Activation of a Novel Gene in 3q21 and Identification of Intergenic Fusion Transcripts with Ecotropic Viral Insertion Site I in Leukemia

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Abstract

We have identified a novel gene, GR6, located within the leukemia breakpoint region of 3q21, that is normally expressed in early fetal development but not in adult peripheral blood. GR6 is activated in the UCSD-AML1 cell line and in a leukemic sample, both of which carry a t(3;3)(q21;q26). In UCSD-AML1, we have also identified fusion transcripts between the ecotropic viral insertion site I (EVII) gene in 3q26 and GR6 and between EVII and Ribophorin I that maps 30 kb telomeric to GR6 in 3q21. All fusions splice the 5' ends of the 3q21 genes into exon 2 of the EVII gene, an event that is similar to the normal intergenic splicing of MDS1-EVII and to those previously documented in leukemias with t(3;21) and t(3;12), in which acute myelogenous leukemia 1-EVII fusions and ETV6-EVII fusions, respectively, occur. The Ribophorin I-EVII fusion in particular may be a common occurrence in t(3;3).

Introduction

The involvement of 3q21 and 3q26 in rearrangements in leukemia is well established (1). Translocations, inversions, and deletions in and between 3q21 and 3q26 are seen in 4–6% of AMLs and also in some chronic myelogenous leukemias, therapy-related leukemias, and MDSs. In many of these cases, the zinc finger transcription factor, the EVII gene, which maps to 3q26, has been shown to be aberrantly activated (2–5). Breakpoints within 3q26 that can effect this activation have been mapped over large regions, up to several hundred kb either 5' or 3' to EVII. Regulation of expression of the EVII gene appears complicated. In normal tissues, EVII and a gene of unknown function, MDS1, located 170–300 kb upstream, have been shown to exist both as separate transcripts and as spliced products, where the 5' end of MDS1 is spliced into exon 2 of EVII (6). Because exon 2 of EVII is otherwise not translated, this intergenic splicing produces a radically different 5' protein sequence. The complexities of the MDS1/EVII gene organization and regulation in 3q26 have not been reported for other human genes.

In contrast to 3q26, the precise role of sequences in 3q21 is less well described. Breakpoints here are clustered; the 10 that have been mapped are located within a segment no more than 30 kb in size (7–9). The RBPHI gene maps 20 kb telomeric to this region, an observation that has led to the hypothesis that an associated enhancer is responsible for the activation of EVII (7). However, several additional transcriptional units have been described within an 80-kb segment, immediately proximal to RBPHI and spanning the breakpoint region (9). These putative genes are novel, of unknown function, and generally expressed at low levels in normal tissues. The density of genes and the dispersion of breakpoints suggests that leukemia rearrangements may make a number of different transcriptional alterations possible. Here, we describe several of these alterations in t(3;3)(q21; q26), seen in the leukemia-derived cell line, UCSD-AML1 (10), and in a leukemia sample.

A novel gene, GR6, within 3q21, has been characterized and shown to be normally expressed in early fetus but not in adult lymphocytes or lymphoblastoid cells. GR6 is, however, activated in the leukemia-derived cell line, UCSD-AML1, and in the one additional leukemic sample tested. In addition, GR6 and RBPH1 separately participate in intergenic splicing events with the EVII gene in the UCSD-AML1 cell line. From information on the locations of other leukemic breakpoints in 3q21, the occurrence of at least the RBPH1-EVII-spliced product may be a common event in t(3;3)(q21;q26).

Materials and Methods

Cell Lines. The leukemia-derived UCSD-AML1 cell line, carrying t(3;3)(q21;q26), has been described previously (10). The lymphoblastoid cell line CCM-1 (received from M. V. Olsen, University of Washington, Seattle) was used as a normal control. Cells were grown in RPMI 1640 with 15% fetal bovine serum. For the UCSD-AML1 cell line, 100 units/ml granulocyte macrophage colony-stimulating factor was added to the medium.

