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T-cell Receptor β-Chain Gene Expression in B-lineage Acute Lymphoblastic Leukemia

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The T-cell receptor β-chain (Tβ) gene expression was examined in 16 children with B-lineage acute lymphoblastic leukemia (ALL), including eight patients with rearrangement of the Tβ gene as well as immunoglobulin (Ig) heavy chain gene rearrangement. In contrast to the 1.3 kb full-length transcripts of the Tβ gene observed in T-lineage leukemia and lymphoma cells, no transcript of the Tβ gene was detected in 10 patients, including four with Tβ gene rearrangement. Low levels of Tβ transcripts were found in three patients with Tβ gene rearrangement and two patients without Tβ gene rearrangement, but those transcripts were truncated. In contrast to those findings, a single patient with Tβ gene rearrangement showed abundant 1.3 kb Tβ transcripts. These data indicate that Tβ gene expression is not restricted to T-lineage cells and demonstrate the heterogeneity of B-lineage ALL at the expression level of the Tβ gene. Our findings also suggest that Tβ gene expression is not always accompanied with Tβ gene rearrangement.

Key words: B-lineage acute lymphoblastic leukemia — T-cell receptor β-chain gene — Expression

Since the first cloning of the T-cell receptor β-chain (Tβ) gene,[1] many patients with lymphoid neoplasms or other hematologic diseases have been analyzed.[2] The results of DNA analyses have demonstrated that rearrangement of the Tβ gene is a useful marker for determining the lineage and clonality of T-cell malignancies.[2] However, it has become apparent that Tβ gene rearrangement is not specific to T-lineage malignancies and that it occurs in 25–40% of patients with B-lineage acute lymphoblastic leukemia (ALL).[3–5] Analyses of Tβ gene expression in leukemia and lymphoma have shown that most T-lineage malignancies have abundant Tβ transcripts,[6–9] but B-lineage ALL with Tβ gene rearrangement has no Tβ transcripts at all.[5] Recently, however, Calman and Peterlin reported that human B cells without Tβ gene rearrangement produced low levels of truncated Tβ transcripts.[10] To determine whether Tβ gene expression is restricted to T cells and whether it is always accompanied with Tβ gene rearrangement, we analyzed leukemic cells from 16 patients with B-lineage ALL. In parallel studies, we also examined Tβ gene expression in four T-lineage malignancies in order to define the differences in Tβ gene expression between T-lineage and non-T-lineage malignancies.

MATERIALS AND METHODS

Patients Samples of bone marrow or peripheral blood from 19 ALL patients and a lymph node specimen from one non-Hodgkin's lymphoma (NHL) patient were obtained at either diagnosis or relapse before initiation of treatment. Mononuclear cells were separated by Ficoll-Hypaque gradient centrifugation. Since four patients were positive for CD3, they were categorized as T-lineage. The other 16 patients were initially diagnosed as B-lineage because they lacked T cell associated antigens and demonstrated B cell associated antigens. Among the 16 patients with B-lineage ALL, 13 had common acute lymphocytic leukemia antigen (CALLA) and three showed an HLA-DR$^+$, CD19 (B4)$^+$, CD10(CALLA)$^-$ phenotype. Studies using monoclonal antibodies were carried out as described previously.[11]

DNA Extraction and Southern Blot Analysis High-molecular-weight DNA was extracted from the mononuclear cells of each patient. The DNA (5–10 μg) was digested with the appropriate restriction endonuclease, size-fractionated by 0.6% agarose-gel electrophoresis, and transferred to nitrocellulose or nylon filters.[12] The filters were hybridized to nick-translated ^{32}P-labeled immunoglobulin (Ig) and Tβ gene probes.[13] These filters

were washed at the appropriate stringency and autoradiography was performed.

RNA Extraction and Northern Blot Analysis RNA was prepared by the modified method of Favaloro *et al.*[14] The RNA (20 μg) was denatured in glyoxal and dimethylsulfoxide, electrophoresed on 1% agarose gels, and transferred to nylon filters.[15] The filters were hybridized to ^{32}P-labeled Tβ and Ig μ heavy chain (Cμ) gene probes. These filters were washed stringently; the final two washes were done for 30 min at 65° in 0.1×SSC, 0.2% SDS. The filters were then autoradiographed.

