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Original Article

BAFF-R is Expressed on B-cell Lymphomas Depending on their Origin, and is Related to Proliferation Index of Nodal Diffuse Large B-cell Lymphomas

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B-cell activating factor receptor (BAFF-R) is one of three known receptors for BAFF. BAFF-R is required for B-cell maturation and survival. We tried to determine the normal pattern of BAFF-R expression in non-neoplastic and neoplastic B- and T-cells. We used immunohistochemistry to evaluate the expression pattern of BAFF-R in non-neoplastic and neoplastic lymphoid tissues of routinely fixed paraffin-embedded samples, and examined the relationships among BAFF-R and expressions of CD10, bcl-6, MUM-1, and MIB-1. BAFF-R expression was detected on B-cells of the mantle zones, some cells within germinal centers, and scattered cells in the interfollicular areas of reactive lymph nodes. BAFF-R expression was only found in B-cell lymphoma (60/120, positive samples/examined samples), but not in T/NK cell lymphoma (0/10) or Hodgkin lymphoma (0/10). The proportions were as follows : follicular lymphoma (14/16), diffuse large B-cell lymphoma (DLBCL) (27/61), mantle cell lymphoma (4/4), and Burkitt lymphoma (0/4). According to Hans' criteria, DLBCLs were subclassified into germinal center B-cell-like (GCB) and non-germinal center B-cell-like (non-GCB) types. Interestingly, in nodal lymphomas, in the GCB subgroup (n = 12), 9 of 12 (75%) were positive for BAFF-R, while 6 of 20 (30%) were positive in the non-GCB subgroup (n = 20) ($p < 0.05$). In addition, expression of BAFF-R related to lower MIB-1 index was associated with GCB-type DLBCL. In conclusion, BAFF-R was only found in some B-cell lymphomas, which was closely associated with the expression pattern in normal counterparts, although BAFF-R expression on follicular lymphoma is different from that on germinal center cells, which is similar to bcl-2. BAFF-R was rather specifically related to low growth activity of GCB-type DLBCL of nodal origin. 〔*J Clin Exp Hematopathol 50(2) : 121-127, 2010*〕

Keywords: BAFF-R, diffuse large B-cell lymphoma, immunohistochemistry

INTRODUCTION

B-cell activating factor belonging to the tumor necrosis factor family (BAFF) is a fundamental survival factor for B-cells, and BAFF functionality is indispensable for B-cell maturation. BAFF is a trimeric membrane-bound or soluble factor, and is produced by monocytes, macrophages, neutrophils, and dendritic cells.[1,2]

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Three receptors for BAFF have been determined : B-cell maturation antigen (BCMA), transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI), and the BAFF-receptor (BAFF-R). All three receptors are expressed on B-cells, while TACI is also expressed on activated T-cells. Ligands of TACI and BCMA are not only BAFF but also a proliferation-inducing ligand (APRIL). However, the only ligand of BAFF-R is BAFF. TACI is known to negatively control B-cell homeostasis and T-cell independent immune responses as determined from studies on TACI-deficient mice. BCMA was recently reported to be essential for the survival of plasma cells. Thus, only BAFF-R is a significant receptor in the successful survival and maturation of B-cells.[1-4] To the best of our knowledge, the distribution of BAFF-R in normal and malignant human lymphoid tissues has not been clarified yet.

Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous group, with morphological subtypes that include centroblastic, immunoblastic, T-cell/ histiocyte-rich, and anaplastic,

according to the WHO classification.[5] The cell origin of DLBCL is thought to be peripheral B-cells of either germinal center or post- germinal center cells,[6] and, interestingly, these subgroups are closely related to patient prognosis.[7] We tried to examine the relationship between BAFF-R and these subgroups of DLBCL with special reference to nodal and extranodal origins. DLBCLs were subclassified into GCB and non-GCB subgroups, which were determined by the expressions of three antigens : CD10, bcl-6, and MUM-1. CD10 is a key marker of germinal center cells, and is found in GCB-type DLBCL, Burkitt lymphomas, and follicular lymphoma. Bcl-6 is highly expressed in germinal center B-cells and tumors derived from germinal centers, such as follicular lymphoma. MUM-1 is a lymphoid-specific member of the interferon regulatory factor of transcription factors, and the protein is normally expressed in plasma cells and a minor subset of germinal center cells. Differences in BAFF-R expressions between sub-groupings of DLBCL, such as GCB versus non-GCB and nodal origins versus extranodal origins, have not yet been investigated in detail.

