Gene Expression Profiling of Acute Myeloid Leukemia with Translocation t(8;16)(p11;p13) and MYST3-CREBBP Rearrangement Reveals a Distinctive Signature with a Specific Pattern of HOX Gene Expression

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Abstract

Acute myeloid leukemia (AML) with translocation t(8;16)-(p11;p13) is an infrequent leukemia subtype with characteristic clinicobiological features. This translocation leads to fusion of MYST3 (MOZ) and CREBBP (CBP) genes, probably resulting in a disturbed transcriptional program of a myelomonocytic precursor. Nonetheless, its gene expression profile is unknown. We have analyzed the gene expression profile of 23 AML patients, including three with molecularly confirmed MYST3-CREBBP fusion gene, using oligonucleotide U133A arrays (Affymetrix). MYST3-CREBBP cases clustered together and clearly differentiated from samples with PML-RARA, RUNX1-RUNXIT1, and CBFI3-MYH11 rearrangements. The relative expression of 46 genes, selected according to their differential expression in the high-density array study, was analyzed by low-density arrays in an additional series of 40 patients, which included 7 MYST3-CREBBP AML cases. Thus, genes such as prolactin (PRL) and protooncogene RET were confirmed to be specifically overexpressed in MYST3-CREBBP samples whereas genes such as CCND2, STAT5A, and STAT5B were differentially underexpressed in this AML category. Interestingly, MYST3-CREBBP AML exhibited a characteristic pattern of HOX expression, with up-regulation of HOXA9, HOXA10, and cofactor MEIS1 and marked down-regulation of other homeobox genes. This profile, with overexpression of FLI3, HOXA9, MEIS1, AKR7A2, CHD3, and APRA2, partially resembles that of AML with MLL rearrangement. In summary, this study shows the distinctive gene expression profile of MYST3-CREBBP AML, with overexpression of RET and PRL and a specific pattern of HOX gene expression. (Cancer Res 2006; 66(14): 6947-54)

Introduction

Chromosomal translocations resulting in fusion proteins are a common finding in acute myeloid leukemia (AML). The most frequent fusion products, PML-RARA, RUNX1-RUNXIT1 (AML-ETO), and CBFB-MYH11, found in ~25% of de novo AML cases, constitute abnormal translocation factors causing a disturbed program of myeloid differentiation. Moreover, each of these translocations defines a specific leukemia subtype associated with a favorable prognosis (1, 2). In this setting, translocation t(8;16)(p11;p13) is an infrequent recurrent chromosomal abnormality found in both de novo and therapy-related AML cases after treatment with topoisomerase II inhibitors (3–6). These patients present with specific clinical and biological features, such as a blast population with a myelomonocytic stage of differentiation, frequent extramedullary involvement, severe coagulation disorder, and a poor outcome (3, 5, 6). At the molecular level, translocation t(8;16) fuses MYST histone acetyltransferase (monocytic leukemia)-3 (MYST3; formerly named MOZ) and CREB binding protein (Rubinstein-Taybi syndrome; CREBBP, or CBP) genes, both encoding proteins with histone acetyltransferase activity (4, 7–9). MYST3 has been shown to modulate gene transcription through activation of the transcription factor complex RUNX1 (8, 10). Moreover, the protein complex MYST3-RUNX1 has been found to increase during normal monocytic differentiation. In its turn, CREBBP protein also regulates transcription by means of histone acetyltransferase activity and by binding to several proteins with key cell cycle functions, such as p53 and nuclear factor κB (8, 9). Therefore, an inhibition of RUNX1-mediated transcription by MYST3-CREBBP fusion protein has been hypothesized to be the main mechanism of leukemogenesis in this AML variety (10). However, the precise pathways disrupted by this chimerical protein are mostly unknown.

Analysis of gene expression profile might contribute to refine the classification of AML based on biological grounds and to assign the prognostic risk of a given subtype more accurately (11–14). Furthermore, genomic analysis of AML might provide a deeper insight into the underlying disease mechanisms.

In this study, we have examined the gene expression profile of AML with the MYST3-CREBBP fusion gene to determine the specific signature of this leukemia compared with other well-defined AML subtypes and to define possible molecular pathways involved in the pathogenesis of this leukemia.

