

[ ORIGINAL ARTICLE ]

# Expression of Master Regulators of T-cell, Helper T-cell and Follicular Helper T-cell Differentiation in Angioimmunoblastic T-cell Lymphoma

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## Abstract:

**Objective** It has been postulated that the normal counterpart of angioimmunoblastic T-cell lymphoma (AITL) is the follicular helper T-cell (TFH). Recent immunological studies have identified several transcription factors responsible for T-cell differentiation. The master regulators associated with T-cell, helper T-cell (Th), and TFH differentiation are reportedly BCL11B, Th-POK, and BCL6, respectively. We explored the postulated normal counterpart of AITL with respect to the expression of the master regulators of T-cell differentiation.

**Methods** We performed an immunohistochemical analysis in 15 AITL patients to determine the expression of the master regulators and several surface markers associated with T-cell differentiation.

**Results** BCL11B was detected in 10 patients (67%), and the surface marker of T-cells (CD3) was detected in all patients. Only 2 patients (13%) expressed the marker of naïve T-cells (CD45RA), but all patients expressed the marker of effector T-cells (CD45RO). Nine patients expressed Th-POK (60%), and 7 (47%) expressed a set of surface antigens of Th (CD4-positive and CD8-negative). In addition, BCL6 and the surface markers of TFH (CXCL13, PD-1, and SAP) were detected in 11 (73%), 8 (53%), 14 (93%), and all patients, respectively. Th-POK-positive/BCL6-negative patients showed a significantly shorter overall survival (OS) than the other patients (median OS: 33.0 months vs. 74.0 months,  $p=0.020$ ; log-rank test).

**Conclusion** Many of the AITL patients analyzed in this study expressed the master regulators of T-cell differentiation. The clarification of the diagnostic significance and pathophysiology based on the expression of these master regulators in AITL is expected in the future.

**Key words:** angioimmunoblastic T-cell lymphoma, follicular helper T-cell, BCL11B, Th-POK, BCL6

(Intern Med 56: 2851-2856, 2017)

(DOI: 10.2169/internalmedicine.8570-16)

## Introduction

Angioimmunoblastic T-cell lymphoma (AITL) is a T-cell lymphoma composed of clusters of atypical medium-sized or large neoplastic lymphocytes with clear-to-pale cytoplasm

and the infiltration of reactive lymphocytes, eosinophils, plasma cells, histiocytes and follicular dendritic cells (1).

During T-cell maturation, naïve T cells comprise two distinct cell types: CD4-positive and CD8-negative helper T cells (Th), and CD4-negative and CD8-positive cytotoxic T cells. Following antigen stimulation, naïve Th cells differen-

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Received: November 18, 2016; Accepted: March 6, 2017; Advance Publication by J-STAGE: September 25, 2017

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**Table 1. Findings of Biopsied Samples and Epstein-Barr Viral Infection of the 15 Patients with Angioimmunoblastic T-cell Lymphoma.**

Patient	Age/ Sex	Biopsy location	TCR C $\beta$ 1 rearrangement	Representative karyotype	EBER-ISH
1	61/M	Lymph node	ND	46,XY	+
2	68/F	Lymph node	TCR J $\beta$ -	t(1;14)(q21;q32.3) [3/21]	+
3	65/F	Lymph node	+	46,XX	-
4	57/F	Subcutaneous nodule	+	47,XX,+3 [6/8] 48,idem,+?21[1/8]	-
5	85/F	Lymph node	ND	46,XX	-
6	68/F	Skin/ Lymph node	- (PB)	46,XX,del(9)(q?),add(14)(q32) [1/20]	-
7	81/F	Lymph node	ND	46,XX	+
8	70/M	Lymph node	NE	47,XY,add(4)(q21),del(5)(q?),+add(6)(p11), del13(q?),add(15)(p11),add(19)(q13) [2/20]	+
9	38/M	Lymph node	ND	46,XY,add(1)(p11),add(4)(p11),add(8)(q24), del(9)(q?),11,add(14)(q32),15,add(18)(q21), add(19)(p13),add(21)(q22),-22,-22,+4mar [2]	-
10	68/M	Lymph node	+	No metaphase	-
11	64/F	Lymph node	ND	47,XX,add(1)(q21),del(2)(q?), +der(7)(1;7)(q12;q32),add(10)(p11.2), add(13)(p11.2) [1/15]	-
12	75/F	Lymph node	ND	46,XX	-
13	63/F	Skin	ND	ND	-
14	83/F	Lymph node	ND	46,XX,inv(9)(p24q21) [1/20]	-
15	68/F	Lymph node	ND	No metaphase	-

ND: no data, NE: not evaluable, PB: peripheral blood, EBER-ISH: Epstein-Barr virus-encoded RNA *in situ* hybridization

tiate into several subtypes of effector Th cells: Th type 1 (Th1), Th type 2 (Th2), follicular helper T cells (TFH), regulatory T cells (Treg), interleukin-17-producing T cells (Th17), central memory T cells, and effector memory T cells (2).

