Advances in Brief

The *HMG-I* Oncogene Causes Highly Penetrant, Aggressive Lymphoid Malignancy in Transgenic Mice and Is Overexpressed in Human Leukemia

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Abstract

HMG-I/Y **is overexpressed in human cancer, although a direct role for this gene in transformation has not been established. We generated transgenic mice with** *HMG-I* **targeted to lymphoid cells. All seven informative founder** *HMG-I* **mice developed aggressive lymphoma by a mean age of 4.8 months. Tumors express T-cell markers and are transplantable. We also demonstrate that** *HMG-I* **mRNA and protein are increased in human acute lymphocytic leukemia samples. Our results show that** *HMG-I* **functions as an oncogene and suggest that it contributes to the pathogenesis of leukemia and other cancers with increased** *HMG-I* **expression.**

Introduction

Although *HMG-I/Y* expression is increased in a variety of human cancers and portends a poor prognosis in some tumors (1–4), the contribution of this gene to malignant transformation is unknown. The *HMG-I/Y* gene encodes the HMG-I and HMG-Y protein isoforms (1–3), which function as architectural chromatin-binding proteins involved in regulating gene expression (1–3, 5–8). Interestingly, this gene is located on the short arm of chromosome 6, in a region known to be involved in rearrangements, translocations, and other abnormalities correlated with human cancers (1–3). We showed previously (9) that *HMG-I/Y* is a c-Myc target gene involved in Burkitt's lymphoma, an aggressive childhood malignancy that develops as a consequence of deregulated c-*myc* expression. *HMG-I/Y* genes have oncogenic properties in cell lines derived from various tissues (9–12). In addition, decreasing HMG-I/Y proteins blocks transformation in human cancer cell lines (9, 12, 13). These studies suggest that *HMG-I/Y* may function as an oncogene important in those cancers associated with increased *HMG-I/Y* expression. To further explore the role of *HMG-I/Y* in neoplastic transformation, we generated transgenic mice overexpressing *HMG-I* in lymphoid tissue. Here, we report that 100% of the *HMG-I* transgenic mice develop lymphoid tumors. Our findings provide the most direct evidence that overexpression of *HMG-I* leads to malignancy.

Materials and Methods

Construction of Transgenic Mice. cDNA encoding murine HMG-I was excised from pBS-I (9) with *Bam*HI and *Sal*I and inserted into the *Sal*I restriction sites of the vector pHSE3′ (14, 15). This construct was cleaved with *Xho*I to release a DNA fragment containing the HMG-I coding

sequence flanked by the H-2K promoter and immunoglobulin μ intronic enhancer. The transgene was injected into fertilized eggs from B6C57/SJL females and maintained by mating hemizygous animals with wild-type B6C57 mice. Germ-line transmission was assessed by Southern blot analysis of tail DNA.

Quantitative Reverse Transcription-PCR Analysis. Tissues from transgenic mice were stored in TRIzol at $-80°C$, and total RNA was extracted from lymphoid organs according to the manufacturer's instructions (Invitrogen). RNA (10 ng) was used in 20-μl reaction mixtures with SYBR Green PCR Master Kit and TaqMan One-Step reverse transcription-PCR kit (Applied Biosystems) using the 7700 model ABI PRISM sequence detector (Applied Biosystems). The sequences of the forward and reverse primers that amplify *HMG-I* are 5′-AAAGAGCCCAGTGAAGTGCCAAC and 5′-GTCAAA-GAACCCAGACGGG, respectively. The sequences for the forward and reverse primers that amplify the internal control, *GAPDH*, are 5′-CATCTCCGC-CCCTTCTGCTG and 5′-GCTAAGCAGTTGGTGGTGC, respectively. Reaction conditions were 30 min at 48°C, 10 min at 95°C, 40 cycles of 15 s at 95°C, and 45 s at 60°C.

