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Regulation of c-fos gene transcription and myeloid cell differentiation by acute myeloid leukemia 1 and acute myeloid leukemia-MTG8, a chimeric leukemogenic derivative of acute myeloid leukemia 1

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Abstract Both acute myeloid leukemia 1 and c-Fos are regulatory factors of hematopoietic cell differentiation. We identified that the c-fos promoter contains an acute myeloid leukemia 1 binding site at nucleotide positions −6–+14. c-fos promoter activity was induced by transient overexpression of acute myeloid leukemia 1 in Jurkat T-cells, but not by that of the short form of acute myeloid leukemia 1-MTG8, a chimeric acute myeloid leukemia 1 protein. In 32Dcl3 myeloid cells, stable overexpression of acute myeloid leukemia 1-MTG8 blocked the c-fos gene transcription and cell differentiation, but that of acute myeloid leukemia did not. These data suggest that acute myeloid leukemia 1 and acute myeloid leukemia 1-MTG8 reciprocally regulate the myeloid cell differentiation, possibly by the way of regulating c-fos gene transcription.

Key words: Acute myeloid leukemia 1; Acute myeloid leukemia 1-MTG8; c-fos; Transcription; Myeloid cell differentiation

1. Introduction

The process by which multiple types of terminally differentiated blood cells are produced from a common pluripotent hematopoietic stem cell is controlled in part by transcription factors that regulate the expression of lineage-specific genes [1,2]. One transcription factor that plays a central role in hematopoiesis is the polyomavirus enhancer binding protein 2 (PEBP2), also known as core binding factor (CBF). PEBP2/CBF is composed of α and β subunits [3]. The α subunit shares sequence similarity with the *Drosophila* segmentation gene *runt* [4]. The Runt domain of PEBP2α harbors both the DNA binding and dimerization activities [5,6]. The β subunit of PEBP2/CBF, PEBP2β, interacts directly with the α subunit and increases its DNA binding affinity [6,7]. This effect on DNA binding is essential for PEBP2α to function in vivo [8].

Three mammalian genes, termed PEBP2αA [9], PEBP2αB [10] and PEBP2αC [11] have been shown to encode the α subunit of PEBP2/CBF. It has been suggested that PEBP2αB, also known as acute myeloid leukemia 1 (AML1), is an important factor in the regulation of hematopoietic cell differentiation [12]. Disruption of the AML1 gene in mice yields a phenotype: impaired hematopoiesis of all cell lineages in the fetal liver [12,13]. AML1 was originally identified at the breakpoint of the 8 to 21 chromosome translocation *t(8;21)* [14], which encodes the fusion protein AML1-MTG8 and is associated with human acute myeloid leukemia [15,16]. Two alternate AML1-MTG8 transcripts, the short and long forms, arise as a consequence of alternative splicing events. Only the long form contains two putative zinc finger domains and proline-rich regions in the C-terminal part of the protein [17]. Overexpression of the long form of AML1-MTG8 in myeloid progenitor cells prevents granulocyte colony stimulating factor (G-CSF)-induced differentiation [18,19]. However, the function of the short form is not yet known.

Although AML1 and AML1-MTG8 are known to play a key role in hematopoietic cell development, the target genes regulated by AML1 or AML1-MTG8 are not much known. The consensus DNA sequence recognized by the Runt domain of AML1 or AML1-MTG8, (Pu/T)ACCPuCA [3,5] is present in the enhancers and promoters of several mammalian genes, including the T-cell receptor genes [20], the myeloperoxidase gene [21], granulocyte macrophage colony stimulating factor [22] and the interleukin-3 gene [23]. Abnormal expressions of these genes are thought to be associated with leukemogenesis.

c-Fos, a component of the AP-1 transcription factor complex is also widely recognized as a key regulator involved in the development of bones, teeth and hematopoietic cells [24–27]. The c-fos mRNA levels were shown to be elevated during myeloid cell differentiation and in terminally differentiated myeloid cells [28]. c-fos gene transcription is modulated by several regulatory gene elements, including the serum response element (SRE) [29], sis inducible element (SIE) [30], AP1/cAMP response element [31] and others [32]. Although the c-fos promoter has been studied extensively, there are still a number of issues that remain unresolved with respect to its regulation.

