Yersinia enterocolitica Serotype O:3 Alters the Expression of Serologic HLA-B27 Epitopes on Human Monocytes

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The expression of serologic HLA-B27 epitopes on leukocytes of patients with reactive arthritis or ankylosing spondylitis has been shown to be modified in the course of the disease. The purpose of this work was to study whether phagocytosis of arthritis-triggering microbes in vitro alters the expression of HLA-B27 molecules on human antigen-presenting cells and to characterize the underlying mechanisms. Human monocytes and HLA-B27- or HLA-A2-transfected human U-937 cells were exposed to Yersinia enterocolitica serotype O:3. The expression of different epitopes of HLA-B27 was monitored by using immunofluorescence, and their synthesis was determined by quantitative immunoprecipitation. Our results show that phagocytosis of Y. enterocolitica serotype O:3 changed the expression of serological HLA-B27 epitopes. This was due to the decreased synthesis of HLA-B27 molecules. The expression of the ME1 epitope, which has been shown to be important for T-cell recognition in patients with reactive arthritis, was decreased. Down-regulation of epitopes important for T-cell recognition may impair the elimination of arthritis-triggering microbes and lead to persistent infection. In addition, Y. enterocolitica serotype O:3 seemed to alter the repertoire of peptides presented by the HLA-B27 molecules on human monocytes. This may have a role in the pathogenesis of reactive arthritis via an autoimmune mechanism.

Reactive arthritis is often self-limiting polyarthritis, but in certain patients the disease develops into a chronic inflammatory arthritis or sacroilitis (24). The association of reactive arthritis with HLA-B27 suggests that the pathogenetic mechanisms underlying this disease may be similar to those of other HLA-B27-associated spondylarthopathies (1). The basis for HLA-B27 association in seronegative spondylarthopathies is not clear.

Microbes that trigger reactive arthritis are facultative or obligate intracellular pathogens, and thus the major histocompatibility complex (MHC) class I-mediated pathway of antigen presentation is probably significant in clearing the arthritis-triggering primary infections and in initiating the arthritic process (15). Persistence of microbial structures has been suggested to be important for the development of arthritis (10). CD8-positive and B27-restricted Yersinia-specific, Salmonella-specific, or autoreactive cytotoxic lymphocytes have been cloned from the synovial fluid of patients with Yersinia-triggered and Salmonella-triggered reactive arthritis (15). This emphasizes the role of T cells in the development of the disease. Microbes associated with the development of seronegative spondylarthropathies may also directly interact with HLA-B27 (8, 19, 48).

Earlier studies have shown that certain HLA-B27 epitopes are modified in patients with reactive arthritis and ankylosing spondylitis (2, 20, 29). In the present study, we wanted to characterize the mechanisms behind this modification. Altered expression of epitopes that are critical for T-cell recognition on antigen-presenting cells may have a role in the pathogenesis of HLA-B27-associated diseases via modified antigen presentation. Down-regulation of epitopes important for antigen presentation may also favor the survival of arthritis-triggering microbes in the body.

MATERIALS AND METHODS

Bacteria. The strain of Yersinia enterocolitica serotype O:3 used (4147/83) was a stool isolate from a patient developing reactive arthritis as a result of infection. The strain contains a virulence-associated 72-kb plasmid. Other arthritis-triggering bacteria used in this study were Y. enterocolitica serotype O:9 (strain EF-8239 from Culture Collection of University of Gothenburg [CCUG], Gothenburg, Sweden), Yersinia pseudotuberculosis serotype I (strain EF-5885 from CCUG), Y. pseudotuberculosis serotype III (strain EF-244 from CCUG), and Salmonella enteritidis (strain 8822/88, isolated from a patient who developed reactive arthritis after gastrointestinal infection). In addition, a plasmid-cured derivative of Y. enterocolitica serotype O:3 obtained after the bacteria were cultured on magne- 
sium-oxalate agar at 37°C was used (9). The presence or absence of the virulence plasmid of Yersinia bacteria was verified by autoagglutination (23). As control bacteria, we used Streptococcus pyogenes (strain 8184, American Type Culture Collection [ATCC], Rockville, Md.) and enteroinvasive Escherichia coli (strain RHE-3459, Central Public Health Laboratory, Colindale, London, United Kingdom). S. pyogenes was chosen as a control bacterium because it can cause postinfectious joint complications (rheumatic fever) which are not linked to HLA-B27. Also, S. pyogenes does not contain lipopolysaccharide. E. coli has lipopolysaccharide but does not induce reactive arthritis. Stock cultures were maintained at −40°C in 20% (vol/vol) glycerol-Trypticase soy broth. The Yersinia bacteria were grown in RPMI 1640 medium mimicking the extracellular conditions of the body or in Luria-Bertani broth (LB). The resulting bacterial cultures were suspended in saline, harvested by centrifugation, and washed three times in saline. The bacteria were killed with heat (1 h, 100°C) and stored in phosphate-buffered saline (PBS) at 4°C. E. coli was grown in LB and killed with heat like Y. enterocolitica serotype O:3. S. pyogenes was grown on blood agar plates for 2 days. The resulting bacteria were harvested, killed with heat, and suspended in saline. S. enteritidis was grown in LB, washed once with NaCl, and stored in glycerol- 
Trypticase soy broth at −40°C. Live bacteria were washed twice with PBS before use.

