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Marker Profiles of Human Leukemia and Lymphoma Cell Lines*

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Summary. By means of the multiple marker analysis, a total of 55 human leukemia-lymphoma cell lines which included 15 T-cell, 30 B-cell, four myelomonocytic-cell, and six non-T, non-B cell lines was characterized for their marker profiles. The multiple markers used included a number of cell surface markers as detected by either rosette or immunofluorescence tests, enzyme assays, cytogenetic analysis, and certain functional assay. Based on the criteria previously defined it was found that all the cell lines were proved to represent original leukemia-lymphoma of ALL, AML, CLL, CML, in blastic phase or variety of lymphomas. The monoclonality, a "frozen" state at a specific stage of differentiation-maturation, and cytogenetic marker in each leukemia-lymphoma cell line were remarkable common properties and were stable for years of cultivation. Similar, if not identical, general characteristics were observed in the study on 344 cases of uncultured fresh leukemia-lymphomas by the multiple marker analysis. While no single marker specific to any type of tumor was found, the study offers not only a basis for better understanding of the biology of leukemia-lymphoma but also an insight into normal hematopoietic cell differentiation in man.

Key words: Leukemia-lymphoma – Cell line – Surface marker – Hematopoietic differentiation

Introduction

Since a permanent cell line from an African Burkitt lymphoma was established 15 years ago for the first time (Pulfertaft 1964), numerous numbers of human hematopoietic cell lines from a variety of sources have been established and Characterized (Moore 1972; Nilsson and Pontern 1975; Minowada 1978). Nevertheless, most of these cell lines are so-called "normal" B-lymphoblastoid cell lines which are char-

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acterized by the presence of immunoglobulin synthesis, Epstein-Barr virus (EBV) infection, and normal cytogenetic constitution. From time to time, true leukemia-lymphoma-derived cell lines were, however, established with great difficulties (Moore and Kitamura 1968; Minowada et al. 1972). Among many contribution.; resulting from the studies of such proven leukemia-lymphoma cell lines, recognition of various immunologic subtypes of leukemias and lymphomas is of special significance. It permits not only accurate diagnosis but also leads to a better treatment of these hematopoietic malignancies. In particular, such immunologic identification of tumor cells involved in lymphomas would resolve many of the problems encountered in the existing classification of lymphoma.

The present study describes marker profiles of a total of 55 human leukemia-lymphoma cell lines which include 29 lines of lymphoma origin. Despite continuous effort at searching an antigen specific to leukemia or lymphoma, all markers thus far studied turned out to be of normal gene products. Hence, an attempt was made to correlate the observed heterogeneity in the marker profiles of leukemia-lymphoma cells with a conceptional and hypothetical schcnie of normal hematopoietic cell differentiation (Minowada et al. 1977).

Materials and Methods

A total of 55 proven leukemia-lymphoma cell lines was used in the present study. Origin, establishment and general characteristics of these cell lines were reported individually or in summary in a series of reports (Minowada et al. 1972, 1977; Minowadii 1978: Lok et al. 1979). Many of the cell lines were generously provided to our laboratory by a number of colleagues who established and characterized them. All ccll lines wcrc maintained in RPMI medium 1640 supplemented with 5 10% (v/v) of heat-inactivated fetal calf serum. The cells in culture for various analyses were kept in an exponential growth phase and cell viability was generally nvcr 90% at the time of study. Mycoplasma and other microbial infections in the cell lines were monitored and all ccll lines were negative for the infection. In addition, several dozens of so-called normal R-lymphohlastoid cell lines were also studied For comparison.

Over 300 cases of various types of leukemias were also studied by the multiple marker analysis. Leukemia specimens were either bone marrow aapirates or peripheral blood and mononuclear cells from them were isolated For examination by standard Ficoll-Hypaque density gradient centrifugation. The mononuclear cells were washed three times with phosphate-buffered saline and wcrc used For analysis.

