Molecular Genetic Analysis of Three AIDS-Associated Neoplasms of Uncertain Lineage Demonstrates Their B-Cell Derivation and the Possible Pathogenetic Role of the Epstein-Barr Virus

By Daniel M. Knowles, Giorgio Inghirami, Angela Ubriaco, and Riccardo Dalla-Favera

Each of three individuals with acquired immunodeficiency syndrome (AIDS) developed a pleomorphic malignant neoplasm in which a precise histopathologic diagnosis could not be rendered. In each case, the tumor cells expressed leukocyte common antigen and a variable constellation of antigens associated with B- and T-cell activation (HLA-DR, T9, T10, BL2, BL3, Ki-24, BLAST-2). They lacked all B cell, T cell, myeloid, and monocyte lineage-restricted antigens, resulting in their classification as hematopoietic neoplasms of uncertain lineage. However, antigen receptor gene rearrangement analysis demonstrated that each of these neoplasms exhibited clonal immunoglobulin heavy chain and kappa light chain gene rearrangements and lacked T-cell receptor beta chain gene rearrangements and therefore were B cell-derived non-Hodgkin’s lymphomas (NHL) representative of an equivalent, relatively mature stage of B-cell differentiation. In contrast with most AIDS-associated NHLs, each of these three neoplasms lacked c-myc gene rearrangements and contained Epstein-Barr virus (EBV) proteins and/or sequences. These studies demonstrate that these three AIDS-associated neoplasms of uncertain lineage exhibit a strikingly similar constellation of distinctly uncommon morphologic, immunophenotypic, and molecular genetic characteristics that distinguishes them substantially from the vast majority of NHLs that have been reported to occur in association with AIDS. The consistent presence of EBV proteins and/or DNA sequences suggests that the Epstein-Barr virus played a pathogenetic role in the development of these three AIDS-associated neoplasms. Finally, these studies further illustrate the utility of antigen receptor gene rearrangement analysis in the diagnosis and classification of hematopoietic neoplasms of uncertain lineage.

A N INCREASED INCIDENCE of non-Hodgkin’s lymphoma (NHL) is a major clinical manifestation of the acquired immune deficiency syndrome (AIDS).1,2,3 Indeed, the Centers for Disease Control now includes the occurrence of diffuse, aggressive intermediate or high-grade NHL in an individual seropositive for the human immunodeficiency virus (HIV) among the criteria diagnostic for AIDS.4 An analysis of 89 AIDS-associated NHLs seen at one institution during 1981 to 1986 demonstrated that approximately 70% were high grade (small, noncleaved cell or large cell, immunoblastic, plasmacytoid) and the remaining 30% were intermediate grade (diffuse large cell) lymphomas.5 Many arose in unusual extranodal sites, including, for example, the skin, maxilla, lung, anus and rectum.6 They nearly always expressed monotypic surface immunoglobulin and/or B cell-restricted and associated antigens,7,8,9 suggesting a B-cell derivation.

We have encountered 3 individuals with AIDS who developed a malignant neoplasm thought to represent an NHL by clinical criteria but in which a precise histopathologic diagnosis was difficult to render initially due to the undifferentiated and/or pleomorphic appearance of the tumor cells. Furthermore, although the tumor cells in each neoplasm expressed leukocyte common antigen, suggesting a hematopoietic origin, they lacked B cell, T cell, myeloid-, and monocyte-lineage-restricted antigens, preventing us from assigning the neoplasms to a specific cell lineage and thereby rendering definitive diagnoses. Hematopoietic neoplasms of uncertain lineage are of considerable interest since so little about them is known because of their rarity. Furthermore, such neoplasms may present a diagnostic dilemma and be confused with lymphocyte-depleted Hodgkin’s disease or an undifferentiated carcinoma because of their overlapping clinicopathologic features.

