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Application of a T Cell Receptor Antibody βF1 for Immunophenotypic Analysis of Malignant Lymphomas

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One hundred sixty-five non-Hodgkin's lymphomas (101 B, 63 T, one histiocytic) were immunostained with an antibody (βF1) reactive with a common framework determinant on the β-subunit of the T cell receptor (TCR). βF1 stained T lymphomas exclusively, including 53% of peripheral T cell lymphomas but only 33% of T lymphoblastic lymphomas. When expression of βF1 and CD3 were considered together, 4 types of T lymphoma were delineated: 1) βF1+CD3+; 2) βF1+CD3−; 3) βF1−CD3+, and 4) βF1−CD3−. The first represented lymphomas with classical T immunophenotype. The second might represent T lymphomas with aberrant loss of CD3 expression. The third might represent T lymphomas with a putative second TCR or cases with an immature phenotype expressing cytoplasmic CD3 only. The fourth type included cases that may be derived from natural killer cells instead of T cells, cases of T lymphoma with aberrant loss of both βF1 and CD3, and some cases of immature T cell (lymphoblastic) lymphoma. βF1−CD3− lymphomas exhibited a remarkable predilection for the nasal region. βF1 is useful in studying T cell lymphomas and distinguishing a novel immunophenotype frequently expressed by nasal lymphomas. (Am J Pathol 1988, 132: 365–371)

THE DEMONSTRATION OF surface markers using leucocyte monoclonal antibodies has contributed significantly to the study of malignant lymphomas. The diagnosis of T cell lymphomas can sometimes be difficult, however, because of the lack of markers for monoclonality and the cross-reactivity of some "T cell markers" with cells of other lineages.[1-6] The problem is compounded further by the frequent loss of one or more T cell markers and the occasional expression of natural killer (NK) cell markers in peripheral T cell lymphomas, particularly those of the nasal region.[7-15] The exact lineage of lymphoid malignancies expressing both T cell and NK cell markers is still unsettled.[16-21]

The T cell receptor (TCR) is a heterodimer of covalently linked alpha and beta chains, and is closely associated with the CD3 molecule on the T cell surface.[22-24] It occurs in the vast majority of T lymphocytes, and can serve as a specific marker of cell differentiation.[22,23,25,26] In this study, 165 cases of malignant lymphoma were stained with an anti-αβ TCR antibody (βF1)[14,27-28] and 2 CD3 antibodies, among others. The aim was to study the value of βF1 in diagnosing T lymphomas and in revealing their immunophenotypic heterogeneity. It was also hoped that βF1 might help to clarify the nature of the many T cell lymphomas of the nasal region that lacked CD3.[12,13,15]

Materials and Methods

Tissues

Fresh tissues from 165 cases of non-Hodgkin's lymphoma obtained from the Department of Morbid Anatomy, Prince of Wales Hospital and Institute of Pathology, Queen Elizabeth Hospital, Hong Kong, were studied. Part of the tissue was fixed in neutral

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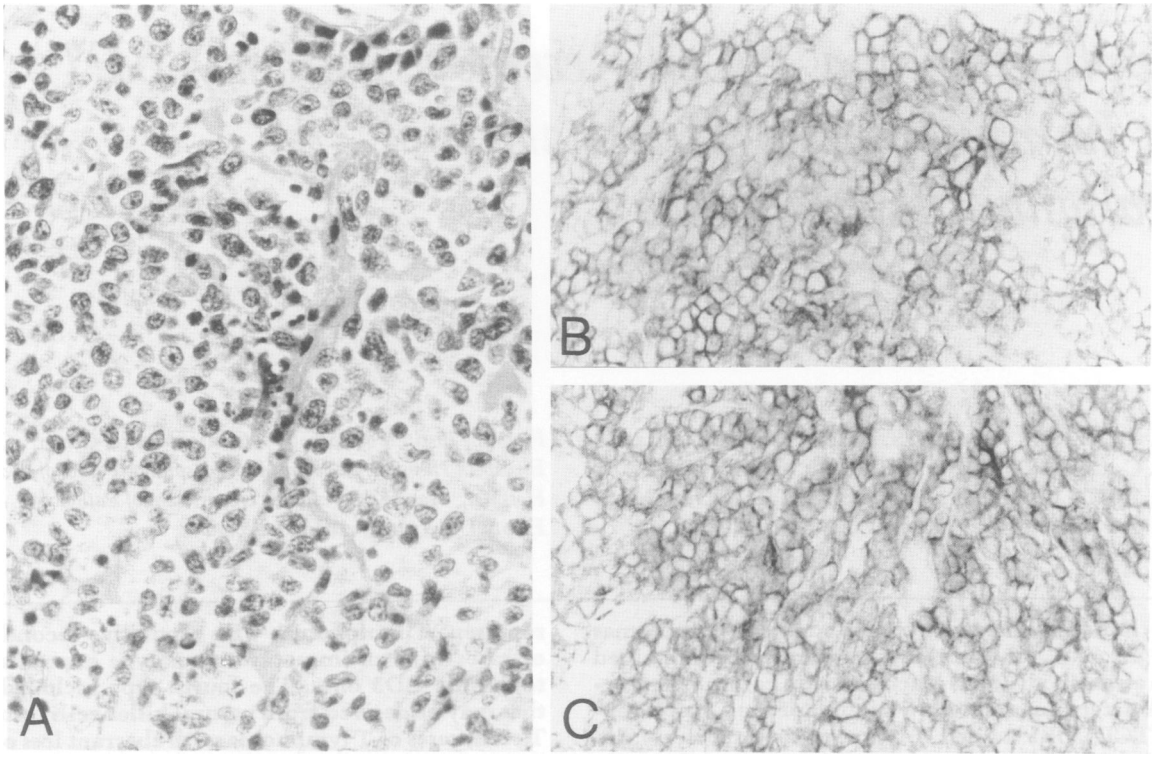

