Clin. exp. Immunol. (1986) **65**, 354–362.

Expression of Tac antigen in B cell lymphomas

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(Accepted for publication 26 March 1986)

SUMMARY

In a series of 55 cases of B cell derived non-Hodgkin's lymphoma the reactivity of two distinct anti-Tac monoclonal antibodies was examined using a sensitive immunoperoxidase technique on cryostat sections. Eighteen out of the thirty-five cases of B cell lymphomas of low or intermediate grade of malignancy were found to be reactive while six out of 20 cases of high-grade malignancy lymphomas showed a positive immunostaining. No correlation was found between anti-Tac reactivity and surface immunoglobulin phenotype, T65 antigen, or calla expression. These findings showed that IL2 receptor expression is not restricted to activated T cells, and raise the question of the possible role of IL2 in the regulation of malignant B cell clone expansion.

Keywords Tac antigen B cell lymphomas

INTRODUCTION

Uchiyama, Broder & Waldman (1981) described a surface antigen of human T cells, termed Tac antigen, which is expressed by T cells activated by mitogens, soluble antigens and alloantigens. Further investigations have revealed the identity of the cellular IL2 binding structure and Tac antigen (Robb & Greene 1983). Moreover, it has been reported that Tac antigen was also expressed on leukaemic cells from patients with human T cell lymphotropic virus associated adult T cell leukaemia (Waldmann *et al.*, 1985).

Very recently, this antigen has also been found on the cell membrane of normal B cells activated *in vitro* by either anti-μ antibody or *Staphylococcus aureus* Cowan strain I (SAC), as well as on EBV-transformed B cells (Boyd *et al.*, 1985; Mitler *et al.*, 1985; Muraguchi *et al.*, 1985; Nakagawa *et al.*, 1985; Tsudo, Uchiyama & Uchino, 1984; Waldmann *et al.*, 1984). Furthermore Hsu (1985) reported that Tac antigen was also expressed by a minor subpopulation of B cells in normal lymphoid tissue. In addition, Tac antigen has been detected on neoplastic B cells, such as hairy cells of B cell genotype (Korsmeyer *et al.*, 1983) and chronic lymphocytic leukaemia cells of B cell type (Lantz *et al.*, 1985).

Little attention has been given to the expression of the Tac antigen in B cell lymphomas. In this study, we examined the reactivity of 55 cases of non-Hodgkin's B cell derived lymphomas for two distinct anti-Tac monoclonal antibodies (MoAb) by using a highly sensitive immunoperoxidase technique. Our study provides some evidence that Tac antigen is present in one-third of B cell lymphomas of various histological types.

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MATERIALS AND METHODS

Tissue specimens

Neoplastic lymphoid tissue. Fresh samples of lymph nodes (42 cases), skin (three cases), stomach (two cases), colon (one case), kidney (one case), thyroid gland (one case), spleen (four cases), lung (one case), and oropharyngeal tumor (one case), removed for diagnostic purposes, were sent to the laboratory immediately after excision. In each case, the biopsy specimen was divided into two portions. One part was snap-frozen in liquid nitrogen and stored at −70°C until sectioned. Another part was fixed in Dubosq-Brazil's fluid and processed routinely for histopathological assessment. Sections were stained with haematoxylin and eosin, PAS, and by the Gordon-Sweet method for reticulin, and Giemsa stain.

Controls. Non neoplastic lymphoid tissues including spleen (three cases), reactive lymph nodes (eight cases) and thymus (three cases), were used as controls.

Selection of the cases

All lymphomas included in this study were classified according to the Kiel classification (Lennert *et al.*, 1978). After immunohistochemical study, 55 cases were considered as B cell lymphomas on the basis of monotypic SIg and the presence of common B cell antigens defined by TO15 (CD22) MoAb (Stein, Gerdes & Mason, 1982) BL14 MoAB (Brochier *et al.*, 1984) and SB3 MoAb (Laurent, unpublished) respectively.

