[CANCER RESEARCH 53, 4489–4492, October 1, 1993]

Advances in Brief

Potential Topoisomerase II DNA-binding Sites at the Breakpoints of a t(9;11) Chromosome Translocation in Acute Myeloid Leukemia[1]

M. Negrini, C. A. Felix, C. Martin, B. J. Lange, T. Nakamura, E. Canaani, and C. M. Croce[2]

Jefferson Cancer Institute and Jefferson Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania 19107 [M. N., T. N., E. C., C. M. C.], and Division of Oncology, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania 19104 [C. A. F., C. M., B. J. L.]

Abstract

We have examined a t(9;11)(p22;q23) chromosome translocation in an acute myeloid leukemia of an infant. The breakpoints on the two chromosomes occurred within introns of the involved genes: *AF-9* on chromosome 9, and *ALL-1* on chromosome 11. Sequence analysis identified heptamers flanking the breakpoints on both chromosomes 9 and 11, suggesting that the V-D-J recombinase was involved in the translocation. The presence of an N-region between the two chromosomes supports the hypothesis that a mistake in V-D-J joining was involved in the genesis of the translocation and indicates that terminal deoxynucleotidyl transferase was expressed in the cells from which this acute myeloid leukemia originated. In addition, potential topoisomerase II DNA-binding sites were found near the breakpoints of both chromosomes, suggesting the involvement of altered topoisomerase II activity in this translocation. Altered topoisomerase II activity in the presence of an active V-D-J recombinase may be a pathogenetic mechanism of acute myeloid leukemia with rearrangements at 11q23.

Introduction

Approximately 70% of ALLs[3] in infants, 60% of AMLs in infants, 90% of monoblastic AML in young children, and 6% of ALL and AML in older children and adults have abnormalities of chromosomal band 11q23 (1–4). More than 50% of the cases of topoisomerase II inhibitor-associated secondary AML also have abnormalities of chromosomal band 11q23 (5, 6). Translocations involving chromosome 11 at band q23 and at least 13 different reciprocal partners have been described (4, 7).

The most common 11q23 translocation in both *de novo* AML during infancy and secondary AML is the t(9;11)(p21;q23) (8–10). Most 11q23 breakpoints occur within a discrete 8-kilobase cluster region of the *ALL-1* gene (11–14). The human *ALL-1* gene has regions of homology with the *Drosophila Trithorax* gene; *i.e.*, the positive regulator of homeobox genes within the *Antennapedia* and *Bithorax* complexes and regulates thoracic body segmentation (15, 16). The presence of zinc finger motifs in the *ALL-1* product suggests that the gene encodes a DNA-binding transcription factor protein (15, 16), but the role of *ALL-1* in hematopoiesis and leukemogenesis is unknown (17). The sequence of the *AF-9* gene also suggests that the AF-9 protein is localized in the nucleus (18).

Secondary AMLs that are characterized by translocations involving chromosomal band 11q23 are associated with chemotherapeutic use of inhibitors of topoisomerase II, most commonly the epipodophyllotoxins, etoposide and teniposide (10, 19, 20). Secondary AML also occurs after therapy with the intercalating topoisomerase II inhibitors dactinomycin and anthracyclines (21).

The V-D-J recombinase has been implicated in several translocations where one or even both genes are neither immunoglobulin (*Ig*) nor *TCR* loci yet contain appropriate recombinase-like recognition signals (22–24). Heptamer and nonamer-like V-D-J recombinase recognition sequences are present within few base pairs of the breakpoints on both chromosomes 4 and 11 in ALLs with the t(4;11) chromosomal translocation (25). In lymphoid leukemias, malignant transformation may occur during developmental stages when the V-D-J recombinase is active and immune receptor genes are rearranging. At that time, the *ALL-1* gene heptamer- and nonamer-like sequences may be potential substrates for the V-D-J recombinase (25).