In the present study, we examined BAFF-R expression in not only B-cell lymphomas but also T-cell lymphomas and Hodgkin lymphomas, and the neoplastic cells of this latter group are also thought to be germinal center B-cells.

MATERIALS AND METHODS

Tissues

Formalin-fixed paraffin-embedded tissues of reactive hyperplasia of lymph nodes and malignant lymphomas were selected from our surgical pathologic file (Table 1). Neoplastic lymphoid tissues from 140 patients with lymphomas were examined in the present study. The examined lymphomas consisted of 5 cases of B-lymphoblastic lymphoma (B-LBL), 4 of B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma (B-CLL/SLL), 4 of mantle cell lymphoma (MCL), 16 of follicular lymphoma (FL), 61 cases of diffuse large B-cell lymphoma (DLBCL) (32 : nodal, 29 : extranodal), 14 of marginal zone B-cell lymphoma (MZL), 2

Table 1. Reactivity of BAFF-R in 140 neoplastic lymphoid tissues according to immunohistochemistry

Type of lymphoma	Positive samples /Examined samples
B-lymphoblastic lymphoma	0/5
Chronic lymphocytic leukemia/Small lymphocytic lymphoma	4/4
Mantle cell lymphoma	4/4
Follicular lymphoma	14/16
Grade 1	5/5
Grade 2	6/6
Grade 3	3/5
Diffuse large B-cell lymphoma	27/61
nodal	15/32
extranodal	12/29
Marginal zone B-cell lymphoma	9/14
Lymphoplasmacytic lymphoma	2/2
Plasma cell myeloma	0/10
Burkitt lymphoma	0/4
Angioimmunoblastic T-cell lymphoma	0/5
Peripheral T-cell lymphoma, unspecified	0/5
Hodgkin lymphoma	0/10
Nodular lymphocyte predominant Hodgkin lymphoma	0/4
Mixed cellularity classical Hodgkin lymphoma	0/3
Nodular sclerosis classical Hodgkin lymphoma	0/3
Total	60/140

of lymphoplasmacytic lymphoma (LPL), 10 of plasma cell myeloma (PCM), 4 of Burkitt lymphoma (BL), 5 of angioimmunoblastic T-cell lymphoma (AITL), 5 of peripheral T-cell lymphoma, unspecified (PTCL), and 10 of Hodgkin lymphoma (HL). FL consisted of 5 cases of grade 1, 6 of grade 2, and 5 of grade 3. HL consisted of 4 cases of nodular lymphocyte predominant Hodgkin lymphoma (NLP-HL), 3 of nodular sclerosis classical Hodgkin lymphoma (NS-CHL), and 3 of mixed cellularity classical Hodgkin lymphoma (MC-CHL).

Immunohistochemistry

Immunohistochemical analysis was performed by the avidin-biotin peroxidase complex method. In brief, deparaffinized 3-μm-thick tissue sections were placed in a microwave oven in 10 mM citrate buffer (pH6.0) for 10 min for antigen retrieval. After tissue sections were blocked with 0.3% hydrogen peroxidase in phosphate-buffered saline for 10 min at room temperature, each section was incubated overnight at 4°C with antibodies against CD10 (56C6, 1:50 ; Novocastra, Newcastle upon Tyne, UK), bcl-6 (PG-B6p, 1:50 ; DAKO, Carpinteria, CA, USA), MUM-1 (MUM1p, 1:40 ; DAKO), and Ki-67 (MIB-1, 1:1,000 ; Novocastra). After washing, samples were incubated with Envision+system labeled Polymer-HRP anti-mouse (DakoCytomation, Kyoto, Japan) for 30 min. Diaminobenzidine with H_2O_2 was used as the chromogen and hematoxylin as the nuclear counter stain. BAFF-R (8A7, 1:1 ; Kobata *et al*.[3]) antibody stainings were performed using a Ventana benchmark machine (Ventana HX system, BenchMark ; Ventana Japan, Tokyo, Japan). Buffer CC2 (Ventana iVIEW DAB Universal Kit) was used for antigen retrieval. Primary antibodies were incubated for 30 min and the DAB detection kit (Ventana iVIEW DAB Universal Kit) was used for the stainings. Expressions of BAFF-R were examined immunohistochemically in all neoplastic lymphoid tissues, but expressions of CD10, bcl-6, MUM-1, and MIB-1 were examined in DLBCL only.