Anti-Tac monoclonal antibodies

Two distinct anti-IL2 receptor MoAb were used in this study. The first, a murine anti-IL2 receptor

Table 1. Monoclonal antibodies

Antibody	Specificity	CD	Source
Anti-B cell MoAb			
Anti-IgM	μ chain	—	Dako
Anti-IgD	δ chain	—	Dako
Anti-IgG	γ chain	—	Seward
Anti-IgA	α chain	—	BRL
Anti-kappa	κ chain	—	Seward
Anti-lambda	λ chain	—	Dako
TO15	pan B cell antigen	CD22	Dako
SB3	pan B cell antigen	NC*	Sanofi
BL14	pan B cell antigen	NC*	Immunotech (France)
Anti-T cell MoAb			
ST1	T65 antigen	CD5	Sanofi
Leu 5a	E^+ T lymphocytes	CD2	Becton-Dickinson
Leu 4	T3 antigen	CD3	Becton-Dickinson
Leu 3a	T helper induced	CD4	Becton-Dickinson
OKT8	T suppressor/cytotox.	CD8	Ortho
OKT6	Cortical thymocytes	CD1	Ortho
Anti-activated T cell MoAb			
33 B 31	Human IL2 receptor	CD25	INSERM U119
2A3	Human IL2 receptor	CD25	Becton-Dickinson
Miscellaneous MoAb			
IOT5a	Calla (gp 100)	CD10	Immunotech (France)
IOT2a	HLA-DR	—	Immunotech (France)
R4/23	Dendritic reticulum cell	—	Dako

* Not yet clustered.

MoAb was purchased from Becton Dickinson (Sunnywale, CA). According to the manufacturer's specifications, this IgG1 antibody is derived from 2A3 clone (Urdal *et al.*, 1984). The second, a rat anti-IL2 receptor antibody (33B31), was prepared by D.O. (Inserm U119). Briefly, male rats were immunized i.p. at 3-week intervals with 4×10^7 three day-PHA-stimulated blast T cells. Three days before fusion, the rats were challenged i.v. and their spleen cells were hybridized with the non-secreting mouse myeloma X63-Ag-8-653 cell line according to the procedure previously described Rebai & Malissen, 1983). The MoAb was assessed as being directed against the IL2-receptor of human T-cells by several lines of evidence: tissue distribution, immunoprecipitation, cross competitive studies with an anti-IL2-receptor MoAb B1 19.9 previously described (Hemmler *et al.*, 1983), and inhibition of IL2 binding on its high affinity receptor (Olive *et al.*, 1986).

Table 2. Distribution of Tac antigen among various subtypes of low or intermediate grade malignancy B-cell lymphomas (35 cases): correlations with other cell markers

Histopathological types	SIg phenotype	TO15 (CD22)	SB3	ST1	IOT5a (CALLA)	Anti-Tac 2A3	Anti-Tac 33B31
Lymphocytic	MDK	+	+	+	−	+	+
	MDλ	+	+	+	−	+	+
	Mλ	+	+	+	−	+	+
	DK	+	+	+	−	+	−
	MDK	+	+	+	−	+	−
	MK	+	+	+	−	−	NT
Hairy cell leukaemia*	K	+	+	−	−	+	+
	MK	+	+	−	−	+	+
	MDλ	+	+	−	−	+	+
	Mλ	+	+	−	−	+	+
Lymphoplasmacytic lymphoma	GK	+	+	−	−	+	+
	MK	+	+	−	−	+	+
Diffuse centrocytic	MK	+	+	−	−	+	+
	Mλ	+	+	+	−	+	+
	M	+	+	+	−	+	+
	λ	+	+	+	−	+	−
	MDλ	+	+	+	−	−	−
	MK	+	+	+	−	−	−
	MK	+	+	+	−	−	−
Diffuse	DK	+	+	−	−	+	+
centroblastic-centrocytic	−	+	+	−	−	+	+
	MK	+	+	−	+	NT	+
	Gλ	+	+	−	NT	−	−
	Mλ	+	+	−	−	−	−
	MK	+	+	NT	NT	NT	−
Follicular centrocytic	Gλ	+	+	−	+	−	−
or follicular centroblastic-	MDK	+	+	−	+	−	−
centrocytic	MDK	+	+	−	+	−	−
	MK	+	+	−	+	−	−
	GK	+	+	−	+	−	−
	Mλ	+	+	−	+	−	NT
	MK	+	+	−	+	−	−
Follicular and diffuse centrocytic	MK	+	+	+	−	NT	−
Unclassified low grade	MDλ	+	+	−	−	+	−
	GK	+	+	+	−	−	−

