Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org
by University of California - Los Angeles on 02/16/09. For personal use only.

Molecular Genetics of Acute Lymphoblastic Leukemia

Michael A. Teitell[1] and Pier Paolo Pandolfi[2,3]

[1]Departments of Pathology and Pediatrics, Jonsson Comprehensive Cancer Center, Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research, and California NanoSystems Institute, David Geffen School of Medicine, University of California, Los Angeles, California 90095-1732; email: mteitell@ucla.edu

[2]Departments of Medicine and Pathology, Harvard Medical School, Boston, Massachusetts 02115

[3]Division of Cancer Genetics and Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts 02215; email: ppandolf@bidmc.harvard.edu

Annu. Rev. Pathol. Mech. Dis. 2009. 4:175–98

First published online as a Review in Advance on September 10, 2008

The *Annual Review of Pathology: Mechanisms of Disease* is online at pathmechdis.annualreviews.org

This article's doi:
10.1146/annurev.pathol.4.110807.092227

Copyright © 2009 by Annual Reviews.
All rights reserved

1553-4006/09/0228-0175$20.00

Key Words

translocation, copy number variation, mouse modeling, oncogene addiction, targeted therapy

Abstract

Acute lymphoblastic leukemia (ALL) is mainly a disease of childhood that arises from recurrent genetic insults that block precursor B and T cell differentiation and drive aberrant cell proliferation and survival. Recurrent defects including chromosomal translocations, aneuploidies, and gene-specific alterations generate molecular subgroups of B- and T-ALL with differing clinical courses and distinct responses to therapy. Recent discoveries arising from genome-wide surveys and adoptive transfer of leukemia-initiating cells have uncovered multiple gene copy number aberrations and have yielded new insight into at least one type of ALL-originating cell. Our understanding of the pathogenesis of ALL has benefited from genetically modified mouse models that recapitulate cellular transformation at specific developmental stages of lymphoid lineage cells. Here, we review the spectrum of genetic aberrations that promote acute B and T cell leukemias and the mechanisms of cell transformation and malignant progression that are reinforced by mouse models of human ALL.

Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org
by University of California - Los Angeles on 02/16/09. For personal use only.

AML: acute myeloid leukemia

INTRODUCTION

Acute Lymphoblastic Leukemia

Acute leukemias comprise a diverse collection of mainly precursor-stage lymphoid and myeloid cell malignancies. An estimated 18,700+ new cases of acute leukemia are predicted for 2008 in the United States alone (1). Almost three-fourths of childhood leukemia (ages 0–19) is acute lymphoblastic leukemia (ALL), whereas acute myeloid leukemia (AML) is the most common form of acute leukemia in adults. Current protocols for diagnosing and treating ALL have achieved overall cure rates, defined as the absence of disease for at least 10 years, of more than 80% in children, although certain molecular subtypes and adults with ALL still have a relatively poor prognosis (2, 3).

The causes that underlie the vast majority of ALL cases are unknown. A small percentage of cases associate with Down syndrome and with inherited predisposing genome instability syndromes, such as ataxia-telangiectasia, Bloom syndrome, and Nijmegen breakage syndrome. Collectively, molecular analysis of archived neonatal blood spots (known as Guthrie cards), studies of leukemia development in monozygotic twins, and screening of umbilical cord blood samples implicate an in utero–initiating lesion for some early childhood ALL cases that harbor a *TEL-AML1* (*ETV6-RUNX1*) fusion gene, as discussed below (4–8). A host of often-conflicting epidemiologic and environmental associations have been suggested for the remainder of childhood ALL cases (9). Two hypotheses involving an abnormal response to infection in early childhood, based upon peak ALL prevalence at 2–5 years of age, increased association with developed countries, and occasional geographical case clustering, have also been advanced (4, 10).

Although root causes have not yet been defined, recurrent genetic defects in ALL have been identified. These include chromosomal translocations that deregulate gene expression or create novel fusion genes, numerical chromosome copy number aberrations (especially hyperdiploidy), and gene-specific mutations. Most often, ALL is subtyped and studied on the basis of a particular underlying genetic abnormality. This approach is consistent with data from microarray expression analysis, which shows that aberrant expression of transcription-factor oncogenes defines distinct molecular, biological, and clinical subtypes of ALL (11). Genetic lesions thought to initiate ALL usually affect either (*a*) a key transcription factor or chromatin-modifying factor at or near the apex of a regulatory hierarchy or (*b*) a membrane-proximal signaling pathway component. A specific genetic lesion, along with a permissive cell of origin—which may be from a hematopoietic stem cell (HSC) possessing multilineage potential (12) or from a later-stage lymphoid precursor—combines with the local microenvironment (13) to generate the biological context for the subtype of acute leukemia that forms. Abnormal levels of DNA methylation also occur and associate with silencing of WNT pathway signaling (14), $P15^{INK4B}$ and $P16^{INK4A}$ tumor suppressors (15), the TP53 target gene $P21^{CIP1}$ (16), and overexpression of *miR-128* (17), suggesting that epigenetic deregulation may be an important contributor to the overall malignant phenotype and patient outcome in ALL.

The World Health Organization provides current diagnostic criteria for ALL as a precursor B cell acute lymphoblastic leukemia/lymphoma (B-ALL/B-LBL) or as a precursor T cell acute lymphoblastic leukemia/lymphoma (T-ALL/T-LBL) (18). This classification scheme does not subdivide ALL into molecular subtypes or into distinct stages of precursor lymphocyte development. A similar entity, termed mature B cell acute lymphoblastic leukemia or Burkitt lymphoma, arises from reciprocal chromosomal translocations between *immunoglobulin* (*IG*) heavy- or light-chain loci and *MYC*, resulting in aberrant *MYC* activation in peripheral germinal-center B cells; this type of leukemia is not further discussed herein (see Reference 19).

B-ALL is an aggressive malignancy of small- to medium-sized precursor B cells. It originates

in the bone marrow (BM) of children and adults and potentially in fetal hemogenic sites in *TEL-AML1*+ B-ALL, and it shows distinct histologic features (summarized in Reference 18). Of the ALL cases that are newly diagnosed in the United States each year, approximately 80–85% are B-ALL phenotype, and the remainder are T-ALL phenotype. B-ALL tumor cells are usually sIG−, CD10+, CD19+, CD24+, cytoplasmic CD79+, and terminal deoxynucleotidyl transferase (TdT)+, with more variable expression of lymphoid lineage CD20, CD22, and CD45 and myeloid lineage CD13 and CD33 biomarkers. Most B-ALL molecular subtypes have a good outcome, with an overall complete remission rate of 95% for children and 60–85% for adults. Human T-ALL mirrors B-ALL histologically, with TdT+ tumor cells that variably express CD1A, CD2, CD3, CD4, CD5, CD7, and CD8, patterns that usually reflect transformation at—or differentiation blockade at—distinct stages of intrathymic T cell development (18). Chromosomal translocations involving *T cell receptor* (*TCR*) α/δ (14q11.2), *TCR*β (7q35), or *TCR*γ (7p14-15) loci with a variety of partner genes are seen in ~33% of T-ALL cases. With current treatment protocols, both B-ALL and T-ALL patients show a median survival of ~60 months.

ALL-promoting chromosomal translocations often involve transcription factors or chromatin modifiers that regulate normal B- and T-lineage maturation; these include factors that control development before the earliest stages of HSC differentiation (**Figure 1**). Pre-multipotent progenitor (MPP) translocations involve *TAL1* [*T cell acute leukmemia 1*; also known as *SCL* (*stem cell leukemia hematopoietic transcription factor*)], required for hematopoietic lineage commitment from hemangioblast precursors; *AML1* (*RUNX1*), which controls the emergence of definitive HSCs in fetal hemogenic sites; *MLL*, which regulates the establishment of functional HSCs; and *TEL* (*ETV6*), which maintains adult HSC survival (20). It is curious that specific pre-MPP transcription-factor deregulation generates either B-lineage-specific (*AML1*, *MLL*, and *TEL*) or T-lineage-specific (*TAL1*) ALL. Alterations in post-MPP-stage transcription-factor genes that regulate early lymphocyte development also generate B-ALL or T-ALL. Translocations of *EBF* or *E2A* B-lineage-initiating genes and inactivation of the *PAX5* B-lineage commitment gene result in B-ALL, whereas gain-of-function mutations of the *NOTCH1* T-lineage commitment gene and *MYB* duplication or translocation promote T-ALL. **Table 1** summarizes major genetic lesions, clinical correlations, and presumed mechanisms of action that have been causally linked with ALL development.

