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Optimal Use of Biomarkers in Oncology: Expression of Activation-induced Cytidine Deaminase (AID/AICDA) in Follicular Lymphoma

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Abstract

Follicular lymphoma (FL), which originates in germinal center B-lymphocytes, has been recognized to be a heterogeneous entity in some patients developing progressive or transformed diseases. Secondary genetic events after t(14;18) translocation have been associated with this histological transformation, such as c-myc amplification and/or translocation. Activation-induced cytidine deaminase (AID/AICDA) is required for somatic hyper-mutation and class switch recombination of immunoglobulin genes, and c-myc translocation of the germinal centre derived B-cell lymphoma. The role of AID in FL pathogenesis has not been established. Here we tried to identify the significance of AID associated with c-myc in the progression of FL, and showed that switched-off AID or a low expression of AID after c-myc amplification might correlate to rapidly progressive FL as well as to overall clinical outcomes.

Keywords: Follicular lymphoma; t (14;18) (q32;q21); Activation-induced Cytidine Deaminase (AID/AICDA); c-myc

Introduction

Follicular lymphoma is a representative indolent lymphoma. It is known that the disease develops frequently in middle age with an average age of 60 years at diagnosis, and progresses slowly, with an average survival rate of 7-10 years [1]. On the other hand, about 30% of follicular lymphoma is phenotypically transformed into diffuse large cell B cell lymphoma during the indolent clinical course [2]. Phenotypically transformed cases often deteriorate clinically [3], and a variety of genetic abnormalities is thought to be involved in the deterioration. Recently it has been reported that cases harboring c-myc translocation [t(8;14)(q24;q32), t(2;8)(p12;q24), and t(8;22)(q24;q11.2)], in particular, exhibit a markedly poor prognosis [4,5]. We previously reported that activation-induced cytidine deaminase (AID/AICDA), postulated to be necessary for c-myc translocation, was closely related with the proliferation of follicular lymphoma cells and aggravation of clinical manifestations [6]. Genetic abnormalities related with the advancement of follicular lymphoma, including those in our findings, are outlined with a focus on the *c-myc* and *AID* genes in this review.

Genetic abnormalities related with the onset and advancement of follicular lymphoma (focused on c-myc)

Follicular lymphoma, derived from germinal center B cells [7], expresses pan-B-cell markers (CD19, CD20, and CD79a), complement receptors (CD21 and CD35), and germinal center B-cell markers (CD10 and bcl-6), and 75%-90% of cases are accompanied by the translocation of t(14;18)(q32;q21) [8]. This chromosomal translocation is dysregulated by the translocation of the *bcl-2* gene from 18q21 to the proximity of the enhancer of the immunoglobulin gene (*IgH*) at 14q32, and bcl-2 overexpression leads to the circumvention of apoptosis and plays an important role in tumorigenesis [9]. However, since it was reported that bcl-2-IgH transgenic mice developed no follicular lymphoma and t(14;18)(q32;q21) translocation was also detected in the peripheral blood in healthy subjects [10,11], all cases harboring this translocation do not always develop follicular lymphoma. This chromosomal translocation alone is insufficient for tumorigenesis and a so-called "second hit" is, in general, considered necessary for onset. Meanwhile, when follicular lymphoma is transformed into diffuse large cell B-cell lymphoma, most cases harbor genetic expression of germinal center-type B-cell lymphoma and maintain bcl-2 expression [12,13]. Tumors with these histological changes are considered to need an additional genetic abnormality as well as a *c-myc* gene translocation and amplification [14,15], translocation of the *bcl-6* gene [16], mutation of the *TP53* gene [17], inactivation of the *p16* gene [18], and amplification of the *c-REL* gene, which have all been suggested to date [13]. Among them, it was reported that B-cell lymphoma harboring t(14;18)(q32;q21) and c-myc translocation (dual translocation or "double hit" lymphoma) had a markedly poor prognosis [4,5]. Although c-myc translocation was first recognized as a genetic abnormality in Burkitt lymphoma [19], it was detectable in 5%-15% of diffuse large cell B-cell lymphoma and 3% of follicular lymphoma [20-22]. Although there is a rare case report that translocation of both bcl-2 and c-myc was simultaneously detected in the pathohistological diagnosis of follicular lymphoma [22], bcl-2 translocation occurs in the bone marrow and c-myc translocation is a genetic abnormality occurring at the germinal center of peripheral lymph nodes [23]. Therefore, it is generally considered that c-myc translocation occurs additionally to t(14;18)(q32;q21) translocation. This "double hit" B-cell lymphoma is categorized as aggressive B-cell lymphoma (B-cell lymphoma, unclassifiable with features intermediate between DLBCL and BL; BCLU), which has features intermediate between DLBCL and BL pathologically, according to the 4th edition of the WHO classification of lymphoma revised in 2008. However, since some cases advance slowly [6], a group of different biological features is present in this disease. It remains largely unknown what kind of genetic abnormalities these cases have, including genes involved in the translocation and amplification of the *c-myc* gene.

