Reversal of Tumorigenicity and the Block to Differentiation in Erythroleukemia Cells by GATA-1

Kevin S. Choe, Farshid Radparvar, Igor Matushansky, Natasha Rekhtman, Xing Han, and Arthur I. Skoultchi

Department of Cell Biology, Albert Einstein College of Medicine, Bronx, New York 10461

ABSTRACT

Oncogenic transformation usually inhibits normal cell differentiation processes. Certain chemical agents can force some tumor cells to resume their differentiation program and undergo cell cycle arrest, an approach termed differentiation therapy. Mouse erythroleukemia (MEL) cells represent an important cell culture model system for investigating the principles of differentiation therapy. MEL cells are malignant erythroblasts that are blocked from differentiating into mature erythroid cells because of inappropriate expression of the transcription factor PU.1, which binds to and represses GATA-1, a key transcriptional stimulator of red blood cell differentiation. We report here that the block to differentiation in MEL cells can be overcome by providing the cells with additional GATA-1. A conditionally active form of GATA-1 can trigger the cells to differentiate, undergo terminal cell division, and lose their tumorigenicity. We also show that the gene for the cell cycle inhibitor p21 is transcriptionally regulated by GATA-1 and is a likely downstream effector of GATA-1 that helps to promote differentiation and proliferation arrest.

INTRODUCTION

The normal process of differentiation involves increasingly restricted proliferative capacity and usually leads to cell cycle exit. Malignant transformation frequently inhibits terminal differentiation, and many tumors fail to express markers of differentiated cells. The concept of treating cancers by forcing tumor cells to reenter their normal terminal differentiation program was supported by early work with MEL cells, which showed that treatment of these tumor cells with DMSO leads to erythroid differentiation and loss of tumorigenicity (1). The most successful clinical application of the differentiation therapy approach is the treatment of APL with ATRA, which promotes differentiation of leukemic promyeloocytes into mature granulocytes and often causes a complete remission in patients. ATRA targets the aberrant, chimeric transcription factor promyelocytic leukemia-retinoic acid receptor α present in APL. Arsenic trioxide is another agent used in APL patients who develop ATRA resistance (2). Hybrid polar compounds such as HMBA and SAHA are other types of differentiation therapy agents, originally identified in studies with MEL cells (3), that induce terminal differentiation in various transformed cells in culture (4), can prevent formation of tumors in mice (5), and may also be effective in APL (6). There is evidence that agents such as ATRA, arsenic trioxide, and SAHA interfere with transcriptional repression mechanisms, thereby altering the transcriptional program of the tumor cells so as to favor differentiation over proliferation (7, 8).

To test directly the role of transcription factors in reversal of the tumor phenotype in MEL cells, we have manipulated the activity of GATA-1, a key regulator of erythroid differentiation. MEL cells are highly malignant tumor cell lines established from Friend virus-induced erythroleukemias in the mice (9). They are blocked near the proerythroblast stage of differentiation. When these cells are treated with certain chemical agents such as HMBA, they resume erythroid differentiation, accumulate hemoglobin and other erythrocyte-specific proteins, and undergo terminal cell division, causing them to lose their tumorigenicity. An important event in the emergence of the erythroleukemias in Friend virus-infected mice is proviral insertion by the spleen focus-forming virus (a component of Friend virus) at the Spi-1 locus, which leads to deregulated expression of the PU.1 transcription factor (10–12). PU.1 is an Ets-family transcription factor important in myeloid and B-cell differentiation (13, 14); it has no known role in erythroid differentiation. However, its role in erythroleukemogenesis is supported by results showing that expression of PU.1 leads to immortalization of bone marrow-derived erythroblasts (15) and that transgenic mice expressing PU.1 in erythroid cells develop erythroleukemias (16).

An early event in chemical induction of MEL cell differentiation is the down-regulation of PU.1 levels (17–20). By stably transfecting MEL cells with an expression vector encoding exogenous PU.1, we showed that the decline in PU.1 is a necessary step in HMBA-induced reentry of MEL cells to differentiation (20). We also reported that PU.1 binds directly to GATA-1 and represses its transcriptional activity (21). These observations led us to investigate the possibility that providing MEL cells with additional GATA-1 would be sufficient to overcome the differentiation block imposed by PU.1 and trigger their terminal differentiation. By using a conditionally active form of GATA-1, we show here that GATA-1 alone can induce MEL cells to differentiate and to lose their tumorigenic properties. In addition, we provide evidence that the cell cycle inhibitor, p21, may be an important target gene and downstream effector of GATA-1 in this process.