Statistical analysis

We used Fisher's exact test to identify correlations for categorical data. A p value of 0.05 or less was considered as statistically significant in all analyses.

RESULTS

Immunohistochemistry of non-neoplastic lymphoid tissue

Lymphocytes were positive for BAFF-R in the mantle zone, marginal zones of the secondary lymphoid follicles, some germinal center cells, and scattered interfollicular cells (Fig. 1).

Immunohistochemistry of the neoplastic lymphoid tissue

The expression of BAFF-R on malignant lymphomas is summarized in Table 1. BAFF-R expression was only found in B-cell lymphomas (60/120 sampled), but not in T/NK cell lymphomas (0/10) or in HLs (0/10).

For the B-cell lymphomas, BAFF-R[8] was detected in all of the examined cases of MCL (4/4) and CLL/SLL (4/4), and most of those of MZL (9/14) and FL (14/16) (Fig. 2). Approximately half (44.3%) of DLBCLs (27/61) (15/32 : nodal, 12/29 : extranodal) were positive for BAFF-R (Fig. 3). BAFF-R was detected predominantly on the lymphoid component of lymphoplasmacytic lymphomas but not on plasmacytic cells. Similarly, the malignant plasma cells of multiple myeloma (0/10) were negative for BAFF-R.

None of the B lymphoblastic lymphoma (0/5) was positive for BAFF-R. BL (0/4), and cases of NLPHL (0/4) were also negative for BAFF-R. Reed-Sternberg cells of classical HL were negative for BAFF-R.[9]

Immunohistochemistry of BAFF-R and germinal center markers in DLBCL

In nodal DLBCLs, BAFF-R was expressed in 15 of 32 (47%) cases, CD10 was expressed in 5 of 32 (16%), bcl-6 protein was expressed in 20 of 32 (63%), and MUM-1 was expressed in 21 of 32 (66%) (Table 2). In extranodal DLBCLs, BAFF-R was expressed in 12 of 29 (41%) cases, CD10 was expressed in 8 of 29 (28%), bcl-6 protein was expressed in 16 of 29 (55%), and MUM-1 was expressed in 12 of 29 (41%) (Table 3). In DLBCLs (nodal + extranodal), BAFF-R was expressed in 27 of 61 (44%) cases, CD10 was expressed in 13 of 61 (21%), bcl-6 protein was expressed in 36 of 61 (59%), and MUM-1 was expressed in 33 of 61 (54%) (Table 4).

According to Hans' criteria, 12 nodal DLBCLs were of GCB-type and 9 (75%) of these were positive for BAFF-R. Twenty nodal DLBDLs were of non-GCB-type and 6 (30%) of these were positive for BAFF-R (Table 2). In addition, 14 extranodal DLBCLs were of GCB-type and 8 (57%) of these were positive for BAFF-R. Fifteen extranodal DLBCLs were of non-GCB-type and 4 (27%) of these were positive for BAFF-R (Table 3). Furthermore, 26 DLBCLs (nodal + extranodal) were of GCB-type and 17 (65%) of these were positive for BAFF-R. Thirty-five DLBCLs (nodal + extranodal) were of non-GCB-type and 10 (29%) of these were positive for BAFF-R (Table 4).

