IL-2 Receptor Expression in Human Lymphoid Lesions

Immunohistochemical Study of 166 Cases

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Interleukin-2 (IL-2) receptor expression is a feature of T-cell activation and T-cell neoplasia. Expression of the IL-2 receptor in human lymphoid lesions was studied in a series of 166 immunophenotyped cases, including nodal and extranodal reactive lymphoid proliferations (44 cases), low-grade B-cell lymphomas (27 cases), intermediate and high grade B cell lymphomas (42 cases), peripheral T-cell lymphomas (13 cases), Hodgkin's disease (12 cases), histiocytic proliferations (15 cases), nonhematopoietic tumors (16 cases), and miscellaneous lesions (7 cases). Low levels of receptor expression were seen in reactive lymphoid lesions, low-grade B-cell lymphomas, and nonhematopoietic tumors (20%, 7%, and 25% of cases, respectively, with greater than 10% positive cells). High levels of receptor expression were seen in cases of peripheral T-cell lymphoma and histiocytic proliferations (86% and 100% of cases, respectively, with greater than 10% positive cells). Intermediate levels of expression were seen in Hodgkin's disease (including Reed–Sternberg cells) and some cases of intermediate and high-grade B-cell lymphomas (58% and 50% of cases, respectively, with greater than 10% positive cells). IL-2 receptor expression is not confined to T-cell neoplasia, but is also a feature of neoplastic and nonneoplastic histiocytic proliferations, Hodgkin's disease, and some intermediate and high-grade B-cell lymphomas. Biologic and therapeutic implications are discussed. (Am J Pathol 1987, 126:506–512)

INTERLEUKIN-2 (IL-2, T-cell growth factor) is a T-cell–derived lymphokine that stimulates the growth of T cells by interaction with a specific cell surface receptor.[1,2] The IL-2 receptor is a 55,000 molecular weight glycoprotein that is expressed on lectin or antigen stimulated T cells, but not on resting T cells.[2,3] IL-2 receptor is expressed on the neoplastic T cells of adult T-cell lymphoma-leukemia (ATL) associated with HTLV-I infection and on HTLV-I–infected cell lines.[4] IL-2 and its receptor play a central role in T-cell activation and possibly T-cell neoplasia. The development of monoclonal antibodies that specifically bind to the IL-2 receptor (anti-Tac) make possible studies of the cellular distribution of the IL-2 receptor.[5,6]Although initially thought to be confined to T lymphocytes, subsequent studies have demonstrated expression on some activated B lymphocytes[7,8] and on cells of monocyte-macrophage lineage.[9]

In an effort to define the role of expression of IL-2 receptors in human lymphoproliferative disorders, we studied a series of 166 cases of various neoplastic and nonneoplastic lesions, utilizing a monoclonal antibody immunohistochemical assay for the IL-2 receptor on frozen tissue. The cases studied represented a broad spectrum of lesions, including reactive nodal lymphoid proliferations, 21 cases; reactive extranodal lymphoid proliferations, 23 cases; non-Hodgkin's lymphoma of low-grade B-cell types, 27 cases; non-Hodgkin's lymphoma of intermediate and high-grade B-cell types, 42 cases; non-Hodgkin's lymphoma of peripheral T-cell types, 13 cases; Hodgkin's disease, 12 cases; histiocytic proliferations, 5 cases; miscellaneous lesions, 7 cases; and nonhematopoietic tumors, 16 cases. All cases were fully immunophenotyped. The results indicate that IL-2 receptor expression is

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present in a variety of human lymphoid proliferations, including T-cell lymphomas, neoplastic and nonneoplastic histiocytic proliferations, Hodgkin's disease, and some intermediate and high-grade B-cell lymphomas. IL-2 receptor expression may play a role in a wider variety of lymphoproliferative disorders than previously appreciated.

Materials and Methods

Tissue

Tissue was obtained at surgical biopsy (164 cases) or autopsy (2 cases). Tissue for histology was fixed in 10% neutral buffered formalin and processed for paraffin embedding. Tissue for IL-2 receptor study and immunophenotyping was snap-frozen and stored at −70 C.