MATERIALS AND METHODS

Cell Culture, Plasmids, and DNA Transfection. Clone DS19 MEL cells were grown in DMEM supplemented with 10% fetal bovine serum as described previously (20, 21). The expression vector for producing the GATA-1-ER fusion protein was constructed by subcloning a BamHI-NcoI DNA fragment encoding GATA-1-ER into a modified pEBB vector digested with the same enzymes. The vector pEBB-puro was generated by blunt-end ligation of the SalI fragment of pPGK-PURO into HindIII-digested pEBB (21). Stable transfectants of MEL cells were prepared as described previously (20). Transfectants were selected and maintained in growth medium containing 5 μg/ml puromycin. Cell differentiation was tested by culturing in the presence of either 5 mM HMBA or 10−5 M β-estradiol (20, 22). Benzidine staining and plasma clot assays were performed as described previously (20, 23). Cell growth was measured by counting aliquots of the cultures with a Coulter counter. Cells were maintained at a density of <2 × 106 cells/ml at all times by dilution with fresh growth medium, including appropriate additives.

Injection of Cells into Mice. Transfected MEL cells expressing GATA-1-ER were grown in the presence or absence of β-estradiol for 5 days. Cells
were washed once with PBS, and the indicated amounts of cells were injected s.c. in the flank region of 6-week-old male DBA/2 mice (Taconic Farms).

Antibodies and Immunoblotting. Immunoblot assays were performed on 50 μg of total protein extract as described previously (24, 25). The following antibodies were used: rat monoclonal anti-GATA-1 (N6), rabbit polyclonal anti-PU.1 (T21), anti-CDK2 (M2), anti-CDK4 (C22), anti-CDK6 (C21), and anti-p27 (M197) antibodies, all from Santa Cruz Biotechnology; rabbit polyclonal anti-c-Myc (O6340) from Upstate Biotechnology; mouse monoclonal anti-p21 (65951A) from PharMingen; rabbit polyclonal anti-hemoglobin (55447) from ICN; and mouse monoclonal anti-c-Myb, a gift from Timothy Bender (University of Virginia).

Northern Blotting. Assays were performed on 10 μg of total cellular RNA isolated by the hot-phenol method as described previously (20). p21 cDNA obtained from an expression vector (24) was labeled with [α-32P]dCTP and used as the probe. Blots were hybridized at 42°C for 12 h and then washed six times in a solution of 0.1% SDS and decreasing concentrations of SSC (2× to 0.1×).

Reporter Assays. U2OS cells were cultured in DMEM with 10% fetal bovine serum. One day before transfection, 4 × 10^6 cells were plated in each well of 24-well plates. Cells were transfected with Lipofectamine Plus (Life Technologies, Inc.), as recommended by the manufacturer. DNA mixtures for transfection contained 50 ng of pEBB-puro vector DNA. Luciferase activity was determined as described in "Materials and Methods." Values in reporter assays represent at least two independent transfections. Error bars represent the SE. All experiments were performed at least twice.

RESULTS

Generation of MEL Cell Lines Expressing a Conditionally Active GATA-1. To test whether introducing additional GATA-1 into MEL cells would trigger their differentiation, we prepared MEL cell lines stably transfected with an expression vector encoding a conditionally active form of GATA-1. A GATA-1-ER gene was constructed by fusing coding sequences from GATA-1 and the ligand binding domain of the human estrogen receptor (Fig. 1A). The sequences encoding the GATA-1-ER fusion protein were inserted downstream of the EF1 α promoter in the pEBB expression vector (27), which we have shown to produce high level expression in MEL cells (20). The vector also contained a PGK-puro cassette, allowing for selection of transfectants in puromycin.

To test the transcriptional activity of the GATA-1-ER fusion protein and its dependence on estrogen and to compare its activity with that of GATA-1, we performed reporter assays with a luciferase gene driven by a GATA-1-responsive promoter (Fig. 1B). The ability of GATA-1-ER to transactivate the reporter was strongly stimulated by estrogen to levels similar to that achieved by GATA-1. Furthermore, the activity of the fusion protein, like that of GATA-1, was repressed by PU.1.