We and others have shown that Southern blot hybridization analysis for antigen receptor gene rearrangements is a highly objective, specific, and sensitive method by which to determine the lineage and the clonality of lymphoid neoplasms, including those that express immature, anomalous, and ambiguous phenotypes.8,10-16 Southern blot hybridization analysis using appropriate DNA probes is similarly useful in detecting viral sequences, oncogenes, and chromosomal translocations17 and thereby investigating pathogenetic mechanisms of neoplasia. Therefore, we used this approach to investigate the lineage, clonality, and pathogenesis of these three AIDS-associated neoplasms of uncertain lineage. The results of our studies suggest that they represent a distinct and unusual group of uncommonly occurring B-cell NHLs associated with AIDS whose pathogenesis may be related to Epstein-Barr virus (EBV) infection. These results further support our contention that the vast majority of AIDS-associated NHLs are B-cell neoplasms5 and also further demonstrate the utility of antigen receptor gene rearrangement analysis in the differential diagnosis of hematopoietic neoplasms of uncertain lineage.

CASE REPORTS

Patient no. 1. A 31-year-old homosexual white man presented in February 1987 with a pericardial effusion positive for mycobacterium tuberculosis. The patient returned 2 months later with a malignant pleural effusion,
interpreted as a probable large cell lymphoma, and he was
diagnosed with AIDS in October 1985 on the basis of HIV-
associated seropositivity and pneumocystis carinii pneumonia.
The patient returned in September 1987 with HIV-associated
malignant lymphoma, and the patient was begun on a
multidrug chemotherapeutic regimen. The patient was unres-
sponsive to therapy, became icteric, developed renal failure
and ascites, became comatose, and died in July 1987, 7
months after his initial presentation.

Patient no. 2. A 47-year-old homosexual white man was
diagnosed with AIDS in January 1987 on the basis of HIV
seropositivity and pneumocystis carinii pneumonia.
The patient returned 3 months later with generalized peripheral
and abdominal lymphadenopathy. A left axillary lymph node
biopsy was interpreted as a malignant neoplasm, probably
malignant lymphoma, and the patient was begun on a
multidrug chemotherapeutic regimen. The patient was unres-
sponsive to therapy, became icteric, developed renal failure
and ascites, became comatose, and died in July 1987, 7
months after being diagnosed with AIDS.

Patient no. 3. A 40-year-old homosexual white man was
diagnosed with AIDS in October 1985 on the basis of HIV
seropositivity and cutaneous Kaposi’s sarcoma. An incisional
biopsy of an enlarged right submandibular gland was inter-
preted as a malignant neoplasm, probably malignant lymphoma,
and the patient was placed on a multidrug chemotherapeutic
regimen. The patient returned 5 months later with further weakness and cachexia, progressive Kaposi’s
sarcoma, and a large malignant pleural effusion. The patient became hypotensive and died ten days later, 6 months after
being diagnosed with AIDS.

MATERIALS AND METHODS

Pathologic samples. Malignant pleural effusions from patients
1 and 2 and lymph node biopsies from patients 2 and 3 were available fresh, sterile, and unfixed. Viable mononuclear cell suspensions
isolated from patients 2 and 3 were snap frozen in isopentane and dry ice, and other representative portions were fixed in formalin and embedded in paraffin. Cytospin
preparations of the two malignant pleural effusions and hematoxylin
eosin stained sections of the lymph node biopsies were examined morphologically.

Immunophenotypic analysis. The immunophenotypic profiles of the neoplasms occurring in these 3 patients were delineated by direct and indirect immunofluorescent cytofluorometric analysis of the isolated tumor cells in suspension using a model 420 fluorescent
activated cell sorter (Becton-Dickinson, Mountain View, CA) and/or by immunohistochemical analysis of cryostat tissue sections
using an avidin-biotin-immunoperoxidase technique.18 We analyzed the malignant cells in each of the three neoplasms for their expression
of surface and cytoplasmic immunoglobulin, sheep erythrocyte
rosettes, terminal deoxynucleotidyl transferase, and a large panel of
B-cell, T-cell, myeloid, and monocyte lineage associated antigens.
This panel included leukocyte common antigen, BA1, BA2 (Hybro-
techn, San Diego, CA), B1, B2, B4, J5, MY7, MY9 (Coulter, Hialeah FL), Leu1, Leu7, Leu9, Leu11, Leu13, LeuM1, LeuM3 (Becton-
Dickinson, Mountain View, CA), OKB1, OKB2, OKB4, OKB7, OKT3, OKT4, OKT6, OKT8, OKT9, OKT10, OKT11, OKM1, OKM5 (Ortho Pharmaceutical, Raritan, NJ), BL1, BL2, BL3, BL4, BL7, BL9, HLA-DR, IL2-R (United Biomedical, Lake Success, NY), Ki-1, Ki-24 (courtesy Prof Harald Stein) and BLAST-2 (courtesy Dr Lee Nadler). In addition, we analyzed the malignant