BAFF-R expression and proliferation index assessed by MIB-1 immunostaining in DLBCL

BAFF-R expression was correlated with a low proliferation index assessed by MIB-1 immunostaining in nodal

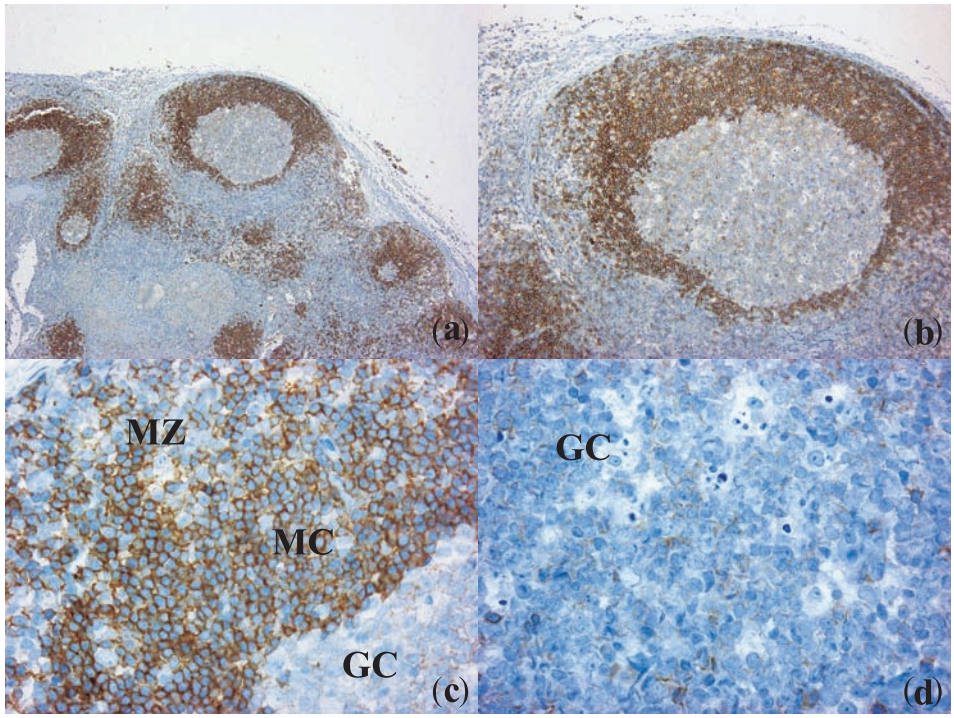

Fig. 1. The expression of BAFF-R in normal lymphoid tissue according to immunohistochemistry (IHC) on paraffin-embedded sections. (***1a***, ***1b***) BAFF-R reacts with lymphocytes in the mantle zone of the secondary lymphoid follicles in the lymph node. (*1a*) ×40, (*1b*) ×100. (***1c***, ***1d***) Lymphocytes in the mantle zone (*MC*) and marginal zone (*MZ*) are positive for BAFF-R. In germinal center (*GC*), BAFF-R expression is very weak or faint. (*1c*) & (*1d*) : ×400.

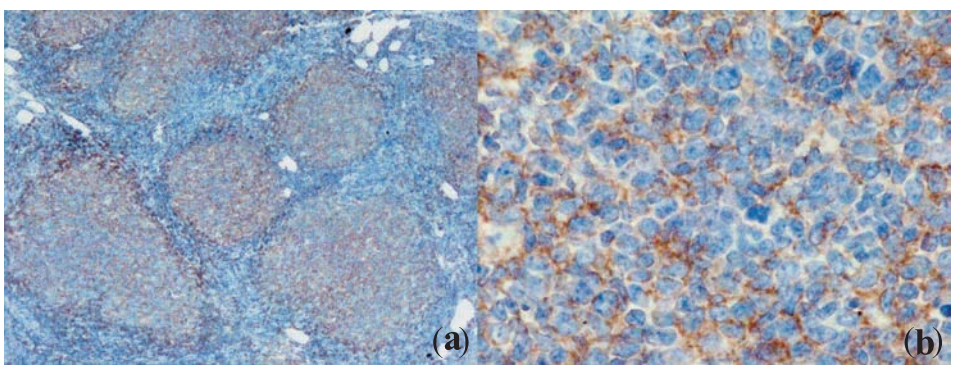

Fig. 2. BAFF-R is expressed on most follicular lymphomas. (*2a*) ×40 ; (*2b*) ×400.