Total RNA was isolated from patient leukemia samples (10^6 to 10^8 cells) and mouse T and B cells using TRIzol and RNAEasy (Qiagen). RNA (100 ng) was used in 20-μl reactions using TaqMan One-Step reverse transcription-PCR kit (Applied Biosystems). The sequences for the forward and reverse primers that amplify *HMG-I* are 5′-AGGAAAAAGGATGGCACTGAGAA and 5′-CCCTGAGGTCTCTTAGGTTTTGG, respectively. The sequence for the specific *HMG-I* probe is 5′-CTCCTTCTGACTCCCTCCCAGCGC. Human phosphoprotein was used as a control with commercially available primers and probes (Applied Biosystems). Reaction conditions were 30 min at 50°C, 10 min at 95°C, 40 cycles of 15 s at 95°C, and 45 s at 60°C. Reverse transcription-PCR reactions were performed in triplicate, and experiments were performed at least twice.

Fluorescence-Activated Cell-Sorting Analysis. Cells from lymphoid organs were analyzed using a FACScan analyzer (15).

Transfer of Tumors to Mice. Splenocytes (10^7 or 10^8) from transgenic mice or control, nontransgenic littermates were injected i.p. into nu$-/-$ or rag$-/-$ mice. Mice that died underwent necropsy. Mice that showed signs of tumor growth were sacrificed and underwent necropsy. Mice without evidence of tumor were observed for 20–24 weeks, sacrificed, and analyzed.

Western Analysis. Western analysis was performed (9, 10) with the anti-HMG-I antibody (1:200 dilution).

Histopathological Analysis. Tissues were fixed in 10% formalin and embedded in paraffin. Sections (5 μm) were stained with H&E.

Hematological Analysis. Blood smears were obtained by tail vein puncture every 2–4 weeks after the age of 6–7 months and at necropsy. Complete blood counts were obtained at necropsy by Coulter counter calibrated for mice.

B- and T-Cell Sorting. Splenocytes (5×10^7 cells) were separated into B and T cells using MACS CD45R (B220) and MACS CD90 (Thy1.2) antibodies and magnetic microbead sorting (Mitenyi Biotec).

Immunohistochemistry. Immunohistochemistry for terminal deoxynucleotidyltransferase was performed using commercially available antibodies (Supertech #C-99300) and a DAKO autostainer.

