Aberrant Expression of the Myeloid Zinc Finger Gene, MZF-1, Is Oncogenic

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ABSTRACT

The zinc finger gene MZF-1 is preferentially expressed in primitive hematopoietic cells and plays an important role in regulating myelopoiesis. Regulators of development are potential targets for neoplastic transformation. This study investigated whether unregulated expression of MZF-1 could function as an oncogene. Retroviral transduction and subsequent overexpression of MZF-1 resulted in loss of contact inhibition, loss of substrate dependence, and more rapid cell cycling in NIH 3T3 cells. The MZF-1-transformed 3T3 cells formed aggressive tumors in athymic mice. Disruption of the tight lineage- and stage-specific regulation of MZF-1 can result in neoplastic transformation of embryonic fibroblasts. Therefore, MZF-1 represents a novel oncogene.

INTRODUCTION

Differentiation is a complex process by which a pluripotent stem cell gives rise to mature cells of unique phenotypes. Although developmental gene expression can be regulated at many levels (1), much is regulated at the level of transcription (2, 3; reviewed in Refs. 4–6). Therefore, transcriptional regulators are responsible for many of the phenotypic changes during the differentiation of pluripotent cells. One accessible and continuous model of development is hematopoiesis, in which marrow stem cells undergo differentiation to mature peripheral blood lineages. Many hematopoietic phenotypic changes are controlled by transcriptional regulators (4). Transcriptional regulators can be classified into families based on conserved amino acid sequences, often in the DNA binding domain (5, 6).

One of the families of transcriptional regulators that control blood cell development is the zinc finger proteins (4, 7–10). These proteins bind specific DNA sequences by a unique peptide loop in which cysteines and histidines or cysteines alone chelate a central zinc ion (8). This zinc ion is important to maintain the peptide structure that allows this finger domain to interact with DNA.

Zinc finger genes can be separated into several classes by the constitution of their finger domains. One such class, called C2H2, is exemplified by Krupple, a Drosophila gap gene (11). The Krupple class is characterized by finger domains having the conserved peptide motif CX2CX3FX5LX2HX3H, in which the two conserved cysteines and two histidines chelate the essential zinc ion. In addition, this class of zinc finger genes also has a highly conserved region called the H-C link (TGEKPYX) that lies between the finger domains.

One member of the Krupple class of zinc finger genes, MZF-1, plays an essential role in regulating hematopoiesis. It was isolated from a cDNA library made from a patient with chronic myelogenous leukemia with the use of degenerate oligonucleotides from the H-C link (12). The gene encodes a 485-amino acid protein containing 13 zinc finger domains. Of the other Krupple zinc finger genes, it is most related to PLZF, KID-1, and GLI-1 (13–15). There is evidence that PLZF and GLI-1 are important in human neoplasia (13, 15).

MZF-1 has been demonstrated to be important in the regulation of hematopoiesis. MZF-1 is preferentially expressed in primitive myeloid cell lines (12). CRNA in situ hybridization of normal marrow revealed that MZF-1 was expressed only in early myeloid cells (9). MZF-1 may be necessary for the transition from progenitor to mature myeloid cells, because antisense but not sense oligonucleotides to MZF-1 markedly inhibited granulocyte-colony-stimulating factor-driven granulocyte colony formation (9).

Recently, the consensus DNA binding sites for the two zinc finger regions of MZF-1 were isolated (16). These consensus DNA binding sites have been identified in the promoters of several genes that are differentially expressed in myelopoiesis. Therefore, MZF-1 is probably one of the genetic regulators of the cascade of gene expression that occurs during myelopoiesis. Such nodal genetic regulators in hematopoiesis are potential targets of neoplastic transformation when regulated aberrantly (4).

Therefore, we investigated whether disrupting the tight lineage- and stage-specific expression of MZF-1 could transform embryonic fibroblasts neoplastically. We retrovirally transduced MZF-1 into NIH 3T3 cells, where it is not normally expressed, and assessed transformation potential. In this study, MZF-1 was found to aggressively transform 3T3 cells.