DLBCL. Among BAFF-R-positive samples (n = 15), the average MIB1 index was 37.3%, while it was 52.4% in BAFF-R-negative samples (n = 17) (p = 0.041) (Table 5) (Fig. 4). Among GCB-type DLBCL samples (n = 12), the average MIB1 index was 36.7%, while it was 50.5% in non-GCB samples (n = 20) (p = 0.070) (Table 5) (Fig. 5).

In contrast, in extranodal DLBCL, BAFF-R expression was not correlated with a low proliferation index assessed by MIB-1 immunostaining in DLBCL. Among BAFF-R-positive samples (n = 12), the average MIB1 index was 62.5%, while it was 52.9% in BAFF-R-negative samples (n = 17) (Table 6). Among GCB-type DLBCL samples (n = 14), the average MIB1 index was 55.0%, while it was 58.7% in non-GCB samples (n = 15) (Table 6).

DISCUSSION

In reactive lymph nodes, BAFF-R expression was de-

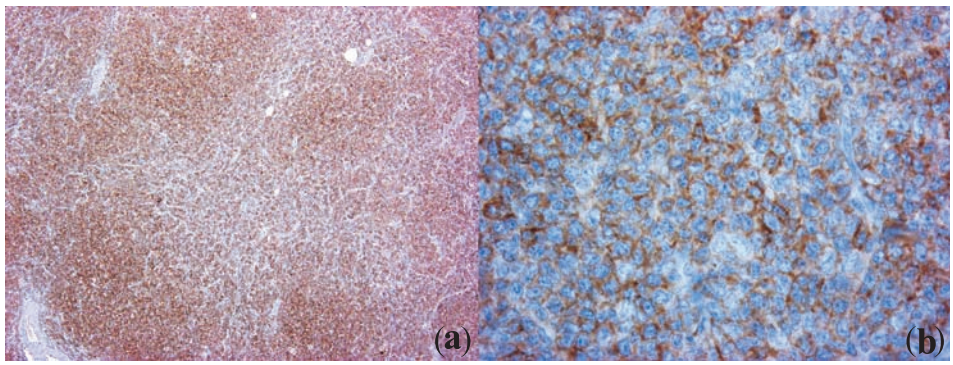

Fig. 3. BAFF-R is expressed on some diffuse large B-cell lymphomas (*3a*) ×40 ; (*3b*) ×400.

Table 2. Relationship between BAFF-R and germinal center markers in DLBCL (nodal)

Marker/Immunological subgroup	BAFF-R		Total	P-value
	+	−		
CD10 (+)	5 (100%)	0 (0%)	5	0.015
bcl-6 (+)	8 (40%)	12 (60%)	20	0.261
MUM-1 (+)	9 (43%)	12 (57%)	21	0.398
GCB	9 (75%)	3 (25%)	12	0.017
non-GCB	6 (30%)	14 (70%)	20	
Total	15 (47%)	17 (53%)	32	

DLBCL, diffuse large B-cell lymphoma ; BAFF-R, B-cell activating factor belonging to the tumor necrosis factor family receptor ; GCB, germinal center B-cell lymphoma ; non-GCB, non-germinal center B-cell lymphoma

Table 3. Relationship between BAFF-R and germinal center markers in DLBCL (extranodal)

Marker/Immunological subgroup	BAFF-R		Total	P-value
	+	−		
CD10 (+)	4 (50%)	4 (50%)	8	0.432
bcl-6 (+)	9 (56%)	7 (44%)	16	0.076
MUM-1 (+)	4 (33%)	8 (67%)	12	0.363
GCB	8 (57%)	6 (43%)	14	0.099
non-GCB	4 (27%)	11 (73%)	15	
Total	12 (41%)	17 (59%)	29	

DLBCL, diffuse large B-cell lymphoma ; BAFF-R, B-cell activating factor belonging to the tumor necrosis factor family receptor ; GCB, germinal center B-cell lymphoma ; non-GCB, non-germinal center B-cell lymphoma

Table 4. Relationship between BAFF-R and germinal center markers in DLBCL

Marker/Immunological subgroup	BAFF-R		Total	P-value
	+	−		
CD10 (+)	9 (69%)	4 (31%)	13	0.042
bcl-6 (+)	17 (47%)	19 (53%)	36	0.384
MUM-1 (+)	13 (39%)	20 (61%)	33	0.284
GCB	17 (65%)	9 (35%)	26	0.004
non-GCB	10 (29%)	25 (71%)	35	
Total	27 (44%)	34 (56%)	61	

