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# Therapy-related myeloid leukemia. A model for leukemogenesis

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A B S T R A C T

Therapy-related acute myeloid leukemia (t-AML) is a distinctive clinical syndrome occurring after exposure to chemotherapy or radiotherapy. t-AML arises in most cases from a multipotential hematopoietic stem cell or, less commonly, in a lineage committed progenitor cell. The prognosis for patients with t-AML is poor, as current forms of therapy are largely ineffective. Molecular analysis and gene expression profiling analysis of t-AML has revealed that there are distinct subtypes of t-AML that have a characteristic gene expression pattern. Establishing the molecular pathways involved in t-AML may facilitate the identification of selectively expressed genes that can be exploited for the development of urgently-needed targeted therapies.

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Therapy-related myelodysplastic syndrome and acute myeloid leukemia (t-MDS/t-AML) is a well recognized clinical syndrome occurring as a late complication following cytotoxic therapy.[1,2] These neoplasms are the direct consequence of mutational events induced by cytotoxic therapy. Several distinct cytogenetic and clinical subtypes of t-MDS/t-AML are recognized that are closely associated with the nature of the preceding treatment. A spectrum of morphologic abnormalities is observed.[2]

t-AML represents an important model for cancer. The incidence of t-AML is rising, as a result of the increasing number of cancer survivors at risk of developing this disorder and the changes in therapeutic trends. Secondly, t-AML provides a unique opportunity to examine the effects of mutagens on carcinogenesis in humans, as well as the role of genetic susceptibility to cancer.[3] Finally, the mechanisms of leukemogenesis that are uncovered in t-AML will likely apply to those subtypes of AML *de novo* which share the same cytogenetic abnormalities, e.g., AML *de novo* with abnormalities of chromosome 5 or 7. In this chapter, we review the clinical and genetic characteristics of t-MDS/t-AML.

## Clinical characteristics

Between 1972 and July 2001, 306 consecutive patients referred to the University of Chicago were confirmed to have a diagnosis of t-MDS/t-AML.[4] All patients had received chemotherapy (CT), radiation therapy (RT), or combined modality therapy (CMT) for an antecedent disorder. The clinical characteristics of the patients are shown in Table 1. The series included 165 women and 141 men. The median age at the time of initial primary disease diagnosis was 51 years (range, 3-83 years). There were 171 (56%) patients with a primary hematological malignancy, with nearly equal numbers of patients with Hodgkin's disease (HD, 77; 25% of the entire series) and non-Hodgkin's lymphoma (NHL, 70; 23%). One hundred and seventeen (38%) patients had a solid tumor as the primary malignancy. Breast cancer was the most common among these (32 patients; 10%). Importantly, we also studied 18 (6%) patients who had not had a prior malignancy, but who received cytotoxic therapy for treatment of autoimmune disorders, or immunosuppressive therapy for an organ transplant.

One hundred and twenty-one patients (40%) had only CT, and 43 (14%) had received only RT (Table 1). In most cases, the RT-only patients had received radiation to large ports encompassing areas of active hematopoiesis within the central skeleton and pelvis. One hundred thirty-nine patients (46%) had been treated with CMT, either concurrently as part of the

**Table 1. Primary diagnoses and primary cytotoxic therapy in 306 t-MDS/t-AML patients.**

| *Primary Diagnosis* | *No. of Patients* | *Chemotherapy Only (%)* | *Radiotherapy Only (%)* | *Combined Modality Therapy (%)* |
|---|---|---|---|---|
| No malignancy | 18 | 12 (67)[a] | 2 (11) | 4 (22) |
| Hematologic Malignancy | 171 | 69 (40) | 5 (3) | 97 (57) |
| Hodgkin's disease | 77 | 18 (23) | 4 (5) | 55 (71) |
| Non-Hodgkin's lymphoma | 70 | 33 (47) | 1 (1) | 36 (51) |
| Myeloma | 23 | 17 (74) | 0 | 6 (26) |
| Other | 1 | 1 (100) | 0 | 0 |
| Solid Tumor | 117 | 40 (35) | 36 (32) | 38 (33) |
| Breast | 32[c] | 11 (35) | 5 (16) | 15 (48) |
| Ovary | 15 | 12 (80) | 1 (7) | 2 (13) |
| Prostate | 13[c] | 0 | 11 (100) | 0 |
| Lung | 9 | 5 (56) | 2 (22) | 2 (22) |
| Cervix | 7 | 0 | 4 (57) | 3 (43) |
| Other[b] | 41 | 12 (30) | 13 (32) | 16 (39) |
| Totals | 306[c] | 121 (40) | 43 (14) | 139 (46) |