Results

Construction of Transgenic Mice and Transgenic Expression. The *HMG-I* transgene was targeted to lymphoid cells by the murine H-2K promoter and immunoglobulin μ enhancer, which drive expres-
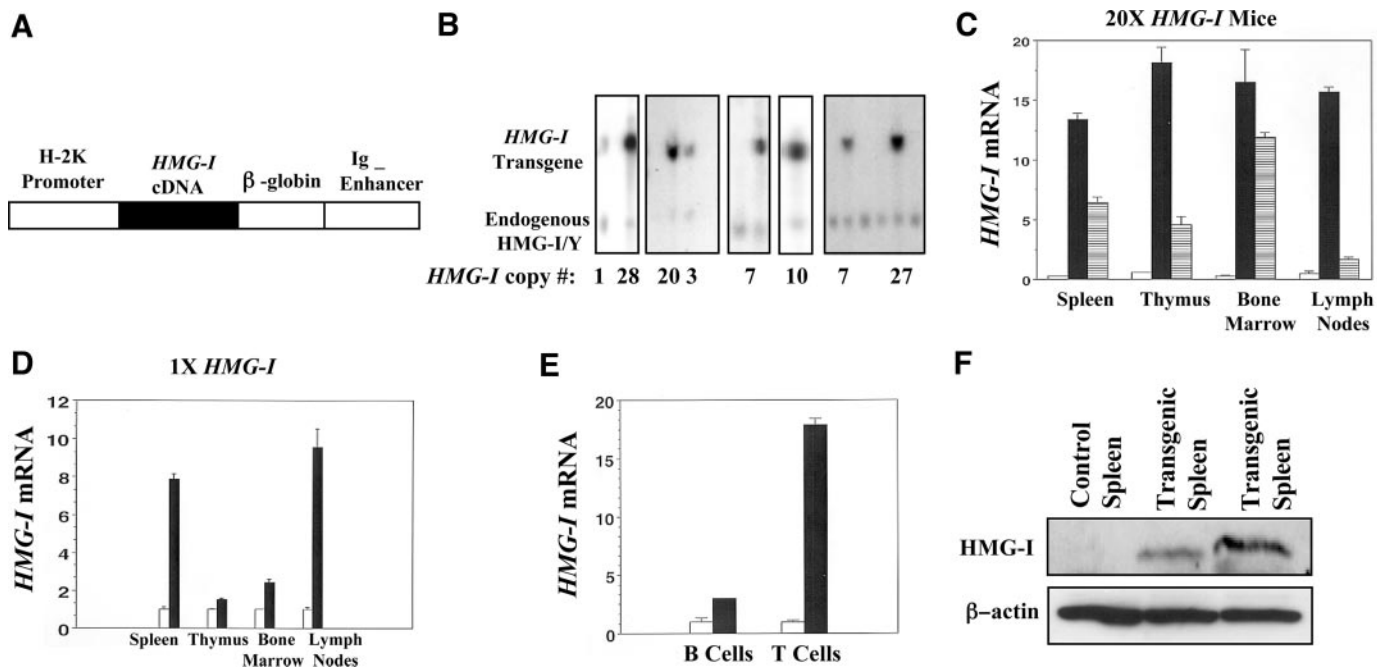
Fig. 1. The *HMG-I* transgenic mouse: construct and transgene expression. *A,* the *HMG-I* transgene. The H2-K promoter, *HMG-I* cDNA, β-globin splice donor/acceptor sequences, and the immunoglobulin heavy chain μ intronic enhancer are shown. *B,* the *HMG-I* transgene and endogenous gene by Southern analysis. Copy number was determined by comparing the intensity of the band from the transgene with that of the endogenous *HMG-I* gene by PhosporImager in at least two experiments. *C,* *HMG-I* mRNA expression by reverse transcription-PCR in lymphoid tissue of transgenic mice with 20 copies of the transgene (20× *HMG-I*) and control littermates. The *solid bars* show relative *HMG-I* mRNA in a transgenic mouse (age, 10.5 months) with widespread disease and a leukemia phenotype. The *hatched bars* show *HMG-I* mRNA from another transgenic mouse (age, 12.5 months) with less extensive disease. The *open bars* show a control littermate in which *HMG-I* mRNA was assigned a value of 1. *Bars* represent the mean ± SD. Note that *HMG-I* expression correlates with disease involvement. *D,* *HMG-I* mRNA expression by reverse transcription-PCR in lymphoid tissue from a transgenic mouse (age, 3.5 months) carrying 1 copy of the transgene (1× *HMG-I*) with lymphoma (■) compared with a control littermate (□) arbitrarily assigned a value of 1. Note that this founder had findings consistent with B-cell disease, which could account for the absence of thymic involvement. *E,* *HMG-I* mRNA expression in B and T cells from splenocytes of a transgenic and control mouse by reverse transcription-PCR. Note the increased *HMG-I* mRNA expression in B cells (4-fold) and T cells (18-fold) in the *HMG-I* mouse. *F,* HMG-I protein levels in splenocytes from *HMG-I* mice with 20 copies of the transgene and a control littermate. Note the marked increase in HMG-I protein in the transgenic animals. The mouse with the most extensive disease and more tumor cells/sample has more HMG-I protein (*right lane*).

sion in B and T cells (Fig. 1*A*; Refs. 14 and 15). We generated eight independent founders with 1–28 copies of the *HMG-I* transgene (Fig. 1*B*). Seven founders developed lymphoid tumors; the eighth died at 2 months, and tissue autolysis precluded further analysis.