A multiple marker analysis used in the present study included a number of cell surface markers, terminal deoxynucleotidyl transferase, and cytogenetic analysis. The surface markers were dctcctcd by two major methods. One was the rosette assay, which included rosette formation with sheep erythrocytes (E). with bovine erythrocytes-IgG antibody complex (EA) and with hovinc erythrocyte-IgM antibody-complement complex (EAC), respectively. Only E rosette was found to be a specific and definitive marker for T cells. Both EA and EAC were not specific to any single lineage within the hematopoietic cell types, and they were, therefore. considered as non-definitive markers. Another major method was immunofluorescence using various specific antibody preparations. Cell surface immunoglobulins (Smlg) or cytoplasmic immunoglobulins (Cylg) was detected by direct immunofluorescence using fluorescein-conjugated goat anti-human immunoglobulin chain-specific antibody. The presence of immunoglobulins (Smlg or/and Cylg) was a definitive and specific marker of the B cells. A T-cell-specific antigen (T-Ag) (Tsubota et al. 1977) was detected by indirect membrane immunofluorescence using specific rabbit anti-T-cell antibody as a primary reagent followed by fluorescein-conjugated goat anti-rabbit globulins as the secondary reagent. A myelomonocyte-specific antigen (MAg-1) (Sagawa et al. 1979) was detected similarly by indirect membrane immunofluorescence. Both T-Ag and MAg-1 were regarded each as a definitive marker to respective lineage (T-cell and myelomonocyte, respectively) in the hematopoietic ccll differentiation. Both antigen specific to an la-like gp 28.30 molecules *(In)* (Schlossman et al. 1976) and antigen associated primarily with common form of acute lymphoblastic leukemia (cALL) (Greaves et al. 1975) were detected by indirect membrane immunofluoresence with respective

antisera. These two antigens were. nevertheless. of non-definitive marker category, since their expression was found beyond a single lineage in the hematopoietic differentiation. Details of production and characteristics of each rabbit-specific antibody were reported previously (Tsubota et al. 1977: Koyama et al. 1977; Koshiba el al. 1978; Sagawa et al. 1979). Results of terminal deoxynucleotidyl transferase, EBV infection, and cytogenetic analyses were cited from previous reports (Minowada et al. 1977. 1978, 1980).

Results

Using the definitive and non-definitive markers as described in Materials and Methods, a total of 55 leukemia-lymphoma cell lines representing original tumors was subgrouped into four groups (Table I).

Group I

T-cell leukemia-lymphoma line has a common definitive marker, i.e., T-Ag. There were 15 such T-cell lines (nos. 1-15) in which E receptor, in spite of being another definitive marker for T cells, was undetectable in five cell lines. In connection to hypothetical scheme for normal hematopoietic cell differentiation which had been previously proposed (Minowada et al 1978, 1980), the 15 T-cell leukemia-lymphoma lines could be assigned to a respective compartment (Table I, Fig. I). Other markers, such as cALL, Ia, TdT, and EAC were apparently non-specific to the T-cell lineage, though they were used to divide the entire T-cell differentiation stage into three compartments. As shown in Fig. I, *T-Blast I* (nos. 1-6) should have cALL antigen and TdT, but *T-Blast* It (nos. 7–12) has only TdT. Neither cALL antigen nor TdT are expressed in the *T-Cell* compartment (no. 14).

Except for MOLT-IO which was an unusual lymphoma-derived cell line, the absence of Ia-like antigen was found to be a common feature of all T-cell lines.

Table 1. Fifty-five human leukemia-lymphoma cell lines: A total of 55 proven human leukemia-lymphoma cell lines was subcategorized into four categories based on the presence of definitive T-lymphoid, B-lymphoid. or myeloid marker. or absence of these three markers. According to the respective marker profile. each cell line was further classified for its position of differentiation stage relative to a hypothetical scheme of hematopoietic cell differentiation (Minowada et al 1980)

