Epstein-Barr Virus and Breast Cancer: Search for Antibodies to the Novel BFRF1 Protein in Sera of Breast Cancer Patients

Epstein-Barr virus (EBV), a widely diffused herpesvirus, is the etiologic agent of infectious mononucleosis. It has been associated with different tumors of lymphoid and epithelial origins, i.e., Burkitt’s lymphoma, Hodgkin’s disease, lymphoproliferative disorders that develop in immunocompromised subjects, and nasopharyngeal carcinoma (1). Furthermore, an association between breast cancer and EBV has been suggested. Some investigators reported detecting EBV DNA in breast cancer tumor cells, whereas others could not find any viral sequence. Recently, it has been shown that EBV is able to infect breast cancer-derived epithelial cells, thus adding a biologic element to this association by suggesting a route for the passage of EBV from circulating B lymphocytes to breast epithelium (2–6). However, the biologic relevance of EBV in the pathogenesis of breast cancer remains obscure, and the analysis of the status of EBV infection in breast cancer patients might be useful to shed a light on the possible role of EBV. Studies based on polymerase chain reaction and in situ hybridization do not provide information on the status of EBV infection, and the wide diffusion of the virus in the general population makes classical serology useless in elucidating the possible association between EBV infection and breast cancer.

We recently identified an EBV gene, called BFRF1 (7). This gene encodes a protein expressed in the early phase of the replicative cycle. We also demonstrated that BFRF1 is antigenic in humans, since antibodies to this protein are detected in sera of patients with nasopharyngeal carcinoma and Burkitt’s lymphoma but not in healthy donors.

In the present study, we extended the epidemiologic survey. We studied the humoral response to BFRF1 in patients affected by different diseases related and unrelated to EBV, and we evaluated its potential as a new marker to follow the status of EBV infection. Among the serum samples screened, 71 were obtained from women affected by breast cancer. The tumor cells of these patients were evaluated previously for estrogen and progesterone receptor status; 38 of the samples were found to be positive for either one or both receptors, and the remaining 33 were found to be negative. This factor seemed to be important, since it has been reported that EBV is detected more frequently in steroid hormone receptor-negative tumors, which are associated with poorer outcome (4). Sera were diluted 1:10, and the search for antibodies to BFRF1 was performed by immunofluorescence assay on cells transfected to express BFRF1, as reported previously (7).

As shown in Table 1, 48 of 359 serum samples were found to be BFRF1 seropositive. It is interesting that 46 (95.8%) of the 48 samples belonged to patients affected by neoplastic diseases in which EBV plays a role as a cofactor in the tumorigenesis—i.e., nasopharyngeal carcinoma, Burkitt’s lymphoma, or lymphoproliferative disorders in immunocompromised subjects.

These data seem to confirm our previous observation that BFRF1 seropositivity is highly restricted to cancers known to be associated with EBV and that presumably a prolonged viral replication is necessary to elicit a detectable humoral response to BFRF1, since only one of 24 patients with infectious mononucleosis was found to be seropositive. On the other hand, the lack of BFRF1-positive sera among the 71 breast cancer patients, regardless of the hormonal receptor status, argues against an active role of EBV in the development of this tumor. This consideration is in keeping with the recent study conducted by McCall et al. (5), who reported that they could not detect EBV sequences in breast cancer lesions and who questioned the biologic significance of the association reported by other authors, although they acknowledged that further studies were needed to clarify that issue.

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REFERENCES


Table 1. Summary of BFRF1 seroprevalence in individuals infected with EBV*

<table>
<thead>
<tr>
<th>Subjects assayed</th>
<th>No. of cases</th>
<th>No. BFRF1 seropositive †</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngeal carcinoma</td>
<td>40</td>
<td>31 ‡</td>
<td>77.5</td>
</tr>
<tr>
<td>Burkitt’s lymphoma</td>
<td>15</td>
<td>7 ‡</td>
<td>46.7</td>
</tr>
<tr>
<td>Other lymphomas</td>
<td>85</td>
<td>8</td>
<td>9.4</td>
</tr>
<tr>
<td>HIV+</td>
<td>67</td>
<td>6</td>
<td>9.0</td>
</tr>
<tr>
<td>HIV−</td>
<td>18</td>
<td>2</td>
<td>11.1</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>36</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>71</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infectious mononucleosis</td>
<td>24</td>
<td>1</td>
<td>4.2</td>
</tr>
<tr>
<td>Hemophilic HIV+</td>
<td>30</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Healthy donors</td>
<td>58</td>
<td>1 †</td>
<td>1.7</td>
</tr>
</tbody>
</table>

*EBV = Epstein-Barr virus; HIV = human immunodeficiency virus.
† a versus b P < 0.0001 by Fisher’s exact test; odds ratio = 196.3, 95% confidence interval = 50.3 to 765.6. c versus b P < 0.0007 by Fisher’s exact test; odds ratio = 49.8, 95% confidence interval = 8.9 to 276.6. No statistically significant difference was found in BFRF1 seropositivity between patients with lymphoma and healthy donors. All P values are two-sided.


NOTES

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