*a numbers in parentheses are percentages for each row of data according to primary therapy. b smaller diagnostic groups were not further subdivided by primary therapy. c in 3 patients, the primary therapy was incompletely known.*

initial treatment plan (54 patients) or sequentially, for treatment of relapsed disease (53 patients). For 32 of the CMT patients, the treatment records were incomplete with regard to concurrent or sequential therapy.

Overall, 224 patients (73%) were first diagnosed with t-MDS; 98 were later observed to progress to t-AML, but follow-up bone marrow data were incomplete in another 54 (18%) patients. The median time for progression from t-MDS to t-AML was 4 months; the interquartile range (IQR, 25$^{th}$-75$^{th}$ percentiles) was 2.0-8.0 months. Eighty-two (27%) patients presented with overt t-AML. Of the 121 patients who had received only CT, 93 (77%) presented with t-MDS. Thirty-six of these 93 t-MDS patients progressed to t-AML. Twenty-eight (23%) of the CT only patients presented with overt t-AML. Of the 43 patients who had received only RT, 28 patients (65%) presented with t-MDS and 15 (35%) with t-AML. Among the remaining 139 patients who had previously received both CT and RT, 103 patients (74%) presented with t-MDS and 36 (26%) with t-AML. Fifty-one of the 103 patients presenting with t-MDS progressed to t-AML, 33 remained with t-MDS, and 19 had incomplete hematology follow-up. The type of primary diagnosis (non-malignant, hematological malignancy, or solid tumor) was associated with the clinical presentation ($p$=0.011). In a pairwise comparison, patients with solid tumors were more likely to present with overt t-AML (38%) than patients with hematologic malignancies (19%; $p$<0.001) or those with non-malignant disorders (22%; $p$=0.29).

The median latency overall was 62 months (IQR, 35-107 months), but this varied from 28 to 136 months for different subgroups. Patients with non-malignant primary diagnoses had longer latency intervals ($p$=0.01). Younger patients also tended to have longer latency intervals ($p$<0.0001), and this association remained when the 18 patients with non-malignant conditions were excluded ($p$<0.0001). However, this apparent association could be due in part to competing risks as older patients died from other age-related causes before the development of t-MDS/t-AML.

## Cytogenetic analyses

Table 2 summarizes the clonal cytogenetic abnormalities observed in the patients. Twenty-four patients (8%) had no abnormality detected, and 282 (92%) patients had one or more abnormal clones detected. The most common abnormalities involved loss of a whole chromosome 5 or 7 (–5, –7) or both, a deletion of the long arm of these chromosomes [del(5q) or del(7q)], occurring in 214 (70%) patients. Monosomy 7 (–7) was present in 102 (33%) patients and monosomy 5 (–5) in 36 (12%) patients. The most common

**Table 2. Cytogenetic abnormalities in 306 patients with t-MDS/t-AML.**

| Karyotype | No. of patients (%) |
|---|---|
| Normal karyotype | 24 (8) |
| Clonal abnormalities | 282 (92) |
| Clonal abnormalities of chromosomes 5, 7, or both (+/- other abnormalities) | 214 (70) |
| Abnormal chromosome 5 only | 63 (21) |
| Abnormal chromosome 7 only | 85 (28) |
| Abnormal chromosomes 5 and 7 | 66 (22) |
| Recurring balanced rearrangements[a] | 31 (10) |
| t(11q23) | 10 (3) |
| t(3;21) or t(8;21) or t(21q22) | 8 (3) |
| t(15;17) | 6 (2) |
| inv(16) | 6 (2) |
| t(8;16) | 1 (0.3) |
| Other clonal abnormalities [b] | 39 (13) |

*[a]One patient with an abnormality of chromosome 5 and t(3;21), and one patient with an abnormality of chromosome 7 and inv(16) are listed twice in the table. [b]Includes 8 patients with +8, 3 patients with –13/del (13q), and 1 patient each with del(20q), del(11q), +11, +21, or –Y.*

structural chromosomal abnormality was a del(5q) in 59 (19%) patients.

