Analysis of T-Cell Differentiation Antigens in Acute Lymphatic Leukemia Using Monoclonal Antibodies

By Benjamin Koziner, David Gebhard, Thomas Denny, Susan McKenzie, Bayard D. Clarkson, Denis A. Miller, and Robert L. Evans

Leukemic cells in 134 patients with ALL were analyzed by a panel of mouse monoclonal antibodies. Two antibodies are reactive with all peripheral blood T cells but define different surface antigens (Leu-1 and Leu-4). Two other antibodies react with antigens that are restricted to suppressor/cytotoxic T cells (Leu-2) and to helper T cells (Leu-3). We also used antibodies to the receptor for sheep red blood cells (SRBC) (Leu-5) and to a human "TL-like" antigen that is found on most thymocytes but not in peripheral T cells (Leu-6). An antibody to the human p29,34 "Ia-like" molecule was also tested. Of the 134 ALL patients, 17 had a predominance of SRBC-rosetting (Leu-5+) lymphoblasts ("T" ALL), expressing different surface phenotypes defined by this panel of monoclonal antibodies.

DISSECTION OF THE phenotypic heterogeneity of ALL has resulted in the recognition of clinically significant prognostic categories of this disease and has been recently proposed to reflect normal maturational sequences in the thymic lineage in those cases expressing T-cell surface markers.

However, the predominant number of ALL patients have leukemic cells that lack the conventional markers, surface immunoglobulin and receptor for sheep red blood cells (SRBC), and therefore cannot be assigned to the T- or B-cell lineages. These "null" lymphoblasts have high levels of terminal deoxynucleotidyld transferase (TdT) and usually are reactive with antibodies to human "Ia-like" antigens. Moreover, the expression of TdT and Ia is frequently associated with the recognition of a surface antigen (CALLA) that is generally restricted to this ALL subtype. This antigen may also be found on a subpopulation of TdT+ lymphoblasts in normal bone marrow (BM), suggesting that it defines a stage of early lymphocyte differentiation. TdT+ "null" ALL cells have been conventionally distinguished from TdT+ T lymphoblasts by their failure to form SRBC rosettes.

These phenotypes were not readily classifiable according to a scheme of sequential stages of normal differentiation proposed. Moreover, the lymphoblasts in 8 of 113 patients not expressing conventional B- or T-cell markers ("null" ALL) reacted with the monoclonal anti-T-cell antibodies. This study suggests that the classification of lymphoblasts in ALL based on the reactivities observed with this panel of mouse monoclonal antibodies is not easily reconciled with current models of normal T-cell differentiation. However, it should be emphasized that the precise sequence of antigenic expression by cells undergoing thymic differentiation is still not fully known, and further phenotypic analysis of ALL cells might contribute to an improved understanding of this malignancy.

These studies were undertaken to determine the value of applying additional T-cell surface markers in the analysis of ALL lymphoblasts for the phenotypic classification of this disease. These markers are derived from studies in which human leukocyte antigens, which are preferentially expressed on thymocytes or T cells, were defined and characterized by mouse monoclonal antibodies.

