Chapter 2
Genetic Modeling of Human Blood Cancers in Mice

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2.1 Introduction

Leukemia is a broad term describing a spectrum of diseases involving white blood cells and is divided into four categories: acute or chronic myelogenous and acute or chronic lymphocytic leukemia (CLL). Acute leukemia is characterized by the rapid proliferation of immature blood cells that cannot carry out their normal functions. Acute leukemia generally occurs in children and young adults and needs immediate treatment because of the rapid progression and accumulation of the malignant cells in the body. Chronic leukemia is distinguished by the excessive and slow build-up of relatively mature white blood cells, which can still carry out some of their normal functions. Chronic leukemia mostly occurs in older people but can theoretically occur in any age group. Whereas acute leukemia must be treated immediately, chronic forms are sometimes monitored for some time before treatment to ensure maximum effectiveness of therapy. Classification of leukemia into myeloid or lymphoid form is based on the type of abnormal white blood cells found most in the blood or bone marrow. Acute lymphocytic leukemia (also known as acute lymphoblastic leukemia, or ALL) is the most common type of leukemia in young children and

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also affects adults, especially those age 65 and older. CLL most often affects adults over the age of 55. CLL sometimes occurs in younger adults, but it almost never affects children.

There is no single known cause for all different types of leukemia. Four possible causes are (1) natural or artificial ionizing radiation, (2) certain kinds of chemicals, (3) some viruses, and (4) genetic predispositions. Leukemia, like other cancers, can result from somatic mutations in the DNA, which leads to disruption of the regulation of cell death, proliferation, and differentiation. These mutations may occur spontaneously or as a result of exposure to radiation or carcinogenic substances (such as benzene, hair dyes, etc.), and sensitivity of humans to these cancer-causing agents are likely to be influenced by genetic factors. Viruses have also been linked to some forms of leukemia. For example, certain cases of ALL are associated with viral infections by either the human immunodeficiency virus (HIV, responsible for AIDS) (Murray et al., 1999) or human T-lymphotropic virus [HTLV-1 and HTLV-2, causing adult T-cell leukemia/lymphoma (TCL)] (Poiesz et al., 2001). Fanconi anemia is also a risk factor for developing acute myelogenous leukemia (Bhatia et al., 2007). All these risk factors end up causing aberrant activation or inactivation of cellular genes that control normal cell proliferation and differentiation. In human blood cancers, formation of a fusion gene from two normal cellular genes, which is caused by chromosomal translocation, is a frequent way to abnormally activate a cellular gene that becomes oncogenic after forming a chimeric gene with another cellular gene. Large numbers of mouse models of human blood cancers are generated by expressing these chimeric or active oncogenes in mice. Mouse leukemia models provide powerful tools to investigate the disease mechanisms and help to develop new therapies.

2.2 Mouse Leukemia Models

In principle, leukemia mouse models are generated based on three major mechanisms: (1) expressing human oncogene(s) in hematopoietic progenitor cells, (2) inactivating tumor suppressor gene(s) (including DNA repair genes) in hematopoietic cells, and (3) combining these two methods. Described below are examples of established mouse models for different forms of human blood cancers.

2.2.1 Modeling Acute Myeloid Leukemia

Expression of a human acute myeloid leukemia-inducing gene in mouse bone marrow cells using retrovirus. Fusion genes involving transcriptional coactivators and generated through chromosomal translocations are frequently found in human acute myeloid leukemia (AML). Examples of these fusion genes are MLL/CBP (Satake et al., 1997; Sobulo et al., 1997; Taki et al., 1997), MLL/

p300 (Ida et al., 1997), MOZ (monocytic leukemia zinc finger)/CBP (Borrow et al., 1996), MOZ/p300 (Chaffanet et al., 2000; Kitabayashi et al., 2001b), MORF/CBP (Panagopoulos et al., 2001), and MOZ–TIF2 (Carapeti et al., 1998; Liang et al., 1998). Each of these fusion proteins contains one or more histone acetyltransferase (HAT) domain(s) that function to modify chromatin by acetylation of the N-terminal histone tail. Because MOZ–TIF2 is a common and well-understood fusion oncogene causing human AML, here we use this fusion gene as an example to describe the retroviral bone marrow transduction/transplantation mouse model of AML induced by MOZ–TIF2.

