically with SEB. Flow cytometry was used to evaluate the effect of the therapy on T cell subsets and T cell receptor (TCR) Vβ expression.

Results—Mice injected with SEB developed arthritis significantly faster than saline treated control animals, and developed more severe clinical features. Mice treated with SEB after the onset of CIA were also observed to progress more rapidly to a severe arthritis than mice treated with saline alone. The level of anti-CII antibody was not affected by SEB injection. Flow cytometric analysis of TCR expression in mice 21 days after injection of CIA showed decreased expression of Vβ6 and Vβ8 cells in SEB treated mice, compared with collagen immunised control mice. Injection of SEB alone caused a decrease in Vβ8, but not Vβ6, T cells compared with the values in normal DBA/1 mice. No significant variations in the T cell repertoire were detected 70 days after CIA immunisation.

Conclusions—Treatment with the bacterial enterotoxin SEB before the induction of arthritis did not suppress the immunological or arthritogenic response to CII in DBA/1 mice, despite the modulation of the Vβ8 T cell subset. Treatment of mice with established arthritis using SEB provoked a more severe disease course.

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Collagen induced arthritis (CIA) in mice is an experimental disease model which resembles rheumatoid arthritis (RA) with respect to both the histopathological features of arthritis and immunogenetic regulation by the major histocompatibility complex (MHC). A close parallel is observed between the class II MHC (HLA-DR) association in RA and the strict MHC association seen in CIA. The immunogenetic analysis of susceptibility to CIA in mice indicates that both the MHC (H-2) phenotype and the T cell repertoire may be critical in the development of autoimmunity. Recent evidence suggests the potential role of the minor lymphocyte stimulating (Mls) genes in CIA susceptibility. The Mls locus acts in the selection of the T cell repertoire, as T cells that recognise Mls antigens in context with self MHC are clonally deleted in the thymus, and it has been suggested that a dysfunction in the Mls system may result in the preservation of self reactive T cells. CIA is associated with H-2d, which is characterised by the absence of I-E. Thus H-2d mice express Vβ8 and Vβ6 T cells, with the exception of the CIA resistant SWR strain (because of a gene deletion). The role of the Vβ8 subset in the development of CIA is controversial, as SWR mice are also complement deficient. Although a recent report suggested that the depletion of Vβ8 cells was effective in preventing the onset of CIA, this finding was not confirmed in a similar study. Despite these variable findings, a limited number of Vβ genes in the ‘autoimmune’ T cell receptor (TCR) repertoire may be responsible for the arthritogenic response to collagen.

The action of the Mls antigen system in T cell selection is mimicked by the activities of staphylococcal enterotoxins. In vivo administration of staphylococcal enterotoxin B (SEB) to neonatal mice causes a complete depletion of mature Vβ8 and Vβ3 T cells by day 10, in contrast with the preservation of cells expressing Vβ6. This clonal deletion presumably arises as a result of neonatal tolerance of SEB. In contrast, enterotoxins are strongly mitogenic in vitro, and expand particular Vβ T cell subsets. The mitogenic profile of SEB indicates that Vβ3, Vβ7, Vβ8, and Vβ17 T cells are clonally expanded, and while in vivo administration of SEB does not alter the absolute number of lymph node T cells, increased Vβ8 expression occurs in a dose dependent manner. However, it has been suggested that SEB induced Vβ8 cells may enter a state of profound anergy, characterised by failure to proliferate in response to anti-Vβ8, SEB, or IL-2 in vitro. This anergy may be confined to the CD4 T cell subset, leaving activity intact in Vβ8 CD8 T suppressor/cytotoxic cells. An influence on the CD4 T cells is supported by findings that SEB
in vivo is immnosuppressive to antibody generation\textsuperscript{16} and the delayed type hypersensitivity response.\textsuperscript{17} The present study used CIA as an experimental model to examine the hypothesis that superantigenic modification of the T cell repertoire may alter the activity of self reactive cells and change susceptibility to autoimmune disease.

