Brief report

Overexpression of *CEBPA* resulting from the translocation t(14;19)(q32;q13) of human precursor B acute lymphoblastic leukemia

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Subtle variation in the expression or function of a small group of transcription factors can drive leukemogenesis. The CEBPA protein is known to regulate the balance between cell proliferation and differentiation during early hematopoietic development and myeloid differentiation. In human myeloid leukemia, *CEBPA* is frequently inactivated by mutation and indirect and posttranslational mechanisms, in keeping with tumor suppressor properties. We report that CEBPA is activated by juxtaposition to the immunoglobulin gene enhancer upon its rearrangement with the immunoglobulin heavy-chain locus in precursor B-cell acute lymphoblastic leukemia harboring t(14;19)(q32;q13). Overexpression of apparently normal CEBPA RNA or protein was observed in 6 patients. These data indicate that *CEBPA* may exhibit oncogenic as well as tumor suppressor properties in human leukemogenesis. (Blood. 2006;108:3560-3563)

Introduction

The CCAAT/enhancer-binding protein (CEBP) belongs to a subfamily of transcription factors sharing a basic region–leucine zipper (bZIP) motif within their carboxy terminal end. They can homo- and heterodimerize through the bZIP motif. Alternative splicing and multiple translational initiation sites add further complexity to the family picture.[1]

CEBPA, the founder member of the family, is encoded from a gene composed of a single exon localized to the chromosomal band 19q13. Expression studies and knock-out experiments have demonstrated its essential role in the control of balance between proliferation and differentiation in a range of tissues, including hematopoietic stem cells and different stages of myeloid differentiation.[2-4] CEBPA controls the expression of myeloid genes and interacts with many protein partners such as CDK2, CDK4, CDKN1A/p21, E2F, and the SPI1/PU.1 transcription factor. The interaction with E2F is essential for the repression of *MYC* expression and induction of granulocytic differentiation. Besides the full-length 42-kDa protein, an internal translational initiation site leads to the synthesis of a smaller 30-kDa product. This product fails to inhibit E2F and to down-regulate *MYC* and acts as a dominant-negative form.[5,6]

In line with its essential role in myeloid differentiation, inactivation of *CEBPA* is observed in human myeloid leukemic samples.[1] Mutations of *CEBPA* are observed in about 8% of acute myeloid leukemia (AML). They comprise 2 classes: mutations within the carboxyterminal part of the protein, resulting in the functional inactivation of the transcription factor; and mutations that occur within the 5′ part of the gene, allowing the synthesis of only the short, dominant-negative 30-kDa CEBPA protein. The latter situation is also observed in rare constitutive mutations of *CEBPA*, which are associated with the occurrence of familial AML. Both constitutive and somatic mutations are frequently associated with mutation or loss of the second copy of the *CEBPA* gene, related to progression of the oncogenic process.[7,8]

More frequently, *CEBPA* is indirectly inactivated in AML.[1] Patients with t(8;21)(q22;q22) express the RUNX1-ETO fusion protein, which disrupts the positive autoregulation of the *CEBPA*

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A complete list of the members of the Groupe Francophone de Cytogénétique Hématologique appears in "Appendix."

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Table 1. Hematologic, individual, and cytogenetic data of patients with t(14;19)(q32;q13)

Patient no.	Sex	Age, y	WBC count, × 10^9/L (% blasts)	Hb level, g/L	Platelet count, × 10^9/L	Survival	Immunophenotype	Karyotype*
P1	F	7	13.4 (92)	75	167	12 y	Early pre-B/pre-B?†	46, XX,t(14;19)(q32;q13)[2]/45,idem,der(16)t (16;17)(q11;q11),−17[14]
P2	F	26	4.5 (55)	100	50	Unknown	Early pre-B/pre-B?†	46,XX,dup(1)(q21q31),t(14;19)(q32;q13)[2]
P3	M	22	6.8 (26)	53	17	5 mo (d)	Early pre-B ($CD10^+$, Igc^-)	46,XY,t(14;19)(q32;q13)[9]
P4	M	40	4.9 (67)	55	27	5 mo (d)	Pro-B ($CD10^-$, Igc^-)	46,XY,t(14;19)(q32;q13)[12]/46,idem,idic(8)(p11)[6]
P5	F	38	16.2 (72)	104	37	3 mo	Early pre-B ($CD10^+$, Igc^-)‡	46,XX,del(7)(p?15),t(14;19)(q32;q13)[20]
P6	M	76	11 (77)	126	57	5 mo (d)	Pre-B ($CD10^-$, Igc^+)	46,XY,t(14;19)(q32;q13)[7]
P7	F	38	94 (46)	120	168	22 d (d)	Early pre-B ($CD10^+$, Igc^-)§	46,XX,t(9;22)(q34;q11)[9]/46,idem,i(7)(p10)[2]/ 47,idem,+8,t(14;19)(q32;q13)[8]/48,idem,+6, t(8;9)(q?;q11),+der(22)t(9;22)[21]§
P8	F	41	1.5 (16)	82	145	9 mo	Early pre-B/pre-B?†	46,XX,t(14;19)(q32;q13)[10]

