BLOOD REVIEWS
Haematological Malignancies

Immunologic Classification of Lymphoma and Lymphoid Leukemia

K. A. Foon, R. P. Gale

SUMMARY. **Important insights into lymphocyte differentiation and the cellular origins of lymphoma and lymphoid leukemia have been gained through the use of monoclonal antibodies that define cell surface antigens and molecular probes that identify immunoglobulin and T cell receptor genes. Results of these studies have been combined with markers such as surface membrane and cytoplasmic immunoglobulin on B lymphocytes, sheep erythrocyte receptors on T lymphocytes, and cytochemical stains. Utilising all of the above markers, it is now clear that acute lymphoblastic leukemia (ALL) is heterogeneous. Furthermore, monoclonal antibodies that identify B cells such as the anti-B1 and anti-B4 antibodies in combination with studies of immunoglobulin gene rearrangement have demonstrated that virtually all cases of non-T-ALL involve B lymphocytes. At least six distinct subgroups of non-T-ALL can now be identified. T-ALL is subdivided by the anti-Leu-9, anti-Leu-1, and additional antibodies that separate T lymphocyte subsets into three primary subgroups. Monoclonal antibodies are also useful in the subclassification of non-Hodgkin's lymphoma, and certain distinct markers can be correlated with morphologic classification.**

Recent advances in immunology have led to important insights into lymphocyte differentiation and the cellular origin of lymphoma and lymphoid leukemia. It is now possible to precisely define stages of human lymphocyte differentiation utilising highly specific monoclonal antibodies that define cell surface antigens and molecular probes that identify rearrangement of immunoglobulin and T cell receptor genes. These can be combined with more traditional cell markers such as surface membrane (SmIg) and cytoplasmic immunoglobulin (CIg) on B lymphocytes, sheep erythrocyte receptors on T lymphocytes, and cytochemical stains. In this review, we summarise advances in the classification of lymphoma and the lymphoid leukemias and their importance in our understanding normal lymphoid differentiation and therapeutic implications.

K. A. Foon, Division of HematolOgy and Oncology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI and R P Gale, the Division of Hematology and Oncology, Department of Internal Medicine, and the Transplantation Biology Unit, University of California, Los Angeles.

Cell Markers

B Lymphocytes

B lymphocytes are usually identified by the presence of SmIg. Progenitors of B lymphocytes, commonly referred to as 'pre-B cells' are present in fetal liver and normal bone marrow; the cells display cytoplasmic μ-heavy chain (Cμ) but lack intracytoplasmic light chain and SmIg. B and pre-B lymphocytes may also have receptors for the third component of complement (C'3) and for the Fc portion of IgG. Fc and C'3 receptors are not specific for the B cell lineage and are found in other cells such as monocytes and some nonhematopoietic cells. Similarly, histocompatibility-related antigens (Ia or HLA-DR) are also found on the surface of B cells, but are not unique to them.[1-4] Plasma cells are the most mature B lymphocytes; they lack detectable SmIg but have CIg. Unlike the CIg found in pre-B lymphocytes, CIg in plasma cells includes both heavy and light chains.

A number of heteroantisera and, more recently, monoclonal antibodies that identify B cell-associated

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Table 1 Monoclonal Antibodies Reactive with Human B Lymphocytes

Antibody (subclass)	Pattern of Reactivity	Molecular Weight of Antigen (kd)	Cluster Designation	Reference
anti-B1	B lymphocytes, malignant B cells	35	CD20	8
anti-B2	B lymphocytes, malignant B cells (receptor for Epstein-Barr virus and C3d)	140	CD21	9, 10
anti-B4	B lymphocytes, malignant B cells	40	CD19	7
BA-1	B lymphocytes, granulocytes, malignant B cells	45, 55, 65	CD24	11, 12
FMC1	B lymphocytes, malignant B cells	NR	NA	13
FMC7	<50% B lymphocytes, some malignant B cells	NR	NA	14
J5, BA-3	Granulocytes, most non-T-ALL, Burkitt's lymphoma, follicular lymphoma, some lymphoblastic lymphoma and T-ALL	100	CD10	4–6
anti-PCA-1 and anti-PCA 2	Plasma cells, malignant plasma cells, weakly on monocytes and granulocytes	NR	NA	15
anti-PC-1	Plasma cells, malignant plasma cells	28	NA	16

NR, not reported; NA, not applicable.
The anti-B series, anti PC-1, and anti PCA-1 are available through Coulter Immunology, Hialeah, Florida; BA-1 through Hybritech Inc., San Diego, California; and the OKB series through Ortho System, Inc., Raritan, NJ.

