Establishing a KSHV+ Cell Line (BCP-1) From Peripheral Blood and Characterizing Its Growth in Nod/SCID Mice


Kaposi’s sarcoma-associated herpesvirus (KSHV or HHV-8) sequences are present in primary effusion lymphomas (PEL). KSHV+ cell lines have been established from such lymphomas. Here we report the first description of the establishment of a KSHV+, EBV− cell line (BCP-1) from the peripheral blood of a patient with PEL. Using this cell line and a KSHV+, EBV− PEL cell line (HBL-6) previously established from ascitic fluid, we investigated whether in nonobese diabetic/severe combined immunodeficiency disease (Nod/SCID) mice tumors representing PEL can be established. When injected intravenously (IV) into Nod/SCID mice, BCP-1 and HBL-6 infiltrated organs, with only occasional macroscopic tumor formation. Intraperitoneal injections (ip) led to the development of ascites and diffuse infiltration of organs, without obviously solid lymphoma formation, resembling the diffuse nature of human PEL. To investigate a possible mechanism for the peculiar phenotype of PEL, we examine the presence of adhesion molecules and homing markers on PEL cells before and after growing in mice. Both BCP-1 and HBL-6 cells lack expression of important cytoadhesion molecules including CD11a and CD18 (LFA1 α and β chains), CD29, CD31, CD44, CD54 (ICAM-1), and CD62L and E (L and E selectins).

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From the Chester Beatty Laboratories, Institute of Cancer Research, London, UK; the Department of Pathology and School of Public Health, Columbia University, New York, NY; the Clinical Sciences Department, London School of Hygiene and Tropical Medicine, University of London, London, UK; the Department of Pathology, Stanford University School of Medicine, Stanford, CA; and the Department of Pathology, Mount Sinai School of Medicine, New York, NY.

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Address reprint requests to Chris Boshoff, Chester Beatty, Laboratories, 237 Fulham Rd, London, SW3 6JB, UK or to Yuan Chang, Department of Pathology, College of Physicians and Surgeons of Columbia University, 630 W 168th St, New York, NY.

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severe combined immunodeficiency disease (Nod/SCID) mice. Both BCP-1 and HBL-6 lack most adhesion molecules and homing markers, which may help to explain the peculiar body distribution of PEL.

MATERIALS AND METHODS

Nod/SCID mice. All animal experiments were approved by the British Home Office and the Ethical Committee for animal procedures of the Institute of Cancer Research (ICR). Nod/SCID mice, bred at the ICR, were kept in containment level 2 cabinets, four mice per cage, with all food and water autoclaved.

Isolation of human peripheral-blood mononuclear cells and generation of KSHV cell line in vitro. The cell line BCP-1 was derived from the peripheral-blood mononuclear cells (PBLs) of a HIV seronegative patient with a PEL who previously had Kaposi’s sarcoma. The lymphoma was KSHV+ and EBV−, with clinical and morphologic features as previously reported. Blood was collected during the course of standard diagnostic procedures under sterile conditions. PBLs were isolated from heparinized blood by isopycnic centrifugation on Ficoll-Hypaque (Pharmacia Fine Chemicals, Piscataway, NJ). The cells were plated at a concentration of 5 × 10^6 cells per mL in 96-well plates without cyclosporin. Cells were grown in RPMI 1640 supplemented with 20% fetal bovine serum (FBS) and 20% T-stim media (Collaborative Biomedical Products, Bedford, MA) at 37°C in the presence of 5% CO₂ and 95% humidity. After 45 days a single clone, BCP-1, was visible. This clone was amplified and cultured without T-stim media.

HBL-6 is a cell line established from the ascitic effusion of an HIV seropositive patient with PEL. This cell line contains both KSHV and EBV. The histology of the primary tumor was previously described.

Both lines are negative for cytomegalovirus, HHV-6, and HIV by polymerase chain reaction (PCR). CB33 is an EBV-immortalized, but not transformed, LCL (gift from Ricardo Dalla-Favera).