DLBCL, diffuse large B-cell lymphoma ; BAFF-R, B-cell activating factor belonging to the tumor necrosis factor family receptor ; GCB, germinal center B-cell lymphoma ; non-GCB, non-germinal center B-cell lymphoma

Table 5. Average of MIB-1 index of BAFF-R, GCB, and non-GCB (nodal DLBCL)

BAFF-R/Immunological subgroup	Average of MIB-1 index	P-value
BAFF-R (+)(n= 15)	37.33%	0.041
BAFF-R (-) (n= 17)	52.35%	
GCB (n= 12)	36.67%	0.070
non-GCB (n= 20)	50.50%	

DLBCL, diffuse large B-cell lymphoma ; BAFF-R, B-cell activating factor belonging to the tumor necrosis factor family receptor ; GCB, germinal center B-cell lymphoma ; non-GCB, non-germinal center B-cell lymphoma

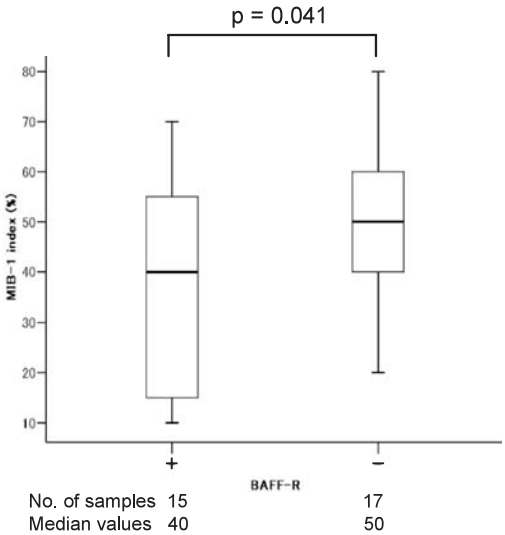

Fig. 4. MIB-1 index according to BAFF-R

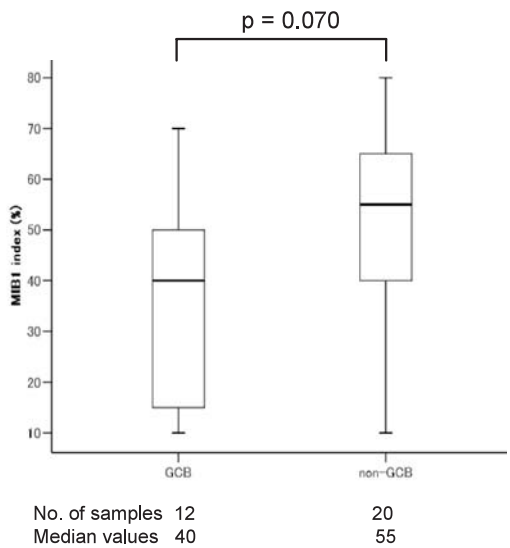

Fig. 5. MIB-1 index according to phenotype

Table 6. Average of MIB-1 index of BAFF-R, GCB, and non-GCB (extranodal DLBCL)

BAFF-R/Immunological subgroup	Average of MIB-1 index	P-value
BAFF-R (+)(n = 12)	62.50%	0.315
BAFF-R (−) (n = 17)	52.94%	
GCB (n = 14)	55.00%	0.698
non-GCB (n = 15)	58.67%	

DLBCL, diffuse large B-cell lymphoma ; BAFF-R, B-cell activating factor belonging to the tumor necrosis factor family receptor ; GCB, germinal center B-cell lymphoma ; non-GCB, non-germinal center B-cell lymphoma

tected on B-cells of the mantle zones, some of the cells within germinal centers, and scattered cells in the interfollicular areas. In germinal centers, BAFF-R expression was very weak or faint (Fig. 1). BAFF-R expression exhibited similar patterns between non-neoplastic lymph node and malignant lymphomas. However, a difference is that FL expressed BAFF-R (Fig. 2). This result is similar to the fact that bcl-2 expression is detected in FL. BAFF-R might have a similar mechanism to that of bcl-2. In BL, neither BAFF-R nor bcl-2 was detected. The reason for this is unclear. According to this finding, BAFF-R might not be expressed at the early stage of germinal centers.