Activation-induced cytidine deaminase (AID/AICDA)

Activation-induced cytidine deaminase (AID/AICDA) is an enzyme involved in somatic mutation and class switch of immunoglobulin, and its expression is regulated mostly at the germinal center [23]. Its action is to change the components of nucleic acid from cytosine to uracil, and AID expression suppresses topoisomerase 1 expression. As a result of this structural change of DNA, DNA is cleaved [24]. Later research revealed that the cleavage of DNA by AID expression was necessary for c-myc translocation [23], and the level of AID expression correlated with the frequency of c-myc translocation in a mouse model developing plasmacytoma [25]. Furthermore, it has been suggested that ectopic AID expression is induced by the trigger of chronic inflammation by HCV and *Helicobacter pylori* infection, and genetic mutation by AID expression may lead to carcinogenesis in some solid cancers [26]. Zaheen et al. reported that the amount of DNA cleavage increased according to the expression level of AID, which resulted in accelerated apoptosis and reduced cell proliferation in a cell line derived from germinal centre B-cells [27], suggesting that AID inhibits tumor cell proliferation although its presence is necessary for tumorigenesis and tumor advancement, a sort of contradictory situation. Meanwhile, when AID is overexpressed at the normal germinal center, B cells per se stop their cell cycle due to DNA injury and are subjected to apoptosis. At somatic mutation and class switch of immunoglobulin, appropriate reaction to DNA injury is induced and a certain level of cell proliferation seems to be maintained [28].

Reports of AID expression in follicular lymphoma

The following reports discussed the significance of AID expression in follicular lymphoma. Smit et al. reported that *AID* gene expression was observed only in nine of 36 clinical samples of follicular lymphoma (25%) [29]. Interestingly, they also reported that *AID* gene expression significantly increased in 3 of 7 cases that histologically advanced from follicular lymphoma at grade 1-2 to grade 3 or diffuse large cell B-cell lymphoma. Their report suggested that AID was in part involved in the histological advancement of follicular lymphoma.