BM: bone marrow

MPP: multipotent progenitor

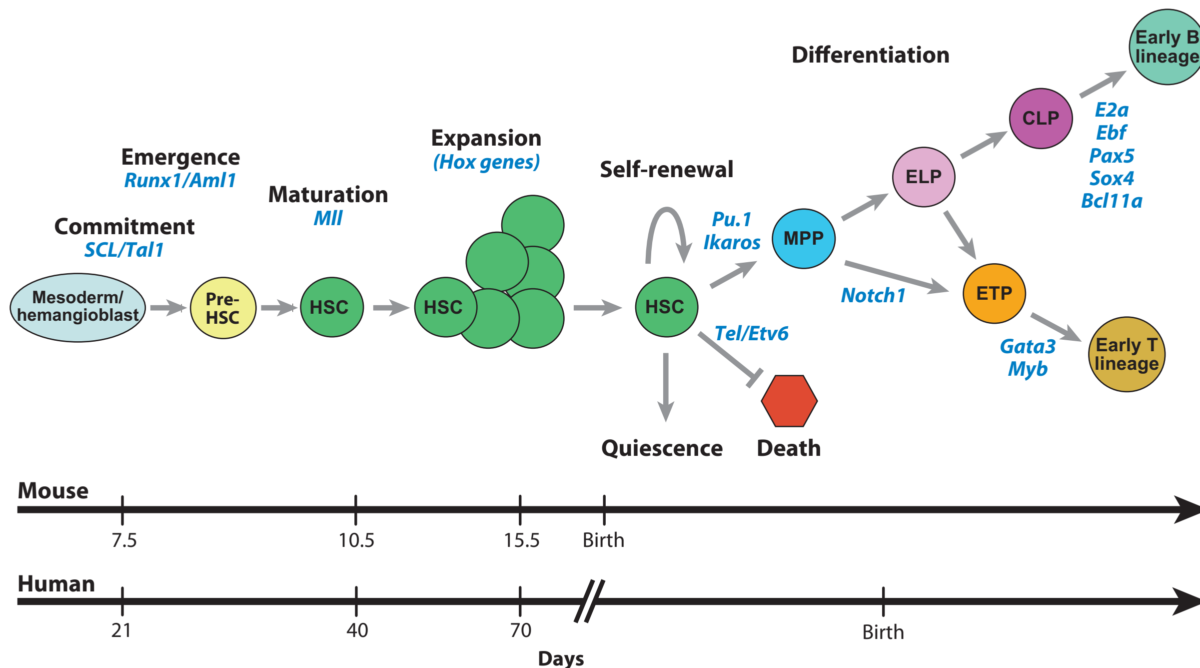
Mouse Models of Human Acute Lymphoblastic Leukemia

Candidate B- and T-ALL-promoting genes have been studied in mice with genetically modified BM and adoptive transfer and with transgenic and gene-knockin and -knockout technologies. Mice have also been used for cancer gene discovery through the use of a wide range of forward genetic methods, including ethylnitrosourea and gene trap mutagenesis, proviral insertion mutagenesis, and Cre-lox-mediated chromosomal inversions and deletions. Some mouse models are generated to resemble B- and T-ALL based on equivalent genetic lesions in humans, whereas others develop unanticipated tumors that resemble or phenocopy key aspects of ALL. Genetic manipulations not seen thus far in human ALL cell lines or in samples occasionally generate equivalent pre-B-LBL or pre-T-LBL tumors in mice. Some of these models link to pathways and mechanisms known to promote human ALL, providing an opportunity to develop new insights into acute leukemogenesis. Informative models (discussed below) have been valuable for molecular validation of identified human lesions, for dissecting molecular mechanisms and companion lesions during tumor initiation and progression, and in some cases for preclinical therapeutic evaluations.

Pre-B-LBL is the tumor that represents human B-ALL/B-LBL in the mouse models

Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org by University of California - Los Angeles on 02/16/09. For personal use only.

Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org
by University of California - Los Angeles on 02/16/09. For personal use only.



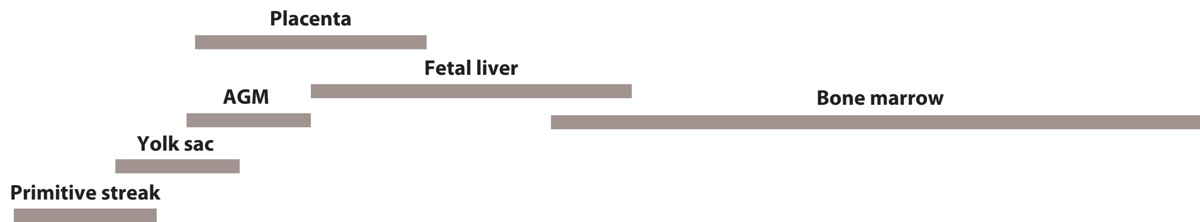


Figure 1

Transcription factors and chromatin modifiers regulate early hematopoietic development before generation of a multipotent progenitor (MPP) and are implicated by chromosomal translocation in promoting B cell acute lymphoblastic leukemia (*Runx1/Aml1*, *Mll*, and *Tel/Etv6*) or T cell acute lymphoblastic leukemia (*SCL/Tal1*). Members of the *Hox* gene family have been shown to expand the hematopoietic stem cell (HSC) pool size in vitro and in vivo and are targets of *Mll*-translocated fusion genes. During later development, alterations in key transcription-factor genes that control early B- or T-lineage initiation, commitment, or precursor differentiation also result in lineage-specific ALL. Depicted are approximately equivalent stages in mouse and human definitive hematopoiesis, which originate from the primitive streak mesoderm. Abbreviations: AGM, aorta–gonad–mesonephros region; ELP, earliest lymphoid progenitor; CLP, common lymphoid progenitor; ETP, early T-lineage progenitor. Figure modified from Reference 20.

of human cancer consortium classification scheme (21). This leukemia is a high-grade neoplasm of small- to medium-sized, round, uniform cells with abundant mitoses and apoptotic bodies; it originates from precursor B cells in the BM. A leukemic phase with spread to peripheral lymphoid and nonlymphoid tissues occurs frequently. By flow cytometry the tumor cells are sIG−, B220+, CD19+, and CD43+/−, and by immunohistochemistry the cells are TdT+. Tumor cells are clonal and contain *Igh* (but usually not *Igl*) gene rearrangements. Due to the differences in their immunohistochemical staining profiles, we can distinguish between mature B lymphoblastic lymphomas, such as mouse-equivalent diffuse large B cell lymphoma and Burkitt-like lymphoma, and mouse pre-T-LBL.

Table 1 Major genetic lesions in B cell and T cell acute lymphoblastic leukemias

Genetic lesion	Associated clinical features	Presumed mechanism of action
B-ALL		
Hyperdiploidy (>50)	20% with FLT3 activation; good prognosis	
BCR-ABL t(9;22)	Poor prognosis; associated *IKZF1* or *CDKN2A* deletions; imatinib resistance develops rapidly	Constitutive tyrosine kinase; interacts with RAS, AKT, JAK/STAT pathways
MLL rearrangements	Improved outcome with high-dose cytarabine for some rearrangements; *MLL-AF4* poor outcome	Chimeric TF; some upregulate hENT1 cytarabine transporter
TEL-AML1 t(12;21)	Good prognosis with intensive chemotherapy that includes asparaginase	Prenatal translocation, chimeric TF, represses AML1 target genes
PAX5	Most frequent target of somatic mutation	Translocated (rare) or deleted TF
E2A-PBX1 t(1;19)	Intensified chemotherapy improves prognosis	Chimeric TF
E2A-HLF	Aggressive disease; adolescents; hypercalcemia; disseminated intravascular coagulation	Chimeric TF with anti-apoptotic SLUG induction; dimerize E2A proteins
T-ALL		
NOTCH1 t(7;9)	GSI sensitive or resistant tumors; associated *PTEN* mutation confers GSI resistance	Gain-of-function change to increase ICN1 and induce targets (e.g, *MYC*)
FBW7	GSI insensitive	Inactivating mutation of SCF-type E3 ubiquitin ligase stabilizes ICN1, MYC
HOX rearrangements	HOX11 T-ALL has better prognosis than other T-ALL molecular subtypes	Elevated expression; HOX11 inhibition of PP2A and PP1 phosphatases
TAL1/SCL t(1;14)	Data for both good and poor outcomes	Dimerize E47 and HEB transcription factors, blocking T cell differentiation
LYL1 t(7;19)		Dimerize E2A and HEB transcription factors, blocking T cell differentiation
MYB t(6;7)		Gene duplication; elevated expression blocks T cell differentiation
LMO1/2 t(11;14)		Binds TAL1/SCL, silent in T cells
CALM-AF10 t(10;11)	TCR γ/δ T-ALL; poor prognosis	*HOXA* cluster, *BMI1* gene induction

Abbreviations: GSI, γ-secretase inhibitor; TF, transcription factor.

Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org
by University of California - Los Angeles on 02/16/09. For personal use only.

Pre-T-LBL is the mouse tumor classification that is analogous to human T-ALL/T-LBL. The histology of pre-T-LBL is similar to that described for pre-B-LBL. Immunophenotypic analysis indicates that tumor cells originate by transformation at distinct stages of intrathymic T cell development with immature, CD3+, CD4−CD8−, CD4+CD8+, CD4+ or CD8+, TCR+, and cytTdT+ staining patterns (21). Alternatively, transformation initiates earlier in development with subsequent blockade at a distinct thymocyte precursor stage. Tumor cells are clonal, and the *Tcrβ* gene is typically rearranged.