**Methods**

**ANIMALS**

Female DBA/1 (H-2\textsuperscript{b}) LacJ mice (seven to eight weeks old) were obtained from Jackson Labs (Bar Harbor, Maine), and housed in the Department of Laboratory Animal Resources at Wayne State University, in accordance with NIH animal care guidelines. Mice were housed randomly, and identified by ear tags. All procedures commenced following a two week period of quarantine.

**INDUCTION AND ASSESSMENT OF COLLAGEN INDUCED ARTHRITIS**

Bovine type II collagen was solubilised at 2 mg/ml in 0-01 mol/l acetic acid overnight at 4°C, and emulsified with an equal volume of cold Freund’s complete adjuvant (FCA) containing 2 mg/ml Mycobacterium tuberculosis H37Ra (Difco, Detroit). Mice were injected intradermally at a single site at the base of the tail with 100 μl of cold emulsion as described elsewhere.\textsuperscript{18} Mice were monitored daily for examination of the onset of disease, which was usually characterised by erythema and oedema in a single paw. After the onset of arthritis, the joints were measured with a constant tension caliper (Schnelltaster System, Kroplin, FRG) to follow the progression of joint swelling during the course of the disease. Each limb was assigned a joint index according to the following score: 0 = normal; 1 = joint swelling and erythema; 2 = visible joint distortion; 3 = ankylosis. Animals affected with arthritis were clinically assessed five times per week until 10 weeks after immunisation, and paw measurements were made three times per week. Mice without signs of arthritis 10 weeks after immunisation were considered disease negative.

**TREATMENT WITH STAPHYLOCOCCAL ENTEROTOXIN B**

SEB (Toxin Technology, Sarasota, FL) was dissolved in sterile saline solution to a concentration of 400 μg/ml. The table summarises the groups of mice and their treatments. Ten DBA/1 mice (group 1) were prophylactically injected intraperitoneally with 100 μl (40 μg) of SEB one day before immunisation with collagen (this dose has been reported as effective in modulating \textsuperscript{VB} T cell populations in vivo).\textsuperscript{19} Ten control mice received 100 μl of sterile saline (vehicle control) and immunisation with collagen (group 2), while six control mice received 100 μl (40 μg) of SEB and immunisation with FCA alone (group 3). Separate groups of four DBA/1 mice (groups 4–6) were immunised and treated by these same three procedures but underwent flow cytometric analysis at day 21. Control normal (unimmunised untreated), DBA/1 mice which received sterile saline alone were included in the assessment (group 7). To examine the influence of SEB on established arthritis, DBA/1 mice were immunised with CII and at the first signs of visible joint disease, the animals were injected with either 100 μl (40 μg) of SEB (group 8) or sterile saline (group 9).

**FLOW CYTOMETRIC ANALYSIS**

Four mice were sacrificed at day 21 or day 70 after immunisation, lymph nodes (inguinal and popliteal) removed, and single cell suspensions made for flow cytometric analysis using techniques described previously.\textsuperscript{19} Spleen cells were not examined, because the spleen population does not appear to participate in the development of CIA.\textsuperscript{20} Cells (10\textsuperscript{6}) were resuspended in 100 μl phosphate buffered saline (PBS) containing 2% fetal calf serum (FCS), 20 mmol/l sodium azide and an appropriate dilution of the primary antibody to CD5 (Lyt1; rat IgG2a from ATCC clone 53-7.313, prepared as described previously\textsuperscript{15}), CD4 (L3T4; rat IgG1 from ATTC clone GK1.5, prepared as described previously\textsuperscript{15}), CD8 (Lyt2.1; IgG3 mouse monoclonal antibody 49-31.1, Cedarlane, Ontario), or 100 μl of PBS/FCS alone. After incubation on ice for 20 minutes, the cells were washed by the addition of 2 ml of cold PBS, centrifuged at 1500 g for 10 minutes, and resuspended in 100 μl PBS/FCS containing either 1/100 dilution of fluorescein isothiocyanate (FITC) conjugated goat anti-mouse Ig (Tago), or 1/10 dilution of goat anti-rat Ig F(ab\textsuperscript{2}) (Jackson). Cell suspensions were analysed using a fluorescence activated cell sorter. Dead cells, erythrocytes, and granulocytes were excluded from the analysis by the construction of appropriate gates based on forward and 90° scatter. Re-analysis of the mononuclear cell population for fluorescence intensity determined the percentage of positive cells for each cell marker. Appropriate corrections for background staining and autofluorescence were included in the analysis.

