SEPTIN6, a Human Homologue to Mouse Septin6, Is Fused to MLL in Infant Acute
Myeloid Leukemia with Complex Chromosomal Abnormalities Involving
11q23 and Xq24

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Abstract

MLL1 is a recurring translocation in pediatric acute myeloid leukemia (AML). We showed that the MLL gene on 11q23 was fused to the SEPTIN6 gene on Xq24, a human homologue to mouse Septin6, in three de novo infant AML with complex chromosomal abnormalities involving 11q23 and Xq22-24. SEPTIN6 consisted of at least 12 exons and was predicted to encode at least two types of proteins by alternative splicing. Expression of 2.3-, 3.1-, and 4.6-kb SEPTIN6 transcripts was simultaneously detected in fetal lung, liver, and brain, in all of the adult tissues except brain, and in acute lymphoblastic leukemia and AML cell lines. However, the expression of an ~2.7-kb transcript was detected alone in fetal heart and adult brain. The SEPTIN6 protein is homologous to septin family members including CDCREL1 and AFI17q25/MSF, which generate fusion products with MLL. The MLL-SEPTIN6 fusion proteins contain almost the entire septin protein, similar to MLL-CDCREL1 and MLL-AFI17q25/MSF. Notably, all of the three patients were diagnosed with M1 or M2. Combined present results and literatures suggest that AML with the MLL-SEPTIN6 fusion gene is a subset of infant AML, which differentiate into the myeloid lineage, although AML with other MLL fusion genes is capable of differentiating into the myelomonocytic or monocytic lineage.

Introduction

A large number of leukemias have been found to be associated with specific chromosomal aberrations (1). Recent studies have demonstrated that several chromosomal rearrangements and the molecular abnormalities are strongly associated with distinct clinical subgroups and can predict clinical features and therapeutic responses (1–3). Recurring translocations involving chromosome 11 band q23 (11q23), observed in acute leukemia or myelodysplastic syndrome, are characterized by the presence of a variety of partner chromosomes (1–3). At least 40 chromosomal regions for partners of 11q23 have been observed, such as t(4;11), t(9;11), and t(11;19). The MLL gene is also called ALL-1 and HRX has been identified in 11q23 translocations (4, 5), and its rearrangement is found in the majority of infant and therapy-related leukemias (1, 3). Up to now, at least 28 partner genes for MLL have been cloned from leukemia cells with various types of 11q23 translocations and formed fusion transcripts with MLL t(X;11) is a recurring chromosomal translocation observed in AML, and the AFX gene on Xq13 was identified previously as a fusion partner of MLL with t(X;11)(q13;q23) (6). There has been a limited number of reports of pediatric AML with t(X;11)(q22–24;q23) (Refs. 7, 8), but no partner gene on Xq22–24 has been identified yet. In this study, we identified the SEPTIN6 gene on chromosome Xq24 as a novel fusion partner of the MLL gene in three patients with infant AML.

Materials and Methods

Patients. Patient 1, a 3-month-old girl, was diagnosed as having AML-M2. Her WBC count was 163,200/μl. Leukemic cells expressed CD4, CD13, CD15, and CD33, and were cytogenetically characterized as 46, XX, t(5;11) (q13;q23), add(X)(q22) in 12 BM cells, as 46, XX, t(5;11) in 6 cells, as 47, XX, t(5;11), add(X)(q22), +t(X;11) in 1 cell, and as 46, XX in 1 cell. She achieved a complete remission with chemotherapy and received unrelated BM transplantation but died of hepatic complications 9 months after diagnosis. Patient 2, a 7-month-old boy, was diagnosed as having AML-M2. His WBC count was 608,000/μl. Leukemic cells expressed CD4, CD13, and CD33, and were cytogenetically characterized as 46, XY in 20 PB cells. By FISH analysis, his karyotype was found to be characterized as 46, XY, ins(X;11)(q22–24; q23). He achieved a complete remission with chemotherapy and received autologous BM transplantation, and survives 35 months after diagnosis without relapse. Patient 3, a 6-month-old girl, was diagnosed as having AML-M1. Her WBC count was 58,500/μl. Leukemic cells expressed CD4, CD13, CD33, and HLA-DR, and were cytogenetically characterized as 46, X, add(X)(q27), del(11q23) in 20 BM cells. She achieved a complete remission with chemotherapy and received unrelated cord blood stem cell transplantation but died of respiratory complications 11 months after diagnosis. Samples of patient 1, and patients 2 and 3 were obtained from BM and PB, respectively, at diagnosis.