MOLECULAR PATHOGENESIS OF B CELL ACUTE LYMPHOBLASTIC LEUKEMIA

Constitutive Abelson Tyrosine Kinase Activity with *BCR-ABL*

The Philadelphia chromosome (Ph) is a short der(22) chromosome resulting from a t(9;22)(q34;q11) that occurs in 20–40% of adults and in 5% of children with B-ALL (22, 23). A reciprocal translocation causes a head-to-tail fusion of the breakpoint cluster region (*BCR*) gene on chromosome 22 with the cellular homolog of the Abelson (*c-ABL*) viral

CML: chronic myeloid leukemia

oncogene on chromosome 9, thereby placing the *BCR-ABL* oncogene under the control of the ubiquitously expressed *BCR* promoter (24). *BCR-ABL* encodes two main BCR-ABL fusion oncoproteins of distinct molecular weights, p190 and p210, that arise from different translocation breakpoints in the *BCR* gene. The p210 isoform is expressed in ~33% of adult Ph+ B-ALL, with the other 66% of adult Ph+ B-ALL expressing the p190 isoform. Approximately 90% of childhood Ph+ B-ALL cases express p190. The source for the preferential association of distinct BCR-ABL isoforms in specific patient populations is unknown. In chronic myeloid leukemia (CML), the Ph is thought to originate in HSCs, whereas the Ph in B-ALL—at least in childhood cases—appears to arise in lymphoid lineage precursors, consistent with the notion that distinct target cells and BCR-ABL isoforms dictate the leukemia subtype that ultimately forms (25).

BCR-ABL is a deregulated, constitutively active nonreceptor tyrosine kinase, and this kinase activity is required for cell transformation (26). Normally, the ABL tyrosine kinase is present in a closed inactive conformation that is activated by a three-step unlatching mechanism (27). Unlatching exposes the ABL activation loop to weak Tyr-412 autophosphorylation or to more robust phosphorylation by the Src tyrosine kinase Hck, thereby increasing ABL kinase activity two- to threefold (28). In contrast, increased ABL tyrosine kinase activity in BCR-ABL appears attributable to inclusion of a BCR oligomerization domain and is further heightened by in vitro deletion of a repressive Src homology 3 (SH3) domain in ABL. BCR-ABL aberrantly enhances RAS-MAPK (mitogen-activated protein kinase) pathway activation, which is essential for transforming activity through autophosphorylation, generation of a high-affinity binding site at Tyr-177, and complex formation through the SH2 domain of the granzyme B2 (GRB2) adaptor protein with GRB-associated binding protein 2 (GAB2) and son of sevenless (SOS) (29, 30). Excessive phosphatidylinositol 3–kinase (PI3K)-AKT pathway signaling has also been linked to BCR-ABL downstream effects through a GAB2-SH2 domain interaction (31), implicating two signal transduction pathways that control cell proliferation, size, survival, and activation as the main leukemia-promoting mechanism for BCR-ABL.

Imatinib mesylate (STI-571; marketed as Gleevec®) is a small-molecule inhibitor that blocks a small group of tyrosine kinases, including BCR-ABL. It is used as frontline therapy for chronic-phase CML and forms part of the treatment regimen for Ph+ ALL (32–34). Imatinib acts as a competitive inhibitor for ATP cofactor binding and locks BCR-ABL in an inactive conformation (35, 36). CML in remission maintained on imatinib can become treatment resistant over time, usually as a result of secondary mutations in the BCR-ABL oncoprotein (37, 38); this phenomenon has spawned the development of a second generation of inhibitors, including dasatinib, nilotinib, and INNO-406, to override imatinib resistance (39). Unlike CML, durable responses to imatinib in Ph+ ALL are uncommon (40, 41), and treatment requires added conventional agents with or without BM transplantation. Potential sources for increased Ph+ ALL imatinib resistance include increased genome instability, which causes more rapid emergence of BCR-ABL kinase mutations than in chronic-phase CML, and additional mutations that synergize with BCR-ABL, such as deletion of the *CDKN2A* (*INK4A-ARF*) tumor-suppressor locus at 9p21, found in ~30% of patients (42, 43). $P16^{INK4A}$ is an inhibitor of CYCLIN-D-dependent kinases, and this inhibition prevents the phosphorylation of RB and RB-related P107 and P130 transcription factors to block entry into the S phase of the cell cycle (44). Functional inactivation of the RB pathway by deletion or epigenetic silencing of $P15^{INK4B}$ and $P16^{INK4A}$ also occurs in most cases of childhood T-ALL (15). $P14^{ARF}$ inhibits the histone demethylase 2 (HDM2) E3 ubiquitin ligase, which blocks TP53 ubiquitination and proteosomal degradation and stabilizes TP53 levels to regulate the program that controls cell-cycle arrest or apoptosis due to oncogene-induced stress (44). Mice deficient in $p16^{Ink4a}/p19^{Arf}$

Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org by University of California - Los Angeles on 02/16/09. For personal use only.

develop aggressive pre-B-LBL, which may resemble a method for acquired independence from BCR-ABL "oncogene addiction" in a sizable number of imatinib-resistant Ph+ ALL cases (45).

A frequent additional complementing lesion that may contribute to relatively poor prognosis and to BCR-ABL treatment resistance is deletion of the *IKZF1* locus, which encodes the nuclear protein IKAROS (46). *IKZF1* deletions were recently identified using single nucleotide polymorphism (SNP) arrays, and results show that haploinsufficiency, homozygous loss, or expression of a dominant-negative IKAROS isoform occurs in ∼84% of pediatric BCR-ABL+ B-ALL. *IKZF1* deletions are largely restricted to BCR-ABL+ B-ALL, suggesting a direct contribution to this ALL molecular subtype. However, similar deletions have also been identified with the conversion of CML to ALL during lymphoid blast crisis. The mechanism of deletion has been suggested (but not explicitly demonstrated) to involve aberrant recombination-activating gene (RAG)–mediated recombination, as sites internal to deletion breakpoints contain heptamer recombination signal sequences that RAG recognizes during V(D)J recombination. This suggestion has been bolstered by the detection of randomly inserted nucleotides, suggesting further modification by TdT at sites of deletion. IKAROS, a lymphoid-restricted zinc-finger-encoded transcription factor with several alternatively spliced forms of undetermined significance, associates with chromatin-remodeling complexes and is considered a master regulator of lymphocyte differentiation (47). Mice with reduced *Ikaros* expression have a partial block at the pro–B cell stage in development (48), suggesting a tumorigenic role in blocking precursor B cell maturation. The same genomic screen identified less-frequent DNA copy number abnormalities in *CDKN2A*, *PAX5*, *C20orf94*, *RB1*, *MEF2C*, *EBF1*, *BTG1*, *DLEU*, *FHIT*, and *ETV6* genes in B-ALL cases with, and in some cases without, BCR-ABL driver translocations. Overall, these results indicate the potential for additional molecular mechanisms beyond BCR-ABL mutation in the aggressive pathogenesis and targeted therapy resistance of Ph+ ALL.

RAG: recombination-activating gene

The oncogenic properties of BCR-ABL have been extensively evaluated in mice using a variety of genetic approaches. 5-fluorouracil-treated mouse BM infected with a *BCR-ABL*^{p210} retrovirus, followed by reconstitution into lethally irradiated hosts, yields B-ALL, T-ALL, or CML, largely depending on strain (49). Similarly, transgenic mice expressing *BCR-ABL*^{p190} or *BCR-ABL*^{p210} develop B-ALL, T-ALL, or CML, likely depending upon the promoter and genetic background used. Mice expressing a fused *Bcr-v-abl* gene develop B-ALL or T-ALL. "Tet-off" mice that express *BCR-ABL*^{p210} when tetracycline is removed from their drinking water generate B-ALL, which is reversed with the addition of tetracycline to resuppress *BCR-ABL*^{p210} expression. These results demonstrate oncogene addiction for the initiating molecular lesion and resembles the success of imatinib and its derivatives in humans. Mice with a *BCR-ABL*^{p190} knockin into exon 1 of the endogenous *Bcr* locus by homologous recombination develop B-ALL. Although the p210 isoform results in few B-ALL cases in humans, adoptive transfer of *BCR-ABL*^{p210}-expressing, p19^{ARF}-null pre–B cells in mice accelerates pre-B-LBL formation and increases imatinib resistance, potentially resembling the *INK4A-ARF* deleted subset of imatinib-resistant human BCR-ABL+ B-ALL cases (50). Overall, mice expressing a variety of *BCR-ABL* oncogene isoforms using adoptive transfer, transgenic, tetracycline-inducible, or gene-knockin technologies develop mainly B-ALL, T-ALL, or CML, with variable penetrance and strain dependence (51).

Mixed Lineage Leukemia Has Multiple Translocation Partners

The *mixed lineage leukemia* (*MLL*) gene encodes a ∼430-kDa, multidomain, trithorax-group methyltransferase that forms part of a larger multiprotein nuclear transcription complex. MLL methylates histone H3 lysine 4 (H3K4)

Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org
by University of California - Los Angeles on 02/16/09. For personal use only.

Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org
by University of California - Los Angeles on 02/16/09. For personal use only.

and positively (or negatively) regulates gene expression (especially *HOX* family gene expression) to control skeletal patterning and HSC and early hematopoietic progenitor cell development (52) (**Figure 1**). The MLL protein is cleaved after translation to generate 320-kDa amino-terminal and 180-kDa C-terminal portions, which self-associate to form the mature protein.

