VOLUME 23 · NUMBER 26 · SEPTEMBER 10 2005

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Molecular Genetics of Acute Lymphoblastic Leukemia

Scott A. Armstrong and A. Thomas Look

From the Department of Pediatric Oncology, Dana-Farber Cancer Institute; and the Division of Hematology/Oncology, Children's Hospital, Harvard Medical School, Boston, MA.

Submitted May 24, 2005; accepted June 1, 2005.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Scott A. Armstrong, MD, PhD, Children's Hospital, Karp Research Labs, Rm 08211, 1 Blackfan Circle, Boston, MA 02115; e-mail: Scott.Armstrong@childrens.harvard.edu.

0732-183X/05/2326-6306/$20.00

DOI: 10.1200/JCO.2005.05.047

ABSTRACT

From its beginnings two decades ago with the analysis of chromosomal translocation breakpoints, research into the molecular pathogenesis of acute lymphoblastic leukemia (ALL) has now progressed to the large-scale resequencing of candidate oncogenes and tumor suppressor genes in the genomes of ALL cases blocked at various developmental stages within the B- and T-cell lineages. In this review, we summarize the findings of these investigations and highlight how this information is being integrated into multistep mutagenesis cascades that impact specific signal transduction pathways and synergistically lead to leukemic transformation. Because of these advances, fueled by improved technology for mutational analysis and the development of small-molecule drugs and monoclonal antibodies, the future is bright for a new generation of targeted therapies. Best illustrated by the successful introduction of imatinib mesylate, these new treatments will interfere with disordered molecular pathways specific for the leukemic cells, and thus should exhibit much less toxicity and fewer long-term adverse effects than currently available therapeutic modalities.

J Clin Oncol 23:6306-6315. © 2005 by American Society of Clinical Oncology

INTRODUCTION

Great strides have been made in the understanding of the molecular pathophysiology of acute lymphoblastic leukemia (ALL). The cloning and characterization of recurrent chromosomal translocations has allowed the identification of genes critical for the leukemogenic process.[1] Furthermore the presence of particular translocations often has prognostic importance and can be used to stratify patients into those who require more-intensive therapy. The use of gene expression analysis to characterize the differences in gene expression between leukemias with different chromosomal aberrations has solidified the notion that specific chromosomal abnormalities specify unique leukemias.[2-4] More recently, mutations in specific signaling molecules have been identified in B-precursor and T-precursor ALL that might be targeted with small molecule inhibitors.[5-7] These developments have generated much excitement about the possibility for development of therapies that are designed based on the specific genetic aberrations present in individual leukemias. This review will outline some of the more recent findings delineating the molecular genetics of ALLs. Although the review is divided into adult, childhood, and infant ALL, data are accumulating in which similar molecular defects share similar pathophysiology across the different age groups.[8] Molecular pathophysiology will be described in the age group in which the genetic abnormalities are the most common.

CHILDHOOD ALL

B-Precursor ALL

B-precursor ALL is the most common form of acute leukemia in children and thus represents the most common malignancy of childhood. As a group, children diagnosed with B-precursor ALL have a good prognosis. Recent treatment protocols from groups in Europe and the United States demonstrate an event-free survival of

approximately 80% for children between the ages of 1 and 18 years.[9-12] While this represents a remarkable improvement over the dismal cure rates only 30 years ago, most believe that further improvement will require the development of new therapeutic approaches—approaches that will likely come from a better understanding of the molecular pathophysiology of leukemia. Furthermore, long-term adverse effects remain a troublesome problem for the increasing numbers of survivors of childhood leukemia.[13]

Recurrent chromosomal abnormalities are a hallmark of lymphoblastic leukemias and provide insight into the molecular mechanisms of leukemogenesis. The most common translocation found in childhood B-precursor ALL is the t(12;21)(p13;q22). Although standard karyotypic analysis does not identify most *TEL-AML1* translocations, molecular techniques demonstrate the presence of this translocation in approximately 25% of childhood ALL (Fig 1). Microarray-based gene expression studies have shown that *TEL-AML1*–rearranged ALLs represent a unique biologic subset of B-precursor ALL.[3] Elegant epidemiologic data demonstrating the presence of the *TEL-AML1* translocation in neonatal blood spots shows that the translocation is present in blood cells at birth, up to 5 to 10 years before the development of leukemia.[14] These data provide convincing evidence that the *TEL-AML1* translocation is the initiating event in this leukemia.

The TEL-AML1 fusion protein generated by the t(12;21) contains the basic helix-loop-helix domain of TEL, fused to the DNA-binding and transactivation domains of AML1. Both the *TEL* and *AML1* genes are found in other leukemia-associated translocations. *TEL* was originally cloned as a fusion partner of the platelet-derived growth factor receptor β gene (*PDGFR*β) encoded by the t(5;12) in chronic myelomonocytic leukemia[15] and is found in other translocations associated with genes such as *MN1*, *ABL*, and *EVI1* in AML, and with *JAK2* in T-ALL.[16] AML1 is the DNA-binding component of the AML1/CBFβ transcription factor complex, the most frequent target of myeloid-associated translocations, including the t(8;21), t(3;21), and inv(16).[17] The prominent role of AML1 (also known as RUNX1) in the pathogenesis of human leukemias is reinforced by the identification of inherited or acquired mutations in AML1 in acute myelogenous leukemias (AMLs)[18]; and the presence of genomic amplifications of the *AML1* locus in childhood ALL.[19]

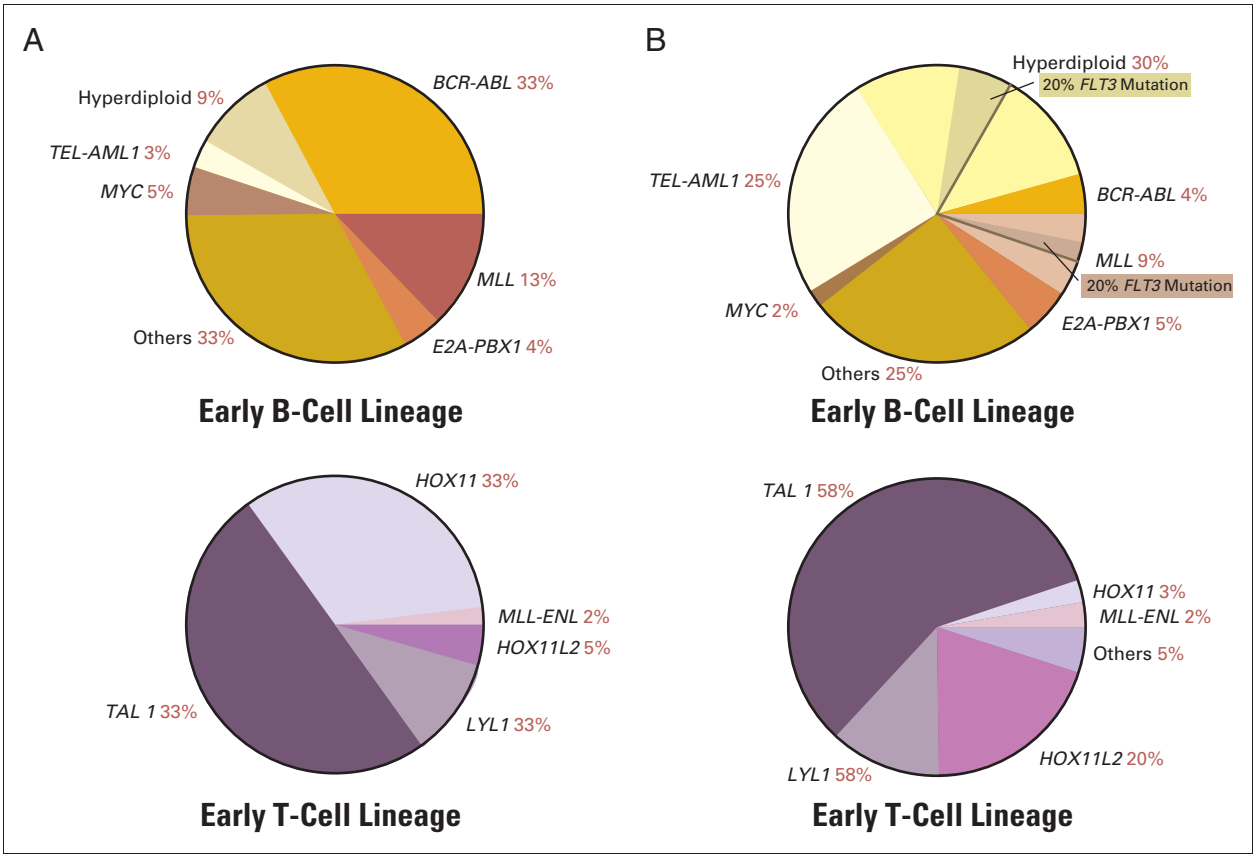

Fig 1. Chromosomal abnormalities in acute lymphoblastic leukemia. The relative frequencies of chromosomal aberrations found in lymphoblastic leukemias are shown for (A) adult and (B) childhood (right) acute lymphoblastic leukemias. The groups are divided into early B-cell lineage and early T-cell lineage.