Peptide extract. Y. enterocolitica serotype O:3 was grown, killed with heat, and suspended in saline as described above. The suspension was sonicated with a Soniprep 150 Ultrasonic Disintegrator (MSE Scientific Instruments, Sussex, England) for 60 s and treated thereafter with proteinase K (100 μg/ml) for 2 h at 57°C and then for 2 h at room temperature (Boehringer GmbH, Mannheim, Germany) and DNase, grade II (100 μg/ml) (Boehringer). The sonicate was centrifuged at 13,000 × g for 10 min, and the peptides were collected. The
peptide extract was diluted in saline (1 mg/ml) and boiled at 100°C for 5 min to inactive proteinase K.

Monocyte isolation. Monocytes from healthy blood donors (Finnish Red Cross, Turku, Finland) or healthy laboratory personnel were isolated as described elsewhere (52). Briefly, human peripheral blood mononuclear cells were isolated by Ficoll-Paque gradient centrifugation (Pharmacia LKB Biotechnology AB, Uppsala, Sweden), and monocytes were allowed to adhere to plastic tissue culture chambers for 1 h. Thereafter, nonadherent cells were washed off. The purity of monocyte populations was determined by using monoclonal antibodies (MAbs) ME1 (4) and BB7.2, respectively (32, 37, 38). Two days before the experiments, the transfectants were removed from the selection medium and the cells were maintained in culture medium (RPMI 1640 medium supplemented with 10% fetal calf serum). Maturation of the cell line was induced by using phorbol 12-myristate 13-acetate (PMA) (Sigma). The cells were incubated in medium with 10 ng of PMA per ml for 30 min, washed twice with Hanks’ balanced salt solution (HBSS), and incubated in culture medium at 37°C overnight.

Incubation with bacteria and peptide extract. Monocytes and transfected U-937 cells were allowed to phagocytose the bacteria in RPMI 1640 medium supplemented with 10% AB serum without antibiotics for 1 h. Then the plates were washed three times with HBSS without antibiotics to wash away the bacteria which were not phagocytosed by the cells. Thereafter, the cells were allowed to process the bacteria in culture medium for different periods as described previously (52) (Table 1). Usually the incubation times for monocytes of one individual were 1 h, 1 or 2 days, and 7 days, but several other incubation times between these were also tested. Control monocytes were incubated in the same way but without any contact with bacteria. Peptide extract (10 μg/ml) was incubated with the monocytes, like the bacteria. Then the cells were detached by using 5 mM EDTA in Ca++-Mg++-free HBSS and scraping with a rubber policeman.

Incubation of monocytes with cycloheximide, brefeldin A, or chloroquine. Monocytes were exposed to bacteria in medium containing 10 μg of cycloheximide (3-[3-chloroethyl]-10-hydroxyethyl)glutarimide; Sigma) per ml. The incubation was continued for an additional 1 h, 4 h, or 1 day after feeding in the same medium. Thereafter, the cells were detached and stained with MAbs against HLA-B27. For brefeldin A experiments, monocytes were isolated and incubated in RPMI 1640 medium with 10% AB serum and brefeldin A (Sigma) (10 μg/ml) for 1 h. Then the monocytes were exposed to the bacteria and reacted with the peptide extract and incubated for 1 h after washes in the continuous presence of brefeldin A (3.3 μg/ml). To block the activity of the lysosomal compartment of the cells, monocytes were incubated in RPMI 1640 medium with 10% AB serum and chloroquine (Sigma) (100 μM) for 1 h. Then the monocytes were exposed to the bacteria and incubated in the presence of chloroquine (100 μM) for 1 h.

