The B7/BB1 Antigen Is Expressed by Reed-Sternberg Cells of Hodgkin's Disease and Contributes to the Stimulating Capacity of Hodgkin's Disease-Derived Cell Lines

By Jan Delabie, Jan L. Ceuppens, Peter Vandenberghe, Mark de Boer, Lieve Coorevits, and Chris De Wolf-Peeters

The B7/BB1 molecule has recently been found to be expressed on professional antigen-presenting cells and to be the natural ligand for CD28 and CTLA-4 on T cells. On binding of B7/BB1, CD28 transduces a signal that synergizes with triggering of the T-cell antigen receptor, resulting in enhanced cytokine secretion. In view of the data supporting an antigen-presenting function of Reed-Sternberg cells, we evaluated the expression of B7/BB1 in lymph nodes affected by Hodgkin's disease. B7/BB1 was found to be strongly expressed by the Reed-Sternberg cells in all 47 cases of Hodgkin's disease studied. Moreover, Reed-Sternberg cells were frequently surrounded by CD28-expressing T cells. Evidence for a functional role of B7/BB1 on Reed-Sternberg cells was obtained by our findings that T-cell proliferation and interleukin-2 (IL-2) production in the primary allogeneic mixed lymphocyte reaction (MLR), using the B7/BB1-expressing Hodgkin's disease-derived cell lines L428 and KM-H2 as stimulators, could be partially blocked by adding anti-B7 monoclonal antibody. B7/BB1 expression was also evaluated in a group of non-Hodgkin's lymphomas (n = 46). Whereas B7/BB1 was not expressed by the neoplastic cells of most non-Hodgkin's lymphomas, including T-cell–rich B-cell lymphoma (n = 11), it was present on the neoplastic cells of anaplastic large-cell lymphoma (Ki-1 lymphoma) (n = 5) and follicular lymphoma (n = 4). Our data provide further evidence for an accessory cell function of Reed-Sternberg cells. The accessory cell function of Reed-Sternberg cells might lead to pronounced T-cell activation in vivo, which might contribute to the Hodgkin's syndrome. In addition, our study indicates that B7/BB1 may be a useful marker for differentiating Hodgkin's disease from morphologically similar conditions such as T-cell–rich B-cell lymphoma.

MATERIALS AND METHODS

Monoclonal antibodies: Anti-B7 mouse monoclonal B7-24 (IgG2a) was produced as previously described. Purified IgG was used for blocking of MLRs and F(ab)2 fragments were used for immunohistochemistry and flow cytometry. Also, anti-CD28 antibody Leu-28 (Becton Dickinson, Mountain View, CA) was used for immunohistochemistry and flow-cytometric analysis.

The following monoclonal antibodies were used only in flow-cytometric studies: anti-Leu-3a (CD4), anti-Leu-2a (CD8), anti-Leu-M3 (anti-CD14), anti-LLA-DR, anti-Leu-M7 (anti-CD13), anti-Leu-54 (CD54), anti-LFA-1α (CD11a), and anti-LFA-1β (CD18) (all from Becton Dickinson); and anti-LFA-3 (CD58, clone AICD58-1) and anti-ICAM-1 (CD54, clone 84H10) (both from Immunotech, Luminy, France). Clones producing anti-LFA-3 (clone TS2/9), anti-LFA-1β (clone CD18) (clone TS1/}

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Table 1. Tissues Studied for B7/BB1 Expression