HMG-I expression is increased in lymphoid tissues of the transgenic mice compared with that of control littermates (Fig. 1, *C* and *D*).

Those organs with extensive invasion by malignant cells have the highest levels of *HMG-I* mRNA. We assessed *HMG-I* expression in T and B lymphocytes from a mouse with 20 copies of the transgene. We showed increased *HMG-I* mRNA in the T cells (18-fold) and B cells (3-fold) compared with those cells from a control littermate (Fig. 1*E*). HMG-I protein is also increased in the splenocytes of transgenic mice

Table 1 *Microscopic findings from HMG-I transgenic mice*

Generation-mouse no.	Sex	Age at necropsy (mo)	Spleen	Thymus	BM[a]	Lymph node	GALT	Liver	Kidney	Lung
I-1	M	8.50	+	+	−	+	ND	ND	ND	−
II-1	M	7.50	+	+	−	−	−	−	−	−
III-1	F	9.25	+	−	+	+	+	−	+	−
III-2	F	8.50	+	+	+	+	+	+	−	−
III-3	F	8.50	+	+	+	+	+	+	+	+
III-4	M	9.50	+	+	+	+	+	+	−	−
III-5	F	7.00	+	−	+	+	−	−	−	−
III-6	M	14.50	+	ND	+	−	+	−	−	+
III-7	M	15.25	+	+	+	+	−	+	+	+
III-7	M	10.00	+	+	+	+	+	−	−	−
III-8	F	8.75	+	+	+	+	+	+	−	−
III-9	F	8.25	+	+	+	+	+	−	−	+
III-10	F	8.75	+	+	+	+	+	−	+	−
III-11	M	6.00	+	+	+	+	−	−	−	−
III-12	F	10.00	+	+	+	+	+	+	−	−
III-14	F	8.00	+	+	+	+	+	+	+	+
III-15	F	10.25	+	+	+	+	+	−	−	−
III-16	M	10.50	+	+	+	+	+	+	−	−
III-17	M	12.50	+	+	ND	−	−	−	−	−
III-18	F	10.50	+	+	+	+	+	−	−	−
III-19	M	7.25	+	+	+	+	+	−	−	−
III-20	F	12.50	+	+	+	+	+	+	+	−
III-21	M	12.50	ND	ND	+	+	+	+	+	−
III-22	F	6.25	+	+	+	+	+	+	+	−

[a] BM, bone marrow; GALT, gut-associated liver tissue; ND, not done.

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(Fig. 1*F*). The mouse with the most extensive disease had higher HMG-I protein levels, which probably reflects a higher proportion of tumor cells in the sample (Fig. 1*F, right lane*).

Lymphoid Malignancy in 100% of *HMG-I* Transgenic Mice. The seven founders all developed organomegaly and died between 1 and 8.5 months of age, with a mean age of death of 4.8 ± 2.6 months. Histopathological analysis showed lymphoma in all cases (Fig. 2, *A*−*G*). There was no correlation between onset of disease and copy number. The founder with 20 copies of the transgene was successfully bred to establish a transgenic line of mice; the rest died before sexual maturity or were infertile.