The panel of monoclonal antibodies used included (1) anti-Leu-1: reacts with a 67,000–70,000 dalton antigen, which is distributed on all thymocytes, all peripheral blood (PB) T cells, and 80%–90% of SRBC-rosetting cells; (2) anti-Leu-2: reacts with 25%–45% of SRBC-rosetting cells in the PB of normal individuals, and 55%–85% of thymocytes; (3) anti-Leu-3: reacts with 45%–75% of PB SRBC-rosetting cells, 80%–90% of thymocytes, and has not been found to react with leukocytes outside the thymic lineage. Whereas the majority of thymocytes are Leu-2+3+, each of these antigens belongs to one of the two non-overlapping T-cell subsets that together comprise the population of Leu-1+ cells. As initially demonstrated with the original anti-TH2 serum, it has been shown using monoclonal antibodies of another series that Leu-2+3− (TH2+) cells have suppressor/cytotoxic functions and Leu-2−3+ (TH1−) cells have helper functions in a variety of assays in vitro; (4) anti-Leu-4: recognizes a 25,000-dalton molecule distributed to all PB SRBC-rosetting cells and about 30%–60% of thymocytes. It has not been found on leukocytes outside the thymic lineage; (5) anti-Leu-5: blocks SRBC rosette formation by T cells and non-T-cells and defines a 55,000-dalton antigen that has the same distribution as the SRBC receptor on lymphocytes; (6) anti-Leu-6: reacts with about 70% of thymocytes and is not found on PB.
SRBC-rosetting cells or other subpopulations of leukocytes. Anti-Leu-6 exhibits competitive binding with the NA-1 antibody of McMichael et al., which precipitates two molecules of 44,000 and 12,000 daltons;\(^7\) (7) anti-Ia: recognizes a 29,000- and 34,000-dalton "Ia-like" antigen on human mononuclear cells.

**MATERIALS AND METHODS**

**Clinical Material**

Fresh cell suspensions of BM and/or PB lymphoblasts in 134 consecutive patients with ALL seen by the pediatric (83 cases) and adult (51 cases) Hematology Services at Memorial Hospital from January 1980 to December 1981 were subjected to surface marker analysis. All patients had active leukemia at the time of the study. Although a majority of patients had leukemic cell counts above 10,000 cells/cu mm, some had lower counts but with a predominance of leukemic elements confirmed by examination of cytocentrifuge smears of the cell suspensions analyzed. The FAB (French-American-British) scheme was used for the morphological classification of lymphoblasts.\(^6\)

**Marker Studies**

Lymphocyte preparation and immunofluorescent staining was performed as previously reported.\(^7\) A polyvalent rabbit antiserum to human immunoglobulin and fluorescein-conjugated F(ab')\(_2\) fragments of specific antisera to heavy chains were purchased from Cappel Lab., Cochranville, Pa.) on a cytofluorograph System 30L (Ortho Instruments, Westwood, Mass.) or a fluorescence activated cell sorter (FACS IV) (Becton Dickinson, Sunnyvale, Calif.). A quantity of 1 x 10\(^5\) cells were incubated at 4°C for 1 hr with 100 \(\mu\)l of a 1:300 dilution of the respective monoclonal antibodies prepared as ascitic fluid. The cells were washed 3 times and then mixed with 50 \(\mu\)l of fluorescein-conjugated goat anti-mouse antibody at 1:20 dilution, incubated for 30 min, washed 3 times, and analyzed on the cytofluorograph or cell sorter. Background fluorescence was obtained by labeling cells with ascitic fluid containing an IgG\(_{1}\) protein, which does not react with human leukocyte antigens, or fluorescein-conjugated goat anti-mouse antibody alone. For a leukemic population to be considered reactive with the different Leu antibodies, more than 25% of the neoplastic cells had to display positive staining. In those cases in which between 10% and 25% of the leukemic cells exhibited reactivity, a +/- qualification was used. When less than 10% of the leukemic cells stained with any of the different Leu antibodies, that population was considered non-reactive.

**RESULTS**

The phenotypic categorization of the 134 patients tested with the Leu panel of mouse anti-human T-cell antibodies will be expressed in terms of the conventional surface markers, surface immunoglobulin, and SRBC rosetting. The lymphoblasts in 113 of the 134 patients lacked both of these surface markers and are therefore termed "null" ALL cells by this criteria. Of these 113 patients, 105 also lacked those cell surface markers defined by Leu antibodies 1 through 6. However, 8 of the 113 (3 untreated and 5 in relapse) had detectable amounts of one of these markers. Thus, as shown in Table 1, 4 patients with "null" ALL had the Leu-1+, 2- or +/−, 3- or +/−, 4- or +/−, 5−, 6−, Ia− phenotype (patients 1-4) and 4 were Leu-1−, 2−, 3− or +/−, 4− or +/−, 5− 6+, Ia+ (patients 5-8). When compared with the former, this latter phenotype characterized a younger group of patients (median age 8.5 versus 15.5 yr) with lower white counts (mean 19.8 versus 94.5 x 10\(^3\) cells/cu mm) (Table 2).