MATERIALS AND METHODS

Cells. Early passage NIH 3T3 cells were the gift of Dr. Jay Tischfield of The Indiana University Medical Center (Indianapolis, IN). They were grown in DMEM plus 10% FCS and antibiotics. Growth curves were obtained by suspending 50,000 cells in 1 ml of the appropriate medium in a number of 30-mm culture dishes. The total cell number for each experimental condition was counted daily with the use of a hemacytometer.

Retroviral Synthesis and Gene Transduction. pLXSN, a Moloney leukemia virus-based expression vector, was the gift of Dr. Dusty Miller of the Fred Hutchinson Cancer Research Center (Seattle, WA; 17). This retroviral expression vector has a multiple cloning site after the Moloney LTR,4 followed by the simian virus 40 promoter driving neuomycin phosphotransferase. The presence of the neomycin phosphotransferase (neo) gene allows the selection of transduced cells with G418. The cDNA clone ZNF1.8 containing the entire open reading frame of MZF-1 was subcloned into the EcoRI site of pLXSN (12). The LNL6 retrovirus containing the Moloney leukemia virus backbone with neo driven off theLTR promoter was used as a negative transformation control.

The pLXSN subclone, termed pLXSN-MZF, and LNL6 were transinfected into the amphotropic packaging cell line PA317 with the use of Lipofectin, according to the supplier’s instructions (BRL, Gaithersburg, MD). PA317 cells were also the gift of Dr. Dusty Miller (17). After 72 h, supernatants were collected and passed through a 0.45-mm sterile filter. These retroviral supernatants containing LXS-MZF or LNL6 were stored at −70°C in 2-ml aliquots. The titer of these supernatants ranged from 3 X 105 to 2 X 106 infectious particles/ml, as determined by G418-resistant 3T3 cell colonies.

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4 The abbreviations used are: LTR, long terminal repeat; kDa, kilodalton.
To infect 3T3 cells, 100,000 3T3 cells were grown overnight in a 100-mm culture dish. The medium was removed, and 4 ml of retroviral supernatant supplemented by 8 μg/ml of polybrene was added. Cells were incubated for 2 h, the viral supernatant was removed, and the cells were exposed to freshly thawed viral supernatant twice more, as before. The cells were then placed back in their normal growth medium for 48 h before selection for 2 weeks with G418 at 1 mg/ml (active). After the initial 2-week selection, cells were maintained in 0.5 mg/ml G418.

The presence or absence of a helper virus was determined with the use of the S+L- assay for two randomly selected LXSN-MZF supernatants (18). Helper virus was not found to be present.

Individual 3T3-transformed cells were isolated with the use of limiting dilution into 96-well plates. The initial presence of a single cell/well was checked visually with the use of an inverted microscope. Wells with a single colony were trypsinized to isolate clones. For most of these experiments, two clones, designated 3T3/MZF 1 and 2, were used for comparison to 3T3/LNL cells and the G418-selected, but uncloned, parent 3T3/MZF cell line. Although all 3T3/MZF clones expressed some MZF-1 at the RNA level, these two clones were chosen on the basis of having a consistently high level of MZF-1 RNA expression. 3T3/LNL cells were used to control for the effect of retroviral transduction and G418 selection in the focus formation assays, soft agar cloning assays, and nude mouse tumor formation.

**Assay for Loss of Contact Inhibition.** The ability of the 3T3 cell lines to form foci that contained cells that had lost contact inhibition was assayed by plating 1000 cells in a 100-mm culture dish and allowing cells to grow to confluency. The dishes were washed in PBS and stained with 1% crystal violet in methanol; foci of piled up cells then become visible microscopically and could be counted. 3T3/LNL cells were used to control for the possibility that retroviral infection and G418 selection produced a loss of contact inhibition. In preliminary experiments, however, there was no difference between 3T3/LNL cells and the normal 3T3 cells in focus formation assays.