Analysis of the clonal cytogenetic abnormalities based upon the primary diagnosis and the primary therapy is shown in Table 3. There was a significant difference among the 3 primary diagnosis categories in the fraction of patients with abnormalities of chromosomes 5 and/or 7 (83%, 75%, and 59% for no malignancy, hematologic malignancy, and solid tumor, respectively, p=0.007). Clonal abnormalities of chromosomes 5 or 7 or both were most common among patients with multiple myeloma (83%) and non-malignant primary disorders (83%), and less common among patients with solid tumors (59%). Abnormalities of Nos. 5 or 7 or both were found in 19 (59%), 9 (60%), and 5 (38%) patients with breast, ovarian, or prostate carcinoma, respectively. In contrast, 75% of patients with malignant lymphoma (HD, 73%, and NHL, 76%) had an abnormality of chromosomes 5 or 7.

Abnormalities of chromosomes 5 or 7 or both were observed in 172 of 224 patients (77%) presenting with t-MDS compared to 42 of 82 (51%) presenting with overt t-AML. However, balanced rearrangements occurred more frequently in the

**Table 3. Primary diagnosis, primary therapy and clonal cytogenetic abnormalities in 306 patients with t-MDS/t-AML.**

| *Clinical Feature* | *No. of patients* | *Abnormal 5 (%)* | *Abnormal 7 (%)* | *Abnormal 5 & 7 (%)* | *Balanced[b] Rearrangement (%)* | *Other Abnormalities (%)* | *Normal %* |
|---|---|---|---|---|---|---|---|
| Primary diagnosis[c] | | | | | | | |
| No malignancy | 18 | 1(6)[a] | 13 (72) | 1 (6) | 1 (6) | 1 (6) | 1 (6) |
| Hematologic malignancy | 171 | 32 (19) | 49 (29) | 47 (27) | 9 (5) | 25 (15) | 9 (5) |
| Hodgkin's disease | 77 | 13 (17) | 26 (34) | 17 (22) | 4 (5) | 14 (18) | 3 (4) |
| Non-Hodgkin's lymphoma | 70 | 12 (17) | 15 (21) | 26 (37) | 4 (6) | 9 (13) | 4 (6) |
| Myeloma | 23 | 7 (30) | 8 (35) | 4 (17) | 0 | 2 (9) | 2 (9) |
| Other | 1 | 0 | 0 | 0 | 1(100) | 0 | 0 |
| Solid tumor | 117 | 29 (25) | 23 (20) | 18 (15) | 17 (15) | 16 (14) | 14 (12) |
| Breast | 32 | 6 (19) | 10 (31) | 3 (9) | 7 (22) | 4 (13) | 2 (6) |
| Ovary | 15 | 5 (33) | 1 (7) | 3 (20) | 3 (20) | 3 (20) | 0 |
| Prostate | 13 | 3 (23) | 0 | 2 (15) | 1 (8) | 4 (31) | 3 (23) |
| Lung | 9 | 1 (11) | 2 (22) | 1 (11) | 3 (33) | 2 (22) | 0 |
| Cervix | 7 | 2 (29) | 2 (29) | 1 (14) | 0 | 0 | 2 (29) |
| Other | 41 | 12 (29) | 7 (17) | 8 (20) | 5 (12) | 2 (5) | 7 (17) |
| Totals | 306 | 62 (20) | 85 (28) | 66 (22) | 27 (9) | 42 (14) | 24 (8) |
| Primary Therapy | | | | | | | |
| CT only | 121 | 21 (17) | 38 (31) | 25 (21) | 11 (9) | 15 (12) | 11 (9) |
| RT only | 43 | 14 (33) | 6 (14) | 6 (14) | 6 (14) | 5 (12) | 6 (14) |
| CMT | 139 | 26 (19) | 40 (29) | 34 (24) | 14 (10) | 18 (13) | 7 (5) |