Materials and Methods

Leukemia samples. Twenty-three AML patients were selected for a global gene expression profile analysis using the Affymetrix HU133A array (Affymetrix, Inc., Santa Clara, CA; subset A of patients, Supplementary Table A). These cases included three MYST3-CREBBP AML cases, together with other 20 samples of different leukemia subtypes classified according to WHO criteria (15) as acute promyelocytic leukemia with t(15;17)(q22;q12) (PML-RARα; n = 3); AML with t(8;11)(q22;q22) (RUNX1-RUNXIT1; n = 3); AML with inv(16)(t(16;16) (CBFI-MYH11; n = 3); AML with t(9;11)(p22q23) (MLL3-MLL; n = 1); acute monocytic leukemias (n = 8); and two cases of AML with multilineage dysplasia. In 10 of these 23 cases, an internal tandem...
duplication of the FLT3 gene was detected whereas mutations of nucleo-
phosmin (NPM1) gene were found in 6 cases (Supplementary Table A). Two cases with MYST3-CREBBP rearrangement and one monocytic-differentiated AML (cases 1, 3, and 18) followed exposure to topoiso-
merase II inhibitors. Cases 1 and 18 also presented amplification of MLL gene.

To confirm the findings of the previous global gene expression profile study, a second subset of 40 AML patients (subset B, Supplementary Table B) was studied using TaqMan low-density arrays (Applied Biosystems, Foster City, CA; see below). This subset of patients included the three MYST3-CREBBP AML cases previously studied by high-density array and four additional MYST3-CREBBP samples with no appropriate material for the genome-wide assay. In addition, an independent set of 33 AML samples was included in this study. These samples corresponded to AML with well-
differentiated phenotype (AML with that in the remaining AML samples was done using a t test comparing two groups, with a significance level of 0.05. In addition, an ANOVA test was also used to compare the relative expression of these genes after defining different AML categories (significance level, 0.05).

Results

High-density Array Analysis

Unsupervised analysis. After applying a variation filter, the resulting 2,683 genes were visualized by hierarchical clustering method (Fig. 1A). Two main branches were seen in the dendrogram, corresponding mainly to cases with myeloid and monocytic differentiation, respectively. Samples clearly grouped in five clusters, which were constituted by cases of AML with well-defined gene rearrangements [i.e., MYST3-CREBBP (cluster 1), RUNX1-RUNX1T1 (cluster 2), CBFβ-MYH11 (cluster 3), and PML-RARα (cluster 4), and, on the other hand, AML with multilineage dysplasia (cluster 5)]. In contrast, the remaining samples (no. 13-21), defined by their monocytic differentiation and the absence of the above-mentioned fusion proteins, were distributed among the different clusters of the array forming a heterogeneous group. One of the samples harboring a CBFβ-MYH11 rearrangement, with a minimally differentiated phenotype (M0 subtype), segregated from two other cases with the same molecular alteration but presenting with a myelomonocytic phenotype.

Supervised analysis. We applied supervised methods based on the six different AML categories (clusters 1-5 and a sixth group containing monocytic-lineage leukemias) drawn from the unsu-
ervised analysis. First, the analysis with a random-variance F test yielded 1,205 genes with a significant different expression level among AML subgroups. A hierarchical cluster done with this set of genes is presented in Fig. 1B. Afterwards, we selected 63 genes

overexpressed and 60 genes underexpressed in MYST3-CREBBP samples with a ratio of mean expression equal or higher than twice the observed in each of the other groups. The 63 genes specifically overexpressed in MYST3-CREBBP samples (Supplementary Table D; Supplementary Fig. A1) included the oncogene RET, genes involved in chromatin remodeling and transcription (HOXA10 and PPARG), and genes with a known function in DNA damage repair (DDB2) and apoptosis (DAP). Other genes such as IRAK1, expressed in response to cell injury, NICAL, implied in neuronal development, and prolactin (PRL), involved in signal transduction, were also upregulated. In addition, 60 genes specifically down-regulated in MYST3-CREBBP leukemias (Supplementary Table D; Supplementary Fig. A2) included genes involved in cell cycle regulation, such as cyclin D2 (CCND2) and two members of the RAS oncogene family (RAB6A and RAB8A).

As an additional method to study possible shared patterns of gene expression between MYST3-CREBBP and other AML, we selected those genes with high or low expression in MYST3-CREBBP leukemias and a similar pattern of expression in one of the other AML categories (Supplementary Tables E and F; Supplementary Fig. B). This analysis revealed that MYST3-CREBBP leukemias had 33 genes overexpressed in common with AML of monocytic lineage (i.e., AKR7A2, CHD3, and AK2) and 19 with PML-RARα, but only a minority of genes in common with other AML subtypes.

Finally, when MYST3-CREBBP cases were compared with the other samples as a group using a t test, 237 genes (53 overexpressed and 184 underexpressed) showed a differential expression (Supplementary Tables G and H). Using this analysis, a high expression of the aforementioned gene RET could be observed. Additionally, an overexpression of genes with a role in transcription (SATB1), genes involved in apoptosis (OPTN), and CEBPa, a crucial gene in the myeloid differentiation process, was observed.