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin’s disease</td>
<td></td>
</tr>
<tr>
<td>Nodular sclerosis</td>
<td>27</td>
</tr>
<tr>
<td>Lymphocyte predominance</td>
<td>5</td>
</tr>
<tr>
<td>Mixed cellularity</td>
<td>10</td>
</tr>
<tr>
<td>Lymphocyte depletion</td>
<td>5</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td></td>
</tr>
<tr>
<td>B-cell type</td>
<td></td>
</tr>
<tr>
<td>Small lymphocytic lymphoma</td>
<td>2</td>
</tr>
<tr>
<td>(chronic lymphocytic lymphoma)</td>
<td></td>
</tr>
<tr>
<td>Follicular center-cell lymphoma</td>
<td>4</td>
</tr>
<tr>
<td>Mantle-cell lymphoma</td>
<td>3</td>
</tr>
<tr>
<td>Diffuse large-cell lymphoma</td>
<td>5</td>
</tr>
<tr>
<td>Immunoblastic lymphoma</td>
<td>2</td>
</tr>
<tr>
<td>Small noncleaved cell lymphoma</td>
<td>2</td>
</tr>
<tr>
<td>T-cell–rich B-cell lymphoma</td>
<td>11</td>
</tr>
<tr>
<td>Histiocyte-rich B-cell lymphoma</td>
<td>5</td>
</tr>
<tr>
<td>T-cell type</td>
<td></td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma</td>
<td>5</td>
</tr>
<tr>
<td>Lymphoblastic lymphoma</td>
<td>2</td>
</tr>
<tr>
<td>Anaplastic large-cell lymphoma</td>
<td>5</td>
</tr>
</tbody>
</table>

18), and anti–HLA-DR (clone L243) were obtained from ATCC (Rockville, MD) and grown in our laboratory. These monoclonal antibodies were used as purified IgG for blocking of MLR experiments.

Immunohistochemistry. The lymph node samples used in this study are listed in Table 1. The study included tissue samples of 47 cases of Hodgkin’s disease, covering the four histologic subtypes, and 46 cases of non-Hodgkin’s lymphoma. All tissue samples were snap-frozen in liquid nitrogen-cooled isopentane and stored at −70°C until used for immunohistochemistry. Acetone-fixed cryostat sections (4 μm) were used. A three-step ABC technique was used for immunodetection according to Hsu et al.25 The ABC complex was peroxidase-conjugated (Dakopatts, Glostrup, Denmark). Aminoethylcarbazole and H2O2 were used as peroxidase substrates. Controls consisted of replacement of the primary antibody by an irrelevant monocolonal antibody of similar isotype or use of chromogen alone.

Cell lines. Hodgkin’s disease cell line KM-H2 was kindly provided by Dr S. Fukuhara (Kyoto, Japan) and Hodgkin’s disease cell line L428 was obtained from Dr V. Diehl (Köln, Germany). These cell lines have been previously characterized.23,24 Both cell lines were grown in RPMI-1640 medium (GIBCO, Paisley, Scotland), supplemented with 10% fetal calf serum, 2 mmol/L L-glutamine, 100 U/mL penicillin, and 100 μg/mL streptomycin.

Flow-cytometric analysis of cell surface antigens. Cells were suspended in 100 μL of phosphate-buffered saline (PBS) containing 1% bovine serum albumin (Sigma Chemical, St Louis, MO). The cell suspension was incubated for 30 minutes at 4°C with a saturating amount of monoclonal antibodies identifying the surface antigens of interest. When unconjugated monoclonal antibodies were used, the cells were further incubated after two washes with fluorescein isothiocyanate (FITC)-labeled F(ab’), fragments of goat antimouse IgG (Becton Dickinson) at 4°C for 30 minutes. After two washes, cells were fixed with 1% paraformaldehyde, and analy-

Fig 1. Hodgkin’s disease, nodular sclerosis subtype. Reed-Sternberg cells express the B7/BB1 antigen. (ABC-peroxidase staining with monoclonal antibody B7-24; original magnification × 500.)
sis was performed on a FacScan flow cytometer (Becton Dickin-
son).

T-cell separation. Peripheral blood mononuclear cells of
healthy donors were isolated on Ficoll-Hypaque (density, 1.077)
gradients. Monocytes were removed by cold agglutination and T
lymphocytes were further purified using complement-fixing mono-
clonal antibodies and two cycles of lympho-KWIK-T treatment
(One Lambda, Los Angeles, CA), as previously reported. The cell
preparations contained more than 97% CD3+ and less than 1%
CD16+ cells. CD14+ monocytes were not detected. The purified
cells did not proliferate in response to an optimal concentration of
immobilized OKT3 or to recombinant IL-2 alone (10 U/mL).