IL-2 Receptor Study

IL-2 receptor expression was assayed by an immunohistochemical method on acetone-fixed frozen sections, utilizing the monoclonal antibody IL-2-R1 (Coulter Immunology, Hialeah, FL) and the avidin–biotin peroxidase technique.[10] Sections were lightly stained with hematoxylin for cellular identification. Sections were examined without knowledge of the histologic diagnosis or results of immunophenotyping. IL-2 receptor expression was graded as follows: 0, no reactive cells; +, few reactive cells (less than 10%); ++, 10–50% reactive cells; +++, greater than 50% reactive cells.

Immunophenotypic Analysis

Immunophenotyping was performed on frozen sections by a standard immunohistochemical method utilizing the avidin-biotin-peroxidase technique.[10] Monoclonal antibodies utilized were Leu 1 (pan-T), Leu 4 (pan-T), and anti-immunoglobulins IgM, kappa and lambda (Becton-Dickinson, Mountain View, Calif); S-34 (HLA-DR) and MoS-1, (monocyte-macrophage) (courtesy of Dr. Alexandra Dimitriu-Bona, New York, NY); and B1 (pan-B) and T11 (pan-T) (Coulter Immunology, Hialeah, Fla).

Table 1 — Lesions Studied

Reactive lymphoid proliferations, nodal		21
Reactive hyperplasia	11	
Atypical hyperplasia	3	
AIDS or ARC*	4	
Necrotizing lymphadenitis	2	
Dermatopathic lymphadenitis	1	
Reactive lymphoid proliferations, extranodal		23
Skin	6	
Gastrointestinal	7	
Breast	3	
Lung	2	
Parotid	3	
Kidney	1	
Paranasal sinus	1	
Low-grade B-cell lymphoma		27
Small lymphocytic	10	
Follicular, small cleaved cell	8	
Follicular, mixed small cleaved and large cell	9	
Intermediate and high-grade B-cell lymphoma		42
Diffuse, small cleaved cell	4	
Diffuse, mixed small and large cell	8	
Diffuse, large cell	23	
Immunoblastic	6	
Undifferentiated	1	
T-cell lymphoma		13
Diffuse, mixed	4	
Diffuse, mixed, high content of epithelioid histiocytes	2	
Immunoblastic	5	
Adult T-cell lymphoma/leukemia	1	
Cutaneous T-cell lymphoma	1	
Hodgkin's disease		12
Histiocytic proliferations		5
True histiocytic lymphoma	1	
Granulomatous disease (sarcoid, toxoplasmosis, atypical mycobacteriosis)	3	
Fibrous histiocytoma	1	
Miscellaneous lesions		7
Null cell lymphoma	3	
Castleman disease	2	
Thymoma	1	
Extramedullary plasmacytoma	1	
Nonhematopoietic tumors		16
Metastatic melanoma	3	
Metastatic carcinoma	3	
Neuroblastoma	1	
Ewing's tumor	1	
Soft-tissue sarcoma	6	
Benign soft-tissue tumors	2	

*Acquired immunodificiency syndrome or AIDS-related complex.

Results

Reactive Lymphoid Proliferations, Nodal and Extranodal

Forty-four reactive lymphoid proliferations were identified, 21 nodal and 23 extranodal (Table 1). All were polyclonal by immunophenotypic analysis. The proportion of cells staining for IL-2 receptor ranged from 0 to less than 50% (Table 2). Thirty-five of 44 cases demonstrated fewer than 10% positive cells. No case had greater than 50% positive cells. In nodal lesions, positive cells were scattered predominantly in the paracortex with a few positive cells in the germinal centers. Positive cells had the morphology of small or large lymphocytes; occasional positive histiocytelike cells were also noted.

Table 2—IL-2 Receptor Expression

Lesion*	% IL-2 receptor staining cells†				Total cases
	0	<10	10–50	>50	
Reactive lymphoid proliferation, nodal	4	10	7	0	21
Reactive lymphoid proliferation, extranodal	4	17	2	0	23
B-cell lymphoma, low-grade	5	20	2	0	27
B-cell lymphoma, intermediate and high grade	9	12	18	3	42
T-cell lymphoma	0	2	4	7	13
Hodgkin's disease	1	4	5	2	12
Histiocytic proliferations	0	0	2	3	5
Miscellaneous lesions	1	4	2	0	7
Nonhematopoietic tumors	7	5	4	0	16

*See Table 1 for details of lesions studied.
†Number of cases in each category.