Table 2 Monoclonal Antibodies Reactive with Human T Lymphocytes

Antibody	Pattern of Reactivity	Molecular Weight of Antigen (kd)	Cluster Designation	Reference
OKT6, NA1/34, anti-Leu-6	Thymocytes	45	CD1	21
OKT11, anti-T11, anti-Leu-5	Pan-T lymphocyte (E receptor)	40–50	CD2	23, 24
OKT3, anti-T3, anti-Leu-4	Pan-T lymphocyte (mitogenic)	20, 20, 25	CD3	21
OKT4, anti-T4, anti-Leu-3	T helper/inducer	55	CD4	21, 22
OKT1, anti-T1, anti-Leu-1, T101	Pan-T lymphocyte, pan-thymocyte	65	CD5	21, 25, 26
3A1, anti-Leu-9 (4H9), WT1	Pan-T lymphocyte, pan-thymocyte	40	CD7	27–29
OKT5, OKT8, anti-T8, anti-Leu-2	T cytotoxic/suppressor	32–43	CD8	22
Anti-Tac	Interleukin-2 receptor	55	CD25	31
Anti-TQ1	Subset of T inducer cells	NR	NA	31
OKT9, 5E9	Thymocytes, lymphoblasts, monocytes (anti-transferrin)	90	NA	20, 21
OKT10	Thymocytes	45	NA	20

NR, not reported; NA, not applicable.
The OKT series of antibodies are available through Ortho Systems, Inc., Raritan, NJ; Leu series through Becton-Dickinson Co., Mountainview, California; anti-T through Coulter Immunology, Hialeah, Florida; and T101 through Hybritech, Inc., San Diego, California.

antigens have been described (Table 1).[4–16] For a more detailed description of these antibodies see reference 17. Where applicable, the nomenclature and clusters of differentiation (CD) defined by the Second International Workshop on Human Leukocyte Differentiation Antigens are shown.[18,19]

T Lymphocytes

T lymphocytes were initially identified by their ability to spontaneously bind sheep erythrocytes (E rosette). T lymphocytes also react with T cell-specific antisera and T cell monoclonal antibodies which may also be used to identify T lymphocytes, and have proven to be more sensitive and discriminatory (Table 2).[20–31] Many of these antibodies react with immature T cells; others react with more mature T cells. Some of these antibodies identify antigens found on all T cells, whereas others occur only on T cell subsets.

A summary of the more frequently referenced antibodies useful for the classification of lymphoma and lymphoid leukemia, and their cluster designations is shown in Table 3.

Table 3 Frequently Referenced Antibodies with Cluster Designations

Cluster Designation	Antibody
CD1	OKT6, anti-Leu-6, NA1/34
CD2	OKT11, anti-T11, anti-Leu-5, 9.6
CD3	OKT3, anti-T3, anti-Leu-4, UCHT-1
CD4	OKT4, anti-T4, anti-Leu-3
CD5	OKT1, anti-T1, anti-Leu-1, 10.2, T101
CD7	anti-Leu-9, 3A1, WT1, 4A
CD8	OKT5, OKT8, anti-T8, anti-Leu-2
CD10	anti-J5, BA-3, anti-CALLA
CD19	anti-B4
CD20	anti-B1
CD21	anti-B2
CD24	BA-1
CD25	anti-Tac

Immunoglobulin and T Cell Receptor Genes

Recombinant DNA technology has provided important insights into antibody diversity and antigen-specific T cell receptors.[32] Immunoglobulins are composed of heavy and kappa and lambda light chains, encoded by genes on chromosome 14, 2 or 22, respectively.[33–36] Immunoglobulin genes are encoded by

discontinuous segments of DNA.[37,38] At one point in development, a potential antibody-producing cell must productively rearrange variable, diversity and joining genes (VDJ) which are then linked to the constant region locus. Immunoglobulin gene rearrangements are hierarchal; μ heavy chain rearrangements precede light chain rearrangements; kappa light chain rearrangement precedes lambda light chains rearrangement.[38] These rearrangements can be detected by Southern blot analyses of DNA from B-cells using appropriately radiolabeled heavy or light chain probes. Heavy chain rearrangements have been identified in non-B cells; light chain rearrangements appear to be restricted to B-cells.[38,39] Clonal rearrangements of light chain genes are therefore an extremely sensitive tool to identify B-cell malignancies.