Gene Probes The human Ig gene probes were the J_H probe (3 kb embryonic *Eco*RI-*Hind*III fragment containing the Ig heavy chain joining region),[16] the Cκ probe (2.5 kb embryonic *Eco*RI fragment containing the Igκ light chain constant region)[17] and the Cμ probe (1.3 kb embryonic *Eco*RI fragment containing the constant region of μ).[18] The human Tβ gene probe (Cβ probe) was a *Bgl*II-*Eco*RV fragment of the cDNA clone YT-35 that contained the constant region of the Tβ gene.[1] J_H and Cκ germ-line clones were kindly provided by Dr. P. Leder and Cμ germ-line clones by Dr. T. H. Rabbitts. YT-35 was donated by Dr. T. W. Mak.

Results

Ig and Tβ Gene Configuration The Ig heavy chain (IgH) gene configuration was analyzed with the J_H probe after *Eco*RI, *Bam*HI or *Hind*III digestion, and all 16 B-lineage ALL patients were found to have IgH gene rearrangement. Thirteen out of the 16 B-lineage ALL samples were analyzed with the Cκ probe after *Bam*HI digestion. One patient showed rearrangement, three showed deletion of both alleles, and the others showed the germ-line configuration.

The Tβ gene configuration of the B-lineage ALL samples was analyzed after *Bam*HI or *Eco*RI digestion, and eight out of the 16 showed rearrangement of the Tβ gene. Three T-lineage ALL samples and one T-lineage NHL sample also showed Tβ gene rearrangement. Table I summarizes the results on Ig and Tβ gene configuration in the B-lineage ALL patients together with the results of the phenotypic studies.

Tβ Gene Expression We examined RNA samples from 20 patients and two cell lines; one was the T-cell line Jurkat and the other was the B-cell line Jijoye. Jurkat showed Tβ gene rearrangement and Jijoye showed the germ-line configuration of the Tβ gene. As seen in Fig. 1, lane 2, Jurkat produced large quantities of the full-length 1.3 kb mRNA of

Table I. Surface-antigen Expression, Rearrangements of Ig and Tβ Genes and Expression of Tβ Gene in B-lineage ALL

Patient No.	Phenotype[a]								Ig genes[b]		Tβ gene[b]	Tβ gene[c]
	HLA-DR	CD19	CD10	CD20	sIg	CD7	CD5	CD2	JH	Cκ	Cβ	Expression
1	+	+	+	−	−	ND	0	0	R	G	R	−
2	+	40	+	−	−	2.6	ND	0	R	G	R	++
3	+	+	+	28	−	ND	0	0	R	G	R	+
4	+	−	+	−	−	ND	1.0	0	R	G	R	+
5	+	+	+	−	−	ND	0.7	1.9	R	G	R	+
6	+	+	+	−	−	2.0	ND	2.0	R	G	R	−
7	+	+	+	−	−	ND	4.8	0	R	D	R	−
8	+	+	+	−	−	ND	1.7	ND	R	G	R	−
9	+	+	+	−	−	4.0	ND	0	R	ND	G	−
10	+	+	+	29	−	2.0	ND	6.0	R	G	G	−
11	+	−	+	−	−	11	ND	0.9	R	ND	G	−
12	49	+	+	21	−	ND	4.0	3.0	R	G	G	−
13	+	+	+	−	−	ND	0	ND	R	D	G	−
14	+	+	−	−	−	3.8	ND	0.9	R	D	G	−
15	+	+	21	19	−	2.2	ND	0	R	R	G	+
16	+	+	−	−	−	9.0	ND	2.0	R	ND	G	+

a) A minus sign denotes < 10% positive cells and a plus sign >50% positive cells; numbers are specific percentages of positive cells.

b) G denotes germ-line, R rearrangement and D deletion.

c) ++ denotes high expression level, + low expression and − no expression.

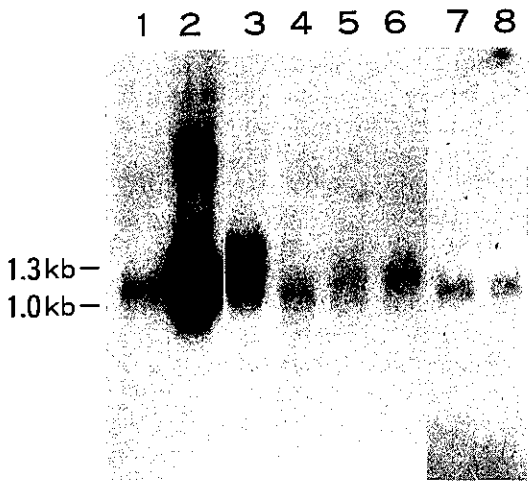

Fig. 1. Tβ gene expression in B-lineage ALL (patients identified in Table I). Lane 1 is the sample from B-cell line Jijoye, lane 2 from T-cell line Jurkat, lane 3 from Patient 2, lane 4 from Patient 3, lane 5 from Patient 4, lane 6 from Patient 5, lane 7 from Patient 15, and lane 8 from Patient 16.