Since both Runt proteins and c-Fos are playing essential roles in the development of hematopoietic cells, we examined, in this study, whether these proteins are functionally associated in the regulation of hematopoietic cell differentiation.

2. Materials and methods

2.1. Cell culture

A Jurkat human T-cell leukemia cell line (ATCC TIB-152) was grown in RPMI 1640 medium (Gibco BRL) supplemented with 10% fetal bovine serum (FBS, Gibco BRL) and penicillin-streptomycin (Gibco BRL). A murine IL-3-dependent myeloid progenitor cell line (32Dcl3) derived from a normal bone marrow long term culture [33] was maintained in Iscove's modified Dulbecco's medium (IMDM, Gibco BRL) supplemented with 10% FBS and 0.25 ng/ml of IL-3 (Sigma) and cultured in the presence of 5 ng/ml of recombinant human G-CSF (Sigma) for the induction of granulocytic differentiation.

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Viable cells excluding trypan blue were counted with a hemocytometer.

2.2. Transient transfection and luciferase assays

Jurkat T-cells (2×10^6 cells) were transfected with 0.25 μg of reporter plasmid and 0.25–2 μg of each expression vector per sample using LipofecTAMINE reagent (Gibco BRL) as instructed by the manufacturer. The luciferase reporter plasmid has the full length promoter region (−711–+45) of the human c-fos gene (pFos-lcf). pCMVβ-gal was included as an internal control for the transfection efficiency. Luciferase activity was measured with an AutoLumat LB953 luminometer (Berthold) using a Promega luciferase assay system kit.

2.3. Gene construction and establishment of stable cell lines

AML1 and AML1-MTG8 (short form) expression vectors were constructed by the insertion of each cDNA into a 6×His-tagged pRc-CMV vector (Invitrogen). After transfection of the AML1 and AML1-MTG8 expression vectors into 32Dcl3 cells, we selected stable transformants on incubating the transfected cells in the presence of G418 (800 μg/ml) for 2 weeks and performing limiting dilutions to obtain clonal isolates.

2.4. Electrophoretic mobility shift assay (EMSA)

Protein-DNA binding reactions were performed as described previously [22]. The DNA probe was labelled with γ-[^{32}P]ATP (Amersham) in a standard T4 polynucleotide kinase (Boehringer, Mannheim) reaction. For supershift and competition assays, the proteins were preincubated with PEBP2α, PEBP2β or competitors and then mixed with DNA probe

2.5. Northern blot analysis

Total RNA was isolated from cultured cells using the RNeasy mini kit (QIAGEN), separated on a 1% agarose-formaldehyde gel and transferred onto a nylon membrane (Hybond N+, Amersham). For Northern blotting, the MPO and β-actin cDNA probes were generated by RT-PCR and the rat c-Fos cDNA template was obtained by *Bgl*II-*Xho*I digestion of the pFos (SP65) plasmid [34]. The various probes were labelled with α-[^{32}P]dCTP (Amersham) using the rediprime system (Amersham). The membrane with cross-linked RNA was hybridized with denatured DNA probes.