**Assay for Loss of Substrate Dependence.** The ability of the 3T3 cell lines to grow independent of substrate was assayed by overlaying 30-mm culture dishes with 1 ml of molten 0.3% agar in DMEM plus 20% FCS and antibiotics. This initial layer of agar prevented the 3T3 cells from sinking to the bottom of the culture dish and attaching before the solidification of the top agar matrix. After the lower agar layer solidified, various dilutions of each cell type were overlain in 1 ml of molten 0.3% agar in DMEM plus 20% FCS and antibiotics. G418 at 0.5 mg/ml was added to agar cultures that contained retrovirally transduced NIH 3T3 cells. Agar cultures were incubated for 2 weeks, by which time macroscopic colonies had formed. Colonies containing more than 50 cells were counted as positive on an inverted microscope at ×10 magnification. 3T3/LNL cells were used to control for the possibility that retroviral infection and G418 selection produced a loss of substrate dependence. However, there was no difference between the behavior of these cells and that of normal 3T3 cells in soft agar cloning assays.

**Tumorigenicity in Athymic Mice.** To assay for the oncogenicity of 3T3/ MZF cells, 500,000 cells were injected s.c. into athymic (nu/nu) mice (female, 12 weeks old; Charles River Laboratories, Cambridge, MA) per cell line. Mice were kept in a sterile environment and observed twice weekly for the formation of tumors. Mice that had tumors were sacrificed, autopsies were performed, and tissue was taken for histological examination and Southern blot and PCR analysis, as described below. The Southern blot and PCR analyses were performed to ascertain that the tumor cells originated from retrovirally transduced 3T3 cells. Because neo was used to probe for the presence of the LXSN retrovirus, normal 3T3 cells were used as a negative control instead of 3T3/LNL cells.

**PCR Analysis of Retroviral Insertion.** Retroviral insertion into the genomic DNA of the tumors produced in mice was analyzed by the PCR as described previously (19). Sequences from neo were amplified and Southern blotted as above. A radiolabeled oligonucleotide with sequence from the neo gene internal to the PCR primers was hybridized to the blot, and the presence of neo was analyzed by autoradiography.

**Western Analysis.** Rabbit polyclonal antiserum was raised to the ZN1-4 recombinant protein (16) portion of MZF-1. Anti-MZF-1 polyclonal but not preimmune serum was able to detect recombinant MZF-1 in Western blot assays. This MZF-1 antiserum, termed anti-MZF, was used to detect MZF-1 protein in the retrovirally transduced 3T3/MZF cells in a Western analysis as a control for the possibility that the 3T3/MZF cells were not synthesizing MZF-1 protein. MZF-1 is not normally expressed in embryonic fibroblasts.

Whole cell lysates were prepared from equal numbers of 3T3, 3T3/MZF, 3T3/MZF 1, and 3T3/MZF 2. Washed cell pellets were resuspended in 10X cell pellet volume in 1X Laemli buffer; samples were boiled for 5 min and then microfuged for 10 min at 4°C. Ten μl of the cell lysate were size fractionated on a 10% SDS-polyacrylamide gel and transferred to Immobilon-P at 1.5 ml/cm² with the use of semidry electrophoretography. Filters were blocked for 1 h at room temperature with 3% BSA in PBS and then incubated in 1:100 anti-MZF in 3% BSA/PBS for 45 min. The membrane was then washed six times in 0.1% BSA/1% Tween-20 in PBS and incubated at room temperature with 1:5000 protein A-horseradish peroxidase (Amersham, Arlington Heights, IL) in 3% BSA/PBS for 20 min. The membrane was then washed six times in the above wash solution, and peroxidase activity was detected by enhanced chemiluminescence, according to the manufacturer's instructions (Amersham). The presence of equal protein loading in different lanes was established by Coomassie blue staining.