More than 40 different balanced chromosomal translocations have been identified as partners for *MLL* in ALL. The five most common *MLL* rearrangements, present in ~80% of *MLL*-translocated leukemia, are t(4;11)(q21;q23)-encoding MLL-AF4, t(9;11)(p22;q23)-encoding MLL-AF9, t(11;19)(q23;p13.3)-encoding MLL-ENL, t(10;11)(p12;q23)-encoding MLL-AF10, and t(6;11)(q27;q23)-encoding MLL-AF6 (53). An 8.3-kb breakpoint cluster region between exons 8 and 13 is the site for most *MLL* rearrangements, which always produce in-frame fusion proteins with variable fusion partners. All MLL fusion proteins retain AT-hook and CxxC zinc-finger motifs, which are required for transformation, and all except the MLL-PTD (partial tandem repeat) fusion lose the C-terminal SET [su(var)-3-9, Enhancer-of-Zeste, trithorax] domain.

MLL fusions with AF4, AF9, and ENL recruit small serine-/proline-rich proteins with nuclear localization signals, which may generate unique chimeric transcriptional transactivators. Some MLL fusion partner proteins have no transcriptional activity but do contain dimerization domains, which may generate dominant-negative chimeric proteins that inhibit the usual functioning of bound and sequestered transcription regulators. Rare MLL-ELL fusions by t(11;19)(q23;p13.1) bring in an RNA elongation factor that may influence transcription. Recent studies with *MLL-ENL* or *MLL-AF9* retrovirally infected, hematopoietic lineage biomarker–negative (Lin−) human umbilical cord blood cells that were adoptively transferred into sublethally irradiated immunodeficient mice generated pre-B-LBL- or AML-equivalent lesions (13). Serial tumor transplantation identified a primitive cell type with lymphoid and myeloid lineage bipotential and with unrearranged *IGH* genes as the leukemia-initiating cell (or cancer stem cell) required for leukemia maintenance, with distinct fusion gene type and culture conditions favoring either lymphoid or myeloid leukemia upon transplantation. Overall, these findings indicate that the cell of origin, microenvironment, and particular *MLL* fusion gene dictate the self-renewing capability of the tumor and the leukemia subtype that forms. Even with these new cellular findings, exactly how the MLL fusion proteins promote leukemogenesis remains largely unknown, although *HOX* genes, which control HSC pool expansions (54, 55), are likely critical targets in the process.

An In Utero Leukemia Precursor Expresses TEL-AML1

The most frequent genetic lesion in pediatric ALL is a karyotype-cryptic t(12;21)(p13;q22). This lesion originates from microclustered breakpoint regions of *TEL*(*ETV6*) intron 5 and *AML1*(*RUNX1*) intron 1 or 2 in 20% of pediatric and ~3% of adult B-ALL cases, resulting in a *TEL-AML1* (*ETV6-RUNX1*) fusion gene. t(12;21) arises mainly in utero during fetal hematopoiesis in a B cell precursor to generate a covert preleukemia clone, suggesting that *TEL-AML1* is an initiating lesion (5). This notion is supported by monozygotic twin studies in which TEL-AML1+ precursor clones migrated transplacentally, followed by B-ALL development at distinct postnatal ages but with the same *TEL-AML1* fusion sequence, suggesting that a randomly timed secondary lesion was required for transformation in each twin. Complementary leukemogenic lesions include postnatal deletion of the untranslocated *TEL* allele and of 11q23, which contains a large number of candidate tumor–promoting genes including *MLL*; this holds true in a subset of *TEL-AML1* B-ALL cases (56).

TEL-AML1 is a leukemogenic, chimeric transcription factor that encodes the amino-terminal basic helix-loop-helix (bHLH)

domain of the ETS family member TEL, which is fused to the AML1 DNA-binding Runt and transactivation domains (57). In mice, *Aml1* is required for definitive embryonic hematopoiesis (58, 59), whereas *Tel* is required for maintenance of definitive adult-type hematopoiesis (60) (**Figure 1**). Mouse xenograft studies using fractionated *TEL-AML1*-patient BM samples suggest that TEL-AML1 functions to enhance self-renewal and survival of an *IGH* clonally rearranged CD34+CD38−/lowCD19+ B cell precursor, thereby generating a preleukemia cancer–initiating cell of origin (6). TEL-AML1 may generate a preleukemia clone by repression of usually activated AML1 target genes or by TEL inhibition of other ETS family proteins via binding through the TEL's pointed domain (61, 62). The frequent loss of the untranslocated *TEL* allele may be required because TEL overexpression in cell lines generates a G_1 cell-cycle arrest (63). Transduction of mouse BM cells with a MSCV-TEL-AML1 retrovirus, followed by adoptive transfer, generates a low frequency of pre-B- and pre-T-LBL with wild-type donor cells and a higher frequency of an undetermined leukemia type from $p16^{Ink4a}/p19^{Arf}$-deficient BM cells (64).

Inactivation or Translocation of PAX5

In the mouse BM, IKAROS and titered levels of PU.1 transcription-factor expression enable HSC-to-CLP (common lymphoid progenitor) differentiation. The B-lineage is initiated by early B cell factor (EBF) and *E2a* gene–splice variant proteins E47 and E12 during the CLP to pre-pro–B cell transition (65). Pre-pro–B cells retain myeloid potential, which is abolished by subsequent expression of the B-lineage commitment transcription factor PAX5 (66, 67). *Pax5*−/− mice lose all B cell development beyond the early pro–B cell stage, are severely runted, and die in the early postnatal period (68).

SNP arrays and genomic DNA sequencing of pediatric B-ALL samples identified somatic deletions and point mutations targeting the *PAX5* gene in ∼32% of cases, which caused reduced PAX5 transcriptional activity in reporter assays (69). This survey also identified less-frequent deletions of *E2A (TCF3)*, *EBF1*, *LEF1*, *IKAROS* (*IKZF1*), and *AIOLOS* (*IKZF3*) transcription-factor genes, several of which have identified roles in controlling early B cell differentiation. Rare *PAX5* translocations in pro–B cell stage ALL, including *PAX5-ETV6*, *PAX5-EVI3*, *PAX5-ENL*, and others, have been described, with *PAX5-ENL* inhibiting the transcriptional activity of PAX5 (70). Although it is not yet proven that *Pax5* gene alterations promote pre-B-LBL in mouse modeling, a common action of these mutations, deletions, and translocations may be to block B cell differentiation, either by lack of PAX5 function or by dominant-negative PAX5 fusion protein activity on PAX5 target-gene transcription. Because differentiation blockade is a critical aspect of ALL development, altered PAX5 may participate in this process, as shown by targeted inactivation of *Aiolos* and *Ikaros* lymphocyte transcription factors in mice. AIOLOS, IKAROS, HELIOS, EOS, PEGASUS, and DAEDALUS are members of a Krüppel-like zinc-finger transcription-factor family that binds DNA and regulates B and T cell development and function (71, 72). *Aiolos*−/− mice result in hyperproliferation and constitutive B cell activation, with pre-B-LBL developing in ∼20% of mice (73). Alternatively spliced *Aiolos* isoforms lacking a full complement of DNA-binding domains in normal and leukemic human B cells have been reported, but their role in human B-ALL has not been identified (74).

E2A-PBX1 Chimeric Transcription Factor

As we discussed briefly above, *E2A* encodes class I bHLH E47 and E12 E-box transcription factors that regulate the CLP to pre-pro–B cell transition in early B cell development. A t(1;19)(q23;p13) fuses the *PBX1* class II divergent *HOX* gene to *E2A* in 3–5% of B-ALL cases

CLP: common lymphoid progenitor

Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org by University of California - Los Angeles on 02/16/09. For personal use only.

ICN1: intracellular portion of NOTCH1

and in 25% of cases with a pre–B cell stage ALL phenotype (75). This rearrangement generates a fusion gene that encodes a chimeric transcription factor from the amino-transactivation domains, AD1 and AD2, of E2A and of the DNA-binding domain of PBX1 (76). Unlike PBX1, E2A-PBX1 is a transcriptional activator for reporter constructs that contain PBX1-binding sites; it also binds to a subset of endogenous *PBX* target genes in vitro (77). E2A-PBX1 may contribute to leukemogenesis by binding and sequestering normal partners of the PBX proteins, such as HOX proteins, and by sequestering E2A coactivators, leading to the repression of E2A target genes and to uncontrolled cell-cycle progression, as shown by in vitro foci-forming assays.

E2A-HLF Chimeric Transcription Factor

A rare t(17;19)(q22;p13) brings together the amino-terminal transcription-activating AD1 and AD2 domains of E2A with the C-terminal basic region and the leucine-zipper DNA-binding and dimerization domains of the PAR (proline- and acidic amino acid–rich protein) subfamily bZIP (basic leucine zipper) transcription factor known as HLF (hepatic leukemia factor) (78, 79). The novel chimeric transcription factor E2A-HLF promotes aggressive, treatment-resistant pro–B cell stage ALL that shows unique clinical associations including adolescent presentation, hypercalcemia, and disseminated intravascular coagulation (DIC) (80). E2A-HLF requires homodimerization and DNA binding to promote in vitro NIH3T3 cell–foci formation and to cause mainly T cell malignancies in transgenic mouse models (81, 82). Leukemogenic mechanism(s) likely relate to aberrant induction of SLUG, an antiapoptotic DNA damage–induced zinc-finger transcription factor that may inhibit proapoptotic BH3-only BCL2–family member expression (83) as well as probable dominant-negative interference by dimerization and sequestration of E2A proteins that regulate cell-cycle and early B-lineage-fate decisions.