Seventeen of the 134 patients (14 untreated and 3 in relapse) had leukemic cells that rosetted with SRBC and are therefore provisionally classified as "T" ALL. Leukemic cells from these patients exhibited a striking heterogeneity in their quantitative and qualitative reactivity with Leu-1 through 6. As shown in Table 1, different phenotypic patterns resulted from the analyses of only 17 patients. Patient 9, who presented with a low leukemic count, L1 morphology, and no mediastinal mass, had leukemic cells only showing reactivity with anti-Ia and anti-Leu-5. The leukemic cells in patients 10 and 11 were reactive with anti-Leu-5 and anti-Leu-3 alone or combined with anti-Leu-2, but unreactive with other markers of thymocytes or mature T cells. Both were pediatric cases presenting with L1 morphology and mediastinal masses. The lymphoblasts in patients 12–17 displayed reactivities suggestive of a thymocyte stage. However, in patients 12 and 13, although the cells expressed Leu-1 and Leu-6, they were reactive with Leu-2 but not with Leu-3. Moreover, the cells in patients 14–17 were not reactive with Leu-6 and did not coexpress Leu-2 and Leu-3 consistently. Although the lymphoblasts in patients 18–25 could be assigned to a mature T-cell stage because of Leu-4 antigen expression, a heterogeneity of phenotypic reactivities was detected not fully consistent with this developmental stage. For instance: (A) Leu-4 was coexpressed with Leu-6 in patients 22 and 23; (B) there was a lack of reactivity with anti-Leu-1, anti-Leu-2, and anti-Leu-3 in case 18 and only with the latter two antibodies in patients 19 and 24; (C) there was coexpression of Leu-2 and Leu-3 with Leu-4 and absence of Leu-6 in patients 20–22 and 24.

In only 10 of 17 patients with "T" ALL, the lymphoblasts formed SRBC rosettes that were heat stable at 37°C. Moreover, the leukemic cells in 13 of 16
patients studied formed a considerable proportion of EAC rosettes. Neither SRBC rosette at 37°C or EAC rosette formations correlated with any particular phenotypic expression as defined by the Leu monoclonal antibodies. Clinically, 16/17 of the “I” ALL patients studied had a predominance of Ia lymphoblasts, markedly different from the incidence of this FAB type (4/8) observed in the group of “null” ALL showing Leu reactivity. Moreover, while only 1 of the 8 patients in the “null” Leu-reactive group presented with a mediastinal mass, this feature was observed in 13/17 patients of the “T” ALL group. Interestingly, the 2 patients presenting with the lowest leukemic counts and absence of mediastinal mass had as main phenotypic features of the neoplastic cells expression of Ia with lack of anti-Leu-1 reactivity.

DISCUSSION

Using a panel of mouse monoclonal antibodies to human T-cell differentiation antigens, we have studied the lymphoblasts of 134 ALL cases by indirect immunofluorescence analysis on a FACS or a cytofluorograph. It was the aim of these studies to relate the surface phenotypes of malignant T cells to a scheme of normal T-cell differentiation, and thereby to make inferences regarding the maturational stages and/or developmental pathways from which the malignant cells arose.

To interpret these data, the known distribution of Leu-1 through 6 on normal hematopoietic cells should first be summarized. Leu-1 is expressed by 100% of T cells and 95% thymocytes. Leu-2 and Leu-3 are each expressed by distinct, nonoverlapping subpopulations of T cells, but are both found on the majority of thymocytes.9,10 Leu-4 is found on 100% of T cells and approximately 30%-60% of thymocytes.11 Leu-5 is expressed by all T cells, 90% of thymocytes, and is also found on a small subpopulation of mononuclear cells that lack other T-cell surface markers.14 Leu-6 is expressed by the majority of thymocytes and is not found on T cells.15