No	Cell line	Origin	Markers detected		Compartment at differentiation stage
			Definitive	Non-Definitive	
I	T-cell leukemia-lymphoma lines				
1	CCRF-C'EM	ALL	T-Ag	cALL, TdT	T-Blast I
2	RPMI 8402	ALL	T-Ag	cAll, TdT, EAC	T-Blast I
3	HPB-ALL	ALL	T-Ag	cALL, TdT, EAC, E	T-Blast I
4	DND-41	ALL	T-Ag	cALL. TdT, EAC. E	T-Blast I
5	HPB-MLT	ATL	T-Ag	cALL, TdT, EAC, E	T-Blast I
6	HD-Mar 2	HD?	T-Ag	cALL, TdT, EAC. E	T-Blast I
7	MOLT 1-4	ALL	T-Ag	TdT, EAC. E	T-Blast II
8	JM	ALL	T-Ag	TdT, EAC, E	T-Blast II
9	MOLT-I I	ALL	T-Ag	TdT, EAC, E	T-Blast II
10	TALL-I	ALL	T-Ag	TdT, E	T-Blast II
11	P12/Ich.	ALL	T-Ag	EAC. E	T-Blast II

Table 1. (continued)

No.	Cell line	Origin	Markers detected		Compartment at differentiation stage
			Definitive	Non-Definitive	
12	CCRF-HSB-2	ALL	T-Ag		T-Blast II
13	Peer	ALL	T-Ag		T-Blast II
14	SKW-3	CLL	T-Ag	E	T-Cell
15	MOLT-10	ALL	T-Ag	TdT, cALL, Ia	T-Blast I(?)
II. B-cell leukemia-lymphoma lines					
16	NALM-1	CML-BP	Cylg	Ia, cALL, TdT, Ph'	Pre-B-Blast
17	NALM 6 15	ALL	Cylg	Ia, cALL, TdT	Pre-B-Blast
18	NALM 17, 18	ALL	Cylg	Ia, cALL, TdT	Pre-B-Blast
19	LAZ-221	ALL	Cylg	Ia, cALL, TdT	Pre-B-Blast
20	HPB-Null	ALL	Cylg	Ia, cALL	Pre-B-Blast
21	KOPN 1 8	ALL	Cylg	Ia, cALL,	Pre-B-Blast
22	U-698-M	LS	SmIg	Ia, cALL	B-Blast I
23	Raji	BL	SmIg	Ia, cALL, EAC, EBV	B-Blast I
24	B35M	BL	SmIg	Ia, cALL, EAC, EBV	B-Blast I
25	HR1K	BL	SmIg	Ia, cALL, EA, EBV	B-Blast I
26	Daudi	BL	SmIg	Ia, cALL, EA, EBV	B-Blast I
27	B46M	BL	SmIg	Ia, cALL, EA, EBV	B-Blast I
28	EB-3	BL	SmIg	Ia, cALL, EBV	B-Blast I
29	Namalva	BL	SmIg	Ia, cALL, EBV	B-Blast I
30	BJAB	BL	SmIg	Ia, cALL, EAC	B-Blast I
31	DND-39	BL	SmIg	Ia, cALL, EAC	B-Blast I
32	DG-75	BL	SmIg	Ia, cALL	B-Blast I
33	Ramos	BL	SmIg	Ia, cALL	B-Blast I
34	Chevallier	BL	SmIg	Ia, cALL	B-Blast I
35	SU-DHL-4	LY	SmIg	Ia, cALL	B-Blast I
36	BALL-1	ALL	SmIg	Ia, EA	B-Blast II
37	BALM 1, 2	ALL	SmIg	Ia, EAC, EBV	B-Blast II
38	BALM 3 5	LB	SmIg	Ia, EA	B-Blast II
39	Ogun	BL	SmIg	Ia, EAC, EBV	B-Blast II
40	AL-1	BL	SmIg	Ia, EAC, EBV	B-Blast II
41	SL-1	BL	SmIg	Ia, EAC, EBV	B-Blast II
42	NK-9	BL	SmIg	Ia, EAC, EBV	B-Blast II
43	RPMI 8226	MM	SmIg	Ia	Plasma C.
44	U-266	MM	SmIg	Ia	Plasma C.
45	ARH-77	MM	SmIg	Ia, EAC	Plasma C.
III. Myelomonocytic leukemia-lymphoma lines					
46	HL-60	APL	MAg-I	EA, EAC	Promycl.
47	ML 1 3	AML	MAg-I	EA	Myclobl.
48	KG-1	AML	MAg-I	EA, Ia	Pre.-My. Bl.
49	U-937	LY	MAg-I	EA	Monoblast
IV. Non-T, non-B leukemia-lymphoma lines					
50	K-562	CML-BP		EA	Pre-Ery. Bl.
51	Reh	ALL		Ia, cALL, TdT	Pre-Ly. Bl.
52	KM-3	ALL		Ia, cALL, TdT	Pre-Ly. Bl.
53	NALL-1	ALL		Ia, cALL, TdT	Pre-Ly. Bl.
54	NALM-16	ALL		Ia, cALL, TdT	Pre-Ly. Bl.
55	SU-DHL 1	Ly			Pre-Mo. Bl.

