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The T Lymphoblastic Malignancies

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Acute lymphoblastic leukemia (ALL) has long been recognized as a heterogeneous disease on the basis of its clinical presentation, course, and response to therapy [17, 21, 57]. As early as 1932, it was noted that a subgroup of patients with ALL presented with mediastinal enlargement, and therefore it was suspected that the origin of the tumor was within the thymus [13]. It was further noted that the majority of these patients were adolescent males and their survival was significantly shorter than that of patients with the nonmediastinal form of ALL [25]. However, despite this variability in clinical presentation and course, the malignant lymphoblasts in these subgroups were morphologically indistinguishable.

The development of immunologic techniques defining human B lymphocytes (surface or intracytoplasmic immunoglobulin), T lymphocytes (sheep erythrocyte rosettes or T cell heteroantisera), and human null lymphocytes (lack of immunoglobulin or T cell markers) has begun to elucidate the cellular origin of the malignant lymphocyte [4, 11, 18, 24, 55, 62]. Table 1 depicts several markers used to define the cell surface phenotype of the malignant lymphocyte. The most frequent form of ALL, affecting about two-thirds of patients, is the 'null cell' or common type of ALL. The surface of null cells bears neither B nor T cell markers, although they are not totally devoid of surface antigens [12, 49]. An antigen common to these tumor cells (CALLA) appears to be a specific tumor-associated antigen for this disease and for the tumor cells of a percentage of patients with the blastic phase of chronic myelogenous leukemia [12, 39, 49]. A small number of patients (5%–10%) who have been thought to have null cell ALL have lymphoblasts that are, in fact, precursors of mature B lymphocytes [8, 60]. These lymphoblasts have IgM in their cytoplasm and are thought to represent an early stage of B cell development. In addition, they frequently express the CALLA antigen. Very rarely, lymphoblasts in ALL (1%–2%) are mature B cells expressing surface immunoglobulin (sIg) [20]. The null, pre-B, and B cell forms of ALL all share an antigen termed 'Ia-like' [1, 19, 54]. The human Ia-like antigen is a gene product of the HLA-D region which present on the surface of normal peripheral blood B cells, a fraction of null cells, monocytes, and activated T cells [1, 15, 54]. The remaining 20% of patients with ALL have lymphoblasts that lack all the previously described markers but react with sheep erythrocytes (E rosettes) and anti-T cell heteroantisera [2, 3, 9, 27, 34]. The reactivity of the lymphoblasts from patients possessing mediastinal ALL with

Table 1. Markers used to define the cell surface phenotype of the malignant lymphocyte

	Ia	Surface Ig	Cytoplasmic Ig	CALLA	E rosette	T cell antigen	Terminal transferase
Null	+	0	0	+	0	0	+
Pre-B	+	0	+	+	0	0	+
B	+	+	0	0	0	0	0
T	0	0	0	0	+	+	+

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sheep erythrocytes and T cell antisera has confirmed the previously suggested T cell lineage of this disease.

As cell surface phenotyping became more widespread, it was rapidly recognized that patients with T cell ALL represented a distinct clinical entity [28, 56, 59]. These patients were commonly older adolescent males who presented with mediastinal enlargement. In addition, it was noted that the lymphoblast count tended to be much higher than in the non-T cell forms of ALL, but severe anemia was infrequent. It appeared that the malignant T lymphoblast was frequently capable of infiltrating the skin, CNS, and testicles. More importantly, these patients responded significantly less well to standard therapy for ALL than did patients with the common null cell form.

Although many patients with T cell ALL presented with a classic clinical picture, significant clinical heterogeneity was noted even within the T cell-derived tumors. With the impressive evidence for functionally relevant T cell subsets in murine systems, it was logical to assume that T cell subsets existed in man. Preliminary evidence for human T cell subsets was suggested by cell surface phenotyping with several widely used markers. Utilizing the differential reactivity of the T lymphocyte markers, including sheep erythrocyte rosettes, complement receptors, and receptors for the Fc portion of immunoglobulin, several laboratories suggested that there was T lymphoblast heterogeneity. Borella et al. [3] demonstrated that thymocytes and leukemic T lymphoblasts formed stable rosettes at 4° C and 37° C, in contrast to peripheral blood normal T lymphocytes, which form stable rosettes at 4° C. This observation suggested that T leukemic blasts were thymic in origin. Subsequently, it was shown that a proportion of T lymphocytes lacked the E rosette receptor but did have reactivity for T cell heteroantisera [33]. When the surface of T lymphocytes were studied for the presence of receptors for the subunits of complement, it was shown that some T lymphocytes bore the receptor for C3 and others did not [22, 26, 51]. Finally, it has been demonstrated that a percentage of normal T lymphocytes and malignant T lymphoblasts bear a receptor for the Fc portion of human immunoglobulin [37, 42]. Moretta and his colleagues have shown that a proportion of T lymphocytes possess a receptor for the Fc portion of IgG and the remaining T lymphocytes possess a receptor for the Fc portion of IgM [35]. These Fc receptors have been correlated with T cell functions [36], although the Fc phenotype on the T cell has been shown tc be altered by cellular activation [41]. While these surface markers have provided strong evidence for the existence of human T cell subsets, they have not yet permitted the delineation of clinically relevant subgroups of T cell ALL.