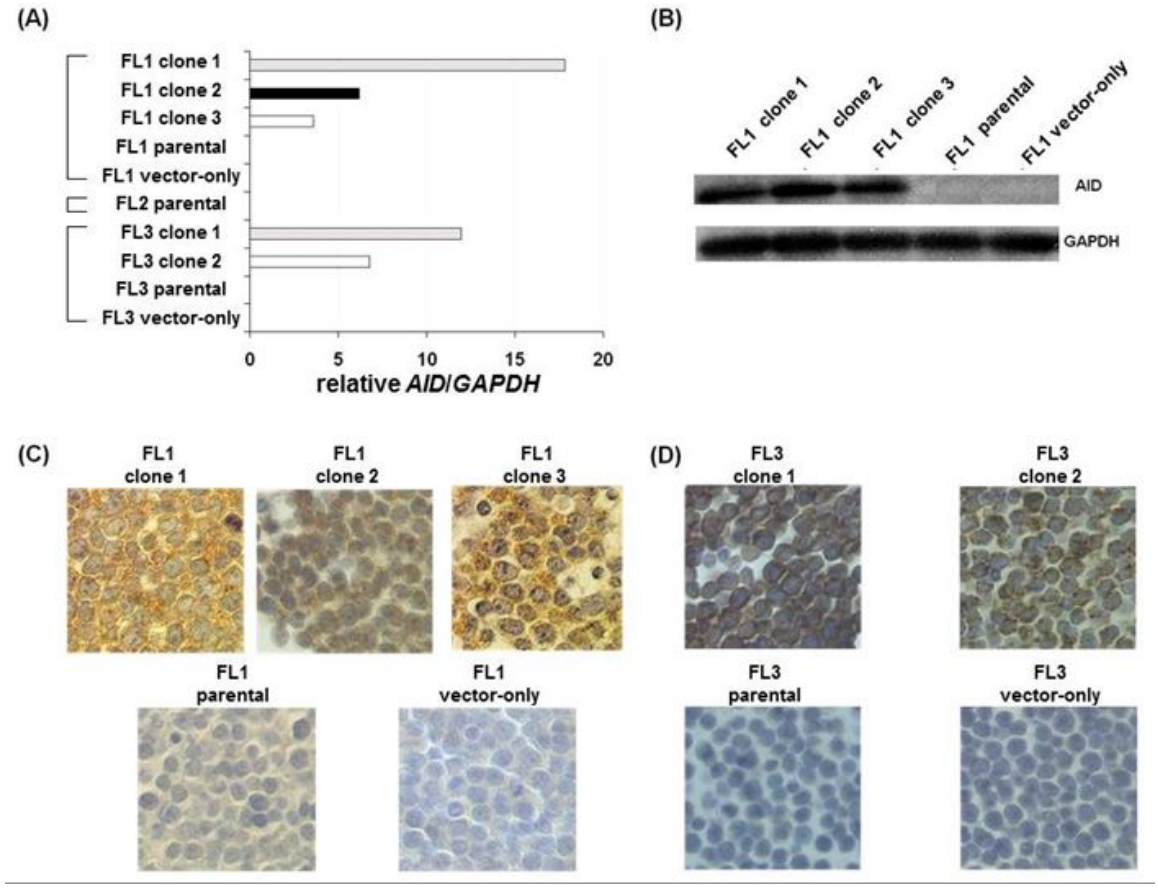

Figure 1: Re-introduction of the *AID* gene to the cell line positive for c-myc and negative for AID established from the patient at the progressive stage of follicular lymphoma. The cell line established from two patients (FL1 and FL3: both positive for c-myc and negative for AID) was infected with a lentivirus vector (CSII-CMV-IRBsd), and a cell line positive for AID was established. From FL1 and FL3, 3 and 2 clones were established, respectively. AID expression was confirmed by (A) real-time PCR (F1 and F3), (B) Western blotting (F1), and (C) immunostaining (F1 and F3).

On the other hand, Hardianti et al. reported that *AID* gene expression was observed in 10 of 15 clinical samples of follicular lymphoma (67%) [8]. Furthermore, they also reported that AID expression disappeared after the somatic mutation of immunoglobulin.

These results suggested the possibility that AID expression became unnecessary for cell maintenance after regulation of the immunoglobulin gene by AID as reported by Zaheen et al. [27]. Meanwhile, Willenbrock et al. reported that scoring of AID staining of pathohistological specimens of follicular lymphoma revealed intense AID expression (staining) in grade 3 follicular lymphoma, but AID expression had no correlation with prognosis or disease stages [30]. Taken together, there are various reports on AID expression in follicular lymphoma, and we think that AID expression changes as this lymphoma advances histologically and clinically.