Non-Hodgkin's Lymphoma, Low-Grade B-Cell Types

Twenty-seven non-Hodgkin's lymphomas of low grade B cell type were identified, including small lymphocytic, 10; follicular small cleaved cell, 8; and follicular mixed small cleaved and large cell, 9 (Table 1). The proportion of cells staining for IL-2 receptor ranged from 0 to less than 50%. Twenty-five of 27 cases demonstrated fewer than 10% positive cells. Only 2 cases demonstrated more than 10% positive cells. In the follicular lymphomas, the positive cells were predominantly interfollicular in distribution; in the small lymphocytic lymphomas, the positive cells were scattered. In all types of low-grade B-cell lymphomas, the distribution of IL-2 receptor-positive cells appeared similar to that of admixed T cells, rather than the neoplastic B lymphocytes.

Non-Hodgkin's Lymphoma, Intermediate and High-Grade B-Cell Types

Forty-two non-Hodgkin's lymphomas of intermediate and high-grade B-cell type were identified, including diffuse small cleaved cell, 4; diffuse mixed small and large cells, 8; diffuse large cell, 23; large cell immunoblastic, 6; and undifferentiated, 1. The lymphoma cells in all cases were of B-cell origin, as evidenced by monoclonal immunoglobulin and/or reactivity with pan-B-cell monoclonal antibodies. The proportion of cells staining for IL-2 receptor ranged from 0 to greater than 50%, 21 of 42 cases demonstrating greater than 10% positive cells and 3 cases, greater than 50%. In contrast to the low-grade B-cell lymphomas, staining of both tumor cells and reactive cells was observed (Figure 1).

Non-Hodgkin's Lymphoma of T-Cell Type

Thirteen cases of non-Hodgkin's lymphoma of T-cell type were identified. The histologic types included diffuse mixed small and large cell, 4; diffuse mixed small and large cell with high content of epithelioid histiocytes (Lennert), 2; large cell immunoblastic, 5; adult T cell lymphoma-leukemia, 1; and cutaneous T-cell lymphoma, 1. All cases demonstrated expression of one or more pan-T-cell antigens on immunophenotyping. The proportion of cells staining for IL-2 receptor ranged from fewer than 10% to greater than 50%. Eleven of 13 cases demonstrated greater than 10% positive cells, and 4 of 13 cases demonstrated greater than 50% positive cells. Staining of both neoplastic lymphocytes and admixed histiocyte-like cells was observed.