Leukemic Cell Lines. B-precursor ALL (REH and NALM26), B-ALL (BALM14, BALM9, BJAB, and A4/FUK), and AML (SN-1) cell lines were analyzed by Northern blot analysis. Acute monocytic leukemia (THP-1, CTS, P31/FU, IMS/M1, and KOC-48), AML (YNH-1, ML-1, Kasumi-3, KG-1, P39/Tsu, inv-3, NB-4, and HEL) and acute megakaryoblastic leukemia (CMS and CMY) cell lines were also analyzed by RT-PCR.

Southern Blot Analysis. High molecular weight DNA was extracted from either BM or PB at diagnosis, and 10 μg of DNA was analyzed with a 0.9-kb BamHI fragment (MLL probe), as reported previously (9).

cDNA Panhandle PCR. Total RNA was extracted from either BM or PB cells at diagnosis using Isogen (Wako Pure Chemical Industries, Ltd., Osaka, Japan) and analyzed by modifed cDNA panhandle PCR method as described previously (10, 11). In brief, first-strand cDNAs were synthesized with MLL-random hexamer oligonucleotides, MLL-N. After primer 1 extension with MLL-1, and extension in stem-loop templates, the sample was amplified by first PCR with ALL-6A and MLL-1. Then, one-twenty fifth of the products were used for nested PCR with MLL-3 and ALL-8S. The products (5 μl) were electrophoresed in a 3% agarose gel. The MLL-random hexamer oligonucleo-

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3 The abbreviations used are: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; BM, bone marrow; PB, peripheral blood; RT-PCR, reverse transcription-PCR; FISH, fluorescence in situ hybridization; ORF, open reading frame.
tides and primers used were as follows: MLL-N, 5'-TCGAGGAAAAAGATGCAGAGGAAGGGAATGTCTCNNNNNN-3'; MLL-1, 5'-TGAAGACAGTGGTGACGCTCT-3'; ALL-6A, 5'-GTCAGAGCAGACAGCAAAAGA-3'; MLL-3, 5'-GTCAGAAAACCTCCACATCA-3'; and ALL-8S, 5'-TGTTGAGCACAA AATGTTGAG-3'.

RT-PCR. Total RNA (4 μg) was reverse transcribed to cDNA in a total volume of 33 μl with random hexamers by using the Ready-To-Go You-Prime First-Strand Beads (Pharmacia Biotech, Tokyo, Japan). Conditions and reagents for PCR have been already described (9). The primers used were as follows: ALL-7S, 5'-TTCTCACACCTCCTCACAAT-3'; SEPS6-2A, 5'-GGGTACGAGCAAGATAATCA-3'; ALL-9A, 5'-GGAAAGGCTCACAACAG-3'; SEPS6-S, 5'-TGTTGACAGTTCCTCCCGTGG-3'; SEPS6-4A, 5'-GGTCCAGAGACATTGTCG-3'; SEPS6-11KA, 5'-CTTGTTGACAGGAAAAAGGTTG-3'; and 24R1, 5'-TGAGAACCCTCGGTAAAAGGCTAAA-3'.

Nucleotide Sequencing. Nucleotide sequences of phage clones, PCR products, and, if necessary, subcloned PCR products, were analyzed as described previously (9).

Screening of the cDNA Library. The 556-bp SEPTIN6 cDNA probe spanning exons 1–4 (nucleotides 230–765) was used for screening a cDNA library derived from human placenta (Ref. 9; Clontech Laboratories, Inc., Palo Alto, CA).

FISH Analysis. Chromosomal mapping of the BAC clone RP13–163A20 was performed by the FISH method (12). FISH analysis of the patients' leukemic cells using a YAC clone specific to 11q23 (13HH4) and RP13–163A20 was carried out as described previously (12).