The antigen-specific T-cell receptor is a heterodimer formed by a 40–50 kilodalton (kd) α subunit (Tα), and a 40–45 kd β subunit (Tβ).[40] It is associated with three 20–25 kd peptide chains identified by the T3 monoclonal antibody.[40] Recently, cDNA clones to the Tβ and Tα receptors have been isolated.[41-43] The human Tβ receptor gene has been localised to chromosome 7[44] and the human Tα receptor gene to chromosome 14.[45]

Tβ gene rearrangements have been detected in malignant human T-cells by Southern blotting.[46-48] This technique can detect as few as 1% tumour cells in a mixed cell population;[46] it is a sensitive diagnostic marker for T-cell diseases. Interestingly, rearrangements of the Tβ antigen receptor are reported in 25% of patients with non-T ALL,[49] and in a small portion of leukemic B cells.[50] This is similar to the rearrangement of immunoglobulin heavy chain genes in approximately 10% of the leukemic T cell population studied.[39]

Classification of the Lymphoid Leukemias and Lymphomas

Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is heterogeneous. The first surface markers used to differentiate subclasses of ALL were E rosettes,[51,52] which identify a T cell subclass (15–20% of cases) and SmIg which identifies a B cell subset (< 5% of cases). Both T and B cell subgroups have an unfavourable prognosis.[53,54] The next important advance in identifying ALL was development of an antiserum to the common ALL antigen (CALLA).[55] CALLA or CD10 reactivity identified a non-B, non-T subclass of ALL patients (approximately 70% of cases) with a more favourable prognosis than T-ALL, B-ALL, or non-B, non-T ALL without CD10.[54] Other markers such as Ia antigen were commonly found on non-T-ALL and could help differentiate non-T from T-ALL.[56] By testing for cytoplasmic μ heavy chain, a subset designated pre-B ALL has been identified.[57] Except for the presence of cytoplasmic μ, this subset expresses the same surface markers as the CD10-positive form of non-T-ALL; it appears, however, to have a less favourable prognosis.[58]

With the development of monoclonal antibodies, it became evident that the T cell subset of ALL was heterogeneous.[59-61] More recently, studies of immunoglobulin gene rearrangements and monoclonal antibodies that identify B cell-associated antigens have demonstrated that most cases of non-T-ALL derive from the B cell lineage.[62,63] We review these data and present a new classification for ALL based on these recent observations.

Non-T-Acute Lymphoblastic Leukemia

Two important areas of research have prompted a reassessment of non-T-acute lymphoblastic leukemia (non-T-ALL). First, monoclonal antibodies that recognise B cell-associated antigens have been identified; many are present on non-T-ALL cells. The most specific of these antibodies is probably anti-B4 which reacts with 95% of cases of non-T-ALL.[11,63] Second, clonal rearrangements of immunoglobulin genes provide strong evidence for the B cell lineage of most cases of non-T-ALL.[62,63]

Although Ia antigen is present on most non-T-ALL, and CD10 is present on 75% of cases of non-T-ALL, these antigens are also identified on approximately 10% of cases of T-ALL. Therefore, B cell-associated antigens (Table 1), which are not identified on T-ALL cells, are the most useful in distinguishing non-T-ALL. The CD20 and CD19 antigens are model antigens for this discussion.

Less than 5% of cases of ALL express SmIg (usually IgM); these cells are typically classified as B-ALL. These cells generally express other B cell antigens, including CD20, CD19, and Ia. B-ALL in children is probably a leukemic phase of non-Hodgkin's or Burkitt's lymphoma.[52,53] Another marker that identifies a subset of non-T-ALL is cytoplasmic μ (Cμ) heavy chain; κ and λ light chains, and SmIg, are typically absent.[57] These cells are considered pre-B cells. As indicated, most cases of non-T-ALL involve pre-B cells; thus Cμ is useful in determining the level of differentiation of pre-B cells. Pre-B cells that synthesise μ heavy chain are the most mature cells of this group.

Nadler and co-workers[63] recently classified 138 patients with non-T-ALL on the basis of monoclonal antibodies and immunoglobulin gene rearrangements. They divided these cases into four major subgroups. The first subgroup was Ia antigen-positive, representing 5% of cases. Another subgroup expressed the Ia and B4 antigens representing 15% of cases. The third subgroup expressed the Ia, CD19, and CD10 antigens, comprising one third of the cases. Finally, one half of the cases of non-T-ALL were Ia, CD19, CD10, and CD20 positive. The fourth group was further subdivided into cases with and without Cμ. We propose that cases with Cμ be placed in a separate group (group V) assuming that they are more mature.