Although the mechanisms of leukemogenesis induced by TEL-AML1 remains obscure, recent data have demonstrated the importance of both TEL and AML1 for normal hematopoiesis, thus suggesting that the presence of the TEL-AML1 fusion protein leads to disordered hematopoietic development as a critical component. *Tel*-deficient mice die at approximately day 11 of embryogenesis associated with defective yolk sac angiogenesis, thus establishing Tel as an important regulator of development.[20] Recently, studies in mice using conditional inactivation of *Tel* alleles have shown that *Tel* is required for definitive hematopoiesis.[21,22] In addition, the observation that loss of the normal *TEL* allele frequently accompanies TEL-AML1 fusion in ALL cases suggests that the leukemogenic effects of TEL-AML1 could be mediated, at least in part, through loss of function of the normal TEL protein.[23-25] The absence of definitive hematopoiesis in mice lacking either AML1 or CBFβ further supports an essential role for the AML1-CBFβ complex in normal hematopoiesis.[17,26-29] These results also suggest that a lack of expression of genes normally activated by AML1 may be important in leukemogenesis.

TEL-AML1 expression is associated with an excellent prognosis, with event-free survival rates approaching 90%.[24,30-32] In addition, the favorable prognostic impact of TEL-AML1 is independent of age and leukocyte count and was consistently favorable among patients treated on several different protocols.[31,32] Thus, TEL-AML1 expression identifies a large subset of B-precursor ALL patients who may be candidates for less-intensive therapy.

Another common chromosomal aberration found in B-precursor ALL is the presence of more than 46 chromosomes (hyperdiploid ALL). As with *TEL-AML1*–rearranged ALL, gene expression studies demonstrated that hyperdiploid ALL represents a separate genetically defined subset of B-precursor ALL[3]. But, the lack of a recurrent abnormality in specific genes identifiable by karyotypic analysis has prevented the identification of initiating events in this leukemia. Potential insight into the mechanism of leukemogenesis in hyperdiploid ALL came recently when activating mutations in the receptor tyrosine kinase FLT3 were identified in approximately 20% of hyperdiploid ALL.[6,33] This finding is intriguing not only in that it points to activated tyrosine kinases as potential oncogenes in hyperdiploid ALL, but also in that it suggests that small-molecule tyrosine kinase inhibitors might be of benefit to patients with this leukemia. Given that patients with hyperdiploid ALL have an extremely good prognosis with event-free survival rates near 90%, it will be a challenge to determine how to incorporate such therapeutics into treatment regimens.

The t(1;19)(q23;p13) encoding the E2A-PBX fusion protein is present in about 6% of all B-precursor ALLs and in 25% of cases with a preB (cytoplasmic immunoglobulin-positive) immunophenotype.[34-36] The t(1;19)(q23;p13) fuses the transactivation domain of the bHLH transcription factor *E2A* on chromosome 19, to the homeobox (*HOX*) gene *PBX1* on chromosome 1.[37-39] E2A contains a bHLH domain responsible for sequence-specific DNA binding and dimerization, and plays a critical role in lymphocyte development.[40,41] Given that *E2A*-deficient mice show significant defects in lymphoid development and the t(1;19) impairs one copy of the *E2A* locus, loss of E2A function may contribute to leukemogenesis in this subtype of ALL. Furthermore, given the clear role of *HOX* genes in leukemogenesis, and the ability of PBX1 to alter *HOX* gene dependent regulatory programs, dysregulation of PBX1 function likely contributes to leukemogenesis.[42]

T-Precursor ALL

bHLH, HOX, *and other developmental genes.* Transcription factor genes are the preferred targets of chromosomal translocations in the acute T-cell leukemias. Notable examples include the bHLH genes *MYC*,[43-45] *TAL1*(*SCL*),[46-48] and *LYL1*,[49] which are essential for the development of other lineages such as erythroid cells (*TAL1*), but with the exception of *MYC*, they are not normally expressed in T-lymphoid cells. When rearranged near enhancers within the *TCR*β-chain locus on chromosome 7, band q34, or the α/δ-chain locus on chromosome 14, band q11, these regulatory genes become active, and their protein products bind inappropriately to the promoter or enhancer elements of downstream target genes.

A useful model of aberrant transcription factor expression in T-ALL is provided by *TAL1* activation due to the t(1;14) or to an intragenic deletion upstream of the gene, changes that characterize as many as one fourth of all cases of childhood T-ALL.[50] Because the TAL1 protein forms a pentameric DNA-binding complex with E2A, LMO2, GATA1 and LDB1,[51] its ectopic expression in T cells might be expected to activate specific sets of target genes that are normally quiescent in T-cell progenitors. Alternatively, TAL1 might be leukemogenic via a dominant-negative effect, since overexpression of TAL1 can lead to a functional inactivation of E2A homodimers or E2A-HEB heterodimers, presumably by sequestering E2A in the aforementioned pentameric complex. This model is supported by the observations that E2A-deficient mice develop T-ALL,[52,53] and that mice expressing the E2A inhibitor Id in the thymus also develop T-ALL.[54] Moreover, mice that express TAL1 mutant proteins able to heterodimerize with E2A, but unable to bind DNA, develop a form of T-ALL that is indistinguishable from that produced by the full-length SCL protein.[55-57]

In addition to genes encoding bHLH proteins, additional classes of regulatory genes are rearranged near *TCR* loci, including those encoding the proteins LMO1

(formerly known as RBTN1 or TTG1) and LMO2 (formerly known as RBTN2 or TTG2) within the cysteine-rich LIM family.[58,59] Although present in high concentrations in the central nervous system,[60] these proteins are only minimally expressed or absent altogether in T cells and their progenitors. Both LMO1 and LMO2 possess zinc-finger–like structures in their LIM domains but lack the DNA-binding domains common to other transcription factors in this family, suggesting that the LIM domain functions in protein-protein rather than protein-DNA interactions. Conceivably, it could even mediate the action of other transcription factors, as indicated by the ability of LMO2 to bind to the bHLH protein TAL1 in vitro.[61,62] Moreover, LMO1 induces thymic lymphomas in transgenic mice whose thymocytes bear the *LMO1* gene under the control of a proximal *Lck* promoter.[63] In this context, inappropriate expression of a LIM family protein appears to have selectively transformed a rare subset of $CD8^+$, $CD4^-$, $CD3^-$ thymocytes. The t(11;14)(p15;q11) and t(11;14)(p13;q11) are thought to affect similar T-cell developmental pathways by inducing ectopic expression of either LMO1 or LMO2.

In a recent gene therapy trial in infants with X-linked severe combined immune deficiency due to underproduction of the common gamma subunit of the interleukin (IL) -2 receptor, two children whose immune systems had been reconstituted successfully using a retroviral vector carrying a cDNA for the common γ chain gene have developed T-ALL. Strikingly, the malignant cells from both of these patients showed that the retroviral particle had integrated near the *LMO2* gene, leading to its overexpression in the malignant lymphoblasts.[64-66] This observation indicates that *LMO2* can be activated iatrogenically by the nearby insertion of a highly active retroviral promoter, as well as by chromosomal translocation.