Sequence Analysis. Sequencing within the 3q21 breakpoint region has been described (9). Twenty-five kb of sequence spanning 12 kb telomeric to the UCSD-AML1 breakpoint to 13 kb centromeric, has been submitted to the GenBank database (accession no. AF008191). In this sequence, Grail analysis (11) predicted exons at nucleotides 7,176–7,797, 8,573–8,744, and 10,246–10,368, and the GR6 gene was determined to extend from nucleotide 6,404 to 10,488. For brevity, Fig. 1c gives the nucleotide/amino acid sequence of only the GR6 exons. Table I lists the names, sequences, and nucleotide numbers (from the GR6 exon sequences in Fig. 1c) of the primers used in RACE and RT-PCR experiments used to determine the structure of GR6.

RNA Isolation. Total RNA was isolated from 2 x 10^8-10^9 cells, from 7–8-week whole fetuses and from adult lymphocytes by standard guanidinium thiocyanate procedures (12). Poly(A)+ RNA was isolated from 0.2–1.0 mg of total RNA using Mini-Oligo(dT) Cellulose Spin Columns (5 Prime → 3 Prime). RNA quality was checked on 0.8% agarose denaturing gels (13). Poly(A)+ RNA for sample no. 32 was prepared from a leukemic sample carrying t(3;3)(q21;q26).4 Northern blots containing 2 μg of poly(A)+ RNA were prepared from whole fetus, adult lymphocytes, and cell lines. Additional Northern blots containing RNA from adult cells, 18–24-week fetal tissues, and cancer cell lines were purchased from Clontech.

RT-PCR. Five μg of total RNA were treated with DNase I (amplification grade; Life Technologies, Inc.) following the manufacturer's directions. DNase I-treated RNA was used in reverse transcription reactions as follows: 10 nm each dNTP, 100 pmol of random hexamers, RNA, and 200 units Moloney murine leukemia virus reverse transcriptase (Life Technologies, Inc.) in total
Fig. 1. Structure of the GR6 gene. a, location and orientation of the GR6 gene in 3q21, relative to the breakpoint in the leukemia-derived cell line UCSD-AML1 (10) and to the previously described novel genes GR2, P2, and 1B1 (9) and the RBPH1 gene, located telomeric to the NotI site (7). Note that GR5, P2, and RBPH1 are all transcribed in the telomere-to-centromere direction. b, enlargement of the GR6 gene structure, showing exons 1–4 and the observed alternative splicing products. c, sequence of the GR6 exons. Boundaries of the exons are indicated above the nucleotide sequence. The amino acid sequence of the ORF in exon 4 is shown below the nucleotide sequence. *5*, 5'tO@ codon. The complete nucleotide sequence, including introns, can be found in GenBank database (accession no. AF008192). d, RT-PCR showing activation of GR6 in leukemia. Lane 1, normal lymphocytes; Lane 2, UCSD-AML1 cell line [with t(3;3)]; Lane 3, CGM-1 lymphoblastoid cell line; Lane 4, 7–8-week fetus; Lane 5, leukemic sample 32 [with t(3;3); Ref. 19]. GR6 included 30 cycles of amplification; actin with 17 cycles of amplification is shown for comparison. +, reactions with reverse transcriptase; −, without reverse transcriptase.
Table 1 Primers used in the determination of the GR6 gene structure and in the identification of fusion transcripts

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<th>Product nucleotide nos.</th>
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* Exons 1–4 refer to the GR6 gene.

b GR6 primers GR6A and GR6B were used in the RT-PCR experiments shown in Fig. 1d.

c GR6 primers SAC15D and GR6AR were used with the EVIl primer EVIK in the RT-PCR experiments of Fig. 2a.

Fusion Transcripts with EVIl in Leukemia

Characterization of the GR6 Gene. A previous report described gene identification within an 80-kb segment of 3q21, spanning a number of leukemia breakpoints (9). As part of this work, a 25-kb segment surrounding the breakpoint from the leukemia-derived cell line UCSD-AML1 was completely sequenced. Analysis of this sequence using the GRAIL exon identification software predicted three exons, located approximately 1 kb telomeric to the UCSD-AML1 breakpoint (Fig. 1). Sequences of the predicted exons were used to design primers for RACE and RT-PCR experiments (described below). Comparisons of these results with the genomic sequence determined exact exon boundaries and the complete structure of the gene, which we have called GR6. GR6 is composed of 4 exons (Fig. 1b): exon 1, of undetermined length (RACE has not been extended further 3'); and exons 2–4, of 121 bp, 109 bp, and 1.6 kb, respectively. Cloning and sequencing of the following RT-PCR and RACE products determined this structure: (a) an 800-bp RACE product contained part of exon 1, spliced directly to exon 4; (b) three consecutive 3' RACE products of 600, 450, and 250 bp connected the 3' end of the 800-bp RACE product with the poly(A) tail of the gene. The 250-bp RACE product contained a 30-nucleotide poly(A) tail that was not encoded by the genomic sequence; (c) a 1.0-kb RACE product and a 600-bp RT-PCR product contained part of exon 3, the entire exon 3a, and part of exon 4; (d) a 300-bp RT-PCR product contained part of exon 3, spliced directly to exon 4; and (e) a 350-bp RT-PCR product contained part of exon 1, the entire exon 2, plus part of exon 3.