MOLECULAR PATHOGENESIS OF T CELL ACUTE LYMPHOBLASTIC LEUKEMIA

Activation of NOTCH1 Signaling

Four human *NOTCH* genes encode unusual type I transmembrane receptors that function in signal transduction and control of metazoan development. To date, altered *NOTCH1* is the only family member implicated in T-ALL (84, 85). NOTCH1 has an extracellular domain composed of 36 epidermal growth factor (EGF)-like repeats, 3 LIN12/NOTCH repeats, and 1 juxtamembrane heterodimerization domain. Newly synthesized NOTCH1 is cleaved by a furin-like protease to generate a heterodimer of extracellular and transmembrane/cytoplasmic (TM) subunits that are noncovalently attached to form the mature NOTCH1 receptor at the cytoplasmic membrane. The intracellular portion of NOTCH1 (ICN1) has one RAM domain, seven ankyrin-like repeats, one transactivation domain, and one C-terminal PEST (proline-, glutamic acid–, serine-, and threonine-rich) domain. NOTCH1 signaling initiates with binding by a DELTA/SERRATE/LAG-2 family member on the surface of an interacting cell. This interaction induces intramembrane proteolysis with ADAM-like metalloprotease cleavage, then γ-secretase cleavage, which is followed by release of ICN1 into the cytoplasm. Released ICN1 translocates to the nucleus, where it forms a transcription complex with CSL (CBF1, also known as RBP-J, Suppressor of Hairless, and LAG-1), mastermind-like (MAML) family members, and other cofactors including p300, RNA pol II–containing complexes, and additional histone modifiers. Nuclear ICN1 is short-lived and is targeted for transcription-linked ubiquitin-mediated degradation by its C-terminal PEST domain.

NOTCH1 was discovered from a t(7;9)(q34;q34.3) that occurs in $<1\%$ of T-ALL cases (86). Translocated *NOTCH1* encodes a partial NOTCH1 receptor that lacks the extracellular portion and retains TM and

Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org by University of California - Los Angeles on 02/16/09. For personal use only.

ICN1 subunits, including the juxtamembrane heterodimerization domain. This truncated form requires γ-secretase proteolysis, but not ligand binding, to release active ICN1 from the membrane, suggesting that γ-secretase inhibitors (GSIs)—currently used mainly for treating Alzheimer disease—may be an effective therapy for *NOTCH1*-altered T-ALL. With such a low patient frequency, *NOTCH1* alterations were considered a minor pathway to T-ALL until gain-of-function mutations were discovered in ∼55% of translocation-negative T-ALL cases (87). DNA sequencing showed *NOTCH1* heterodimerization–domain missense mutations and PEST-domain mutations and deletions involving one or both domains in *cis* in all immunophenotypic and molecular T-ALL subtypes. Heterodimerization domain missense mutations also cause ligand-independent NOTCH1 cleavage, removing this prerequisite to cleavage by γ-secretase. C-terminal PEST domain deletions stabilize ICN1 by removing an SCF^{FBW7} (SKP1, CUL1, F-box protein) E3-ligase phosphodegron sequence, resulting in increased ICN1 stability and enhanced reporter assay activity. Therefore, leukemogenesis from *NOTCH1* translocations and mutations likely arises from augmented transcription of ICN1 target genes, such as *MYC* (88), and from signaling-pathway activation, such as enhanced mTOR (mammalian target of rapamycin) signaling through *PTEN* (phosphatase and tensin homolog) repression and heightened PI3K-AKT pathway activity (89), to promote precursor T cell growth. Because of the central role of NOTCH in T-lineage development, these alterations likely originate and deregulate the earliest intrathymic T cell progenitors, which drive T-ALL formation when coupled to secondary transforming alterations such as loss of the transcriptional repressor *IKAROS*.

In nonmalignant T cells, NOTCH1 signaling upregulates *MYC* and *HES1* (Hairy and Enhancer-of-Split) transcription factors, causing antagonistic binding on the *PTEN* promoter, with *HES1* repression dominating *MYC* induction and resulting in *PTEN* downregulation with augmented PI3K-AKT pathway signaling (88) (**Figure 2**). PTEN is a tumor suppressor with lipid and protein phosphatase activity that opposes the receptor tyrosine kinase–PI3K-induced activation of AKT. As soon as the NOTCH pathway is silenced by cessation of ligand-bound stimulation and ICN1 proteolysis, *PTEN* expression returns to baseline, and signaling through the PI3K-AKT pathway is again modulated by PTEN. However, gain-of-function *NOTCH1* mutations and mutational loss of *PTEN* are associated with resistance to GSIs in T-ALL (90), possibly because the malignant clone transfers its oncogene addiction from constitutive NOTCH1 signaling to constitutive PI3K-AKT signaling (91). *PTEN* is mutated and is the most consistently downregulated gene in GSI-resistant T-ALL cell lines. All molecular subtypes of primary T-ALL patient samples also show *PTEN* repression, with PTEN-silencing alterations in NOTCH1-activated T-ALL seen both at diagnosis and as a secondary event during disease progression. These important results suggest that concurrent treatment with both GSI and therapy targeting PI3K-AKT signaling may be required for personalized treatment of specific gain-of-function NOTCH1 T-ALL cases. Consistent with the selective role of NOTCH in early T-lineage development, no NOTCH alterations have been identified in B-ALL to date.

GSI: γ-secretase inhibitor

Transgenic mice expressing *ICN1*, lacking the PEST proteolysis domain, and driven by the T-lineage-specific *Lck* proximal promoter favor TCRαβ+ CD8+ over CD4+ thymocyte maturation (92), with ∼20% of mice developing CD4+CD8+ pre-T-LBL (93). Interestingly, proviral insertion mutagenesis identified *Ikaros* as the main disrupted target gene that cooperates with and accelerates ICN1-induced T-ALL, showing a striking similarity to *IKAROS* deletion in BCR-ABL+ B-ALL (46). Targeted removal of the *Ikaros* DNA-binding domain is embryonic lethal, but 100% of hemizygous mice develop thymic-based T cell lymphoproliferations, followed by clonal CD4−CD8−, CD4+ or CD8+, TCR+ pre-T-LBL (94).

Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org by University of California - Los Angeles on 02/16/09. For personal use only.

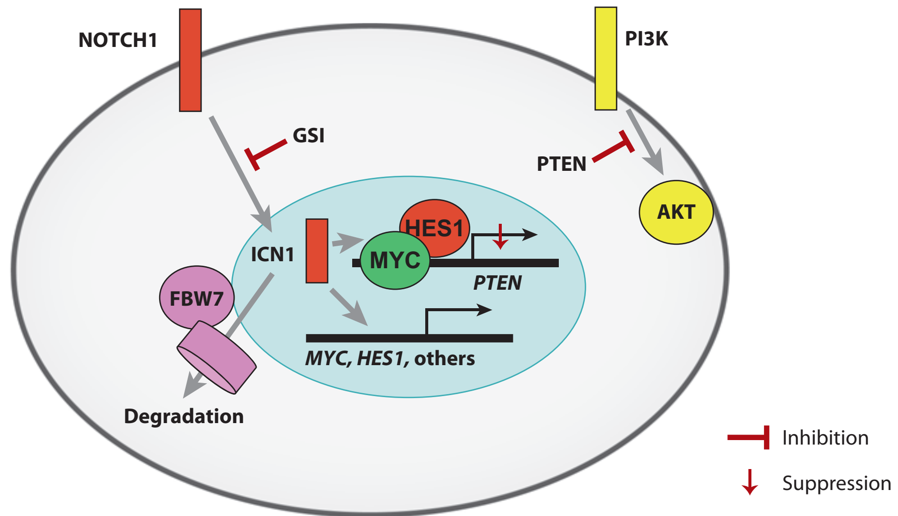


Figure 2

FBW7 (F-box- and WD repeat domain–containing 7) or PTEN (phosphatase and tensin homolog) functional loss leads to γ-secretase inhibitor (GSI) resistance in *NOTCH1* gain-of-function T cell acute lymphoblastic leukemia (T-ALL). Ligand-independent activating *NOTCH1* lesions, including truncation by chromosomal translocation and mutations in *NOTCH1* heterodimerization and PEST (proline-, glutamic acid–, serine-, and threonine-rich) domains, lead to constitutive NOTCH1 pathway activation following γ-secretase cleavage/release from the membrane and increased intranuclear intracellular portion of NOTCH1 (ICN1). A transcriptional binding/activation complex is formed among ICN1 and CSL (CBF1, also known as RBP-J, Suppressor of Hairless, and LAG-1), mastermind-like (MAML), p300, and other cofactors, which results in upregulation of *MYC* among many ICN1 target genes. *HES1* (Hairy and Enhancer-of-Split) is also a NOTCH1-induced target gene, and both it and MYC bind to the *PTEN* promoter, resulting in HES1-mediated suppression of *PTEN* overpowering MYC-mediated induction (88). SCF^{FBW7} (SKP1, CUL1, F-box protein) E3 ligase–mediated ubiquitination through the ICN1 C-terminal PEST domain targets ICN1 for proteosomal degradation and cessation of NOTCH1 pathway signaling. However, mutation of the FBW7 protein substrate recognition subunit of SCF-type E3 ubiquitin ligase, or PEST-domain mutations in ICN1 that block ubiquitination, stabilize ICN1 and maintain inappropriate NOTCH1 signaling pathway activation, which opposes GSI therapy. Transient repression of the *PTEN* tumor suppressor and decreased *MYC* expression are inhibited through ICN1 maintenance. Homozygous loss of *PTEN* renders NOTCH1-activated T-ALL samples resistant to GSI through constitutive PI3K (phosphatidylinositol 3–kinase)-AKT signaling, which now cannot be reversed by proteolytic removal of ICN1, to support robust cell proliferation, survival, and size growth (153).