HOX11, *HOX11L2*, and also major *HOX* genes complete the list of developmental genes that are inappropriately placed under the control of *TCR* loci. Located on chromosome 10, band q24,[67-70] *HOX11* encodes a homeodomain transcription factor that can bind DNA and transactivate specific target genes.[71] It is most closely related to *Hlx*, a murine homeobox gene expressed in specific hematopoietic cell lineages and during mouse embryogenesis,[72] and it is distantly related to the *antennapedia* homeobox genes of *Drosophila*, which regulate segment-specific gene expression along the anteroposterior axis of the fly embryo.[73] A specific role of *HOX11* in mammalian development was demonstrated by homozygous disruption of this gene, which blocked the formation of the spleen in otherwise normal mice.[74] In the mouse, *Hox11* is normally expressed in specific regions of the branchial arches and ectoderm of the pharyngeal pouches of the developing hindbrain, as well as from a single site corresponding to the splanchnic mesoderm beginning on embryonic day 11.5.[74] Because the nervous system develops normally in these mice, the roles of Hox11 proteins in branchial arch and hindbrain structures appear to be compensated for by other transcription factors expressed by the cells; however, the role of Hox11 in cellular organization at the site of splenic development is absolutely essential for the genesis of this organ. Lymphoid and other types of hematopoietic cells, normally lacking expression of Hox11 proteins, were not affected by loss-of-function mutations in this gene, except for the presence of asplenia-related Howell-Jolly bodies in circulating erythrocytes. Activation of *HOX11* expression by chromosomal translocations, either the t(10;14)(q24;q11) or the t(7;10)(q35;q24), in developing T cells must therefore interfere with normal regulatory cascades to promote malignant transformation. Interestingly, *HOX11* expression by T-ALL blasts is associated with a favorable prognosis in children treated with modern intensive therapy, possibly because these leukemias have a gene expression signature reflecting an arrest at the early cortical thymocyte stage with downregulation of anti-apoptotic proteins such as BCL2 and $BCLX_L$.[4]

In addition, the *HOX11L2* gene, located at chromosome 5 band q35, has been found to be activated by translocation near the *BCL11B* locus as a result of the t(5;14)(q35;q32), or by fusion to the *TCRδ* locus as a result of the t(5;14)(q35;q11). Although neither of these translocations is commonly recognized with use of conventional cytogenetic techniques, almost 20% of childhood T-ALL patients demonstrated a *HOX11L2* gene translocation by fluorescence in situ hybridization.[75] Although some studies have suggested that T-ALL patients whose lymphoblasts overexpress *HOX11L2* have a poor prognosis, this finding appears to be eliminated in children who receive more-intensive therapy.[76]

More recently, a new recurrent translocation has been recognized that targets and dysregulates expression from the whole HOXA cluster.[77] Thus, this translocation mimics the global *HOXA* gene dysregulation characteristic of T-ALLs with *MLL* gene fusions, as discussed in the next section. Gene expression analysis demonstrates that this subgroup shares aspects of the gene expression signature characteristic of *HOX11*- and *HOX11L2*-overexpressing T-ALLS.

Fusion genes in T-ALL. Although most chromosomal translocations in T-ALL patients lead to inappropriate activation of structurally intact cellular proto-oncogenes such as *MYC*, *TAL1*, *HOX11* or *LMO2*, some can produce fusion genes. *MLL-ENL* fusion results from the translocation t(11;19)(q23;p13), and is associated with acute myeloid leukemia, B-cell precursor ALL, and T-ALL. Strikingly, in one series, all 11 T-ALL patients with the *MLL-ENL* fusion became long-term survivors, suggesting that this rearrangement is associated with a good prognosis.[78] Gene expression array analysis showed that these cases overexpress major

HOX genes such as *HOXA9* as well as *MEIS1*, resembling the expression signature identified in B-lineage leukemias with *MLL* fusion genes.[79] The *CALM-AF10* fusion gene was initially identified in the U937 cell line, which was established from a patient with histiocytic lymphoma and shown to differentiate along the macrophage lineage in vitro.[80] Subsequently, *CALM-AF10* was found in patients with a wide spectrum of hematologic malignancies, but most commonly in patients with T-ALL.[81-84] *CALM-AF10* fusions were identified in 12 (9%) of 131 consecutive patients with T-ALL. Of note, all of the patients with *CALM-AF10* fusions had either immature T-cell lymphoblasts that expressed no *TCR* genes or γ/δ-positive lymphoblasts. None of the patients with *CALM-AF10* fusions expressed *TCR*α/β, suggesting that such fusions are restricted to the *TCR*γ/δ lineage.[85]

NOTCH1 *gene mutations in T-ALL.* Very rare cases of T-ALL harbor chromosomal translocations that produce a truncated and activated form of *NOTCH1*, a gene that normally encodes a transmembrane receptor, as shown in Figure 2, that is involved in the regulation of normal T-cell development and may other tissues during embryologic development.[86] The NOTCH-1 protein is generated as a pro-protein that is synthesized and then cleaved into a heterodimer by a furin-like protease. This heterodimer migrates to the cell membrane where signals from its ligands, which consist of Delta-Serrate-Lag2 family proteins, lead to further cleavages, including a final step catalyzed by the enzyme gamma-secretase. This final step generates an intracellular NOTCH protein, which translocates to the nucleus and forms a complex with the CSL protein and Mastermind cofactors to initiate transcription.[87-89] *NOTCH-1* had previously been shown to be truncated and activated by a rare t(7;9) in T-cell ALL[86] and the same activated fragment was shown to induce T-cell ALL in mouse models.[90-92] To uncover more frequent types of NOTCH1-activating mutations, we[7] tested several T-cell leukemia cell lines with a drug known to inhibit gamma-secretase and found evidence of cell-cycle arrest that was subsequently proven to be *NOTCH-1* specific. We were able to identify specific mutations in sequences encoding both the heterodimerization and PEST domains of NOTCH1 in these cell lines, and subsequently in over 50% of primary patient T-cell ALL samples, including samples from all of the molecular subtypes of T-cell leukemia (Fig 3).

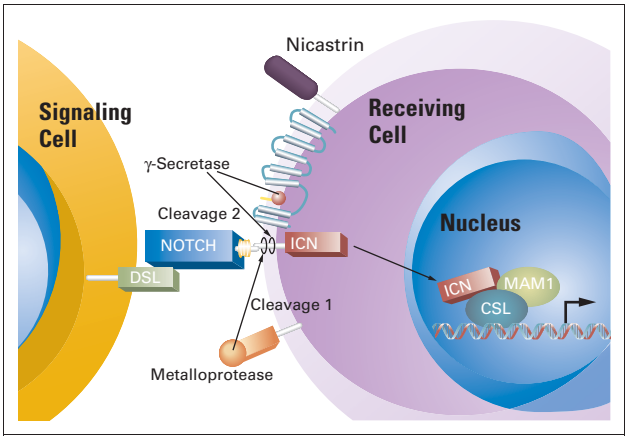

Fig 2. Activation of notch signaling via extracellular and intracellular proteolytic cleavage and nuclear translocation of the intracellular NOTCH domain (ICN). Interaction with delta serrate ligand (DSL) stimulates NOTCH extracellular cleavage by metalloproteases and intracellular cleavage by gamma-secretase. After proteolytic cleavage, the ICN moves to the nucleus where it interacts with Mastermind-like proteins (MAM1) and the CSL (CBF1 in humans, Su[H] in *Drosophila*, and Lag-1 in *Caenorhabditis elegans*) DNA-binding component to regulate gene expression.