**Low-density Array Analysis**

**Supervised analysis.** Forty-six genes were selected according to their differential expression in MYST3-CREBBP samples in the high-density array and/or their relevant oncogenic role in leukemia. The relative expression of these genes was analyzed in 40 AML patients (subset B, Supplementary Table B). To define the group of genes characteristic of MYST3-CREBBP subtype, a t test with two groups was used to compare the gene expression in MYST3-CREBBP samples and the remaining AML patients. Twenty-two genes were significantly overexpressed in MYST3-CREBBP samples whereas three genes were underexpressed in this group of leukemias (Table 1). Subsequently, an ANOVA test was used to compare the gene relative expression among the seven AML categories defined by their underlying molecular abnormality (A, MYST3-CREBBP; B, PML-RARα; C, RUNX1-RUNX1T1; D, CBFβ-MYH11;...
E, MLL-translocated samples; F, MLL partial tandem duplication; and G, miscellaneous). The ANOVA test yielded five different gene expression profiles. First (profile 1, Fig. 2A), a group of nine genes (PRL, C20orf103, RET, GGA2, FLT3, GA2, AKR7A2, SURF1, and LM02) were found to be highly expressed in MYST3-CREBBP AML with absent or low expression in the remaining samples. Genes such as FLT3, HOXA9, MEIS1, AKR7A2, CHD3, and APBA2 composed a second pattern of expression (profile 2, Fig. 2B), with high expression level in both MYST3-CREBBP and AML with monocytic phenotype. In the third profile observed (profile 3, Fig. 2C), some genes had a high expression level in MYST3-CREBBP and were variably expressed in other AML categories. This group included SATB1, LM02, CEBPz, SURFI, HIST1H2A, DDB2, and LGALS3 genes.

Another group of genes were characteristically down-regulated in the MYST3-CREBBP leukemia subtype compared with other AML categories, including CCND2, STAT5A, and STAT5B (profile 4, Fig. 2A). A decrease in expression levels of CREBBP was seen in MYST3-CREBBP subtype, but the difference did not reach statistical significance in the ANOVA test comparing the AML subgroups. Finally, a low or absent expression of Wilms' tumor 1 (WT1) gene was distinctly observed in both MYST3-CREBBP and RUNX1-RUNX1T1 cases (profile 5, Fig. 2B).

### Table 1. Genes with a significant differential expression level (overexpressed and underexpressed) in MYST3-CREBBP samples according to the low-density array study

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<th>Symbol</th>
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<th>Symbol</th>
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### Mutational Status of RET Gene
Due to the distinctly overexpression of RET gene observed in MYST3-CREBBP samples, mutations of this gene were screened by direct sequencing of exons 8 to 16, where somatic and germ-line mutations associated with human diseases have previously been described (24). None of the five MYST3-CREBBP samples that could be analyzed harbored mutations of RET gene, and only neutral polymorphisms at codons 769 and 836 were found (data not shown).

### Expression of Homeobox Genes
Given the high expression of several homeobox (HOX) genes observed in MYST3-CREBBP, we did an unsupervised analysis on the whole series of patients focused on the relative level of expression of the HOX genes present in the array. Several patterns of HOX genes expression were seen in different AML categories (Fig. 4A). Thus, overexpression of 5’-HOX genes (HOXA9, HOXB9, and HOX10) was characteristically found in all MYST3-CREBBP samples and most cases of monocytic AML. Other HOX genes (HOX-A2 and HOX-B7) showed a high expression in the group of monocytic leukemias whereas their expression was low in MYST3-CREBBP AML. In contrast, HOX genes were underexpressed in good-risk cytogenetic AML.

Ten genes of the HOX family were subsequently studied by low-density arrays. With this method, the distinctive pattern of HOX expression according to AML subtypes was confirmed (Fig. 4B). Thus, good-prognosis AML showed a lower expression of all HOX analyzed. On the contrary, a high expression of all the HOX genes studied was detected in MLL-rearranged, partial tandem duplication, and monocytic-phenotype AML. In addition, MYST3-CREBBP AML showed a high expression of HOXA9 and MEIS1 but a lower expression of the remaining HOX genes.