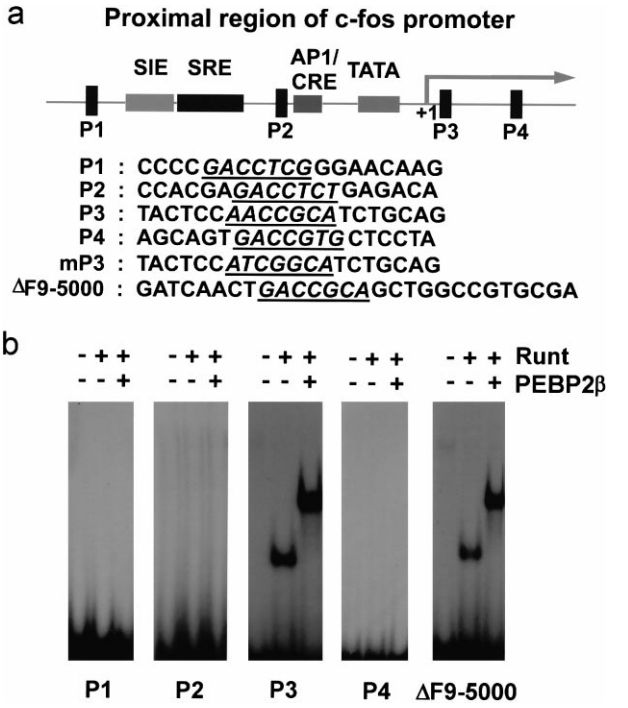

Fig. 1. (a) Schematic representation of the proximal region of the c-fos promoter and the probe sequences used in EMSA. The transcription initiation site is indicated by +1 and the transcriptional regulatory sites are indicated above the rectangle by SIE, SRE, AP1/CRE and TATA. The AML1 binding consensus motif is underlined in P1, P2, P3 and P4. The mP3 indicates the mutated P3 site (A→T and C→G). (b) DNA binding assays of purified Runt protein. Each probe was indicated at the bottom of the panels. Purified PEBP2β protein was added to the reaction mixture to give rise to an additional shifted complex. The absence (−) or presence (+) of Runt and PEBP2β is indicated above each panel.

3. Results

3.1. Identification of AML1 binding site within the c-fos promoter

The computer-aided nucleotide sequence analysis suggested that the c-fos gene promoter contains a putative AML1 binding sequence. Thus, we tested whether the c-fos gene is a target gene for AML1. We screened upstream sequences of the c-fos gene for the consensus AML1 binding sequence. The upstream regions of the c-fos gene contain four putative AML1 binding related sites, denoted as P1 (−493–−476),

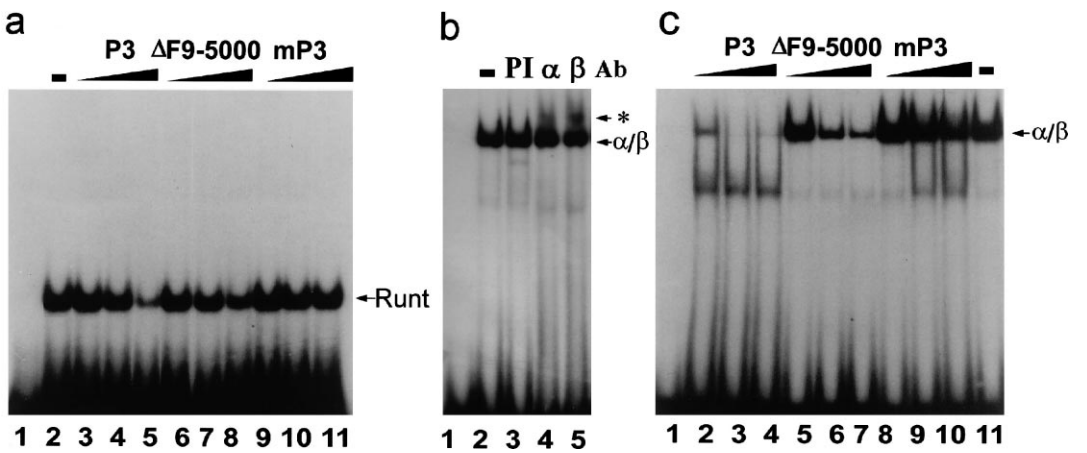

Fig. 2. Supershift and competition assays. (a) Purified Runt protein was mixed with ^{32}P-labelled P3 probe in the absence (lane 2) and presence of increasing amounts (5, 10 or 50 molar excess) of competitors (lanes 3–5, P3; lanes 6–8, ΔF9-5000; lanes 9–11, mP3) and incubated at 30°C for 15 min. The reaction products were analyzed by electrophoresis on a 6% non-denaturing polyacrylamide gel. (b) Jurkat T-cell nuclear extracts were pre-incubated with pre-immune (lane 2), PEBP2α (lane 3) or PEBP2β (lane 4) specific antibody. PI means preimmune serum and * denotes the supershifted band. (c) Jurkat T-cell nuclear extracts were mixed with P3 probe in the presence of competitors (lanes 2–4, P3; lanes 5–7, ΔF9-5000; lanes 8–10, mP3) or in the absence of a competitor (lane 11). Lane 1 (a–c) is the no protein control lane.