INFANT ALL

Leukemias bearing translocations involving chromosome 11q23 are found in leukemic blasts from > 70% of leukemias in patients younger than 1 year of age whether the immunophenotype is designated AML or ALL.[93] Some infant leukemias express antigens characteristic of both lymphoblasts and monoblasts, and are sometimes designated acute biphenotyic leukemias. Infants diagnosed with ALL harboring an 11q23 rearrangement have a particularly poor prognosis as compared to other children with ALL.[94] The association of 11q23 rearrangements with either ALL or AML is unique in that most other translocations tend to be associated with leukemias of a particular hematopoietic lineage. These observations prompted the name mixed-lineage leukemia (*MLL*) for the gene on 11q23.

The *MLL-AF4* gene generated by the t(4;11)(q21;q23) was cloned in the early 1990s. *MLL-AF4* encodes a protein of 2304 amino acids, with the NH_2-terminal 1439 amino acids derived from *MLL* on chromosome 11, and COOH-terminal 865 amino acids from the *AF4* gene on chromosome 4.[95-98] Subsequently, more than 40 different translocations have been identified, all of which produce a fusion protein possessing the NH_2-terminus of MLL fused to COOH-terminus of the fusion partner.[99] Although *MLL* translocations can be found in either ALL or AML, particular translocations are associated with hematopoietic lineage with the t(4;11) found most often in ALL and the t(9;11)(p21;q23) AML. But this specificity is not absolute in that the t(9;11) is also frequently identified in blasts designated as ALL. The association of particular translocations with a specific immunophenotype suggests that the fusion partner plays a role, but the molecular details of this association are unclear.

The *MLL* gene encodes a 3969 amino acid DNA-binding protein that possesses multiple protein motifs including an NH_2-terminal DNA binding domain, transcriptional activation and repression domains, and a COOH-terminal SET domain that contains histone methyltransferase activity.[100,101] Of interest, the MLL protein is

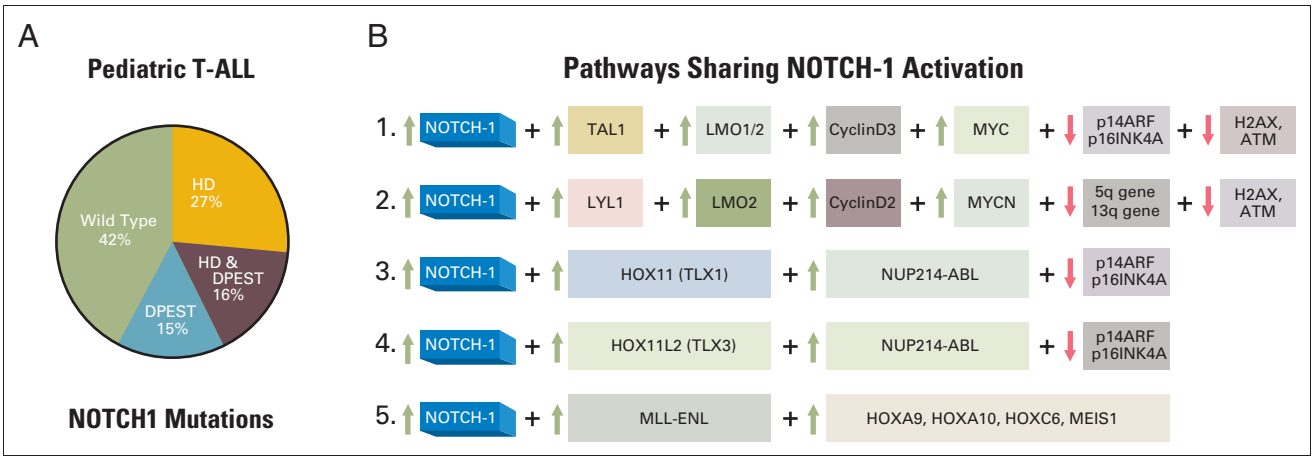

Fig 3. Frequency of *NOTCH1* mutations and the role of multistep molecular pathways in the pathogenesis of T-ALL. (A) *NOTCH1* mis-sense mutations were identified within the heterodimerization domain (HD) in 27% of childhood T-ALL blasts, truncating mutations that deleted the PEST destruction box (DPEST) were identified in 15%, and both regions were simultaneously mutated in the same *NOTCH1* gene in 16% of cases, providing evidence for multi-hit mutagenesis affecting a single oncogene in primary T-ALL samples at diagnosis. Only 42% of cases had unmutated *NOTCH1* genes. (B) These mutations were shown to occur in each of the at least five multistep molecular pathways that can lead to the transformation of T-cell progenitors during development, suggesting that some form of NOTCH pathway disruption may be required as a first step regardless of the additional genes that ultimately become mutated. *HOX11*$^+$, *HOX11L2*$^+$ and *TAL1*$^+$ cases show high levels of *MYC* expression and share the loss of the tumor suppressor genes *p16/INK4A* and *p14/ARF* on chromosome 9p. *HOX11*$^+$ and *HOX11L2*$^+$ often have a novel *NUP214-ABL* episomal fusion gene, which may render these T-ALLs sensitive to imatinib. *LYL1*$^+$ cases show high levels of expression of *N-MYC* and frequently have deletions affecting as yet unidentified loci on chromosomal arms 5q and 13q. Finally, *MLL-ENL*$^+$ cases have low levels of expression of *MYC* and other genes involved in cell growth and proliferation. This subset of T-ALL cases express high levels of HOXA9, HOXA10, and HOXC6, in concert with the *HOX* gene regulator *MEIS1*, which is different from other T-ALL cases.

cleaved into two subunits by a recently identified novel protease.[102-104] Analysis of *Mll* knockout mice suggests that *Mll* plays an important role in development and hematopoiesis through maintenance of appropriate homeotic (*Hox*) gene expression.[105-108] The ability of *Mll* to regulate *Hox* gene expression suggests that its role in both hematopoiesis and leukemogenesis may be mediated by altering patterns of *Hox* gene expression. Multiple studies have demonstrated the ability of *Hox* genes to induce leukemia in mice,[109] and the t(7;11)(p15;p15) translocation found in some human acute myeloid leukemias results in a fusion of the *HOXA9* gene to the nucleoporin *NUP98*.[110,111] Given the apparent importance of *HOX* genes in leukemogenesis, it seems likely that translocations involving *MLL*, a known regulator of *HOX* genes, alters expression of *HOX* genes that are critical for leukemogenesis.

We recently found the receptor tyrosine kinase FLT3 to be highly expressed in *MLL*-rearranged ALL as compared with other acute leukemias.[2] This prompted further assessment of FLT3 in this disease, in which we found approximately 20% of *MLL*-rearranged ALL samples to possess activating mutations in the activation loop region.[5] These data support the idea that leukemogenic fusion proteins such as MLL fusions cooperate with activated kinases to promote leukemogenesis (Fig 4).[112] Furthermore, FLT3 inhibitors appear to have activity against *MLL*-rearranged and hyperdiploid ALL, in vitro and in murine models.[5,113] Clinical trials to assess the efficacy of FLT3 inhibitors in *MLL*-rearranged ALL are in development.

ADULT ALL

B-Precursor ALL

Unlike adult B-precursor ALL, in which t(9;22) is identified in approximately 33% of cases, this translocation encoding the BCR-ABL fusion protein is found in only 5% of childhood cases (Fig 1).[34,114] This difference in frequency partially accounts for the difference in outcome between adults diagnosed with B-precursor ALL as compared with children diagnosed with B-ALL because both children and adults with *BCR-ABL* rearranged

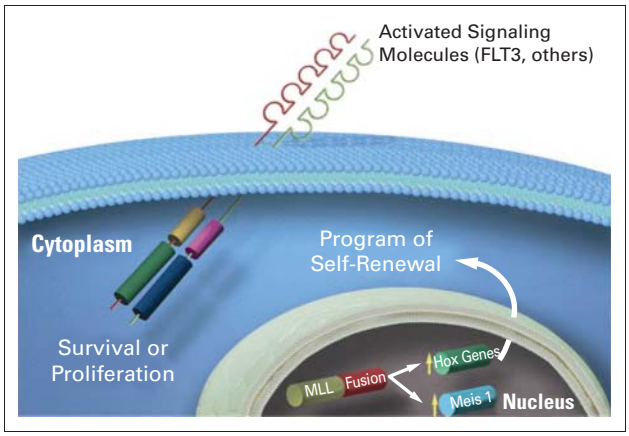

Fig 4. Multi step pathogenesis of *MLL*-rearranged lymphoblastic leukemias. *MLL* translocations induce self-renewal in hematopoietic progenitors as a first step in leukemogenesis. The presence of FLT3 mutations in *MLL*-rearranged ALLs support activation of FLT3 or other kinases as cooperating events in this disease. Clinical trials designed to assess the efficacy of FLT3 inhibitors in *MLL*-rearranged ALL are being developed.