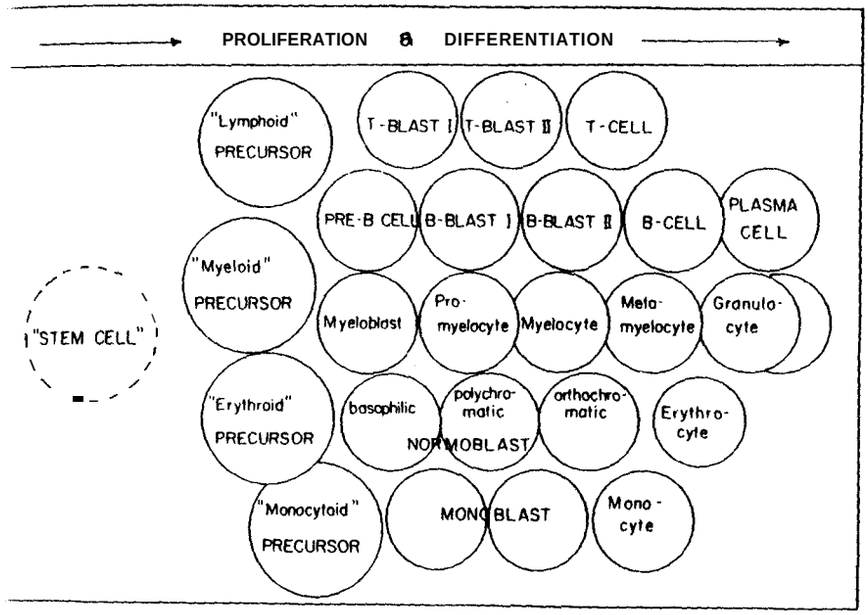

Fig. 1. This Scheme of human hematopoietic cell differentiation does not include the megakaryocyte lineage Each compartment has a particular marker combination beside each definitive marker, such as T-Ag for T-cell lineage. Ig for B-cell lineage or MAg-1 for myeloidmonocytoid lineage

MOLT-10 was an exceptional T-cell line with T-Ag in which a fraction (10–30%) of population at a given time expressed both la-like antigen and cALL antigen, though the cell line appeared to a monoclonal population on the basis of cytogenetic markers.

Group II

B-cell leukemia-lymphoma line has a common definitive tnarker, i.e., immunoglobulin, such as Smlg, Cylg, or both. There were 30 such B-cell lines (nos. **16–45)** listed in Table 1. An la-like antigen was obligatory in all 30 B-cell lines, but it was not the definitive marker for the B-cell lineage. Other markers, such as cALL, TdT, EA, and EAC were apparently non-specific to the B-cell lineage. though they were useful to divide the entire B-cell differentiation stage into five separate compartments as shown in Fig. I. The ***Pre-B Cell*** (nos. **16–21)** without detectable Smlg has both cALL and la-like antigen, but not always positive for TdT. The ***B-Blast I*** (nos. **22–35)** has Smlg, **cALL,** and **la-like** antigens. Many of the Burkitt lymphoma-derived cell lines (nos. 23–29, African Burkitt lymphomas) had EBV infection, but it was not specific to either Burkitt lymphoma or ***B-Blast*** I category. ***B-Blast II*** (nos. 36-42) is similar to ***B-Blast*** I except for the absence of cALL. The ***B-Cell*** compartment is in fact a compartment indistinguishable in membrane phenotype from both ***B-Blast II*** and ***Plasma Cell*** and there is no cell line in the ***B-Cell*** compartment. The *Plasma Cell* has no specific positive marker; nonetheless, there are three cell lines in this compartment (nos, **43–45).** It was based on the fact that

the Ig produced by the lines were identical to those found in patients myeloma proteins.