Table 4 Classification of non-T-ALL

	Antigens					
	Ia	CD19	CD10	CD20	Cytoplasmic μ	Surface Membrane Immunoglobulin
Group I	+	−	−	−	−	−
Group II	+	+	−	−	−	−
Group III	+	+	+	−	−	−
Group IV	+	+	+	+	−	−
Group V	+	+	+	+	+	−
Group VI	+	+	+/−	+	−	+

Table 5 Classification of T-ALL

	Antigens						
	CD7	CD5	CD2	CD3	CD4	CD8	CD1
Group I	+	+ (90%)	+ (75%)	−	−	−	−
Group II	+	+	+	+ (25%)	+ (90%)	+ (90%)	+
Group III	+	+	+	+	+/−†	+/−†	−

* Found on virtually all T-ALL cells.
† No longer simultaneous expression of T4/Leu-3 and T8/Leu-2 as found in Group II.

The final and most differentiated group, group VI, represents SmIg-positive B-ALL (Table 4).

T-Acute Lymphoblastic Leukemia

T-acute lymphoblastic leukemic (T-ALL) represents 15% to 25% of cases of ALL. Clinical features associated with T-ALL include a high blast cell count, predominance of male patients, older patients (15–20 years), and mediastinal masses. T-ALL was originally identified by E rosette formation. The most sensitive marker for T-ALL is probably the CD7 pan-T 40 kilodalton (kd) antigen. This antigen is present on most thymocytes and T cells but not on non-T-ALL or B cell lymphomas or leukemias.[27–29] In a study of 23 patients with T-ALL, all cases expressed CD7.[28] Interestingly, CD7 reacts with a small proportion of cases that appear to be myeloid leukemias.[64] In addition, an unusually high incidence of CD10, Ia, and CD24 expression has been reported in adults with T-ALL.[65] Recently, rearrangement of the Tβ receptor gene in cases of T-ALL has been reported.[46–50]

Further subclassification of T-ALL is controversial. Reinherz and colleagues proposed a subclassification for T-ALL according to the level of thymic differentiation.[59] Several elements of their subclassification of T-ALL have been confirmed; others are controversial. The most primitive thymocytes, referred to as early or stage I thymocytes, react with T9 and T10 antibodies and account for approximately 10% of the thymic cells. In their study, Reinherz and co-workers reported that most T-ALL cells express antigens found on early thymocytes. The next level of thymic differentiation, which included the majority of thymocytes, is referred to as common or stage II. These cells lose T9, retain T10, and acquire CD1, CD4, and CD8 antigens. Approximately 20% of cases of T-ALL express this phenotype. Mature stage III thymocytes no longer express CD1 but segregate into CD4 or CD8 subsets similar to peripheral blood T lymphocytes. Only rarely did Reinherz, et al find T-ALL cells with the phenotype of mature thymocytes or circulating T lymphocytes. In a more recent study, Roper and co-workers[61] confirmed many of the findings reported by Reinherz, but reported some major differences. In this study, only one third of the T-ALL patients had the phenotype of early or stage I thymocytes; most had the phenotype of either intermediate or late stage thymocytes. In Table 5 we summarize these data and propose a scheme for the classification of T-ALL. The common marker for all of the subgroups is CD7. Nearly all cells also express CD5 and most express CD2 that identifies the E-rosette receptor.

Although Roper and co-workers[61] studied clinical correlations between these three groups of T-ALL, they found no unique clinical features among the subgroups and no differences in remission duration or survival. However, the groups were too small for statistically valid conclusions. Presently we believe it useful to subclassify T-ALL using this system so that data from a number of institutions can be analysed for clinical correlations between the subgroups of T-ALL.

Non-Hodgkin's Lymphoma

The non-Hodgkin's lymphomas are a diverse group of neoplasms whose pathologic classification are controversial. It is even more difficult to correlate pathologic classification with immunologic classification. There are, however, a number of immunologic patterns that emerge, and we will attempt to place them within the non-Hodgkin's lymphoma working classification[66] as well as the Rappaport classification.[67]

Follicular or Nodular Lymphomas

The follicular or nodular lymphomas most likely represent neoplastic proliferation of lymph node-derived follicular center B lymphocytes. The cell type may be a small cleaved cell (nodular lymphocytic poorly differentiated lymphoma by the Rappaport classification), mixed small cleaved and cleaved or non-cleaved large cell (nodular mixed), or predominantly large cell (nodular histiocytic). The first two cell types fall within the working classification as low-grade lymphoma, whereas the latter cell type as an intermediate grade lymphoma. While the predominantly small cleaved cell will almost always express high density monoclonal SmIg, larger cells may be SmIg negative.[68,69] However, the small cleaved and large cells will routinely express Ia, CD19, and CD20 antigens and will often express the CD21 antigen.[69] Interestingly, more than half of these cases will also express CD10,[69,70] Follicular lymphoma cells may be found in the patient's peripheral blood as a 'leukemic' phase of the disease (formerly referred to as lymphosarcoma cell leukemia). These cells can usually be differentiated from chronic lymphocytic leukemia (CLL) cells as they may express CD10, which is not expressed on CLL cells; they do not express the CD5 pan-T antigen found on CLL cells; and they generally will have a low percentage of mouse erythrocyte rosette formation (see below).[71,72]

