Cytokine BAFF Gene Variation Is Associated with Survival of Patients with T-cell Lymphomas

Kan Zhai1, Xiaobo Tian3, Chen Wu1, Ning Lu2, Jiang Chang1, Liming Huang1, Tongwen Zhang1, Yuling Zhou1, Yan Qiao1, Dianke Yu1, Wen Tan1, Jieping Chen3, and Dongxin Lin1

Abstract

**Purpose:** Cytokine BAFF is a potent molecule for the activation and survival of B cells, and it also plays an important role in T-cell function. Genetic polymorphism (rs9514828C>T) in BAFF has been associated with elevated BAFF transcription. We sought to determine whether rs9514828 is associated with T-cell lymphoma (TCL) survival.

**Experimental Design:** BAFF rs9514828 genotypes and survival of TCL were analyzed in the discovery group including 150 patients, and the results were replicated in an independent validation group of 120 patients. Kaplan–Meier analysis was conducted to compare survival among different genotypes. Cox proportional hazard models were used to identify independent significant variables. Luciferase reporter gene assays were conducted to examine the function of rs9514828 variant.

**Results:** We found that BAFF rs9514828 polymorphism was significantly associated with TCL survival. In pooled analysis of two independent groups, the favorable rs9514828 TC and TT genotypes had significantly better five-year survival rates compared with the CC genotype (47% and 53% vs. 22%, \( P = 2.27 \times 10^{-5} \) for log-rank test). Multivariate Cox regression analysis showed that rs9514828 was an independent prognostic factor, with HRs for patient death being 0.48 [95% confidence interval (CI), 0.32–0.71] for the CT and 0.47 (95% CI, 0.23–0.93) for the TT genotypes. Reporter gene assays indicated that the rs9514828T allele had significantly higher promoter activity than the rs9514828C counterpart.

**Conclusion:** These findings suggest that functional polymorphism in BAFF might be a genetic determinant for the survival of patients with TCL. Clin Cancer Res; 18(8); 2250–6. ©2012 AACR.

Introduction

T-cell non–Hodgkin lymphomas (TCL), several entities with great clinical, histologic, and biologic heterogeneity, represent approximately 12% of all malignant lymphomas (1). The incidence of peripheral TCL (PTCL) and natural killer/TCL (NKTCL) is relatively higher in Asian countries than that in Western countries, with approximately 15% to 20% of all malignant lymphomas (2). High prevalence of PTCL and NKTCL in Asian countries may reflect particular exposure or genetic susceptibility to pathogenic agents such as human T-cell virus 1 and Epstein-Barr virus (3). Clinical outcome of patients with PTCL and NKTCL is usually worse than that of patients with aggressive B-cell lymphoma, not only because of more frequent adverse clinical features at diagnosis, a lower response rate to chemotherapy, and a higher incidence of relapses, but also because of the association of T-cell phenotype itself with a poor prognosis independent of other prognostic factors (4). The International Prognostic Index (IPI) and Prognostic Index for PTCL unspecified, which are based on age, performance status, lactate dehydrogenase (LDH), stage, extranodal involvement, and bone marrow involvement, have been used in clinic as prognostic indices for PTCL and NKTCL, however, they are not so satisfactory for all patients (5, 6), suggesting that there might be other factors determining prognosis of these diseases. In recent years, evidence has been accumulated to show that genetic variations such as single-nucleotide polymorphisms (SNP) in both tumor and host genomes may play a role in treatment outcome and survival of patients with cancer (7–9). However, to the best of our knowledge, little has been known about the association between genetic polymorphisms and TCL survival.

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Several genetic variations have been identified in the development and progression of B-cell malignancies (10–14). We have shown that overexpression of BAFF promotes B-cell–mediated cell proliferation and survival, making it a potent molecule for B-cell proliferation and survival. BAFF has been described as a member of TNF superfamily ligand that is expressed on the cell surface or cleaved and secreted. It has been characterized as a key cytokine involved in the activation and survival of B and T cells, and genetic variations in the BAFF gene have been shown to affect BAFF expression. In this study, we found for the first time that functional single-nucleotide polymorphism in BAFF (rs9514828), resulting in significantly elevated BAFF promoter activity, was independently associated with better survival of patients with T-cell lymphomas (TCL), a group of malignancies that genetic determinants for their survival were largely unknown. Thus, the single-nucleotide polymorphism rs9514828 may be a prognostic biomarker for TCLs. In addition, this study suggests that cytokine BAFF may be a target for the treatment of TCLs.