Transfected MEL cell clones were isolated and screened for expression of the GATA-1-ER fusion protein by Western blotting with an antibody to GATA-1. The GATA-1-ER protein has a predicted molecular mass of 85 kDa and migrates more slowly in polyacrylamide gels than GATA-1 (Fig. 1C). Two independent GATA-1-ER-expressing clones (GER-4 and GER-21) were selected for additional study.

Induction of Erythroid Differentiation and Terminal Cell Division by GATA-1-ER. Treatment of MEL cells with chemical inducers of differentiation such as HMBA leads to a gradual accumulation of hemoglobinized cells as an increasing percentage of cells undergo differentiation. Although the molecular target(s) of HMBA action has not been defined, it is a potent inducer that causes a very high proportion of treated MEL cells to undergo differentiation. We compared the effects of HMBA and estrogen treatment on differentiation of MEL cells and the two GATA-1-ER transfectants by measuring production of hemoglobinized, benzidine-positive cells, and by Western blotting for hemoglobin in cellular protein extracts. Treatment of GATA-1-ER transfectants with either HMBA or estrogen caused 90–95% of the cells to become benzidine positive (Fig. 2A). The kinetics of appearance of benzidine-positive GATA-1-ER cells was very similar with the two agents, and the final percentage differentiation was also very similar to that obtained in MEL cells treated with HMBA. Estrogen did not induce differentiation of the parental MEL cells. Immunoblotting experiments showed gradual accumulation of hemoglobin induced by estrogen treatment, and the final level of hemoglobin accumulation was similar to that induced in MEL cells by HMBA (Fig. 2B).

Certain agents, e.g., hemin, can induce MEL cells to accumulate low levels of hemoglobin without inducing terminal cell division (28). Therefore, it was important to determine whether estrogen treatment of GATA-1-ER transfectants induced loss of proliferative capacity. Untreated MEL cells or MEL cells treated with estrogen grow exponentially with a doubling time of ~12 h, whereas MEL cells treated with HMBA cease growth after 2–3 days and about three to four population doublings. Untreated GATA-1-ER transfectants also grow exponentially with doubling times similar to untreated MEL cells, but...
estrogen treatment, as with HMBA treatment, caused them to stop dividing after 2–3 days (Fig. 2C), indicating they had undergone terminal cell division.

The foregoing assays of differentiation and proliferative capacity were performed in the continuous presence of inducing agents. An important feature of the in vitro differentiation of MEL cells is that treatment of the cells with inducers such as HMBA leads initially to cells that are not overtly differentiated but that are irreversibly committed to differentiate. Such cells no longer require the presence of the inducer to execute the terminal differentiation program. In contrast to untreated MEL cells, committed MEL cells have a very limited proliferative capacity and can undergo a maximum of five to six cell divisions, similar to normal committed erythroid precursors called Colony Forming Unit-Erythroid. To determine whether activation of GATA-1-ER in MEL cell transfectants induces irreversible commitment to differentiate, the cells were treated with either estrogen or HMBA for various times as indicated. C. MEL cells and GATA-1-ER transfectants were cultured in the presence or absence of estrogen or HMBA, and cell numbers were measured at the indicated times. D. a GATA-1-ER transfectant (clone 4) or MEL cells were cultured in the presence of estrogen (Est) for 48 h and then plated in plasma clot in the absence of estrogen. Colonies were photographed after 4 days of incubation at 37°C. All colonies shown in the left panel stained positive with benzidine, whereas those in the right panel did not stain positive (data not shown). On the other hand, MEL cells treated with estrogen produced very large, benzidine-negative colonies, like those produced by untreated MEL cells (Fig. 2D, right panel). The kinetics of accumulation of committed cells in the transfectants induced with estrogen was shown.