MAbs, immunofluorescence staining, and flow cytometry. Monocytes were stained by a double-immunofluorescence technique as described previously (52). MAbs and their specificities are listed in Table 2. Cells which appeared to be weakly positive in flow cytometry analysis after staining with MAbs HLA-ABC-m3 were not HLA-B27 positive but had some of the HLA-B27-cross-reacting epitopes, usually HLA-B7 (Table 2). ME1 is a conformational epitope, and amino acid substitutions at positions 67 or 69 to 71 disrupt the binding of ME1 to HLA-B27 (5, 6, 27, 42). The B7M2 epitope is not disrupted by a Tyr67 mutation like the ME1 epitope (5). It has been shown previously that the reactivity of B27M1 and B7M2 is partly dependent on the presence of the peptide in the HLA-B27 complex (17, 49). The reactivity of ME1 is enhanced when empty HLA-B27 molecules are incubated with peptides, but ME1 can also react slightly with empty HLA-B27 molecules alone (49, 50). MAb FD705 is specific for HLA-B27 and does not show any cross-reactivities (33). The HLA-B7-specific MAb BB7.2 seems to bind to the HLA-B7 molecule from the top across the peptide-binding groove, or it may recognize an HLA α2 configuration that depends on the α1 α-helix or the bound peptide (26).

Analyses were performed with a FACScan flow cytometer (Becton Dickinson & Co., Mountain View, Calif.). Monocytes were gated according to their size and granularity. This correlated well with the expression of monocyte-specific CD14. Routinely, 10,000 cells were analyzed per sample. A 5% or greater change in the positive cell population or a shift of 100 U in the mean fluorescence intensity was considered to be significant. The expression of tissue antigens on

TABLE Experimental design

<table>
<thead>
<tr>
<th>Antigen</th>
<th>No. of subjects studied whose monocytes were exposed to the following bacteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Monocytes from individuals were divided, and some of the cells were exposed to Y. enterocolitica serotype O:3. Monocytes from individuals were divided, and one portion of the cells was exposed to Y. enterocolitica serotype O:5.</td>
</tr>
</tbody>
</table>
**RESULTS**

**Arthritis-triggering bacteria and expression of MHC class I molecules.** We found that *Y. enterocolitica* serotype O:3 was able to reduce the expression of all HLA-B27 epitopes except B27M2 on human monocytes and on the HLA-B27-transfected U-937 cells. Both the percentage of positive monocytes and the mean fluorescence intensities decreased. The initial level of expression of B27M2 on monocyctic cells is already very low.

Examples of the decreases of expression are shown in Fig. 1, and an example of the expression of the B27M2 epitope is shown in Fig. 2. The decrease occurred without a concomitant change in the overall expression of MHC class I complexes in monocytes from 21 of 31 individuals which were studied after short incubation periods (from 1 h to 1 day) (Table 3). The effect of *Y. enterocolitica* serotype O:3 on the ME1 epitope was observed only if the epitope was in a certain background (HLA-B27) because the expression of HLA-B27-cross-reacting epitopes on HLA-B7-positive monocytes was not reduced. The expression of the peptide-dependent B27M2 epitope was increased, especially after 1 day of incubation (Fig. 2). The most significant changes were observed in patients with ankylosing spondylitis or a history of reactive arthritis. Certain individuals were tested up to 10 times and no variation between experiments was observed. *Y. enterocolitica* serotype O:9, *Y. pseudotuberculosis* serotypes I and III, a plasmid-cured derivative of *Y. enterocolitica* serotype O:3, and *S. enteritidis* decreased the expression of ME1, B27M1, and HLA-ABC-m3 epitopes, like the virulent *Y. enterocolitica* serotype O:3. When monocytes of three individuals were exposed to both live and heat-killed *Yersinia* bacteria in three separate experiments, live bacteria induced more-significant changes than the heat-killed bacteria. Live *S. enteritidis* also had a more significant effect than the heat-killed *Salmonella* bacteria. An example of the change induced by live *S. enteritidis* using MAbs FD705 is shown in Fig. 3.