**RESULTS**

NIH 3T3 cells were retrovirally transduced to assess oncogenicity of forced MZF-1 expression. To verify the insertion of intact retrovirus, Southern analysis of two LXSN-MZF-infected 3T3 cell clones was performed (Fig. 1A). DNA was digested with ASP718, which cuts within the LTR of the retrovirus, allowing for size determination of the integrated provirus. The blot was probed with radiolabeled neo.
MZF-1-transduced 3T3 cells revealed that MZF-1 was expressed in the NIH 3T3 cells (Fig. 1A). This was as expected, because MZF-1 is generally not expressed outside of hematopoietic cells (12). In two LXSN-MZF-infected clones, MZF-1 transcripts of approximately 4.5 kb were observed, indicating that the integrated virus expressed intact MZF-1 mRNA.

The hypothesis that MZF-1 expression transforms 3T3 cells implies that MZF-1 protein is synthesized in the transduced cells. Western analysis was used to assess whether the retrovirally transduced 3T3 cells synthesized MZF-1 protein. Rabbit polyclonal antiserum was raised against recombinant MZF-1 protein. This antiserum, termed anti-MZF, but not preimmune serum recognized recombinant MZF-1 protein on Western analysis. To assess whether MZF-1 protein was expressed in the MZF-1-transduced 3T3 cells, whole cell lysates from 3T3, 3T3/MZF, 3T3/MZF 1, and 3T3/MZF 2 subjected to SDS-PAGE were probed with preimmune and anti-MZF sera (Fig. 1C). Western blot analysis revealed that anti-MZF but not preimmune serum bound to a 53-kDa protein in all 3T3 cells retrovirally transduced with MZF-1. This 53-kDa species, the size of the putative MZF-1 protein, was not present in the parent, untransduced 3T3 cells. Therefore, a protein of the size of MZF-1, recognized by MZF-1 antiserum, is expressed in all 3T3/MZF cell lines but not in normal 3T3 cells. These data taken together show that intact MZF-1 was transduced and expressed in the NIH 3T3 cell line.

Next, the effect of MZF-1 expression on the growth of transduced 3T3 cells was determined. Growth curves of the control 3T3 and MZF-1-transduced 3T3 cells revealed that MZF-1-transduced cells grew at a faster rate than did control 3T3 cells (Table 1). 3T3 cells had a doubling time of 12 h when measured on the steepest part of the growth curve (0–2 days). When all 3T3/MZF cell lines were averaged, they had a doubling time of 7 h when on the exponential portion of their growth curve (also 0–2 days). The MZF-1-transduced cells had a much higher plateau, indicating that they were able to tolerate a higher cell density. The G418-selected but uncloned 3T3 cells had an average of 3.2 foci/plate. In addition, there was no difference in focus formation between normal 3T3 and 3T3/LNL cells. The parent 3T3/MZF cells averaged 234 foci/plate, the 3T3/MZF 1 cells, 231 foci/plate, and the 3T3/MZF 2 cells, 174 foci/plate. Therefore, 3T3 cells transduced with MZF-1 produced a loss of contact inhibition. Loss of substrate dependence by 3T3/MZF cells was assayed by colony growth on a layer of soft agar. When 3T3/MZF cells were plated in soft agar, they formed macroscopic colonies in 2 weeks (Fig. 2). An example of a 3T3/MZF agar colony is shown in Fig. 2B. Normal 3T3 or control 3T3/LNL cells did not produce any colonies in soft agar. However, 3T3/MZF parent cells had an average soft agar cloning efficiency of 43%, and the 3T3/MZF 1 cells and 3T3/MZF 2 cells both had efficiencies of 35% (Table 1). 3T3 cells overexpressing MZF-1 are able to grow without adhering to a substrate. The 3T3/LNL cell line served as an internal control for the possibility that retroviral integration and G418 selection might have produced the 3T3-MZF oncogenic transformation. As with the focus formation assay, there was no difference in the soft agar colony formation of 3T3 cells compared with that of 3T3/LNL cells.