* All cases were also reactive with Leu M5 MoAb detecting hairy cells and macrophage associated antigen (Becton-Dickinson).

NT = not tested.

Immunohistochemical studies

A three step immunoperoxidase procedure was performed using the method described by Stein *et al.* (1982) with some modifications. Briefly, frozen sections were air-dried for 2 h and fixed in acetone at room temperature for 10 min. Slides were stained immediately, or wrapped in aluminium foil and stored at −20°C for 2 to 30 days, until immunostaining.

In the first incubation a series of 20 MoAb (See Table 1) was used at optimal dilution, varying from 1:100 to 1:1000. After washing, the sections were incubated with a peroxidase-conjugated rabbit antimouse Ig (Dako) diluted to 1:15. As a third layer, we used a peroxidase-conjugated swine antirabbit Ig (Dako) diluted to 1:15. Normal human serum (diluted to 1:3) was added to the second and third antisera to avoid cross reactivity with human Ig.

Finally, cytochemical detection of peroxidase activity was carried out according to the method of Graham & Karnovsky. Sections were mounted in Eukitt. Control sections consisted of (1) detection of endogenous peroxidase activity which is not inhibited in this technique (2) immunostaining after omission of the MoAb.

RESULTS

Benign hyperplastic lymph nodes, spleen and normal thymus

Lymph nodes. Immunostainings with Pan-B (TO15, BL14 and SB3) and Pan-T(leu-4, ST1) monoclonal antibodies were in agreement with previous studies (Stein, Gerdes & Mason 1982). The germinal centres were stained with all Pan-B antibodies, but the follicular mantle zone was more intensely stained than the germinal centre. Some B lymphocytes were also scattered within the paracortical area. However the majority of lymphocytes within this last area were reactive for Pan-

Table 3. Distribution of Tac antigen among various subtypes of high grade malignancy B-cell lymphomas (20 cases): correlations with other cell markers

Histopathological types	SIg phenotype	TO15 (CD22)	SB3 (CD21)	ST1 (CD5)	IOT5a (CALLA)	Anti-Tac 2A3	Anti-Tac 33B31
Centroblastic and immunoblastic	MK	+	+	−	−	+	+
	MK	+	+	−	−	+	+
	GK	+	NT	−	−	+	NT
	Gλ	+	+	−	−	+	+
	MDK	+	+	−	−	+	+
	MK	+	+	NT	NT	NT	−
	MK	+	+	−	−	−	−
	MK	+	+	−	−	−	−
	MK	+	+	+	−	NT	−
	MDK	+	+	−	−	NT	−
	GK	+	+	−	−	−	−
	GK	+	+	−	−	−	−
	Mλ	+	+	−	−	−	−
Lymphoblastic	−	+	+	−	−	−	−
	Mλ	NT	+	−	−	−	−
	M	+	+	−	+	−	−
	M	+	+	−	+	−	−
Unclassified high grade	−	+	+	−	−	+	+
	MK	+	+	−	−	−	−
	−	+	+	−	−	−	−*

* This case showed a mixed phenotype with a clear reactivity with OKT8.

T antibodies, and T helper (Leu-3a+) cells outnumbered T-suppressor (OKT8) cells. Some T lymphocytes were also present within the germinal centres.