MOZ belongs to the MYST family of HATs and was first cloned as a fusion partner of CBP as a consequence of t(8;16)(p11;p13) chromosomal translocation associated with the French–American–British M4/M5 subtype of AML (Borrow et al., 1996). MOZ regulates transcriptional activation mediated by the hematopoietic transcription factor, Runx1 (AML1) (Kitabayashi et al., 2001a), and a related osteogenic transcriptional factor, Runx2 (Kitabayashi et al., 2001a). TIF2 belongs to p160 nuclear receptor transcriptional coactivator family (NRCoAs) (Glass et al., 1997; Horwitz et al., 1996), which includes SRC-1, TIF2/GRIP1, and ACTR/RAC3/pCIP/AIB-1. p160 family coactivators have a conserved N-terminal bHLH–PAS domain, a centrally located receptor interaction domain (RID), and a C-terminal transcriptional activation domain (AD). The RID contains three conserved motifs, LXXLL (where L is leucine and X is any amino acid), that are required to mediate interactions between coactivators and liganded nuclear receptors (Ding et al., 1998; Heery et al., 1997; Torchia et al., 1997). TIF2 can directly interact with CBP via its three conserved LXXLL motifs (Demarest et al., 2002; Torchia et al., 1997). P160 family members interact with nuclear receptors and enhance transcriptional activation by the receptor via histone acetylation/methylation (Leo and Chen, 2000).

In the MOZ–TIF2 fusion protein, MOZ retains the C4HC3-type PHD zinc finger domain and the HAT (MYST) domain and TIF2 retains the CBP interaction domain (CID) and CBP-independent activation domain (called AD2) of TIF2. MOZ–TIF2 lacks the C-terminus of MOZ and the PAS–bHLH DNA-binding/protein heterodimerization domain, and nuclear RID of TIF2 (Deguchi et al., 2003). To assess the transforming properties of MOZ–TIF2 in vivo, the *MOZ–TIF2* gene was cloned into the MSCV retroviral vector (see Fig. 1.2 in Chapter 1 for the viral vector structure); mouse bone marrow cells transduced with the MOZ–TIF2 containing retrovirus were transplanted into irradiated syngeneic mice (Deguchi et al., 2003). Recipients receiving bone marrow transduced with either the *MOZ–TIF2(I)* or the *MOZ–TIF2(II)* variant fusion genes developed fatal hematopoietic malignant disease, with high white blood cell (WBC) counts and splenomegaly. In addition, the mice demonstrated the presence of peripheral blood and bone marrow blasts and extensive tissue infiltration of organs including the liver, spleen, and lungs by leukemic blasts (Deguchi et al., 2003). This study provides sufficient evidence

showing that MOZ–TIF2, which is associated with human AML, induces similar disease in mice.

Transgenic AML mouse model. A good example of transgenic AML model is to express the *CBFβ–SMMHC* gene in mice. *CBFβ–SMMHC* resulted from the inversion of chromosome 16 inv(16)(p13.1;1q22), which breaks and joins the *CBFβ* gene with the myosin gene *MYH11* (Liu et al., 1993, 1996) and causes about 12% of human AML. To avoid embryonic lethality caused by expression of the *CBFβ–SMMHC* gene[6–10], a conditional *CBFβ–SMMHC* knock-in mouse was generated to analyze the preleukemic effects of CBFβ–SMMHC in hematopoiesis and AML development in adult mice. The *CBFβ–SMMHC* gene caused appearance of abnormal progenitor cells that are leukemic precursors. Mice expressing CBFβ–SMMHC developed AML with a median latency of approximately 5 months. Interestingly, the number of CBFβ–SMMHC-expressing hematopoietic stem cells (HSCs) was maintained at a normal level, but their ability to differentiate into multiple lineages of blood cells was severely impaired. This AML model is key for the study of early target genes in progenitor cells and provides an in vivo validation system for studying cooperative oncogenes and for testing candidate drugs for improved treatment of AML.

