Expression of the c-kit Receptor in Human Lymphomas Is Restricted to Hodgkin’s Disease and CD30+ Anaplastic Large Cell Lymphomas

By Antonio Pinto, Annunziata Gloghini, Valter Gattei, Donatella Aldinucci, Vittorina Zagonel, and Antonino Carbone

The product of the proto-oncogene c-kit is a transmembrane receptor protein that plays an important role in the regulation of normal and neoplastic hematopoiesis via the interaction with its specific ligand termed stem cell factor. To examine whether c-kit product is possibly involved in the pathogenesis of human lymphomas, we analyzed the expression of the c-kit protein in neoplastic cells from a variety of lymphoid tumors by immunostaining of lymph node frozen sections with the 17F11 antibody, detecting an extracellular epitope of the c-kit receptor, and of c-kit RNA by Northern blot hybridization. Of 24 nonHodgkin’s lymphomas (NHL) of B- and T-cell phenotype, none expressed immunodetectable c-kit protein that was also not evidenced in lymphoid cells of reactive lymph nodes and normal tonsils. In contrast, c-kit protein was expressed by Reed-Sternberg cells and their mononuclear variants from 11 of 21 Hodgkin’s disease (HD) cases, and in tumor cells from 11 of 16 cases of CD30+ anaplastic large cell lymphoma (ALCL). c-kit specific mRNA was also detected in lymph node tissues from HD and ALCL cases but not in neoplastic tissues from NHL other than ALCL. In addition, c-kit/CD30+ tumor cells were evidenced by flow cytometry in a patient displaying massive bone marrow involvement by ALCL. With the exclusion of lymphocyte predominance cases of HD that resulted c-kit negative, no apparent correlation was found between c-kit expression and the other histologic subtypes of HD or the immunologic phenotype of tumor cells (B, T, nonB-nonT) in both HD and ALCL. The highly restricted expression of the c-kit product among human lymphomas to HD and ALCL provides a further biologic link between these two closely related lymphoma entities.

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Table 1. Cases of Non-Hodgkin’s Lymphoma Other Than ALCLs Selected for Study

<table>
<thead>
<tr>
<th>Working Formulation</th>
<th>No. of Tested Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade</td>
<td></td>
</tr>
<tr>
<td>A. Small lymphocytic</td>
<td>3</td>
</tr>
<tr>
<td>B. Follicular predominantly small cleaved cell</td>
<td>5</td>
</tr>
<tr>
<td>Intermediate grade</td>
<td></td>
</tr>
<tr>
<td>E. Diffuse small cleaved cell</td>
<td>3</td>
</tr>
<tr>
<td>F. Diffuse mixed, small and large cell</td>
<td>1</td>
</tr>
<tr>
<td>G. Diffuse large cell</td>
<td>3</td>
</tr>
<tr>
<td>High grade</td>
<td></td>
</tr>
<tr>
<td>H. Large cell, immunoblastic</td>
<td>4</td>
</tr>
<tr>
<td>J. Small noncleaved</td>
<td>4</td>
</tr>
<tr>
<td>Miscellaneous</td>
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</table>

Neoplastic cells in all lymphoma cases tested were not stained by the monoclonal anti-c-kit receptor antibody 17F11.

MATERIALS AND METHODS

Tissue samples. The study included tissue samples of 21 cases of HD (13 nodular sclerosis, 3 mixed cellularity, 1 lymphocyte depletion, and 4 lymphocyte predominance), 16 cases of “nonsecondary” ALCL, and 24 cases of non-Hodgkin’s lymphoma (NHL) other than ALCL. Tissues from two reactive lymph nodes and two tonsils were also included in the study. One part of the material was fixed in Bouin’s solution for histologic examination. A portion of unfixed tissue was snap frozen in liquid nitrogen directly after surgical removal and stored at -80°C. The cases that formed the basis of the study were retrieved from the files of the Division of Pathology at the Centro di Riferimento Oncologico (Aviano, Italy). Pathologic specimens of NHL were classified according to the Working Formulation (WF) (Table 1). The Rye modification of the Lukes and Butler classification was used to classify HD; the morphologic criteria for identifying ALCL were those described by Agnarsson and Kadin. The differential expression of CD45, epithelial membrane antigen (EMA) and CD15 was also used in the diagnostic assessment. Of the study were retrieved from the files of the Division of Pathology at the Centro di Riferimento Oncologico (Aviano, Italy). Pathologic specimens of NHL were classified according to the Working Formulation (WF) (Table 1). The Rye modification of the Lukes and Butler classification was used to classify HD; the morphologic criteria for identifying ALCL were those described by Agnarsson and Kadin.