Tumors uniformly demonstrate loss of heterozygosity (LOH) of the wild-type *Ikaros* allele. Although increased levels of IKAROS isoforms lacking DNA-binding domains are seen in B-ALL, T-ALL, and CML in blast crisis, their role(s) in human ALL has not yet been determined (74). Additional *ICN1*-transgenic and *ICN1*-modified BM with adoptive transfer mouse models of NOTCH1 gain-of-function signaling also develop CD4+CD8+ pre-T-LBL, often in cooperation with c-MYC (95–98).

Gene knockout of *Pten* is embryonic lethal in mice, whereas *Pten*-heterozygous CD-1-strain mice survive and develop thymocyte expansions followed by pre-T-LBL at high frequencies (99). Analyzed tumors demonstrate LOH at the wild-type *Pten* locus. Inbred 129Sv- and C57BL/6 *Pten*$^{+/-}$–strain mice do not develop T cell leukemia/lymphoma, indicating that strain-specific effects contribute to *Pten* tumor suppression (100). Multiple human tumor types and patients with Cowden disease, Bannayan-Zonana syndrome, and Lhermitte-Duclos

Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org by University of California - Los Angeles on 02/16/09. For personal use only.

syndrome demonstrate diverse types of *PTEN*-inactivating mutations, although *PTEN* is rarely mutated or lost in human lymphoid malignancies.

Inactivation of the SCF^{FBW7} E3 Ubiquitin Ligase

FBW7 (F-box- and WD repeat domain–containing 7) is a protein substrate recognition subunit of the SCF-type E3 ubiquitin ligases and is mutated in a wide range of human cancers, where it functions as a tumor suppressor (101). Known FBW7 substrates for degradation include JUN, CYCLIN E, and key members of the NOTCH signaling pathway including γ-secretase, ICN1, and the ICN1 transcriptional target *MYC* (102). Missense mutations in key arginine substrate-binding residues are the mechanism for FBW7 malfunctioning in T-ALL (103–106). These FBW7 mutations, along with mutations centered around T^{2512} in the ICN1 PEST domain, block FBW7-mediated ICN1 and possibly MYC degradation, leading to excessive NOTCH pathway signaling (**Figure 2**). T-ALL lines and relapsed T-ALL cases containing *FBW7* mutations are insensitive to GSIs, suggesting a mechanism for drug resistance that is potentially related to stabilization of MYC expression (106). FBW7 mutations may also coexist with NOTCH1 heterodimerization–domain mutations to further augment NOTCH pathway signaling. Mice with deletion of *Fbw7* are embryonic lethal, HSC-restricted *Fbw7*-knockout mice develop pancytopenia, and adoptive transfer of *Fbw7*-null HSCs impairs long-term HSC repopulating activity; most animals develop a CD4+CD8+ pre-T-LBL, probably due to c-MYC accumulation (107). Collectively, these results suggest that FBW7 is a tumor suppressor in T-ALL associated with T-ALL promotion, relapse, and drug resistance.

Deregulation of Homeobox Genes

HOX genes regulate axial patterning and cellular differentiation during embryonic development. All *HOX* genes encode transcription factors that have in common a 61-amino-acid helix-turn-helix DNA-binding homeodomain. The class I *HOX* genes (*HOXA-D)* cluster at four chromosomal loci (7p15, 17q21, 12q13, and 2q31), whereas class II *HOX* genes, also termed non-*HOX* genes or divergent *HOX* genes, are dispersed throughout the genome. To date, the only class I *HOX* genes with a suggested role in T-ALL belong to the *HOXA* cluster. One molecular subtype implicates an inv(7)(p15q34) that associates with elevated *HOXA10* and *HOXA11* expression (108, 109). Elevated expression is from juxtaposition to *TCRβ* enhancers with a postulated role in T-ALL from simple overexpression versus disordering of the usual developmental expression and silencing patterns within the *HOXA* gene cluster.

Class II *HOX* genes encode DNA-binding HOX protein cofactors, are not involved in homeotic transformations, have a more restricted pattern of expression than class I genes, and are implicated in organogenesis or cell-type differentiation. *HOX11* (also known as *T cell leukemia*, *homeobox 1*, and *TLX1*) is a class II orphan *HOX* gene that mouse knockout studies show is normally required for survival of splenic precursors during organogenesis (110, 111). *HOX11* is not expressed during T cell development, and it undergoes a t(10;14)(q24;q11) or t(7;10)(q34;q24), which induces elevated thymocyte expression by juxtaposition to *TCRα/δ*- or *TCRβ*-loci-regulatory elements in ~5% of pediatric to 30% of adult T-ALL (112). Aberrant *HOX11* expression may also occur by loss of negative regulatory elements with cytogenetic rearrangements or by loss of silencing DNA methylation. HOX11-containing T-ALL has a better prognosis than (*a*) other T-ALL subtypes and (*b*) a CD4+CD8+ precursor T cell phenotype. A mechanism for HOX11-mediated transformation has not been fully established, although transcription-independent inhibition of PP2A and PP1 signaling phosphatases, which alters RB phosphorylation and deregulates G_1/S cell-cycle growth-control genes, may be

Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org
by University of California - Los Angeles on 02/16/09. For personal use only.

Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org
by University of California - Los Angeles on 02/16/09. For personal use only.

involved (113, 114). About 20% of CD-1-strain mice with an *Eμ-HOX11* transgene develop IGM+IGD+ B cell lymphoma and not pre-B- or pre-T-LBL (115). An association between *HOX11* expression and B cell cancers in humans has not yet been established.

HOX11L2 (*TLX3*) is another well-studied class II orphan *HOX* gene that undergoes a t(5;14)(q35;q32), bringing it under the influence of *TCRα-/δ*-regulatory elements downstream of *BCL11B* (a gene expressed throughout T cell development) in ~20% of children and ~5% of adults with T-ALL (116). Microarray studies indicate that *HOX11+* and *HOX11L2+* T-ALL gene-expression patterns cluster together, suggesting a potential common mechanism of action, although HOX11L2+ T-ALL cases have a less favorable outcome and a broader immunophenotype than HOX11+ T-ALL cases (11, 108).

Mutation or Translocation of TAL1 and LYL1

TAL1 encodes a class II bHLH transcription factor that is a master regulator of hematopoietic lineage commitment (**Figure 1**) and is essential for the development of mouse HSCs; however, its continued expression is dispensable for definitive HSC functions (117). *TAL1* is a target for translocation or mutation in ~25% of childhood T-ALL cases (118–120), with t(1;14)(p32;q11), t(1;14)(p34;q11), and deletions aberrantly activating *TAL1* during thymocyte maturation, promoting transformation. An interesting hypothesis for its contribution to T-ALL is its inhibition of the function of class I bHLH E47 and HEB (TCF12) transcription factors through heterodimer formation, thereby blocking normal T cell differentiation. Support for this potential mechanism comes from (*a*) $E2a^{-/-}$ mice, which develop pre-T-LBL (121); (*b*) transgenic mice lacking the TAL1 DNA-binding domain that develop pre-T-LBL (122); and (*c*) accelerated pre-T-LBL in *TAL1*-transgenic mice on $E2a^{-/-}$ or $Heb^{-/-}$ backgrounds (123). Thymocyte-expressing CD2 promoter *Tal1/Scl*–transgenic mice fail to develop T-lineage malignancies unless crossed with *N-Ras*-transgenic or *p53*-null mice (124). In contrast, proximal *Lck* promoter–driven *Tal1* transgenics develop pre-T-LBL (125). Transgenics lacking the *Tal1* DNA-binding domain still develop CD8+ pre-T-LBL, again suggesting that the *Tal1* tumor-promoting effect likely arises from interference with additional trans-acting factors, such as E2A proteins (122, 126).

LYL1 encodes another class II bHLH transcription factor that forms heterodimers with class I bHLH proteins, such as E2A (E47 and E12) and HEB. *LYL1* was identified from a t(7;19)(q35;p13) in a T cell leukemia line and is aberrantly expressed in only a few T-ALL cases (11, 127, 128). LYL1 has an unknown cellular function, but it has an overlapping expression pattern with TAL1 and shares 90% sequence identity with the bHLH domain of TAL1. LYL1 cannot replace TAL1 in driving early hematopoietic development and HSC commitment. LYL1-transgenic mice developed CD4+CD8+ pre-T-LBL, probably through dimerization with E2A, inhibition of CD4 promoter activity, and downregulation of a subset of E2A/HEB target genes, suggesting a block in differentiation as a component of T cell transformation (129).

MYB Duplication and Translocation

MYB is the cellular homolog of the *v-Myb* oncogene of the avian myeloblastosis virus. Gene knockout studies show that MYB is required for mouse T cell development (130, 131). A t(6;7)(q23;q34), juxtaposing *MYB* to *TCRβ* regulatory elements, and a *MYB* gene duplication, caused by ALU-mediated homologous recombination, were detected in 8–15% of T-ALL cases, leading to *MYB* overexpression and a blockade in T cell differentiation that was reversed with *MYB* knockdown (132–134).