Soft agar assays. Cells (1 × 10^4) were suspended in a 0.35% agar solution in RPMI 1640 supplemented with 10% FBS and overlaid onto a 0.5% agar solution in RPMI 1640 containing 10% FBS in 35-mm plates prepared the previous day. After incubation for 1 day, 2 mL of RPMI 1640 supplemented with 10% FBS was added. Colonies in soft agar were counted 12 days after plating. Cloning efficiency is the number of colonies ×100 divided by the number of cells plated. Each determination was repeated three times in separate experiments.

Establishment of mouse tumors and ascites. Four- to 6-week-old Nod/SCID mice were injected intravenously (iv; 10^7 cells/tail vein injection), intraperitoneally (ip; 5 to 6 × 10^6 cells/injection), and subcutaneously (sc; 5 to 6 × 10^6 cells/injection) with either cell line (see Table 2). A total of 32 mice were injected. If animals developed ascites or solid tumors greater than 2 cm or became ill they were killed. Tumors and other organs were fixed in 10% buffered formalin for histology and immunohistochemistry or snap frozen in liquid nitrogen for DNA or RNA extraction. Tumors and ascites were also used to prepare viable cell suspensions for cell-surface phenotype analysis and cell culture.

Histopathology and immunohistochemistry. Formalin-fixed tissues were embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Immunohistochemistry was performed with antibodies to the following antigens: epithelial membrane antigen (EMA; Dako, Glostrup, Denmark), CD3 (Dako), CD20 (L26; Dako), CD30 (Ber H2; Dako), CD43 (Leu 22; Becton Dickinson, Mountain View, CA), and an antibody specific to the interleukin-6 (IL-6) homolog encoded by KSHV (vIL-6). In situ hybridization (ISH) for EBV (EBER) was performed as previously described.

Cell surface immunofluorescence (FACS analysis) of cell lines, tumor cell suspensions, and ascites. Cell suspensions from tumors were established as previously described. Cell lines, cell suspensions, and ascites were stained with unconjugated and fluorescein isothiocyanate (FITC)-conjugated monoclonal antibodies (MoAbs) specific for cell-surface or cytoplasmic antigens, followed by direct or indirect fluores-

Table 1. Cloning Efficiencies of Experimental Cell Lines

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Cloning Efficiency (%)</th>
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</thead>
<tbody>
<tr>
<td>BCP-1</td>
<td>11.5 (2.0)</td>
</tr>
<tr>
<td>HBL-6</td>
<td>9 (1.2)</td>
</tr>
<tr>
<td>CB33</td>
<td>0</td>
</tr>
<tr>
<td>NIH3T3</td>
<td>0.8 (0.3)</td>
</tr>
</tbody>
</table>

![Fig 1. BCP-1 (A) and HBL-6 (B) cells grow in soft agar and form loose disaggregated colonies.](image-url)
ence analysis on a FACS 440 (Becton Dickinson) as previously described. The MoAbs used were CD10 (Serotec, Kidlington, Oxford, UK), CD19 (FMC 63; Selinus, Hawthorne, Victoria, Australia), CD20 (Dako), CD23 (Dako), CD22 (SeraLab, Crawley, Sussex, UK), CD79a (Dako), CD79b (SN8; gift from B.K. Seon, Roswell Park Cancer Institute, Buffalo, NY), CD39 (AC2), CD72 (BU40), CD25 (Dako), CD30 (Dako), CD38 (BA-6; Serotec), CD3 (Dako), CD5 (Dako), CD25 (Dako), CD7 (Dako), CD13 (Dako), CD14 (UCHM1; Sigma, St Louis, MO), CD11a (Becton Dickinson), CD11b (Serotec), CD11c (Dako), CD18, CD29 (8A2 recognizes β1-subunit of integrin receptors; gift from Nick

Fig 2. BCP-1 cells circulating through and forming microscopic tumor deposits in kidney (A) and liver (B) after ip inoculations in Nod/SCID mice. Mitotic figures are prominent.