Figure 1—Peripheral T cell lymphoma of the skin. **A**—The infiltrate consists of medium-sized cells possessing round, indented to elongated nuclei with dense chromatin and small nucleoli. Vascularity is rich. (H&E, ×400) **B,C**—Membrane staining with βF1 and Leu4 (anti-CD3) respectively. (ABC immunoperoxidase, ×200)

buffered formalin and processed for paraffin blocks. Four-micron sections were cut and stained with hematoxylin and eosin (H&E). The rest was snap frozen in liquid nitrogen (−170 C) and stored at −70 C for subsequent immunohistochemical staining.

Monoclonal Antibodies

βF1 was obtained from T cell Sciences, Inc, Cambridge, MA. It is a murine IgG1/Kappa monoclonal antibody that reacts with a common framework determinant on the TCR β-subunit, and recognizes the αβ TCR complex. The derivation and characterization of βF1 have been described.[27,28] A wide panel of leucocyte monoclonal antibodies was also used as described previously,[5,10,12,13] with the addition of anti-Leu4 (CD3) obtained from Becton Dickinson (Mountainview, CA) and anti-T2 (CD7) from Dakopatts (Copenhagen, Denmark).

Immunohistochemical Staining

Six-micron sections were immunostained with the antibodies using the avidin-biotin-peroxidase complex (ABC) technique.[29] Counterstaining with hematoxylin or methyl green was performed as deemed necessary.

The lymphoma was considered to express the immunologic marker when more than half of the neoplastic cells showed membrane staining (Figure 1). B lymphomas were characterized by expression of one or more pan-B markers (CD19, CD20, CD22) and/or light chain restriction. The diagnosis of T lymphoma was made if the lymphoma cells expressed one or more T cell markers (CD2, CD3, CD4, CD7, CD8).

Results

There were 101 B lymphomas, 63 T lymphomas, and 1 true histiocytic malignancy (CD11+, CDw14+, EBM11+). Sixty-three percent of T lymphomas were extranodal, 27 cases of which occurred in the nasal region. With the exception of 6 cases of T lymphoblastic lymphoma, all T lymphomas were of the peripheral T cell type.[30-32]

The neoplastic cells of the B lymphomas and the single case of true histiocytic malignancy did not stain with βF1, while the scattered reactive small cells in the background did (Figure 2). βF1 stained 2 of the 6 cases of T lymphoblastic lymphoma and 30 (53%) of 57