Malignant Lymphoma, Small Lymphocytic

Malignant lymphoma, small lymphocytic (diffuse lymphocytic well-differentiated lymphoma in the Rappaport classification) is a low-grade malignancy and some cases may be identical to CLL. Also, included within this subclassification are the plasmacytoid lymphocytic subgroups with and without an IgM monoclonal gammopathy; some of these cases are similar to Waldenström's macroglobulinemia (described below). Surface markers on these small lymphocytic cells include low intensity SmIg, mouse erythrocyte receptors, C'3 and receptors for the Fc portion of IgG and Ia, CD19, CD20, CD21, CD24, and other B cell antigens. These features are similar to CLL and the cells also express the CD5 pan-T antigen.

Malignant Lymphoma, Diffuse Small Cleaved Cell and Diffuse Mixed Small and Large Cell

Malignant lymphoma, diffuse small cleaved cell (diffuse lymphocytic poorly differentiated lymphoma in the Rappaport classification) is an intermediate prognostic group. The cells are B lymphocytes that (similar to follicular lymphoma cells) usually display large amounts of monoclonal SmIg. Unlike follicular lymphoma cells, however, they do not usually express CD10.[70] Similar to follicular lymphoma cells, they do not express the CD5 antigen as do cells from most small lymphocytic lymphomas and CLL. However, all of these cell types have in common the expression of Ia, CD19, CD20, CD21, and other B cell antigens.[69]

The diffuse mixed small and large cell (diffuse mixed lymphocytic-histiocytic) lymphomas have not been extensively studied but are most likely predominantly B cell diseases. They are also considered an intermediate grade prognostic group.

Malignant Lymphoma, Diffuse Large Cell and Large Cell Immunoblastic

In the working classification, the diffuse large cell lymphomas are considered within the intermediate prognostic group, whereas large cell immunoblastic lymphoma is a high-grade malignancy. By the Rappaport classification, both of these cell types would be described as histiocytic. This is clearly a misdesignation since 80–90% of cases represent clonal expansions of malignant B cells.[73] A high percentage of these cells express T9 and T10 antigens.[68] Fifty-seven cases of diffuse large cell lymphoma were recently studied and divided into the following subgroups: (1) CD20, CD19, and SmIg positive; CD21 negative (50%), (2) CD20, CD19, SmIg, and CD21 positive (30%), (3) CD20 and CD19 positive; SmIg and CD21 negative (10%), and (4) CD20 and SmIg positive, and CD21 negative (10%).[74] These data suggest that most of these lymphomas's represent the malignant counterpart of B cells at the mid-stage of differentiation. Ten to 20% of cases are T cell lineage; 2% are derived from the monocyte-myeloid lineage. Recently, clonal rearrangement of the Tβ receptor has been described in patients with T-derived non-Hodgkin's lymphoma.[47,48]

Malignant Lymphoma, Lymphoblastic

Malignant lymphoma, lymphoblastic or lymphoblastic lymphoma is a high-grade malignancy. The nuclear membrane is characteristically deeply subdivided imparting either a lobulated (convoluted) appearance or a fine linear (nonconvulated) subdivision in a round nucleus. Lymphoblastic lymphoma represents approximately one-third of the cases of non-Hodgkin's lymphomas in children and 5% of cases in adults. The disease is more prevalent in males; these patients often have a mediastinal mass. In some cases, the disease may evolve into a leukemic phase morphologically indistinguishable from T-ALL. The malignant cells are T cells, form E rosettes, react with T cell antisera,[75–77] and have rearrangements of the Tβ receptor.[78] Studies with monoclonal antibodies have demonstrated marked heterogeneity. Lymphoblastic lymphoma cells differ from T-ALL in that the cells rarely express the surface markers common to immature thymocytes (group I);[79] phenotypes are equally divided among group II and group III T-ALL. Interestingly in 40% of cases, the cells are reported to express CD10; CD10 expression is less common in T-ALL (10%).[70]