Fig 3. Solid lymphoma established in Nod/SCID mouse after iv injection with HBL-6 cells. (A) EBER ISH showing intense localization of signal (black chromagen) in nuclei of tumor cells indicating coinfection by EBV (60× magnification). (B) Polyclonal rabbit antiserum against KSHV vIL-6. A minority of cells express detectable protein (red chromagen), which is restricted to the cytoplasmic compartment (with exclusion of nuclei). (60× magnification; Mayer’s hematoxylin counterstain). (C) EMA is strongly expressed in anaplastic tumor cells characterized by large pleomorphic nuclei and abundant mitotic activity (60× magnification; Mayer’s hematoxylin counterstain). (D) Leukocyte common antigen (LCA) is not generally expressed in tumor cells consistent with the null immunophenotype association with PEL and derived cell lines (60× magnification; Mayer’s hematoxylin counterstain).
Table 2. Injection Sites and Results of KSHV Cell Lines in Nod/SCID Mice

<table>
<thead>
<tr>
<th>Injection Site</th>
<th>No. of Mice Injected</th>
<th>No. of Mice With Ascites</th>
<th>No. of Mice With Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>ip Injections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCP-1</td>
<td>6</td>
<td>6 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>HBL-6</td>
<td>6</td>
<td>6 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>sc Injections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCP-1</td>
<td>4</td>
<td>0 (0%)</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>HBL-6</td>
<td>4</td>
<td>0 (0%)</td>
<td>4 (100%)</td>
</tr>
<tr>
<td>iv Injections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCP-1</td>
<td>6</td>
<td>0</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>HBL-6</td>
<td>6</td>
<td>0</td>
<td>2 (33%)</td>
</tr>
</tbody>
</table>

Kovach, Harbor View Medical Centre, Seattle, WA), CD49d (HP2/1; gift from Sanchez-Madrid, Hospital de la Princesa, Madrid, Spain), 9EG7 (this antibody recognizes an epitope on integrin chain β1, which is only accessible after activation of this integrin; gift from Dietmar Vestweber, WestFalische, Munster, Germany), CD31 (HC1/6; Serotec), CD44, CD49e (Serotec), CD54 (ICAM-1; Becton Dickinson), CD88 (LFA-3; ATCC Hybridoma, ATCC, Bethesda, MD), CD42L (L-selectin; Becton Dickinson), CD62E (R & D Systems, Minneapolis, MN), EMA (ICR-1; gift from C. Dean, ICR, London), terminal deoxynucleotidal transferase (TdT; SeraLab), CD34 (QBend-10; Quantum Biosciences, Cambridge, UK), CD43 (DFT-1; Serotec), CD45 (Sigma), and HLA-DR (L.243; Becton Dickinson).

EBV latent gene expression. EBV latent and lytic gene expression in HBL-6 cells (EBV+; KSHV+) was investigated by immunocytochemistry on acetone-ethanol-fixed cytospin preparations and by immunoblotting of protein extracts. BCP-1 (KSHV+; EBV-) and B958 (EBV+; KSHV-) cell lines were used as negative and positive controls, respectively. For phenotyping, EBV-latent antigens were detected by anticomplement immunocytochemistry using polyclonal human antisera with high titre activity to EBV nuclear antigens EBNA1-6 (CP) and EBNA-2 (JT), and by standard three layer immunoalkaline phosphatase sera with high titre activity to EBV latent gene expression. Such vascularity surrounding KSHV+ lymphomas induced in SCID mice was also recently reported by another group.28

Two of the six mice injected iv with HBL-6 developed solid tumors, but none of the BCP-1 iv-injected mice developed visible tumors or ascites (Table 2).

Histologic examination of the SCID mice xenograft tumors showed a diffuse infiltrate of neoplastic lymphoid cells. The constituent cells were medium-to-large and contained nuclei with unevenly distributed chromat and prominent nucleoli. Many cells showed plasmacytoid features characterized by eccentrically placed nuclei and amphophilic cytoplasm. Immunohistochemical studies showed the neoplastic lymphoid cells to express the activation antigen CD30 (Ki-1), the hematoxylinic studies showed the neoplastic lymphoid cells to express the activation antigen CD30 (Ki-1), the hematolymphoid antigen CD43, as well as EMA (Fig 3). The cells lacked CD20 and CD3 reactivity. These immunohistochemical findings are identical to those described in PEL. Although tumor masses developed after sc injections, these could be caused by tumor cell restriction within the tissue plane, rather than tumor aggregation.