Northern Blot Analysis. An aliquot (1 μg) of mRNA derived from each cell line and multiple human tissue Northern blots (Clontech Laboratories, Inc.) were analyzed with the 32P-labeled same cDNA probe as used for screening a cDNA library (9).

Results

Cloning and Identification of the MLL Fusion cDNA. Southern blot analysis of DNA prepared from the leukemic cells of the patients using MLL probe revealed chromosomal breakpoints within the breakpoint cluster region of the MLL gene at 11q23 (Fig. 1A). To clone the chimeric transcripts, we performed cDNA panhandle PCR analysis of total RNA from BM mononuclear cells of patient 1 and obtained a PCR product, which represented a fusion transcript of MLL (Fig. 1, B and C). This product, 336 bp in size, contained a fusion of a 108-bp sequence of exon 8 in the MLL gene at the 5' region to a 117-bp sequence, which did not match the MLL gene or the partner genes of MLL cloned previously (3). To prove that this fusion product was indeed expressed in the leukemic cells from patient 1, we performed RT-PCR analysis using ALL-7S and SEPS6-2A, and obtained 306-bp and 198-bp transcripts (Fig. 1B). The 306-bp product contained a fusion of a 191-bp sequence of exons 7 and 8 in the MLL gene at the 5' region to a 115-bp sequence within the 117-bp sequence of the product of the panhandle PCR. The 198-bp product contained a fusion of a 83-bp sequence of exon 7 in the MLL gene at the 5' region to a 115-bp sequence within the 117-bp sequence of the product of panhandle PCR. The ORF was preserved in both types of fusion transcripts. These results indicate that this MLL fusion product was alternatively spliced.

Isolation and Characterization of the SEPTIN6 Gene. The novel sequence was compared with known sequences in public databases and found to be highly homologous to mouse Septin6 (GenBank accession no. AB203622) and two clones, KIAA0128 (D50918) and FLJ22936 fss (AK026589). FLJ22936 fss was 65 bp longer at the 5' end and region, and these two clones were different from each other at the 3' noncoding region. Thus, we assumed the sequence combined the common region between the two clones with the 5' 65-bp region in FLJ22936 fss, and designed a sense primer, SEPS6-S, at the 5' region in FLJ22936 fss, and an antisense primer, SEPS6-10A, at the 3' region in the common region (Fig. 2A). An RT-PCR analysis of the THP-1 cell line using these two primers yielded a 1361-bp product as expected, which enabled us to predict ORF of the gene and confirm the 3' end of the gene, but not to confirm the 5' end.

To confirm the 5' end of the gene and the complete ORF, a 556-bp PCR product at the 5' region of the 1361-bp sequence was used as a probe to screen a cDNA library derived from human placenta. We isolated overlapping clones by several rounds of screening. Although the frame is open all of the way to the 5' end of the clones, two independent clones had the same 5' end of sequences; therefore, we concluded that the ATG at nucleotides 266–268 was the initiation codon.

The overlapping clones and the PCR product were assembled into two types of contiguous sequences resulting in total cDNA sizes of 2059 nt (type I; GenBank accession no. AF403058) and 2695 nt (type II; AF403059). They were then compared with known genomic sequences in public databases and found to contain at least nine com-

Fig. 1. Identification of the MLL-SEPTIN6 chimeric transcripts. A, rearrangements of the MLL gene by Southern blot analysis with HindIII digestion. Rearranged bands are indicated by arrows. N, normal peripheral lymphocyte; Pt1–3, leukemic cells from the patients 1–3. B, analysis of t(X;11)(Q24;Q23) by RT-PCR (Lanes 1–4). (The arrowhead indicates the band of the fusion transcript.) Longer fragment of 306 bp from patients 1 and 2, and shorter fragment of 198 bp from patients 1, 2, and 3 are indicated by arrows. M, 1-kb DNA ladder (Life Technologies, Inc.); Lanes 1 and 2, patient 1; Lanes 3, patient 2; Lane 4, patient 3. C, partial sequence of the junction of each fusion transcript.
mon exons at the 5' region in addition to some additional exons at the 3' region (Fig. 2A).