**Translational Relevance**

BAFF is a key cytokine involved in the activation and survival of B and T cells, and genetic variations in the BAFF gene have been shown to affect BAFF expression. In this study, we found for the first time that functional single-nucleotide polymorphism in BAFF (rs9514828), resulting in significantly elevated BAFF promoter activity, was independently associated with better survival of patients with T-cell lymphomas (TCL), a group of malignancies that genetic determinants for their survival were largely unknown. Thus, the single-nucleotide polymorphism rs9514828 may be a prognostic biomarker for TCLs. In addition, this study suggests that cytokine BAFF may be a target for the treatment of TCLs.

BAFF is a key cytokine involved in the activation and survival of B and T cells, and genetic variations in the BAFF gene have been shown to affect BAFF expression. In this study, we found for the first time that functional single-nucleotide polymorphism in BAFF (rs9514828), resulting in significantly elevated BAFF promoter activity, was independently associated with better survival of patients with T-cell lymphomas (TCL), a group of malignancies that genetic determinants for their survival were largely unknown. Thus, the single-nucleotide polymorphism rs9514828 may be a prognostic biomarker for TCLs. In addition, this study suggests that cytokine BAFF may be a target for the treatment of TCLs.

Cytokine BAFF (also known as B-cell activating factor), is a member of TNF superfamily ligand that is expressed on the cell surface or cleaved and secreted. BAFF has been described as a potent molecule for B-cell proliferation and survival, which plays important roles in the immune system, especially in the B-cell arm. However, previous studies have shown that overexpression of BAFF promotes B-cell–mediated autoimmune disorders and is implicated in the development and progression of B-cell malignancies (10–14). Several genetic variations have been identified in BAFF and some variant genotypes have been shown to be associated with BAFF transcription and high risk of B-cell lymphoma (15–17). The rs9514828C to T change in the promoter region of BAFF has been previously associated with elevated transcription of BAFF, and the variant rs9514828T allele seemed more prevalent in patients with familial chronic lymphocytic leukemia than in controls (18). Interestingly, accumulating evidence has shown that BAFF also plays a role in promoting T-cell proliferation and survival (19–23). Although overexpression of BAFF might have harmful effects such as the association with the development of B-cell–mediated autoimmune disorders and malignancies, it might otherwise favor cytotoxic T cells to protect against some types of cancer because antitumor T cells play a pivotal role in immune surveillance of cancer cells. To test this hypothesis, we examined whether rs9514828 SNP is associated with overall survival of patients with TCL.

**Patients and Methods**

**Patients**

This study consisted of 2 stages of test and validation. The test group consisted of 150 patients collected at Tumor Research Institute, Chinese Academy of Medical Sciences in Beijing (China) between January 1992 and April 2009, and the validation group included 120 patients recruited at Southwest Hospital, the third Military Medical University in Chongqing (China) between January 1994 and September 2009. All patients were unrelated ethnic Han Chinese and diagnosed with histologically confirmed TCL. In this study, we classified TCL as T-acute lymphoblastic leukemia/lymphoblastic lymphoma (T-ALL/LBL), PTCL, anaplastic large-cell lymphoma (ALCL), mycosis fungoides, and adult T-cell leukemia/lymphoma (ATCL). The tumor staging was defined with Ann Arbor system (24). Most patients with TCL were treated with CHOP (cyclophosphamide–adriamycin–vincristine–prednisone)-based regimen as the first-line chemotherapy. Forty-nine patients with T-ALL/LBL were treated with hyper-CVADA/B (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone plus high-dose methotrexate-cytarabine) regimen. Eight patients treated with CHOP-based regimen in test group also received stem cell transplantation. Overall survival time of patients was measured from the date of diagnosis to the date of last follow-up or death. Whether and when a patient had died were obtained from inpatient and outpatient records, patients' families, or local Public Security Census Register Office through follow-up telephone calls. The last date of follow-up was February 28, 2011. Patients alive on the last follow-up date were considered censored. At recruitment, personal data from each participant about demographic information and clinical characteristics were collected via clinical record. This study was approved by the Institutional Review Board of both Chinese Academy of Medical Sciences Cancer Institute and The Third Military Medical University Southwest Hospital.