The majority of mice injected iv with either BCP-1 or HBL-6 did not develop visible macroscopic tumors, but postmortem examination of several tissues (sampled up to 16 weeks after inoculations; Fig 4 and 5) showed the presence of diffuse infiltrates of single or small clumps of KSHV-infected cells, as determined by histology and vIL-6 immunohistochemistry (Fig 4). This was confirmed by PCR and Southern blot analyses (Fig 5) in which various organs were shown to contain KSHV. The human origin of the infiltrating infected cells was confirmed by PCR amplification of human ERV-3 sequences from KSHV+ tissues (ERV-3 is an endogenous human retrovirus present at two copies per genome in humans). Tissues from those mice injected with HBL-6 also contained EBV as evidenced by EBER ISH and EBV-specific PCR.

These data show that both cell lines have the capacity to form tumors in Nod/SCID mice and that ip injection gives rise to an
effusion tumor similar to that observed in human PEL, including ascites and diffusion of lymphoma cells in various organ systems, but seldom macroscopic lymphoma formation.

**Cell surface immunophenotype.** The immunophenotype profile was essentially similar for the cell line established from peripheral blood (BCP-1) and did not change upon xenotransplantation in Nod/SCID mice (Table 3; Fig 6). For the coinfected cell line HBL-6 surface phenotype also did not change after xenotransplantation.

Both lines lacked T-cell and the majority of B-cell markers, although HBL-6 cells expressed CD79a, a marker which identifies the α-chain of the B-cell receptor. Both lines expressed B-cell activation markers including CD23, CD25, and CD38 and were, as the previously described PEL lines, EMA+. Both lines lacked expression of several important adhesion and homing molecules including ICAM-1 (CD54), L- and E-selectin (CD62L and E), CD31, CD44, and CD11a and CD11c. The activation marker CD38 was absent on native BCP-1 cells, but repeatedly became upregulated after growth in the peritoneal cavity of mice.

Normal plasma cells also lack expression of most B-cell antigens and CD11a, CD45, CD62L, CD49e while expressing CD38. By FACS analyses, there is no surface Ig expression on...
BCP-1 cells; however, heavy chain IgG is expressed as seen on Western blotting (data not shown), indicating internal rather than surface expression.

HBL-6 cells displayed a restricted EBV antigen profile limited to EBNA-1 expression, similar to BL. With polyclonal antisera (CP), strong granular staining similar to that seen on the EBV
\[1\]
B958 cell line was present in all nuclei (Fig 7a and b, see page 1675). HBL-6 cells were negative with MoAbs to EBNA-2 and LMP-1 and -2 (Fig 7c and d).

Clonality of BCP-1 cells. To investigate the relationship, at a molecular level, between the KSHV
\[1\]
PEL cells and the BCP-1 cell line derived from the peripheral blood, we analyzed the VDJ segments of the Ig heavy chain gene from the KSHV
\[1\]
PEL cells and that from the BCP-1 cell line. PCR amplification showed VDJ products of similar length when analyzed on ethidium bromide–stained polyacrylimide gel. Subsequent DNA sequence analysis showed identical sequences (Fig 8) of both 97-bp amplicons, indicating a clonal identity between the PEL cell line and the BCP-1 cells derived from peripheral blood.

Cytogenetic analysis of BCP-1. Previous analyses have shown that both the HBL-6 cell line and its parental tumor
\[15\] have a normal c-myc allele configuration. Cytogenetic analysis of BCP-1 also revealed no c-myc rearrangements, although this cell line does possess a complex karyotype involving chromosomes X, 12, and 14. Chromosome painting showed that the der(x) correspond to t(x;14,12) (q12; q11;q22-23; q23-24) (Fig 9, see page 1675).