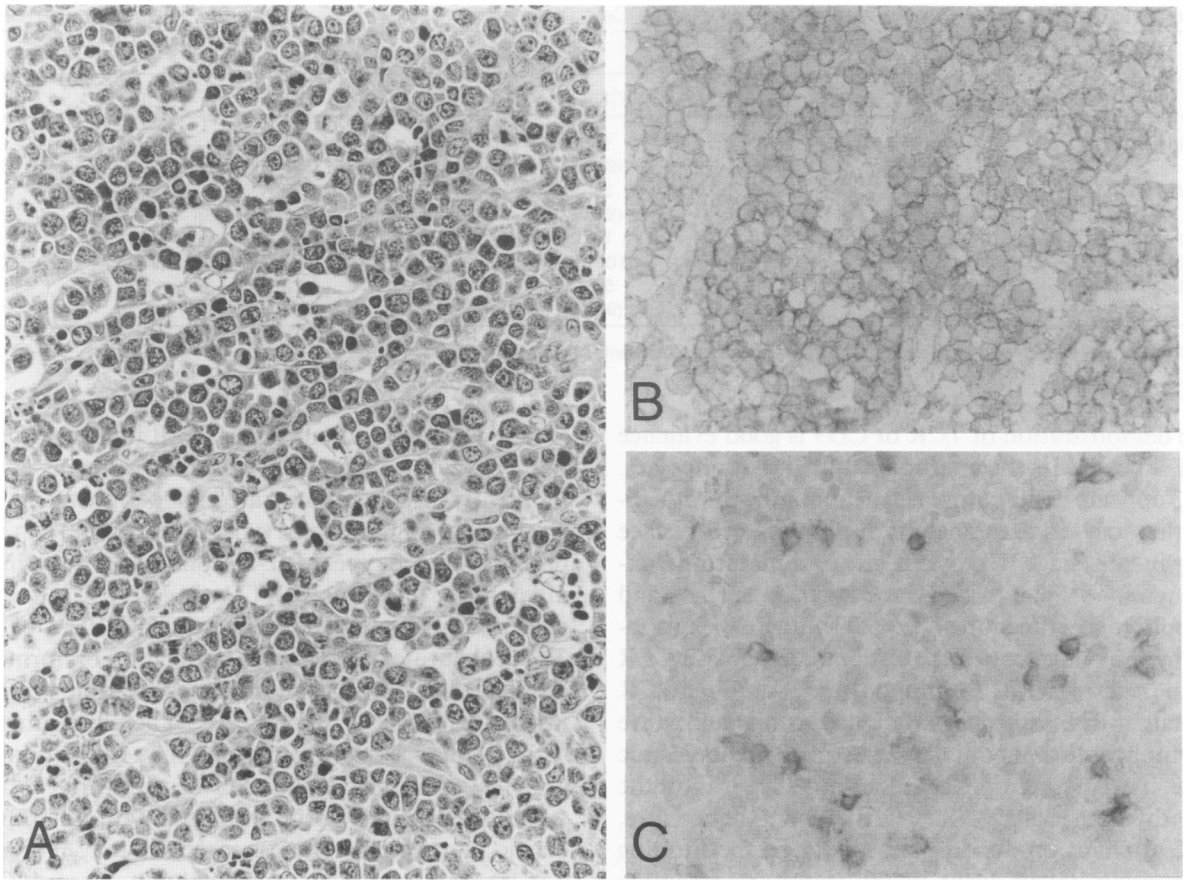

Figure 2—Burkittlike B cell lymphoma. **A**—Monotonous population of medium-sized cells with interspersed histiocytes. (H&E, ×150) **B**—Lymphoma cells show membrane staining with the CD19 antibody B4. (ABC immunoperoxidase, ×150) **C**—Lymphoma cells are not stained by βF1 while some reactive small lymphocytes are stained. (ABC immunoperoxidase, ×150)

cases of peripheral T cell lymphoma (Tables 1 and 2, Figure 1). Among the βF1-negative T lymphoblastic lymphomas, 1 had the phenotype of a mature thymocyte (case 3), while another had the phenotype of a primitive T lymphoblast (case 4). Two other βF1-negative cases had aberrant T phenotypes not corresponding to that of normal thymocytes (cases 5 and 6). For peripheral T cell lymphomas, βF1 was demonstrated more frequently in the nonnasal (80%) than nasal (22%) area. Similar to βF1, CD3 was expressed more frequently in nonnasal (80%) than in nasal (33%) T lymphomas. The difference was more striking between nasal and nodal lymphomas. There was no discrepancy in expression of CD3 antigen as determined by anti-T3 and anti-Leu4, except in 9 cases, that were T3-Leu4+. It could not be determined with certainty in most cryostat sections whether the CD3 staining was on the cell surface, in the cytoplasm, or both, because the rim of cytoplasm was often thin. In cases with more cytoplasm, the staining was on the cell membrane.