Two colour flow cytometry was used to determine TCR expression. Cells (10\textsuperscript{6}) were resuspended in an appropriate dilution of FITC conjugated antibody to CD3 (Clone 500A2, hamster IgG; Pharmingen, CA). One of the following phycoerythrin conjugated anti-\textsuperscript{VB} sera library (Pharmingen, CA) were added: \textsuperscript{VB}2 (Clone B20.6, rat IgG2a), \textsuperscript{VB}3 (Clone

**Experimental treatment protocol**

<table>
<thead>
<tr>
<th>Group</th>
<th>Immunisation</th>
<th>Treatment</th>
<th>Assessment</th>
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<tbody>
<tr>
<td>1</td>
<td>Type II collagen + FCA</td>
<td>40 μg SEB</td>
<td>Clinical</td>
<td>10</td>
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<tr>
<td>2</td>
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<td>Saline</td>
<td>Clinical</td>
<td>10</td>
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<tr>
<td>3</td>
<td>FCA</td>
<td>40 μg SEB</td>
<td>Clinical</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>Type II collagen + FCA</td>
<td>40 μg SEB</td>
<td>Flow cytometry (day 21)</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>Type II collagen + FCA</td>
<td>Saline</td>
<td>Flow cytometry (day 21)</td>
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<tr>
<td>6</td>
<td>FCA</td>
<td>40 μg SEB</td>
<td>Flow cytometry (day 21)</td>
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<tr>
<td>7</td>
<td>Saline</td>
<td>Flow cytometry (day 21)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Type II collagen + FCA</td>
<td>40 μg SEB</td>
<td>Clinical (after onset)</td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td>Type II collagen + FCA</td>
<td>Saline</td>
<td>Clinical (after onset)</td>
<td>12</td>
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FCA = Freund’s complete adjuvant; SEB = staphylococcal enterotoxin B.
KJ-25, hamster IgG), Vβ5.1, 5.2 (Clone MR9-4, mouse IgG1), Vβ6 (Clone RR4-7, rat IgG2b), Vβ7 (Clone TR310, rat IgG2b), Vβ8.1, 8.2 (Clone MR5-2, mouse IgG2a), Vβ9 (Clone MR10-2, mouse IgG1), Vβ11 (Clone RR3-15, rat IgG2b), or Vβ14 (Clone 14-2, rat IgM). After incubation and washing, cells were resuspended in PBS and analysed by flow cytometry. Two dimensional analysis of the mononuclear cell population for red and green fluorescence determined the percentage of cells dual positive for the pan T cell CD3 marker and the library of Vβ markers.

ANTIBODY RESPONSES TO TYPE II COLLAGEN
The antibody responses to CII were assessed using an enzyme linked immunosorbenent assay (ELISA) assay described previously. ELISA plates were coated overnight at 4°C with 3 μg/well of CII. Plates were washed three times with PBS/Tween, and blocked by the addition of 5% bovine serum albumin (BSA)/PBS. Serum samples diluted 1/200 in PBS/BSA were dispensed in triplicate. A standard serum was titrated on each plate, and negative controls were included in the assay. The plates were incubated overnight at room temperature, and washed three times with PBS/Tween. Goat anti-Ig conjugated with alkaline phosphatase was added, and incubation continued for one hour at 37°C. After the plates were washed, 100 μl of paranitrophenyl phosphate solution in diethanolamine buffer was added to each well, and the reaction allowed to proceed for 20 minutes in the dark. The plates were read at 405 nm using a Photometer (Molecular Devices), and the data analysed using the SOFTmax analytical software package. Antibody levels were expressed as units derived from the standard curve.