All of the descendants of the founder mouse with 20 copies of the transgene (1 second generation and 22 third generation) were sacrificed and analyzed histopathologically when they developed signs of disease (abnormal lymphoblasts in the peripheral blood, decreased activity, and/or organomegaly). Four mice also developed rectal (3) or cervical (1) prolapse. There were abnormal lymphoblasts infiltrating the prolapsed organ, which probably contributed to the prolapses. All transgenic mice with 20 copies of the *HMG-I* transgene from three generations developed lymphoid malignancy at a mean age of 9.6 ± 2.4 months. Histopathological analysis (Table 1) showed lymphoma in the spleen of all mice analyzed (23 of 23). In most cases, lymphoma was found in the thymus (20 of 22), bone marrow (21 of 23), lymph nodes (21 of 24), and gut-associated lymphoid tissue (18 of 23). Blood smears (Fig. 2*G*) showed abnormal, circulating lymphoblasts (19 of 21), and blood counts showed a pronounced leukocytosis (8 of 15). The presence of abnormal lymphoblasts in the bone marrow, spleen, and peripheral blood in most mice (17 of 18) suggests a leukemia-like process. Abnormal lymphoblasts were observed in the liver (11 of 23), kidneys (8 of 23), and lungs (5 of 24). All mice had at least two organs affected, and most had multiorgan involvement. These findings indicate aggressive, widespread disease in the *HMG-I* transgenic mice.

To determine the phenotype of the transformed cells from the line of mice with 20 copies of the transgene, fluorescence-activated cell-sorting analysis was performed and showed CD3+, CD4−, CD8+, and αβTCR+ T-cell markers (Fig. 3*A*). Cells are negative for the Natural Killer 1.1 (NK 1.1) and terminal deoxynucleotidyltransferase (data not shown), consistent with a mature T-cell phenotype (16). A homogenous population of cells with a single T-cell receptor rearrangement was observed in four of seven mice, including Vβ2 (one of seven), Vβ8.2 (two of seven), and Vβ6 (one of seven), as expected for clonal disease (Fig. 3*B*). The founder with 1 copy of the transgene had no gross thymic abnormalities with lymphoma involving the spleen, bone marrow, and lymph nodes. *HMG-I* mRNA was increased in the spleen, bone marrow, and lymph nodes, but not the thymus (Fig. 1*D*). The absense of thymic involvement in this founder suggests B-cell disease. The remaining founders had thymic disease, consistent with a T-cell phenotype. The basis for the preponderance of T-cell disease in the HMG-I mice is not known, although it is possible that factors present in T cells facilitate or enhance expression of the *HMG-I* transgene.

Tumors from the *HMG-I* Mice Are Transplantable. Mice that received injection with splenocytes from the transgenic mice developed lymphoma and died after 8–16 weeks, depending on the number of cells injected. Splenocytes (10^7) from an *HMG-I* mouse with lymphoma were injected into a nu−/− mouse, which developed lymphoma after 16 weeks. When 10^8 splenocytes from another transgenic mouse with lymphoma were injected into five rag−/− mice, all developed organomegaly and died after 8 weeks with lymphoma. Fluorescence-activated cell-sorting analysis from the tumor cell-injected mice showed that the lymphoid tumors had the same T-cell markers as the original tumor. None of the control mice injected with
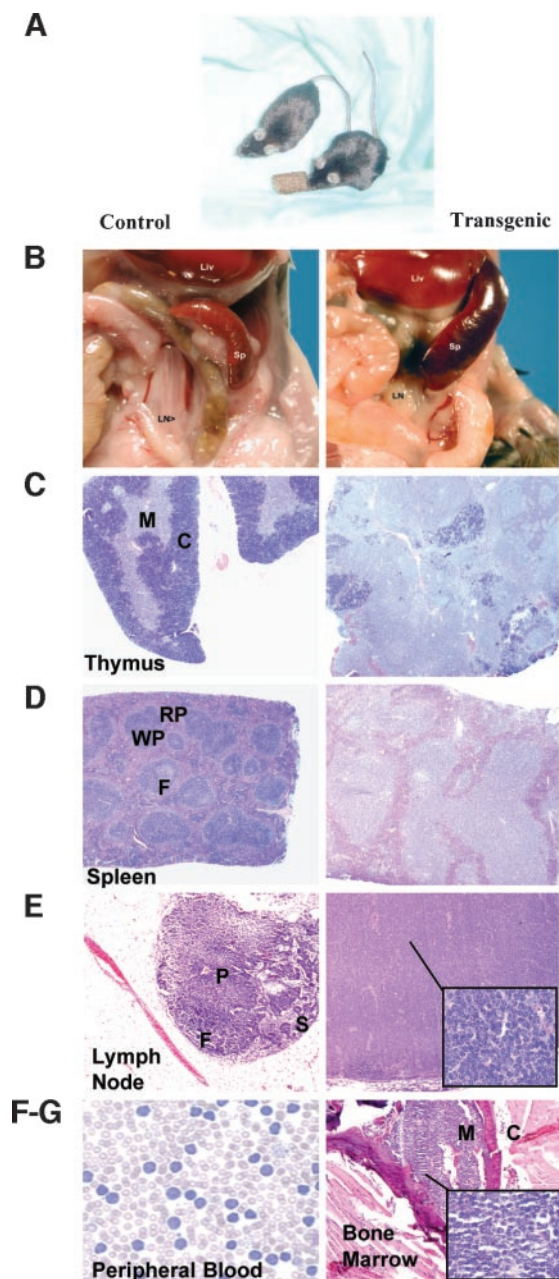