Previously, these subtypes of effector Th cells were classified according to their pattern of cytokine secretion and expression of surface antigens, including chemokine receptors. Recent immunologic studies, however, have identified several transcription factors responsible for T-cell differentiation. The master regulators associated with T-cell, Th, Th1, Th2, TFH, Treg, and Th17 differentiation are reportedly BCL11B (3, 4), Th-POK (5), T-Bet (6), GATA3 (7), BCL6 (8, 9), FOXP3 (10), and ROR $\gamma$ t (11), respectively.

The detection of the expression of these master regulators has contributed to the identification of the normal counterparts of some histological subtypes of T-cell lymphoma. For example, the normal counterpart of some adult T-cell leukemia patients was reported to be Treg because of the detection of FOXP3 expression (12). In addition, we previously reported the postulated that the normal counterparts of 10 peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS) patients were Th1 (T-BET-positive), Th2 (GATA3-positive), TCM (CCR7- and CD62L-positive), and TFH (BCL6-positive) (13).

The neoplastic cells of AITL are thought to originate from effector Th cells because these tumor cells express surface antigens such as pan-T-cell (CD3), effector-T-cell (CD45RO) (14), and Th (CD4) markers. Regarding the subtypes

of effector Th cells, several immunohistochemical studies (15-18) have shown that the neoplastic cells of AITL express the transcriptional factors and surface antigens associated with TFH, such as BCL6, CXCL13, PD-1, and SAP. A gene expression profile analysis also demonstrated a molecular link between AITL and TFH cells (19, 20). These results indicate that the neoplastic cells of AITL are derived from TFH cells.

In this study, to identify the postulated normal counterpart of AITL with respect to the master regulators of T-cell differentiation, we immunohistochemically analyzed the expression of BCL11B, Th-POK, and BCL6. Furthermore, we compared the results with those for previously known markers of these cells in AITL patients.

## Materials and Methods

### Patients

The study population comprised 15 Japanese patients with histopathologically diagnosed AITL at the hospital of Kyoto Prefectural University of Medicine and Kyoto Minami Hospital between 1990 and 2012. These patients were 4 men and 11 women who ranged in age from 38 to 85 years (Table 1, Figure A). The clinical data of patients No. 1-4, 6, and 9-15 were previously reported (21). Ten patients (No. 2, 4, 6, 8-13, 15) were treated with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) regimen as first-line therapy. Two patients received stem cell transplantation.

**Table 2. Clinical Characteristics of the 15 Patients with Angioimmunoblastic T-cell Lymphoma.**

Patient	LDH (IU/L)	Ann Arbor Stage	PS	Extranodal sites	WBC ( $\times 10^4/\mu\text{L}$ )	Hb (g/dL)	Platelet count ( $\times 10^4/\mu\text{L}$ )	IgA (mg/dL)	PIAI	ATPI	Survival (months)
1	1682H	IVB	0	Pleural effusion Ascites	35,200	5.5	28.4	ND	H	H	179
2	191	IIISB	0	-	9,400	9.9	35.8	528	H	HI	37
3	556H	IIISA	0	-	7,100	11.3	13.2	373	H	L	145+
4	226	IIISB	0	Skin	9,000	9.7	4.2	168	H	L	74+
5	264H	IVA	0	Pleural effusion Hepatomegaly	7,100	6.6	1.8	ND	H	HI or H	9+
6	315H	IVA	0	Skin	7,500	12.9	30.2	348	L	L	78+
7	242H	ND	0	ND	6,600	10.2	14.7	1,292	H	HI	ND
8	193	IIIA	0	-	4,900	14.0	18.5	554	L	LI	110+
9	198	IVB	0-1	-	4,300	14.9	25.5	111	L	L	72+
10	238	IIISA	0	Pancreas	7,600	11.5	17.5	1,378	L	HI	93+
11	993H	IVB	1	Hepatomegaly	8,700	11.2	0.3	410	H	LI	4
12	477H	IVB	4	Bone marrow	19,300	8.4	4.3	950	H	H	62+
13	277H	IVB	0	Skin	7,280	10.5	27.3	423	H	HI	45
14	276H	IA	0	-	8,200	14.9	15.9	367	L	L	33+
15	279H	IVB	0	Ileum	6,300	11.1	17.1	70	H	L	52