WBC indicates white blood cell; Hb, hemoglobin; (d), dead; and Igc, cytoplasmic IgM,
*Normal population omitted from the karyotype.
†$CD10^+$, Igc not done.
‡All analyzed myeloid markers (myeloperoxidase, CD13, CD33, CD117, CD65) were negative for all patients, except for P5 ($CD13^+$).
§All karyotypes were analyzed from bone marrow, except for P7 (peripheral blood).

promoter, suppressing CEBPA protein expression. The RUNX1-MDS1-EVI1 fusion oncoprotein, expressed in patients with t(3;21)(q26;q22), and the CBFB-MYH11 fusion protein, expressed as a result of inv(16)(p13q22), indirectly suppress CEBPA protein expression through translational inhibition of the *CEBPA* mRNA and loss of CEBPA protein.[1] A comparable mechanism is observed in chronic myelogenous leukemia, in which the expression of heterogeneous nuclear RNPE2 (hnRNPE2) is responsible for the translational inhibition of *CEBPA* in blast crisis. More recently, functional inactivation of the CEBPA protein has been described in association with *FLT3* internal tandem duplication.[9] Together, these data support a tumor suppressor role for the *CEBPA* gene in myeloid malignancies.

Chromosomal translocations are frequently observed in hematologic malignancies, representing an important step in the leukemic transformation process. A number of chromosomal translocations, particularly in lymphoid malignancies, result in ectopic or enhanced expression of genes located within the vicinity of the chromosomal breakpoints.[10] This leads to overexpression of a protein, usually of normal sequence, although functionally significant mutations have been reported.[11]

In human precursor-B acute lymphoblastic leukemia (BCP-ALL), translocations involving the immunoglobulin heavy-chain locus *(IGH)* at chromosomal band 14q32 is a rare but recurrent event. One such translocation, t(14;19)(q32;q13), has been previously described in 6 patients with BCP-ALL, in which the breakpoint on chromosome 19 differs from the t(14;19)(q32;q13) identified in mature B-cell malignancies.[12] The Groupe Francophone de Cytogénétique Hématologique (GFCH) has collected 8 additional patients for hematologic, cytogenetic, and molecular studies. Here we report that this translocation involves the *CEBPA* gene on chromosome 19, resulting in a marked up-regulation of its expression and the production of an apparently normal CEBPA protein.

Study design

Patient details are shown in Table 1. Samples were obtained after patients provided informed consent in accordance with the Declaration of Helsinki. Fluorescence in situ hybridization (FISH) analysis was performed as previously described,[13] using either bacterial artificial chromosomes (BACs) or commercially available *IGH* probes (LSI IGH; Abbott Diagnostics, Rungis, France).[14] Immunologic, molecular, and quantitative polymerase chain reaction (PCR) analyses were performed as previously described.[15,16] The fusion *CEBPA-Cmu* transcript was amplified using standard reverse transcription (RT)–PCR techniques with the primers CEBPA3 (AGGGGTGGAAACATAGGGACTT) and C1 (CCAACGGCCACGCTGCTC).