B-ALL have a poor prognosis.[114-116] Due to this poor prognosis with standard ALL-directed chemotherapy, bone marrow transplantation is often recommended for patients in first remission.[117] This is one of the few situations where bone marrow transplant is clearly beneficial for children with ALL in first remission.

T-Precursor ALL

As noted in the T-Precursor ALL subsection in Childhood ALL, the activation of oncogenic transcription factors defines distinct molecular subsets of T-ALL with prognostic significance in children. We studied cryopreserved lymphoblasts collected at diagnosis from 52 adults with T-ALL to determine whether overexpression of these oncogenes is of comparable importance in the pathogenesis and treatment responses of adults with T-ALL. We found that the molecular pathways leading to adult T-ALL were very similar to those identified in childhood T-ALL, except that HOX11 was expressed by 33% of adult T-ALL cases, compared with only 3% of T-ALLs arising in children (Fig 1). In addition, HOX11L2 overexpression was under-represented in adult T-ALL compared with childhood cases (5% *v* 20% of cases; Fig 1). As in children, adults T-ALLs with aberrant expression of *HOX11* had a significantly better leukemia-specific survival rate than did those without this feature.[118] Thus, we propose that patients with *HOX11*$^+$ T-ALL could be treated effectively with regimens of intensive chemotherapy and spared from the toxicity associated with very intensive therapy followed by rescue with autologous or allogeneic stem cell transplantation.

PROSPECTS FOR TARGETED THERAPY

Small-Molecule Inhibitors of Tyrosine Kinase Receptors

Tyrosine kinases are recognized as valid therapeutic targets in multiple types of cancer including leukemia, and inhibition of constitutively active kinases has clear therapeutic benefit.[119-122] Kinase inhibition is highly successful in the treatment of chronic myelogenous leukemia (CML), in which imatinib mesylate, a small-molecule inhibitor of the BCR-ABL kinase, is remarkably effective.[119] Imatinib induces complete hematologic remission in approximately 95% of patients, and complete cytogenetic responses in approximately 75% of patients with chronic phase CML.[123] Imatinib also has significant activity in patients with *BCR-ABL*–positive ALL, in which remission is frequently achieved with imatinib alone.[124] Unfortunately these responses are transient, with most patients experiencing a relapse of their disease within months. The transient nature of the responses has prompted a number of clinical trials in adults and children in which imatinib will be incorporated into multi-agent chemotherapy for patients with *BCR-ABL*–positive ALL.[125] These early trials combining imatinib and chemotherapy are of significant interest; it is likely that other kinase inhibitors currently in development for both leukemias and other cancers also will need to be combined with either chemotherapy or other targeted therapy because resistance to single-kinase inhibitors is becoming an expected outcome.[126] Because multiple inhibitors are in clinical development, the imatinib trials will provide the groundwork for future combinations.

Small-Molecule Inhibitors of the NOTCH Pathway

As noted in the T-Precursor ALL subsection in Childhood ALL, we recently identified mutations involving the extracellular NOTCH1 heterodimerization domain or C-terminal PEST domain in the majority of human T-ALLs, including leukemias from all of the previously defined molecular oncogenic subtypes. The mutations cause increased NOTCH1 signaling, and T-ALL cell lines bearing such mutations are growth arrested by NOTCH pathway inhibitors. These findings greatly expand the role of activated NOTCH1 in the molecular pathogenesis of human T-ALL, and provide a strong rationale in for targeted therapies of this disease that interfere with NOTCH signaling because mutationally activated forms of NOTCH1 are still dependent on enzymatic cleavage for activity (Fig 2). On the basis of these findings, a novel clinical trial of a potent NOTCH pathway inhibitor has been opened recently at the Dana-Farber Cancer Institute to target specifically the NOTCH pathway in children and adults with relapsed or refractory T-ALL or T-lymphoblastic lymphoma.

CONCLUSIONS

Molecular studies of recurrent genetic abnormalities found in ALL blasts have provided tremendous insights into molecular pathogenesis. The discovery and ongoing characterization of fusion oncogenes encoded by chromosomal translocations provides a foundation upon which the study of leukemogenesis continues to build. Recent studies assessing gene expression profiles of lymphoblastic leukemias have demonstrated convincingly the dividing of cases into biologic subsets, and in some cases identified potential therapeutic targets that are under investigation. Finally, the identification of aberrant signaling pathways represents a fertile ground of future study, given the proven success of small molecule tyrosine kinase inhibitors like imatinib mesylate for the treatment of leukemia. The incorporation of such targeted agents into ALL treatment represents a major focus for clinicians and scientists involved in the study of ALL, and the addition of such therapies should improve the therapeutic index for ALL therapy.

Acknowledgment

We thank Eric Smith and Adolfo Ferrando for help in designing figures. We would also like to thank Jason Berman and Doris Dodson for help with editing and references. Finally, we would like to dedicate this review to the

memory of the late Stanley J. Korsmeyer, a beloved colleague, friend and mentor, for his enduring contributions to the understanding of leukemia biology and treatment.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

REFERENCES

1. Rowley JD: The critical role of chromosome translocations in human leukemias. Annu Rev Genet 32:495-519, 1998

2. Armstrong SA, Staunton JE, Silverman LB, et al: MLL translocations specify a distinct gene expression profile that distinguishes a unique leukemia. Nat Genet 30:41-47, 2002

3. Yeoh EJ, Ross ME, Shurtleff SA, et al: Classification, subtype discovery, and prediction of outcome in pediatric acute lymphoblastic leukemia by gene expression profiling. Cancer Cell 1:133-143, 2002

4. Ferrando AA, Neuberg DS, Staunton J, et al: Gene expression signatures define novel oncogenic pathways in T cell acute lymphoblastic leukemia. Cancer Cell 1:75-87, 2002

5. Armstrong SA, Kung AL, Mabon ME, et al: Inhibition of FLT3 in MLL. Validation of a therapeutic target identified by gene expression based classification. Cancer Cell 3:173-183, 2003

6. Armstrong SA, Mabon ME, Silverman LB, et al: FLT3 mutations in childhood acute lymphoblastic leukemia. Blood 103:3544-3546, 2004

7. Weng AP, Ferrando AA, Lee W, et al: Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. Science 306:269-271, 2004

8. Kohlmann A, Schoch C, Schnittger S, et al: Pediatric acute lymphoblastic leukemia (ALL) gene expression signatures classify an independent cohort of adult ALL patients. Leukemia 18:63-71, 2004

9. Gaynon PS, Trigg ME, Heerema NA, et al: Children's Cancer Group trials in childhood acute lymphoblastic leukemia: 1983-1995. Leukemia 14:2223-2233, 2000

10. Maloney KW, Shuster JJ, Murphy S, et al: Long-term results of treatment studies for childhood acute lymphoblastic leukemia: Pediatric Oncology Group studies from 1986-1994. Leukemia 14:2276-2285, 2000

11. Schrappe M, Reiter A, Zimmermann M, et al: Long-term results of four consecutive trials in childhood ALL performed by the ALL-BFM study group from 1981 to 1995. Berlin-Frankfurt-Munster. Leukemia 14:2205-2222, 2000