Together, these data suggest the existence of several alternatively spliced GR6 mRNAs (Fig. 1, b and c): an mRNA in which exon 1 is spliced directly to exon 4; an mRNA in which exons 3 and 4 are spliced in sequence or two mRNAs, one in which exons 1–3 are spliced in sequence or one in which exons 3 and 4 are spliced in sequence (these last two mRNAs cannot be distinguished in the experiments described here). All splice sites conform to the consensus GT/AG. The RT-PCR product for the first transcript (in which exon 1 of GR6 is spliced directly into exon 4) was always much more intense than the other two (data not shown), suggesting that this is the major normal GR6 transcript. This is consistent with the identification by RACE of only this transcript (the other two were identified by RT-PCR).

Exon 4 contains a 450-bp ORF, with the initiation methionine at nucleotide 968 (Fig. 1c). No homologies to known genes, expressed sequence tags, or other sequences were found in Blast searches with the GR6 transcripts, with the exception of a 50-bp Alu segment within exon 2. All hybridizations to Northern blots containing 2 μg of poly(A)+ RNA from a variety of fetal and adult tissues and several cancer cell lines and using RACE and RT-PCR products as probes were negative.

Normal GR6 Expression and Activation in Leukemia. The negative Northern results suggested GR6 may be expressed only at low levels, raising the possibility that GR6 may be specifically activated in leukemia. This was investigated by RNA expression studies in a large number of hematopoietic cell lines and in a variety of hematopoietic cell types. A nearly full-length GR6 transcript could be found in all of these cells, and its expression was found to be significantly increased in several leukemia cell lines. The results of these studies are reported elsewhere (15).
levels. RT-PCR analysis was used to explore this possibility (Fig. 1d). RT-PCR using GR6A and GR6B primers (within exons 1 and 4, respectively) was weak in normal lymphocytes and negative in a lymphoblastoid cell line (Lanes 1 and 3). Results were similar with other cell lines, including both normal and tumor-derived cell lines lacking 3q21 rearrangements (data not shown). However, normal human 7–8-week embryo showed strong levels of GR6 product (Lane 4). This is the only evidence of GR6 expression in material carrying a normal 3q21 region that we have found. GR6 is also expressed in the UCSD-AML1 leukemia cell line (Lane 2), in which the 3q21 breakpoint lies approximately 1 kb 3' to GR6. In neither fetal tissues nor the UCSD-AML1 cell line is GR6 expression detectable by Northern analysis. Similar results were obtained with patient material that showed a t(3;3)(q21;q26) (sample no. 32; Lane 5). These data indicate that breakpoints outside the GR6 gene, i.e., the UCSD-AML1 breakpoint is 3' to GR6 and the sample no. 32 breakpoint is 5' (see Discussion and Fig. 3), can both effect aberrant activation of GR6. This observation is similar to that with breakpoints surrounding the EVII gene in 3q26.