RESULTS

Histopathology. The neoplasm in patient 1 consisted of a
monotonous population of large, round tumor cells contain-
ing a small amount of acidophilic cytoplasm and round, regular nuclei with prominent nucleoli. The neoplasms in patients 2 and 3 consisted of malignant cells displaying considerable pleomorphism (Figs 1, 2). The cells were generally round or ovoid to polygonal in shape and contained abundant acidophilic to amphophilic cytoplasm without evidence of phagocytosis and nuclei that ranged from large, round, and regular to highly irregular and hyperconvoluted with one or more prominent nucleoli. Multinucleated cells were scattered throughout both neoplasms; some nuclei resembled those of the Reed-Sternberg cells of Hodgkin's disease. Mitotic figures were numerous.

**Immunophenotype.** The tumor cells comprising each of the three neoplasms (a) expressed leukocyte common antigen, suggesting a hematopoietic origin; (b) lacked all B cell (surface and cytoplasmic immunoglobulin, B1, B2, B4, BA1, BA2, BL1, BL7, BL9, Leu 14), T cell (Leu1, Leu9, T3, T4, T6, T8, T11), and myeloid/monocyte (MY7, MY9, OKM1, OKM5, LeuM1, LeuM3) lineage-associated antigens investigated; and (c) expressed a variable constellation of antigens associated with B- and T-cell activation (HLA-DR, BL2, BL3, Ki-24, BLAST-2, T9, T10) (Table 1). Occasional hematopoietic neoplasms of obscure derivation express the Ki-1 antigen, but these three neoplasms were Ki-1 negative. The lack of expression of any lineage-restricted antigens by these three neoplasms precludes their assignment to the B-cell, T-cell, monocyte, or myeloid lineage, resulting in their classification as hematopoietic neoplasms of uncertain lineage.

**Antigen receptor genes.** The neoplastic cells comprising each of the three neoplasms exhibited clonal rearrangements of the immunoglobulin heavy-chain gene upon hybridization of EcoRI and HindIII digested DNAs to a JH probe and BamHI-digested DNAs to a C\(_{\lambda}\) probe. In addition, each neoplasm exhibited clonal rearrangements of the kappa light-chain gene upon hybridization of BamHI- and HindIII-digested DNAs to a J\(_{\kappa}\) probe and clonal rearrangement and/or deletion of the kappa light-chain gene upon hybridization of BamHI-digested DNAs to a C\(_{\kappa}\) probe. In each case, the lambda light-chain gene remained in the germline configuration. There was no evidence of clonal rearrangements of the T-cell receptor beta chain gene upon hybridization of EcoRI- and BamHI-digested DNAs to a T\(_{\beta}\) probe (Table 2, Figs 3, 4).

In summary, antigen receptor gene rearrangement analysis unequivocally demonstrated that the tumor cells in each of these three neoplasms underwent rearrangement of the immunoglobulin heavy chain and kappa light chain but not the lambda light chain or the T-cell receptor beta chain gene loci. These results indicate that these three neoplasms considered to be of uncertain lineage by immunophenotypic analysis are of B-cell lineage derivation and represent an approximately equivalent, relatively mature stage of B-cell differentiation.

**Epstein-Barr virus sequences and proteins.** We initially investigated the presence of EBV sequences by Southern blot hybridization analysis using DNA probes for the EBNA-1 and Oripl, and the EBNA-2 genes since these regions are usually present in EBV-infected cells. We detected hybridization bands in the genomic EBV pattern in each of the three neoplasms (Table 3, Fig 5). Since >90% of the cells in each pathologic sample were tumor cells, our results strongly suggested that the EBV sequences are contained within the malignant cells. However, the intensity of the EBNA-1 and EBNA-2 hybridization bands of these three neoplasms was weaker than those of EBV-infected B lymphoblastoid cell line JY25 used as a positive control, causing us to consider, alternatively, that these results could be related to the presence of large numbers of copies in a minor, residual

![Fig 1.](image) The lymph node obtained from patient 2 was entirely replaced by a pleomorphic neoplastic cell population. The cells contain abundant acidophilic to amphophilic cytoplasm and large round and regular to markedly irregular nuclei. Nucleoli are prominent. Mitotic figures are numerous (original magnification ×500).