DISCUSSION

We describe the establishment of a KSHV
\[1\], EBV
\[2\]
cell line (BCP-1) from the peripheral blood of a patient with PEL. BCP-1 and a KSHV/EBV dually infected cell line (HBL-6), established from an effusion of another patient with PEL, both grow in soft agar and form tumors in mice, indicating transformed phenotypes
\[16\].

Clonal analysis of the KSHV
\[1\] PEL and the BCP-1 cell line showed identical IgH VDJ segments, providing molecular evidence for the derivation of the BCP-1 cells from the original effusion lymphoma. This finding indicates that PEL cells circulate in the peripheral blood and that cell lines can be derived from these; furthermore, they circulate and infiltrate numerous organs in Nod/SCID mice.

BCP-1 has a complex karyotype concordant with that previously shown in PEL cell lines derived from malignant effusions, but no breakpoints common to other PELs have been identified
\[9\]. HBL-6 cells show certain similarity to EBV
\[1\] BL cells in that they have a restricted expression of EBV latent antigens (only EBNA-1), but, unlike the latter, they lack c-myc rearrangements. However, HBL-6 cells show evidence of transformation, and this suggests that KSHV can replace c-myc activation as a further step toward a transformed phenotype in the presence of

Fig 5. Southern blot (A) and PCR (B) for KSHV in various mouse tissues. (Note Southern blots were done independently of PCR and do not represent blotting of PCR products.) MW, molecular markers. Lane 1: Southern blot and PCR-positive ascitic cells from HBL-6 ip-injected mouse. Lane 2: Southern blot and PCR-positive tumor cells from HBL-6 iv-injected mouse. Lane 3: PCR-positive small intestine from HBL-6 iv-injected mouse. Lane 4: Southern blot and PCR-positive testis from HBL-6 iv-injected mouse. Lane 5: Southern blot and PCR-positive kidney from HBL-6 iv-injected mouse. Lane 6: PCR-positive heart from HBL-6 iv-injected mouse. Lane 7: Southern blot and PCR-positive lungs from HBL-6 iv-injected mouse. Lane 8: PCR-positive spleen from HBL-6 iv-injected mouse. Lane 9: Blank. Lane 10: PCR-positive kidney from BCP-1 iv-injected mouse. Lane 11: PCR-positive (weakly) lung from BCP-1 iv-injected mouse. Lane 12: PCR-positive (weakly) liver from BCP-1 iv-injected mouse. Lane 13: PCR-positive thymus from BCP-1 iv-injected mouse.
EBNA-1 expression. KSHV+ BCP-1 cells also lack c-myc rearrangements, are EBV−, and show evidence of transformation, indicating that KSHV by itself is potentially sufficient to transform B cells. HBL-6 and BCP-1 have the capacity to generate tumors after injection into NOD/SCID mice, providing further evidence that these cells are transformed (Table 2). Differences were apparent, however, between the two cell lines in tumor-forming capacity and resulting tumor phenotypes, which were dependent on the site of injection.

When injected iv into immunodeficient mice, BCP-1 and HBL-6 infiltrated organs, with only occasional macroscopic tumor formation, whereas ip injections led to the development of ascites without solid lymphoma formation, resembling the diffuse nature of human PEL.

The major difference in cell surface antigen expression between the HBL-6 and BCP-1 cell lines is the presence of the integrins CD49d, CD49e, and CD58 on HBL-6 but not on BCP-1. CD49e, a component of the fibronectin receptor very late activation antigen 5 (VLA-5; CD49e/CD29 or α6β1), has been shown to correlate with the capacity of malignant human B lymphocytes to disseminate in SCID mice. VLA-4 (CD49d/CD29 or α4β1) is also involved in B-cell migration, especially on activated endothelium, through its ligand VCAM-1. The expression of these α-integrins on HBL-6 cells only is consistent with the higher capacity of this line to form solid tumors distal to the site of inoculation in mice.

The presence of Ig gene rearrangements along with the immunophenotype described suggest that these PEL cell lines (and mouse-induced neoplasms) belong to the B-cell lineage with plasmacytic differentiation. The only true “aberrancies” regarding normal plasma cells seem to be the expression of CD23 and lack of CD49d and surface Ig expression. KSHV infection either arrests cells at this stage of differentiation or infects and transforms these mature B cells.