**BAFF rs9514828 genotype analysis**

Genomic DNA samples were extracted from peripheral blood lymphocytes (75.2%) and paraffin-embedded biopsy tissues (24.8%) of patients. BAFF rs9514828 genotypes were analyzed by PCR-based RFLP method. The PCR primers used to amplify the DNA fragment containing the rs9514828 SNP were 5′-cagagttctgaggctttaagtccgc-3′ and 5′-gggacagtcaaccagggattg-3′. The PCR products were digested with restriction enzyme BstUI (New England Biolabs) and subjected to 3.5% agarose gel electrophoresis to determine their genotypes. The samples were tested twice by different persons, and the results were 99.6% concordant.

**Luciferase reporter gene assays**

A 2,134-bp DNA fragment corresponding to the BAFF 5′-untranslated region and 5′-flanking region and containing the C allele at −871 nucleotide position relative to the transcriptional start site (rs9514828C allele) was generated by PCR with primers of 5′-cagagttctgaggctttaagtccgc-3′/5′-taagatctttctttcagcctgaagc-3′ and subcloned into the pGL3-Basic vector (Promega). The resultant plasmid was designated as p-T. The p-C construct was then site-specifically mutated to create the p-T construct, which contains the T at −871 position (rs9514828T allele). These 2 constructs were restriction mapped and sequenced to confirm their authenticity. Jurkat E6-1, HuT 102, and HEK-293 cells were transduced with the p-T construct and then subjected to luciferase reporter gene assays to determine the transcriptional activity of BAFF promoter region.
lines was provided by ATCC through short tandem repeat profiling, karyotyping, and cytochrome c oxidase I testing. We seeded 5 × 10^5 Jurkat E6-1, HuT 102, or HEK-293 cells per well in 48-well plates and transfected them with an empty pGL3-Basic vector (a promoterless control), p-C or p-T construct. pRL-SV40 plasmid (Promega) was cotransfected as a normalizing control. For each plasmid, 3 independent transfections were carried out and each was done in triplicate. After 48 hours of incubation in RPMI-1640 with 10% FBS in a humidified, 5% CO_2 incubator at 37°C, cells were collected and analyzed for the luciferase activity with a Dual-Luciferase Reporter Assay System (Promega).

**Statistical analysis**

Cox regression under a log-additive genetic model was conducted for BAFF genotypes with adjustment for covariates that might influence patients' survival including sex and IPI score. HRs and their 95% confidence intervals (CI) were calculated. Kaplan–Meier survival estimates were plotted and P values were assessed using log-rank tests. The survival package in R was used to conduct the analyses of TCL-related death. The Student t test was used to examine the differences in luciferase reporter gene expression. All statistical tests were carried out in a 2-sided manner and P less than 0.05 was considered as statistical significance.

**Results**

**Patient characteristics**

The basic clinical characteristics of patients in the test and the validation panels are shown in Table 1. In this study, the most common subtype of TCL was PTCL (61.1%), followed by ALCL (18.9%) and T-ALL/LBL (18.1%), although their distributions were somewhat different between the test and the validation groups. By the time of final analysis on February 28 2011, 68 patients (45.3%) in the test group died of TCL and the median survival time was 39 months. Among the patients in the validation group, 54 (45%) died of the cancer with the median survival time of 46 months. For pooled sample of