Collaborative induction of AML with multiple oncogenes. It is generally believed that multiple genetic alterations are required for the initiation and progression of malignant diseases. There are many examples that show the failure of a single AML-inducing oncogene to efficiently induce AML, as evident by no induction of leukemia or induction of leukemia with low penetrance and long latency. Additional genetic events (secondary "hits") are needed to promote the pathogenesis of leukemia. In this case, coexpression of more than one oncogene in the same hematopoietic progenitor cells helps to successfully induce human AML in mice.

The PML–RAPα fusion oncogene is found in acute promyelocytic leukemia (APL). APL comprises about 5–10% of cases of AML, and approximately 90% of APL patients are associated with a balanced t(15;17)(q22;q21) reciprocal chromosomal translocation. This translocation results in the fusion of the *PML* gene on chromosome 15 to the retinoic acid receptor alpha (*RARα*) gene on chromosome 17, forming two new oncogenes, PML–RARα and RARα–PML. The *RARα* gene encodes a hormone-inducible nuclear receptor that has been shown to be involved in myeloid development (Collins et al., 1990; Dawson et al., 1994; Onodera et al., 1995; Tsai and Collins, 1993). Both PML–RARα and RARα–PML play roles in APL phathogenesis.

To induce APL in mice, a transgene containing a human PML–RARα cDNA under the control of sequence that regulates the promyelocyte-specific expression of the human CG gene allows expression of PML–RARα in the early myeloid cells of the transgenic mice (Grisolano et al., 1997). At the early stage, these transgenic mice were found to have altered myeloid development with an expansion of myeloid cells in their bone marrows and spleens. After a long latent period, approximately 30% of the transgenic mice developed

leukemia, with massive splenomegaly, high percentage of immature myeloid cells in peripheral blood and bone marrow of the mice (Grisolano et al., 1997). In addition, approximately 40% of human APL patients are found to contain an activating mutation in the *FLT3* gene, containing internal tandem duplication (ITD) in the juxtamembrane domain. ITDs in FLT3 (FLT3–ITD) are found in 27% of all AML cases (Stirewalt et al., 2001; Yamamoto et al., 2001; Yokota et al., 1997) and 37% of APL patients (Kottaridis et al., 2001). FLT3–ITDs induce a myeloproliferative disease in a murine bone marrow transplantation model but are insufficient to induce AML (Kelly et al., 2002b). This low frequency and long latency of APL pathogenesis induced by PML–RARα or FLT3–ITDs can be overcome by coexpression of both genes in the same animal. In this model, bone marrow cells derived from hCG-PML–RARα transgenic mice (Grisolano et al., 1997) were transducted with the FLT3–ITD retrovirus, followed by transplantation of transduced cells into lethally irradiated syngeneic recipient mice. These recipients developed APL-like disease with complete penetrance and a short latency. The pathogenesis of this disease resembles the APL-like disease that occurs with a long latency in the PML/RARα transgenic mice, suggesting that activating mutations in FLT3–ITD services as the additional mutations in APL progression in the hCG-PML–RARα transgenic mice.

Another example is the Ras oncogene. Ras mutations are commonly found in AML. N-ras and K-ras mutations are found in 4 (Callens et al., 2005) and 10% of APL patients (Bowen et al., 2005), respectively. Overexpressing oncogenic K-ras under the control of its endogenous promoter in the mouse hematopoietic system, K-ras induces a myeloproliferative disease, but it is not sufficient to induce AML (Braun et al., 2004; Chan et al., 2004). To test whether K-ras serves as a cooperative secondary genetic event in induction of AML, LSL-K-ras G12D mice (Jackson et al., 2001), in which K-ras expression is controlled by the conditional knock-in Lox-stop-Lox, were crossed with cathepsin G-PML–RARα mice (Grisolano et al., 1997) to generate LSL-K-ras $G12D^{+/-}$/cathepsin G-PML–$RAR\alpha^{+/-}$ mice (KP mice). Subsequently, these mice were crossed with Mx-1–Cre mice (Kuhn et al., 1995) to generate triple-transgenic LSL-K-ras $G12D^{+/-}$/cathepsin G-PML–$RAR\alpha^{+/-}$/Mx-1–$Cre^{+/-}$ mice (KPM mice). K-ras expression was induced by deletion of the Lox-stop-Lox with Cre, whose expression was induced with polyinosinic–polycytidylic acid (pI–pC) (Chan et al., 2006). Mice expressing oncogenic K-ras and PML–RARα developed an APL-like disease with a high penetrance and short latency compared to cathepsin G-PML–RARα transgene mice (Chan et al., 2006).