Cycloheximide, brefeldin A, and chloroquine were used to characterize the mechanisms behind the changes in cell surface expression. Cycloheximide is a protein synthesis inhibitor; brefeldin A blocks the traffic of newly synthesized molecules from the endoplasmic reticulum through the Golgi complex to the cell surface and leads to mixing of the trans-Golgi network with the recycling endosomal system; and chloroquine inhibits lysosomal degradation and the recycling of molecules from the plasma membrane through acidic endosomes. Cycloheximide did not modify the effect induced by *Y. enterocolitica* serotype O:3, although the basal level of the MHC class I expression reduced gradually after the monocytes were treated with cycloheximide (not shown). Brefeldin A abrogated the effect of *Y. enterocolitica* serotype O:3 on the ME1 and FD705 epitopes.

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**TABLE 2. Antibodies used in this study**

<table>
<thead>
<tr>
<th>Designation</th>
<th>Class</th>
<th>Specificity</th>
<th>Amino acid residue(s) critical for binding*</th>
<th>Reference(s) or source</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-ABC-m3</td>
<td>IgG2a</td>
<td>HLA-B27, HLA-B7</td>
<td>67–71, 41, 43</td>
<td>45; Serotec®</td>
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<tr>
<td>ME1</td>
<td>IgG1</td>
<td>HLA-B27, HLA-B7, HLA-Bw22, HLA-Bw42</td>
<td>4, 27, 30; ATCC</td>
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<tr>
<td>B27M1</td>
<td>IgG2a</td>
<td>HLA-B27, HLA-B7, HLA-Bw42</td>
<td>77–81</td>
<td>12; ATCC</td>
</tr>
<tr>
<td>B27M2</td>
<td>IgM</td>
<td>HLA-B27, HLA-Bw47</td>
<td>33; One Lambda INC</td>
<td></td>
</tr>
<tr>
<td>FD705</td>
<td>IgG2b</td>
<td>HLA-B27</td>
<td>5, 26, 30, 44; ATCC</td>
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</tr>
<tr>
<td>BB7.1</td>
<td>IgG1</td>
<td>HLA-B7, HLA-Bw42</td>
<td>67, 166, 169</td>
<td>32, 37, 38; ATCC</td>
</tr>
<tr>
<td>BB7.2</td>
<td>IgG2b</td>
<td>HLA-A2, HLA-Aw69</td>
<td>58</td>
<td>38; Incat Corp.®</td>
</tr>
<tr>
<td>W6/32</td>
<td>IgG2a</td>
<td>Monomorphic class I HLA</td>
<td>31; ATCC</td>
<td></td>
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<tr>
<td>4D12</td>
<td>IgG1</td>
<td>HLA-B5</td>
<td>14; ATCC</td>
<td></td>
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<tr>
<td>G3C10</td>
<td>IgG1</td>
<td>HLA-B27</td>
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<td>C3I0</td>
<td>IgG2b</td>
<td>CD14</td>
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<td>3G6</td>
<td>IgG1</td>
<td>Chicken T cells (negative control)</td>
<td>36; our laboratory</td>
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</tr>
<tr>
<td>1B2</td>
<td>IgG1</td>
<td>Vascular adhesion protein 1 (negative control)</td>
<td>36; our laboratory</td>
<td></td>
</tr>
<tr>
<td>1D3</td>
<td>IgM</td>
<td>Chicken lymphocytes (negative control)</td>
<td>36; our laboratory</td>
<td></td>
</tr>
</tbody>
</table>

* Amino acid residues 67 to 71 and 77 to 81 are in the αα α helix, and residues 166 to 169 are in the α2 α helix. Residues 41 and 43 belong to the solvent-accessible connecting loop, and amino acid residue 32 is at the bottom of the peptide-binding groove.

† Oxford, United Kingdom.

‡ Canoga Park, Calif.

§ Stillwater, Minn.
Y. enterocolitica

Y. enterocolitica serotype O:3 down-regulates the mean fluorescence intensity (MFI) of HLA-B27 on monocytes exposed to Y. enterocolitica. The MFI of control monocytes stained with MABs against different HLA-B27 epitopes is 1. Results are presented as relative MFI ratios. The incubation time is 1 h, and the results are from two independent experiments. Relative MFI values for control monocytes stained with the indicated MABs (open bars) and for monocytes exposed to the bacteria (closed bars) are shown.

Control bacteria and expression of MHC class I molecules.

Monocytes were exposed to S. pyogenes and E. coli to analyze whether the effects of Y. enterocolitica serotype O:3 were specific to reactive-arthritis-triggering microbes. S. pyogenes reduced specifically the expression of ME1 or HLA-ABC-m3 epitopes in only 2 of 14 individuals during the first day of incubation (Table 3), but it did not considerably change the overall expression of the peptide-dependent B27M1 and B27M2 epitopes (not shown). The expression of HLA-B27 epitopes on monocytes exposed to S. pyogenes also stayed at the level of control cells during the 1-week follow-up time after a small initial fall in a few individuals. E. coli did not decrease the expression of HLA-B27 epitopes as often as the arthritis-triggering bacteria (Table 3). The expression of HLA-A2 was not decreased specifically after an incubation with S. pyogenes or E. coli (Table 3; Fig. 4).