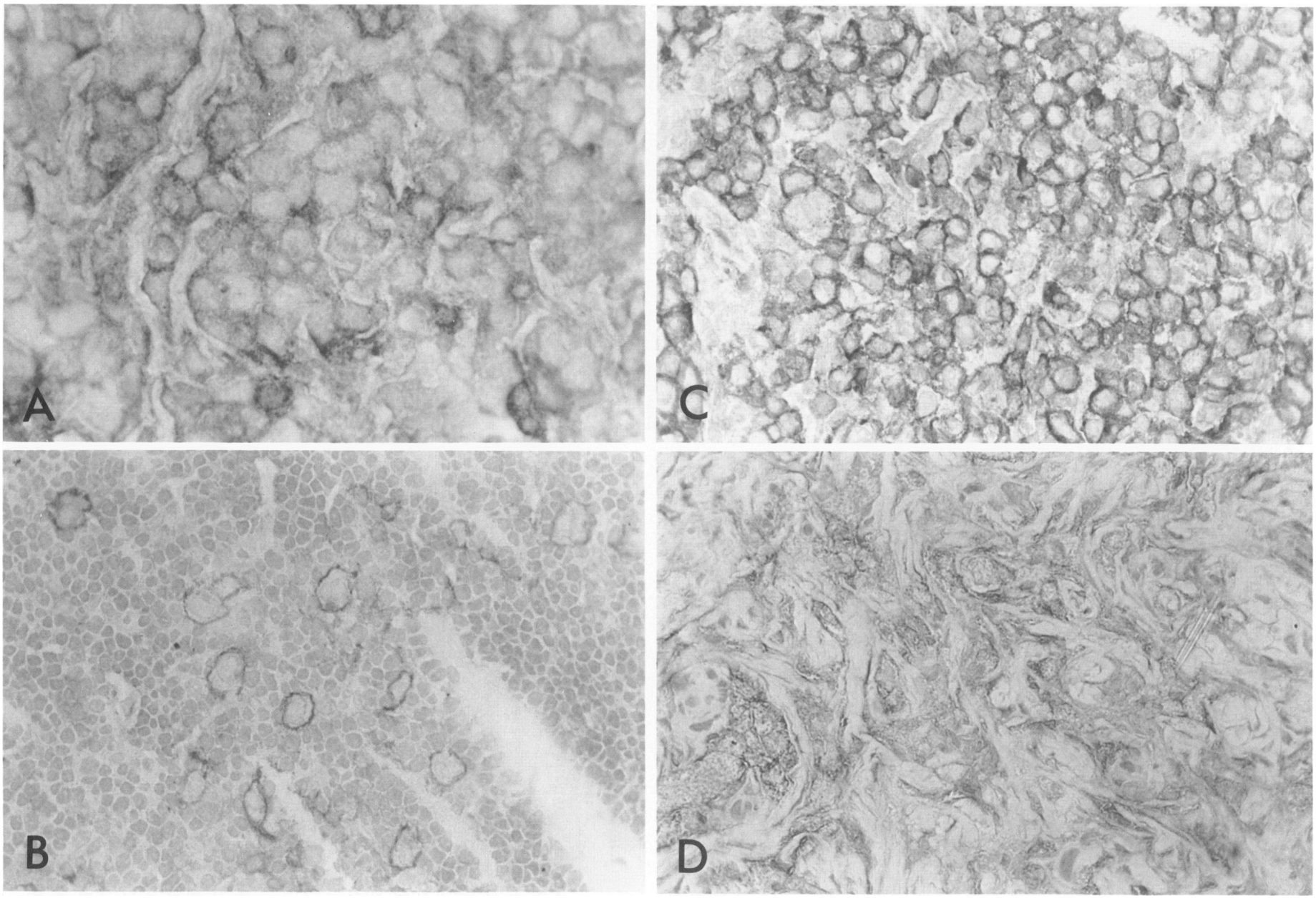
Hodgkin's Disease

Twelve cases of Hodgkin's disease were identified. The proportion of cells staining for IL-2 receptor ranged from 0 to greater than 50%. Seven of 12 cases demonstrated greater than 10% positive cells. A single case did not demonstrate staining. Reed–Sternberg cells and mononuclear Reed–Sternberg-like cells stained strongly (Figure 1). Scattered lymphocytes and histiocyte-like cells were also stained in most cases.

Histiocytic Proliferation

A variety of neoplastic and nonneoplastic histiocytic proliferations were studied, including "true" histiocytic lymphoma, 1; granulomatous disease, 3 (sarcoidosis, 1; toxoplasmosis, 1; atypical mycobacterial

Figure 1—Lymphoid lesions stained for IL-2 receptor expression with the monoclonal antibody IL-2 R1. (Avidin–biotin peroxidase, counterstained with hematoxylin). **A**—Non-Hodgkin's lymphoma, high-grade B-cell (large cell immunoblastic) showing staining of neoplastic cells. (×400) **B**—Hodgkin's disease showing staining of Reed–Sternberg cells. (×250) **C**—True histiocytic lymphoma showing intense staining of neoplastic histiocytes. (×250) **D**—Fibrous histiocytoma of the skin showing staining of storiform spindle cells. (×250)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disease, 1); and a fibrous histiocytoma of the skin. The cells in all cases demonstrated reactivity with monoclonal antibodies to monocyte-macrophage restricted antigens (MoS-1). The proportion of cells staining for IL-2 receptor ranged from less than 50% to nearly 100%. All 5 cases of histiocytic proliferations demonstrated greater than 10% positive cells, and 3 of 5 cases demonstrated greater than 50% positive cells. The case of "true" histiocytic lymphoma demonstrated the most intense staining observed in this series (Figure 1). Immunophenotyping of this case demonstrated reactively with monoclonal antibodies to monocyte-macrophage restricted antigens but not pan-T-cell antigens. Erythrophagocytosis was also present. Staining of the fibrous histiocytoma of the skin was also striking, with intense staining of the storiform spindle cells (Figure 1).

