IMMUNOBIOLOGY

HLA-B8 and HLA-A3 Coexpressed With HLA-B8 Are Associated With a Reduced Risk of the Development of Chronic Myeloid Leukemia


Chronic myeloid leukemia (CML) is characterized by the chromosomal translocation t(9;22) resulting in the chimeric bcr-abl oncogene that encodes the P210 fusion protein, which contains a unique amino acid sequence. If peptides derived from the leukemia-specific part of P210 are expressed in HLA molecules on the cell membrane of leukemic cells, an immunological response may occur. Recent studies using synthetic peptides identical to the bcr-abl fusion region showed that some peptides are capable of binding to HLA-A3, -A11, and -B8 molecules. Cytotoxic T-cell responses have been induced against bcr-abl-derived synthetic peptides bound to HLA-A3 and -B8. We hypothesized that if antigen processing of the P210 fusion protein leads to presentation of peptides from the fusion region by major histocompatibility complex (MHC) molecules in vivo, this may be reflected in a diminished incidence of CML in individuals expressing HLA-A3, -A11, or -B8. Consequently, lower frequencies of these antigens would be expected in patients with CML compared with unaffected individuals. A case-control study and a meta-analysis were performed to test this hypothesis. The multicenter case-control study compared patients with CML from the data base of the European Group for Blood and Marrow Transplantation (EBMT) with unaffected individuals from the registry of Bone Marrow Donors Worldwide. Patients and controls were matched per country. The meta-analysis consisted of five studies reported in the literature. The multicenter case-control study consisting of 1,899 patients and 512,363 bone marrow donors as controls yielded odds ratios (ORs) of 0.90 (95% confidence interval [CI], 0.80 to 1.00) for HLA-A3, 1.16 (95% CI, 1.02 to 1.33) for HLA-A11, and an OR of 0.73 (95% CI, 0.65 to 0.82) for HLA-B8. Coexpression of HLA-A3 and -B8 gave an OR of 0.51 (95% CI, 0.40 to 0.67). This can be translated into a protective effect of 27% for HLA-B8, 10% for HLA-A3, and 49% protection for the combination of HLA-A3 and HLA-B8. The meta-analysis comprising 463 CML patients and 4,912 controls showed a 29% risk reduction for individuals expressing HLA-B8 (OR of 0.71; 95% CI, 0.52 to 0.97), but an OR of 1.19 (95% CI, 0.90 to 1.56) for HLA-A3 and an OR of 1.09 (95% CI, 0.80 to 1.50) for HLA-A11. In conclusion, these results indicate that HLA-B8 expression, in particular when HLA-A3 is coexpressed, is associated with a diminished incidence of CML. A biological mechanism may be that presentation of bcr-abl breakpoint peptides in these HLA molecules can induce a protective immune response.

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MATERIALS AND METHODS

Patients and methods. A multicenter case-control study and a meta-analysis addressing the hypothesis whether there are diminished frequencies of HLA-A3, -A11, or -B8 in CML patients was performed. The frequencies of individuals coexpressing two of these HLA molecules were also compared between patients and controls. The same analysis was performed for control purposes on HLA-A2, an antigen not reported to have a binding motif for bcr-abl-derived peptides and for HLA-A1, also without a binding motif for the fusion protein, but in linkage disequilibrium with HLA-B8. To assess a possible protective effect of the A1B8 haplotype itself, also the frequencies of the combination HLA-A1 positive/HLA-B8 negative phenotype and of the...
The multicenter case-control study comprised 1,899 patients, consisting of patients who underwent bone marrow transplantation obtained from the data base of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT), restricted to 10 countries with at least 15 patients, of untransplanted patients from two centers also contributing to EBMT, and 512,363 controls, matched per country as present in the Bone Marrow Donors Worldwide Registries.13-15 All HLA data from the EBMT have been reviewed and checked by one of the authors (D.N.).

The results of studies previously reported in literature were combined in a meta-analysis. These studies were obtained by searching the MEDLINE data base and checking references in text books. Studies were included in which at least the frequencies of the HLA-A3, -A11, (-A1 and -A2), and HLA-B8 typings in CML patients were compared with those in controls. The meta-analysis consisted of 463 patients with CML and 4,912 controls.