The fact that 10–20% of acute myeloid leukemias carry Ig or *TCR* gene rearrangements suggests that V-D-J recombinase activity may be present in the precursor cells of the myeloid leukemias (26). However, it is possible that different lineages of 11q23 leukemias may involve different pathogenetic mechanisms. Topoisomerase II has been implicated in illegitimate DNA recombination (27, 28), and because of the association of topoisomerase II inhibitors with secondary leukemias with rearrangements at 11q23, we investigated whether topoisomerase II DNA binding sites may play a role in translocations affecting region 11q23 in AMLs by characterizing the sequence of the genomic breakpoints of a t(9;11) chromosome translocation in a *de novo* AML.

Materials and Methods

Informed consent was obtained and genomic DNA was prepared by standard methodology from the primary leukemic cells of an infant male. Cells were of French-American-British M5 morphology. Southern blot analysis with the B859 probe was used to localize the 11q23 translocation breakpoint. This 859-base pair *Bam*HI fragment of *ALL-1* cDNA spans exons 5–11 (15), the region of the *ALL-1* gene breakpoint cluster for *de novo* ALL and AML. Five μg of genomic DNA were digested to completion with 15 units of *Bam*HI, size fractionated on an 0.8% agarose gel, and transferred to nitrocellulose using standard methodology. The filter was hybridized with the 859-base pair *Bam*HI fragment of human *ALL-1* cDNA that was radiolabeled with [^{32}P]dCTP by nick translation (29).

Restriction fragments were subcloned into Bluescript plasmid vector (Stratagene, La Jolla, CA), and sequencing was performed using an ABI automated sequencer and manually using Sequenase version 2.0 (United States Biochemical, Cleveland, OH). The genomic sequence at the breakpoint junctions was assessed for the presence of potential recombinase-like recognition signals and topoisomerase II DNA binding sites using known sequence data (24, 30).

Results

We have examined the leukemic cells of patient 704, a male infant carrying a t(9;11)(p22;q23) chromosome translocation for rearrangements of the *ALL-1* gene by using an *ALL-1* cDNA (B859) probe that allows the detection of breakpoints within the *ALL-1* 8-kilobase breakpoint cluster region (11, 15). Southern blot analysis showed the presence of the normal *ALL-1* allele and of both derivative chromosomes

Received 8/16/93; accepted 8/27/93.

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[1] This study was supported by an Outstanding Investigator Award (CA39860) to C. M. C. from the National Cancer Institute and an Award from the Falck Medical Research Trust. C. M. is a recipient of a fellowship from the Ministerio de Educacion y Ciencia of Spain.

[2] To whom requests for reprints should be addressed, at Jefferson Cancer Institute, Thomas Jefferson University, Bluemle Life Science Bldg, Room 1050, 233 S. 10th Street, Philadelphia, PA 19107.

[3] The abbreviations used are: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; TCR, T-cell receptor; cDNA, complementary DNA.

that resulted from the translocation (Fig. 1). A partial *Sau*3A genomic library was constructed in the *EMBL3* λ phage vector and screened with the B859 *ALL-1* probe. One positive clone (704-10A) contained the translocation breakpoint. The breakpoint in the *ALL-1* gene on chromosome 11q23 was mapped to the intron between exons 6 and 7 (Fig. 2). Southern blot analysis with genomic probes derived from clone 704-10A of DNAs from somatic cell hybrids containing chromosomes 9 or 11 as the only human material, confirmed that the translocation was a t(9;11) (data not shown). Furthermore, hybridization of the λ clone 704-10A with *AF-9* cDNA probe (18) demonstrated that the breakage on chromosome 9 in patient 704 occurred in the *AF-9* gene. The breakpoint region was subcloned into the Bluescript vector and sequenced. About 3 kilobases of the sequence surrounding the der(11) breakpoint were determined. On the basis of the DNA sequence, the breakpoint in the *AF-9* gene on chromosome 9p22 was localized to an intron.