12. Silverman LB, Declerck L, Gelber RD, et al: Results of Dana-Farber Cancer Institute Consortium protocols for children with newly diagnosed acute lymphoblastic leukemia (1981-1995). Leukemia 14:2247-2256, 2000

13. Robison LL, Bhatia S: Late-effects among survivors of leukaemia and lymphoma during childhood and adolescence. Br J Haematol 122:345-359, 2003

14. Greaves MF, Wiemels J: Origins of chromosome translocations in childhood leukaemia. Nat Rev Cancer 3:639-649, 2003

15. Golub TR, Barker GF, Lovett M, et al: Fusion of PDGF receptor beta to a novel ets-like gene, tel, in chronic myelomonocytic leukemia with t(5;12) chromosomal translocation. Cell 77:307-316, 1994

16. Golub TR, Barker GF, Stegmaier K, et al: Involvement of the TEL gene in hematologic malignancy by diverse molecular genetic mechanisms. Curr Top Microbiol Immunol 211:279-288, 1996

17. Okuda T, van Deursen J, Hiebert SW, et al: AML1, the target of multiple chromosomal translocations in human leukemia, is essential for normal fetal liver hematopoiesis. Cell 84:321-330, 1996

18. Song WJ, Sullivan MG, Legare RD, et al: Haploinsufficiency of CBFA2 causes familial thrombocytopenia with propensity to develop acute myelogenous leukaemia. Nat Genet 23:166-175, 1999

19. Dal Cin P, Atkins L, Ford C, et al: Amplification of AML1 in childhood acute lymphoblastic leukemias. Genes Chromosomes Cancer 30:407-409, 2001

20. Wang LC, Kuo F, Fujiwara Y, et al: Yolk sac angiogenic defect and intra-embryonic apoptosis in mice lacking the Ets-related factor TEL. EMBO J 16:4374-4383, 1997

21. Wang LC, Swat W, Fujiwara Y, et al: The TEL/ETV6 gene is required specifically for hematopoiesis in the bone marrow. Genes Dev 12:2392-2402, 1998

22. Hock H, Meade E, Medeiros S, et al: Tel/Etv6 is an essential and selective regulator of adult hematopoietic stem cell survival. Genes Dev 18:2336-2341, 2004

23. Cave H, Cacheux V, Raynaud S, et al: ETV6 is the target of chromosome 12p deletions in t(12;21) childhood acute lymphocytic leukemia. Leukemia 11:1459-1464, 1997

24. McLean TW, Ringold S, Neuberg D, et al: TEL/AML-1 dimerizes and is associated with a favorable outcome in childhood acute lymphoblastic leukemia. Blood 88:4252-4258, 1996

25. Takeuchi S, Seriu T, Bartram CR, et al: TEL is one of the targets for deletion on 12p in many cases of childhood B-lineage acute lymphoblastic leukemia. Leukemia 11:1220-1223, 1997

26. Sasaki K, Yagi H, Bronson RT, et al: Absence of fetal liver hematopoiesis in mice deficient in transcriptional coactivator core binding factor beta. Proc Natl Acad Sci U S A 93:12359-12363, 1996

27. Wang Q, Stacy T, Binder M, et al: Disruption of the Cbfa2 gene causes necrosis and hemorrhaging in the central nervous system and blocks definitive hematopoiesis. Proc Natl Acad Sci U S A 93:3444-3449, 1996

28. Wang Q, Stacy T, Miller JD, et al: The CBFbeta subunit is essential for CBFalpha2 (AML1) function in vivo. Cell 87:697-708, 1996

29. Niki M, Okada H, Takano H, et al: Hematopoiesis in the fetal liver is impaired by targeted mutagenesis of a gene encoding a non-DNA binding subunit of the transcription factor, polyomavirus enhancer binding protein 2/core binding factor. Proc Natl Acad Sci U S A 94:5697-5702, 1997

30. Borkhardt A, Cazzaniga G, Viehmann S, et al: Incidence and clinical relevance of TEL/AML1 fusion genes in children with acute lymphoblastic leukemia enrolled in the German and Italian multicenter therapy trials: Associazione Italiana Ematologia Oncologia Pediatrica and the Berlin-Frankfurt-Munster Study Group. Blood 90:571-577, 1997

31. Rubnitz JE, Downing JR, Pui CH, et al: TEL gene rearrangement in acute lymphoblastic leukemia: A new genetic marker with prognostic significance. J Clin Oncol 15:1150-1157, 1997

32. Rubnitz JE, Pui CH, Downing JR: The role of TEL fusion genes in pediatric leukemias. Leukemia 13:6-13, 1999

33. Taketani T, Taki T, Sugita K, et al: FLT3 mutations in the activation loop of tyrosine kinase domain are frequently found in infant ALL with MLL rearrangements and pediatric ALL with hyperdiploidy. Blood 103:1085-1088, 2004

34. Pui CH: Childhood leukemias—Current status and future perspective. Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi 36:322-327, 1995

35. Kamps MP, Look AT, Baltimore D: The human t(1;19) translocation in pre-B ALL produces multiple nuclear E2A-Pbx1 fusion proteins with differing transforming potentials. Genes Dev 5:358-368, 1991

36. Raimondi SC, Behm FG, Roberson PK, et al: Cytogenetics of pre-B-cell acute lymphoblastic leukemia with emphasis on prognostic implications of the t(1;19). J Clin Oncol 8:1380-1388, 1990

37. Mellentin JD, Murre C, Donlon TA, et al: The gene for enhancer binding proteins E12/E47 lies at the t(1;19) breakpoint in acute leukemias. Science 246:379-382, 1989

38. Nourse J, Mellentin JD, Galili N, et al: Chromosomal translocation t(1;19) results in synthesis of a homeobox fusion mRNA that codes for a potential chimeric transcription factor. Cell 60:535-545, 1990

39. Kamps MP, Murre C, Sun XH, et al: A new homeobox gene contributes the DNA binding domain of the t(1;19) translocation protein in pre-B ALL. Cell 60:547-555, 1990

40. Sigvardsson M, O'Riordan M, Grosschedl R: EBF and E47 collaborate to induce expression of the endogenous immunoglobulin surrogate light chain genes. Immunity 7:25-36, 1997

41. Murre C, McCaw PS, Vaessin H, et al: Interactions between heterologous helix-loop-helix proteins generate complexes that bind specifically to a common DNA sequence. Cell 58:537-544, 1989

42. Chang CP, Shen WF, Rozenfeld S, et al: Pbx proteins display hexapeptide-dependent cooperative DNA binding with a subset of Hox proteins. Genes Dev 9:663-674, 1995

43. Erikson J, Finger L, Sun L, et al: Deregulation of c-myc by translocation of the alpha-locus of the T-cell receptor in T-cell leukemias. Science 232:884-886, 1986

44. McKeithan TW, Shima EA, Le Beau MM, et al: Molecular cloning of the breakpoint junction of a human chromosomal 8;14 translocation involving the T-cell receptor alpha-chain gene and sequences on the 3′ side of

MYC. Proc Natl Acad Sci U S A 83:6636-6640, 1986

45. Shima EA, Le Beau MM, McKeithan TW, et al: Gene encoding the alpha chain of the T-cell receptor is moved immediately downstream of c-myc in a chromosomal 8;14 translocation in a cell line from a human T-cell leukemia. Proc Natl Acad Sci U S A 83:3439-3443, 1986

46. Begley CG, Aplan PD, Davey MP, et al: Chromosomal translocation in a human leukemic stem-cell line disrupts the T-cell antigen receptor delta-chain diversity region and results in a previously unreported fusion transcript. Proc Natl Acad Sci U S A 86:2031-2035, 1989

47. Chen Q, Cheng JT, Tasi LH, et al: The tal gene undergoes chromosome translocation in T cell leukemia and potentially encodes a helix-loop-helix protein. EMBO J 9:415-424, 1990

48. Xia Y, Brown L, Yang CY, et al: TAL2, a helix-loop-helix gene activated by the (7;9)(q34;q32) translocation in human T-cell leukemia. Proc Natl Acad Sci U S A 88:11416-11420, 1991