Synthesis of HLA molecules.

In metabolic labelling experiments, the synthesis of HLA-B27 decreased 26% after the cells were fed with Y. enterocolitica serotype O:3, while the synthesis of HLA-A2 increased up to threefold compared to that of the control cells (Fig. 5A). During the same 3-h incubation period, the expression of HLA-B27 on the surface of U-937 cells exposed to Y. enterocolitica decreased (mean fluorescence intensity on a linear scale decreased from 48 to 23). Despite the increase in HLA-A2 synthesis, no significant increase in the expression of HLA-A2 was seen (mean fluorescence intensity changed from 30 to 28) (Fig. 5B).

that in most of the individuals studied there was a decrease and in certain individuals there was no change in expression level. Values are means ± standard errors of the means. The relative MFI values for control monocytes stained with the indicated MABs (open bars) and for monocytes exposed to the bacteria (closed bars) are shown. (B) Y. enterocolitica serotype O:3 decreases the percentage of HLA-B27-positive monocytes (experimental values were subtracted from the control value so that the zero line represents the level of positive monocytes of the controls; values are means ± standard deviations). Results for monocytes of all individuals studied with MAB HLA-ABC-m3 have been included in the figure regardless of the fact that in most of the individuals studied there was a decrease and in certain individuals there was no change in the level of expression. Results are means ± standard errors of the means. Relative MFI values for control monocytes stained with the indicated MABs (open bars) and for monocytes exposed to the bacteria (closed bars) are shown.

FIG. 1. (A) Y. enterocolitica serotype O:3 down-regulates the mean fluorescence intensity (MFI) of HLA-B27 on monocytes exposed to Y. enterocolitica. The MFI of control monocytes stained with MABs against different HLA-B27 epitopes is 1. Results are presented as relative MFI ratios. The incubation time is 1 h, and the results are from two independent experiments. Results for all subjects studied with these MABs are included in the figure regardless of the fact that in most of the individuals studied there was a decrease and in certain individuals there was no change in expression level. Values are means ± standard errors of the means. The relative MFI values for control monocytes stained with the indicated MABs (open bars) and for monocytes exposed to the bacteria (closed bars) are shown. (B) Y. enterocolitica serotype O:3 does not down-regulate the expression of HLA-B27 epitopes on HLA-B27-transfected U-937 cells. The MFI of control monocytes stained with MABs against different HLA-B27 epitopes is 1. Results are presented as relative MFI ratios (means ± standard deviations). The incubation time is 1 h, and the results are from two independent experiments. Relative MFI values for control monocytes stained with the indicated MABs (open bars) and for monocytes exposed to the bacteria (closed bars) are shown.
In the present study, we investigated whether phagocytosis and processing of reactive-arthritis-triggering bacteria in vitro would change the expression of HLA-B27 molecules on human antigen-presenting cells. We found that arthritis-triggering microbes decreased the expression of epitopes which have been shown to be important for T-cell recognition in reactive arthritis (15, 46). Arthritis-triggering microbes also changed the three-dimensional structure consisting of the HLA-B27 molecule and the bound peptide which is recognized by antibodies or cytotoxic T cells. Interestingly, the changes in expression of HLA-B27 were most significant in patients with ankylosing spondylitis and in individuals with a previous history of reactive arthritis (unpublished data). This suggests that this phenomenon has a role in the pathogenesis of reactive arthritis.

The effects of bacteria were found to be specific for certain epitopes if the epitopes were in a particular background. The explanation for this may be the HLA-B27-specific cysteine at position 67. This residue forms part of the peptide-binding B-pocket in HLA-B27 which binds the second amino acid residue relative to the amino terminus of the peptide that associates with the MHC class I molecule (13, 25). Cysteine 67 associates with the MHC class I molecule (13, 25). Cysteine 67 has been shown to be oxidized in HLA-B27 has been shown to carry an unusually reactive thiol group (51). This group may be modified by low-molecular-weight compounds such as nitric oxide and superoxide ions, which are produced by activated phagocytes. Such a modification most probably alters the specificity of the cleft, so that wrong self-peptides will be presented to T cells (51). In addition, the cysteine at position 67 has been shown to be oxidized by homocysteine originating from arthritis-triggering bacteria. This modification leads to a modified T-cell response (7).