Immunohistochemistry. Deparaffinized and cryostat sections were used for immunophenotyping with MoAbs (I2F1, CD3, CD4, CD5, CD9, CD10, CD13, CD15, CD20, CD22, CD24, CD25, CD30, CD43, CD45, CD45R, CD45RO, CD68, CD71, CD74, CDw34, HLA-DR, LN3, MB2, anti-α and λ immunoglobulin (lg) light chains, EMA, antivimentin, anticytokeratin MoAb MNB116, and BNH9). Sources and specificities of the antibodies used in this study have been reported in detail previously. Immunochemistry was performed with the avidin-biotin-peroxidase complex (ABC-px) or alkaline phosphatase antialkaline phosphatase (APAAP) methods as previously described. In addition, for BerH2 (CD30), antivimentin, anti-CD3, and BNH9 MoAbs, the ABC-px method was performed with the ABC Elite kit (Vector Laboratories, Burlingame, CA).

Staining with anti-c-kit antibody. Frozen sections were stained by the APAAP technique with the monoclonal antibody 17F11 (Immunotech, Marseille, France) recognizing an epitope of the extracellular domain of P145 c-kit protein. Negative control experiments were performed by incubating sections with irrelevant isotype-matched mouse lg and by omitting the primary antibody.

Flow cytometry. BM cells from a patient affected by ALCL displaying BM involvement were stained by two colors immunofluorescence as described. The simultaneous expression of c-kit protein and CD30 antigen was studied by incubating cells with 17F11 antibody followed by phycocyaninated rabbit F(ab)2-antimouse lg (Dakopatts, Glostrup, Denmark) and subsequently with fluorescein isothiocyanate-conjugated Ber-H2/CD30 antibody (Dakopatts). BM cells were also stained with HPCA-2/CD34, MY9/CD33, and LeuM1/CD15 antibodies. Viable, antibody-labeled cells were identified according to their forward and right angle scattering, electronically gated and analyzed for surface fluorescence on a FACS Scan flow cytometer (Becton-Dickinson Immunocytometry Systems, San Jose, CA).

RNA preparation, Northern blotting and hybridization. Frozen tumor material was pulverized by a microdisembitter (Microdismembrator II, Braun, Milan, Italy) and total cellular RNA was extracted by the guanidium thiocyanate method. Briefly, frozen tumor samples were extracted with 4 mol/L guanidium thiocyanate containing 0.5% sarcosyl, 25 mmol/L sodium citrate, 0.1 mol/L 2-mercaptoethanol, and phenol-chloroform, and precipitated in isopropanol. RNAs were size fractionated on 1% agarose containing 2.2 mol/L formaldehyde in morpholino propane-sulfonic acid buffer and blotted onto nylon transfer membranes (Boehringer Mannheim, Mannheim, Germany). Equal loading of the lanes and integrity of RNAs was documented by ethidium bromide stained gels. Filters were then hybridized in 50% formamide at 42°C with 2 X 10⁶ cpm/mL of 32P-labeled c-kit specific cDNA probe (1.25-kb Stu I/Stu 1 c-kit fragment in pUC 119) and SCF cDNA probe (0.9-kb HindIII BamHI fragment in pBluescript SK+) kindly provided by L. Pegoraro (University of Turin, Italy). After washings to a final stringency of 0.1 X standard sodium citrate (SSC), 0.1% sodium dodecyl sulfate, filters were exposed to Kodak X-ray film.
Expression of c-kit receptor protein in human lymphomas.

Expression of c-kit receptor was investigated by immunostaining with the 17F11 MoAb of frozen sections from HD (n = 21), ALCL (n = 16) and other NHL (n = 24). Neoplastic cells from all NHL cases other than ALCL, including low, intermediate and high-grade lymphomas according to the WF were negative (Table 1). Lymphoid cells from two reactive lymph nodes and two normal tonsils were also unreactive with the 17F11 MoAb, which conversely stained endothelial cells, and epithelial cells in tonsil tissues (data not shown). In contrast, Reed-Sternberg (RS) cells from 11 cases of HD (Table 2) and tumor cells from 11 cases of ALCL (Table 3), showed a consistent reactivity with the 17F11 antibody. Reactivity with the anti c-kit receptor MoAb 17F11 was overall higher in ALCL (8 of 11 cases showing strong reactivity) than in HD (4 of 11 cases display-

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**Table 3. c-kit Expression and Immunophenotype in Anaplastic Large Cell Lymphoma**