When the expression of βF1 and CD3 were considered together, 4 types of peripheral T cell lymphoma could be delineated (Table 3). Type I expressed both βF1 and CD3. Most lymphomas of this type did not express NK markers (NKH1 and/or Leull/CD16). Type II expressed βF1 but not CD3, and the single case of this type did not express NK markers. Type III expressed CD3 but not βF1; 2 of the 4 cases expressed NK markers. Type IV expressed neither βF1 nor CD3. Many of the nasal lymphomas belonged to this type, and also expressed NK markers.

Discussion

TCR is closely associated with the CD3 molecule, and acts as a receptor for antigen recognition.[22-24,26,33]

Table 1—βF1 Expression and Immunophenotypes of 6T Lymphoblastic Lymphomas

Case	βF1	CD3	CD1	CD2	CD4	CD5	CD7	CD8
1	+	+	+	+	+	+	+	+
2	+	+	+	+	+	+	+	−
3	−	+	+	+	+	+	+	+
4	−	−	−	−	−	−	+	−
5	−	+	−	−	−	+	−	−
6	−	+	−	+	−	−	+	−

Table 2—Expression of T Cell Antigens and TCR in Peripheral T Cell Lymphomas

	Number (%) of positive cases						
	βF1	CD3*	CD2	CD4	CD5	CD7	CD8
Nodal (N = 18)	17 (94%)	16 (89%)	17 (94%)	17 (94%)	10 (56%)	4/17 (24%)	2 (11%)
Nasal (N = 27)	6 (22%)	9 (33%)	24 (89%)	14 (52%)	5 (19%)	3/22 (14%)	– (0%)
Other extranodal sites (N = 12)	7 (58%)	8 (67%)	12 (100%)	6 (50%)	7 (58%)	4/11 (36%)	4 (33%)
Total (N = 57)	30 (53%)	33 (58%)	53 (93%)	37 (65%)	22 (39%)	11/50 (22%)	6 (11%)

* CD3 positivity was defined by positive staining of neoplastic cells with anti-T3 and/or anti-Leu4.

The demonstration of TCR or CD3 is good evidence of T lineage. In the maturation of T lymphocytes, CD3 appears in the cytoplasm at about the intermediate thymocyte stage (stage II), but on the cell surface only in late (stage III) thymocytes and mature T lymphocytes.[34–36] The discordance between surface and cytoplasmic expression of the CD3 antigen is explanable by the obligatory coexpression of CD3 with TCR on the cell surface of T lymphocytes.[37] Although TCR β-chain mRNA appears in the cytoplasm of immature T lymphocytes at about the same time as cytoplasmic CD3, TCR α-chain mRNA does not appear until the late thymocyte stage (Stage III).[34,35,38,39] Therefore, TCR α-chain production appears to be the limiting maturation-linked event in the transport, assembly and cell surface membrane insertion of the TCR-CD3 complex.[36]

Though antibodies to TCR have been quite used widely for the immunologic study of T cells,[26,34,40–42] they have not been used widely to characterize lymphoproliferative diseases.[14,19,27,43] Recently, 3 monoclonal antibodies, βF1, βF2, and WT31, were compared for the immunohistochemical study of malignant lymphoid cells, and βF1 was found to give the best results.[28] In the present study, βF1 was evaluated on a large number of malignant lymphomas including a group of nasal lymphoma with distinct immunophenotypes.

None of the B cell and histiocytic lymphomas expressed βF1, attesting the specificity of βF1 for determining the T cell lineage of a neoplasm.

There is normally an obligatory requirement for the coexpression of TCR and CD3.[34,37] In general, βF1 and CD3 are either both expressed or both absent in the peripheral T cell lymphomas. There are, however, some exceptions. Four types can therefore be delineated: βF1+CD3+ (type I), βF1+CD3− (Type II), βF1−CD3+ (type III) and βF1−CD3− (type IV). The first type has an immunophenotype corresponding to that of normal T lymphocytes, and NK markers are expressed only rarely. The second type (βF1+CD3−) is rare and shows an aberrant T cell immunophenotype, probably explanable by loss of antigens as has frequently been demonstrated in peripheral T cell lymphomas.[7–14] The third type (βF1−CD3+) can represent a novel type of T-lymphomas possessing a different TCR such as γδ-TCR or γγ′-TCR.[44–51] Cells expressing the putative second TCR instead of αβ-TCR constitute only a minor population of normal T lymphocytes, but may be increased in some primary immunodeficiency diseases.[49–50] Therefore, further study of this group of lymphomas may lead to a better understanding of the function of the minor TCRs. Another possibility to be discussed with T lymphoblastic lymphomas is that such cases may represent a more immature phenotype with cytoplasmic CD3 expression only.