Studies in which other monoclonal antibodies to T-cell antigens have been used to analyze cell suspensions in “T” ALL have shown a marked heterogeneity of T-cell antigen expression. Reinherz et al. reported
Table 2. Clinical Characterization of 25 ALL Cases Showing Reactivity With the Leu Monoclonal Antibodies

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/Sex</th>
<th>WBC 10^7 Cells/cu mm</th>
<th>PB Blasts Plus Lymphs (%)</th>
<th>BM Blasts Plus Lymphs (%)</th>
<th>FAB Class</th>
<th>Medastinal Mass</th>
<th>Time of Study</th>
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<td>92</td>
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<td>Relapse</td>
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<td>Untreated</td>
</tr>
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<td>Relapse</td>
</tr>
<tr>
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<td>12M</td>
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<td>100</td>
<td>96</td>
<td>L1</td>
<td>No</td>
<td>Untreated</td>
</tr>
<tr>
<td>5</td>
<td>8M</td>
<td>2.0</td>
<td>25</td>
<td>92</td>
<td>L1</td>
<td>No</td>
<td>Relapse</td>
</tr>
<tr>
<td>6</td>
<td>9F</td>
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<td>96</td>
<td>90</td>
<td>L1</td>
<td>No</td>
<td>Relapse</td>
</tr>
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<td>Relapse</td>
</tr>
<tr>
<td>8</td>
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<td>Relapse</td>
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<td>L1</td>
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<td>Untreated</td>
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</table>

SRBC-R, sheep erythrocyte rosette; SmIg, surface membrane immunoglobulin; NA, not available; FAB class, French-American-British classification.

on 25 cases of “T” ALL. Fifteen appeared to pertain to an early thymocyte stage by expression of OKT10 and/or OKT9. Five of the 25 cases were reactive with OKT6, equivalent to our Leu-6 reagent, suggesting that these cells arose from a thymic stage of development. In this group of patients there was variable expression of OKT4, OKT5, and OKT8, which correspond to the helper and suppressor/cytotoxic subsets, respectively. There was only one case with a mature thymocyte phenotype expressing OKT3 reactivity. Using the same panel of reagents, Bernard et al. have described a significant degree of phenotypic heterogeneity in the neoplastic T cells from 21 patients with lymphoblastic lymphoma. Moreover, one-third of these patients had malignant cells that were not readily classifiable according to their proposed scheme of intrathymic differentiation. This report by Bernard et al. and recent work by Greaves tend to suggest that while “T” ALL mostly reflects an early thymic phenotype, T-lymphoblastic lymphoma displays predominantly the phenotype of cortical thymocytes. Haynes et al. found at least five general patterns of phenotypic expression that could relate to hypothetical stages of thymic differentiation using an array of antibodies of similar reactivity to the Leu reagents, further stressing the marked heterogeneity of phenotypic expression in “T” ALL.

This information and evidence derived from other systems suggests that there are three major stages of thymic differentiation that are associated with the following phenotypes: Leu-1+, 2−, 3−, 4−, 5+, 6− (early thymic); Leu-1+, 2−, 3−, 4−, 5+, 6+ (thymic); Leu-1+, 2−, 3−, 4−, 5+, 6− (late thymic and T cell). This agrees with a model proposed by Reinherz et al. except for the expression of Leu-1 (elsewhere termed OKT1), which was suggested to be expressed only in late thymic differentiation and on T cells. One might therefore predict the following Leu phenotypes on malignant cells: Leu-1−, 2−, 3−, 4−, 5+, 6− (non-T-cells); Leu-1+, 2−, 3−, 4−, 5−, 6− (non-T-cells); Leu-1+, 2−, 3−, 4−, 5+, 6− (early thymocytes); Leu-1+, 2+, 3+, 4−, 5+, 6+ (thymocytes); Leu-1+, 2−, 3+, 4+, 5+, 6− (helper T cells); Leu-1+, 2+, 3−, 4+, 5+, 6− (suppressor T cells).