To study the expression of fusion transcripts in leukemic cells from patient 1, we performed RT-PCR analysis for RNA from the leukemic cells using primers ALL-7S and one of the antisense primers, SEP6–11KA and 24RA1, which corresponded to chimeric transcripts fused to type I and II. However, no PCR product was obtained, suggesting that the quality of mRNA from the leukemic cells of patient 1 was not good. We next performed RT-PCR using primers SEP6–8SS and one of the same antisense primers, and detected a 346-bp product only when primers SEP6–8SS and SEP6–11KA were used, suggesting that a fusion transcript was formed by type I (data not shown).

Computer analysis indicated a type I encoding a 427-amino acid protein, and a type II encoding a 434-amino acid protein with an estimated molecular mass of 48.8 kDa and 49.7 kDa. Each product revealed highly significant homology to mouse Septin6 protein (95.8% identity; Fig. 2B). Therefore, we designated this gene SEPTIN6 as a human homologue of mouse Septin6. Motif analysis using the PSORT II and Pfam database revealed a coiled-coil region at the COOH region and a GTP-binding domain, which is highly conserved among septin family proteins. This domain was conserved in each isoform. The fusion partner genes of MLL, CDCREL1, and AF17q25/MSF, which also belong to the septin family, were homologous to this novel gene (Fig. 2C).

Chromosomal Assignment of the SEPTIN6 Gene. To assign the chromosomal location of the SEPTIN6 gene, we found a BAC clone (RP13–163A20) after comparing SEPTIN6 with known genomic sequences in public databases. Surprisingly, the BAC clone showed specific signals at Xq24 but not at 5q13 in all of the metaphase male cells tested (Fig. 3, A and B). We next performed a FISH analysis of leukemic interphase cells of patient 1 using a YAC clone specific to 11q23 (13HH4) and RP13–163A20, and detected three signals of 13HH4 and RP13–163A20, respectively (Fig. 3C). Only one of the three signals was found to be fused. These results suggest that the chromosome aberration in patient 1 was not a reciprocal t(5;11)(q13;q23) but a complex chromosomal abnormality including t(X;11)(q24;q23).

Studies of Other Cases with Xq22–24 Breakpoints. We found that SEPTIN6 was located at Xq24. To detect the MLL–SEPTIN6 chimeric transcripts in the other patients, we performed RT-PCR analysis of the leukemic cells from two patients with complex chromosomal abnormalities involving 11q23 and Xq22–24. We obtained PCR products of 306 bp from patient 2 and 198 bp from patients 2 and 3, which were the same chimeric transcripts as obtained from patient 1, using primers ALL-7S and SEP6–2A (Fig. 2B). However, we could not detect reciprocal PCR products (SEPTIN6–MLL) using primers SEP6–S and ALL-9A in these three patients by RT-PCR (data not shown). We also detected only the expression of SEPTIN6 type I from the leukemic cells of patient 3 by RT-PCR, like patient 1. No expression of two isoforms was detected from the leukemic cells of patient 2 by RT-PCR (data not shown).

We also performed FISH analyses of leukemic metaphase cells of patient 2 and leukemic interphase cells of patient 3 using a YAC clone 13HH4 and RP13–163A20. Three signals of 13HH4 and RP13–163A20 were detected in patient 3, similarly to patient 1 (data not shown). However, no split signals of RP13–163A20 were detected, despite 3 signals of 13HH4, in patient 2 (Fig. 3D). One signal of RP13–163A20 was found to be fused to a split signal of 13HH4 on der(X), suggesting that the split signals were too close to discriminate by FISH analysis or that one of the split signals of RP13–163A20 on der(X) was deleted.