Acceleration of AML development with a chemical mutagen. As pointed out above, some oncogenes are, by themselves, insufficient to transform cells and induce leukemia. However, genetic modifications or changes of the model-making procedures, or the oncogene itself, or even mouse background would dramatically increase the penetrance of leukemogenesis. Mouse model of *AML1–ETO*-induced AML is such an example.

AML1–ETO (also known as RUNX1-ETO) is a fusion gene resulted from translocation between chromosomes 8 and 21. The translocation is highly associated with human AML and is present in up to 40% of leukemias of the French–American–British M2 subtype (Hess and Hug, 2004). AML1 is a key regulator of normal blood formation and is frequently altered in leukemias. However, it has been difficult to clarify the role of AML1–ETO in leukemogenesis, because AML1–ETO alone is not sufficient to cause AML, and AML1–ETO transgene causes embryonic lethality (Okuda et al., 1998, 2000). To bypass the embryonic lethality caused by AML1–ETO, conditional and inducible transgenic models, and bone marrow transplantation system were used to express AML1–ETO in mice; all these strategies were unable to reliably induce AML even after 24 months (de Guzman et al., 2002; Fenske et al., 2004; Higuchi et al., 2002; Rhoades et al., 2000), suggesting that induction of AML by AML1–ETO requires additional genetic events. However, when stem cells were transduced with AML1–ETO and transplanted into lethally irradiated recipient animals, the stem cell compartment expanded dramatically (de Guzman et al., 2002). Similarly, direct targeting of AML1–ETO expression to stem cells by using the SCA-1 promoter enhanced myeloid progenitor expansion (Fenske et al., 2004). These results imply that retroviral insertion sites or large numbers of leukemia-initiating progenitors provide the additional "hits" for AML1–ETO-induced leukemia. To assess the ability of AML1–ETO to induce leukemia in the context of cooperating mutations, animals expressing AML1–ETO were mutagenized with the alkylating agent *N*-ethyl-*N*-nitrosourea (ENU). In two independent systems, mutagenized AML1–ETO-expressing mice developed myeloid leukemia or granulocytic sarcoma at frequencies greater than ENU-treated wild-type animals (Higuchi et al., 2002; Yuan et al., 2001). These results confirm that AML1–ETO predisposes a myeloid precursor population to cellular transformation (Hess et al., 2004).

The AML1–ETO mouse model provides an excellent assay system to investigate AML1–ETO downstream signaling pathways. AML1–ETO was found to suppress cell proliferation by inhibiting its targeting genes, including cyclin D3 and CDK4 (Bernardin-Fried et al., 2004; Burel et al., 2001; Lou et al., 2000), and impair cell cycle in the transition of G1 to S phase (Burel et al., 2001). In addition, an AML1–ETO truncated protein (loss of C-terminal Nervy homology regions 3 and 4 domain), which binds the corepressor complexes associated with N-CoR (nuclear receptor corepressor) and SMRT (silencing mediator for retinoid and thyroid hormone receptor) (Lutterbach et al., 1998), can induce high penetrance of leukemia with a short disease latency (mean survival of 20 weeks) in the retroviral transduction/transplantation model (Yan et al., 2004). In this study, the results also showed that expression of cyclin A and D3 was increased in truncated AML1–ETO-transformed cells compared with full-length AML1–ETO-transformed cells. Taken together, these studies demonstrate that AML1–ETO alone is not sufficient to cause leukemia, and additional genetic changes that cooperate with AML1–ETO are required for the

development of AML. Obviously, AML1–ETO mouse models of AML will be helpful in study of genetic pathways involved in AML development.