The fourth type (βF1−CD3−) is noteworthy. Sixty-one percent of lymphomas of this type expresses 1 or more NK markers, and many occur in the nasal region, as demonstrated in the authors' previous study.[13] Recent studies[17,18,52] suggest that lymphocytes with NK-like activities (nonmajor histocompatibility-restricted cytoxicity) may include: 1) nonmajor histocompatibility-restricted cytotoxic T lymphocytes, which are CD3+NK+, and 2) true natural killer cells, which are CD3−NK+. The exact lineage of the NK cells remains unresolved, but cases of large granular lymphocyte proliferation with a similar phenotype of CD3−NK+ do not show rearrangement of the gene for the beta chain of TCR.[16–19,21] However, it is of interest that when purified normal natural killer cells (CD3− TCR− NK+) are cultured with interleukin-2, the majority of the cells become CD3+ TCR+ NK+,[19] although different results are observed in neoplastic large granular lymphocyte proliferations.[17,53] Whether these cases of βF1−CD3−NK+ lymphoma represent true T cell or NK cell neoplasms remains to be clarified (these cases have been provisionally designated "peripheral T cell lymphomas" in this study because of their expression of CD2 and/or CD4). The distinctive group of βF1−CD3−NK+ nasal lympho-

Table 3—Analysis of 4 Subtypes of Peripheral T Cell Lymphoma

		Nasal	Nodal	Other extranodal sites
Type I βF1+CD3+	NK+*	1	2	1
(N = 29)	NK−	5	14	6
Type II βF1+CD3−	NK+	−	−	−
(N = 1)	NK−	−	1	−
Type III βF1−CD3+	NK+	1	−	1
(N = 4)	NK−	2	−	−
Type IV βF1−CD3−	NK+	14	−	−
(N = 23)	NK−	4	1	4

* NK+, NKH1+Leu11+ or NKH1−Leu11+ or NKH1+Leu11−.

mas may serve as a good model for studying the relationship between T cells and NK cells. There are also some cases of βF1−CD3− peripheral T cell lymphoma that do not express NK markers, and they may represent lymphomas with aberrant loss of surface antigens.

Since T-beta gene rearrangement and expression occur later than CD7 expression in T cell development, βF1 may fail to react with early T cell neoplasms, as in the case that expresses only CD7.[54] In the present series, the 2 cases with a more mature immunophenotype express βF1, and 3 CD3+ cases are βF1−. The latter phenotype may be due to expression of a TCR other than αβ with CD3,[39,44–51] or sole expression of cytoplasmic CD3. The expression of CD3 in the cytoplasm corresponds to an early stage of T cell maturation.[34,35,55] However, because lymphoblasts have scanty cytoplasm, cytoplasmic and/or surface CD3 expression cannot be distinguished in this study using cryostat sections alone.[35,55] Detection of surface antigen without simultaneous detection of intracellular antigen would require the use of fresh unfixed cells in suspension.[35,55,56]

The present series also shows discrepancy in immunohistochemical results of 2 CD3 antibodies, anti-T3 (Coulter) and anti-Leu4 (Becton Dickinson). Nine cases expressed only Leu4 but not T3. Differences in reactivity of 2 other CD3 antibodies (OKT3 and UCHT1) in T cell neoplasms also have been reported.[57] It is possible that different CD3 antibodies recognize different epitopes on the CD3 molecule. Therefore it may be necessary to use more than one antibody to detect CD3 expression.

In summary, βF1 is a specific and fairly sensitive marker of T cell neoplasms. It may help to define different subtypes of T lymphoma that represent the neoplastic counterparts of minor populations of T cells. It also helps to define a novel type of lymphoma occurring frequently in the nasal region that may represent neoplasm of natural killer cells.

Addendum

Since submission of this manuscript, Picker et al also reported on the discordant expression of CD3 and T cell receptor beta-chain antigens in T lineage lymphomas.[58] The discordance is attributed to aberrant phenotypic expression in the neoplastic state probably due to abnormal gene expression. Compared with the results of Picker et al, there is a lower rate of expression of βF1 in peripheral T cell lymphomas of this series. This is probably due to the high proportion of nasal lymphomas among the peripheral T lymphomas.