The number of Tac-positive cells varied greatly from one case to another (from 5% to 20%). But, whatever their abundance, positive cells were mainly found within the paracortical area and their size corresponded mainly to small lymphocytes. Germinal centres also contained a few positive cells. In addition to the membrane-staining of lymphoid cells, there were also some larger cells showing a cytoplasmic labelling. These cells were found in both paracortical area and germinal centres where they were better seen and clearly identified as macrophages. In all investigated lymph nodes the staining noted with 2A3 anti-IL2 receptor was always stronger than that with 33 B 31 anti-Tac antibody. It was interesting to note that lymph nodes from patients with EB virus infection showed atypical hyperplasia with numerous large sized Tac positive immunoblasts. By contrast, hyperplastic lymph nodes from two homosexual men contained very few Tac positive cells.

Spleen. Antibodies directed against B or T lymphocytes showed the immunostaining previously described (Stein, Gerdes & Mason 1982). Anti-Tac antibodies in the three investigated specimens stained only a few lymphocytes scattered within the periarterial lymphoid sheets and to a lesser extent in germinal centres. The marginal zone did not contain a larger number of Tac-positive cells than the preceding areas.

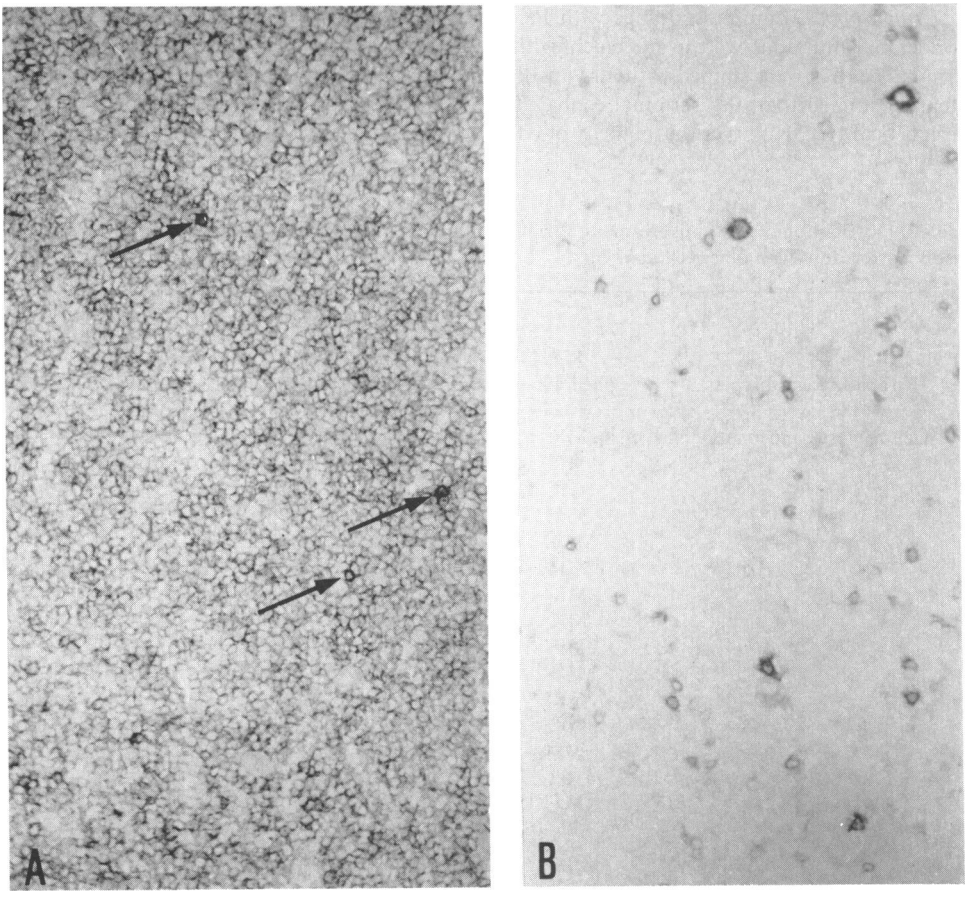

Fig. 1. (A) Anti-Tac reactive chronic lymphoid leukemia cells: immunostaining with anti-IL2 receptor MoAb. All neoplastic cells are labelled. Note the stronger staining of some cells (× 25). (B) Anti-Tac negative chronic lymphoid leukaemia cells. Only reactive-T lymphocytes scattered among neoplastic cells are labelled (frozen section stained with anti-IL2 receptor × 25).