Results and discussion

Conventional chromosomal analysis identified 8 patients with t(14;19)(q32;q13). Apart from 1 child, the patients were adults (median, 38 years; range, 22-76 years) with ALL, ranging from pro-B to pre-B immunophenotype. Myeloid markers tested were essentially negative (Table S1, available at the *Blood* website; see the Supplemental Materials link at the top of the online article). Data from the Leukaemia Research Acute Leukemia Cytogenetics Database has shown an incidence of less than 0.5% and approximately 2% for this translocation in B-lineage childhood and adult ALL, respectively. The involvement of the *IGH* locus was confirmed by FISH (data not shown). Extensive FISH mapping identified a single BAC (RP11-270I13) containing sequences that encompassed the breakpoint within 19q13. Figure 1A shows a representative image from patient P5, which was similar in all 8 patients. No material was available for further study of patients P7 and P8. The clustering of the chromosome 19 breakpoints within the sequences covered by a single BAC indicated the recurrent targeting of an individual gene.

To investigate the potential partner gene, we evaluated the expression by quantitative PCR of 4 genes located in this region of chromosome 19: *LRP3*, *CEBPA*, *CEBPG*, and *PEPD*. The expression levels were normalized against *ABL* and compared with the human cell line U937. The candidate oncogene was *CEBPA*. Its level of expression was at least 2.5 times higher in t(14;19) than control BCP-ALL samples, with a number of t(14;19) patients expressing extremely high levels of *CEBPA* mRNA (Figure 1B; Figure S2 for the 3 other genes).

Recent data[17] have indicated that the t(14;19) translocation breakpoint may be located within the 3′ untranslated region (UTR) of *CEBPA*, suggesting a fusion transcript between *CEBPA* and the *IGH* constant region. RT-PCR analysis of 6 patients (P1 to P6) with primers from *Cmu* and *CEBPA* allowed specific amplification of material from patients P1 and P2 only. Direct sequencing demonstrated the fusion of *Cmu-JH* to the 3′ UTR of *CEBPA*, establishing