References

1. Favara BE, MacCarthy RC, Mieran GW: Histiocytosis X, Pathology of Neoplasia in Children and Adolescents. Edited by M Finegold. Philadelphia, WB Saunders, 1986, pp 126–144
2. Aquel NM, Jones DB, Wright DH: A study of the antigenic profile of histiocytosis X cells: A suggestion of their macrophage derivation. J Pathol 1987, 151:41A
3. Stein H, Lennert K, Feller AC, Mason DY: Immunohistological analysis of human lymphoma: Correlation of histological and immunological categories. Adv Cancer Res 1984, 42:67–147
4. Stein H, Mason DY: Immunological analysis of tissue sections in diagnosis of lymphoma, Recent Advances in Hematology, Vol 4. Edited by AV Hoffbrand. Edinburgh, Churchill Livingstone, 1985, pp 127–169
5. Chan JKC, Ng CS, Lo STH: Immunohistological characterization of malignant lymphomas of the Waldeyer's ring other than the nasopharynx. Histopathology 1987, 11:885–900
6. Boekstegers A, Grundmann E: What's new in natural killer cells? Pathol Res Pract 1985, 180:536–552
7. Weiss LM, Crabtree GS, Rouse RV, Warnke RA: Morphologic and immunologic characterization of 50 peripheral T-cell lymphomas. Am J Pathol 1985, 118: 316–324
8. Grogan TM, Fielder K, Rangel C, Jolley CJ, Wirt DP, Hicks MJ, Miller TP, Brooks R, Greenberg B, Jones S: Peripheral T-cell lymphoma: Aggressive disease with heterogeneous immunotypes. Am J Clin Pathol 1985, 83:279–288
9. Borowitz MJ, Reichert TA, Brynes RK, Cousar JB, Whitcomb CC, Collins RD, Crissman JD, Byrne GE: The phenotypic diversity of peripheral T-cell lymphomas: The Southeastern Cancer Study Group experience. Hum Pathol 1986, 17:567–574
10. Ng CS, Chan JKC, Lo STH, Poon YF: Immunophenotypic analysis of non-Hodgkin's lymphomas in Chinese: A study of 75 cases in Hong Kong. Pathology 1986, 18:419–425
11. Van der Valk P, Willemze R, Meijer CJLM: Peripheral T-cell lymphomas: A clinicopathological and immunological study of 10 cases. Histopathology 1986, 10:235–249
12. Chan JKC, Ng CS, Lau WH, Lo STH: Most nasal/nasopharyngeal lymphomas are peripheral T-cell neoplasms. Am J Surg Pathol 1987, 11:418–429