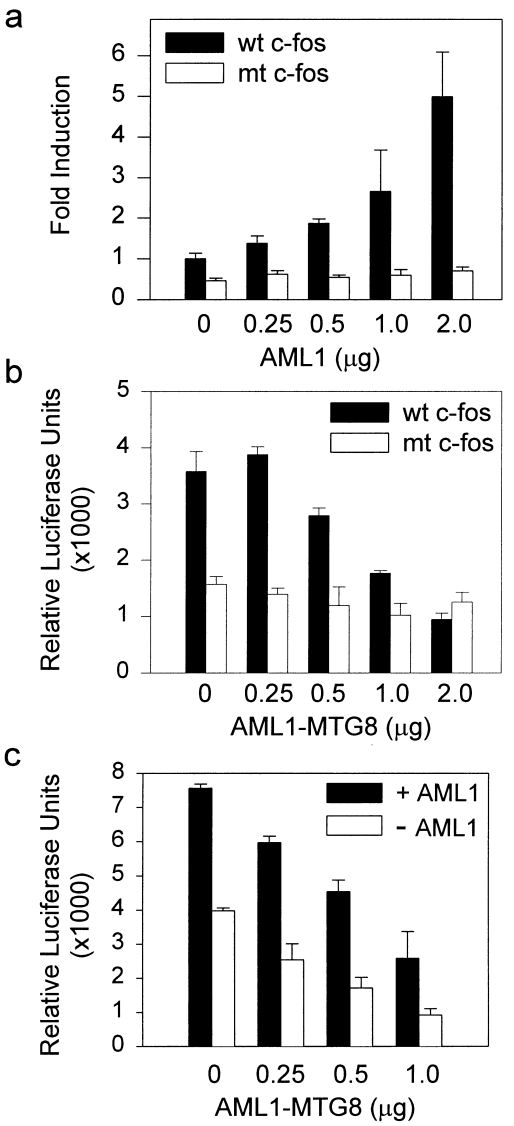

Fig. 3. The effect of AML1 and AML1-MTG8 on the c-fos promoter activity. Jurkat T-cells were co-transfected with the wt c-fos or mt c-fos luciferase reporter gene and increasing amounts of AML1 (a) or AML1-MTG8 (b) expression vector. (c) In a separate experiment, Jurkat T-cells were co-transfected with a wt c-fos luciferase reporter gene and AML1-MTG8 expression vector, without (−AML1) or with (+AML1) the AML1 expression vector. Luciferase activities were normalized to the β-galactosidase activity of each protein extract. Each value represents the mean of four independent experiments. Standard deviations are indicated by error bars.

P2 (−223–−205), P3 (−6–+14) and P4 (+65–+83) (Fig. 1a). Using DNA probes with the nucleotide sequences of these four putative sites, we performed EMSA with purified Runt protein, which is the DNA binding moiety of AML1. Among the sites tested, P3 was the only site that displayed sequence-specific Runt binding activity (Fig. 1b). The protein binding affinity of P3 was comparable with that of ΔF9-5000, a high affinity AML1 binding oligonucleotide [3] (Fig. 1b). In addition, the mobility of both DNA-protein complexes was shifted by the addition of purified PEBP2β protein, as shown previously [6,9]. These data clearly suggest that Runt protein binds directly to the P3 site within the c-fos promoter.