![Fig 2.](image) The neoplasm in patient 3 was similarly composed of large, pleomorphic tumor cells containing abundant acidophilic cytoplasm and round, ovoid, irregular, and bizarre pleomorphic nuclei, many of which contained large prominent nucleoli. The large pleomorphic, multilobated nucleus containing several nucleoli in the cell in the center. Numerous mitotic figures are present (original magnification ×500).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Immunophenotype of Tumor Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LCA, T9, T10, BLAST-2, Ki-24</td>
</tr>
<tr>
<td>2</td>
<td>LCA, HLA-DR, T9, T10, BL2, BLAST-2, Ki-24</td>
</tr>
<tr>
<td>3*</td>
<td>LCA, HLA-DR, T9, BL2, BL3</td>
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</tbody>
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*Not tested for BLAST-2 or Ki-24.

**Table 1. Results of Immunophenotypic Analysis**
nonneoplastic B-cell population. Therefore, we chose to investigate the presence of EBV in the malignant cells directly by determining the presence of EBV proteins in the tumor cells from patients 1 and 2 using an anti-EBNA antiserum. We detected characteristic patchy nuclear fluorescence in the majority of the tumor cells in both of these neoplasms, confirming our results obtained by Southern blotting. Previously, we had been able to show similar complete concordance between EBNA positivity or negativity by immunofluorescence and the presence or absence of EBV sequences by Southern blotting in a study of 16 AIDS-associated NHLs.4 Taken together, these studies demonstrate the presence of EBV proteins and/or sequences in a variable proportion of the malignant cells in each of the three neoplasms. In addition, each neoplasm displayed a single band of different molecular weight when BamHI- and EcoRI-digested DNAs were hybridized to a probe recognizing the EBV termini (data not shown). This finding strongly suggests that the tumor cells in each neoplasm were infected with a single form of EBV and that the monoclonal proliferation occurred after EBV infection.

_C-myc, bcl-1, and bcl-2 rearrangements and HTLV-1 sequences._ Previously, we had demonstrated the presence of c-myc gene rearrangements analogous to those observed in sporadic Burkitt’s lymphomas in 12 of 16 AIDS-associated NHLs of various histologic types. In contrast, none of the three neoplasms investigated here exhibited evidence of c-myc gene rearrangements when studied with the same c-myc probe and enzymes under similar conditions. However, these three neoplasms were similar to other AIDS-associated NHLs that we have studied in that they also lacked bcl-2 locus rearrangements and HTLV-1 DNA sequences. These three neoplasms also lacked bcl-1 gene rearrangements (Table 3).

### Table 2. Results of Antigen Receptor Gene Rearrangement Analysis

<table>
<thead>
<tr>
<th>Patient</th>
<th>JH</th>
<th>Cμ</th>
<th>Jκ</th>
<th>Cλ</th>
<th>Tκ</th>
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<tr>
<td>1</td>
<td>R</td>
<td>R</td>
<td>ND</td>
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<td>R</td>
<td>R</td>
<td>ND</td>
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<td>G</td>
</tr>
</tbody>
</table>

Abbreviations: R, rearranged; G, germline; D, deletion; ND, not done.

DISCUSSION

The three AIDS-associated neoplasms described here exhibit a strikingly similar constellation of distinctly uncommon morphologic, immunophenotypic, and molecular genetic characteristics that distinguishes them substantially from the vast majority of AIDS-associated NHLs reported thus far. First, AIDS-associated NHLs nearly always belong to small noncleaved cell, large-cell immunoblastic plasmacytoid, or diffuse large-cell histopathologic categories.7 Two of the neoplasms described here exhibited considerable cellular pleomorphism, which, although within the morphologic spectrum of large-cell immunoblastic plasmacytoid lymphoma, raised the possibility of lymphocyte-depleted Hodgkin’s disease, a malignant neoplasm of true histiocytic derivation, or an undifferentiated carcinoma. The remaining neoplasm was composed of large undifferentiated-appearing tumor cells. Second, essentially all AIDS-associated NHLs express monotypic surface immunoglobulin and/or B cell-restricted and associated antigens consistent with B-cell lineage derivation. The neoplastic cells comprising the three neoplasms described here expressed leukocyte common antigen and a variety of antigens associated with both B- and T-cell activation but lacked B cell, T cell, and monocyte and myeloid lineage-restricted antigens, resulting in their classification as hematopoietic neoplasms of uncertain lineage.
Nonetheless, despite phenotypic ambiguity, these tumor cells exhibited clonal rearrangement of the immunoglobulin heavy-chain and kappa light-chain genes, consistent with a relatively mature stage of B-cell differentiation. Third, we recently demonstrated that approximately 75% of AIDS-associated NHLs of all histologic types exhibit c-myc gene rearrangements similar to those of sporadic Burkitt’s lymphoma and that about only one-third contain EBV sequences and/or proteins. In contrast, the neoplastic cells comprising the three neoplasms described here contained EBV proteins and/or sequences and lacked c-myc gene rearrangements.