13. Ng CS, Chan JKC, Lo STH: Expression of natural killer cell markers in non-Hodgkin's lymphomas. Hum Pathol 1987, 18:1257–1262
14. Picker LJ, Weiss LM, Medeiros LJ, Wood GS, Warnke RA: Immunophenotypic criteria for the diagnosis of non-Hodgkin's lymphoma. Am J Pathol 1987, 128: 181–201
15. Lippman SM, Grogan TM, Spier CM, Koopmann CF, Gall EP, Shimm DS, Dure BGM: Lethal midline granuloma with a novel T-cell phenotype as found in peripheral T-cell lymphoma. Cancer 1987, 59:936–939
16. Rambaldi A, Pelicci PG, Allavena P, Knowles DM, Rossini S, Bassan R, Barbui T, Dalla-Favera R, Mantovani A: T cell receptor β chain rearrangements in lymphoproliferative disorders of large granular lymphocytes/natural killer cells. J Exp Med 1985, 162:2156–2165
17. Chan WC, Link S, Mawle A, Check I, Brynes RK, Winton EF: Heterogeneity of large granular lymphocyte proliferations: Delineation of two major subtypes. Blood 1986, 68:1142–1153
18. Lauria F, Foa R, Migone N, Giubellino MC, Raspadori D, Buzzi M, Casorati G, Gobbi M, Tazzari PL, Tura S: Heterogeneity of large granular lymphocyte proliferations: Morphological, immunological and molecular analysis in seven patients. Br J Hematol 1987, 66:187–191
19. Pilicci PG, Allavena P, Subar M, Rambaldi A, Pirelli A, Bello MD, Barbui T, Knowles DM, Dalla-Favera R, Mantovani A: T cell receptor (α, β, γ) gene rearrangements and expression in normal and leukemic large granular lymphocytes/natural killer cells. Blood 1987, 70:1500–1508
20. Semenzato G, Pandolfi F, Chisesi T, De Rossi G, Pizzolo G, Zambello R, Trentin L, Agostini C, Dini E, Vespignani M, Cafaro A, Pasqualetti D, Giubellino MC, Migone N, Foa R: The lymphoproliferative disease of granular lymphocytes, a heterogeneous disorder ranging from indolent to aggressive conditions. Cancer 1987, 60:2971–2978
21. Knowles DMII: The human T-cell leukemies: Clinical, cytomorphologic, immunophenotypic, and genotypic characteristics. Hum Pathol 1986, 17:14–33
22. Acuto O, Fabbi M, Bensussan A, Milanese C, Campen TJ, Royer HD, Reinherz EL: The human T-cell receptor. J Clin Immunol 1985, 5:141–157
23. Kronenberg M, Siu G, Hood LE, Shastri N: The molecular genetics of the T-cell antigen receptor and T-cell antigen recognition. Annu Rev Immunol 1986, 4:529–592
24. Minden MD, Mak TW: The structure of the T-cell antigen receptor genes in normal and malignant T-cells. Blood 1986, 68:327–336
25. Freedman AS, Nadler LM: Cell surface markers in hematologic malignancies. Semin Oncol 1987, 14:193–212
26. Acuto O, Reinherz EL: The T-cell receptor, structure and function. N Engl J Med 1985, 312:1100–1111
27. Brenner MB, McLean J, Scheft H, Warnke RA, Jones N, Strominger L: Characterization and expression of the human $\alpha\beta$ T cell receptor by using a framework monoclonal antibody. J Immunol 1987, 138:1502–1509
28. Chan WC, Borowitz M, Wu YJ, IP S: T-cell receptor antibodies in the immunohistochemical studies of normal and malignant lymphoid cells. In press
29. Hsu SM, Raine L: The use of avidin-biotin-peroxidase complex (ABC) in diagnostic and research pathology: Advances in immunohistochemistry; Masson Monographs in Diagnostic Pathology. Vol 7. Edited by RA De-Lellis. New York, Masson Publishing, 1984, pp 31–42
30. Waldron JA, Leech JH, Glick AD, Flexner JM, Collins RD: Malignant lymphoma of peripheral T-lymphocyte origin. Cancer 1977, 40:1604–1617
31. Jaffe ES: Post-thymic lymphoid neoplasia, Surgical Pathology of the Lymph Nodes and Related Organs. Edited by ES Jaffe. Philadelphia, WB Saunders, 1985, pp 218–248
32. Stansfeld AG: Peripheral T-cell lymphomas, Lymph Node Biopsy Interpretation. Edited by AG Stansfeld. Edinburgh, Churchill Livingstone, 1985, pp 300–329
33. Adkins B, Mueller C, Okada CY, Reichert RA, Weissman IL, Spangrude GJ: Early events in T-cell maturation. Annu Rev Immunol 1987, 5:325–365
34. Royer HD, Reinherz EL: T lymphocytes: ontogeny, function and relevance to clinical disorders. N Engl J Med 1987, 317:1136–1142
35. Pittaluga S, Uppenkamp M, Cossman J: Development of T3/T cell receptor gene expression in human pre-T neoplasms. Blood 1987, 69:1062–1067
36. Furley AJ, Mizutani S, Weilbaecher K, Dhaliwal HS, Ford AM, Chan LC, Molgaard, Toyonaga B, Mak T, van den Elsen P, Gold D, Terhorst C, Greaves MG: Developmentally regulated rearrangement and expression of genes encoding the T cell receptor-T3 complex. Cell 1986, 46:75–87
37. Weiss A, Stobo JD: Requirement for the coexpression of T3 and the T cell antigen receptor on a malignant human T-cell line. J Exp Med 1984, 160:1284–1299
38. Haars R, Kronenberg M, Gallatin WM, Weissman IL, Owen FL, Hood L: Rearrangement and expression of T cell antigen receptor and γ genes during thymic development. J Exp Med 1986, 164:1–24
39. van Dongen JJM, Quertemous T, Bartram CR, Wolvers-Tettero ILM, Comans-Bitter WM, Hooijkaas H, Adriaansen HJ, Terhorst C: The T-cell receptor-CD3 complex during early T-cell differentiation, Leucocyte Typing III: White Cell Differentiation Antigens. Edited by AJ McMichael. Oxford, Oxford University Press, 1987, pp 198–199
40. Spits H, Borst J, Tax W, Capel PJA, Terhorst C, Devries JE: Characterization of a monoclonal antibody (WT-31) that recognizes a common epitope on the human T-cell receptor for antigen. J Immunol 1985, 135:1922–1928
41. Allison JP, Lanier LL: Structure, function, and serology of the T-cell antigen receptor complex. Annu Rev Immunol 1987, 5:503–540
42. Schiro R, Delia D, Illeni MT, Berti E, Foa R, Migone N, Cantu-Rajnoldi A, Cattoretti G. Serological analysis of Ti antibodies, Leucocyte Typing III: White Cell Differentiation Antigens. Edited by AJ McMichael. Oxford, Oxford University Press, 1987, pp 188–191
43. Lenier LL, Ruitenberg JJ, Allison JP, Weiss A: Biochemical and flow cytometric analysis of CD3 and Ti