Cell culture for T-cell proliferation studies. T cells (50,000/well)
were mixed with 25,000 or 50,000 irradiated (2,500 rad) KM-H2 or
L428 cells, in the presence or absence of monoclonal antibodies to
B7/BB1, LFA-1/ (CD18) or LFA-3 (CD58), HLA-DR, CD40, or
CD32 and cultured at 37°C and 5% CO2, in flat-bottomed 96-well
microculture plates (Costar, Highwycombe, UK) for 120 hours in
RPMI-1640 supplemented with 2 mmol/L l-glutamine, penicillin
(100 U/mL), streptomycin (100 μg/mL) gentamycin (10 μg/mL),
and 10% autologous plasma. Experiments were performed in qua-
druplicate. At the end of the culture, cells were pulsed with 1 μCi of
[3H]-thymidine (specific activity, 2 Ci/mmol; Amersham, Buck-
inghamshire, UK). Eight hours later, cells were harvested with a
multiple automated sample harvesting apparatus and radioactivity
on the filter papers was counted in a liquid scintillation counter.
Results are expressed as mean cpm ± SEM.

IL-2 production and assay. T cells (500,000/well) were mixed
with 250,000 or 500,000 irradiated (2,500 rad) L428 or KM-H2
cells in the presence or absence of monoclonal antibodies to B7/
BB1, LFA-1/ (CD18), HLA-DR, LFA-3 (CD58), or CD32 and cul-
tured at 37°C and 5% CO2 in 24-well culture plates (Falcon). Anti-
Tac (anti-CD25) monoclonal antibody was added to the cultures to
block IL-2 consumption. IL-2 was assayed by its ability to induce
proliferation of mouse CTLL cells and results are expressed in
international units per milliliter according to the reference prepara-
tion provided by the Biological Responses Modifier Program (Na-
tional Cancer Institute, Frederick, MD).

RESULTS

Immunohistochemical analysis of Hodgkin's disease and
non-Hodgkin's lymphomas. Reed-Sternberg cells in all
cases of Hodgkin's disease studied (n = 47), which covered
the four subtypes, as well as the malignant cells of all cases of
anaplastic large-cell lymphoma (n = 5), expressed B7/BB1 on
the membrane (Figs 1 and 2). In addition, some cytoplasmic
reactivity with the anti-B7/BB1 antibody was also ob-
served in most Reed-Sternberg cells. B7/BB1 was detected
in a subpopulation of malignant cells of the four cases of
follicular lymphoma studied. No reactivity was observed
with the neoplastic cells in the other non-Hodgkin's lym-
phomas tested, including T-cell-rich B-cell lymphoma. In
cases studied, B7/BB1 was expressed by a highly variable
number of infiltrating monocyte-derived cells inter-
spersed between the malignant cells. In those cases in which residual germinal centers were present, B7/BB1 was also expressed by a subset of germinal-center B cells.

In all cases tested, the majority of nonneoplastic T cells expressed CD28. In Hodgkin’s disease, rosettes of CD28 expressing T cells surrounding Reed-Sternberg cells were frequently observed (Fig 3).

Flow-cytometric analysis of Hodgkin’s disease-derived cell lines. Flow-cytometric analysis of Hodgkin’s disease-derived cell lines KM-H2 and L428 showed strong expression of B7/BB1 (Fig 4). KM-H2 also expressed ICAM-1, HLA-DR, and CD40, but not LFA-1 (CD11a/CD18), CD13, CD14, or LFA-3 (CD58). L428 cells expressed LFA-1 (CD11a/CD18), ICAM-1, HLA-DR, CD40, and LFA-3 (CD58), but not CD13 or CD14.