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Test group (N = 150)</th>
<th>Validation group (N = 120)</th>
<th>Pooled sample (N = 270)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>68 (45.3)</td>
<td>54 (45.0)</td>
<td>122 (45.2)</td>
</tr>
<tr>
<td>Survival</td>
<td>82 (54.7)</td>
<td>66 (55.0)</td>
<td>148 (54.8)</td>
</tr>
<tr>
<td>Median survival, month</td>
<td>39</td>
<td>46</td>
<td>40</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>101 (67.3)</td>
<td>81 (67.5)</td>
<td>182 (67.4)</td>
</tr>
<tr>
<td>Female</td>
<td>49 (32.7)</td>
<td>39 (32.5)</td>
<td>88 (32.6)</td>
</tr>
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<td>Age, year</td>
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</tr>
<tr>
<td>≤60</td>
<td>127 (84.7)</td>
<td>109 (90.8)</td>
<td>236 (87.4)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>23 (15.3)</td>
<td>11 (9.2)</td>
<td>34 (12.6)</td>
</tr>
<tr>
<td>Subtype</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>T-ALL/LBL</td>
<td>19 (12.7)</td>
<td>30 (25.0)</td>
<td>49 (18.1)</td>
</tr>
<tr>
<td>PTCL</td>
<td>94 (62.7)</td>
<td>71 (59.2)</td>
<td>165 (61.1)</td>
</tr>
<tr>
<td>ALCL</td>
<td>36 (24.0)</td>
<td>15 (12.5)</td>
<td>51 (18.9)</td>
</tr>
<tr>
<td>Other^a</td>
<td>1 (0.6)</td>
<td>4 (3.3)</td>
<td>5 (1.9)</td>
</tr>
<tr>
<td>Stage^b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>15 (10.0)</td>
<td>28 (23.3)</td>
<td>43 (15.9)</td>
</tr>
<tr>
<td>II</td>
<td>31 (20.7)</td>
<td>37 (30.9)</td>
<td>68 (25.2)</td>
</tr>
<tr>
<td>III</td>
<td>26 (17.3)</td>
<td>15 (12.5)</td>
<td>41 (15.2)</td>
</tr>
<tr>
<td>IV</td>
<td>78 (52.0)</td>
<td>40 (33.3)</td>
<td>118 (43.7)</td>
</tr>
<tr>
<td>IPI score^c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>17 (11.3)</td>
<td>30 (25.0)</td>
<td>47 (17.4)</td>
</tr>
<tr>
<td>1</td>
<td>48 (32.0)</td>
<td>41 (34.2)</td>
<td>89 (33.0)</td>
</tr>
<tr>
<td>2</td>
<td>38 (25.4)</td>
<td>32 (26.7)</td>
<td>70 (25.8)</td>
</tr>
<tr>
<td>3</td>
<td>25 (16.7)</td>
<td>12 (10.0)</td>
<td>37 (13.7)</td>
</tr>
<tr>
<td>4</td>
<td>15 (10.0)</td>
<td>3 (2.5)</td>
<td>18 (6.7)</td>
</tr>
<tr>
<td>5</td>
<td>5 (3.3)</td>
<td>0 (0.0)</td>
<td>5 (1.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (1.3)</td>
<td>2 (1.6)</td>
<td>4 (1.5)</td>
</tr>
</tbody>
</table>

^aOther includes mycosis fungoides and ATCL.

^bDefined with Ann Arbor staging system.

^cIPI comprising of age, stage, extranodal sites, serum LDH level, and ECOG PS.
The genotyping results of rs9514828 SNP in the test group, validation group, and pooled sample are shown in Table 3. The T allele was the minor allele in both test group, validation group, and pooled sample.

Comparison of survival according to clinical characteristics of patient

We first wanted to test whether various clinical characteristics contribute to survival. Patients were grouped according to sex, age (≤60 y or >60 years), subtype (precursor T type or mature T type), stage, LDH level, Eastern Cooperative Oncology Group performance status (ECOG PS), extranodal site, and IPI score. We found that all these characteristics except sex significantly affected patients’ survival when analyzed using univariate Cox regression model. However, when analyzed using multivariate model, subtype and extranodal involvement site became insignificant for overall survival (Table 2). In pooled sample, the median survival time of patients with IPI scores 0/1, 2/3, and 4/5 were 81.0, 20.0, and 7.0 months, respectively.