Identification of GR6-EVI1 and RBPH1-EVI1 Fusion Transcripts in the UCSD-AML1 Cell Line. Fusion transcripts involving the EVII gene have been reported in cases of t(3;21)(q26;q22) (15) and t(3;12)(q26;p13) (16). Fusions have most frequently involved splicing into exon 2 of EVII. Fig. 2b shows that the positions and orientations of GR6, P2, and RBPH1 relative to EVII in the der 3q+ chromosome of the t(3;3) in the UCSDAML1 cell line are shown. RBPH1 is composed of 10 exons (20); only exon one is indicated separately. The four exons of GR6 are indicated. Only exons 1–3 of EVII are shown. Segments of exons 2 and 3 that are not translated in the EVII-alone protein. The novel exon X is located in 3q26. 5' to the EVII gene. The four intergenic transcripts are indicated. c, amino acid sequences of IT1-IT4 fusions. Italicized letters, GR6 sequences in IT1-IT4 fusions. Underlined letters, GR6 sequences in IT1-IT3: underlined exons, exon X sequence in IT1-IT3. IT4 is the RBPH1 fusion transcript. Boldface letters, translation of EVII exons 2 and 3 common to IT1-IT4; underlined, italicized letters, continuation of the remainder of the EVII sequence.
locations of GR6, a previously described novel gene, P2 (9), and RBPH1 (10) in 3q21 have the same orientation as the EVII gene in 3q26 in the UCSD-AML cell line. This suggests that GR6, P2, and RBPH1 could, in principle, participate in forming intergenic fusion transcripts with EVII. To explore this possibility, RT-PCR was carried out between exon 3 of the EVII gene and various exons of GR6 and RBPH1 and segments of the P2 gene (Fig. 2a). Three different intergenic transcripts between EVII and GR6 and one intergenic transcript between EVII and RBPH1 were identified:

(a) IT1 fuses exon 1 of the GR6 gene with exon 2 of the EVII gene. The ORF of this transcript includes 3 amino acids (including methionine) of exon 1 of the GR6 gene, 63 amino acids of exons 2 and 3 of the EVII gene (in normal EVII transcripts this region is not translated; Ref. 5), and 1051 amino acids of the normal EVII protein.

(b) IT2 fuses exon 4 of the GR6 gene with exon 2 of the EVII gene. An ORF of this transcript includes 63 amino acids of exon 4 of the GR6 gene (including methionine) and the same 1104 amino acids of the EVII gene as IT1. The 63 amino acids from the GR6 gene in this transcript are encoded by an ORF different from the major GR6 ORF. This smaller ORF is 200 bp in size (Fig. 1c).

(c) IT3 also fuses exon 4 of the GR6 gene with exon 2 of the EVII gene. But in this case, an 87-bp exon X is located between these two exons. The ORF of the IT3 is the same as the ORF of the IT2, with the addition of 29 amino acids encoded by exon X. Exon X has been localized to 3q26 by analysis of a chromosome 3 hybrid mapping panel (Ref. 8; data not shown); it is not part of the published sequence of the EVII cDNA (17), and it shows no homology to any GenBank sequences in Blast searches.

(d) IT4 fuses inframe exon 1 of RBPH1 to exon 2 of EVII. The ORF of IT4 contains 87 NH2-terminal amino acids of RBPH1 fused to the same 1104 amino acids of EVII.

The predicted protein sequences of all four fusion proteins are shown in Fig. 2c.

Summary. Because of the complexity of these data, some additional details are worth summarizing. No intergenic fusion transcripts involving P2 or any other exons of GR6 or RBPH1 were found, and RBPH1-GR6-EVII tandem fusions were not seen. Limited patient material precluded testing of sample no. 32 for any fusion transcripts. In fusion transcripts IT2 and IT3, it is assumed that the transcription start site is similar to that for IT1, i.e., including the normal exon 1 of GR6. This has not been determined; what has been described is the start of an ORF. 5' RACE from EVII cannot help in these determinations because of the high levels of activated expression of the (apparently) normal EVII transcript (2). In summary, in the UCSD-AML1 cell line, three types of relevant transcripts are seen: normal EVII transcripts produced by breakpoint activation; normal GR6 transcripts similarly produced by breakpoint activation; and fusion transcripts between GR6 and EVII and between RBPH1 and EVII.

Discussion

We have identified a novel gene, GR6, mapping within the leukemia breakpoint region of 3q21, a band frequently associated with t(3;3), inv(3), and del(3q21) in AML, chronic myelogenous leukemia, and MDS. The GR6 gene is composed of four exons, with an ORF of 150 amino acids located within exon 4. It is transcribed telomere to...
The putative GR6 protein shows no homology with any proteins in the databases searched with Blast. Negative Northern results with adult and 18–24-week fetal tissues suggest that GR6 expression is, at best, low in normal tissues. GR6 does, however, show clear expression by RT-PCR in whole 7–8-week fetus, suggesting potential fetal specificity. Most interestingly, it is negative by RT-PCR in fresh adult lymphocytes but clearly expressed in the UCSD-AML1 leukemic cell line and in the one leukemic sample available for testing.