Expression of the SEPTIN6 Gene. To examine the expression of SEPTIN6, we performed Northern blot analysis on poly(A)+ RNA from various human tissues and detected four types of transcripts, ~2.3-kb, 3.1-kb, 4.6-kb, and 2.7-kb (Fig. 4). Expression of the 2.3-kb, 3.1-kb, and 4.6-kb transcripts was detected almost simultaneously in fetal lung, liver, and brain, and in all of the adult tissues tested except brain. On the other hand, expression of the 2.7-kb transcript was detected alone in fetal heart and adult brain. We also performed Northern blot analysis of RNAs of leukemic cell lines. The SEPTIN6 gene was expressed in six leukemic cell lines, including three B-ALL (BALM14, BALM9, and A4/FUK), two B-precursor ALL (REH and NALM26), and one AML cell lines (SN-1). In addition, we examined the expression of SEPTIN6 in 10 AML including 2 acute megakaryoblastic leukemia cell lines and in 5 acute monocyctic leukemia cell lines by RT-PCR using primers SEP6–S and SEP6–4A. The expression of SEPTIN6 was found in all of the cell lines.

Discussion

In the present study, we isolated a novel fusion partner of the MLL gene, SEPTIN6, in three patients of de novo infant AML with chromosomal abnormalities involving 11q23 and Xq22–24. The
t(X;11)(q22–q24;q23) is a rare chromosomal translocation, which has thus far been reported in only five patients (7, 8). All of these patients were diagnosed as having AML, compatible with the three present patients. All three of the patients presented here were classified as FAB-M1 and M2, and two of the three informative patients reported in the literature were classified as FAB-M2 and M5, suggesting that AML with the MLL-SEPTIN6 fusion gene have a tendency to differentiate into the myeloid lineage, although

Fig. 3. FISH analysis of normal metaphase (A, B), leukemic interphase (C), and metaphase (D) nucleus. A, SEPTIN6 gene (RP13–163A20) was assigned to band Xq24 as indicated by an arrow. B, same metaphase spread stained with 4',6-diamidino-2-phenylindole dihydrochloride. A 4',6-diamidino-2-phenylindole dihydrochloride image was inverted and enhanced in terms of band image contrast. C and D, red and green signals indicate the 13HH4 and RP13–163A20, respectively. In patient 1 (C), three signals of each probe were observed. In patient 2 (D), three signals of 13HH4 and one signal of RP13–163A20 were observed. The arrowheads indicate fusion signals.

Fig. 4. Northern blot analysis of RNAs from fetal (A) and adult (B) human tissues, and leukemic cell lines (C).
AML with other MLL fusion genes have a capability to differentiate into the myelomonocytic or monocytic lineage (13). Our patients were all infants, and the three informative patients involved young children, suggesting that AML with t(X;11)(q24;q23) is a subgroup of infant leukemia. Although our two patients died of complications after stem cell transplantation, the remaining patient has been alive for ~3 years. Two of the three patients reported in the literature were long-term survivors. However, the cases reported in the literature may not have the same molecular abnormality described in this work; therefore, the prognosis is uncertain at this time and will have to await the identification of large numbers of cases through molecular analysis.

None of the three patients were characterized as simple reciprocal t(X;11)(q24;q23). Patient 1 may have a three-way chromosome translocation among 5q13, 11q23, and Xq24. Patient 2 had an insertion of 11q23 at Xq22–24. t(10;11) is strongly associated with complex translocations, because the direction of transcription of AF10 is opposite to that of MLL, and t(10;11)(p12;q23) cannot form regular head to tail fusion transcripts (14,15). This may explain why t(X;11)(q24;q23) is often complex and associated with 11q insertions. These results may suggest that the orientation of the SEPTIN6 gene is reversed, telomere to centromere at Xq24.

SEPTIN6 is homologous to septin proteins. The septins are a family of nucleotide-binding proteins originally found in the yeast Saccharomyces cerevisiae as cell division cycle regulatory proteins. These proteins possess a well-conserved central core domain that binds GTP. To date, several genes have been identified as coding septin family proteins, for example, CDC3, CDC10, CDC11, and CDC12 in yeast; Pnut, Sep1, and Sep2 in Drosophila; Nedd5, H5, Diff6, E-septin, and G-septin in mouse; and CDCRELI, AF17q25/MSF, and septin 2-like cell division control gene in human (16). Recently, it was shown that Septin6 was associated with synaptic vesicles in various brain regions, including glomeruli of the olfactory bulb in mice. CDCRELI and AF17q25/MSF were also identified as the fusion partners of MLL (17–20). Septin proteins are associated with actin stress fibers in interphase cells, the cleavage furrow of dividing cells, and the bud neck of budding yeast. In addition, the functions of the septin proteins are considered to be related to the organization of specialized domains within the cells (16).