Thymus. The three specimens showed quite a similar staining pattern. Tac positive cells were found in the medullary area where they represented 20% to 40% of thymocytes. By contrast, within the cortex, positive cells were very scarce. As noted in the lymph nodes or spleen, the staining with 2A3 antibodies was stronger than with 33B 31 anti-Tac antibody.

B cell lymphomas

Twenty-four out of fifty-five cases were reactive for 2A3 anti-IL2 receptor antibody, whereas only twenty cases were found to be positive for 33 B 31 (see Tables 2 and 3).

In 18 out of the 35 cases of B cell lymphomas of low or intermediate malignancy 2A3 anti-IL2 receptor MoAb was found to be reactive (see Table 2). Only six out of 20 cases of high grade malignancy showed a positive immunostaining. Among low or intermediate grade malignancy lymphomas, lymphocytic lymphoma, hairy cell leukaemia and lymphoplasmacytic lymphoma were found to be reactive in all cases but one. In contrast, follicular lymphoma showed no reactivity in a series of seven patients as showed in Table 2. Five out of 13 cases of centroblastic or immunoblastic lymphoma were positive, including the two cases of immunoblastic lymphoma with plasmacytic differentiation. Lymphoblastic lymphoma (Burkitt or non-Burkitt) was found to be unreactive as shown in Table 3.

In all cases, the intensity of the immunostaining of neoplastic cells with TO15 (CD22), SB3 and