Heptamer-like sequences were identified at the breakpoints on both chromosome 9 and chromosome 11 (Fig. 3). This finding suggests that the t(9;11) chromosome translocation in AML also may be catalyzed by the recombinase involved in *Ig* and *TCR* gene rearrangement, similarly to the t(4;11) chromosome translocation in ALL. Extra nucleotides, resembling an N-region, were present at the joining site between the two chromosomes. This observation indicates that the enzyme terminal deoxynucleotidyl transferase was active at the time the translocation took place. Thus, the presence of potential heptamer and nonamer signal sequences at the breakpoints and the presence of an N-region at the joining site suggest that the t(9;11)(p22;q23) chromosome translocation occurred by V-D-J recombination. In addition, sequence analysis indicated the presence of consensus topoisomerase

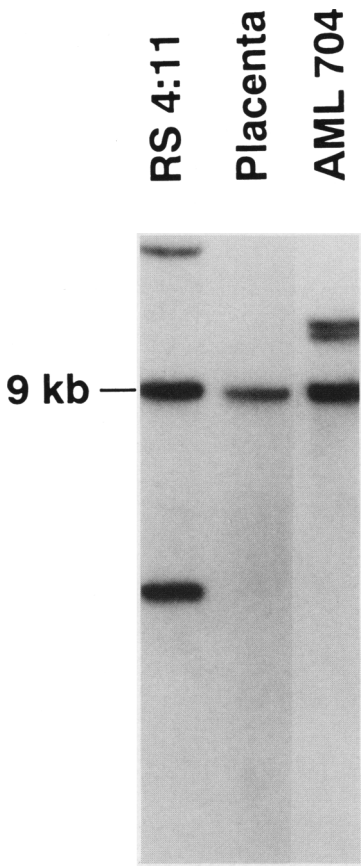

Fig. 1. Southern blot analysis of leukemic cells from patient 704. Genomic DNAs were digested with the restriction enzyme *Bam*HI and hybridized with an ALL-1 cDNA probe (B859). DNAs from the RS4:11 cell line, which carries a t(4;11) chromosome translocation, and from human placenta were used as controls.

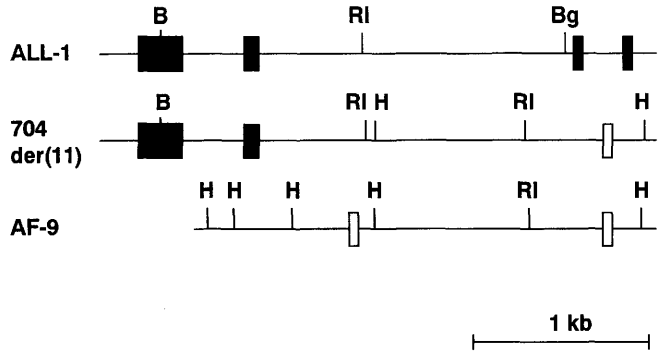

Fig. 2. Schematic representation of the der(11) chromosome of patient 704. Exons are represented by empty (AF-9) or full (ALL-1) boxes. *B*, *Bam*HI; *RI*, *Eco*RI; *Bg*, *Bgl*II; *H*, *Hind*III, *ALL-1* exons are from 5 to 8 and the two *AF-9* exons correspond to nucleotides 1627–1698 and 1699–1770 of the published cDNA sequence (18).

II DNA-binding sites in both the *ALL-1* and *AF-9* loci in close proximity to the breakpoints (Fig. 3). Since both strands of DNA are involved in cleavage by the topoisomerase II dimer, a relationship exists between the strength of cleavage and the match of both strands to the consensus sequence. According to this criterion, the sequences in proximity to the translocation breakpoint that show homology to the consensus are categorized as "strong cleavage sites" (Fig. 4) (30). These sites are the strongest among other potential sites found in the 3 kilobases of sequence analyzed.