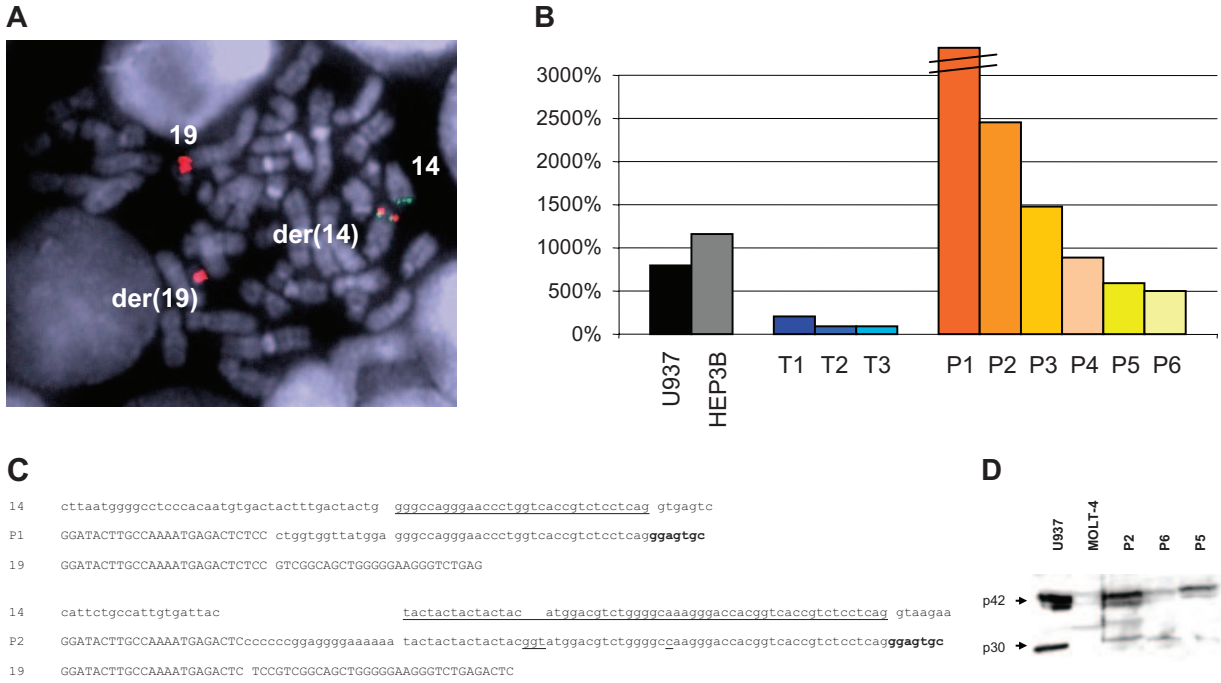

Figure 1. The *CEBPA* gene is targeted by the t(14;19) translocation. (A) A representative FISH image of the t(14;19)(q32;q13) in patient P5. The RP11-270I13 probe produces a red signal on the normal chromosome 19 and a split signal between der(14) and der(19). A green signal from the *IGH* constant region-specific probe[14] identifies chromosomes 14 and der(14). Images were visualized under a Leica DM RXA microscope equipped with a fluorescence epi-illumination 100×/130-0.60 oil-immersion objective lens (Leica, Rueil-Malmaison, France). Leica QFISH software was used to digitally acquire images after capturing them with a Photometrics Sensys camera (Roper Scientific, Evry, France). (B) Quantitative RT-PCR analysis of *CEBPA* expression in t(14;19) patients (P1-P6), 3 control patients with BCP-ALL and the human cell lines U937 (AML) and HEP3B (hepatocellular carcinoma) using gene expression assay no. Hs.00263372_s1 (Applied Biosystems, Foster City, CA). Data are presented as percentage of *ABL* expression. Note that for patient 1 the bar graph is not drawn to scale: the real value is 6672%. Comparable results were obtained when the *GUS* gene was used as a reference. Because *CEBPA* is composed of a single exon, control experiments were performed with omission of the reverse transcriptase from the reaction. The observed Ct values in control experiments were always several cycles higher than in the test experiments. Quantitative RT-PCR analyses of the neighboring genes (*CEBPG*, *PEPD*, and *LPR3*) are shown in Figure S1. P1-P6 indicates t(14;19) samples; T1-T3, control BCP-ALL samples without a chromosome 19 abnormality. (C) Nucleotide sequence alignments of fusion *CEBPA-Cmu* transcripts isolated from patients P1 and P2: chromosome 19 sequences are indicated in uppercase; chromosome 14 sequences, lowercase. The JH segment is underlined on the germline chromosome 14 sequences and was identified as JH4 for P1 and JH6 for P2. The first exon of *IGH* constant (*Cmu*) gene is indicated in bold. Nucleotides underlined in P2 sequences differ from the genomic germline sequences used for comparison. (D) Western blot analyses of 200 μg protein extracted from blast cells of patients P2, P5, and P6. Proteins were separated on a 12% denaturating acrylamide gel, and transferred onto a nylon membrane. Proteins were detected using a goat anti-CEBPA immuneserum (sc 9314; Santa Cruz Biotechnology, Santa Cruz, CA). U937 and MOLT-4 (T-ALL cell line) extracts were used as positive and negative controls, respectively. Arrows indicate the p42 and p30 CEBPA protein species.

unequivocally that *CEBPA* was the gene involved in the t(14;19) (Figure 1C).

To confirm the expression of *CEBPA* at the protein level, whole-cell extracts were analyzed by Western blotting. The CEBPA protein was present as the 2 usual species, p42 and p30, of similar size to the U937 positive control (Figure 1D; Figure S3). Thus, apparently normal CEBPA proteins are expressed in patients with t(14;19). This was expected, as no mutation of the *CEBPA* gene was observed in patients (data not shown).

Our results indicate that *CEBPA* may act as an oncogene in lymphoid malignancies, in contrast to its role as a tumor suppressor in myeloid leukemia. A preliminary report has indicated that additional members of the *CEBP* family are involved in translocations with *IGH* in BCP-ALL, which may also exhibit oncogenic properties.[17] Interestingly, our patients with *CEBPA* overexpression did not express myeloid markers, such as CD13 or myeloperoxidase (MPO), suggesting that only a subset of the known CEBPA target genes, mainly defined in a myeloid context, would be activated in a lymphoid context. Their identification would be of great interest. Another possibility is that CEBPA exerts its effect through its interaction with other transcription factors, thereby deregulating a different set of genes. This example from CEBPA strongly supports the emerging paradigm that both an increase or decrease in gene dosage may contribute to the pathogenesis of leukemia.[4]

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