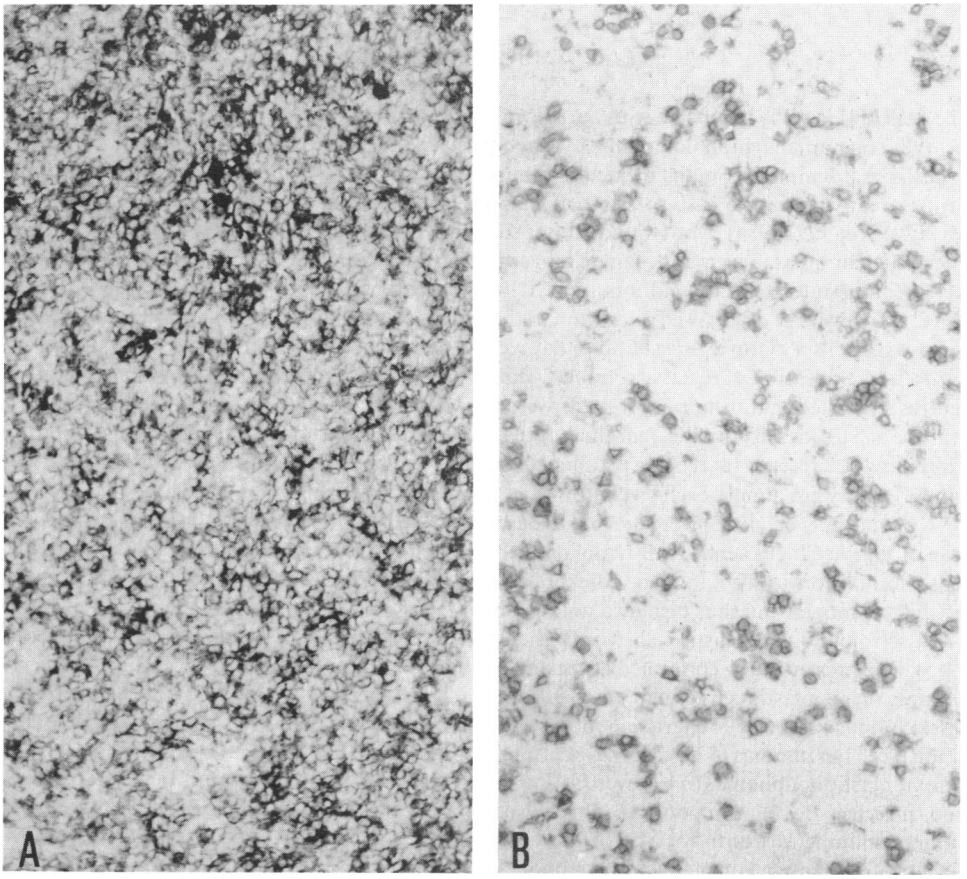

Fig. 2. (A) anti-Tac reactive lymphoplasmacytic cells; immunostaining with anti-IL2 receptor MoAb. All cells are labelled but some cells are moderately positive whereas some others are strongly stained (× 25). (B) Same case stained with Leu-4 Pan-T MoAb. Reactive T cells are quite numerous and the strongly positive cells in Fig. 2A are probably T lymphocytes (× 25).

with anti-IL2 receptor MoAb was compared with the labelling of reactive T cells with Leu-4 (CD3), Leu-5a (CD2), Leu-3a (CD4) and OKT8 (CD8). In the vast majority of cases, neoplastic cells showed a weak anti-Tac membrane staining and some strongly stained reactive lymphocytes scattered among malignant cells were easily detected (see Fig. 1). However, these anti-Tac positive T lymphocytes were clearly less numerous than Leu-4 positive cells and thus represented only a small population of T cells.

In low-grade malignant lymphomas, hairy cell leukaemia and lymphoplasmacytic lymphomas showed a stronger staining than chronic lymphocytic leukaemia or diffuse centrocytic lymphomas (see Fig. 2). In high-grade malignant lymphomas, only two cases (immunoblastic and high-grade unclassified) were strongly stained with the two anti-IL2 receptor MoAb. Apart from these two cases, the staining obtained with 2A3 MoAb was always stronger and the number of positive cells greater than that with 33.B.33 MoAb.

In an attempt to correlate IL2-receptor expression and other differentiation markers, we compared (CD5) and CALLA reactivities with the expression of IL2-receptor. CD5 MoAb was found to be reactive with lymphocytic lymphoma and a majority of diffuse centrocytic lymphomas, while no reactivity was found with follicular lymphomas as we reported previously (Al Saati *et al.*, 1984). No correlation between these reactivities and IL2-receptor expression was found. Surface immunoglobulin phenotype (IgM, IgM, IgG) was also compared to IL2-receptor expression and Tac antigen was found to be co-expressed with any one of these phenotypes.

DISCUSSION

The data of this study are in line with the previous findings by Miyawaki *et al.* (1984), and Takacs *et al.* (1985) on human lymphoid organs. Lymphoid cells reactive with anti-Tac antibodies are present in peripheral lymphoid organs particularly in paracortical area (T zone). Although their number varied greatly from one case to another, our results were in agreement with those reported by Miyawaki *et al.* (1984) who found about 20% of Tac-positive cells in the paracortical and interfollicular areas. The mantle zone and germinal centres contain a few Tac-positive cells which were demonstrated by these authors to be T lymphocytes using double staining with TRITC and FITC (Miyawaki *et al.*, 1984). In addition to the membrane-staining of lymphoid cells, we found in some large cells a cytoplasmic staining that we did not attribute, as others have (Miyawaki *et al.*, 1984), to the diffusion of reactive products. Both the morphology and location within the germinal centres suggested that these positive cells were probably macrophages. Contrary to Hsu (1985) we are unable to identify in the marginal zone of the spleen a subpopulation of B lymphocytes expressing IL2 receptor and being alkaline phosphatase positive. Finally, in the thymus T-activated lymphocytes were almost exclusively found in the medulla (Takacs *et al.* 1985).