Effect of BAFF genotype on patient survival

The genotyping results of BAFF rs9514828 SNP in the test group, validation group, and pooled sample are shown in Table 3. The T allele was the minor allele in both test and validation groups, with the frequency being 0.380 and 0.458, respectively. There was no significant association between this SNP and sex, age, subtype, stage, LDH level, extranodal site, and IPI score (data not shown). However, the genotypes of this SNP were significantly associated with survival of patients with TCL in both test and validation groups. After adjusting for covariates including sex, subtype, and IPI score, the rs9514828CT and TT genotypes were associated with better overall survival, with the HRs being 0.48 (95% CI, 0.32–0.71; P = 0.0002) and 0.47 (95% CI, 0.23–0.93; P = 0.0306) in pooled sample of the test and validation groups. Five-year overall survival rates in pooled sample were 53% (95% CI, 28–79) for patients with the rs9514828TT genotype, 47% (95% CI, 37–57) for patients with the rs9514828CT genotype, and 22% (95% CI, 7–38) for patients with the rs9514828CC genotype (P = 2.27 × 10⁻³ by log-rank test; Fig. 1). In the dominant genetic model, the rs9514828T allele also showed better overall survival than the rs9514828C allele, with the adjusted HR for the rs9514828T allele (CT and TT genotype) being 0.48 (95% CI, 0.33–0.70; P = 0.002; Table 3).

Table 2. Univariate and multivariate Cox regression for overall survival of patients with TCL

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Sex</td>
<td>0.91 (0.62–1.34)</td>
<td>0.6420</td>
</tr>
<tr>
<td>Age</td>
<td>1.83 (1.14–2.94)</td>
<td>0.0118</td>
</tr>
<tr>
<td>Subtype</td>
<td>0.52 (0.34–0.80)</td>
<td>0.0029</td>
</tr>
<tr>
<td>Stage</td>
<td>1.46 (1.23–1.72)</td>
<td>0.0001</td>
</tr>
<tr>
<td>LDH level</td>
<td>1.35 (1.05–1.72)</td>
<td>0.0001</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>1.75 (1.39–2.19)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Extranodal site</td>
<td>1.83 (1.28–2.63)</td>
<td>0.0010</td>
</tr>
<tr>
<td>IPI score</td>
<td>1.36 (1.22–1.52)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Table 3. Five-year survival rate and HRs for death of rs9514828 genotype in patients with TCL in the test group, validation group, and pooled sample

<table>
<thead>
<tr>
<th>Genotype</th>
<th>FYS (%)</th>
<th>HRb (95% CI)</th>
<th>P</th>
<th>FYS (%)</th>
<th>HRb (95% CI)</th>
<th>P</th>
<th>FYS (%)</th>
<th>HRb (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>52 36</td>
<td>1.00 (reference)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>82 45</td>
<td>0.62 (0.36–1.04)</td>
<td>0.0707</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td>16 25</td>
<td>0.74 (0.27–2.01)</td>
<td>0.5493</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT + TT</td>
<td>98 43</td>
<td>0.64 (0.38–1.07)</td>
<td>0.0858</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: FYS, five-year survival rate.

*Number of patients.

1Calculated with multivariate Cox models and adjusted for sex, subtype, and IPI score.
Effect of rs9514828 SNP on BAFF promoter activity

Regulatory sequences with discrete alleles might influence gene expression upon binding transcriptional activators or inhibitors that instruct their regulatory control. To evaluate whether the rs9514828C to T change has effect on the BAFF promoter activity, a set of luciferase reporter gene constructs were made and were transiently transfected into HEK-293, Jurkat E6-1, and HuT 102 cells, the latter 2 are TCL cell lines. As expected, the p-T construct containing the rs9514828T allele drove a significantly higher reporter gene expression than that containing the rs9514828C allele in all the 3 cell lines (all \( P < 0.05 \); Fig. 2), confirming that this SNP is of functional significance.