Deletion of a tumor suppressor gene causes AML. Tumor suppressor genes play critical roles in regulating biological properties of cells, including cell cycle control, apoptosis, proliferation and differentiation, detecting and repairing DNA damage, and protein ubiquitination and degradation (Sherr, 2004). Deletions of tumor suppressor genes are associated with many types of tumors, and examples of tumor suppressor genes are *P53*, *RB*, *INK4a*, *ARF*, *APC*, *PTCH*, *SAMAD4*/*DPC4*, *PTEN*, *TSC1*/*2*, *NF1*, *WT1*, *MSH2*, *MLH1*, *ATM*, *NBS1*, *CHK2*, *BRCA1*/*2*, *FA*, and *VHL* (Sherr, 2004). The best AML model established by the deletion of a tumor suppressor gene is the removal of the *PTEN* gene in mice.

The *PTEN* gene was initially identified based on the observation that a loss of heterozygosity (LOH) at 10q23 was frequently detected in a variety of human tumors, and PTEN was later identified as the corresponding gene (Li et al., 1997). Further studies indicate that PTEN suppresses tumor cell growth by modulating G1 cell cycle progression through negatively regulating the PI3 K/Akt signaling pathway, and a critical target gene of this pathway is the cyclin-dependent kinase inhibitor p27 (KIP1) (Li and Sun, 1998). PTEN has been found to be associated with a series of primary acute leukemias and non-Hodgkin lymphomas (NHLs) as well as many tumor cell lines, and 40% of these cell lines carried PTEN mutations or hemizygous PTEN deletions. On the other hand, one-third of these cell lines had low PTEN transcript levels, and 60% of them had low or absent PTEN protein. Furthermore, a smaller number of primary hematologic malignancies, in particular NHLs, carried PTEN mutations (Dahia et al., 1999). To model AML induced by the deletion of the *PTEN* gene,

Ptenfl/fl mice (Lessard and Sauvageau, 2003) were crossed with Ptenfl/+ mice carrying an Mx-1–Cre (Park et al., 2003) transgene to generate litters containing Mx-1–Cre^{+} and Ptenfl/fl. PTEN deletion was induced by injection of pI–pC to mice at weaning. After the induction of PTEN deletion, mice had an increased representation of myeloid and T-lymphoid lineages in bone marrow and developed myeloproliferative disorder. Notably, the cell populations that expanded in PTEN-deficient mice matched those that became dominant in the acute myeloid/lymphoid leukemia that developed in later stages of myeloproliferative disorder. This study demonstrates that PTEN has essential roles in restricting the activation of HSCs, in lineage fate determination, and in the prevention of leukemogenesis (Zhang et al., 2006).

2.2.2 Modeling Chronic Myeloid Leukemia-Like Diseases

Chronic myeloid leukemia (CML) is represented by myeloproliferative disease induced by the BCR–ABL oncogene that results from the t(9;22)(q34;q22)

chromosomal translocation. Other CML-like diseases are induced by the fusion genes *TEL/PDGFβR* (Golub et al., 1994), *TEL/ABL* (Golub et al., 1995), *TEL/JAK2* (Lacronique et al., 1997), and *H4/PDGFβR* (Kulkarni et al., 2000; Schwaller et al., 2001), which are associated with t(5;12)(q33;p13), t(9;12)(q34;p13), t(9;12)(p24;p13), and t(5;10)(q33;q11.2) translocations, respectively. These fusion genes encode constitutively activated tyrosine kinases and are sufficient to induce myeloproliferative diseases in mice (Daley et al., 1990; Schwaller et al., 1998; Tomasson et al., 2000). Because BCR–ABL oncogene is associated with over 95% of human CML, we describe BCR–ABL-induced mouse CML models in detail in Chapter 7.