3.2. AML1 and AML1-MTG8 bind in a sequence-specific manner to the P3 site within the c-fos promoter.

To determine whether Runt binds in a sequence-specific manner to the P3 site, we performed competition assays using the following oligonucleotide competitors: wild-type P3, ΔF9-5000 and a mutated form of P3 (mP3), in that the A and C residues known as important nucleotides for Runt protein binding, were mutated to T and G, respectively. Addition of excessive unlabelled P3 or ΔF9-5000 competitor to the DNA binding reaction inhibited completely the formation of the P3-Runt complex, whereas the mP3 competitor did not affect the complex formation (Fig. 2a). These data suggest that Runt protein binds to the P3 site in a sequence-specific manner. Thus, we examined whether the native Runt protein can also bind specifically to the P3 site. Cockerill and colleagues [22] showed that the PEBP2α/β complex in the nuclear fraction of Jurkat T-cells binds specifically to the AML1 gene regulatory element using a supershift assay. Our data showed that the protein-DNA complex was shifted by the addition of PEBP2α or β antibody (Fig. 2b). The result also showed that

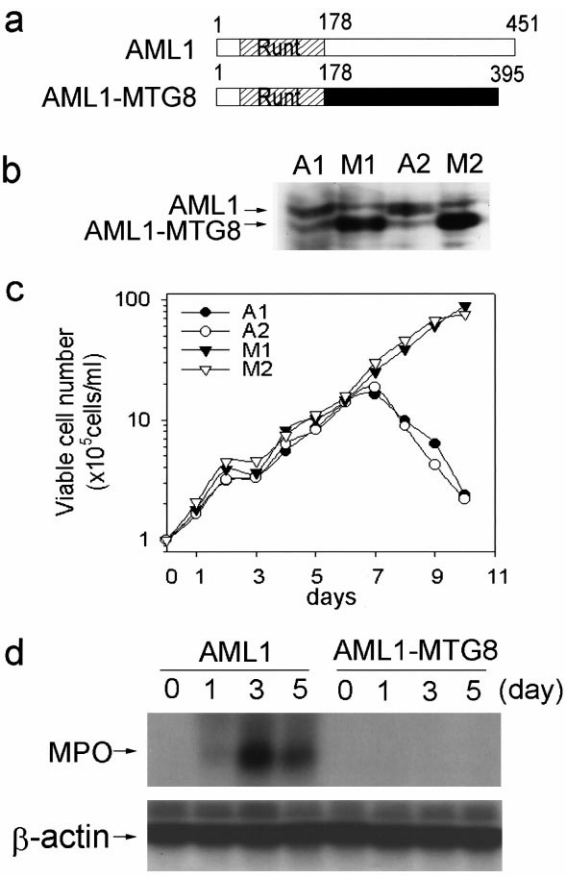

Fig. 4. (a) Schematic structure of AML1 (451 aa) and the short form of AML1-MTG8 (395 aa). (b) Immunoblotting of AML1 and AML1-MTG8. A1 and A2 indicate selected AML1-32Dcl3 clones. M1 and M2 indicate AML1-MTG8-32Dcl3 clones. (c) Growth curves in AML1-32Dcl3 and AML1-MTG8-32Dcl3 cells in response to G-CSF. At each time point (days), viable cells excluding trypan blue were counted using a hemocytometer. Three independent experiments were performed. (d) Northern blot analysis. Total RNA was prepared from AML1-32Dcl3 and AML1-MTG8-32Dcl3 at 0, 1, 3 or 5 days after treatment with G-CSF and analyzed by Northern blotting using ^{32}P-labelled MPO cDNA as a probe. The β-actin mRNA levels were analyzed as an internal control.

the native α/β complex in Jurkat T-cell extracts bound to the P3 site, whereas, the complex formation was inhibited competitively by an excess P3 and ΔF9-5000, but not by mP3 (Fig. 2c). Moreover, the in vitro translated proteins of AML1 and AML1-MTG8, Runt protein family, bound specifically to the P3 site (data not shown). Thus, we concluded that the members of the Runt protein family, AML1 and AML1-MTG8 can bind to the P3 site in a sequence-specific manner.