Discussion

Because rs9514828 has been shown to be a functional SNP in the promoter region of BAFF, a gene that plays a role in promoting proliferation and survival of T cells (19–23), we examined its association with survival of patients with TCL. By choosing TCL as disease model, we might be able to check whether this SNP affects TCL cells directly or normal antitumor T-cell system alternatively. We speculated that if this SNP affects TCL cells predominantly, the T allele would be the risk allele because it prompts TCL cell to survive, otherwise the T allele would be the favorable allele for patient survival because it may prompt antitumor T-cell activation and survival, which in turn may have higher capacity to eliminate TCL cells. Our results showed that rs9514828T allele is the favorable allele for TCL patient survival, confirming our latter hypothesis. To the best of our knowledge, this is the first report investigating germline genetic variation in BAFF and TCL survival.

Previous studies have shown that overexpression of BAFF are implicated in some autoimmune disorders and associated with the development and progression of B-cell malignancies (10–14). In B-cell lymphoma, both autocrine and paracrine expression of BAFF results in degradation and phosphorylation of IK-Bε and activation of NF-κB pathway, and incubation of B lymphoma cells with BAFF causes downregulation of apoptotic proteins Bax and upregulation of antiapoptotic proteins Bcl-2 and Bcl-xL (25). Although overexpression of BAFF might be implicated in B-cell lymphoma development and progression, no such effect has been reported on TCL. However, evidence has been accumulated to show that BAFF also have profound effects on T-cell activation and survival (19–23). Importantly, previous studies in vitro and in vivo in BAFF transgenic mice have shown that BAFF preferentially stimulates T-helper cell 1 (Th1) but suppresses Th2 activity (22, 26), which is well known to be critical important in anticancer immune response. rs9514828 is located in the promoter region of the BAFF gene and the C to T change has been shown to be correlated with elevated promoter activity and BAFF transcription (ref. 18 and this study). In our study, patients with at least one rs9514828T allele (CT or TT genotype) had longer survival time than patients with the rs9514828C allele, which is in line with these previous findings showing BAFF as a Th1 response–promoting cytokine.

The major strength of this study is the 2-stage design in which patients with TCL were recruited from 2 different hospitals for association discovery and validation, which
Prompts antitumor T cells to survive and to differentiate BAFF in individuals carrying the rs9514828T allele, which might be mediated by constitutively higher expression of better overall survival of patients with TCL. This association in the discovery group was only marginally significant and was not significant in T-ALL/LBL subtype (n = 49). Therefore, larger studies are warranted to confirm the effects of rs9514828 SNP in other ethnic patient cohorts. Second, the underlying mechanism for the association between the genetic polymorphism in BAFF and survival of TCL remains to be elucidated although antican-cer T-cell immunity would be involved. In addition, in this study, we recruited both aggressive T-ALL/LBL and relatively indolent mycosis fungoides (3 cases in the validation group). Because the natural histories of these diseases can be quite different, it might affected the median survival time of the test and the validation groups. However, this would not bias our results of survival time associated with BAFF genotypes.

In conclusion, our study showed that rs9514828C>T SNP in the promoter region of the BAFF gene is associated with better overall survival of patients with TCL. This association might be mediated by constitutively higher expression of BAFF in individuals carrying the rs9514828T allele, which prompts antitumor T cells to survive and to differentiate into T\(_{H1}\) effector cells, resulting in higher anticancer T-cell immunity. Our results provide a new insight into TCL prognosis and have potential implication in clinical care of patients with TCL.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors' Contributions
Conception and design: K. Zhai, X. Tian, C. Wu, D. Lin. Development of methodology: K. Zhai, X. Tian, C. Wu, J. Chang, T. Zhang, D. Lin. Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K. Zhai, X. Tian, N. Lu, J. Chang, T. Zhang, Y. Zhou, Y. Qiao, J. Chen. Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K. Zhai, N. Lu, L. Huang, D. Yu, W. Tan, D. Lin. Writing, review, and/or revision of the manuscript: K. Zhai, X. Tian, C. Wu, N. Lu, J. Chen, D. Lin. Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K. Zhai, W. Tan, D. Lin. Study supervision: J. Chen, D. Lin.

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Clinical Cancer Research

Cytokine BAFF Gene Variation Is Associated with Survival of Patients with T-cell Lymphomas

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