2.2.3 Modeling Acute Lymphoblastic Leukemia

ETV6/RUNX1 (TEL/AML1) results from a t(12;21)(p13;q22) chromosomal translocation and is the most common known gene rearrangement in childhood cancer. Twenty-seven percent of childhood ALL samples contain an ETV6/RUNX1 fusion transcript detected by the PCR screening. RUNX1 is a member of the heterodimeric core-binding factor (CBF) family of transcription factors and has been shown to regulate a number of genes relevant to myeloid and lymphoid development (Tenen et al., 1997). RUNX1 contains conserved Runt homology domain (RHD) in the N-terminal half, which can bind to DNA, and this DNA-binding activity is enhanced by interaction with the C-terminal portion of the CBF beta subunit (Fenrick et al., 1999; Kitabayashi et al., 1998; Levanon et al., 1998; Meyers et al., 1993). Recruitment of the AML1 complex to the enhancers of its target genes can be direct or cooperatively with other proteins (Pabst et al., 2001). ETV6 protein contains a helix-loop-helix (HLH) motif and an ETS DNA-binding domain. 12p13 translocations and deletions are highly associated with childhood ALL, suggesting that there is a tumor suppressor gene that is disturbed by these chromosomal changes. Detailed examination shows that the critically deleted region includes two candidate suppressor genes: *ETV6* and *KIP* (Stegmaier et al., 1995). ETV6/RUNX1 forms homodimers and forms heterodimers with the normal ETV6 protein when the two proteins were expressed together (Hess and Hug, 2004). Besides ETV6/RUNX1, ETV6 variably forms fusion genes with other genes, including *ETV6/MN1* (Raynaud et al., 1996), *ETV6/AML1* (Ford et al., 1998), *ETV6/JAK2* (Schwaller et al., 2000), *ETV6/ARNT* (Salomon-Nguyen et al., 2000b), *ETV6/MDS2* (Odero et al., 2002), *ETV6/PER1*, and *ETV6/ABL* (Papadopoulos et al., 1995).

To elucidate the mechanism of lymphoid transformation by ETV6/RUNX1, the ETV6/AML1 coding region was inserted into retroviral vector to allow expression of ETV6/AML1 in lineage-negative donor bone marrow cells in mice (Fischer et al., 2005). Although mice receiving ETV6/RUNX1-transduced bone morrow cells did not develop B cell ALL, ETV6/RUNX1 perturbed B-cell

differentiation by increasing the proportion of pro-B cells with low level of mature lymphoid cells in the blood and spleen, which is consistent with human precursor B cell ALL at an early stage. This mouse ALL model can be used for studying the mechanism of early stage of ETV6/RUNX1-induced ALL. Apparently, better disease models need to be developed with *ETV6/RUNX1* or other *ETV6*-related fusion genes to study the molecular basis of ALL.

2.2.4 Modeling Chronic Lymphocytic Leukemia

CLL is a common type of leukemia. There are about 10,000 new CLL cases in United States every year (Bichi et al., 2002; Landis et al., 1998), and CLL accounts for almost 30% of all adult leukemia cases. Most cases of CLL are of B-cell origin, and a few are of T-cell origin. B-CLL is believed to be derived from $CD5^+$ B lymphocyte through clonal expansion. Several common genomic abnormalities in CLL have been identified, and TCL1 is involved in the pathogenesis of CLL. The *TCL1* gene locates at chromosome 14q32.1 (Virgilio et al., 1994) and is commonly activated by inversions or translocations that juxtapose it to a T-cell receptor locus at 14q11 or 7q35. TCL1 has been found to be overexpressed in sporadic and ataxia telangiectasia-associated T-prolymphocytic leukemia (T-PLL) (Narducci et al., 1997; Thick et al., 1996). TCL1 is also highly expressed in a broad variety of human tumor-derived B-cell lines and in many cases of B-cell neoplasias (Narducci et al., 2000; Takizawa et al., 1998). To elucidate the role of *TCL1* in B-cell development and in B-cell leukemia pathogenesis, TCL1 transgenic mouse has been generated by cloning human *TCL1* coding region into the pBSVE6BK (pEμ) plasmid containing a mouse VH promoter (V186.2) and the IgH-μ enhancer along with the 3′-untranslated region and the poly(A) site of the human beta-globin gene, followed by injecting the *TCL1*-containing construct free from vector sequences into fertilized oocytes from B6C3 mice. In this model, *TCL1* was under the control of a promoter and enhancer whose activity specifically targets expression of the *TCL1* transgene to the B-cell compartment. Eμ-TCL1 transgenic mice developed a disease similar to human CLL. The mice first developed a preleukemic phenotype and later developed a frank leukemia with all characteristics of CLL (Bichi et al., 2002).