Translocation of LMO1 and LMO2

LMO1 (e.g., *RBTN1*, *TTG1*) and *LMO2* (e.g., *RBTN2*, *TTG2*) genes encode cysteine-rich,

tandem LIM–only domain-containing proteins that interact with a variety of nuclear factors, including TAL1 in erythroid cells (135). t(11;14)(p13;q11) and t(7;11)(q35;p13) rearrange the *LMO2* gene to *TCRα/δ* or *TCRβ* loci, which, along with del11(p12;p13) of a negative regulatory sequence, can cause deregulated *LMO2* expression in T-ALL (136–138). Approximately 10% of *Lmo2*-transgenic mice develop CD4−CD8−, CD4+CD8+, CD4+, or CD8+ pre-T-LBL (139). A *CD2* promoter–driven *Lmo2*-transgenic model develops a similar spectrum of *Tcrαβ* and *Tcrγδ* pre-T-LBL in ~75% of mice (140) and accelerates the rate of pre-T-LBL in *Tal1*-transgenic mice (141). DNA mismatch repair (MMR) genes maintain fidelity of genomic replication in mammals. Targeted deletion of the *Msh2* MMR gene results in TdT+RBTN2+TAL1+ pre-T-LBL that spans the CD4−CD8−, CD4+ or CD8+ and CD4+CD8+ developmental spectrum (142, 143). As discussed above, human T-ALL may exhibit genetic defects leading to aberrant *RBTN2* or *TAL1* expression, suggesting a potential role for defective *MSH2* or for additional MMR genes in certain T-ALL cases (144).

CALM-AF10 Fusion Gene

Rare t(10;11)(p13;q14-21) arise in ALL and AML, generating a *CALM-AF10* fusion gene that encodes a chimeric fusion protein (145). CALM (clathrin assembly lymphoid myeloid) is a 652-residue cytoplasmic protein that functions in the assembly of clathrin-coated pits during endocytosis and may also interact with nuclear proteins (146). AF10 is a 1027-amino-acid putative transcription factor that contains a nuclear localization signal and several conserved transcription-factor DNA-interaction domains, including a plant HOX domain and an AT-hook motif, and was first isolated as a fusion partner with MLL (147). CALM-AF10 fusions occur most frequently in *TCRγδ*-expressing T-ALL, typically with all but four amino acids from the C terminus retained from CALM fused to one of four common AF10 fusion sites that retain most of the AF10 coding sequence. The precise mechanism for CALM-AF10-mediated transformation is not known, although the expression of *HOXA* cluster genes, including *HOXA5*, *HOXA9*, and *HOXA10*, along with the polycomb group transcriptional repressor *BMI1*, is induced in *CALM-AF10*-expressing T-ALL cells (148). BMI1 is a potent repressor of the *CDKN2A* (*INK4A-ARF*) tumor-suppressor locus, and *CDKN2A* is deleted in ~70% of T-ALL (149), suggesting a mechanism of altered lymphocyte differentiation coupled to enhanced cell proliferation and survival for *CALM-AF10*-mediated transformation. A *CALM-AF10* model created using retroviral transduction of mouse BM followed by recipient transfer generates ALL with features of myeloid and B cell bilineage differentiation, suggesting transformation of a multipotent lineage precursor cell (150). A second model created using a *Vav*-driven *CALM-AF10* transgene develops a mixed-lineage ALL phenotype as well (151).

CONCLUSION

ALL is mainly a disease of childhood. It is characterized by uncontrolled precursor lymphocyte proliferation, survival, and blocked differentiation that initiates from the BM, thymus, and perhaps fetal hemogenic organs. Despite current therapeutic success, specific molecular subtypes, such as *BCR-ABL+* and *MLL-AF4+* B-ALL, and disease in adults continue to have a poor prognosis. ALL accounts for more deaths due to treatment resistance and relapse than any other childhood malignancy. The proliferating lymphoblasts of ALL are generated by genetic defects of unknown cause at or before permissive stages of transformation during precursor hematopoietic or lymphocyte development. The main molecular genetic mechanisms driving ALL pathogenesis include chromosomal translocations that generate novel fusion genes or that deregulate gene expression, most often from master or key transcriptional regulatory factors, chromosome copy number

Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org
by University of California - Los Angeles on 02/16/09. For personal use only.

alterations (with either hyper- or hypodiploid forms of aneuploidy), and gene-specific mutations. Chimeric transcription-factor or chromatin-modifier fusion proteins may act to induce or repress gene expression by novel gene targeting, by aberrant recruitment of coactivators or corepressors to target genes, or by generating dominant-negative complexes that block regulatory elements from gaining access to target sites. Mechanisms of treatment resistance and tumor progression include secondarily acquired mutations of primary oncogene-addicted lesions with clonal outgrowth over time, gene amplification, and complementing genetic changes in secondary loci such as (*a*) *CDKN2A* tumor-suppressor and *IKAROS* transcription-factor deletions in BCR-ABL+ B-ALL and (*b*) *PTEN* tumor-suppressor loss in NOTCH1 gain-of-function T-ALL. Nongenetic contributors to ALL pathogenesis likely include gene deregulation through altered epigenetic mechanisms, such as repeated patterns of abnormal DNA methylation and possibly effects on post-transcriptional processing due to aberrant microRNA effects on transcript stability and translation, although further work is required to establish the importance of these factors.

Despite the activity of RAG1 and RAG2 during pre-BCR and pre-TCR assembly at post-CLP stages of lymphocyte precursor development, oncogenic translocations into the antigen receptor loci are observed almost exclusively in T-ALL. This is not due to preferential rearrangements of pre-CLP-acting HSC factors in B cells, as common B-ALL rearrangements involve *MLL*, *TEL*, and *AML1*, whereas common T-ALL rearrangements involve *HOX* and *TAL1*(*SCL1*) genes (**Figure 1**). Also, mature B cell transformation of germinal-center B cells, in which activation-induced cytadine deaminase directs DNA double-strand breaks to *IG* and specific non-*IG* loci followed by repair, involves common rearrangements into the *IG* locus for (*a*) *IG-BCL2* in follicular lymphoma, (*b*) *IG-MYC* in Burkitt lymphoma, and (*c*) *IG-BCL6* in diffuse large B cell lymphoma. Why B-ALL is exempt from molecular genetic mechanisms that cause gene rearrangements into the B cell antigen receptor loci, whereas T-ALL and germinal-center B cell lymphomas are not, remains unclear.

SUMMARY POINTS

1. Acute leukemias are driven by (*a*) recurrent chromosomal translocations that generate novel fusion genes or deregulate gene expression, (*b*) numerical chromosome–copy number aberrations, or (*c*) gene-specific mutations.
2. The most commonly altered genes in ALL are transcription factors, which usually sit at or near the apex of regulatory networks that control early hematopoietic and lymphoid precursor development.
3. Therapeutic resistance in oncogene-addicted ALL may develop from companion genetic alterations, such as (*a*) *CDKN2A* (*INK4A/ARF*) or *IKZF1* (*IKAROS*) loss with BCR-ABL translocations and (*b*) *PTEN* loss with gain-of-function NOTCH1 mutations.

FUTURE ISSUES

1. Aside from a small number of cases in which inherited genetic predisposition syndromes or exposure to leukemogenic agents plays an etiologic role, the cause of ALL remains unclear.

Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org by University of California - Los Angeles on 02/16/09. For personal use only.

2. We do not yet know how the various molecular and genetic alterations that initiate and drive acute leukemogenesis control the redistribution of cell-energy resources to meet altered metabolic and biosynthetic demands.
3. It is necessary to determine whether there will be an expanding role for epigenetic and microRNA alterations in acute leukemogenesis through the use of advanced genome-surveying technologies.
4. Whether the amount of cancer-initiating or cancer stem cells present in each molecular subtype of ALL is quantitatively and qualitatively different and whether it parallels tumor aggressiveness and/or treatment response remain to be determined.
5. As yet, we do not know how specific molecular genetic alterations of transcription factors that control early pre-MPP hematopoiesis generate either B-ALL or T-ALL.

Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org
by University of California - Los Angeles on 02/16/09. For personal use only.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

In some cases, review articles were cited over original articles because of space constraints. P.P.P. and M.A.T. are supported by grants from the National Institutes of Health and the National Cancer Institute. M.A.T. is a Scholar of the Leukemia and Lymphoma Society.