Table 1 Comparison of the growth characteristics and the oncogenicity of the control 3T3/LNL cells with the 3T3 cells transduced with MZF-1

<table>
<thead>
<tr>
<th>Doubling time</th>
<th>S phase (%)</th>
<th>Foci/100 mm</th>
<th>Agar cloning (%)</th>
<th>Tumors/mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>3T3/LNL</td>
<td>12h</td>
<td>18</td>
<td>3.2 ± 0.2</td>
<td>0</td>
</tr>
<tr>
<td>3T3/MZF 1</td>
<td>7h</td>
<td>ND</td>
<td>234 ± 7.5</td>
<td>43 ± 1.1</td>
</tr>
<tr>
<td>3T3/MZF 2</td>
<td>8h</td>
<td>49</td>
<td>174 ± 32.5</td>
<td>35 ± 5.2</td>
</tr>
</tbody>
</table>

* 3T3/MZF cell lines grew faster, formed foci, had a high cloning efficiency in soft agar, and formed aggressive tumors in nude mice.

* ND, not done.

* Mean ± SEM.

controls. These studies show that NIH 3T3 cells expressing MZF-1 appeared to be cycling at a faster rate than were their normal counterparts.

The loss of contact inhibition was assayed in 3T3/LNL versus 3T3/MZF cells by focus formation (Table 1). In three experiments performed in duplicate, 3T3/LNL cells were grown to confluence on a 100-mm culture dish and stained with crystal violet. These plates had an average of 3.2 foci/plate. In addition, there was no difference in focus formation between normal 3T3 and 3T3/LNL cells. The parent 3T3/MZF cells averaged 234 foci/plate, the 3T3/MZF 1 cells, 231 foci/plate, and the 3T3/MZF 2 cells, 174 foci/plate. Therefore, 3T3 cells transduced with MZF-1 produced a loss of contact inhibition.

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All 3T3 cell lines transduced with MZF-1 formed tumors in athymic mice. These tumors had the characteristics of aggressive fibro-
OVEREXPRESSION OF MZF-1 IS ONCOGENIC

Fig. 3. Analysis of the tumorigenicity in athymic mice of normal 3T3 versus 3T3/MZF cells. A, a photomicrograph of the histology of a tumor formed in an athymic mouse after injection with 3T3/MZF cells. These tumors had a high grade histology and had an aggressive metastatic potential. B, PCR assessment of whether the tumors formed in the athymic mice still carried an integrated retroviral DNA. By PCR, neo sequences were present in all tumors that were studied (Lanes 1-4). +, a positive control, DNA with known neo sequences present; —, a negative control, DNA without neo sequences.

DISCUSSION

This study investigated the hypothesis that dysregulation of transcription factors that control hematopoietic development can be oncogenic (4). The myeloid zinc finger gene MZF-1 is essential for normal human granulopoiesis (9). Forcing its expression in NIH 3T3 cells resulted in the oncogenic transformation of those cells. The transformation of 3T3 cells by MZF-1 indicates that disrupting the tight lineage- and stage-specific regulation of this myeloid transcription factor can result in neoplastic transformation. In parallel experiments not shown herein, we also retrovirally overexpressed the myeloid-specific transcriptional regulators HOX12 and PU.1 (20–22) in NIH 3T3 cells. The forced expression of these myeloid-specific transcription factors did not change the phenotype of the 3T3 cells. Therefore, oncogenic transformation of embryonic fibroblasts is not a function of every myeloid lineage transcription factor. This finding implies that the aberrant expression of MZF-1 is more deleterious than is the expression of these other myeloid transcription factors, and that the tight regulation of its expression is important to prevent hematopoietic neoplasia. On this basis, aberrant expression of MZF-1 could play a contributing role in leukemia or myelodysplasia. Therefore, the transformation of 3T3 cells by MZF-1 may represent a more general phenomenon that could also include human neoplasia.

It is unlikely that the MZF-1 transformation of the 3T3 cells was caused by retroviral rearrangement, resulting in an aberrant transcript. Southern analysis of the integrated retrovirus demonstrated that the viral DNA was of the appropriate size in both the 3T3/MZF cell lines and the 3T3/MZF tumors. It is unlikely that this viral DNA fragment seen on Southern analysis represented an unintegrated provirus, because G418 selection forces retroviral integration.