*aNumbers in parentheses are percentages for each row of data according to cytogenetic abnormality. b Patients with abnormalities of 5 or 7 or both plus other abnormalities except balanced rearrangements are counted only in the abnormal 5, 7, or both categories. Two patients, one each with abnormal chromosome 5 or 7, are counted only in the balanced rearrangement category because of t(3;21) or inv(16). c P < 0.0001 as measured by Fisher's exact test for the comparison of the 3 major categories of no malignancy, hematological malignancy, and solid tumor (3 X 6 contingency table). d. CT denotes chemotherapy, RT radiation therapy, and CMT combined modality therapy.*

subgroup presenting with t-AML than in those presenting with t-MDS (28% vs 4%, p<0.0001). There was no statistically significant association between age at primary diagnosis and cytogenetic subgroup. Patients with a balanced rearrangement had shorter latencies than all other patients taken together (medians, 28 vs. 67 months, p<0.0001).

Very few patients had received single agent treatment for their primary disorder, and most patients had received more than one class of CT. Thus, conclusions could not be made regarding specific types of CT and associated cytogenetic abnormalities. However, patients who had received topoisomerase II inhibitors were more likely to have a balanced rearrangement or abnormalities not involving Nos. 5 or 7 than patients who did not receive these agents (32% vs. 16%, p=0.002).

## Survival

The median time from diagnosis of t-MDS/t-AML to death was 8 months (95% confidence interval [CI], 7-9 months). The median survival of patients presenting with t-MDS was 8.6 months (95% CI, 7.6-9.9 months) compared to 6.9 months (95% CI, 4.0-8.5 months) for patients presenting with t-AML. Median survival times after diagnosis of t-MDS/t-AML by cytogenetic group were 7 months for chromosome 5 abnormalities, 9 months for chromosome 7 abnormalities, 5 months for both chromosome 5 and 7 abnormalities, 11 months for recurring balanced rearrangements, 9 months for other clonal abnormalities, and 11 months for normal karyotypes (log-rank, $p$=0.017). Patients with abnormalities of both chromosomes 5 and 7 had the worst overall survival compared to all other groups (log-rank, $p$=0.005). The large majority of our patients had abnormalities of chromosomes 5 and/or 7, abnormalities that also portend a poor survival when observed in patients with AML *de novo*. The median survivals of patients with AML *de novo* who had deletions of chromosomes 5 or 7 in the recent CALGB series were 0.3 and 0.5 years despite intensive chemotherapy.[5]

## Gene expression profiling of CD34+ progenitor cells in t-AML patients

To expand our understanding of the molecular basis of t-AML, we performed expression profiling of CD34+ progenitor cells from bone marrow samples from 14 t-AML patients using the Affymetrix platform.[6] Of these, three (21%) had a normal karyotype, three had –7, four had a del(5q) or loss of 5q, one had +13 as the sole abnormality, and one had a t(7;11)(p15;q23) that did not involve MLL. Two patients had recurring translocations involving 3q26.2 together with loss of 5q and 17p.

Although many of the leukemias contained multiple cytogenetic abnormalities, we identified 2 major groups (A and B) with unique expression profiles. Although t-AML patients with abnormalities of chromosomes 5 or 7 have similar clinical and morphological features, surprisingly, these patients did not cluster into the same group. Group A included all patients with –7 but no abnormality of chromosome 5. In contrast, patients with an abnormality of chromosome 5 clustered into one group (Group B). The remainder of the patients with other abnormalities or with a normal karyotype clustered into Group A. We identified 61 genes whose expression pattern is significantly altered, and whose expression best distinguishes the unique groups of t-AML. Forty-six genes were expressed in 50% of the leukemias, but not in the normal control samples (see ref. #6 and the PNAS web site).

## CD34+ progenitor cells in t-AML are blocked at an early stage of differentiation

A common feature that we identified in all t-AMLs examined was the down-regulation of genes required for the function of differentiated hematopoietic cells. Ten genes that are essential for the function of mature neutrophils (myeloperoxidase, and the serine proteases: cathepsin G, neutrophil elastase, proteinase 3, and azurocidin), platelets (platelet factor 4 and proplatelet basic protein), and eosinophils (eosinophil cationic protein and Charcot–Leyden crystal protein) were expressed in normal CD34+ stem cells from control samples but not in t-AML patients. These data provide molecular evidence that the initiating somatic mutation(s) occurs in early progenitor cells, which results in the dysregulation of genes essential for the differentiation of multiple hematopoietic lineages.