In addition to the evidence for T lymphoblast heterogeneity provided by cell surface markers, attempts to demonstrate functional T cell heterogeneity were undertaken. It has been shown that the T lymphoblasts from a very small minority of patients with T cell ALL retain the functional capacities of normal T cells. Broder and his colleagues reported a single patient whose malignant T lymphoblasts could suppress the in vitro synthesis of antibody [6]. Saxon et al. have reported a patient with ataxia telangectasia who developed T cell ALL, and it was demonstrated in vitro that the T lymphoblasts in this patient possessed both suppressor and helper cell functions [53]. This evidence for functionally competent malignant T lymphoblasts in T cell ALL further suggests that both helper and suppressor cell lineages exist in the T cell lymphoblastic malignancies.

Another approach to elucidate the cellular origin of the malignant T lymphoblast is the development of heteroantisera specific for normal human T lymphocytes and malignant T lymphoblasts. Antisera directed against normal human peripheral blood T lymphocytes, thymocytes, and malignant T lymphocytes have provided insight into the cellular origins of the T cell malignancies. An early T cell antiserum developed in our laboratory was prepared against human T lymphoblasts [54]. After absorption with human erythrocytes, fetal hepatocytes, and CLL cells, this antiserum reacted with all normal human thymocytes and the tumor cells from patients with E rosette-positive, Ia antigen-negative leukemia. A similar antiserum with reactivity against thymocytes, T cell lines, and T lymphoblasts was prepared by Chechik et al. by immunizing with thymocytes [10]. These antisera provided the first serologic evidence that the T cell lymphoblastic malignancies were of thymic origin. With these initial observations, several laboratories attempted to identify T cell subset-specific differentiation antigens by immunizations with several different T cell tissues. Borella et al. [5] developed antisera against human thymus, E rosette-positive ALL, E rosette-negative ALL, and fetal brain tissue. Tumor cells from patients with T cell (E^+) ALL reacted with the anti-thymocyte and anti-T-ALL antisera, but did not react with the E rosette-negative ALL antiserum. This approach was further extended by Boumsell and her colleagues, who prepared 11 antisera against various human normal and malignant T cells [L Boumsell et al., in Press, J.I.]. Antigens included Sézary cells, T cell ALL, T lymphoblastic lymphoma cells, T cell CLL cells, and fetal and adult thymocytes. These antisera defined phenotypic subsets of normal and malignant T lymphocytes and provided further evidence for T cell heterogeneity.

Over the last several years, considerable evidence has been accumulated in our laboratory supporting the notion of functional T cell heterogeneity defined by cell surface markers in human systems. One subset-specific heteroantiserum termed TH_2 was developed by immunizing with human peripheral blood T lymphocytes [14]. The TH_2 antiserum was reactive with 20% of peripheral blood

lymphocytes and 80% of human thymocytes. Correlation of the TH_2 phenotype of peripheral blood T lymphocytes with functional T cell subsets was then undertaken. In vitro functional experiments demonstrate that in peripheral blood the TH_2 reactive cells contain both the cytotoxic effector and suppressor cell populations [16, 44]. In contrast, the majority of peripheral blood T lymphocytes are TH_2-unreactive, and functionally they represent the helper cell and feedback regulatory populations [46]. Unlike other T cell markers, the TH_2 antigen is phenotypically stable and is unaltered by cellular activation.