Korsmeyer *et al.* (1983) were the first to describe the expression of Tac antigen on the malignant cells of hairy cell leukaemia, a B lymphoid cell proliferation. Thereafter, it was shown that these cells, in addition to Tac antigen, co-expressed B cell antigens (CD20, CD22) and macrophage associated antigen and thus display a unique phenotype (Falini *et al.*, 1986). Recently, Tac antigen was also found on neoplastic cells from patients with B chronic lymphoid leukaemia (Lantz *et al.*, 1985). The present study confirmed and extended these findings. In fact, IL2 receptor was detected not only on neoplastic cells of hairy cell leukaemia (4/4 cases) and chronic lymphoid leukaemia (5/6 cases) but also in other low-grade non Hodgkin's lymphomas (19/26 cases) as well as some high-grade B cell lymphomas (6/20 cases). It was interesting to note that follicular lymphomas ($n=7$) and lymphoblastic lymphomas ($n=4$) were found to be unreactive with the two anti-Tac MoAb. Among Tac positive B cell lymphomas, there was no correlation with other cell markers. The immunostaining with anti-Tac MoAb, although variable, was often weak, suggesting that the mean density of Tac antigen on malignant lymphoma B cells was generally low. It is thus possible that the incidence of 30% of Tac positive malignant lymphomas we found underestimates the exact incidence of B cell lymphomas expressing the IL2-receptor. Furthermore, our study indicated that anti-Tac MoAb differed in terms of reactivity and 2A3 MoAb was found to be more reactive than 33B31 MoAb.

The mechanism of expression of IL2 receptor on B cell neoplasias remains unclear. Several hypotheses can be discussed. Firstly, the possibility of a transforming gene cannot be ruled out. Regarding this, it must be stressed that Muraguchi *et al.* (1985) reported two Epstein-Barr negative, HTLV I-infected B cell lines which were found to be strongly Tac positive. Secondly, Tac positive malignant B cells could represent a clonal expansion of a minor subpopulation of Tac-positive B lymphocytes in normal lymphoid tissue as suggested by Hsu (1985). As mentioned above, we were unable to identify such a subpopulation in either lymph node or spleen. However, these findings require further investigations since it is now well established that in-vitro activated normal B lymphocytes are able to express IL2 receptor. Thus, Tsudo and co-workers (1984) demonstrated the expression of Tac antigen in about 20% of human B cells activated *in vitro* by *Staphylococcus aureus* Cowan I (SAC). More recently, Muraguchi *et al.* (1985) demonstrated that, in addition to SAC, other polyclonal B cell activators such as phorbolmyristate acetate, Epstien Barr virus or anti-μ chain can induce the expression of IL2-receptor. Similarly, it may be possible that neoplastic B-cells express IL2-receptor as a result of in-vivo activation due to auto-anti-idiotypic anti-Ig as suggested by Lantz *et al.* (1985).

Whether or not IL2-receptor expressed on lymphoma cells are functional, remains to be elucidated. However, Lantz *et al.* (1985) clearly showed that purified recombinant IL2 preparation was able to trigger leukaemic B cells from patients with CLL (6/9 cases) to proliferate after preactivation by SAC or anti-μ chain as it has been shown for normal B cell (Boyd *et al.*, 1985; Mittler *et al.*, 1985; Muraguchi *et al.*, 1985; Nakagawa *et al.*, 1985; Tsudo *et al.*, 1984; Waldmann *et al.*, 1984).

In conclusion, the results presented here showed that IL2 receptor expression is not restricted to activated T cells. In fact, a variety of non-Hodgkin's lymphomas from B cell origin have been found to be reactive with two anti-Tac MoAbs. These findings open the question of a possible role of IL2 in the regulation of malignant clone expansion.

We are particularly grateful to Dr C. Mawas for his helpful comments and suggestions in the preparation of this manuscript. We also wish to thank C. N'Diaye for typing the manuscript.

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