Miscellaneous Lesions

A number of other lymphoproliferative disorders were studied, including maignant lymphomas of null cell phenotype, 3 (large cell, 2; diffuse small cleaved cell, 1); Castleman's lesion, 2; a thymoma; and an extramedullary plasmacytoma. No consistent pattern of IL-2 receptor expression was observed.

Nonhematopoietic Tumors

A series of 16 nonhematopoietic tumors were also studied, including metastatic malignant melanoma, 3: metastatic carcinoma, 3; metastatic neuroblastoma, 1; metastatic Ewing's tumor, 1; malignant soft tissue tumors, 6; and benign soft tissue tumors, 2. IL-2 receptor expression was confined to admixed reactive inflammatory cells; in no case was staining of tumor cells observed. The proportion of cells staining for IL-2 receptor ranged from 0 to less than 50%. Twelve of 16 cases demonstrated fewer than 10% positive cells.

Discussion

Interleukin 2 (IL-2) and its receptor have been identified as a central mechanism in physiologic T-cell activation and proliferation.[1-3] Antigen or mitogen activation of normal T cells results in both secretion of IL-2 and expression of a specific cell surface receptor for IL-2 binding. Expression of the IL-2 receptor has also been identified on neoplastic T cells in adult T-cell leukemia-lymphoma associated with HTLV-I infection. IL-2 receptor expression in this neoplasm is independent of normal physiologic stimuli and at continuously high levels, suggesting a role in maintenance of the neoplastic phenotype.[4] IL-2 receptor expression has subsequently been found not to be limited to T lymphocytes, but to occur on other activated mononuclear cell populations, including staphylococcal or poke weed mitogen-activated normal B cells,[7,8] B-cell lines derived from Burkitt's lymphoma or carrying the Ebstein–Barr or HTLV-I genome,[3] and the cells of hairy-cell leukemia.[11] Activated cells of monocyte-macrophage lineage and the Reed–Sternberg cells of Hodgkin's disease have also been reported to express the IL-2 receptor.[9,12]

The development of monoclonal antibodies to the IL-2 receptor makes possible immunohistologic study of IL-2 receptor expression.[5,6] In order to better define the role of IL-2 receptor expression in human pathologic lymphoid proliferations, we studied a series of 166 cases, using an immunohistochemical assay for IL-2 receptor expression in frozen sections. The monoclonal antibody, anti-IL-2-R1 (Coulter Immunology, Hileah, Fla), specific for the IL-2 receptor glycoprotein, was utilized. Complete immunophenotyping with a panel of monoclonal antibodies was also performed on each case. A spectrum of lesions was studied, including reactive nodal and extranodal lymphoid proliferations, low-grade B-cell lymphomas, intermediate and high-grade B-cell lymphomas, T-cell lymphoma, Hodgkin's disease, histiocytic proliferations, nonhematopoietic neoplasms, and miscellaneous lesions (Table 1).

IL-2 receptor expression was evaluated semiquantitatively (Tables 2 and 3). Low levels of receptor expression (<10% of positive cells in 75–93% of cases) were found in reactive lymphoid proliferations, low-grade B-cell non-Hodgkin's lymphoma, and nonhematopoietic neoplasms. Staining in these cases was confined to apparently reactive cells. The presence of reactive T lymphocytes in B-cell lymphoma and nonhematopoietic neoplasms is well established. The role

Table 3—Summary of IL-2 Receptor Expression

Low levels of receptor expression
Reactive lymphoid proliferations (0.20)*
Non-Hodgkin's lymphoma, low-grade B-cell (0.07)
Nonhematopoietic tumors (0.25)
Intermediate levels of receptor expression
Non-Hodgkin's lymphoma, intermediate and high-grade B-cell (0.50)
Hodgkin's disease (0.58)
High levels of receptor expression
Peripheral T-cell lymphoma (0.85)
Histiocytic proliferations, neoplastic and nonneoplastic (1.00)

*Fraction of cases with greater than 10% IL-2 receptor-positive cells.

of these cells is unclear; however, the expression of IL-2 receptor would indicate some degree of activation. The tumor cells in these cases appeared uniformly negative.