Table 1. HLA Frequencies With OR and 95% CI in Multicenter Case-Control Study

<table>
<thead>
<tr>
<th>Study and Reference No.</th>
<th>CML Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Momigliano Richiardi (1994)13</td>
<td>288</td>
<td>1,092</td>
</tr>
<tr>
<td>Hester (1977)21</td>
<td>43</td>
<td>142</td>
</tr>
<tr>
<td>Pollack (1977)22</td>
<td>60</td>
<td>1,942</td>
</tr>
<tr>
<td>Caruso (1987)23</td>
<td>35</td>
<td>200</td>
</tr>
<tr>
<td>Terasaki (1977)24</td>
<td>37</td>
<td>1,536</td>
</tr>
<tr>
<td>Total</td>
<td>463</td>
<td>4,912</td>
</tr>
</tbody>
</table>

DISCUSSION

Recent in vitro studies have shown that synthetic bcr-abl-derived peptides can be presented in the context of HLA-A3, -A11, and -B8 molecules and can elicit a T-cell response against these peptides.10-12,19 However, no endogenous processing of bcr/abl protein resulting in the presentation of the fusion region in the HLA molecules has been demonstrated. We hypothesized that if the bcr/abl-specific peptides could be processed in vivo in these HLA molecules, the presence of any of these class I antigens may protect an individual against the development of this disease. The results of the multicenter case-control study showed a decreased incidence of individuals expressing HLA-B8 in the CML patient group, corroborating the findings of the in vitro studies. The negative association with HLA-B8 was confirmed in the meta-analysis. The HLA-A3 frequency in patients with CML was lowered only in the very large EBMT case-control study, but not in the meta-analysis. A recently published epidemiologic study showed an association between homozygosity for HLA-A3 and early onset CML.20 However, the strongly diminished incidence of the combination of HLA-A3/HLA-B8 in patients with CML, as found in the presented case-control study, indicates a negative association with both HLA-A3 and HLA-B8.

The discrepancy between the protective effect of HLA-B8 and HLA-A3 and the absence of effect of HLA-A11 may be explained by the inability of tumor-specific peptides to bind to
HLA-A11. Alternatively, peptides with binding affinities for HLA-A11 may be processed, but are unable to elicit an immune response. In the in vitro studies, there were also differences in peptide binding and sensitivity to specific T-cell lines between these HLA molecules.10,12

Although immune responses have been reported for both b2a2 and b3a2-derived peptides in HLA-B8,11 the protective effect of HLA-B8 and HLA-A3 may be underestimated. In vitro T-cell responses have been mainly described against b3a2-derived peptides.12,19 If no or only minor effects are present in the subgroup of patients with the b2a2 translocation, an even stronger protective effect of HLA-A3 and -B8 may be expected for the b3a2 subgroup. Peptides other than the bcr-abl breakpoint region related may also be immunogenic in combination with HLA-A3 and HLA-B8.

To analyze whether the negative association of HLA-A1 with CML was due to the linkage disequilibrium of the HLA-A1B8 haplotype, the frequencies of HLA-A1 positive/HLA-B8 negative, HLA-A1 negative/HLA-B8 positive, and HLA-A1 positive/HLA-B8 positive individuals were compared between patients and controls in the EBMT case-control study. In the EBMT study, the HLA-A1 positive/-B8 negative frequency resulted in an OR of 0.95 (95% CI, 0.83 to 1.09) for patients with CML, the HLA-A1 negative/-B8 positive frequency gave an OR of 0.73 (95% CI, 0.58 to 0.92) for patients with CML compared with controls, whereas the HLA-A1/HLA-B8 both positive combination yielded an OR of 0.75 (95% CI, 0.66 to 0.86). These results illustrate the negative association of HLA-A1 is due to the linkage disequilibrium with HLA-B8.

In summary, the studies presented show a negative association of HLA-B8 and HLA-A3 with CML. The possible mechanism may be that binding of bcr/abl-derived peptides in these HLA molecules lead to an immune response resulting in a protective effect against the development of CML. These findings may have implications for a bcr-abl fusion protein-based immunotherapeutic approach in HLA-A3 and HLA-B8 positive patients with CML. It may be possible to generate either an autologous T-cell immune response against these peptides in vitro using patient lymphocytes or an allogeneic response using donor lymphocytes. In vitro-generated T-cell lines with a specificity against breakpoint specific peptides may be used as part of the treatment of CML.

REFERENCES

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