PIAI: Prognostic Index for AITL (34), ATPI: AITL prognostic index (35), L: low-risk, LI: low-intermediate-risk, HI: high-intermediate risk, H: high risk, ND: no data

Autologous and reduced-intensity allogeneic peripheral blood stem cell transplantations (PBSCTs) were performed in Patient 4, and autologous PBSCT and myeloablative cord blood transplantation were performed in Patient 9.

Informed consent was obtained from each patient in accordance with institutional guidelines. Each patient enrolled in the study was reviewed by two pathologists for confirmation of AITL. The histopathologic diagnosis was in accordance with the World Health Organization Classification of Neoplastic Disorders of the Lymphoid Tissues (1).

## Methods

We subjected 4- $\mu\text{m}$ -thick paraffin-embedded sections of diagnostic lymph node or skin biopsy specimens to immunohistochemical staining using a standard indirect avidin-biotin horseradish peroxidase method and diaminobenzidine (DAB) color development (DAKO Envision™, Carpinteria, and Cell & Tissue Staining Kit; R&D Systems, Minneapolis, USA). In line with previously reported studies, the patients were considered positive if  $\geq 20\%$  of the tumor cells were stained with an antibody (16, 17). Paraffin-embedded lymph nodes with a histological diagnosis of nonspecific lymphadenitis and diffuse large B-cell lymphoma were used as negative and positive staining controls.

Primary antibodies against the following transcription factors were introduced: BCL11B (dilution 1: 100; Novus Biologicals, Littleton, USA), Th-POK (dilution 1:50; Abgent, San Diego, USA), and BCL6 (PG-B6p, dilution 1: 15; DAKO). Primary antibodies against the following surface antigens and chemokine were used: CD3 in clinical use, CD 4 (4B12, dilution 1:70; DAKO), CD8 (C8/144B, no dilution; DAKO), CD45RA (4KB5, dilution 1: 70; DAKO), CD45RO (UCHL-1, dilution 1:70; DAKO), CXCL13 (dilution 15 mg/

mL; R&D Systems), PD-1 (dilution 15  $\mu\text{g}/\text{mL}$ ; R&D Systems) and SAP (SH2D1A, dilution 1: 250; Santa Cruz Biotechnology, Santa Cruz, USA). All antibodies were treated and used in accordance with the manufacturers' instructions.

We analyzed the relationship between the expression of the master regulators and the immunohistochemical and clinical features listed in Tables 2 and 3 using Fisher's exact test. The overall survival (OS) distributions were calculated with the Kaplan-Meier method and compared by the log-rank test.