<table>
<thead>
<tr>
<th>No.</th>
<th>Diagnosis</th>
<th>c-kit</th>
<th>CD30</th>
<th>CD15</th>
<th>BH9</th>
<th>EMA</th>
<th>Immunophenotype</th>
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<tr>
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<td>ALCL</td>
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<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Histio</td>
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<tr>
<td>2</td>
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<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>B</td>
</tr>
<tr>
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<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>T/Histio*</td>
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<td>+</td>
<td>-</td>
<td>+</td>
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<td>T</td>
</tr>
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<td>T</td>
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<td>-</td>
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<td>T</td>
</tr>
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<td>-/+</td>
<td>-</td>
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</tr>
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<td>+/−</td>
<td>-</td>
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<tr>
<td>12</td>
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<td>+</td>
<td>+/−</td>
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<td>+</td>
<td>nonB nonT</td>
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<td>+</td>
<td>−</td>
<td>+</td>
<td>nonB nonT</td>
</tr>
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</table>

Immunophenotype was determined based on the expression of B-, T-, or histiocyte-associated antigens on large anaplastic cells.

Abbreviations: ALCL, anaplastic large cell lymphoma; Histio, histiocyte; w, weak reactivity; ND, not done; +, positive (all tumor cells labeled); +/−, most tumor cells labeled; −/+ , scattered tumor cells labeled; −, negative (no tumor cells labeled).

* Neoplastic cells coexpressed T-cell antigens and the histiocyte associated marker CD68 (see ref 34).

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**RESULTS**

Expression of c-kit receptor protein in human lymphomas.

As a positive control for c-kit transcripts, total cellular RNA extracted from the human erythroleukemia cell line HEL was used.13,17,19

**Fig 1.** (A) RS cells from a case of nodular sclerosing Hodgkin’s disease show membrane and cytoplasmic reactivity with the monoclonal anti–c-kit antibody 17F11. (B) Neoplastic cells from a ALCL case are stained by the anti-CD30 antibody Ber-H2. (C) Neoplastic cells from the same anaplastic large cell lymphoma case stained with the monoclonal anti–c-kit antibody 17F11 show strong membrane reactivity. APAAP technique on lymph node frozen sections (original magnification × 400).
Fig 2. The reactivity pattern of RS cells of Hodgkin's disease (A, B) and their mononuclear variants (C) with the anti-\textit{c-kit} antibody 17F11 shows both membrane and cytoplasmic staining (original magnification \( \times 1,000 \) oil). Tumor cells of ALCL (D) show strong membrane reactivity with the monoclonal anti-\textit{c-kit} antibody 17F11 (original magnification \( \times 400 \)). APAAP technique on lymph node frozen sections.

In HD positive cases, most RS cells (>90%) were stained by the 17F11 antibody (Fig 1A). Similarly, in ALCL, the great majority of CD30+ tumor cells (Fig 1B) displayed a strong membrane reactivity with the anti-\textit{c-kit} receptor 17F11 MoAb (Fig 1C). In the case of RS cells, membrane staining was commonly associated with a cytoplasmic labeling (Fig 2 A-C), whereas in ALCL a prominent staining of tumor cell membranes was observed (Fig 2D). Differences in the staining patterns between RS cells and their mononuclear variants were not perceptible (Fig 2 A-C). Cases of each subtype of HD other than lymphocyte predominance, stained positively for CD30 and CD15 being conversely unreactive with anti-EMA and BNH9 antibodies (Table 2). RS cells showed a non B-non T phenotype in all cases with the exception of cases 13, 18, 19, 21, and 15 in which B- or T-cell antigens were respectively detected, and case 1 in which neoplastic cells coexpressed both B and T markers (Table 2). Tumor cells of ALCL reacted with anti-CD30, CD45, and CD74 MoAbs in all cases, whereas immunoreactivity with anti-vimentin, MB2, LN3, and anti-EMA antibodies was noted in more than half of the cases evaluated (Table 3 and data not shown). In five cases of ALCL, a presumptive T-cell phenotype was assigned based on immunoreactivity of tumor cells with anti-CD43, anti-CD45RO, \( \beta F1 \), and/or anti-CD3 MoAbs, whereas in six cases, ALCL cells showed expression of CDw75 and/or CD20 B-cell–associated antigens (Table 3). In two other cases (no. 1 and 3) ALCL cells expressed the CD68 histioyte-associated antigen along with T-cell markers in one case (no. 3) as previously shown by us\textsuperscript{34} (Table 3). RS cells and variants from all the four cases of lymphocyte predominance subtype showed no reactivity with the 17F11 MoAb, whereas \textit{c-kit} expression did not disclose any apparent correlation with the other histologic subtypes of HD (Table 2) or the supposed lineage derivation of tumor cells (T, B, non T-non B) in both HD and ALCL (Table 2 and 3).