Fig. 2. *HMG-I* transgenic mice develop lymphoid malignancy. *A,* comparison of a *HMG-I* mouse (*right*) with a control mouse (*left*). *B,* gross necropsy findings of a *HMG-I* mouse (*right*) and a control mouse (*left*). Note the marked splenomegaly (Sp) and lymph node (LN) enlargement in the *HMG-I* mouse (spleen weight, 0.46 g in the *HMG-I* mouse *versus* 0.07 g in the control mouse). *C,* comparison of thymus from a control and *HMG-I* mouse. The control mouse has normal thymic architecture with a distinct medulla (*M*) and cortex (*C*), as shown. Note the marked disruption in the thymic architecture by extensive infiltration with abnormal lymphoblasts in the *HMG-I* mouse. *D,* the spleen in the control mouse shows normal architecture with red pulp (*RP*), white pulp (*WP*), and a follicle (*F*), as shown. Note the enlarged spleen from the *HMG-I* mouse with disrupted architecture secondary to infiltration by abnormal lymphoblasts. *E,* the mesenteric lymph node in the control mouse shows normal architecture with a cortical follicle (*F*), paracortical area (*P*), and medullary intercommunicating sinus (*S*), as shown. The architecture in the enlarged lymph node from the *HMG-I* mouse is disrupted with complete effacement by sheets of abnormal lymphoblasts. *F,* circulating, abnormal lymphoblasts in a *HMG-I* mouse with a WBC of >100,000/mm³ (*left*). *G,* bone marrow (*M*) and cortical bone (*C*) from a *HMG-I* mouse showing extensive infiltration with abnormal lymphoblasts.

the same number of splenocytes from a nontransgenic littermate developed lymphoid disease.