Malignant Lymphoma, Small Noncleaved Cell

This category includes Burkitt's lymphoma and other lymphomas previously designated undifferentiated non-Burkitt type (high grade). Burkitt cells from peripheral blood and bone marrow are usually classified as L3 by the French–American–British (FAB) criteria.,[80] Most cases of Burkitts lymphoma from Africa are associated with the Epstein-Barr virus (EBV); these are endemic. Most non-African cases (non-endemic) are EBV negative.[81] Chromosomal abnormalities involving chromosome 8 (carrying the oncogene c-myc) and either 2, 14, or 22 occur in virtually all cases of endemic and non-endemic Burkitt's lymphoma.[82] These are designated t(2;8), t(8;14) and t(8;22), respectively. Usually the light chain class expressed on these cells is correlated with the translocation, i.e., κ in t(2;8) and λ in t(8;22). African Burkitt's lymphoma cells have C'3 and receptors for the Fc portion of IgG in addition to the EBV receptor. American Burkitt's lymphoma cells do not.[81] Phenotyping of cell lines derived from patients with undifferentiated lymphoma of the Burkitt's and non-Burkitt's type have demonstrated heterogeneity.[83] These studies suggest that Burkitt cells follow a divergent pathway of B cell evolution as they are all TdT negative (unlike early B cell non-T ALL). The most primitive of the Burkitt cell lines are Ia and CD20 positive and may or may not express CALLA. Maturation was evident in other Burkitt cell lines by the expression of $C\mu$, surface membrane IgM, and/or IgM secretion. Some of these Burkitt cell lines also expressed the Tac antigen.

Peripheral T Cell Lymphoma

Peripheral T cell lymphoma would usually be classified as malignant lymphoma, large cell immunoblastic (high grade) under the working formulation. However, this tumour has unique features and will be described separately. The term 'peripheral T cell lymphoma' is used to distinguish it from lymphoblastic lymphoma of presumed thymic origin. Peripheral T cell lymphomas are thought to derive from peripheral T lymphocytes in lymph nodes and other, non-lymphoid sites. These lymphomas comprise a broad spectrum of morphologic types of lymphocytes. In all instances the cells have T cell markers admixed with epithelioid histiocytes, plasma cells, eosinophils, and vascular hypertrophy. Clinically, peripheral T cell lymphoma is characterized by generalized lymphadenopathy, weight loss, and a high incidence of pulmonary involvement.[84] Surface markers are usually but not always characteristic of mature T helper cells,[85] including CD4 helper-associated antigen CD3, CD2, and CD5 pan-T antigens. Rearrangement of the Tβ receptor has been reported.[78]

Tγ Lymphoproliferative Disease

Tγ lymphocytes are a subset of T lymphocytes with receptors for the Fc portion of IgG. A high proportion of normal Tγ lymphocytes are large granular lymphocytes. These cells are thought to be responsible for natural killer (NK) and antibody-dependent cell-mediated cytotoxicity. A lymphoproliferative disorder made up of predominantly Tγ lymphocytes has been described; we refer to this as chronic Tγ lymphoproliferative disease.[86] Typically, patients are elderly, males, with increased Tγ lymphocytes infiltrating the bone marrow and spleen.[86,87] Although the disease is not rapidly progressive, neutropenia and recurrent infections are common. Most patients do not require chemotherapy. Variants of this disease, including a more aggressive form have also been described.[88] Clonal chromosomal abnormalities,[89] as well as clonal rearrangement of the Tβ receptor have been reported.[57,90] Cells from chronic Tγ lymphoproliferative disease usually contain acid phosphatase and β-glucuronidase and express the pan-T antigens CD3, CD2, the suppressor-associated antigens CD8, and the NK-associated antigens Leu-7 (HNK-1).

Cutaneous T Cell Lymphoma (Mycosis Fungoides, Sézary Cell Leukemia)

Skin lesions are the most prominent feature of patients with cutaneous T cell lymphoma.[91] Lesions vary from limited plaques to diffuse plaques, tumours, and generalised erythroderma. Rare patients with limited plaque disease and less than 50% with generalised plaques and tumours have extracutaneous disease detected by light microscopy evaluation of peripheral blood and lymph nodes. Special studies including cytogenetic analysis and electron microscopy indicate blood involvement in over half of the patients with limited plaque disease and most patients with generalized plaques and skin tumours.[92] Analysis of the Tβ receptor rearrangement will likely reveal a higher proportion of cases with blood involvement.