Group III

Myelomonocytic leukernis-lymphoma line has a common definitive marker. ic MAg-I antigen. There were four such myelomonocyte lines as the listed nos. 46 19 in Table 1. All four cell lines expressed EA in varying percents. Both HL-60 and ML 1–3 showed positive myeloperoxidase reaction at 100% (data are not shown), whereas KG-I and U-937 were negative or marginal for the myeloperoxidase reaction. Accordingly, it was decided tentatively that the myelocytic differentiation lineage can be divided into several compartments on the basis of both the marker profiles and cytochemistry. The *Promyelocyte* (HL-60), *Myeloblast* (ML 1 3) *Myeloid Precursor* (KG-I) and more *Mature Granulocytes* are those compartments in order of progressive differentiation (Fig. 1). U-937 line was, however, placed into the *Monoblast* compartment, because it derived from a histiocytic lymphoma

Group IV

Non-T, non-B leukemia-lymphoma line lacks all three above mentioned definitive markers. Six cell lines (nos. 50–55) were in this group. Nevertheless, cell lines nos 51–54 were considered to be in a single compartment, viz., *Lymphoid Precursor*. Since all four cell lines were of ALL origin with common marker profiles (In. cALL and TdT). Based on the latest information, K-562 can be placed in a compartment for an *Erythroid Precursor* (Andersson et al. 1979). The SU-HDL-1 (no. 55) which is another unusual cell line lacking all markers was tentatively placed of the compartment of *Monocytoid* Precursor on the basis of its derivation of a histiocytic lymphoma (Epstein and Kaplan 1974).

A total of 344 patients with leukemias were studied by the multiple marker analysis. Table 2 summarizes immunologic subclassification of these leukemias

In view of our hypothesis that the observed heterogeneity of marker profiles among 55 leukemia-lymphoma cell lines was interpreted as reflecting normal hematopoietic cell differentiation scheme, the heterogeneity of marker profiles among these leukemias was similarly correlated with the scheme shown in Fig. 1.

Of 19 T-cell ALLs, six had cALL antigen expression which can be placed in the *T-Blast I* compartment in Fig. 1. The rest of the T-cell ALL were in the *T-Blast II* compartment. Of six B-cell ALLs, two had cALL antigen expression which can be placed in the *B-Blast* Icompartment. Since we did not determine systematically for the pre-B-cell phenotype, all 118 common ALLs were in the *Lymphoid Precursor* compartment. Of seven null-cell ALLs, four had Ia antigen expression which might be placed alternatively in the *Myeloid Precursor*.

A total of 39 AMLs are shown in Table 2. An attempt at subclassification by the multiple marker analysis (Minowada et al. 1980) was made to subclassify AMLs into three subtypes. The type I AML is characterized by the presence of Ia antigen but lacking MAg-I antigen and all other markers. While type II AML expresses both Ia and MAg-I antigens with variable expression for EA and EAC. type III AML expresses only MAg-I antigen which commonly accompanies with expression of EA and EAC. Expression of Ia antigen in the type III AML cells is

Table 2. Immunologic subclassification of 344 patients with leukemias. According to the presence of definitive markers with combinations of other non-definitive markers, four major types of leukemias were further subclassified

Diagnosis	Immunological subtype	% Incidence (No positive/no total)	Remarks
ALL	T	13% (19/150)	cALL$^+$, 32% (6/19)
	B	4% (6/150)	cALL$^+$, 33% (2/6)
	Common	79% (118/150)	
	Null	4% (7/150)	Ia$^+$, 71% (4/7)
AML	I	20% (8/39)	Ia$^+$, 69% (27/39)
	II	49% (19/39)	MAg-1$^+$, 79% (31/39)
	III	31% (12/39)	
CLL	B	99% (100/101)	
	T	1% (1/101)	
CML in BP	Lymphoid	20% (11/54)	
	Mixed	26% (14/54)	cALL$^+$, 46% (25/54)
	Myeloid	54% (29/54)	