***HMG-I* Expression in Human Acute Lymphocytic Leukemia.** We showed previously (9, 10) that overexpression of *HMG-I* leads to a transformed phenotype in human lymphoid cells. HMG-I is
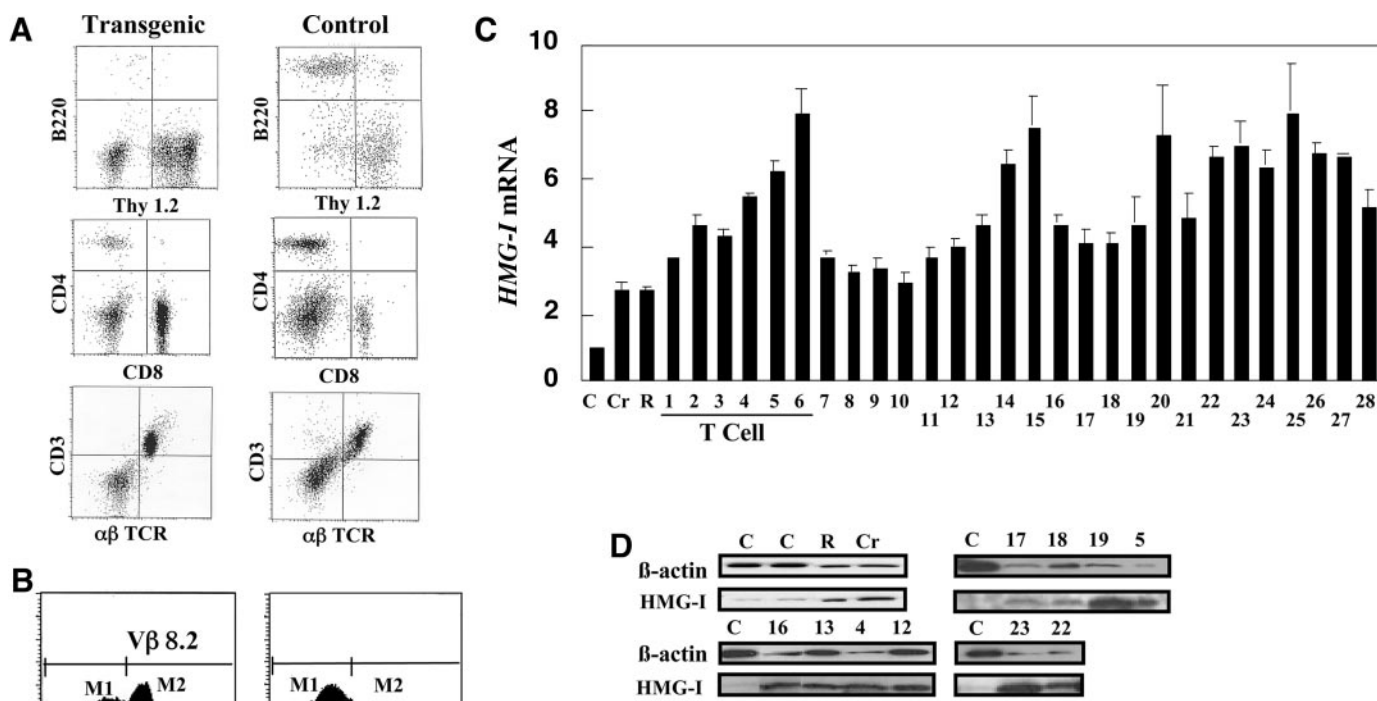
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Fig. 3. Fluorescence-activated cell-sorting (FACS) analysis of tumors from *HMG-I* mice and increased *HMG-I* expression in human leukemia. *A,* FACS of splenocytes from a representative *HMG-I* mouse shows positive thy1.2, CD8, CD3, and αβTCR markers. *B,* evidence for clonality by FACS analysis. Representative *HMG-I* mouse with a homogenous population of T cells with a single Vβ T-cell receptor rearrangement. *C, HMG-I* mRNA is increased in all human lymphoid leukemia samples (28 of 28 samples) and both leukemia cell lines by 2–9-fold compared with the control, EBV-transformed normal human lymphocytes (*C*) by reverse transcription-PCR. The control cells were arbitrarily assigned a value of 1. CRL-8286 cells (*Cr*) are a T-cell leukemia cell line, and REH cells (*R*) are a pre-B acute leukemia cell line. The first six leukemia samples have T-cell markers, and the remaining samples have B-cell markers. *D,* HMG-I protein is increased in all patient samples (10 of 10 samples) and both leukemia cell lines compared with the control (*C*) lymphocytes by Western analysis. The *numbers above the lane* correspond to the patient samples, as identified in *C*.

also increased in Burkitt's lymphoma (9) and five human acute lymphocytic leukemia samples (17). Taken together with our *HMG-I* mice, these findings suggest that *HMG-I* is involved in the pathogenesis of human lymphocytic leukemia. Therefore, we assessed *HMG-I* expression in bone marrow samples from patients with acute lymphocytic leukemia and acute lymphocytic leukemia cell lines. *HMG-I* mRNA was increased in all acute lymphocytic leukemia samples (28 of 28) and both cell lines by 2–9-fold compared with normal lymphocytes (Fig. 3*C*). We also showed increased HMG-I protein levels in the patient samples (10 of 10 samples; Fig. 3*D*) and both cell lines. In all cases, the protein levels correlate with the mRNA.