T-cell-stimulating capacity of Hodgkin’s disease-derived cell lines. KM-H2 and L428 cells were used as stimulators in MLR reactions, with purified T cells from normal donors as responder cells. Purified T cells were used to exclude all helper signals derived from autologous accessory cells. It was found that both KM-H2 and L428 cells strongly stimulated the T-cell proliferation and IL-2 production. To examine the contribution of B7/BB1 in this stimulating capacity, the MLR was performed in the presence or absence of monoclonal antibodies to B7/BB1. As shown in Table 2 and Fig 5, respectively, anti-B7/BB1 antibody partially inhibited the capacity of both Hodgkin’s disease-derived cell lines to stimulate T-cell proliferation and strongly reduced IL-2 production. The stimulatory capacity of these cell lines was similarly reduced by monoclonal antibodies to HLA-DR and to LFA-1/β. Anti-LFA-3 clearly reduced the stimulating capacity of L428 cells, but not of KM-H2 cells. These results correspond with the level of LFA-3 expression by both cell lines. We also analyzed the phenotype of the stimulated T cells. HLA-DR was not expressed on resting T cells (<1% positive cells), but its expression was induced in the MLR with Hodgkin’s disease-derived cell lines on both CD4 (41% ± 7%) and CD8 cells (36% ± 4%) (n = 4). Surprisingly, addition of anti-B7 did not change the number of cells that expressed HLA-DR.

DISCUSSION

B7/BB1 is expressed by professional antigen-presenting cells and provides an important costimulatory signal for T-cell receptor/CD3-mediated T-cell activation via binding to its ligands, CD28 and CTLA-4.1-3,23 In this report, we have shown that Reed-Sternberg cells, irrespective of histologic subtype of Hodgkin’s disease, express the B7/BB1 antigen, and T cells surrounding Reed-Sternberg cells express the B7/BB1 ligand CD28. B7/BB1 was also detected on KM-H2 and L428 Hodgkin’s disease-derived cell lines. The expression of B7/BB1 by Reed-Sternberg cells completes the spectrum of accessory molecules expressed by these cells; previ-
B7/BB1 IN HODGKIN'S DISEASE

Fig 4. Flow-cytometric analysis of B7/BB1 and LFA-3 expression on KM-H2 and L428 cells. Cells were stained with monoclonal antibody B7-24 and monoclonal antibody AICD58-1, respectively, followed by FITC-labeled goat antimouse antibodies. Analysis was performed on a FacScan and results are presented in histograms. (-) Isotype controls; (-----) staining with the monoclonal antibodies indicated.

 Previously it was shown that Reed-Sternberg cells express MHC class II antigens, LFA-3, and ICAM-1. As a first step to study the role of B7/BB1 in the accessory cell function of Reed-Sternberg cells, T-cell proliferation and IL-2 production were studied using allogeneic mixed lymphocyte cultures with Hodgkin’s disease-derived cell lines KM-H2 and L428 as stimulator cells. We showed that T-cell proliferation and IL-2 production induced by these Hodgkin’s disease–derived cell lines can be partially blocked by the anti-B7/BB1 antibodies. T-cell proliferation and IL-2 production were also partially inhibited by anti–HLA-DR, anti–LFA-1β, and anti–LFA-3 in the case of L428, and by anti–HLA-DR and anti–LFA-1β in the case of KM-H2. Our findings confirm and extend previous studies showing that L428 and KM-H2 are potent stimulators of the human allogeneic MLR, which can be blocked by anti–HLA-DR and anti–LFA-1 antibodies. Previously, it was also shown that L428 can present soluble antigen to T cells in an MHC-restricted fashion. Taken together, these functional data, as well as the expression of accessory molecules, including B7/BB1, by Reed-Sternberg cells in situ, strongly indicate that Reed-Sternberg cells in vivo function as antigen-presenting cells. The expression of B7/BB1 in all cases included in this study indicates that the accessory cell function is a common denominator in Hodgkin’s disease. The ability of Reed-Sternberg cells to stimulate T cells strongly, resulting in the direct and indirect production of various cytokines, might explain some of the typical features of the “Hodgkin’s syndrome.” The few T lymphocytes observed in the lymphocytic depletion subtype of Hodgkin’s disease are not in contradiction with a possible accessory cell function of Reed-Sternberg cells. Indeed, lack of T cells in the involved tissues may be explained by the well-documented T-cell deficiency in this subtype of Hodgkin’s disease (reviewed by Maggi et al).