The malignant cells in this disorder are characterised by a cerebriform nucleus. In the skin, the cells are referred to as mycosis fungoides cells and in the peripheral blood as Sézary cells. Sézary and mycosis cells form E rosettes, react with T antisera and anti-T monoclonal antibodies,[93] and have clonal rearrangements of the Tβ receptors.[54,55,85,94] In most cases, the cells express the phenotype associated with normal helper/inducer T lymphocytes (CD5, CD3, CD4)[95] and function as helper T lymphocytes in in vitro assays.[96]

Adult T Cell Leukemia/Lymphoma

Adult T cell leukemia/lymphoma is associated with a human retrovirus designated human T cell leukemia/lymphoma virus-1 (HTLV-1).[97] Virtually all patients tested have antibodies to HTLV-1.[98] Patients with this disease have been identified primarily in Japan, the USA and the Caribbean. In the USA the patients are young (median age 33 years) predominantly black,

and born in the Southeast.[98] Common clinical features include a rapid onset of symptoms with rapidly progressive cutaneous lesions and hypercalcemia. Skin lesions are variable and include small and large discrete or confluent nodules, or nonspecific plaques, papules or patches. Patients have increased bony turnover with abnormal bone scans, elevated alkaline phosphatase and may have lytic bone lesions.[99] Lymphocytosis is common, and circulating malignant cells are present in low numbers in most patients. Peripheral lymphadenopathy is common with retroperitoneal and hilar involvement in approximately 50% of cases. Bone marrow, gastrointestinal, pulmonary, leptomeningeal and hepatic involvement are somewhat less common (20–50%). Response to combination chemotherapy is prompt and often complete, but duration of response is short (median 13 months). Opportunistic infections are extremely common in these patients.

The typical malignant circulating cells have moderately condensed nuclear chromatin, inconspicuous nucleoli, and a markedly irregular nuclear contour in which the nucleus is divided into several lobes.[100] These cells typically express the phenotype of helper/inducer Tγ lymphocytes,[101] and CD25 that identifies the IL-2 receptor.[102] Variability in the expression of CD2 and CD3 have been reported.[101] Clonal rearrangements of the Tβ receptor are identified in cells from patients with adult T cell leukemia/lymphoma.[48,50,78,82] The leukemic cells are reported to suppress B cells Ig secretion,[103] by a complex mechanism involving induction of suppressor cells following activation of normal suppressor cell precursors.[101]

Chronic Lymphocytic Leukemia and Prolymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is a monoclonal proliferation of SmIg-positive B lymphocytes.[104,105] Clonality of CLL has been demonstrated by expression of a single Ig light chain, either κ or λ, on the cell surface membrane.[106] More sophisticated techniques have confirmed clonality by showing unique immunoglobulin idiotype specificities,[107] a single pattern of glucose-6-phosphate dehydrogenase activity,[108] clonal chromosome abnormalities,[109] or immunoglobulin gene rearrangement.[47] The malignant B cell involved in CLL is an intermediately differentiated cell. The cell appears frozen in differentiation and does not mature to the final stage of B cell development, the mature plasma cell. However, recent data have demonstrated that in vitro treatment of these cells with phorbol esters or pokeweed mitogen can induce differentiation into mature immunoglobulin-secreting plasma cells.[110] Under certain circumstances, CLL cells stimulated in vitro with phorbol esters differentiate into cells with cytoplasmic protrusions and other characteristics of hairy cell leukemia.[111]

The B lymphocyte characteristic of CLL displays a relatively small amount of SmIg and this has been used to distinguish CLL from the leukemic phase of nodular and diffuse lymphocytic lymphomas and from prolymphocytic leukemia where the cells generally display considerably more SmIg.[112] Immunoglobulin isotype analyses indicates that most CLL display a single heavy chain class; typically, μ or μ and δ. Less commonly, γ, α, or no heavy chain determinant is found. CLL cells display either κ or λ light chains but never both. B-CLL cells display receptors for mouse erythrocytes, a feature characteristic of immature B lymphocytes.[113] The cells also have the receptor for the Fc portion of IgG and complement with a relative increase of C'3d receptors (CR2) over C'3b receptors (CR1); this is typical of immature B cells.[114] B-CLL cells display several antigens, including Ia and human B cell antigens such as CD19, CD20, CD21 and CD24. One unanticipated finding was that B CLL cells display the CD5 antigen previously thought to be restricted to T lymphocytes. CD5 on CLL cells was first recognised by using heteroantisera[115] and later with the T101 and equivalent monoclonal antibodies.[32] The precise meaning of this anomalous expression of a T cell antigen is unclear; although a normal B cell counterpart has been reported in human tonsil lymph nodes,[116] and stimulation in vitro of normal B cells with phorbol ester may induce expression of this antigen.[117] Recently, the TQ1 antigen, reported to define the inducer of suppression within the T helper subset, was identified on 60 of 75 B-cell patients' cells.[118]

Rearrangement of immunoglobulin heavy and light chains have been reported as expected in B-CLL cells, however, rearrangement of the Tβ receptor has also been reported in approximately 10% of cases of B-CLL.[50] This is analogous to the reported Tβ rearrangement in non-T (pre-B) ALL, and again emphasises that immunoglobulin and Tβ receptor rearrangement alone are not adequate to assign lineage.