3.3. AML1 and AML1-MTG8 reciprocally regulate transcriptional activity of the c-fos gene through the P3 site

To examine whether the interaction of AML1 or AML1-MTG8 with the P3 site regulates c-fos promoter activity, we performed transient transfection assays with the wild- (wt) or mutant-type (mt) c-fos promoter linked to a luciferase reporter gene. The mt c-fos reporter gene contains mP3 sequences replaced in the P3 site. Jurkat T-cells were transfected with a fixed amount of the reporter gene and increasing amounts of an AML1 expression vector. Our results showed that wt c-fos promoter activity was induced by AML1 overexpression (Fig. 3a), whereas mt c-fos promoter activity was not altered. Interestingly, wt c-fos promoter activity was inhibited by overexpression of AML1-MTG8 (Fig. 3b). Moreover, the wt c-fos promoter activity induced by AML1 overexpression was also inhibited by the co-expression of increasing amounts of AML1-MTG8 (Fig. 3c). These results suggested that AML1 and AML1-MTG8 reciprocally regulate the wt c-fos promoter through the P3 site and that the inhibitory effect of AML1-MTG8 can override the inductive effect of AML1 on the c-fos promoter activity.

3.4. AML1 and AML1-MTG8 reciprocally regulate the G-CSF-induced myeloid cell differentiation possibly by a way of regulating c-fos gene transcription

We next examined whether the reciprocal regulation of the c-fos promoter activity by AML1 and AML1-MTG8 is accordingly associated with hematopoietic cell differentiation. To this end, we established the stably transformed 32Dcl3 cell lines, AML1-32Dcl3 and AML1-MTG8-32Dcl3 (Fig. 4a,b). With the AML1-32Dcl3 clones A1 and A2, the number of viable cells increased until 7 days after G-CSF treatment and rapidly decreased thereafter. By contrast, with the AML1-MTG8-32Dcl3 clones M1 and M2, the cells proliferated continuously after treatment with G-CSF (Fig. 4c). Moreover, the myeloperoxidase (MPO) mRNA levels, a marker for myeloid cell differentiation, increased after G-CSF treatment in AML1-32Dcl3 cells, whereas MPO mRNA was not detectable in AML1-MTG8-32Dcl3 cells (Fig. 4d). These data demonstrate that AML1-32Dcl3 cells, as do 32Dcl3 parental cells, undergo the myeloid cell differentiation in response to G-CSF, while in AML1-MTG8-32Dcl3 cells, the G-CSF-induced cell differentiation is blocked. In addition, endogenous c-fos gene transcription was also blocked in AML1-MTG8-32Dcl3 cells treated with G-CSF. By contrast, c-fos mRNA levels were elevated in parental and AML1-32Dcl3 cells under the same conditions (Fig. 5). Thus, it appears that transcriptional regulation of the c-fos gene by AML1 or AML1-MTG8 is functionally associated with the myeloid cell differentiation.

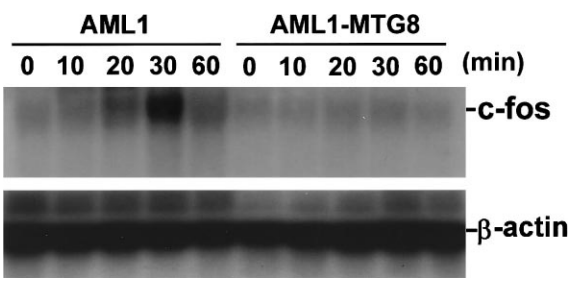

Fig. 5. c-fos mRNA analysis in AML1-32Dcl3 and AML1-MTG8-32 Dcl3 cell lines. Total RNA was isolated from AML1-32Dcl3 and AML1-MTG8-32Dcl3 cells treated with G-CSF at the indicated time points. The RNA-blotted Nylon membrane was hybridized with a ^{32}P-labelled c-fos cDNA probe. As an internal control, the β-actin mRNA level was analyzed on the same blot after stripping.