Within the T cell lymphoblastic malignancies, two clinical entities have been described [23, 31, 38, 39, 50]. T cell ALL and lymphoblastic lymphoma (LL) appear at presentation to be clinically identical, except that the bone marrow is uninvolved in LL. Classically, these patients with LL rapidly progressed to a leukemic picture indistinguishable from that of T cell ALL. However, it has recently been reported that survival is significantly longer in patients with LL than in T-ALL patients treated with similar therapeutic strategies [52, 61]. The difference in survival between T-ALL and LL suggests that there might be distinct biologic differences between these T lymphoblasts. With the clinical and phenotypic evidence for heterogeneity in T cell lymphoblastic malignancies, the TH_2 antiserum was employed to determine the lineage of these malignant T lymphoblasts.

In recent studies, we have reported the TH_2 phenotype of the malignant T lymphoblast in patients with T cell ALL and patients with LL [43; L Nadler et al., in Press, Blood]. The T cell origin of these diseases was confirmed by reactivity of the tumor cells with sheep erythrocytes, specific T cell heteroantisera, the presence of terminal transferase, and the lack of surface immunoglobulin, Ia, and the common ALL antigen. All tumor cells were either TH_2-reactive or TH_2-unreactive. The majority of patients (21 of 26) with T cell ALL were TH_2-unreactive and the majority of patients (7 of 9) with LL were TH_2-reactive. The heterogeneity of the TH_2 phenotype in these diseases suggests that the malignant lymphoblasts in these diseases were derived from different T cell subpopulations.

Correlation of the TH_2 phenotype with the clinical presentation provides further confirmation that the TH_2 antigen divides these diseases into clinically relevant subgroups. For example, T-ALL patients possessing predominantly TH_2^- tumor cells present with the major tumor burden involving bone marrow, lymph node, and spleen. Although the majority of these patients had mediastinal masses, they tended to be smaller and they did not lead to clinical symptoms. In contrast, patients with LL possess predominantly TH_2^+ tumor cells, and presented with respiratory symptoms due to markedly enlarged mediastinal masses and pleural effusions. The subgroup of patients with TH_2^+ T-ALL presented with a different clinical picture. Unlike all other subgroups, these patients were largely female children lacking a mediastinal mass. It was this group of patients that had the very high white blood cell count and severe anemia. It is crucial to emphasize that with small numbers of patients, no definitive clinicopathologic subgroup is suggested by these data. However, the heterogeneity noted suggests that distinct clinical entities will eventually be described. Similarly, although it is too early to correlate the TH_2 phenotype definitively with survival, suggestive trends have appeared. The majority of patients with TH_2^- T-ALL have poor prognoses. In contrast, the majority of patients with LL have TH_2^+ lymphoblasts and have long disease-free survivals. In addition, a subgroup of patients with T-ALL are TH_2^+, and they also appear to have a prolonged disease-free interval. These preliminary data suggest that the TH_2 phenotype of the malignant lymphoblast may correlate with the response to therapy and therefore the disease-free interval.

The evaluation of the TH_2 phenotype on the surface of the malignant T lymphoblast has provided the first evidence that the determination of the T cell subset lineage leads to clinically relevant data. However, the TH_2 antigen is only a single differentiation antigen. To further our understanding of normal and malignant T cell heterogeneity, new, functionally defined differentiation antigens have been sought. The development by Milstein and his colleagues of the technique of somatic cell hybridization producing monoclonal antibodies has begun to provide unique new antisera to subsets of human lymphoid cells [1, 29, 58]. A human thymus-specific antigen has recently been reported by McMichael [32]. In our laboratory, efforts are directed at defining functionally relevant subgroups of T lymphocytes by means of hybridoma antibodies [30, 45, 47, 48]. Unlike conventional antisera, these monoclonal antibodies define a single determinant on a cell. Moreover, they possess titers in excess of 1 : 100,000 and the hybrid line is immortal. Standardization of cell surface phenotyping by monoclonal antibodies is a major advance that will shortly be achieved. In preliminary experiments, these monoclonal antibodies have been used to define the phenotype of the malignant T lymphoblast [EL Reinherz et al., in Press, P.N.A.S.]. These experiments demonstrate that antisera which react with immature thymocytes are present on 12 patients with T cell ALL. Antisera that define more mature T lymphocytes are unreactive with T lymphoblasts. These preliminary experiments suggest that further heterogeneity of T cell ALL exists, and that understanding of the clinical presentation and course of the T lymphoblastic malignancies has only begun. Moreover, the biologic heterogeneity defined in the T cell leukemias and lymphomas will clearly be reflected in their sensitivity to chemotherapy and immunotherapeutic manipulations.

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