Roles of *AID* in advancement of follicular lymphoma

Although treatment results of malignant lymphoma have improved recently, refractory cases are present at a certain rate. In particular, a number of institutes commonly recognize the fact that the prognosis of follicular lymphoma refractory to treatment is critically poor. When follicular lymphoma advances histologically, increased gene expression, including c-myc expression, is necessary, and partial involvement of AID is presumed. However, under the circumstances where AID expression is increased, there are potential inhibiting cell proliferation and tumor advancement [27]. To further verify the hypothesis, we carried out an experiment of a gene transfer of the AID gene again to the established cell strains (the follicular lymphoma cell strains that expressed c-myc strongly with AID shutdown: FL1 and FL3). Interestingly, when 3 and 2 clones established from FL1 and FL3, respectively (Figure 1), were compared with their respective parent strain, these clones showed decreased cell proliferative activity in a negative correlation with the level of AID expression (Figures 2A and 2B).

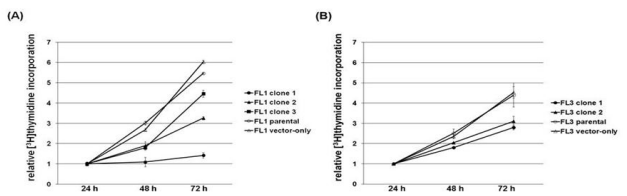

Figure 2: Measurement of cell proliferative activity with [3H] thymidine. (A) Comparison of cell proliferative activity among three clones established from FL1. (B) Cell proliferation was compared between two clones established from FL3. Cell proliferative activity was reduced in all AID-introduced clones compared with the control. The reduced level was comparable to the expression level of *AID* shown in Figure 1 (ref. real-time PCR).

It was suggested that this reduced cell proliferative activity was attributable to the phenomenon of the changes in the cell cycle or accumulation at the G0/G1 phase of the cell cycle of the *AID* gene-reintroduced clone (Figures 3A and 3B). This phenomenon may potentially explain the results of the examinations using clinical samples that we previously discussed. We investigated whether this phenomenon was consistent with malignant lymphoma expressing c-myc, but failed to confirm the similar shutdown of AID in BCLU and Burkitt's lymphoma [6]). There was a possibility that this phenomenon could be observed when follicular lymphoma expressed c-myc. Currently, we are identifying factors involved in the expression and suppression of AID in follicular lymphoma and how AID influences the cell cycle.

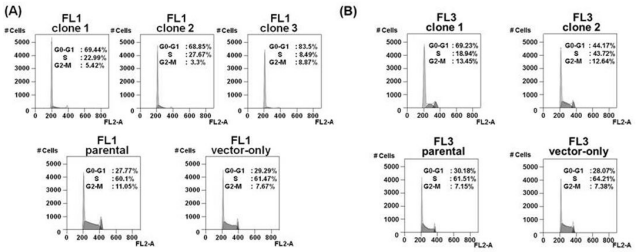

Figure 3: Cell cycle in established clones. (A) The cell cycle was examined in the three clones established from FL1. (B) The cell cycle was examined in the two clones established from FL3. Cells accumulated at the G0/G1 phase of the cell cycle with shortening of the S phase in the AID-introduced clone compared with the control.

Conclusions

Increased c-myc expression in association with histological and clinical advancement of follicular lymphoma is often experienced. Our current study suggested that elimination or attenuation of AID expression following increased c-myc expression potentially showed a rapid increase in tumour cells and aggravation in clinical manifestations. Histologically advanced follicular lymphoma often accompanies a variety of gene abnormalities, and there may be a group having a poor prognosis with AID suppression. Accumulation of such cases may lead to early identification of cases with a poor prognosis, and development of new treatment strategies and drugs.

Disclosure Statement

Authors declare that the research team has no conflict of interest.

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