4. Discussion

In this article, we described four major observations: (i) the c-fos promoter harbors an AML1 binding sequence (−6–+14), (ii) the c-fos promoter activity is stimulated by the overexpression of AML1, but repressed by AML1-MTG8 overexpression, (iii) AML1-32Dcl3 cells undergo the myeloid cell differentiation in response to G-CSF, while the G-CSF-induced cell differentiation is blocked in AML1-MTG8-32Dcl3 cells and (iv) endogenous c-fos mRNA levels are repressed in AML1-MTG8-32Dcl3 cells treated with G-CSF.

There has been ample evidence that AML1 (or AML1-MTG8) and c-Fos play essential roles in the regulation of hematopoietic cell development along with most of the myeloid lineages [12,24,27]. It has been shown that definitive hematopoiesis becomes defective when the AML1 gene was disrupted in mice. With respect to the role of c-Fos, c-fos mRNA was shown to be stably expressed in normal myeloid cells upon the induction of either granulocyte or macrophage differentiation by using G-CSF or M-CSF, respectively. The murine M1 myeloid leukemic cells normally proliferate, but undergo the terminal differentiation as a consequence of stable expression of the c-fos gene in the presence of IL-6. In addition, c-fos antisense oligodeoxynucleotides, but not sense oligodeoxynucleotides, can block the terminal differentiation in the cultured cells [28]. Thus, it is evident that c-Fos, as well as AML1, transcription factors play an important role in the myeloid cell differentiation. It is unclear, however, whether these transcription factors regulate coordinately the myeloid cell differentiation.

Our data reveal that c-fos harbors a novel regulatory gene element, the AML1 binding site. Earlier reports showed that the c-fos gene transcription is regulated by several regulatory elements, among which the SRE plays a major regulatory role in controlling the c-fos promoter activity [29]. At present, it is not clear whether the cooperation between AML1 (or AML1-MTG8) and other transcription factors is important for the regulation of c-fos gene transcription but the possibility still exists.

It is also interesting that c-fos promoter activity is reciprocally regulated by the overexpression of AML1 and AML1-MTG8. The C-terminal regions of AML1 and AML1-MTG8 may determine the reciprocal regulation of the c-fos promoter activity, because the amino acid sequences of AML1 and AML1-MTG8 differ only in this region. The inhibitory effect of AML1-MTG8 can override the inductive effect of AML1

on the c-fos gene expression. This result is consistent with the previous report suggesting that AML1-MTG8, a chimeric leukemogenic version of AML1, exerts a dominant effect over AML1 by competing with AML1 for DNA binding. This dominant effect has been implicated in the inhibition of terminal differentiation of myeloid lineage cells, which results in leukemogenesis [35]. Recently, it was reported that AML1 interacts with the transcriptional co-activator, p300 in its C-terminal region and this results in the induction of myeloid cell differentiation [36]. By contrast, AML1-MTG8 does not interact with p300 because the C-terminal region of this chimeric protein is replaced by other sequences. Thus, it is very likely that transcriptional repression of c-fos gene transcription by binding of AML1-MTG8 may be related to the failure of recruiting transcriptional co-activator to the c-fos promoter.

It has also been shown that AML1 (or AML1-MTG8) and c-Fos are required for the induction of myeloid cell differentiation [19,24]. Consistent with these findings, our data have demonstrated that AML1 and AML1-MTG8 reciprocally regulate the myeloid cell differentiation by the way of regulating c-fos gene transcription. In this experiment, AML1-32Dcl3, a stable cell line that overexpresses AML1 in 32Dcl3 cells, was similar to 32Dcl3 parental cells in views of cell growth pattern, c-fos gene transcription and myeloid cell differentiation induced by G-CSF. The reason may be explained by that the endogenous AML1 levels in the parental cells are sufficient to induce c-fos gene transcription and cell differentiation. By contrast, AML1-MTG8-32Dcl3 cells completely differed from parental or AML1-32Dcl3 cells. This may be due to the fact that overexpression of AML1-MTG8 can override the effect of endogenous AML1 on the c-fos gene transcription and cell differentiation. Thus, it appears that AML1 and AML1-MTG8 reciprocally regulate myeloid cell differentiation through their differential effects on the c-fos gene transcription.

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