It should be emphasized that the precise sequences of appearance and disappearance of Leu-2, Leu-3, and Leu-6 on cells as they mature in the thymus are
unknown, as is their relationship to the induction of
Leu-4 on cells late in thymic differentiation. These
considerations become significant if it is assumed that
malignant transformation sometimes (?) or often)
occur during transition of cells from one stage of
differentiation to another. It is interesting, therefore,
that the two markers that may appear in prethymic or
in early thymic differentiation were generally present
on cells that expressed markers associated with later
stages of T-cell development. Thus, Leu-5 was
expressed by lymphoblasts in 16/17 cases that
expressed either Leu-2, 3, 4, or 6, and Leu-1 was
expressed on the lymphoblasts of 12/17 of these cases.
Moreover, it is questionable that the cases having cells
of Leu-1−, 2−, 3−, 4−, 5−, 6+ phenotype were
derived from the thymus, as the putative murine
counterpart to this antigen, TL−, may be found on
leukemic cells derived from normal cells which are
TL+. 23

The dissociation of Leu-2, 3, 4, and 6 from the
phenotypes anticipated by the proposed sequences of
T-cell development suggest, therefore, that these
schemes are oversimplified, and/or that the oncogenic
events take place during transition from one stage to
the other when the phenotypic expression of these
markers is being determined. This is further compli-
cated by consideration of evidence suggesting that
Leu-2 and Leu-3 are antigen receptors of their respec-
tive subsets, 10, 24 which raises the possibility that at least
a segment of both of these molecules undergoes
somatic mutation in the thymus, and therefore is not
determined until relatively late in thymic differentia-
tion. Thus, the requirements for the generation of
diversity in immunoglobulin V-gene-encoded T-cell
receptors, proposed initially by Jerne, 25 may be rele-
vant to the apparent variability in the expression of
these markers on T leukemia blasts. Interpretation of
our results requires, therefore, much more information
regarding the cell–cell signals that control thymic
differentiation.

As previously described in another group of patients
with T-ALL, not all of the ALL cases with a predomi-
nance of SRBC-rosetting lymphoblasts at 4°C pre-
served this capacity at 37°C. 2 This temperature-depen-
dent stability has been reported to be considered
characteristic of T lymphoblasts and thymocytes, since
it is not present in any other normal or neoplastic T-cell
population. 26 In this study, no relationship could be
established between the heat stability of SRBC rosette
formation on lymphoblasts and the different “T” ALL
phenotypes identified by the Leu-T-cell monoclonal
antibodies.

The finding that Leu-1 was the only antigen
expressed on the cells of 2 cases (patients 1 and 2) that
otherwise lacked other T-cell markers is interesting.
Leu-1 is unique among human T-lymphocyte antigens
thus far detected by monoclonal antibodies because it
is expressed by surface immunoglobulin-bearing leu-
keemic cells from most patients with chronic lympho-
cytic leukemia, but it has not been found in normal B
cells. 4 These findings may be relevant to the phenotype
observed in these three cases of “null” ALL, as both
malignant cell types could cells may represent the
clonal expansion of neoplastic cells at an early stage of
lymphocyte differentiation. Alternatively, expression
of Leu-1 on ALL cells could be induced by leukemic
transformation, which was raised as a possible expla-
nation for the expression of this antigen by surface
immunoglobulin-bearing CLL cells but not by normal
B cells 4 in the “null” ALL category also, the lympho-
blasts in patients 5–7 had the Leu-1−, 2−, 3−, 4−,
5−, 6+, Ia+ phenotype, arguative of an early
thymocyte stage.

This study suggests that the classification of lym-
phoblasts in ALL based on the reactivities observed
with the panel of Leu mouse monoclonal antibodies is
not easily reconciled with current models of normal
cell differentiation. However, it should be empha-
sized that the precise sequence of antigenic expression
by cells undergoing thymic differentiation is still not
fully known and further phenotypic analysis of ALL
cells might contribute to its improved understanding.

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ANALYSIS OF MONOCLONAL ANTIBODIES IN ALL


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