Northern analysis also found that MZF-1 transcripts were of the predicted size. The total population of 3T3/MZF cells exhibited characteristics similar to those of single cell clones of 3T3/MZF cells. Because LXSN-MZF will integrate randomly within the genome, the total population will have a large number of independent integrations. Therefore, it is improbable that a single integration event, in which the retrovirus inserted next to and deregulated another oncogene, produced the transformation. It is recognized that single cell 3T3 clones can spontaneously exhibit a transformed phenotype. However, this most likely did not occur in this investigation, because the 3T3/MZF 1 and 2 clones behaved the same as the parent uncloned population.

The oncogenic transformation of NIH 3T3 cells results in certain classic phenotypic changes. One of these is the loss of contact inhibition, in which cells pile up on one another in foci. In a focus formation assay, 3T3/MZF cells had a marked increase in the number of foci compared with 3T3/LNL cells.

Another characteristic of transformed 3T3 cells is the loss of substrate dependence. 3T3/MZF cells were able to grow well on a soft agar substrate, whereas 3T3/LNL cells were unable to grow when overlain on soft agar. Cloning efficiencies for 3T3/MZF cells were all approximately 30%, indicating that a large number of 3T3/MZF cells formed colonies without substrate. The finding that control 3T3/LNL cells were unable to grow on soft agar is additional evidence that LXSN integration or G418 selection had no part in the transformation seen in the 3T3/MZF cell lines. These cell lines contained retroviral integrants and underwent G418 selection yet were not transformed.

3T3/MZF cells had a higher percentage of the cell population in active cell cycle and a faster doubling time. The 3T3/MZF cells also had a higher plateau of growth, indicating that they could tolerate a higher cell density than could the normal 3T3 cells. Both parent and cloned 3T3/MZF cells also formed high-grade, invasive fibrosarcomas in athymic mice. These tumors were found to harbor the intact original retrovirus. Therefore, the 3T3/MZF cells exhibited characteristics commonly associated with oncogenic transformation of NIH 3T3 cells.

Although this is the first example of the direct transformation of 3T3 cells by a C2H2 zinc finger gene, previous reports implicate this subtype of zinc finger genes in oncogenesis. GLI-1 has significant homology at the amino acid level to MZF-1 in its zinc finger domains; GLI-1 is amplified in some human glioblastomas. In addition, it can transform embryonic rat fibroblasts when the adenoviral oncogene EIA is coexpressed (13). EVI-I is another C2H2 zinc finger gene for which there are data indicating that it might play a role in neoplastic transformation (23). The retrovirally induced overexpression of EVI-I is associated with interleukin-3 independence by some IL-3-depend-
ent murine leukemias. In addition, there is evidence that EVI-1 might play a role in some human leukemias, inasmuch as it is disrupted in rare chromosomal translocations (24). PLZF is a third example of a C2H2 zinc finger gene that might play an important role in oncogenesis. The PLZF protein is fused to the retinoic acid α-receptor because of a chromosomal translocation in a rare form of human promyelocytic leukemia (15). Finally, a Kruppel-like zinc finger gene called Bel-15 is activated by chromosomal translocation in many cases of human diffuse large cell lymphoma (25, 26).

The mechanism by which MZF-1 transforms 3T3 cells is not clear. There is preliminary evidence that MZF-1 functions as a transcriptional repressor in 3T3 cells (27). One potential hypothesis is that MZF-1 might interfere with the normal expression of growth control genes in 3T3 cells. Because the 3T3/MZF cell lines can grow actively even when floating in liquid media, it is possible that genes regulating cell-substrate or cell-cell interaction are affected.

In summary, abnormal expression of the myeloid regulatory zinc finger protein MZF-1 transforms the embryonic fibroblast cell line NIH 3T3. Taken together with the reports mentioned above, this implies that neoplastic transformation can result from aberrant expression of transcriptional regulators of development.

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