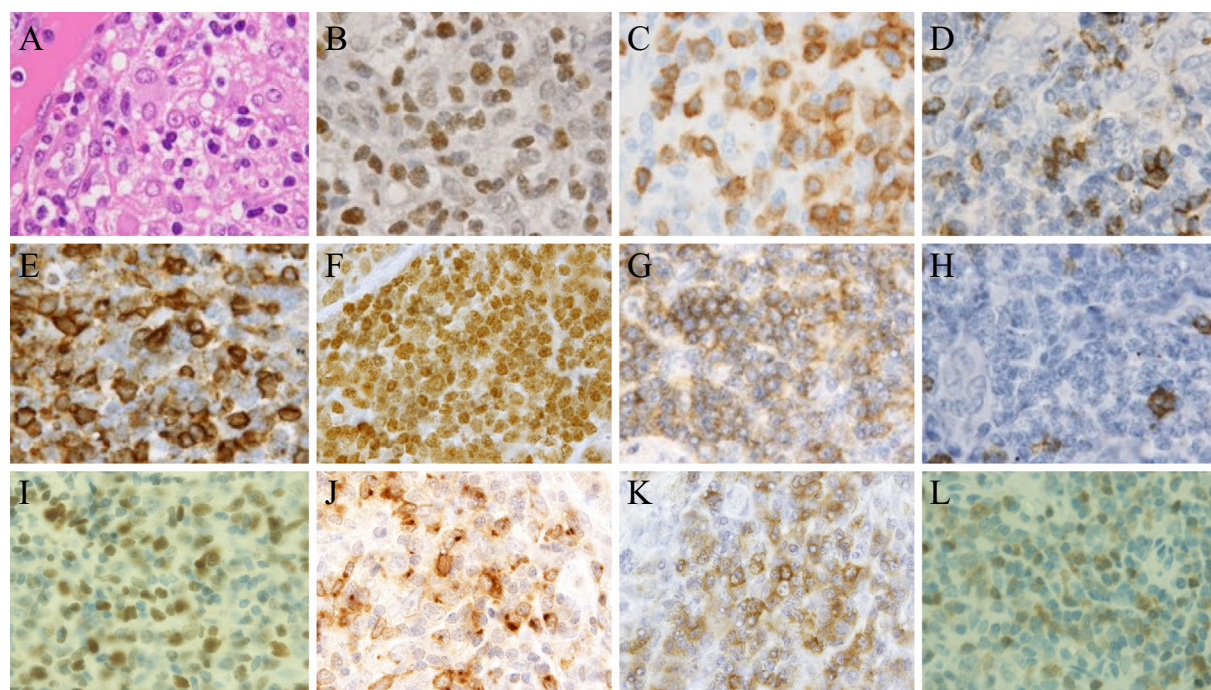
## Results

The immunohistochemical results are shown in Table 3. We first analyzed the expression of the master regulator (BCL11B) and the surface marker (CD3) of T-cells (Fig. 1 B, C). BCL11B was detected in 10 patients, and CD 3 was detected in all AITL patients. We then analyzed the expression of the master regulator of Th (Th-POK) and the surface markers (CD4 and CD8), naïve T-cell antigen (CD45 RA), and effector T-cell antigen (CD45RO) (Fig. 1 D-H). Th-POK was detected in 9 patients, while 7 patients showed the phenotype of the surface antigens of Th, i.e. CD4-positive and CD8-negative. All patients were positive for the effector T-cell marker (CD45RO), and all patients except two were negative for the naïve T-cell marker (CD45 RA) (14). Regarding the expression of the master regulator (BCL6) and the surface antigens of TFH (CXCL13, PD-1 and SAP), BCL6, CXCL13, PD-1, and SAP were detected in 11, 8, 14, and all patients, respectively (Fig. 1 I-L).

Regarding the associations between the expression of these master regulators of T-cell differentiation and the clinical

**Table 3. Results of the Immunohistochemical Analysis.**

Patient	T-cell		Effector T-cell		Th			TFH			
	BCL11B	CD3	CD45RA	CD45RO	Th-POK	CD4	CD8	BCL6	CXCL13	PD-1	SAP
1	+	+	+	+	+	+	-	+	+	+	+
2	-	+	-	+	+	+	-	+	+	+	+
3	+	+	+	+	+	+	+	+	-	+	+
4	+	+	-	+	+	+	+	+	+	+	+
5	+	+	-	+	-	+	+	+	+	+	+
6	+	+	-	+	-	+	-	+	-	+	+
7	+	+	-	+	-	+	-	+	-	+	+
8	-	+	-	+	-	+	-	+	+	+	+
9	-	+	-	+	-	-	-	+	+	+	+
10	-	+	-	+	-	+	-	+	-	-	+
11	-	+	-	+	+	-	-	-	+	+	+
12	+	+	-	+	+	+	+	-	-	+	+
13	+	+	-	+	+	+	+	+	-	+	+
14	+	+	-	+	+	+	-	-	-	+	+
15	+	+	-	+	+	-	+	-	+	+	+
positive rate (%)	67	100	13	100	60	80	40	73	53	93	100



**Figure.** Typical results of the immunohistochemical analysis. All of the antigens except for CD45RA and CD8 were positive. A: Hematoxylin and Eosin staining, B: BCL11B, C: CD3, D: CD45RA, E: CD45RO, F: Th-POK, G: CD4, H: CD8, I: BCL6, J: CXCL13, K: PD-1, L: SAP. A-C: Patient 15, D-H: Patient 14, I-L: Patient 2

cal characteristics shown in Table 2, the elevation of serum lactate dehydrogenase (LDH) beyond the normal upper limit was significantly associated with the BCL11B expression ( $p=0.0170$ ). The patients in this study were divided into three groups based on the expression of Th-POK and BCL6, consisting of double-positive ( $n=5$ ), Th-POK single-positive ( $n=4$ ), and BCL6 single-positive patients ( $n=6$ ). Th-POK single-positive patients showed a significantly shorter OS

than the other 2 groups (median OS: 33.0 months vs. 74.0 months,  $p=0.020$ ). Five of six BCL6 single-positive patients showed negativity of CD8, although this result was not statistically significant ( $p=0.42$ ).