Metabolic labelling and immunoprecipitation experiments showed that the synthesis of the HLA-B27 and HLA-A2 was different after phagocytosis of Y. enterocolitica serotype O:3. This is likely to be responsible for the down-regulation of HLA-B27 expression seen in our experiments after prolonged incubation. The expression of HLA-A2 did not increase, although the synthesis of HLA-A2 was greatly enhanced after phagocytosis of Y. enterocolitica serotype O:3. These results suggest that in addition to inducing changes in the synthesis of HLA molecules, phagocytosis of Y. enterocolitica serotype O:3 modifies the posttranslational modification of MHC class I molecules or the traffic to the cell surface so in HLA-B27 has been shown to carry an unusually reactive thiol group (51). This group may be modified by low-molecular-weight compounds such as nitric oxide and superoxide ions, which are produced by activated phagocytes. Such a modification most probably alters the specificity of the cleft, so that wrong self-peptides will be presented to T cells (51). In addition, the cysteine at position 67 has been shown to be oxidized by homocysteine originating from arthritis-triggering bacteria. This modification leads to a modified T-cell response (7).

Metabolic labelling and immunoprecipitation experiments showed that the regulation of the synthesis of HLA-B27 and HLA-A2 was different after phagocytosis of Y. enterocolitica serotype O:3. This is likely to be responsible for the down-regulation of HLA-B27 expression seen in our experiments after prolonged incubation. The expression of HLA-A2 did not increase, although the synthesis of HLA-A2 was greatly enhanced after phagocytosis of Y. enterocolitica serotype O:3. These results suggest that in addition to inducing changes in the synthesis of HLA molecules, phagocytosis of Y. enterocolitica serotype O:3 modifies the posttranslational modification of MHC class I molecules or the traffic to the cell surface so

TABLE 3. Down-regulation of HLA epitopes on human peripheral blood monocytes

<table>
<thead>
<tr>
<th>Bacterium</th>
<th>HLA-B27</th>
<th>HLA-A2</th>
<th>HLA-B7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y. enterocolitica</td>
<td>21/31b</td>
<td>11/30</td>
<td>4/13</td>
</tr>
<tr>
<td>S. pyogenes</td>
<td>2/14</td>
<td>3/10</td>
<td></td>
</tr>
<tr>
<td>E. coli</td>
<td>8/19</td>
<td>5/17</td>
<td>4/13</td>
</tr>
</tbody>
</table>

b Values are numbers of individuals in whom the expression of the given MHC class I allele decreased without a concomitant change in the overall expression of MHC class I molecules after 1 h to 1 day of incubation divided by the total number of individuals studied. HLA-B27 epitopes are the ones recognized by MAbs ME1, B27M1, HLA-ABC-m3, and FD705; the HLA-B7 epitope is recognized by MAb BB7.1 (HLA-B7-specific epitope); and HLA-A2 epitopes are recognized by MAbs BB7.2 and MA2.2.

P is <0.05 when the specific decrease in the expression of HLA-B27 induced by Y. enterocolitica serotype O:3 is compared to that of control alleles or S. pyogenes. P is <0.08 when the specific decrease of HLA-B27 caused by Y. enterocolitica serotype O:3 is compared to the specific decrease induced by E. coli.
that the newly synthesized MHC molecules do not reach the plasma membrane. Certain DNA viruses have been shown to prevent the expression of MHC class I molecules via mechanisms interfering with posttranslational processing of these glycoproteins as early as 2 h after infection (16). The effect of glycosylation on the expression of MHC class I molecules has been shown to be allele specific (28). In addition, bacteria have been shown to modify the glycosylation of the host cell proteins (47). Experiments conducted in the presence of brefeldin A suggest that Yersinia bacteria may interfere also with the intracellular traffic of HLA-B27 molecules. Brefeldin A, which blocks the transport of molecules from the endoplasmic reticulum through the Golgi complex to the cell surface, reduced the expression of certain HLA-B27 epitopes on human antigen-presenting cells. Down-regulation of epitopes shown to be important for T-cell recognition in patients with reactive arthritis may impair the elimination of arthritis-triggering microbes. An altered repertoire of peptides in the HLA-B27 molecules may lead to the pathogenesis of reactive arthritis via an autoimmune mechanism.

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