49. Mellentin JD, Smith SD, Cleary ML: lyl-1, a novel gene altered by chromosomal translocation in T cell leukemia, codes for a protein with a helix-loop-helix DNA binding motif. Cell 58:77-83, 1989

50. Baer R: TAL1, TAL2 and LYL1: a family of basic helix-loop-helix proteins implicated in T cell acute leukaemia. Semin Cancer Biol 4:341-347, 1993

51. Hsu HL, Cheng JT, Chen Q, et al: Enhancer-binding activity of the tal-1 oncoprotein in association with the E47/E12 helix-loop-helix proteins. Mol Cell Biol 11:3037-3042, 1991

52. Bain G, Engel I, Robanus Maandag EC, et al: E2A deficiency leads to abnormalities in alphabeta T-cell development and to rapid development of T-cell lymphomas. Mol Cell Biol 17:4782-4791, 1997

53. Yan W, Young AZ, Soares VC, et al: High incidence of T-cell tumors in E2A-null mice and E2A/Id1 double-knockout mice. Mol Cell Biol 17:7317-7327, 1997

54. Morrow MA, Mayer EW, Perez CA, et al: Overexpression of the helix-loop-helix protein Id2 blocks T cell development at multiple stages. Mol Immunol 36:491-503, 1999

55. O'Neil J, Billa M, Oikemus S, et al: The DNA binding activity of TAL-1 is not required to induce leukemia/lymphoma in mice. Oncogene 20:3897-3905, 2001

56. Chervinsky DS, Zhao XF, Lam DH, et al: Disordered T-cell development and T-cell malignancies in SCL LMO1 double-transgenic mice: Parallels with E2A-deficient mice. Mol Cell Biol 19:5025-5035, 1999

57. Aplan PD, Jones CA, Chervinsky DS, et al: An scl gene product lacking the transactivation domain induces bony abnormalities and cooperates with LMO1 to generate T-cell malignancies in transgenic mice. EMBO J 16:2408-2419, 1997

58. Boehm T, Foroni L, Kaneko Y, et al: The rhombotin family of cysteine-rich LIM-domain oncogenes: Distinct members are involved in T-cell translocations to human chromosomes 11p15 and 11p13. Proc Natl Acad Sci U S A 88:4367-4371, 1991

59. Royer-Pokora B, Loos U, Ludwig WD: TTG-2, a new gene encoding a cysteine-rich protein with the LIM motif, is overexpressed in acute T-cell leukaemia with the t(11;14)(p13;q11). Oncogene 6:1887-1893, 1991

60. Greenberg JM, Boehm T, Sofroniew MV, et al: Segmental and developmental regulation of a presumptive T-cell oncogene in the central nervous system. Nature 344:158-160, 1990

61. Valge-Archer VE, Osada H, Warren AJ, et al: The LIM protein RBTN2 and the basic helix-loop-helix protein TAL1 are present in a complex in erythroid cells. Proc Natl Acad Sci U S A 91:8617-8621, 1994

62. Wadman I, Li J, Bash RO, et al: Specific in vivo association between the bHLH and LIM proteins implicated in human T cell leukemia. EMBO J 13:4831-4839, 1994

63. McGuire EA, Rintoul CE, Sclar GM, et al: Thymic overexpression of Ttg-1 in transgenic mice results in T-cell acute lymphoblastic leukemia/lymphoma. Mol Cell Biol 12:4186-4196, 1992

64. Hacein-Bey-Abina S, von Kalle C, Schmidt M, et al: A serious adverse event after successful gene therapy for X-linked severe combined immunodeficiency. N Engl J Med 348:255-256, 2003

65. Hacein-Bey-Abina S, Von Kalle C, Schmidt M, et al: LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1. Science 302:415-419, 2003

66. McCormack MP, Rabbitts TH: Activation of the T-cell oncogene LMO2 after gene therapy for X-linked severe combined immunodeficiency. N Engl J Med 350:913-922, 2004

67. Dube ID, Kamel-Reid S, Yuan CC, et al: A novel human homeobox gene lies at the chromosome 10 breakpoint in lymphoid neoplasias with chromosomal translocation t(10;14). Blood 78:2996-3003, 1991

68. Hatano M, Roberts CW, Minden M, et al: Deregulation of a homeobox gene, HOX11, by the t(10;14) in T cell leukemia. Science 253:79-82, 1991

69. Kennedy MA, Gonzalez-Sarmiento R, Kees UR, et al: HOX11, a homeobox-containing T-cell oncogene on human chromosome 10q24. Proc Natl Acad Sci U S A 88:8900-8904, 1991

70. Lu M, Gong ZY, Shen WF, et al: The tcl-3 proto-oncogene altered by chromosomal translocation in T-cell leukemia codes for a homeobox protein. EMBO J 10:2905-2910, 1991

71. Dear TN, Sanchez-Garcia I, Rabbitts TH: The HOX11 gene encodes a DNA-binding nuclear transcription factor belonging to a distinct family of homeobox genes. Proc Natl Acad Sci U S A 90:4431-4435, 1993

72. Allen JD, Adams JM: Enforced expression of Hlx homeobox gene prompts myeloid cell maturation and altered adherence properties of T cells. Blood 81:3242-3251, 1993

73. McGinnis W, Krumlauf R: Homeobox genes and axial patterning. Cell 68:283-302, 1992

74. Roberts CW, Shutter JR, Korsmeyer SJ: Hox11 controls the genesis of the spleen. Nature 368:747-749, 1994

75. Berger R, Dastugue N, Busson M, et al: t(5;14)/HOX11L2-positive T-cell acute lymphoblastic leukemia: A collaborative study of the Groupe Francais de Cytogenetique Hematologique (GFCH). Leukemia 17:1851-1857, 2003

76. Cave H, Suciu S, Preudhomme C, et al: Clinical significance of HOX11L2 expression linked to t(5;14)(q35;q32), of HOX11 expression, and of SIL-TAL fusion in childhood T-cell malignancies: Results of EORTC studies 58881 and 58951. Blood 103:442-450, 2004

77. Soulier J, Clappier E, Cayuela JM, et al: HOXA genes are included in genetic and biological networks defining human acute T-cell leukemia (T-ALL). Blood 106:274-286, 2005

78. Rubnitz JE, Camitta BM, Mahmoud H, et al: Childhood acute lymphoblastic leukemia with the MLL-ENL fusion and t(11;19)(q23;p13.3) translocation. J Clin Oncol 17:191-196, 1999

79. Ferrando AA, Armstrong SA, Neuberg DS, et al: Gene expression signatures in MLL-rearranged T-lineage and B-precursor acute leukemias: Dominance of HOX dysregulation. Blood 102:262-268, 2003

80. Dreyling MH, Martinez-Climent JA, Zheng M, et al: The t(10;11)(p13;q14) in the U937 cell line results in the fusion of the AF10 gene and CALM, encoding a new member of the AP-3 clathrin assembly protein family. Proc Natl Acad Sci U S A 93:4804-4809, 1996

81. Narita M, Shimizu K, Hayashi Y, et al: Consistent detection of CALM-AF10 chimaeric transcripts in haematological malignancies with t(10;11)(p13;q14) and identification of novel transcripts. Br J Haematol 105:928-937, 1999

82. Kobayashi H, Hosoda F, Maseki N, et al: Hematologic malignancies with the t(10;11)(p13;q21) have the same molecular event and a variety of morphologic or immunologic phenotypes. Genes Chromosomes Cancer 20:253-259, 1997

83. Jones LK, Chaplin T, Shankar A, et al: Identification and molecular characterisation of a CALM-AF10 fusion in acute megakaryoblastic leukaemia. Leukemia 15:910-914, 2001

84. Carlson KM, Vignon C, Bohlander S, et al: Identification and molecular characterization of CALM/AF10fusion products in T cell acute lymphoblastic leukemia and acute myeloid leukemia. Leukemia 14:100-104, 2000