The locations and orientations of the GR6 gene, the P2 gene, and the RBPH1 gene in 3q21, relative to the location and orientation of the EVIl gene in 3q26 in the UCSD-AML1 cell line, suggested the possibility of fusion transcripts. These were verified between GR6 and EVIl and between RBPH1 and EVIl. In each of the fusions, additional amino acids and a novel transcription start site are spliced into exon 2 of EVIl. The additional amino acids number 3, 63, and 92 from the GR6 fusions and 87 from the RBPH1 fusion. Exon 2 and the 5’ end of exon 3 of EVIl are not translated in the EVIl protein; the novel start sites, thus, also add 63 amino acids of EVIl sequence to the translations.

Splicing into exon 2 of the EVIl gene is a normal event observed in pancreas and kidney, involving the 3q26 upstream MDSJ gene (6). It is believed that this normal intergenic splicing serves to alter the transactivating properties of the EVIl transcription factor, thus altering regulation of downstream genes (18). Abnormal EVIl exon 2 splicing events have also been observed in leukemia rearrangements involving t(3;21)(q26; q22) (15), in which the chromosome 21 breakpoint occurs in intron 6 of the AML1 gene. In this case, the 5’ end of the AML1 gene is then fused either with exon 2 of EVIl directly or through MDSJ or the gene encoding E1A-associated protein, both upstream of EVIl. Similar aberrant EVIl exon 2 splicing has also been observed in t(3;12)(q26;p13) (16), in which the chromosome 12 breakpoint occurs within the ETv6 gene. In a fashion analogous to the t(3;21), the first two exons of ETv6 are spliced to EVIl or MDSJ-EVIl. Thus, there are several examples of leukemia-associated rearrangements giving rise to potential translation of EVIl exons 2 and 3, suggesting that this may be a critical element in cases with EVIl activation.

A novel feature of the 3q21-EVIl splicing observed here is that the 3q21 breakpoint occurs downstream of the 3’ end of each of the genes that encode the 5’ ends of the fusion products. Thus, it is not the more commonly observed scenario of fusion transcripts produced when a translocation has interrupted a gene. It will be of interest to determine the sequences in 3q21 that promote these intergenic splicing events.

Unresolved is the role that the fusion protein products may play in leukemia. These may include the inappropriate activation of EVIl and the inappropriate function of the EVIl protein. This latter, at least, is strongly suggested by the analysis of normal EVIl and MDSJ/EVIl function (18). Normal EVIl protein is a repressor of promoters containing the AGATA motif, whereas normal MDSJ/EVIl is a strong activator. In addition, the activation function of MDSJ/EVIl protein is contained within the segment encoded by EVIl exons 2 and 3. Thus, the GR6-EVIl and RBPH1-EVIl fusions not only cause expression of EVIl inappropriately but also potentially produce proteins with EVIl transcriptional activator properties.

A second point of interest involves the frequency of these fusion products in leukemias with rearrangements affecting 3q21 and 3q26. Fig. 3 shows the breakpoint locations relative to the GR6, RBPH1, and EVIl genes for a number of cases in which detailed mapping information is available. Several features are noteworthy. First, for all cases of t(3;3)(q21;q26), RBPH1-EVIl fusion can occur. In the cases of t(1;3), RBPH1 is also correctly positioned and oriented for producing a fusion product with a gene from chromosome 1. In contrast, considering all t(3;3), it is possible for the GR6-EVIl fusion to occur only in the UCSD-AML1 example, and GR6 is also oriented incorrectly in both t(1;3). Thus, it may be postulated the fusion of RBPH1 is the critical event in leukemias with t(3;3). The production of additional fusion products may affect some aspects of the leukemia phenotype.

Even RBPH1 fusions, however, are unlikely to be the entire story for 3q21 rearrangements in leukemia. In cases of inv(3), RBPH1 is transcribed in the opposite orientation relative to the breakpoints and EVIl transcription. In these cases, the fusion partners may still be one of several novel transcripts described previously (9) or yet to be discovered in 3q21.

Acknowledgments

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References

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