## Expression profiling reveals distinct molecular profiles in t-AML

In Group A t-AML cases, we observed loss of expression of TAL1, GATA1, and EKLF. TAL1 is a key regulator of early hematopoiesis, whereas GATA1 is essential for the development of both erythroid and megakaryocyte lineages. EKLF regulates expression of the β-globin gene and is

required for erythroid development. Taken together, these results suggest that dysregulation of transcription factors critical to the development of hematopoietic stem cells may contribute to the pathogenesis of this subtype of t-AML.

FLT3, PI3K/PIK3C2B, and BCL2 were highly expressed in Group A leukemias. FLT3 is expressed primarily in human $CD34^+$ stem/progenitor cells, and encodes a member of the type III receptor tyrosine kinase family. Constitutively activating mutations in FLT3 occur in the malignant cells of 25–30% of AML patients. Overexpression of BCL2 interferes with programmed cell death and has been reported to protect $CD34^+$ AML blasts from chemotherapy-induced apoptosis, leading to drug resistance. Downstream targets of the FLT3 kinase include the p85 subunit of PI3K, which phosphorylates the AKT serine/threonine kinase, resulting in expression of antiapoptotic proteins, such as BCL-$X_L$ and BCL2. The coordinated overexpression of FLT3, PI3K, and BCL2 suggests that FLT3 may play a role as a survival factor by regulating the expression of BCL2 through the PI3K pathway.

Group B t-AML cases with –5/del(5q) have high expression of proliferation signature genes, such as the genes encoding cyclin A2, cyclin E2, CDC2, CKS2, BUB1, and MYC. In contrast, the expression of the ICSBP gene (interferon consensus sequence-binding protein) was significantly down-regulated in Group B leukemias when compared with normal individuals. ICSBP functions as a negative regulator of IFN-induced genes, and plays a role in regulating proliferation, differentiation, and apoptosis of hematopoietic cells. A global perspective on gene expression in t-AML provides new insights into the underlying biology of this disease and may facilitate the identification of molecular targets for therapeutic approaches.

## Experimental models for the –5/del(5q) in t-AML

Despite intense efforts, the tumor suppressor genes on chromosomes 5 and 7 involved in the pathogenesis of AML *de novo* and t-AML have not been identified. Moreover, a growing body of experimental evidence is compatible with a haploinsufficiency model in which loss of one allele of the relevant gene(s) on 5q and 7q perturbs cell fate.[7,8] We have initiated a major effort to evaluate the role of haploinsufficiency of genes within the commonly deleted segment of 5q31 in hematopoiesis and leukemogenesis. One such candidate is the early growth response 1 gene (*EGR1*). EGR1, a member of the WT-1 family of transcription factors, is an early response protein in mediating the cellular response to growth factors, mitogens, and stress stimuli, and is downstream of cytokine signaling pathways. EGR1 is a direct transcriptional activator of *p53* and $p21^{Cip1/Waf1}$.[9] Loss of EGR1 function may allow hematopoietic stem cells to bypass p53-mediated senescence or apoptosis, contributing to leukemogenesis.

To evaluate the role of *Egr1* in hematopoiesis, we characterized *Egr1*-deficient mice. $Egr1^{-/-}$ mice display elevated WBCs, with elevated lymphocytes, and decreased neutrophil counts. In addition, $Egr1^{-/-}$ mice have elevated serum EPO levels.