TNF receptor-associated factors (TRAFs) are a family of adapter proteins that link TNF-family receptors (TNFRs) to intracellular signaling pathways. It has been demonstrated that TRAF-family members participate in signaling cascades involved in gene expression, cell proliferation, and control of apoptosis. Elevated expression of some TRAF-family proteins, in particular TRAF1, is found in hematopoietic malignancies such as CLL and NHL (Munzert et al., 2002; Zapata et al., 2000). A study shows that TRAF1 and TRAF2 mediated apoptosis protection (Arron et al., 2002; Lin et al., 2003; Wang et al., 1998), suggesting that these TRAF family members could participate in the

Table 2.1 Examples of mouse models of human blood cancers

Chromosomal translocation	Fusion gene	Leukemia type	Disease frequency	Mouse models (approaches)	Citations
t(15;17)(q22-q11.2-12)	*PML–RARα*	AML	10% (98%)	Transgene, retroviral transduction of bone marrow cells	(Chan et al., 2006; Grisolano et al., 1997; Kelly et al., 2000a; Westervelt et al., 2003)
t(8;21)(q22;q22)	*AML1–ETO*	AML	18% (30%)	Transgene, retroviral transduction of bone marrow cells	(de Guzman et al., 2002; Fenske et al., 2004; Yan et al., 2004)
t(11;17)(q23;q21)	*PLZF–RARα*	AML	Rare	Transgene	(Rego et al., 2006)
inv(16) or t(16;16)	*CBFβ–MYH11*	AML	8% (∼100%)	Conditional transgene	(Kuo et al., 2006)
t(9;11)(p22;q23)	*MLL–AF9*	AML	11% (30%)	Knock-in	(Dobson et al., 1999)
t(6;11)(q27;q23)	*MLL–AF6*	AML	11q23 abnormalities are detected in ∼35% of all AML		(Joh et al., 1997; Poirel et al., 1996)
t(10;11)	*MLL–AF10, CALM–AF10*				(Borkhardt et al., 1995a)
t(11;17)(q23;q21)	*MLL–AF17*				(Suzukawa et al., 2005)
t(11;19)(q23;p13.3)	*MLL–ENL/ENL/EEN*			Retroviral transduction of bone marrow cell	(DiMartino et al., 2000; Rubnitz et al., 1999)
t(4;11)(q21;q23)	*MLL–AF4*			Knock-in	(Chen et al., 2006; Domer et al., 1993)
t(6;9)(p23;q34)	*DEK–CAN*	AML	1%		(Soekarman et al., 1992; von Lindern et al., 1992)

Table 2.1 (continued)

Chromosomal translocation	Fusion gene	Leukemia type	Disease frequency	Mouse models (approaches)	Citations
t(16;21)(p11;q22)	*TLS (FUS)–ERG*	AML	<1%		(Ichikawa et al., 1994; Kong et al., 1997; Panagopoulos et al., 1994)
t(16;21)(q24;q22)	*AML1–MTG16*	t-AML, MDS	<1%		(La Starza et al., 2001; Salomon-Nguyen et al., 2000a)
t(3;21)	*AML1–EVI1* *AML1–EAP* *AML1–MDS1*	AML	<1%	Knock-in	(Maki et al., 2005)
t(7;11)(p15;p15)	*NUP98–HOXA9*	AML	<1%	Retroviral transduction of bone marrow cells	(Kroon et al., 2001; Nakamura et al., 1996)
t(1;11)(q23;p15)	*NUP98–PMX1*	AML			
t(8;16)(p11;p13.3)	*MOZ–CBP*	AML	<1%		(Borrow et al., 1996)
inv(8)(p11q13)	*MOZ–TIF2*	AML	<1%	Retroviral transduction of bone marrow cells	(Deguchi et al., 2003)
t(8;22)(p11;p13)	*MOZ–p300*	AML	<1%		(Imamura et al., 2003; Kitabayashi et al., 2001b)
t(12;22)(p12;q23)	*TEL–MN1*	AML, CML	<1%		(Buijs et al., 1995; Nakazato et al., 2001)

Table 2.1 (continued)