CELL PROLIFERATIVE RESPONSES
Lymph nodes were removed at sacrifice from six mice in groups 1–3, and mitogen responses to concanavalin A (Con A) (Sigma, St Louis, MO), lipopolysaccharide (LPS) (Difco, Detroit, MI) and SEB, and antigen responses to collagen were determined as described previously. Single cell suspensions were made in RPMI-1640 (Gibco, Grand Island, NY) supplemented with 10% FCS. Proliferative responses to Con A, LPS or SEB were measured by culturing 2.5 × 10⁶ cells with 2.5 μg/ml of Con A, 10 μg/ml of LPS, 2.5 μg/ml of SEB, or 25 μg/ml of collagen in RPMI-1640 supplemented with 10% FCS and 40 μmol/l 2-mercaptoethanol in 96 well tissue culture plates (Costar). After three days incubation at 37°C, wells were pulsed with 20 μl/well 3-(4,5-dimethylthiazol-2)-2,5-diphenyltetrazolium bro- mide (MTT) at 10 mg/ml in sterile PBS. Plates were incubated for 24 hours at 37°C, and 180 μl of supernatant removed from each well and replaced with 180 μl of 10% sodium dodecyl sulphate in PBS. After incubation at 37°C for four hours, the optical density of the wells at 590 nm was determined using the microplate spectrophotometer. Proliferation results were expressed as OD₅₉₀ units, corrected for the background proliferative response observed in cultures containing medium alone.

STATISTICAL ANALYSIS
Data were analysed using the SPSS-PC (SPSS Inc., Chicago, IL) statistical software package. The group comparisons were performed using χ² test or the Mann-Whitney test for independent samples of non-parametric data.

**Results**

INFLUENCE OF SEB PRETREATMENT ON COLLAGEN INDUCED ARTHRITIS
Figure 1 shows the effect of SEB injection upon the development of CIA. DBA/1 mice injected with SEB and immunised with collagen developed arthritis significantly faster (mean day of onset 37-4) than control animals injected with saline and immunised with collagen (mean day of onset 56-7) (p < 0.01), although the final disease incidence was similar (80%). Mice injected with SEB and immunised with FCA alone did not develop arthritis. Figure 2 shows the effect of SEB on the severity of the arthritis. Mice injected with SEB and immunised with collagen developed a similar number of involved paws, but significantly more severe clinical disease (assessed by the maximum disease index) than control animals (p < 0.02).

The arthritis in DBA/1 mice treated with a single injection of SEB 40 μg at the onset of disease (fig 3) progressed faster than in control mice treated with saline, with significant differences in the arthritis score occurring from one week after onset and sustained throughout the assessment period (p < 0.05) at week 1, p < 0.02 at week 5.

FLOW CYTOMETRIC ANALYSIS
Figure 4 shows the results of the flow cytometric analysis of lymph node cells from...
mice sacrificed 21 days after injection of CII. All mice immunised with CII showed a marked increase in Ig positive (B) cells compared with saline injected control DBA/1 mice. The Ig positive cell population of CII immunised, saline injected mice (26-5%) was significantly increased (p < 0.025) compared with the normal controls (16-3%). However, the percentage of Ig positive cells in mice immunised with CII and injected with SEB (39-7%) was significantly increased compared with CII immunised, saline injected mice (p < 0.04). DBA/1 mice injected with SEB, but not immunised with CII also demonstrated a significant increase in Ig positive cells (33-0%) (p < 0.05) compared with the normal control mice. There were corresponding significant decreases in the proportion of lymph node CD5 T cells from these populations, and the numbers of CD5 cells from CII immunised, SEB treated mice (51-6%) were significantly reduced compared with CII immunised, saline injected mice (64-5%) (p < 0.05). However, data from T cell phenotyping for CD4 and CD8 did not suggest that either subset was specifically affected by the enterotoxin therapy (fig 4).