The binding of B7/BB1 expressed by Reed-Sternberg cells to CD28 on the membrane of T cells might contribute to the typical rosetting of T cells around Reed-Sternberg cells, a phenomenon that is observed both in vivo and in vitro. The rosetting phenomenon has previously been shown to be also mediated in part by the adhesion molecules LFA-3 and ICAM-1.

B7/BB1 is also expressed by the malignant cells in all cases of anaplastic large-cell lymphoma (so-called Ki-1 lymphoma) studied here. This finding further emphasizes the phenotypic similarities of anaplastic large-cell lymphoma cells and Reed-Sternberg cells and raises the question whether both conditions are related. The expression of accessory molecules by the malignant cells of anaplastic large-cell lymphoma may indicate that these cells also function as accessory cells. As argued for lymphocytic depletion Hodgkin’s disease, the low numbers of T cells present in the involved tissues of anaplastic large-cell lymphoma may be secondary to T-cell deficiency in these cases. However, T-cell deficiency has as yet to be documented in anaplastic large-cell lymphoma. Alternatively, the presence of most tumor cells in the lymph node sinuses, predominantly a traffic area of the lymph node, might also explain why T
Table 2. T-Cell Proliferation in MLRs With KM-H2 and L428 Hodgkin’s Cells as Stimulator Cells

<table>
<thead>
<tr>
<th>Culture Addition†</th>
<th>(3H)-Thymidine Incorporation (% inhibition)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Donor 1</td>
</tr>
<tr>
<td>L428 stimulator cells</td>
<td></td>
</tr>
<tr>
<td>+ none</td>
<td>33,226 ± 1.912</td>
</tr>
<tr>
<td>+ anti-B7</td>
<td>22,076 ± 1.489 (33%)</td>
</tr>
<tr>
<td>+ anti-LFA-3</td>
<td>10,931 ± 1.100 (67%)</td>
</tr>
<tr>
<td>+ anti-LFA-1β</td>
<td>ND</td>
</tr>
<tr>
<td>+ anti-HLA-DR</td>
<td>ND</td>
</tr>
<tr>
<td>+ control MoAb</td>
<td>32,731 ± 1.236 (1%)</td>
</tr>
<tr>
<td>KM-H2 stimulator cells</td>
<td></td>
</tr>
<tr>
<td>+ none</td>
<td>34,727 ± 0.832</td>
</tr>
<tr>
<td>+ anti-B7</td>
<td>20,414 ± 1.068 (41%)</td>
</tr>
<tr>
<td>+ anti-LFA-3</td>
<td>29,594 ± 1.912 (15%)</td>
</tr>
<tr>
<td>+ anti-LFA-1β</td>
<td>22,804 ± 0,726 (34%)</td>
</tr>
<tr>
<td>+ anti-HLA-DR</td>
<td>ND</td>
</tr>
<tr>
<td>+ control MoAb</td>
<td>36,023 ± 2,242 (0%)</td>
</tr>
</tbody>
</table>

Purified T cells (50,000/well) from different donors were cultured with 25,000 or 50,000 irradiated (2,500 rad) KM-H2 or L428 cells in RPMI-1640 with 10% autologous plasma.

Abbreviation: ND, not done.

* Monoclonal antibodies (MoAbs) were added at a concentration of 4 μg/mL. The control MoAb was anti-CD40 for donors 1 and 2, and anti-CD32 for donor 3. Both L428 and KM-H2 cell lines were negative for CD32, but positive for CD40 expression.