Chromosomal translocation	Fusion gene	Leukemia type	Disease frequency	Mouse models (approaches)	Citations
t(1;229)(p13;q13)	*OTT–MAL*	AML	<1%		(Ma et al., 2001; Mercher et al., 2001)
t(5;12)(q33;p12)	*TEL–PDGFRβ*	CMMoL	2–5%	Transgene; retroviral transduction of bone marrow cells	(Ritchie et al., 1999; Sawyers and Denny, 1994; Tomasson et al., 2000; Wlodarska et al., 1995)
t(9;22)(q34;q11.2)	*BCR–ABL*	CML	~ 98%	Retroviral transduction of bone marrow cells; tetracycline inducible system	(Koschmieder et al., 2005; Li et al., 1999)
t(1;19)(q23;p13.3)	*E2A–PBX1*	Pre-B ALL	6% (30%)		(Kamps et al., 1991)
t(17;19)(q22;p13.3)	*E2A–HLF*	Pro-B ALL	1%	Transgene	(Honda et al., 1999; Hunger et al., 1992)
t(12;21)(p12;q22)	*TEL–AML1*	Pre-B ALL	25%	Retroviral transduction of bone marrow cells	(Bernardin et al., 2002; Tsuzuki et al., 2004)
t(9;22)(q34;q11.2)	*BCR–ABL*	ALL	~5% of childhood ALL; 30% of adult B-ALL	retroviral transduction of bone marrow cells; knock-in	(Castellanos et al., 1997; Li et al., 1999)
t(4;11)(q21;q23)	*MLL–AF4*	Pre-B ALL	5%	Knock-in	(Chen et al., 2006; Domer et al., 1993)

Table 2.1 (continued)

Chromosomal translocation	Fusion gene	Leukemia type	Disease frequency	Mouse models (approaches)	Citations
t(9;11)(p22;q23)	*MLL–AF9*	Pre-B ALL	<1%	Knock-in	(Dobson et al., 1999)
t(11;19)(q23;p13.3)	*MLL–ENL*	Pre-B ALL, T-ALL	1%	Retroviral transduction of bone marrow cell	(DiMartino et al., 2000; Rubnitz et al., 1999)
t(X;11)(q13;q23)	*MLL–AFX1*	T-ALL	<1%		(Corral et al., 1993)
t(1;11)(p32;q23)	*MLL–AFP1*	ALL	<1%		(Borkhardt et al., 1995b)
t(6;11)(q27;q23)	*MLL–AF6*	ALL	<1%		(Joh et al., 1997; Poirel et al., 1996)
t(2;5(2p23;q35)	*NPM–ALK*	Lymphoma ALCL, NHL	75%	Retroviral transduction of bone marrow cell; transgene	(Chiarle et al., 2003; Jager et al., 2005; Kuefer et al., 1997; Miething et al., 2003)

The percentage refers to the frequency of the translocations within the disease overall. The values within parentheses refer to the frequency within the morphologic or immunologic subtype of the disease. ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; CMMoL, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome; NHL, non-HodgkinÂ's lymphoma. (Referred and modified from http://emice.nci.nih.gov/emice/mouse_models/organ_models/hema_models/hema_appendix_two.)

apoptosis-resistant phenotype of CLL and NHL. To model TRAF-mediated CLL, transgenic mice, which expressed in lymphocytes a TRAF2 mutant lacking the RING and zinc finger domains located at the N-terminus of TRAF2 (TRAF2DN), developed splenomegaly and lymphadenopathy, as a result of a polyclonal expansion of B lymphocytes (Lee et al., 1997). In addition, transgenic mouse expressing Bcl-2 in B lymphocytes developed age-dependent lymphadenopathy and splenomegaly (Katsumata et al., 1992), associated with lymphoid cell expansions resembling certain human low-grade B-cell malignancies (Katsumata et al., 1992; Strasser et al., 1993). When both TRAF2DN and Bcl-2 transgenic mice were crossed to generate double transgenic mice, the double homozygous mice develop an age-dependent B-cell leukemia and lymphoma, with striking similarities to human CLL. These findings also provide direct evidence that TRAFs contribute to CLL development and that the high coexpression levels of TRAF1 and Bcl-2 commonly found in human CLL contribute to the pathogenesis of this leukemia (Zapata et al., 2000).

2.3 Conclusion

Although many mouse models of human blood cancers (Table 2.1) are available for the study of disease mechanisms and the development of new therapeutic strategies, improvements are needed to more accurately mimic human blood cancers. On the other hand, mouse models of many types of human leukemia induced or accelerated by fusion genes and other mutated genes are not yet available (Table 2.1), and generation of these disease models will be of important value.

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