Fig. 2. Activation of the GATA-1-ER fusion protein in MEL cells leads to erythroid differentiation and terminal cell division. A, MEL cells and GATA-1-ER transfectants (clones 4 and 21) were cultured in the presence of either estrogen (Est) or HMBA, as indicated. Aliquots were removed at the indicated times, and the percentage of the cells staining positive for hemoglobin with the benzidine reagent was scored. B, immunoblot analysis of hemoglobin levels in total protein cell extracts of a GATA-1-ER transfectant (clone 4) or MEL cells treated with either estrogen (Est) or HMBA for various times as indicated. C, MEL cells and GATA-1-ER transfectants were cultured in the presence or absence of estrogen or HMBA, and cell numbers were measured at the indicated times. D, a GATA-1-ER transfectant (clone 4) or MEL cells were cultured in the presence of estrogen (Est) for 48 h and then plated in plasma clot in the absence of estrogen. Colonies were photographed after 4 days of incubation at 37°C. All colonies shown in the left panel stained positive with benzidine, whereas those in the right panel did not stain positive (data not shown).
somewhat slower than with HMBA, but the maximum percentage of committed cells achieved with both treatments was very similar (Fig. 3).

We conclude that activation of GATA-1-ER in erythroleukemia cells triggers a program of erythroid differentiation that includes an irreversible commitment to undergo a small number of terminal cell divisions.

Reversal of Erythroleukemia Cell Tumorigenicity by GATA-1-ER. We also sought to determine whether activation of GATA-1-ER in the transfected erythroleukemia cells caused changes in their capacity to form tumors. s.c. injection of MEL cells into syngeneic DBA/2 mice leads rapidly to formation of tumors at the site of injection and subsequently to death of the mice (1, 29). We grew GATA-1-ER transfected cells for 5 days in the presence or absence of estrogen and then tested their ability to form s.c. tumors. After 2 weeks, 60% of mice injected with $10^3$ untreated cells had palpable tumor masses, whereas none of the mice injected with the same number of estrogen-treated cells had tumors (Table 1). A significant reduction in frequency of tumors by estrogen treatment was also observed when $10^4$ cells were injected. By 3 weeks, even some mice injected with $10^5$ treated cells had tumors, presumably because of outgrowth of cells that had not responded to estrogen treatment in cell culture. However, the average weight of these tumors was in all cases significantly lower than that of tumors arising from untreated cells (Fig. 4). We conclude that activation of GATA-1-ER causes reversal of MEL cell tumorigenicity.

Activation of GATA-1-ER Induces Rapid Down Regulation of Proteins Capable of Blocking MEL Cell Differentiation. The levels of certain proteins have been found to decline rapidly upon chemical induction of MEL cell differentiation. Marked reductions in the levels of three transcription factors, PU.1, c-Myc, and c-Myb, as well as a cell cycle regulator, CDK6, occur primarily in the first 24–48 h after initiating treatment, concomitant with the irreversible commitment of the cells to differentiate (20, 23, 30, 31). Transfection experiments in which each of these proteins has been constitutively expressed in MEL cells show each of the changes is necessary for MEL cell differentiation (20, 32–36). There is also evidence that the declines in c-Myc and c-Myb depend on down-regulation of PU.1 (20). A decline in CDK6 is specifically required because the levels of CDK2 and CDK4, as well as several cyclins, do not decline and constitutive expression of only CDK6 blocks differentiation (23, 36).

To determine whether activation of GATA-1-ER in the transfected cells also induced these changes to occur, protein levels were studied by Western blotting after estrogen treatment. Fig. 5 shows that each of the proteins capable of blocking MEL cell differentiation declined rapidly upon estrogen treatment, with kinetics very similar to that observed upon HMBA treatment of MEL cells. The changes induced upon estrogen treatment of transfected cells are specific because CDK2 did not decline during the treatment and estrogen did not cause these changes in untransfected MEL cells.

Transcription of p21, a Positive Regulator of MEL Cell Differentiation, Is Induced by GATA-1-ER. We and others (24, 37) reported previously that induction of MEL cell differentiation by HMBA is accompanied by a very rapid increase in the level of p21 RNA and protein. Furthermore, we found that inducible expression of a transfected p21 gene triggers MEL cell differentiation, including hemoglobin synthesis and terminal cell division (24). Thus, both GATA-1-ER and p21 are strong, positive regulators of MEL cell differentiation. Therefore, we sought to determine whether the p21 gene is a downstream target of GATA-1-ER. Western blotting experiments showed that p21 levels increase within 2 h of treating GATA-1-ER transfected clones with estrogen (Fig. 6A, left panels). In contrast, p27 is induced much later during estrogen treatment as the cells are undergoing terminal cell division (Fig. 6A, right panels). We also saw this long delay between induction of p21 and p27 in HMBA treated MEL cells (24). p21 is also induced earlier than p27 in primary mouse erythroblasts undergoing erythropoietin-induced terminal differentiation.