### Discussion
AML with MYST3-CREBBP rearrangement is an infrequent leukemia subtype resulting from the fusion of two genes with chromatin-modifying properties. In this regard, inhibition of RUNX1-mediated transcription, possibly through a disturbed histone acetyltransferase activity, has been hypothesized to be the main mechanism of leukemogenesis (10). Nevertheless, the signaling pathways disrupted by the chimerical protein MYST3-CREBBP are mostly unknown and, to the best of our knowledge, no previous studies have focused on the genomic profile of this AML variety. With this purpose, we used high-density microarrays to study a series of 23 AML samples that included three MYST3-CREBBP cases. The unsupervised analysis of the results identified a distinctive gene expression signature associated with the MYST3-CREBBP rearrangement. Thereafter, a group of genes was selected and analyzed using a quantitative approach with low-density arrays. This technology allowed us to study four additional MYST3-CREBBP samples with no appropriate material for the genome-wide assay. Interestingly, this approach confirmed the existence of a characteristic gene expression profile in MYST3-CREBBP AML, clearly distinguishable from that of other well-defined AML subtypes.

The combination of several methods of comparative analysis allowed the identification of groups of genes with a differential expression in distinct AML categories. First, a subset of genes seemed to be highly characteristic of MYST3-CREBBP AML, being up-regulated in these cases and showing a low or absent expression...
in the remaining AML categories. Thus, genes such as PRL, C2orf103, RET, GGA2, ICSBP1, ITGA7, DAP, IRAK1, and PPARG were overexpressed almost exclusively in MYST3-CREBBP cases. Among those genes, PRL and RET have been occasionally reported to be involved in leukemogenesis (24–33). In this regard, an increased expression of prolactin protein in blast populations has been observed in anecdotal cases of monocytic-lineage leukemia as well as in the eosinophilic cell line Eol-1 (25–29). In a recent study, prolactin expression in Eol-1 cells was shown to involve different signaling pathways induced by cyclic AMP whereas inhibition of Jak-STAT5 pathway resulted in up-regulation of prolactin (28). Interestingly, STAT5A and STAT5B genes were found to be significantly underexpressed in our MYST3-CREBBP AML samples, suggesting a negative regulatory effect between prolactin and STAT5 proteins. On its turn, RET gene is a proto-oncogene that encodes a tyrosine kinase receptor expressed during normal myelomonocytic differentiation and, accordingly, has been found to be predominantly expressed in AML of monocytic phenotype (30–32). Moreover, RET mRNA levels are typically low among immature CD34+ hemopoietic progenitors whereas overexpression

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**Figure 2.** Low-density array study: genes significantly overexpressed in MYST3-CREBBP samples (ANOVA test). A, profile 1. Genes specifically overexpressed in MYST3-CREBBP samples, with absent or low expression in the remaining AML categories. B, profile 2. Genes overexpressed in MYST3-CREBBP and monocytic AML, either MLL-rearranged or non-rearranged variants. C, profile 3. Genes overexpressed in MYST3-CREBBP samples with variable expression in other AML categories.
of this protein has been associated with coexpression of adhesion molecules such as CD56 (30). These observations resemble the characteristic phenotype of MYST3-CREBBP AML, defined by common CD34 negativity, high expression of monocyteic antigens, and frequent coexpression of CD56 and NG2 (16). Of note, RET has recently been reported as one of the most characteristic genes in one of the 16 AML clusters defined according to its genomic profile in a recent study by Valk et al. (14). Although most of the cases forming that cluster were monocytic-differentiated leukemias (14), modulation of RET does not seem to be merely attributable to a monocytic differentiation process because, in the present study, the expression level of RET was significantly higher in MYST3-CREBBP cases than in other monocytic-lineage leukemia samples. Somatic and germ-line RET mutations leading to gene activation are responsible for several human diseases, including multiple endocrine neoplasia types 2A and 2B and papillary thyroid carcinomas (24). Nevertheless, mutations of RET as a mechanism of overexpression were discarded in the present MYST3-CREBBP series, in accordance with a previous study analyzing diverse AML subtypes (33).

One of the most striking findings of this study was the similarities observed between MYST3-CREBBP and MLL-rearranged leukemias. MYST3-CREBBP cases presented high levels of homeobox genes (HOX9 and HOX10), their cofactor MEIS1, and the receptor with tyrosine-kinase activity FLT3, all of them typically up-regulated in MLL leukemias (34–36). HOX genes are transcription factors required for a proper hematopoietic development and constitute downstream targets of MLL protein (37). In this regard, MLL-rearranged leukemias are typically characterized by an impaired pattern of HOX expression, and HOX9, HOX10, and the cofactor MEIS1 are up-regulated in virtually all lymphoid, myeloid, and biphenotypic lineage MLL-rearranged leukemia subtypes (38). In addition to the unexpected HOX overexpression in MYST3-CREBBP cases, the results of the present study confirmed previous findings on the pattern of HOX expression in different AML subtypes (39–41). Thus, whereas an overall low expression of HOX genes was observed in cases of AML with favorable cytogenetics, high levels of the members of HOX family HOX9 and HOX10 were seen in MYST3-CREBBP and MLL-rearranged leukemias. In contrast, other HOX genes analyzed, such as HOX3, HOX7, and HOXB5, were expressed at different levels in MLL-translocated cases, MLL with partial tandem duplication, and other monocytic leukemias, but were not expressed in MYST3-CREBBP AML cases.