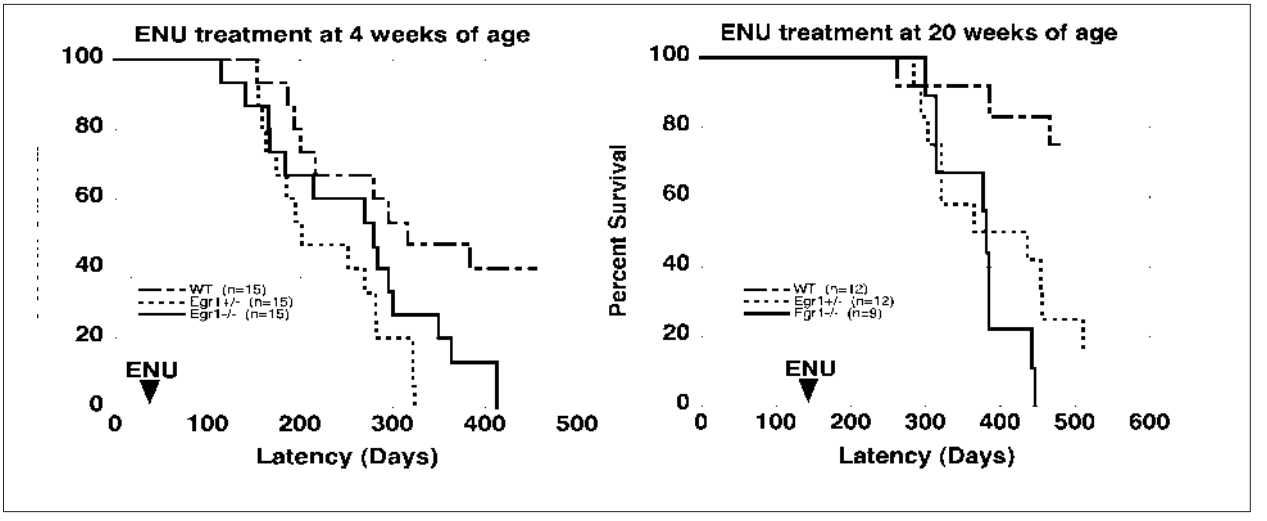


**Figure 1. Survival curves of WT, and Egr1-deficient mice after ENU treatment at 4 weeks (left panel) or 20 weeks (right panel) of age. Egr1-deficient mice developed T cell lymphomas or MPD with ineffective erythropoiesis at an increased rate, and shorter latency than WT littermates. Note: Only 1 mouse in the WT cohort (20 weeks) developed a neoplasm (T cell lymphoma). Two other mice were sacrificed for other disorders.**

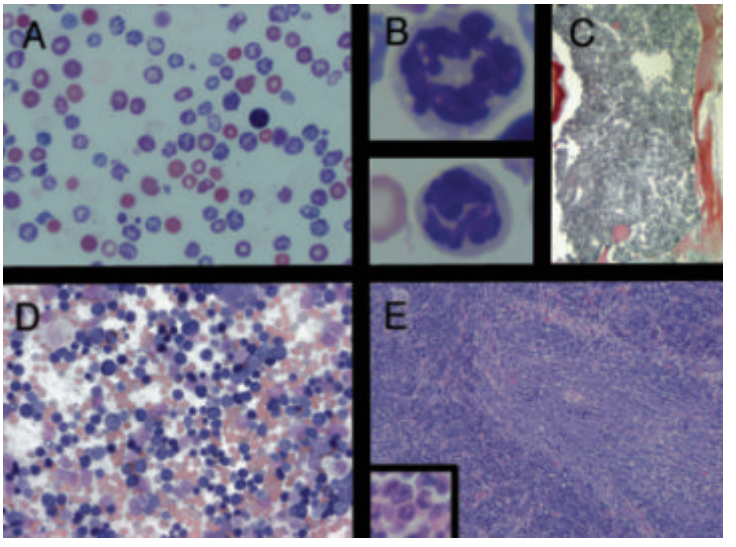


Figure 2. (A, B) Wright-Giemsa stained peripheral blood. (C) H&E stained sternum. (D) Wright-Giemsa stained bone marrow. (E) H&E stained spleen. The MPD developing in Egr1-deficient mice was characterized by elevated WBCs, anemia, and thrombocytopenia, with ineffective erythropoiesis in the bone marrow (D) and spleen (E). Neutrophils appeared hypogranular with hypersegmented nuclei (B). (C, D) The bone marrow was hypercellular with panhyperplasia of the erythroid and granulocytic lineages.