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**Table 1** Reduced frequency of palpable tumors in mice injected with estrogen-treated GATA-1-ER MEL cells

<table>
<thead>
<tr>
<th>No. of cells injected</th>
<th>−Est</th>
<th>+Est</th>
</tr>
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<tbody>
<tr>
<td>$1 \times 10^5$</td>
<td>100% (5/5)</td>
<td>80% (4/5)</td>
</tr>
<tr>
<td>$1 \times 10^4$</td>
<td>100% (5/5)</td>
<td>20% (1/5)</td>
</tr>
<tr>
<td>$1 \times 10^3$</td>
<td>60% (3/5)</td>
<td>0% (0/5)</td>
</tr>
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* MEL cell transfectant GATA-1-ER clone 4 was grown in the presence (+Est) or absence (−Est) of estrogen for 120 h and then the indicated numbers of cells were injected into 5 male DBA/2 mice as described in “Materials and Methods.”

* Two weeks after injection, the number of mice with palpable tumors was scored.

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![Fig. 4](image-url)  
**Fig. 4.** Reversal of MEL cell tumorigenicity by GATA-1-ER. A GATA-1-ER transfected (clone 4) was cultured in the presence or absence of estrogen for 120 h. The indicated number of cells was injected into five syngeneic DBA/2 mice as described in “Materials and Methods.” Mice were sacrificed after 3 weeks, and s.c. tumor masses were excised and weighed.

![Fig. 5](image-url)  
**Fig. 5.** Activation of GATA-1-ER induces down-regulation of specific proteins involved in blocking MEL cell differentiation. A and B, MEL cells and GATA-1-ER transfectants (clones 4 and 21) were treated with estrogen (Est) or HMBA for the indicated amount of time. Total protein cell lysates were prepared, and equal amounts of protein were analyzed by immunoblotting with antisera specific for the indicated proteins as described in “Materials and Methods.”
Accordingly, we pretreated GATA-1-ER transfectants with cycloheximide for 12 h. The cells were further incubated in the presence (+Est) or absence (−Est) of estrogen for the indicated times and then total RNA was prepared and analyzed by Northern blot hybridization for p21 mRNA.

![Fig. 6. p21 mRNA and protein are rapidly induced by GATA-1-ER. A, GATA-1-ER transfectants (clones 4 and 21) were cultured in the presence of estrogen for the indicated times, total protein cell lysates were prepared, and equal amounts of protein were analyzed by immunoblotting for p21 and p27. B, MEL cells and transfectants expressing either a GATA-1-ER or PU.1-ER fusion protein were cultured in the presence of 7.5 μg/ml cycloheximide for 12 h. The cells were further incubated in the presence (+Est) or absence (−Est) of estrogen for the indicated times and then total RNA was prepared and analyzed by Northern blot hybridization for p21 mRNA.](image)

**Fig. 6.** p21 mRNA and protein are rapidly induced by GATA-1-ER. A, GATA-1-ER transfectants (clones 4 and 21) were cultured in the presence of estrogen for the indicated times, total protein cell lysates were prepared, and equal amounts of protein were analyzed by immunoblotting for p21 and p27. B, MEL cells and transfectants expressing either a GATA-1-ER or PU.1-ER fusion protein were cultured in the presence of 7.5 μg/ml cycloheximide for 12 h. The cells were further incubated in the presence (+Est) or absence (−Est) of estrogen for the indicated times and then total RNA was prepared and analyzed by Northern blot hybridization for p21 mRNA.