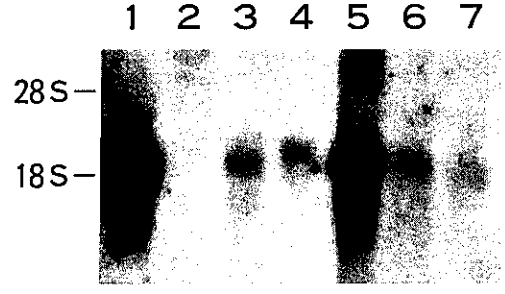

Fig. 2. Cμ gene expression in B-lineage ALL (patients identified in Table I). Lane 1 is the sample from B-cell line Jijoye, lane 2 from T-cell line Jurkat, lane 3 from Patient 1, lane 4 from Patient 2, lane 5 from Patient 3, lane 6 from Patient 4, and lane 7 from Patient 5.

the Tβ gene as well as the truncated 1.0 kb mRNA. This cell line also showed small amounts of high-molecular-weight RNA, which may represent unspliced precursors.[10] Three T-lineage ALL samples also had abundant 1.3 kb mRNA, and one T-lineage NHL presented almost the same expression patterns as the T-cell line Jurkat. The results of Northern blot analysis of Tβ gene expression in the B-lineage ALL patients and the B-cell line Jijoye are shown in Fig. 1. Jijoye expressed low levels of truncated Tβ transcripts (Fig. 1, lane 1). Five patients showed almost the same expression level of truncated Tβ transcripts as the B-cell line Jijoye (Fig. 1, lanes 4–8). As shown in Fig. 1, lane 3, Patient 2 expressed 1.3 kb Tβ transcripts, and the quantity of transcripts was greater than that in Jijoye but less than that in Jurkat. The results of Northern blot analysis are summarized in Table I.

Overall, six B-lineage ALL patients expressed Tβ gene transcripts. Four of them showed Tβ gene rearrangement, and two showed the germ-line configuration of Tβ gene. Tβ transcripts in five patients were truncated, and the quantities of transcripts were much smaller than those in T-lineage malignancies and almost the same as those in Jijoye. Only one patient, who showed Tβ gene rearrangement, expressed the full-length 1.3 kb mRNA, and the amount of transcripts was smaller than that in T-lineage malignancies but much larger than that in Jijoye.

Cμ Gene Expression Cμ gene expression was also analyzed in the children with B-lineage ALL. As shown in Fig. 2, B-cell line Jijoye and Patient 3 expressed high levels of Cμ transcripts. Four other patients, including Patient 2, showed low levels of Cμ gene expression, and T-cell line Jurkat had no Cμ gene transcripts.

Discussion

Based on recent studies, the organization and rearrangement events of the Tβ gene are probably very similar to those of Ig genes.[19–22] Like Ig genes, the first event in rearrangement is a DJ (diversity-joining) joining, and the next step is a VDJ (variable-diversity-joining) joining.[19, 20] Thymocytes and many T-cell lines produce 1.0 kb truncated Tβ transcripts, which probably represent DJ transcripts, as well as presumably functional 1.3 kb transcripts of VDJ recombination.[23–25] In this study, we have demonstrated that all four $CD3^+$ T-lineage malignancies produced 1.3 kb full-length VDJ transcripts of the Tβ gene. These findings are consistent with the results of other studies.[6–9]

Among the 16 B-lineage ALL patients we analyzed, six patients showed Tβ transcripts.

Since the percentage of cells with the T cell phenotype was very low in each case and there were patients who had slightly higher percentages of normal T cells but no Tβ gene transcripts, it is very unlikely that these transcripts were derived from contaminating normal T cells. Therefore these transcripts should be derived from leukemic cells and this indicates that the expression of the Tβ gene is not restricted to T-lineage cells.