Initial studies suggest that *Egr1*-deficient mice have normal numbers of hematopoietic stem cells. *Egr1*$^{+/-}$ and *Egr1*$^{-/-}$ mice treated with N-nitroso-N-ethylurea (ENU), a potent DNA alkylating agent, developed immature T cell lymphomas (CD4$^+$, CD8$^+$) and MPD at an increased rate with a shorter latency as compared to wild-type animals ($P<0.05$, Figure 1). With ENU treatment, 37% of *Egr1*$^{+/-}$ mice and 33% of *Egr1*$^{-/-}$ mice develop MPD, compared to only 7% of wild-type mice. No mutations of the remaining *Egr1* allele were identified in MPDs from *Egr1*$^{+/-}$ mice, suggesting that loss of a single allele is sufficient for disease predisposition.

The MPD is characterized by elevated WBCs (WBC >19×10$^6$/mL), anemia (HGB < 7.5 g/dL), and thrombocytopenia (PLT < 800 K/μL), with ineffective erythropoiesis in the bone marrow and spleen (Figure 2). Dysplastic neutrophils were observed in the bone marrow and peripheral blood with hypersegmented nuclei and a hypogranular cytoplasm. The bone marrow was hypercellular with full maturation of all lineages, and no increase in blasts. The mice presented with severe splenomegely with a dramatic increase in erythropoiesis (Figure 2). Flow cytometric analysis confirmed an expansion in the erythroid (CD71$^+$, Ter119$^+$) and myeloid (Gr-1$^+$, Mac-1$^+$) populations with no increase in stem/progenitor cells (KIT$^+$, CD34$^+$) in the spleen. In other studies, we demonstrated that *Egr1* plays a role in murine stress erythropoiesis (data not shown). Our studies revealed that loss of *Egr1* cooperates with other mutations in the pathogenesis of myeloid neoplasms. *Egr1*-deficient mice may represent the first animal model for AML characterized by –5/del(5q).

## Models for the pathogenesis of t-AML

There is growing evidence that mutations in a limited number of molecular pathways may cooperate in the genesis of leukemia. Gilliland and colleagues have described an emerging paradigm in AML, namely, the cooperation between constitutively activated tyrosine kinases, such as FLT3, and transcription factor fusion proteins.[10] In this model, the activated tyrosine kinase confers a proliferative and/or antiapoptotic activity, whereas the fusion protein impairs normal differentiation pathways but has a limited effect on cellular proliferation. In the context of this model, haploinsufficiency for a gene(s) on 7q and 5q is likely to be the initiating mutation in Group A and B t-AMLs, respectively. In Group A t-AML, loss of *TAL1*, *GATA1*, and *EKLF* expression may result in impaired differentiation, whereas overexpression of *FLT3*, *PIK3C2B*, and *BCL2* result in a proliferative/survival advantage. In Group B, loss of expression of ICSBP may have pleiotropic effects, leading to impaired differentiation and/or a proliferative and survival advantage, whereas increased expression of cell cycle regulatory proteins (CCNA2, CCNE2, CDC2) would be predicted to result in a proliferative advantage.

Pedersen-Bjergaard and collegues have proposed 8 different pathways that are involved in progression to t-AML.[11] Pathway I consists of patients who have abnormalities of chromosome 7, without chromosome 5 abnormalities. These patients often present with mutations of the RAS pathway (*KRAS1, NRAS, NF1, PTPN11*), and methylation promoter of p15 (*CDKN2A*), and they have a poor prognosis. Pathway II comprises patients with a -5/del(5q) with or without

abnormalities of chromosome 7, and a poor prognosis. Genomic instability and complex karyotypes are common in these patients. Mutations of TP53 are often observed in this subgroup. Pathway III consists of patients with translocations at 11q23. Alterations of pathway IV convey the best prognosis for patients with t-AML, and include the t(8;21) or inv(16). Pathway V comprises patients who present with therapy-related acute promyelocytic leukemia with the t(15;17) resulting in the *PML/RARA* fusion and a good prognosis. Pathway VI involves balanced translocations of NUP98 at 11p15. Pathway VII includes t-MDS/t-AML with a normal karyotype. Recently, internal tandem duplications of *FLT3* and *MLL* have been described in these patients. Pathway VIII includes patients with other chromosomal abnormalities. Emerging technologies, such as high throughput proteomics and genomics technologies, may facilitate further delineation of the genetic pathways leading to t-AML.

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