85. Asnafi V, Radford-Weiss I, Dastugue N, et al: CALM-AF10 is a common fusion transcript in T-ALL and is specific to the TCRgammadelta lineage. Blood 102:1000-1006, 2003

86. Ellisen LW, Bird J, West DC, et al: TAN-1, the human homolog of the Drosophila notch gene, is broken by chromosomal translocations in T lymphoblastic neoplasms. Cell 66:649-661, 1991

87. Rand MD, Grimm LM, Artavanis-Tsakonas S, et al: Calcium depletion dissociates and activates heterodimeric notch receptors. Mol Cell Biol 20:1825-1835, 2000

88. Sanchez-Irizarry C, Carpenter AC, Weng AP, et al: Notch subunit heterodimerization and prevention of ligand-independent proteolytic activation depend, respectively, on a novel domain and the LNR repeats. Mol Cell Biol 24:9265-9273, 2004

89. Kimberly WT, Esler WP, Ye W, et al: Notch and the amyloid precursor protein are cleaved

by similar gamma-secretase(s). Biochemistry 42: 137-144, 2003

90. Aster JC, Xu L, Karnell FG, et al: Essential roles for ankyrin repeat and transactivation domains in induction of T-cell leukemia by notch1. Mol Cell Biol 20:7505-7515, 2000

91. Hoemann CD, Beaulieu N, Girard L, et al: Two distinct Notch1 mutant alleles are involved in the induction of T-cell leukemia in c-myc transgenic mice. Mol Cell Biol 20:3831-3842, 2000

92. Feldman BJ, Hampton T, Cleary ML: A carboxy-terminal deletion mutant of Notch1 accelerates lymphoid oncogenesis in E2A-PBX1 transgenic mice. Blood 96:1906-1913, 2000

93. Biondi A, Cimino G, Pieters R, et al: Biological and therapeutic aspects of infant leukemia. Blood 96:24-33, 2000

94. Chen CS, Sorensen PH, Domer PH, et al: Molecular rearrangements on chromosome 11q23 predominate in infant acute lymphoblastic leukemia and are associated with specific biologic variables and poor outcome. Blood 81: 2386-2393, 1993

95. Domer PH, Fakharzadeh SS, Chen CS, et al: Acute mixed-lineage leukemia t(4;11)(q21;q23) generates an MLL-AF4 fusion product. Proc Natl Acad Sci U S A 90:7884-7888, 1993

96. Gu Y, Nakamura T, Alder H, et al: The t(4;11) chromosome translocation of human acute leukemias fuses the ALL-1 gene, related to Drosophila trithorax, to the AF-4 gene. Cell 71:701-708, 1992

97. Tkachuk DC, Kohler S, Cleary ML: Involvement of a homolog of Drosophila trithorax by 11q23 chromosomal translocations in acute leukemias. Cell 71:691-700, 1992

98. Ziemin-van der Poel S, McCabe NR, Gill HJ, et al: Identification of a gene, MLL, that spans the breakpoint in 11q23 translocations associated with human leukemias. Proc Natl Acad Sci U S A 88:10735-10739, 1991

99. Ayton PM, Cleary ML: Molecular mechanisms of leukemogenesis mediated by MLL fusion proteins. Oncogene 20:5695-5707, 2001

100. Milne TA, Briggs SD, Brock HW, et al: MLL targets SET domain methyltransferase activity to Hox gene promoters. Mol Cell 10:1107-1117, 2002

101. Nakamura T, Mori T, Tada S, et al: ALL-1 is a histone methyltransferase that assembles a supercomplex of proteins involved in transcriptional regulation. Mol Cell 10:1119-1128, 2002

102. Hsieh JJ, Ernst P, Erdjument-Bromage H, et al: Proteolytic cleavage of MLL generates a complex of N- and C-terminal fragments that confers protein stability and subnuclear localization. Mol Cell Biol 23:186-194, 2003

103. Hsieh JJ, Cheng EH, Korsmeyer SJ: Taspase1: A threonine aspartase required for cleavage of MLL and proper HOX gene expression. Cell 115:293-303, 2003

104. Yokoyama A, Kitabayashi I, Ayton PM, et al: Leukemia proto-oncoprotein MLL is proteolytically processed into 2 fragments with opposite transcriptional properties. Blood 100:3710-3718, 2002

105. Hess JL, Yu BD, Li B, et al: Defects in yolk sac hematopoiesis in Mll-null embryos. Blood 90:1799-1806, 1997

106. Yu BD, Hess JL, Horning SE, et al: Altered Hox expression and segmental identity in Mll-mutant mice. Nature 378:505-508, 1995

107. Ernst P, Fisher JK, Avery W, et al: Definitive hematopoiesis requires the mixed-lineage leukemia gene. Dev Cell 6:437-443, 2004

108. Ernst P, Mabon M, Davidson AJ, et al: An Mll-dependent Hox program drives hematopoietic progenitor expansion. Curr Biol 14:2063-2069, 2004

109. Owens BM, Hawley RG: HOX and non-HOX homeobox genes in leukemic hematopoiesis. Stem Cells 20:364-379, 2002

110. Borrow J, Shearman AM, Stanton VP Jr, et al: The t(7;11)(p15;p15) translocation in acute myeloid leukaemia fuses the genes for nucleoporin NUP98 and class I homeoprotein HOXA9. Nat Genet 12:159-167, 1996

111. Nakamura T, Largaespada DA, Lee MP, et al: Fusion of the nucleoporin gene NUP98 to HOXA9 by the chromosome translocation t(7;11)(p15;p15) in human myeloid leukaemia. Nat Genet 12:154-158, 1996

112. Gilliland DG, Griffin JD: The roles of FLT3 in hematopoiesis and leukemia. Blood 100:1532-1542, 2002

113. Brown P, Levis M, Shurtleff S, et al: FLT3 inhibition selectively kills childhood acute lymphoblastic leukemia cells with high levels of FLT3 expression. Blood 105:812-820, 2005

114. Ribeiro RC, Abromowitch M, Raimondi SC, et al: Clinical and biologic hallmarks of the Philadelphia chromosome in childhood acute lymphoblastic leukemia. Blood 70:948-953, 1987

115. Crist W, Carroll A, Shuster J, et al: Philadelphia chromosome positive childhood acute lymphoblastic leukemia: Clinical and cytogenetic characteristics and treatment outcome—A Pediatric Oncology Group study. Blood 76:489-494, 1990

116. Fletcher JA, Lynch EA, Kimball VM, et al: Translocation (9;22) is associated with extremely poor prognosis in intensively treated children with acute lymphoblastic leukemia. Blood 77: 435-439, 1991

117. Arico M, Valsecchi MG, Camitta B, et al: Outcome of treatment in children with Philadelphia chromosome-positive acute lymphoblastic leukemia. N Engl J Med 342:998-1006, 2000

118. Ferrando AA, Neuberg DS, Dodge RK, et al: Prognostic importance of TLX1 (HOX11) oncogene expression in adults with T-cell acute lymphoblastic leukaemia. Lancet 363:535-536, 2004

119. Druker BJ, Talpaz M, Resta DJ, et al: Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med 344:1031-1037, 2001

120. Demetri GD, von Mehren M, Blanke CD, et al: Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 347:472-480, 2002

121. Paez JG, Janne PA, Lee JC, et al: EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy. Science 304:1497-1500, 2004

122. Sordella R, Bell DW, Haber DA, et al: Gefitinib-sensitizing EGFR mutations in lung cancer activate anti-apoptotic pathways. Science 305:1163-1167, 2004

123. Druker BJ: Imatinib as a paradigm of targeted therapies. Adv Cancer Res 91:1-30, 2004

124. Ottmann OG, Druker BJ, Sawyers CL, et al: A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. Blood 100:1965-1971, 2002

125. Thomas DA, Faderl S, Cortes J, et al: Treatment of Philadelphia chromosome-positive acute lymphocytic leukemia with hyper-CVAD and imatinib mesylate. Blood 103:4396-4407, 2004

126. Gorre ME, Mohammed M, Ellwood K, et al: Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. Science 293:876-880, 2001