Discussion

Analysis of the sequences at the regions of breakpoints in chromosome translocations can reveal enzymatic mechanisms involved in DNA breakage and nonhomologous recombination. We previously proposed that aberrant V-D-J recombination is involved in chromosomal translocations in B- and T-cell malignancies (22, 23). While the V-D-J recombinase has been implicated in several translocations juxtaposing *Ig* or *TCR* loci to cellular oncogenes, the analysis of t(4;11) chromosome translocations suggested recombinase involvement also in translocations between non-Ig, non-*TCR* genes (25). The heptamer- and nonamer-like sequences at the translocation breakpoints of ALLs with rearrangements at 11q23 are potential substrates for the V-D-J recombinase. The present work suggests V-D-J recombinase involvement not only in *de novo* ALL but also in *de novo* AML with a t(9;11) chromosome translocation. The orientation of the heptamer-like sequences with their 5′ end at the boundary of the breakpoints, as shown on the two normal chromosome sequences (Fig. 3), and the presence of an N-region at the junction between *ALL-1* and *AF-9* genes suggests that the der(11) chromosome represents the "coding junction" of a V-D-J-like recombination (24).

Since secondary leukemias are frequently induced by inhibitors of topoisomerase II, we investigated whether topoisomerase II DNA binding sites may be present in proximity to this t(9;11) breakpoint. Indeed, in the DNA of patient 704 we identified two regions of homology with topoisomerase II binding sites adjacent to the translocation breakpoints. These results suggest that aberrant topoisomerase II activity may be involved in the pathogenesis of myeloid leukemias with translocations at 11q23.

Topoisomerase II catalyzes and regulates double stranded DNA cleavage and religation during replication, condensation, mitotic segregation or strand passage, transcription, and recombination (31, 32). The cleavage and religation reactions enable topoisomerase II to participate in illegitimate DNA recombinations including translocations (28, 33). Yeast strains lacking topoisomerase II have a 200-fold increase in recombination (34). Topoisomerase II has high *in vitro* activity at an *in vivo* hot spot for recombination in the human β-globin

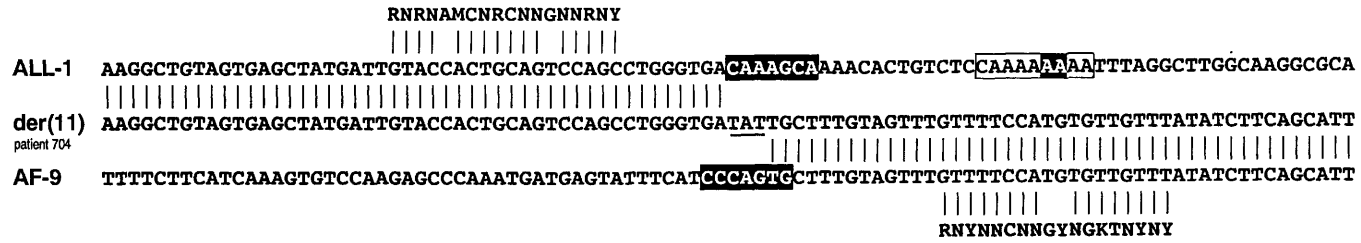

Fig. 3. der(11) genomic breakpoint junction of the t(9;11) chromosome translocation. Regions of homology with preferred eukaryotic topoisomerase II binding sequence in the human β-globin gene (34) are shown. *R*, purine; *Y*, pyrimidine; *N*, any base; *K*, G or T; *M*, A or C. The breakpoint falls between *Eco*RI and *Hind*III restriction sites as shown in Fig. 2. Heptamer-like sequences, found on the *AF-9* gene and the *ALL-1* gene, are shown as *shadowed* nucleotides. A potential nonamer in the *ALL-1* sequence is *boxed*, with the two critical As *shadowed*.