Similar to EBV, KSHV might also transactivate cellular genes involved in B-cell activation because KSHV+ PEL cells and cell lines derived from them also express activation markers CD23, CD25, and CD38. Interestingly, CD38 was negative on the BCP-1 cell line, but upregulated after culturing in a different environment, ie, the peritoneal cavity of immunodeficient mice.

The unusual propensity of PEL to involve predominantly body cavity surfaces could be the result of a peculiar homing pattern induced by KSHV infection. The traffic of lymphocytes to lymphoid and other tissues is controlled in part by the interaction of lymphocyte adhesion molecules called homing receptors with tissue-selective endothelial ligands known as vascular addressins. LFA-1 α- and β-chains (CD11a/CD18), αβ integrin (CD49d/CD29), ICAM-1 (CD54), and L-selectin (CD62L) have all been shown to be involved in the homing of lymphocytes to lymphoid tissues. KSHV+ PELs do not express these molecules in contrast to the EBV+ BLs, EBV+ LCLs, anaplastic large cell lymphomas, and primary central nervous system lymphomas.

The absence of B-cell markers CD10, CD19, CD20, and CD22 on PEL cell lines has already been described. The lack of CD19 expression may also contribute to the effusion phenotype of these lymphomas, as this B-cell antigen has been shown to be involved in the homing of B cells to lymph nodes and in germinal center formation. CD19 is also involved in the spontaneous homotypic adhesion seen in culture, and notably BCP-1 and HBL-6 do not grow in clumps in culture. We further observed that both cell lines lack CD79b, a specific and functional B-cell marker identifying the β-chain of the B-cell receptor, whereas only HBL-6 expresses CD79a.

The absence of CD44 on PEL cells is also noteworthy. CD44 (Pgp-1 also known as Hermes lymph node homing receptor) is a glycoprotein proposed to be the principal cell surface receptor for hyaluronan and involved in lymphocyte trafficking from blood to lymphatic tissues. Different isoforms of CD44 expressed in lymphoid tumor cells have distinct effects on their ability to attach to hyaluronan surfaces and consequently their capacity to form solid tumors in vivo. EBV+ LCLs express CD44, as do most primary lymphomas. In contrast, EBV+ BLs and Burkitt’s cell lines are negative for CD44.

Both lines express EMA (also known as MUC-1 or epoia-
lin), which is expressed on a variety of epithelial cells and also on anaplastic large lymphoma cells. It has been suggested that EMA is an "antiadhesion molecule" involved in the metastatic process (in release of cells from a primary tumor) and in escape from immune surveillance.

It has been postulated that the absence of certain adhesion molecules on neoplastic cells could contribute to lymphomagenesis by conferring on them some degree of protection from immunosurveillance. CD54 and CD58 expressed on B cells have been proposed to interact directly with T cells, and EBV+ cells lacking CD11a/CD18 are poor stimulators of T-cell responses. Notably, CD54, CD58, CD11a, and CD18 are absent on BCP-1 cells, and HBL-6 cells only express CD58.

Apart from EBV and human T-cell leukemia virus (HTLV)-positive cell lines, this is the only other report of a presumably viral-driven and maintained cell line established from human peripheral blood. These cells grow in soft agar and in immunodeficient mice confirming their transformed phenotype and supporting an oncogenic role for KSHV.

Fig 6. Representative example of FACS profiles for BCP-1 and HBL-6 cells and cells obtained from Nod/SCID ascitic fluid. EBV+ Daudi cells were used as a control. Fluorescence intensity is expressed on an arbitrary logarithmic scale. Black histograms represent antibody stained cells, and white histograms are isotype-specific controls for each antibody used. As previously shown, KSHV+ PEL cells lack B-cell markers including CD19, but express EMA. ICAM-1 or CD54 is an important adhesion molecule present on most lymphoma cells and upregulated by EBV LMP-1.

Fig 8. PCR products of Ig heavy chain gene rearrangement analysis.

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