BAFF-R was shown to be required for B-cell maturation and survival, and BAFF-R expression was not observed in T-cell lymphoma or HL.[9] In B-cell lymphoma, BAFF-R was not detected at the immature stage of lymphoblastic lymphomas or the final differentiated stage of plasmacytic lymphomas. In contrast, BAFF-R was found on mature-type lymphomas such as CLL, MCL, FL, and DLBCL. These findings strongly suggest that BAFF-R plays roles in cellular survival and the differentiation of peripheral B-cells, which is related to its expression in non-neoplastic lymph nodes. The lack of BAFF-R on plasmacytic cells indicated that these cells are end-stage B-cells and thus require no differentiation. Furthermore, the lack of BAFF-R on HL may be related to their cellular origin.[9]

In the present series, nodal DLBCL consisted of 12 cases of GCB type and 20 of non-GCB type. The rate of positivity for BAFF-R of the former group was significantly higher than that of the latter group ($p = 0.017$). Extranodal DLBCL consisted of 14 cases of GCB type and 15 of non-GCB type. The rate of positivity for BAFF-R of the former group was higher than that of the latter group, although the difference was not significant ($p = 0.099$). In DLBCL (nodal and extranodal), BAFF-R expression was significantly associated with GCB-type DLBCL ($p = 0.004$). These results show that BAFF-R expression in nodal DLBCL was associated with GCB-type DLBCL. GCB-type DLBCL is thought to originate from germinal centers, and it is known to at least be related to germinal centers, although it is a malignant tumor. BAFF-R was detected on most FLs (87.5%). It is of interest that GCB-type DLBCL showed germinal-center-related molecules by DNA microarray analyses, and there were similar findings from the point of view of BAFF-R.

Some studies have reported a good prognosis of GCB-type DLBCL.[10-12] We focused on the proliferation index (MIB-1 index) of DLBCL, and found that cases of nodal DLBCL that were BAFF-R-positive had a significantly lower proliferation index than those that were BAFF-R-negative. It has been reported that patients with a low proliferation index tend to show a better prognosis than those with a high proliferation index.[13] This is thought to be due to the fact that BAFF-R expression in nodal DLBCL is associated with GCB-

type DLBCL. BAFF-R is required for B-cell maturation and survival, so DLBCL with BAFF-R expression might inhibit initiation of the cell cycle.

In extranodal DLBCL, high BAFF-R expression was not correlated with a low proliferation index. This may indicate that the properties of DLBCL differ between organs. It has also been reported that many genes were found to be differentially expressed in extranodal DLBCL compared with those in nodal DLBCL.[14] The results of the relationship between BAFF-R and MIB-1 index were interesting : BAFF-R was rather strongly associated with low growth activity of GCB-type DLBCL of nodal origin but not with that of extranodal origin. The reason for this finding has not been clarified yet. However, nodal and extranodal lymphomas are quite different in some respects. The MALT lymphoma related to chronic inflammation is specific for extranodal sites, while follicular lymphoma is predominantly of nodal origin, with the exception of the duodenum. The proportions of GCB- versus non-GCB-type DLBCLs in extranodal organs are not uniform : the vast majority of gastric, breast, CNS, testicular, and adrenal DLBCLs are of non-GCB type, whereas thyroid ones are predominantly of GCB type. These findings suggest that the pathogenesis of lymphomas of extranodal sites is not the same as that of nodal ones. If this is the case, nodal and extranodal GCB-type DLBCLs might not be the same. As a matter of fact, although the patients with non-GCB-type DLBCL show poor prognosis in general, patients with gastric DLBCL show excellent prognosis, although most of them are of non-GCB type. BAFF-R is related to the cellular maturation of B-cells, and matured-differentiated cells show low mitotic activity, although the exact mechanisms behind this remain unclear.

In conclusion, BAFF-R was only found in some B-cell lymphomas, and was closely associated with the expression pattern in normal counterparts. BAFF-R was rather strongly associated with low growth activity of GCB-type DLBCL of nodal origin.

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