Traditionally, NHLs were assigned to the B- or T-cell lineage according to their expression of monotypic surface immunoglobulin (SIg) or sheep erythrocyte (E) rosette formation, respectively; SIg and E rosette negative NHLs were termed null cell NHLs. However, the majority of these so-called null-cell lymphomas may be readily assigned to the B- or T-cell lineage according to their expression of a variety of monoclonal antibody defined B and T cell lineage-restricted antigens. The few remaining unclassifiable NHLs represent a clinicopathologically heterogenous group of hematopoietic neoplasms of uncertain lineage. We have identified only 13 such neoplasms from among more than 600 NHLs that we have immunophenotyped during 1980 through 1987. Antigen receptor gene rearrangement analysis has demonstrated that 4 of these 13 neoplasms, including the 3 AIDS-associated neoplasms described here, are derived from the B-cell lineage. Therefore, genotypic B-cell NHLs lacking B cell lineage-restricted antigens have constituted less than 1% of all B-cell NHLs that we analyzed during the past eight years, and this group is nearly entirely accounted for by these three AIDS-associated NHLs.

The tumor cells in each of these three neoplasms exhibit rearranged immunoglobulin heavy- and kappa light-chain genes, suggesting that they represent an approximately
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equivalent, relatively mature stage of B-cell differentiation. The tumor cells are devoid of cell-surface antigens associated with the early and middle stages of B-cell differentiation but express a constellation of antigens that occur in the late stages of B-cell differentiation and/or activation. The tumor cells in one or more of these neoplasms expressed HLA-DR antigens and an HLA-DR associated antigen, BL2.18,41 which are expressed on activated T cells50,41 and on all but terminally differentiated B cells13,40,41 T9, the transferrin receptor,52 T10,40 and BL3,52 distinct antigens that are expressed in the late stages of B-cell differentiation and also on activated T cells50,41; and activation-associated antigens Ki-243 and BLAST-2.4 The mature pattern of rearranged immunoglobulin genes combined with the cell-surface expression of antigens associated with the late stages of B-cell differentiation and/or activation suggests that each of these three neoplasms represents the neoplastic counterpart of a benign equivalent stage of B-cell differentiation, which normally occurs during lymphocyte transformation, i.e., a stage following antigenic stimulation and lying somewhere between a mature B cell and a plasma cell.

The pathogenesis of AIDS-associated NHLs and the relationship between the increased frequency of their development in individuals with AIDS and the severe immunosuppression characteristic of AIDS is not well understood at the present time. It has been suggested that EBV plays a role in AIDS-associated lymphogenesis based on the fact that (a) the immune regulation of EBV infections is defective in patients with AIDS and the AIDS-related complex (ARC)46; (b) multiple clonal B-cell expansions, presumably carrying EBV, have been detected in the benign, hyperplastic lymph nodes of the lymphadenopathy syndrome and in AIDS-associated NHLs; (c) EBV-positive B lymphoblastoid cell lines may be easily established in vitro from the peripheral blood of AIDS patients45; and (d) EBV is known to be involved in the pathogenesis of B-cell NHLs occurring in association with other cellular immune deficiencies.46-50 Nonetheless, we were able to demonstrate EBV sequences and/or proteins in only 6 of 16 (38%) AIDS-associated NHLs, including cases exhibiting Burkitt’s morphology.3 However, we found evidence of c-myc gene rearrangements in 12 of these same 16 NHLs, including cases belonging to intermediate (diffuse large-cell) and high-grade (small non-cleaved cell, large-cell immunoblastic-plasmacytoid) histopathologic categories. The occurrence of c-myc gene rearrangements in the absence of EBV sequences in the majority of AIDS-associated NHLs is similar to sporadic Burkitt’s lymphoma.51 This similarity is enhanced by our observation that AIDS-associated NHLs carry translocations of the c-myc gene and recombinations with the switch region of the immunoglobulin heavy-chain locus,8 which are typical of sporadic Burkitt’s lymphoma.52 Therefore, it is highly likely that c-myc gene rearrangements but not EBV contribute to the pathogenesis of most AIDS-associated NHLs, analogous to sporadic Burkitt’s lymphoma.