## Discussion

We detected the master regulators of T (BCL11B), Th

(Th-POK), and TFH (BCL6) cells in 10 (67%), 9 (60%), and 11 (73%) of the 15 AITL patients, respectively. Many functions of BCL11B have been reported. Physiologically, BCL11B plays critical roles in the differentiation (3, 4) and survival (22) of the T-cell lineage identity. In oncogenesis, several contradictory functions of BCL11B have been reported, such as haploinsufficient tumor suppressor effects (23) and anti-apoptosis effects (24). There have also been conflicting findings concerning the expression of *BCL11B* in T-cell lymphoma/leukemia. While monoallelic *BCL11B* deletions or missense mutations are reportedly found in 9% of T-cell acute lymphoblastic leukemia (T-ALL) (23), *BCL11B* mRNA expression has been reported in 36% (8/22) of T-ALL cell lines (25) and acute type adult T-cell leukemia/lymphoma (26). However, to our knowledge, there have been no previous reports concerning the BCL11B expression in AITL patients.

Th-POK and BCL6 are master regulators of Th and TFH lineage commitment, respectively (5, 8, 9), both of which belong to the poxvirus and zinc finger (POZ) and Krüppel-type (POK) protein family. POK family members often act as oncogenes in various hematological malignancies (27). For example, chromosomal translocation involving *PLZF* [t(11; 17) (q23; q21), *PLZF/RARα* and *RARα/PLZF*] is associated with acute promyelocytic leukemia (28). *LRF* acts as a proto-oncogene and is highly expressed in non-Hodgkin's lymphoma (29). Furthermore, the dysregulation of *Th-POK* (30) and *BCL6* (31) causes non-Hodgkin's T- and B-cell lymphoma, respectively. Very few reports have examined the expression of Th-POK in lymphoma, including AITL. We previously reported that Th-POK was immunohistochemically expressed in 10 of 10 PTCL, NOS patients (13). Although Th-POK is a master regulator of CD4-positive/CD8-negative Th lineage commitment (5), our analysis showed that most (5/6) Th-POK-negative patients were also CD4-positive/CD8-negative. However, previous reports have examined the expression of BCL6 in AITL. Yuan et al. reported that extrafollicular BCL6 expression was observed in all 8 AITL patients they analyzed, with values ranging from 10% to 50% (32), and Dupuis et al. reported BCL6 expression in 16 of 21 (76%) AITL patients (16). Recently, a loss-of-function mutation in *TET2* was reported to be frequent (33-83%) in AITL patients, resulting in the deregulated BCL6 expression caused by hypermethylation at intron 1 of *BCL6* (33).

While CD3, a T-cell marker, was positive for all patients in our study, only 47% (7/15) of the patients featured a set of surface antigens compatible with Th (CD4-positive and CD8-negative). As for TFH markers, CXCL13, PD-1, and SAP were positive for 53% (8/15), 93% (14/15), and all (15/15) patients in our study, respectively, the corresponding values reported by other studies were 86% (25/29) (15), 100% (29/29) (16), 86% (42/49) (18), 100% (23/23) (17), and 86% (59/69) (18), respectively. The presence of a polymorphous infiltrate with reactive inflammatory cells often makes the histological diagnosis of AITL difficult. However,

the detection of master regulators of T-cell differentiation in T-cell lymphomas is essential for determining their normal counterparts. An immunohistochemical analysis combining these conventional surface markers and the master regulators of T-cell differentiation may therefore improve the accuracy of the histological diagnosis of AITL.

Because BCL11B, Th-POK and BCL6 play roles not only as master regulators of T-cell differentiation but also in oncogenesis, as described above, the expression of these regulators might be associated with the pathogenesis and clinical findings of AITL. In the present study, the BCL11B expression was significantly associated with the elevation of the serum LDH level beyond its normal upper limit, and Th-POK-positive/BCL6-negative patients showed a worse OS than other patients. Two recent reports regarding the prognosis of AITL were published by the International Peripheral T-cell Project (Prognostic Index for AITL, PIAI) (34) and Japan (AITL Prognostic Index, ATPI) (35). We analyzed only a limited number of patients in the present study. Further investigations including the findings of these master regulators are needed to clarify the clinical characteristics associated with the pathophysiology of T-cell lymphoma.

**The authors state that they have no Conflict of Interest (COI).**

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