Interestingly, in 5 of 11 \textit{c-kit}+ ALCL cases, neoplastic cells coexpressed the H and Y red blood cell–related antigens detected by the BNH9 MoAb.\textsuperscript{35} In contrast, none of the five \textit{c-kit}− ALCL cases reacted with the BNH9 MoAb which has been previously indicated as a useful reagent for the diagnosis of ALCL in the adults.\textsuperscript{30,35}

Dual fluorescence analysis of tumor cells from an ALCL patient displaying a massive BM involvement is shown in Fig 3. More than 50% of neoplastic cells coexpressed \textit{c-kit} receptors along with CD30 determinants. Tumor cells were CD34, CD33, and CD15 negative (data not shown).

Expression of \textit{c-kit} mRNA in human lymphomas. Northern blot analysis of \textit{c-kit} mRNA expression showed the presence of 5.0-kb specific transcripts in a lymph node sample massively involved by ALCL (case 9) and in tissues from one case of HD (case 13) (Fig 4). Neoplastic cells from both cases strongly immunoreacted with the 17F11 MoAb in tissue sections and the intensities of hybridized bands ap
Fig 3. Coexpression of c-kit protein and CD30 antigen on tumor cells obtained from the BM of an ALCL patient. More than 50% of neoplastic cells are double stained by the anti-c-kit antibody 17F11 (y-axis, red fluorescence) and by the anti-CD30 antibody Ber-H2 (x-axis, green fluorescence).

Fig 4. Detection of 5.0-kb c-kit mRNA transcripts by Northern blot analysis (upper panels). Twenty-five micrograms of total RNA extracted from lymph nodes tissues was loaded in each lane: ALCL c-kit+, Anaplastic Large Cell Lymphoma (case 9); HD-NS c-kit+, Hodgkin’s disease, nodular sclerosing (case 13); ALCL c-kit−, Anaplastic Large Cell Lymphoma (case 8); NHL-G (WF), non-Hodgkin’s lymphoma, type G according to the WF; HEL, RNA extracted from the human erythroleukemia cell line HEL was used as a positive control for c-kit transcripts. Tumor cells from cases 9 and 13 expressed c-kit protein as detected by immunostaining of lymph node frozen sections with the 17F11 antibody, the remaining cases were c-kit− on immunostaining (see Tables 1, 2 and 3). Staining of ribosomal RNA in ethidium bromide gels confirms integrity of RNA and shows comparable RNA loading in single lanes (lower panels).
blood group-related antigen H and Y on ALCL cells,\textsuperscript{35} reacts also with erythroid cells, subpopulations of megakaryocytes, endothelial cells, and epithelial cells.\textsuperscript{33} This staining pattern appears somehow reminiscent of the c-kit distribution in human tissues.\textsuperscript{8,12,15,20,22,27} The biologic relationship between BHN9 and c-kit expression by ALCL cells, if any, remains however unclear and deserves further investigations.

The highly restricted expression of the c-kit receptor to HD and ALCL appears intriguing under several aspects. Although typical cases of ALCL are clinically different and can be distinguished from HD on the basis of pathologic\textsuperscript{28} and cytogenetic criteria,\textsuperscript{37,38} both conditions share a number of phenotype and genotypic features\textsuperscript{28,37,39} and the existence of a continuum between these two neoplastic lesions has been suggested.\textsuperscript{37,39} In addition, transformation of either disease into the other has been described based on immunophenotypic data,\textsuperscript{28,37,38} and evidences indicating the evolution of HD into a "secondary" ALCL have been provided.\textsuperscript{37,38,40} The overlapping phenotypic features of HD and ALCL include the expression of the CD30 molecule and of other activation antigens such as CD25, the inconsistent expression of T- or B-lineage antigens often leading to a "null-cell" overall phenotype,\textsuperscript{28-30,37-40} and the highly heterogeneous status of Ig and T-cell receptor genes in both diseases.\textsuperscript{38,41} In addition, the expression of the intermediate filament-associated protein resilin has recently shown to be highly restricted among human lymphomas to HD and ALCL.\textsuperscript{42} Moreover, as opposed to several other cytokines such as IL-1, IL-3, IL-6 and γ-interferon, which are expressed in both HD and NHL including ALCL,\textsuperscript{53} the expression of the recently identified cytokine IL-9 has been shown to be selectively confined to neoplastic cells of HD and ALCL.\textsuperscript{45} The highly restricted expression of the c-kit product as detected in the present study provides now a further biologic link between these two closely related lymphoma entities.