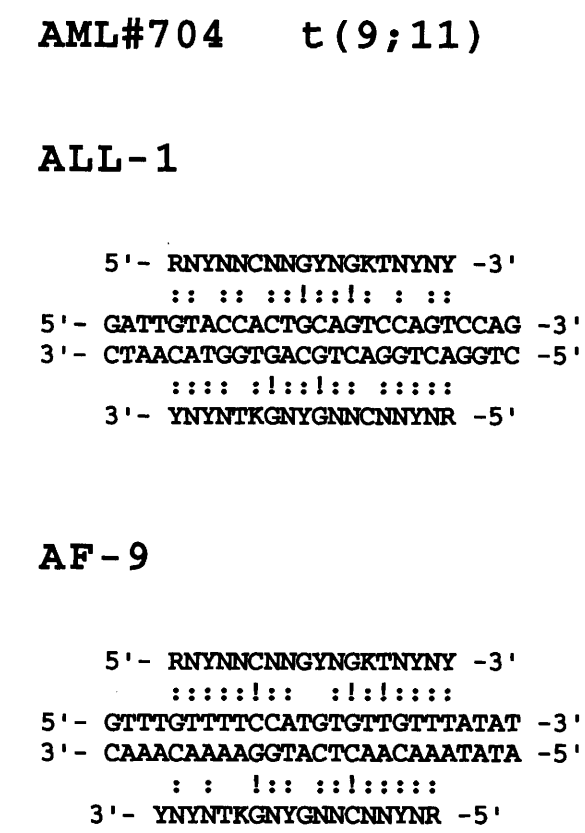

Fig. 4. Homology to the consensus sequence of topopisomerase II DNA-binding sites of the two strands. On *ALL-1*, the "best matched" strand has 8 of 10 (excluding the Ns) matches and the less homologous has 6 of 10 matches. On *AF-9*, the "best matched" strand has 8 of 10 and the less homologous has 5 of 10 matches. These data classify these sites as "strong cleavage sites" (34). *R*, purine; *Y*, pyrimidine; *N*, any base; *K*, G or T; *M*, A or C; :, homology; and !, identity.

gene (30). Topoisomerase II cleavage sites are present in the murine *Igκ* light chain locus at a site of translocation (27).

The epipodophyllotoxins are topoisomerase II inhibitors that interfere with the breakage-reunion reaction of the enzyme. They increase DNA breakage by the formation of a stacking complex involving drug, DNA, and enzyme, thus decreasing religation. Treatment with etoposide causes DNA strand breaks and sister chromatid exchanges. The resulting deletions or rearrangements in essential genes are usually cytotoxic (35–37). The chromosomal aberrations frequently involve human chromosome 11 *in vitro* (38). Topoisomerase II inhibitor chemotherapy occasionally causes leukemia with translocations at 11q23 (21). The results of this study suggest a role of altered topoisomerase II activity not only in the secondary forms of 11q23 leukemia but also in *de novo* AML.

The heptamer- and nonamer-like signal sequences at the regions of the breakpoints of *ALL-1* and the reciprocal partner AF-4 in *de novo* ALL are imperfect. Therefore, enzymes other than the V-D-J recombinase may be necessary for 11q23 translocations (24). The inserted 43-base pair duplicated and inverted sequence as well as the deletion of bases at the t(4;11) breakpoints of the cell line RS4:11, and the additional bases inserted in the region of the MV4:11 breakpoint suggest complex patterns of DNA breakage and repair (25). Conceivably, disrupted topoisomerase II activity; the V-D-J recombinase enzyme system including RAG-1, RAG-2, terminal deoxynucleotidyl transferase and/or other enzymes all may be involved (24, 39).

Pesticide exposure, maternal use of marijuana, and maternal alcohol consumption are independent risk factors for monoblastic AML (40–42). The finding of a common breakpoint cluster region in secondary leukemias and leukemias associated with the other toxins suggests that the *ALL-1* genomic region is vulnerable to chemical injury (43, 44). The finding of topoisomerase II sites at a breakpoint in a *de novo* AML suggests that 11q23 leukemias with different etiologies may have a common pathogenetic mechanism. The AML case described in this work, even though it might not represent a general rule for *de novo* AMLs, may instead reflect a more general situation for secondary leukemias. In order to elucidate this point, it will be necessary to characterize the genomic breakpoints of translocations involving region 11q23 in secondary leukemias.

Acknowledgments

We thank Y. Gu for the B859 probe.

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