The antibody library used for the two colour flow cytometric analysis of T cell receptor expression in mice accounted for 81.7-95.0% of CD3 T cells (fig 5). Immunisation with CII alone did not cause any significant variations in the lymph node TCR Vβ repertoire in comparison with the Vβ distribution seen in normal DBA/1 mice, although the proportion of Vβ8 cells (23-6%) was increased compared with normal (18-7%). In contrast, injection with SEB alone caused a significant decrease (p < 0.05) in Vβ8 cells. DBA/1 mice immunised with CII and injected with SEB also showed a significant decrease in Vβ8 cells, when compared with either CII injected or control DBA/1 mice (p < 0.025 for both determinations). CII immunised DBA/1 mice injected with SEB also showed significantly decreased levels of Vβ6 cells when compared with CII injected, saline injected DBA/1 mice, or normal control mice (p < 0.05). The proportion of Vβ6 T cells in DBA/1 mice injected with SEB alone was not significantly different from that of Vβ6 T cells in normal DBA/1 mice.

In contrast to the analysis 21 days after immunisation, flow cytometric analysis of T cell Vβ receptor expression in mice sacrificed 70 days after CII immunisation showed no significant variations in the T cell repertoire (Vβ2, 3, 5, 6, 7, 8, 9, 11, 14) between the enterotoxin treated mice and controls (data not shown).

**INFLUENCE OF ENTEROTOXIN PRETREATMENT ON THE IMMUNE RESPONSE**

Anti-bovine type II collagen antibody levels, determined by ELISA, indicated that all mice developed a vigorous antibody response to collagen. The amount of anti-CII antibody in SEB treated mice was not significantly different from controls. No remarkable
Figure 5 Flow cytometric analysis of T cell receptor (TCR) Vβ markers on lymph node cells from mice sacrificed 21 days after collagen or control (saline) immunisation: mean percentage of cells staining positive for each Vβ antiseraum. □ = Normal controls; ■ = staphylococcal enterotoxin B (SEB) alone; □ = collagen induced arthritis + saline; □ = collagen induced arthritis + SEB. The SEM of each group (not shown) did not exceed 5% of the mean for any determination.

Discussion

Collagen induced arthritis in mice appears to represent a sound model of rheumatoid arthritis, resembling a number of the immunological and histopathological features of RA. CIA is an MHC restricted disease, occurring only in H-2k and H-2g phenotype mice." This restriction may occur at the level of antigen presentation, as sequences in both the I-A\(\alpha\) and I-A\(\beta\) chains have been implicated in collagen peptide presentation. However, the specificity of collagen responsive T cells may also regulate the development of disease. The CIA resistant SWR (H-2k) strain has a major deletion in the TCR V\(\beta\) genes, which could account for the failure of SWR to develop collagen reactive T cells that participate in the pathogenesis of arthritis. In particular, the V\(\beta\) 8 T cell subset has been implicated in the arthritogenic response to collagen, by studies examining the restricted heterogeneity of TCR V\(\beta\) usage in lymph nodes and joints from CIA mice and using monoclonal antibody immunotherapy to deplete V\(\beta\) 8 T cells from collagen immunised mice.

The role of the V\(\beta\) 8 T cell subset in the development of CIA remains controversial as SWR mice are complement (C5) deficient and may be resistant to arthritis because of the role of complement in the inflammatory process. Nevertheless, the participation of a limited T cell response in the pathogenesis of arthritis remains an attractive hypothesis, particularly considering the recent demonstration of the accumulation of TCR V\(\beta\) 14 cells within the rheumatoid joint. Therefore, modulation of the T cell repertoire using superantigen immunotherapy appeared to represent a viable approach to the treatment of autoimmune disease in which limited TCR usage is responsible for the development of autoimmunity.