no longer detected. It was thus possible to place type I, II, and III AMLs into *Myeloid Precursor*, *Myeloblast*, and *Promyelocyte* compartments, respectively. CMLs in blastic phase were also subtyped into three types according to their membrane phenotypes (Janossy et al. 1976). The lymphoid type of CML in BP is characterized by the same marker profile (Ia, cALL, and TdT positive) with *Lymphoid Precursor* compartment. The myeloid type of CML in BP is characterized by the same marker profiles of either type I, II, or III AML. The mixed type of CML in BP is a mixed phenotype between lymphoid and myeloid types in varying proportions. It was thus possible to place each CML in BP into either *Lymphoid Precursor*, *Myeloid* Precursor, or *Myeloblast/Promyelocyte* compartment.

Discussion

a total number of leukemia-lymphoma cell lines increased, it became apparent that a considerable heterogeneity exists in the marker profiles among them, even those cell lines within the same lineage of hematopoietic differentiation (Minowada et al. 1977). Similar heterogeneity in the marker profiles was repeatedly documented in a large series of study with fresh leukemia-lymphomas (Greaves et al. 1977, 1978; Greaves and Janossy 1978; Minowada et al. 1977, 1980; Thierfelder et al 1979). Unlike earlier reports for the presence of leukemia antigens, all cell surface markers so far studied were considered to be of normal gene products which can be found in the cells during various stages of hematopoietic cell differentiation (Janossy et al. 1977; Greaves 1978; Metzgar and Mohanakumor 1978). Moreover, many of the antigens which were restricted in their expression to one type of mature peripheral hematopoietic cells were found to be expressed on the leukemia-lymphoma cells as well as normal immature hematopoietic cells. These antigens include Ia-like gp 28,30 antigens (Billing et al. 1976; Schlossman et al. 1976; Janossy et al. 1977) and cALL antigens (Greaves 1978; Greaves and Janossy 1978;

Minowada et al. **1978).** The cell types in which these antigens were expressed were often beyond a single differentiation lineage and it was concluded that these antigens are of differentiation-linked natures. It was in the same situation for TdT activity that the enzyme activity is found not only in immature T cells but also in the immature lymphoid precursor cells (Bollum **1979).**

On the basis of these observations, a number of investigators have attempted to correlate the observed heterogeneity of the marker profiles of leukemia-lymphomas to the scheme of normal hematopoietic cell differentiation (Greaves 1978; Minowada 1978; Thierfelder el al. 1979; Minowada et al. 1980; Reinherz and Schlossman 1980; Nilsson et al. 1980).

Our model for a hematopoietic cell differentiation as presented in this study (Fig. 1) was based on the multiple marker analysis of **55** leukemia-lymphoma cell lines and 344 cases of leukemias. The monoclonality of human leukemia-lyphomas so far studied is a remarkable feature and it seems to represent a particular marker profile of normal counterpart at a specific point in the hematopoietic differentiation. Assuming a single pluripotential stem-cell compartment, each lymphoid. myeloid, monocytoid, erythroid. arid megakaryocytoid differentiation can emerge from it. With this concept in mind, each marker can now be distributed with some certainty on the scheme. It is thus possible that each leukemia-lymphoma line or fresh leukemia-lymphoma with the combination of the definitive marker and number of non-definitive markers can be placed at particular stage of **hematopoietic** cell differentiation. This attempt with the current scheme may not be totally correct, but at least it makes reasonable sense in the immunologic membrane phenotypes of leukemia-lymphomas.

Recent advances in methodologies, such as the in vitro culture method, induction for differentiation, and murine hybridoma technology, would certainly facilitate further progress in the study of human hematopoietic cell system and leukemia-lymphoma (Collins et **al. 1978;** Mier et al. **1980;** Kohler et al. **1975).**

Proper usage and experimentation with these permanent leukemia-lymphoma cell lines would continue to be'responsible for further advances in the **leukemia** membrane phenotyping **and** it would provide a realistic basis to resolve some of the difficulties in the existing classification of human lymphomas.

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LEUKEMIA IN LYMPHOMA

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