The functional significance of c-kit protein expression in HD and ALCL remains to be defined, and additional studies are required to ascertain whether tumor cell growth is actually stimulated by SCF or by intracellular signals delivered through the c-kit oncogene product. Even though functional c-kit receptors have been detected on human cell lines from nonhematopoietic tumors,\textsuperscript{70} exogenous SCF had only a minimal effect on their growth.\textsuperscript{71} The autocrine production of SCF, binding of endogenous SCF to intracellular c-kit receptors, or structural alterations of the c-kit receptor leading to its constitutive activation have been suggested to explain the lack of proliferative response to exogenous SCF by these cell lines.\textsuperscript{20} The stimulation of tumor cell growth can be induced by specific growth factors produced by neoplastic cells or by surrounding tissue cells in an autocrine or paracrine fashion. The typical histology of HD in which RS cells are surrounded by a large number of reactive cells and the association of neoplastic cells in ALCL with activated histiocytes and plasma cells in different anatomic sites, suggests a functional relationship between tumor cells and the neighboring tissue components. In particular, fibrosis with a high number of fibroblasts is a common finding characterizing the microenvironmental picture of both diseases\textsuperscript{37,38,43,44} and in addition a distinctive morphologic feature of ALCL, ie, the sinus infiltration.\textsuperscript{28,37,40} May suggest a strict relationship of tumor cells with the accessory cells of the sinus microenvironment, including endothelial cells and possibly fibroblasts.\textsuperscript{40} Indeed, we have previously shown that a great number of fibroblast-like cells and interdigitating reticulum cells are immunodetectable within the collagen bands of nodular sclerosing HD, being often closely associated to RS cells,\textsuperscript{46,47} and in the lymphoid microenvironment surrounding tumor cells in ALCL with fibrosis (Carbone et al., unpublished observation, January 1993). Given the demonstration that stromal cells such as fibroblasts,\textsuperscript{54,48} and endothelial cells\textsuperscript{49} express SCF mRNA and can produce SCF in both soluble and membrane-bound forms,\textsuperscript{6,8} it could be speculated that SCF may act in a paracrine fashion to regulate growth of c-kit-expressing neoplastic cells in HD and ALCL. We were unable to detect SCF transcripts by Northern blot in lymph node tissues from one case of HD and one case of ALCL analyzed, and which conversely expressed c-kit protein and c-kit transcripts. These data however cannot rule out an autocrine hypothesis for SCF/c-kit interaction in HD and ALCL. Small amounts of highly effective cytokines such as IL-6, IL-4, IL-5\textsuperscript{43} and SCF transcripts\textsuperscript{50} have been detected by in situ hybridization\textsuperscript{50} or reverse-transcriptase polymerase chain reaction (RT-PCR) technique\textsuperscript{50} in neoplastic tissues when Northern blot analysis gave negative results.\textsuperscript{39,50} The application of RT-PCR techniques and/or of in situ hybridization appears therefore warranted to exclude beyond any doubt the expression of SCF mRNA by tumor cells in HD and ALCL, even though the possible amplification of fibroblast-derived SCF RNA has to be taken into account. Finally, the possibility of a structural alteration of c-kit receptors, leading to aberrant signal transduction in HD and ALCL tumor cells needs to be explored.

The recently identified cytokine IL-9, is selectively expressed by tumor cells of HD and ALCL\textsuperscript{45,52} and appears to be involved in the autocrine growth of the HD-derived cell line HDLM-2, whose in vitro proliferation is significantly inhibited by anti-IL-9 MoAbs or IL-9 antisense oligodeoxynucleotides.\textsuperscript{52} Similarly, IL-6 is preferentially expressed in HD\textsuperscript{53} and ALCL,\textsuperscript{43,44} and the coexpression of IL-6 and its receptors has been detected in RS cells.\textsuperscript{53} The overlapping and highly restricted expression of c-kit receptors and IL-9 to neoplastic cells of HD and ALCL, and the preferential expression of IL-6 by neoplastic cells of both diseases, suggests that c-kit bound SCF may cooperate with IL-9 and/or IL-6 in promoting tumor growth. Such hypothesis appears reinforced by recent reports showing that SCF synergizes with IL-9\textsuperscript{54} and IL-6\textsuperscript{4,12,35,56} in promoting cell proliferation of various murine and human hematopoietic cell types. Whether c-kit protein and/or SCF are actually involved in the control of tumor cell proliferation in HD and ALCL by paracrine or autocrine mechanisms remains to be ascertained by further studies. Our results and the capacity of SCF to synergize with IL-9 and IL-6 hint in this direction.

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