SEB immunotherapy has already shown the potential for modulation of murine models of autoimmune disease, with positive effects reported in MRL lpr/lpr disease. In that study, V\(\beta\) 8 T cells were reduced in both spleen and lymph nodes from MRL lpr/lpr mice, and the SEB therapy resulted in the improvement of both the clinical and immunological features of murine lupus. However, intra-articular injection of SEB in V\(\beta\) 8.2 transgenic MRL lpr/lpr mice gave rise to a chronic arthritis, suggesting that the chronic joint disease in this model was adversely affected. Our data suggest that staphylococcal enterotoxins were not immunosuppressive in collagen immunised mice at any administration time point examined. DBA/1 mice injected with a single dose of SEB at the time of CII immunisation developed arthritis faster, and exhibited more severe disease signs, than control animals. Administration of SEB subsequent to the appearance of CIA also resulted in a more severe arthritis. The precise cause of the increased disease severity is not clear, as the immune response to collagen was not increased in SEB treated mice. The flow cytometric data indicated changes in both B cells and T cells in enterotoxin treated, CIA immunised mice. As predicted by published studies on the in vivo and in vitro effects of enterotoxins, treatment with SEB before immunisation with CII caused changes in the TCR repertoire of DBA/1 mice. These changes in T cell V\(\beta\) expression were detected 21 days after injection of enterotoxin but were not apparent 70 days after injection. A decrease in TCR V\(\beta\) expression occurred in lymph node cells from both collagen immunised and normal mice in response to SEB injection. The decrease in V\(\beta\) 8 cells is consistent with the elimination of the V\(\beta\) 8 subset reported in both adult and neonatal mice, although Marrack et al demonstrated an increase in adult B10.BR mice injected with SEB. In our study, the V\(\beta\) 3 subset in adult DBA/1 mice was not affected by the immunotherapy, whereas a 1–2% decrease in V\(\beta\) 3 T cells was seen by Marrack’s group.

We did not observe changes in the V\(\beta\) 7 subpopulation, which occur only with high (100 \(\mu\)g) dose treatment. V\(\beta\) 6 T cells were not affected by the injected of SEB in normal DBA/1 mice. However, SEB caused a decrease in the V\(\beta\) 6 subset in mice immunised with CII. This result was not predicted by the known T cell specificity of the enterotoxins. Previous reports have suggested that the modification of the T cell repertoire by SEB acts as an immunosuppressive agent, possibly by the induction of T cell anergy in cells bearing a TCR engaged by the superantigen. However, the phenotypic changes induced by SEB during the response to collagen did not result in immunosuppression and reduced disease. There was no obvious preference in the SEB effects for either CD4 or CD8 T cells in...
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collagen injected mice. Our data suggest that SEB does not suppress the immunological or arthritogenic response to CII, but actually enhances the disease. Furthermore, this arthritic effect occurred irrespective of the time of administration of SEB. It is possible either that collagen reactive Vβ8+ or Vβ6+ T cells, or both, are preserved during SEB immunotherapy, or that the Vβ8 or Vβ6+ T cell population is not essential for the development of CIA, as suggested by Holmdahl et al. However, it is possible also that the effect is independent of specific influences on the T cell repertoire in the DBA/1 mice, as the introduction of enterotoxins in collagen immunised mice may promote increased cytokine activity in synovial cells, and it has been demonstrated that increased levels of interleukins and interferon promote collagen-induced arthritis.44

Our results suggest that the concept of T cell modification using superantigen immunotherapy may be problematic, because the T cell subsets modified in vivo did not correlate completely with the predictions based on in vitro studies, and the nature of the specific autoimmune response may be critical to the outcome of the immunotherapy. The precise immunogenetic aspects of the autoimmune disease may also play a crucial role in the outcome, as a similar approach to the treatment of CIA induced by B10.RIII mice using SEB has demonstrated disease suppression. However, this H-2d strain responds to a different epitope on the CII molecule, and TCR usage in B10.RIII mice immunised with porcine collagen may vary markedly from that in DBA/1 mice injected with bovine collagen. Marked differences between H-2d and H-2k haplotype mice were observed in the response to immunotherapy using monoclonal antibodies directed against the class II MHC molecule, with B10.RIII mice developing a more severe arthritis after the injection of an anti-I-E antibody. At present, the specificity of the T cell autoimmune response in rheumatoid arthritis is unknown, and the response may be directed against several self components. Current reports suggest that the T cell receptor expression in synovial fluid and synovial tissue is polyclonal and varies within the RA population. It will therefore be important to determine the precise nature of the cellular response in RA patients before a superantigen therapy should be considered in human autoimmune disease.

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