expression on normal and malignant T cells, Leucocyte Typing III: White Cell Differentiation Antigens. Edited by AJ McMichael, Oxford, Oxford University Press, 1987, pp 175–178

44. Brenner MB, McLean J, Dialynas DP, Strominger JL, Smith JA, Owen FL, Seidman JG, Ip S, Rosen F, Krangel MS: Identification of a putative second T-cell receptor. Nature 1986, 322:145–149
45. Bank I, De Pintro RA, Brenner MB, Cassimerik J, Alt FW, Chess L: A functional T3 molecule associated with a novel heterodimer on the surface of immature human thymocytes. Nature 1986, 322:179–181
46. Van de Griend RJ, Tax WJM, van Krimpen BA, Vreugdenhil RJ, Ronteltap CPM, Bolhuis RLH: Lysis of tumor cells by CD3+, 4-, 8-, 16+, T-cell receptor alpha-beta- clones, regulation via CD3 and CD16 activation sites, recombinant interleukin 2 and interferon beta. J Immunol 1987, 138:1627–1633
47. Borst J, van de Griend RJ, van Oostween W, Ang SL, Melief CJ, Seidman JG, Bolhuis RLH: A T-cell receptor γ/CD3 complex found on cloned functional lymphocytes. Nature 1987, 325:683–688
48. Brenner MB, McLean J, Scheft H, Riberdy J, Ang SL, Seidman JG, Deulin P, Krangel MS: Two forms of the T-cell receptor γ protein found on peripheral blood cytotoxic T lymphocytes. Nature 1987, 325:689–694
49. Reinherz EL: T-cell receptor. Who needs more? Nature 1987, 325:660–663
50. Ioannides CG, Itoh K, Fox FE, Pahwa R, Good RA, Platsoncas CD: Identification of a second T-cell antigen receptor in human and mouse by an anti-peptide γ-chain-specific monoclonal antibody. Proc Natl Acad Sci USA 1987, 84:4244–4248
51. Weiss A, Newton M, Crommie D: Expression of T3 in association with a molecule distinct from the T-cell antigen receptor heterodimer. Proc Natl Acad Sci USA 1986, 83:6998–7002
52. Lanier LL, Phillips JH, Hackett J Jr, Tutt M, Kumar V: Opinion. Natural killer cells: Definition of a cell type rather than a function. J Immunol 1986, 137:2735–2739
53. Chan WC, Link S, Waldman TA, Mawle A, Check LJ, Winton EF: Type B large granular lymphocyte proliferation: A clinical, immunological and T-cell receptor gene arrangement study. Lab Invest 1987, 56:12A
54. Pittaluga S, Raffeld M, Lipoford EH, Cossman J: 3A1(CD7) expression precedes T-beta gene rearrangements in precursor T (lymphoblastic) neoplasms. Blood 1987, 68:134–139
55. Link MP, Stewart SJ, Warnke RA, Levy R: Discordance between surface and cytoplasmic expression of the Leu4 (T3) antigen in thymocytes and in blast cells from childhood T lymphoblastic malignancies. J Clin Invest 1985, 76:248–253
56. Mirro J, Kitchingman G, Behm FG, Murphy SB, Goorha RM: T-cell differentiation stages identified by molecular and immunologic analysis of the T cell receptor complex in childhood lymphoblastic leukemia. Blood 1987, 69:908–912
57. Pallesen G: Immune phenotypes of human T-cell lymphoma: A study of 35 cases using extensive monoclonal antibody immunohistological staining of frozen biopsies, Monoclonal Antibodies in Hematopathology. Vol 26. Edited by F Grigani, MF Martelli, DY Mason. New York, Raven Press, 1985, pp 335–339
58. Picker LJ, Brenner MB, Weiss LM, Smith SD, Warnke RA: Discordant expression of CD3 and T-cell receptor beta-chain antigens in T-lineage lymphomas. Am J Pathol 1987, 129:434–440

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