SEPTIN6 was expressed almost ubiquitously in this study, being similar to AF17q25/MSF and Nedd5, but different from CDCRELI (17–20). Recently, functional subgroups of the septin family were characterized. For example, AF17q25/MSF was also identified as the fusion partner of MLL. Septin proteins are associated with actin stress fibers in interphase cells, the cleavage furrow of dividing cells, and the bud neck of budding yeast. In addition, the functions of the septin proteins are considered to be related to the organization of specialized domains within the cells (16).

The MLL-SEPTIN6 fusion proteins contain almost the entire septin protein as well as the NH2 terminus of MLL, including the DNA-binding regions, similar to MLL-CDCRELI and MLL-AF17q25/MSF (Fig. 2B; Refs. 17–20). Therefore, a common region, e.g., the GTP-binding domain, might be crucial for the leukemogenesis associated with MLL-SEPTIN fusion proteins. The function of the MLL fusion protein remains unknown, although a few interesting reports have been published. It was shown that MLL-lacZ fusion gene was sufficient to cause leukemia in mice, and it seemed that lacZ could contribute to leukemogenesis through oligomerization of the MLL-lacZ fusion protein (23). Similarly, the coiled-coil region, which is found in CDCRELI as well as AF1p/Eps15, and AF6 located at the COOH-terminus of SEPTIN6 might also contribute to leukemogenesis.
Announcements

MEETING OF THE RADIATION RESEARCH SOCIETY

The annual meeting of the Radiation Research Society will be held at the State University of Iowa, Iowa City, on June 22–24, 1953. The Society will be the guest of the University, and all meetings will be held on the campus. The program will consist of: (1) Two symposia, one on “The Effects of Radiation on Aqueous Solutions,” which includes the following speakers: E. S. G. Barron, Edwin J. Hart, Warren Garrison, J. L. Magee, and A. O. Allen. The second is “Physical Measurements for Radiobiology” and companion talks by Ugo Fano, Burton J. Moyer, G. Failla, L. D. Marinelli, and Payne S. Harris. (2) On Monday night, June 22, a lecture by Dr. L. W. Alvarez on meson physics has been tentatively scheduled. On Tuesday night, June 23, Dr. L. H. Gray of the Hammersmith Hospital, London, will speak on a topic to be announced. Dr. Gray’s lecture is sponsored by the Iowa Branch of the American Cancer Society. Those desiring to report original research in radiation effects, or interested in attending or desiring additional information, please contact the Secretary of the Society, Dr. A. Edelmann, Biology Department, Brookhaven National Laboratory, Upton, L.I., New York.

ERRATUM

The following correction should be made in the article by Beck and Valentine, “The Aerobic Carbohydrate Metabolism of Leukocytes in Health and Leukemia. I. Glycolysis and Respiration,” November, 1952, page 891; substitute for the last paragraph:

The data in Table 8 permit several interesting calculations. If one compares the amount of glucose actually disappearing with the sum of the amount equivalent to lactic acid produced plus that equivalent to O₂ consumption, it is seen that the amount of glucose “cleavage products” exceeds the amount of glucose utilized by 12 per cent in N and 27 per cent in CML and is exceeded by the glucose utilized by 16 per cent in CLL. If the assumption is made that, in this respect, the myeloid and lymphoid cells of leukemia are similar to those of normal blood, it may be that the computed normal figure represents a summation of the myeloid (M) and lymphoid (L) cells that make up the normal leukocyte population. Thus, if M = +0.27 and L = −0.16 and the normal differential is 65 per cent M and 35 per cent L, then

\[ 0.65(0.27) + 0.35(-0.16) = +0.12 \]

a figure identical to the observed +0.12 for normal leukocytes.
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