However, the three AIDS-associated B-cell NHLs described here differ substantially from AIDS-associated NHLs that we have others have described. In particular, in contrast with most AIDS-associated NHLs, these three neoplasms contain EBV proteins and/or sequences and lack c-myc gene rearrangements. In light of their unusual morphologic and immunophenotypic features, their association with severe immune deficiency (AIDS), and the observations outlined above concerning the associations between EBV, AIDS, and/or lymphomagenesis, an intriguing and important question is to what extent did EBV play a role in the pathogenesis of these three unusual AIDS-associated B-cell NHLs.

It is well known that EBV induces normal resting B cells to secrete immunoglobulin, to express surface-membrane activation antigens similar to those expressed by antigen- or mitogen-activated B cells, and to proliferate indefinitely.52 The tumor cells in the three neoplasms described here expressed a variable number of cell-surface antigens associated with B-cell activation. In particular, the tumor cells in both patients tested expressed BLAST-2 in high density. The BLAST-2 cell-surface antigen is absent from unstimulated B cells and is expressed in low density in pokeweed, protein-A, and anti-immunoglobulin-driven B cells but is superinduced in EBV-infected B cells.44 Ki-24 antigen expression is similarly lacking from resting B cells but is induced by EBV.45,53 Therefore, the neoplastic cells comprising these three neoplasms exhibit characteristics comparable to those of EBV-infected B cells in vitro. Furthermore, the EBV genome persists in infected B cells as an episome or by integrating into the cell’s DNA.54 The latently infected growth-transformed cells characteristically express certain EBV genes, including EBNA-1, necessary for EBV episome maintenance,54,55 and EBNA-2, necessary for cell-growth transformation.53 A variable proportion of the malignant cells in each of the three neoplasms described here contained EBNA-1 and EBNA-2 sequences, evidence of the presence of EBV genomes, and displayed a single band of different molecular weight when hybridized to a probe recognizing the EBV termini. These findings strongly suggest that the tumor cells comprising each neoplasm were infected with a single form of EBV and that the monoclonal B-cell proliferation occurred after EBV infection. Taken together, these findings provide strong and compelling evidence that EBV infection played a significant role in the pathogenesis of these three unusual AIDS-associated B-cell NHLs. Obviously, further studies are necessary to prove the extent of the role of EBV in lymphomagenesis in AIDS.

Finally, each one of these three neoplasms represented a morphologic diagnostic dilemma that was largely left unresolved, even following extensive immunophenotypic analysis. A definitive diagnosis was possible in these three cases only after antigen receptor gene rearrangement analysis had been performed. Therefore, the results of our studies further illustrate the utility of antigen receptor gene rearrangement analysis in the diagnosis and classification of hematopoietic neoplasms of uncertain lineage.

ACKNOWLEDGMENT

The authors wish to express their sincere gratitude to Drs Stanley Korsmeyer, Tak Mak, Bernard Poiesz, Michael Cleary, Carlo

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Croce, and Paul Luciw for the DNA probes used in these studies. The authors also wish to thank Drs Eleni Athan, Milayna Subar, and Rosemary Wieczorek for assistance in portions of these studies, Elizabeth Cochrane and Laurie McFall for excellent technical assistance, and Nilda Lopez for assistance in preparation of the manuscript. These studies were partially supported by NIH grants EYO6337 (DMK), CA48236 (DMK), and CA37295 (RDF) and by a grant from the American Cancer Society (DMK). Dr Riccardo Dalla-Favera is a scholar of the Leukemia Society of America and is supported by a senior AIDS fellowship from the Kaplan Cancer Center.

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