Similarities between MYST3-CREBBP and MLL leukemias comprised other genes. Thus, overexpression of AKR7A2, PBX3, NICAL, and IRAK1B genes, observed in MYST3-CREBBP subtype, was also found in AML with MLL rearrangement, as reported in a recent study by Kohlmann et al. (36). Moreover, a coincidental expression of several genes (RET, C20orf103, GGA2, GAGED2, AKR7A2, and AK2) was observed between our MYST3-CREBBP samples and the above-mentioned cluster no. 16 of the study of Valk et al. (14). Of note, 5 of the 11 patients included in this cluster had 11q23 abnormalities.

As a common mechanism of leukemogenesis, chimeric protein PML-RARα in acute promyelocytic leukemia and RUNX1-RUNXIT1 and CBFβ-MYH11, associated to core binding factor leukemias, respectively, induce a constitutive transcriptional repression, leading to a blockage of the normal myeloid differentiation program (42). This contrasts with the presumed function of fusion gene products derived from the rearrangement of MLL with different partners, thought to produce a constitutive transcriptional activation through a gain-of-function mechanism resulting in an inappropriate expression of target genes such as HOX (42). In this context, the gene expression signature of MYST3-CREBBP rearrangement obtained in this study seemed to be similar to that of MLL-rearranged leukemia and markedly different from those of CBF-AML and acute promyelocytic leukemia. Therefore, the leukemogenic effect of MYST3-CREBBP fusion gene could rely on a deregulated modulation of downstream targets, resembling that of MLL chimeras, probably due to impaired histone acetyltransferase activity of the proteins involved in this translocation. Moreover, the adverse prognosis classically associated with this entity differs from that of CBF-AML and acute promyelocytic leukemia and is similar to that of MLL-rearranged AML.

With regard to the underexpressed genes, the CREBBP expression was decreased in MYST3-CREBBP samples, although not reaching a significant difference, thus suggesting a negative regulation of the chimerical protein MYST3-CREBBP over native CREBBP transcript. Additionally, down-regulation of WT1 was observed in MYST3-CREBBP, as well as in RUNX1-RUNXIT1, as compared with the other AML categories. WT1 gene has been shown to be overexpressed in >90% of AML cases and it has recently been proposed as a molecular marker for minimal residual disease studies in AML (43). However, the low levels of WT1 in MYST3-CREBBP leukemias observed in our study would hamper this strategy in the follow-up of the minimal residual disease in this group of leukemia.

In summary, the double strategy followed, based on the selection of a group of genes according to their differential expression in the high-density array assay and further analysis by real-time PCR in an additional set of patients, allowed the

Figure 3. Low-density array study: genes significantly underexpressed in MYST3-CREBBP samples (ANOVA test). A, profile 4. Genes specifically underexpressed in MYST3-CREBBP samples. B, profile 5. WT1 gene was found to be characteristically underexpressed in MYST3-CREBBP samples as well as in RUNX1-RUNXIT1 cases.
assessment of gene profile in a group of seven MYST3-CREBBP patients. Of note, a distinctive gene expression signature of MYST3-CREBBP leukemias was observed, characterized by the overexpression of homeobox genes HOXA9, HOXA10, and their cofactor MEIS1; the up-regulation of the oncogenes RET and PRL; and the decreased expression of genes such as CCND2, STAT5, and WT1. This profile harbors some similarities with that of MLL-rearranged leukemias, thus suggesting a partially common leukemogenic pathway.

Acknowledgments
Received 12/22/2005; revised 4/28/2006; accepted 5/16/2006.

Grant support: Instituto de Salud Carlos III grant V-2003-REDG008-0 (M. Camo’s, J. Esteve, J. Nomdedeu, and E. Montserrat); Generalitat de Catalunya grant 2002XT/00031; CICYT SAF 05/585 (E. Campo); and Fondo de Investigaciones Sanitarias grants N-2004-FS041085 (J. Esteve) and FIS 03/0423 (M. Rozman).

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We thank all the staff of the Hemopathology Unit and Montse Sánchez from the Genomics Unit for their excellent work.

References
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