We also analyzed Cμ gene expression in these B-lineage ALL patients in order to define differentiation stages of leukemic cells more precisely. Patient 3 showed almost the same expression level of Cμ transcripts as the B-cell line Jijoye. In contrast, four other patients (Patients 1, 2, 4 and 5) expressed much lower levels of Cμ transcripts. Phenotypically, the only difference between Patient 3 and the other patients is the presence of CD20. Twenty-eight percent of bone marrow cells from Patient 3 reacted with anti-CD20 antibody, but other patients' cells did not. These results are concordant with the previous findings that B-lineage cells carrying CD20 appear at later stages of maturation.[26]

Although Patient 2 had rearranged Tβ genes and expressed 1.3 kb full-length Tβ transcripts, the lineage of Patient 2 is more likely to be B-lineage on the basis of phenotypical and genotypical analyses of his bone marrow cells. More than 90% of his bone marrow cells demonstrated HLA-DR as well as CD24 (BA-1, data not shown) and 40% was positive for CD19. No T-lineage associated marker such as CD7 or CD2 was detected. In addition, Ig gene rearrangement, as well as a low level of Cμ gene expression, was also observed. These findings are indistinguishable from those in other B-lineage ALL cells as demonstrated above. Based on these findings, we prefer to categorize Patient 2 as B-lineage ALL, and to conclude that some B-lineage ALL could express the 1.3 kb full length transcripts of the Tβ gene. The lack of lineage specificity is somewhat analogous to the demonstration of Igκ light chain gene rearrangement in T-lineage cells.[27] However, another possible explanation is that no definite single lineage determination is possible in Patient 2.

As demonstrated in a number of human and murine T-cell lines, IgH gene rearrangement in T-cell lines involves the D and J segments but not the V segment of the IgH gene.[28–30] Further, analysis of Tβ gene rearrangement in B-lineage leukemias suggests that these also involve predominantly the DJ segments and not the V segment.[30] However, Pelicci *et al.* reported that the Tβ gene rearrangement in two B-lineage tumors involved both the C and V regions, indicating that VDJ joining occurred in these tumors.[31] In our study, Patient 2 showed Tβ gene rearrangement and expressed 1.3 kb transcripts, which represent VDJ transcripts. These findings, together with those of Pelicci *et al.*, indicate that in some B-lineage cells a full VDJ rearrangement of the Tβ gene can occur.

Five B-lineage ALL patients had small amounts of Tβ transcripts, and the size of those transcripts was intermediate between the 1.0 kb DJ and the 1.3 kb full-lenght VDJ transcripts. These intermediate-sized transcripts are seen in T-cell precursors without rearrangement of the Tβ gene.[6, 7] Calman and Peterlin reported that human B cells also showed intermediate-sized transcripts with the germ-line configuration of the Tβ gene.[10] Based on these findings, these transcripts must be germ-line transcripts. Among our five patients, two (Patients 15 and 16) showed the germ-line configuration of the Tβ gene, so their transcripts must be derived from an unrearranged Tβ gene.

In the patients (Patients 3, 4 and 5) with rearranged Tβ genes, the size of the transcripts was not parallel to the size of VDJ or DJ transcripts and was parallel to that of germ-line transcripts. However, since two patients showed rearrangement of both alleles of the Tβ gene (data not shown), it is unlikely that their truncated transcripts are germ-line transcripts. At this time, the precise composition of these transcripts is not clear, and further studies including sequencing analysis will be needed. As mentioned before, there is some evidence for intermediate-sized transcriptions from the unrearranged Tβ gene in T-lineage ALL, but it is very rare for T-lineage ALL with Tβ gene rearrangement to show only intermediate-sized transcripts.[6, 7] Based on the data of published cases including our four cases, only one out of 33 T-lineage ALL patients showed intermediate-sized Tβ transcripts with rearrangement of the Tβ gene.[6–9]

On the other hand, in our studies three out of four B-lineage patients with Tβ gene rearrangement and expression showed intermediate-sized transcripts. Therefore it seems likely that intermediate-sized Tβ transcripts of a rearranged gene may be predominant in B-lineage ALL.

Overall, six out of 16 B-lineage ALLs expressed Tβ gene transcripts and two of six patients did not show Tβ gene rearrangement. In five of them, the size and expression level of transcripts were quite different from those of T-lineage leukemia/lymphoma and one patient showed 1.3 kb full length transcripts. These findings suggest that Tβ gene expression is not restricted to T-lineage cells and is not always accompanied with Tβ gene rearrangement.

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