Discussion

The results of our studies clearly show that *HMG-I* overexpression is responsible for malignant transformation *in vivo*. The early onset of tumors, widespread disease, and 100% penetrance demonstrate that *HMG-I* overexpression causes aggressive disease in mice. The mechanisms involved in transformation by *HMG-I* are unknown. The onset of tumors after 4 months suggests that more than one genetic event is involved. Because HMG-I proteins function in transcriptional regulation (1–3, 5–8), overexpression of HMG-I may lead to transformation by altering expression of genes involved in regulation of cell growth. Recent studies also show that HMG-I proteins may contribute to genomic instability (18). Preliminary data with spectral karyotyping analysis of cell lines overexpressing *HMG-I* and tumor cells from our transgenic mice suggest that overexpression of HMG-I is correlated with an increased frequency of translocations, polyploidy, and other chromosomal abnormalities observed in cancer.[5]

[5] L. M. S. Resar, unpublished results.

HMG-I/Y is a c-Myc target gene important in the transformed phenotype in Burkitt's lymphoma (9). Our *HMG-I* transgenic mice are phenotypically similar to transgenic mice overexpressing c-*myc* in lymphoid tissue (19, 20). c-*myc* transgenic mice develop lymphoma between 4 and 14 months of age. In contrast to the *HMG-I* mice, the c-*myc* transgene was targeted only to B cells, and these mice therefore develop B-cell disease. To our knowledge, *HMG-I* is the only c-Myc target gene to exhibit malignancy in a transgenic mouse model. These results further suggest that HMG-I is critical for c-Myc function in transformation.

HMG-I may also function independent of c-Myc in some malignancies. For example, there are cancers known to express high levels of HMG-I protein without concurrent elevations in the c-Myc protein (12). Analysis of the *HMG-I/Y* promoter showed that *HMG-I/Y* is also regulated by transcription factors other than c-Myc (9). Thus, in some cancers, factors other than c-Myc may enhance *HMG-I/Y* expression. It is possible that other mechanisms, such as gene amplification, may enhance *HMG-I/Y* expression in cancer, although this has not yet been demonstrated.

Because *HMG-I* overexpression occurs in aggressive human malignancy, including Burkitt's lymphoma (9), we investigated human acute lymphoid leukemia samples to determine whether our *HMG-I* mouse model is applicable to human disease. Notably, we observed that *HMG-I* expression was increased in all lymphoid leukemia samples studied. A larger, more comprehensive study is needed to determine the prevalence of *HMG-I* overexpression in human lymphoid malignancy and whether *HMG-I* expression correlates with prognosis in this disease.

In summary, we show that overexpressing *HMG-I* in lymphoid tissue leads to an aggressive T-cell leukemia and lymphoma in transgenic mice. We also show that *HMG-I* is overexpressed in human

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lymphoid leukemia. Our findings demonstrate that *HMG-I* functions as an oncogene *in vivo* and suggest that it is important in the pathogenesis of human leukemia. The *HMG-I* transgenic mouse should provide a valuable model for human lymphoid malignancy and a useful tool for identifying the mechanisms through which overexpression of *HMG-I* leads to transformation. Because increased *HMG-I* expression occurs in a wide range of aggressive human cancers, this model should enhance our understanding of cancer biology relevant to tumors of various origins. Understanding the mechanisms that underlie transformation may also identify novel therapeutic targets for malignancy associated with *HMG-I* overexpression.

Acknowledgments

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