† T-cell proliferation was measured after 5 days of culture by (3H)-thymidine incorporation. (3H)-thymidine incorporation is expressed in mean cpm ± SEM. % Inhibition in comparison to control cultures without added antibodies is given in parentheses.

Our cases of Hodgkin’s disease and anaplastic large-cell lymphoma are not admixed with the tumor cells in anaplastic large-cell lymphoma.

Previous studies have shown that Epstein-Barr virus infection may induce B7/BB1 expression in B cells.1 In view of the recent evidence that Epstein-Barr virus is found in a large number of cases of Hodgkin’s disease and anaplastic large-cell lymphoma,31,32 B7/BB1 expression in these conditions might be induced by the Epstein-Barr virus. However, this would mean that Epstein-Barr virus is present in all of our cases of Hodgkin’s disease and anaplastic large-cell lymphoma studied, which is unlikely as judged from the reported incidence of infection.33

Of interest is the absence of B7/BB1 expression on the neoplastic cells of T-cell–rich B-cell lymphomas. The absence of B7/BB1 on tumor cells of T-cell–rich B-cell lymphoma, as well as on histiocyte-rich B-cell lymphoma, but with expression on Reed-Sternberg cells in all of our cases of Hodgkin’s disease, suggests that B7/BB1 is a useful diagno-
tic marker for distinguishing these entities, which may morphologically appear similar.\textsuperscript{34,35}

In our series, B7/BB1 was also expressed by a subpopulation of neoplastic cells of follicular lymphomas, but not by the other non-Hodgkin's lymphomas studied, with the exception of anaplastic large-cell lymphoma. B7/BB1 expression in follicular lymphomas was also reported by Freeman et al.\textsuperscript{36} However, these investigators also noted B7/BB1 expression in diffuse large-cell lymphomas, in contrast to our results. The discrepancies may be attributed to the use of the Northern blot technique on RNA extracts of total tissue in the study by Freeman et al. It is likely that the presence of B7/BB1-expressing monocyte-derived cells, as variably seen in all our cases, may have accounted for the presence of B7/BB1 transcripts in their RNA preparations of tumor tissue. The expression of B7/BB1 on a subset of neoplastic cells of follicular lymphoma is interesting, and mimicks well the expression of the B7/BB1 molecule on a subset of germinal-center cells in secondary lymph follicles.\textsuperscript{4} B7/BB1 expression by germinal-center cells may be important for T-cell/B-cell cooperation.\textsuperscript{4} The expression of B7/BB1 in follicular lymphomas might indicate that the tumor cells have retained the ability to interact with T cells.

It remains to be demonstrated whether, by acting as accessory cells, Reed-Sternberg cells directly raise a cell-mediated cytotoxic response against the cells proper, as recently demonstrated for B7/BB1-transfected melanoma cells.\textsuperscript{37} The presence of mummified or apoptotic Reed-Sternberg cells, frequently observed in Hodgkin's disease, seems to corroborate such a hypothesis. Cell-mediated cytotoxic killing of Reed-Sternberg cells might explain the relative indolent clinical behavior of most subtypes of Hodgkin's disease. The aggressive clinical behavior of non-Hodgkin's lymphomas, such as histiocyte-rich B-cell lymphoma,\textsuperscript{35} the neoplastic cells of which are phenotypically related to Reed-Sternberg cell variants of lymphocyte predominant Hodgkin's disease, but which do not express B7/BB1, might be due to lack of accessory cell function and hence deficient cell-mediated cytotoxic killing of the malignant cells. Finally, the lack of B7/BB1 expression on most non-Hodgkin's lymphomas suggests that B7/BB1 transfection of lymphoma cells, as has been done for mouse melanoma cells,\textsuperscript{38} might provide a useful approach to the induction of effective antitumor responses.

In conclusion, this study has provided further evidence for the accessory cell function of Reed-Sternberg cells. Despite recent evidence indicating a heterogenous origin of the Reed-Sternberg cell,\textsuperscript{39} the accessory cell function may be characteristic of the Hodgkin's syndrome.

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