In 3% to 10% of patients with CLL, the disease may evolve into a diffuse histiocytic lymphoma (Richter's syndrome). This may be associated with loss of the TQ1 antigen.[118] Most data suggest that this evolution involves transformed follicular center B cells rather than histiocytes or macrophages. Some transformations represent evolution of the malignant clone with expression of the same monoclonal immunoglobulin and karyotypic abnormality present in the original CLL clone.[119] In other cases, the lymphoma cells have different markers and immunoglobulin gene rearrangements than the original CLL cells; these cases probably represent the concomitant development of a B cell lymphoma or a histiocytic malignancy in patients with CLL.[120,121]

Prolymphocytic leukemia (PL) is related to CLL and is also likely to be derived from cells from the medullary cords of the lymph node. Immunoglobulin

gene rearrangements of heavy and light chains have been reported.[122] Patients with PL generally have extremely high blast counts and splenomegaly but lack significant lymphadenopathy. Prolymphoblasts are likely activated cells and appear morphologically immature with a fine lacy nuclear chromatin and one to two nucleoli; they may contain intracytoplasmic granules. These cells generally have higher density SmIg than CLL cells; they have Ia and CD19 antigens and may form rosettes with mouse erythrocytes.[72] PL cells from 14 consecutive patients reacted with the FMC7 monoclonal antibody that recognises an antigen found on one-half of normal B lymphocytes, while cells from only five of 20 patients with CLL reacted with this antibody.[7]

Approximately 5% of cases of CLL and PL result in a malignant proliferation of T rather than B cells. These cells react with T antisera and anti-T monoclonal antibodies reflecting the phenotypes of mature T lymphocytes; they lack SmIg and other B cell markers.[123,124] Many of these patients have diffuse organ and skin involvement.[123]

Hairy Cell Leukemia

Hairy cell leukemia (leukemic reticuloendotheliosis) is characterised by invasion of the bone marrow and spleen by morphologically distinct mononuclear cells with 'hairy' cytoplasmic projections.[125] These cells usually contain an isoenzyme of acid phosphatase (isoenzyme 5) that is resistant to tartrate; this isoenzyme is not unique to hairy cells. Surface markers of hairy cells are most consistent with a monoclonal proliferation of B lymphocytes.[126] SmIg with a single light chain is frequently identified,[126] as are B cell-associated antigens. Interestingly, the PCA-1 antigen (but not the PC-1 antigen) typically on plasma cells, is identified on hairy cells; these data suggest that hairy cells may be pre-plasma cells.[127] Perhaps the most convincing evidence for the B cell origin of hairy cells comes from studies of immunoglobulin genes which indicate clonal rearrangement of heavy chain genes and at least one light chain.[128,129] Most cases of hairy cell leukemia demonstrate CD25 typically identified on select T cell malignancies and activated T cells.[129]

Myeloma and Related Disorders

The malignant B cells of Waldenström's macroglobulinemia, heavy chain disease, and multiple myeloma represent a further step in the maturation of medullary cord B cells.[104] Like CLL cells, cells from patients with Waldenström's macroglobulinemia express SmIg and Ia, CD20, and CD19 antigens.[11] Unlike CLL cells, however, these cells express the PCA-1 antigen and do not express the CD21 antigen nor rosette with mouse erythrocytes.[72] The plasma cell and its malignant counterpart, the myeloma cell, represent the most differentiated B lymphocytes. These cells synthesise large quantities of immunoglobulin and have CIg, but usually lack SmIg and the Ia, CD20, CD21, and CD19 antigens.[130] Plasma cells and myeloma cells, like other mature B lymphocytes, usually lack CD10, but a recent study has suggested that rare cases of CD10-positive myeloma represent an aggressive subtype with a poor prognosis.[131] Interestingly, plasma cells and myeloma cells stain intensely with the OKT10 monoclonal antibody as well as the anti-PCA-1 and anti-PC-1 antibodies.[132,133]

Conclusion

The exciting advances in molecular biology and the hybridoma technology over the past 10 years have led to major advances in our understanding of the cellular origin of lymphoma and leukemia and will likely lead to a better understanding of the etiology of these diseases. Utilising these techniques it is now possible to more accurately diagnose and classify these disorders; these data may also have therapeutic implications. It is also possible to use molecular probes to detect minimal residual disease. In the future, monoclonal antibodies conjugated to isotopes, drugs, and/or toxins will likely have a role in the therapy of certain leukemias and lymphomas. We look forward to this exciting new era in cancer therapy and diagnosis.

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