Intermediate levels of expression (>10% of positive cells in 50–58% of cases) were found in cases of intermediate and high-grade B-cell lymphoma and Hodgkin's disease. In contrast to low-grade B-cell non-Hodgkin's lymphoma, staining of morphologically recognizable neoplastic cells was observed in the intermediate and high-grade tumors. Staining of Reed–Sternberg cells and the related mononuclear cells of Hodgkin's disease was also observed, as previously reported by others.[9,12]

High levels of expression (>10% positive cells in 85–100% of cases) were observed in T-cell lymphomas and histiocytic proliferations. The T-cell lymphomas include a spectrum of peripheral T-cell neoplasms, including a case of adult T-cell leukemia lymphoma associated with HTLV-I. The histiocytic proliferations included neoplastic ("true" histiocytic lymphoma, fibrous histiocytoma) and nonneoplastic (granulomatous) lesions. The most intense staining observed in the entire series was observed in the case of "true" histiocytic lymphoma (Figure 1). This lesion demonstrated a monocyte-macrophage phenotype on immunophenotypic analysis. The fibrous histiocytoma and granulomatous lesions also stained strongly. The expression of IL-2 receptor on the epitheloid histiocytes of granulomas is of interest, because T lymphocytes appear to be important in granuloma formation.

Our data and earlier studies support the view that IL-2 receptors are expressed on a variety of activated and neoplastic cell types, including T cells, some B cells, and monocyte-macrophages. IL-2 production by activated T lymphocytes may have a broader function in the immune system than originally proposed with stimulation of activated B cells and monocyte-macrophages in addition to T cells. The precise physiologic role of the IL-2 receptor on B cells and monocyte-macrophages is not known.

The role of IL-2 receptor expression in lymphoid neoplasia is of major interest. In adult T-cell lymphoma-leukemia associated with HTLV-I, a high level of IL-2 receptor expression appears to be part of the neoplastic phenotype and may play a role in the unrestrained proliferation of these cells. Our observations suggest that IL-2 receptor expression may also play a role in other neoplasms, including some intermediate and high-grade B-cell lymphomas, histiocytic proliferations, T-cell lymphomas, and Hodgkin's disease. In contrast, IL-2 receptor expression does not appear to play a role in low-grade B-cell non-Hodgkin's lymphoma or the nonhematopoietic neoplasms studied.

The use of anti IL-2 as a diagnostic reagent in immunopathology appears limited. In most circumstances, the pattern of IL-2 receptor staining does not definitely distinguish reactive from neoplastic proliferations. Very high levels of IL-2 receptor expression (>50% of the cells), however, were seen only in neoplastic conditions (3 of 42 intermediate and high-grade B-cell lymphoma, 7 of 13 T-cell lymphoma, 2 of 12 Hodgkin's disease) and in histiocytic proliferations, both neoplastic and nonneoplastic (3 of 5).

There has been recent considerable interest in possible therapeutic application of IL-2 or antibody to the IL-2 receptor. The administration of monoclonal anti-IL-2 receptor (anti-Tac) has been attempted in adult T-cell lymphoma leukemia in which the neoplastic cells express IL-2 receptor at high levels. Transient response in two patients and a remission lasting 6 months in a third patient were observed.[3] The demonstration of IL-2 receptors on B-cell lymphomas, Hodgkin's disease, and histiocytic proliferations may broaden the applicability of this approach.

The physiologic significance of expression of IL-2 receptor-related proteins on non-T-cell neoplasms is unclear. Transfection of Tac cDNA into non-T cells results in expression of only low affinity, nonfunctional IL-2 binding sites, whereas transfection into T cells results in expression of both functional high-affinity as well as low-affinity sites.[13–16] Investigation of the affinity and functional characteristics of the IL-2 receptors expressed on non-T-cell neoplasms would therefore be of interest.

In summary, the expression of IL-2 receptors was studied in a spectrum of human lymphoid lesions. IL-2 receptor expression was found at low levels in reactive lymphoid lesions, low-grade B-cell lymphomas, and nonhematopoietic tumors. IL-2 receptor expression was found at intermediate levels in intermediate and high-grade B-cell lymphoma and Hodgkin's disease. IL-2 receptor expression was found at high levels in T-cell lymphomas and histiocytic proliferations. IL-2 receptor expression may play a role in a variety of lymphoproliferative disorders.

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