**DISCUSSION**

Recent progress indicates that many transcription factors exist in large multiprotein complexes (40). Some of these complexes contain more than one sequence-specific DNA binding protein. There are now many examples of direct protein-protein interactions between such DNA binding transcription factors. We and others have shown that PU.1 and GATA-1 interact directly through their DNA binding domains (21, 41, 42). This interaction results in repression of each factor’s ability to stimulate transcription. Several mechanisms for the inhibition have been proposed (21, 43), but the precise mechanism(s) operating in vivo remains to be fully elucidated. Regardless of the mechanism, it seems likely that this mutual antagonism of the two factors is important in lineage commitment decisions in hematopoietic progenitors. Studies by Nerlov and Graf (44) have shown that the stoichiometry of PU.1 and GATA-1 is important in determining the differentiation status of avian multipotent precursor cells, and we have shown that the stoichiometry of the two factors is important in erythropoiesis in *Xenopus* embryos (21).

The studies reported here indicate that the stoichiometry of PU.1 and GATA-1 is also crucial in determining whether erythroleukemia cells proliferate and form tumors or undergo differentiation and terminal cell division. Deregulated expression of PU.1 in erythroid precursors causes erythroleukemia in mice (16, 45). The role of PU.1 in oncogenic transformation may be multifaceted, but it is likely to involve the ability of PU.1 to repress GATA-1 and block erythroid differentiation (21). Our findings strongly support this view. We found that simply providing MEL cells with additional functional molecules of GATA-1 caused them to reinitiate erythroid differentiation, undergo terminal cell division, and lose their tumorigenic properties in mice. Thus, the stoichiometry of these two mutually antagonistic transcription factors is important not only during normal development but also during leukemogenesis.

It appears that the MEL cells may be exquisitely sensitive to the levels of PU.1 and GATA-1. We cannot be certain about the relative levels of GATA-1-ER and endogenous GATA-1 in the transfectants because we do not know the relative reactivity of the GATA-1-ER fusion protein with the anti-GATA-1 antisem used in immunoblotting. However, if the reactivities of the two proteins are similar, then the level of the fusion protein in the transfectants is less than that of endogenous GATA-1. Nevertheless, that was sufficient to reprogram erythroleukemia cells to undergo terminal differentiation. Because there is evidence that expression of both GATA-1 and PU.1 may be positively autoregulated (46, 47), it is possible that autoregulation of GATA-1 expression, as well as loss of positive effects of PU.1 on its own expression, may play a role in the reprogramming process. For the experiments in this study, we chose to use a conditionally active form of GATA-1 because stable transfectants expressing a constitutively active GATA-1 would be expected to differentiate and undergo terminal cell division and therefore could not be isolated. We do not believe that the GATA-1-ER fusion protein differs in its activities compared with GATA-1. It is no more active than GATA-1 in reporter assays, and it is sensitive to repression by PU.1 (Fig. 1B). Furthermore, other estrogen receptor fusion proteins do not induce differentiation when introduced into MEL cells (K. Choe, unpublished observations).

Regarding the role of PU.1 in erythroleukemia, it should be noted that our results need not imply that repression of GATA-1 is the sole function of PU.1 in leukemogenesis. Because the antagonism between the two factors is mutual, elevating the level of GATA-1 in the tumor cells by transfecting them with the GATA-1-ER expression vector would be expected to inhibit other functions of PU.1 that contribute to the leukemic state of the MEL cells. Recently, we showed that PU.1 can regulate the synthesis of CDK6 mRNA (36). We previously reported that CDK6 activity is required for MEL cell proliferation (24). These findings suggest that in addition to blocking differentiation by repressing GATA-1, deregulated expression of PU.1 in erythroid precursors also stimulates a proliferation program. Increasing the level of functional GATA-1 in MEL cells may oppose this action of PU.1 and reestablish normal cell cycle controls, triggering terminal cell division.

Conversely, we do not think that the role of GATA-1-ER in reversing the leukemic phenotype in MEL cells is limited to opposing the leukemia-promoting functions of PU.1. We found that activation of GATA-1-ER leads to a very rapid induction of the cell cycle inhibitor, p21. The observation that p21 mRNA is also induced by activation of GATA-1-ER and that this can occur from preformed GATA-1-ER molecules in the presence of cycloheximide without ongoing protein synthesis (Fig. 6D) suggest that the p21 gene may be a direct target for regulation by GATA-1. We previously reported that conditional expression of p21 in MEL cells induces hemoglobin synthesis and terminal erythroid differentiation (24). Thus, conditional expression of either GATA-1 or a putative target of GATA-1, the p21 gene, can trigger MEL cells to reenter the erythroid differentiation pathway and lose their leukemic properties.
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REFERENCES


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