LITERATURE CITED

1. Am. Cancer Soc. 2008. Cancer facts and figures 2008. **http://www.cancer.org/downloads/STT/2008CAFFfinalsecured.pdf**. Last accessed July 7, 2008
2. Pui CH, Evans WE. 2006. Treatment of acute lymphoblastic leukemia. *N. Engl. J. Med.* 354:166–78
3. Vitale A, Guarini A, Chiaretti S, Foa R. 2006. The changing scene of adult acute lymphoblastic leukemia. *Curr. Opin. Oncol.* 18:652–59
4. Greaves M. 2006. Infection, immune responses and the aetiology of childhood leukaemia. *Nat. Rev. Cancer* 6:193–203
5. Greaves MF, Wiemels J. 2003. Origins of chromosome translocations in childhood leukaemia. *Nat. Rev. Cancer* 3:639–49
6. Hong D, Gupta R, Ancliff P, Atzberger A, Brown J, et al. 2008. Initiating and cancer-propagating cells in TEL-AML1-associated childhood leukemia. *Science* 319:336–39
7. Maia AT, Van Der Velden VH, Harrison CJ, Szczepanski T, Williams MD, et al. 2003. Prenatal origin of hyperdiploid acute lymphoblastic leukemia in identical twins. *Leukemia* 17:2202–6
8. Wiemels JL, Cazzaniga G, Daniotti M, Eden OB, Addison GM, et al. 1999. Prenatal origin of acute lymphoblastic leukaemia in children. *Lancet* 354:1499–503
9. Buffler PA, Kwan ML, Reynolds P, Urayama KY. 2005. Environmental and genetic risk factors for childhood leukemia: appraising the evidence. *Cancer Invest.* 23:60–75
10. Kinlen L. 2004. Infections and immune factors in cancer: the role of epidemiology. *Oncogene* 23:6341–48
11. Ferrando AA, Neuberg DS, Staunton J, Loh ML, Huard C, et al. 2002. Gene expression signatures define novel oncogenic pathways in T cell acute lymphoblastic leukemia. *Cancer Cell* 1:75–87
12. Wang JC, Dick JE. 2005. Cancer stem cells: lessons from leukemia. *Trends Cell Biol.* 15:494–501

13. Barabe F, Kennedy JA, Hope KJ, Dick JE. 2007. Modeling the initiation and progression of human acute leukemia in mice. *Science* 316:600–4
14. Roman-Gomez J, Cordeu L, Agirre X, Jimenez-Velasco A, San Jose-Eneriz E, et al. 2007. Epigenetic regulation of Wnt-signaling pathway in acute lymphoblastic leukemia. *Blood* 109:3462–69
15. Omura-Minamisawa M, Diccianni MB, Batova A, Chang RC, Bridgeman LJ, et al. 2000. Universal inactivation of both p16 and p15 but not downstream components is an essential event in the pathogenesis of T cell acute lymphoblastic leukemia. *Clin. Cancer Res.* 6:1219–28
16. Roman-Gomez J, Castillejo JA, Jimenez A, Gonzalez MG, Moreno F, et al. 2002. 5′ CpG island hypermethylation is associated with transcriptional silencing of the p21(CIP1/WAF1/SDI1) gene and confers poor prognosis in acute lymphoblastic leukemia. *Blood* 99:2291–96
17. Mi S, Lu J, Sun M, Li Z, Zhang H, et al. 2007. MicroRNA expression signatures accurately discriminate acute lymphoblastic leukemia from acute myeloid leukemia. *Proc. Natl. Acad. Sci. USA* 104:19971–76
18. Brunning RD, Flandrin G, Borowitz M, Swerdlow SH, Matutes E, et al. 2001. WHO histological classification of precursor B cell and T cell neoplasms. In *Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*, ed. ES Jaffe, NL Harris, H Stein, JW Vardiman, pp. 110–17. Lyon: IARC
19. Dalla-Favera R, Bregni M, Erikson J, Patterson D, Gallo RC, Croce CM. 1982. Human *c-myc* oncogene is located on the region of chromosome 8 that is translocated in Burkitt lymphoma cells. *Proc. Natl. Acad. Sci. USA* 79:7824–27
20. Teitell MA, Mikkola HK. 2006. Transcriptional activators, repressors, and epigenetic modifiers controlling hematopoietic stem cell development. *Pediatr. Res.* 59:33–39R
21. Morse HC 3rd, Anver MR, Fredrickson TN, Haines DC, Harris AW, et al. 2002. Bethesda proposals for classification of lymphoid neoplasms in mice. *Blood* 100:246–58
22. Gleissner B, Gokbuget N, Bartram CR, Janssen B, Rieder H, et al. 2002. Leading prognostic relevance of the BCR-ABL translocation in adult acute B-lineage lymphoblastic leukemia: a prospective study of the German Multicenter Trial Group and confirmed polymerase chain reaction analysis. *Blood* 99:1536–43
23. Ribeiro RC, Abromowitch M, Raimondi SC, Murphy SB, Behm F, Williams DL. 1987. Clinical and biologic hallmarks of the Philadelphia chromosome in childhood acute lymphoblastic leukemia. *Blood* 70:948–53
24. Heisterkamp N, Stam K, Groffen J, de Klein A, Grosveld G. 1985. Structural organization of the *bcr* gene and its role in the Ph translocation. *Nature* 315:758–61
25. Chan LC, Karhi KK, Rayter SI, Heisterkamp N, Eridani S, et al. 1987. A novel abl protein expressed in Philadelphia chromosome positive acute lymphoblastic leukaemia. *Nature* 325:635–37
26. Konopka JB, Watanabe SM, Witte ON. 1984. An alteration of the human c-abl protein in K562 leukemia cells unmasks associated tyrosine kinase activity. *Cell* 37:1035–42
27. Harrison SC. 2003. Variation on an Src-like theme. *Cell* 112:737–40
28. Tanis KQ, Veach D, Duewel HS, Bornmann WG, Koleske AJ. 2003. Two distinct phosphorylation pathways have additive effects on Abl family kinase activation. *Mol. Cell Biol.* 23:3884–96
29. Puil L, Liu J, Gish G, Mbamalu G, Bowtell D, et al. 1994. Bcr-Abl oncoproteins bind directly to activators of the Ras signalling pathway. *EMBO J.* 13:764–73
30. Tauchi T, Boswell HS, Leibowitz D, Broxmeyer HE. 1994. Coupling between p210bcr-abl and Shc and Grb2 adaptor proteins in hematopoietic cells permits growth factor receptor–independent link to ras activation pathway. *J. Exp. Med.* 179:167–75
31. Kharas MG, Fruman DA. 2005. ABL oncogenes and phosphoinositide 3–kinase: mechanism of activation and downstream effectors. *Cancer Res.* 65:2047–53
32. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, et al. 2001. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N. Engl. J. Med.* 344:1031–37
33. Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, et al. 1996. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. *Nat. Med.* 2:561–66
34. Traxler P, Bold G, Buchdunger E, Caravatti G, Furet P, et al. 2001. Tyrosine kinase inhibitors: from rational design to clinical trials. *Med. Res. Rev.* 21:499–512
35. Nagar B, Bornmann WG, Pellicena P, Schindler T, Veach DR, et al. 2002. Crystal structures of the kinase domain of c-Abl in complex with the small molecule inhibitors PD173955 and imatinib (STI-571). *Cancer Res.* 62:4236–43

Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org
by University of California - Los Angeles on 02/16/09. For personal use only.

36. Schindler T, Bornmann W, Pellicena P, Miller WT, Clarkson B, Kuriyan J. 2000. Structural mechanism for STI-571 inhibition of abelson tyrosine kinase. *Science* 289:1938–42
37. Gorre ME, Mohammed M, Ellwood K, Hsu N, Paquette R, et al. 2001. Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. *Science* 293:876–80
38. Shah NP, Nicoll JM, Nagar B, Gorre ME, Paquette RL, et al. 2002. Multiple BCR-ABL kinase domain mutations confer polyclonal resistance to the tyrosine kinase inhibitor imatinib (STI571) in chronic phase and blast crisis chronic myeloid leukemia. *Cancer Cell* 2:117–25
39. Shah NP, Tran C, Lee FY, Chen P, Norris D, Sawyers CL. 2004. Overriding imatinib resistance with a novel ABL kinase inhibitor. *Science* 305:399–401
40. Armstrong SA, Look AT. 2005. Molecular genetics of acute lymphoblastic leukemia. *J. Clin. Oncol.* 23:6306–15
41. Druker BJ, Sawyers CL, Kantarjian H, Resta DJ, Reese SF, et al. 2001. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N. Engl. J. Med.* 344:1038–42
42. Heerema NA, Harbott J, Galimberti S, Camitta BM, Gaynon PS, et al. 2004. Secondary cytogenetic aberrations in childhood Philadelphia chromosome positive acute lymphoblastic leukemia are nonrandom and may be associated with outcome. *Leukemia* 18:693–702
43. Primo D, Tabernero MD, Perez JJ, Rasillo A, Sayagues JM, et al. 2005. Genetic heterogeneity of BCR/ABL+ adult B cell precursor acute lymphoblastic leukemia: impact on the clinical, biological and immunophenotypical disease characteristics. *Leukemia* 19:713–20
44. Sherr CJ, McCormick F. 2002. The RB and p53 pathways in cancer. *Cancer Cell* 2:103–12
45. Serrano M, Lee H, Chin L, Cordon-Cardo C, Beach D, DePinho RA. 1996. Role of the INK4a locus in tumor suppression and cell mortality. *Cell* 85:27–37
46. Mullighan CG, Miller CB, Radtke I, Phillips LA, Dalton J, et al. 2008. BCR-ABL1 lymphoblastic leukaemia is characterized by the deletion of Ikaros. *Nature* 453:110–14
47. Ng SY, Yoshida T, Georgopoulos K. 2007. Ikaros and chromatin regulation in early hematopoiesis. *Curr. Opin. Immunol.* 19:116–22
48. Kirstetter P, Thomas M, Dierich A, Kastner P, Chan S. 2002. Ikaros is critical for B cell differentiation and function. *Eur. J. Immunol.* 32:720–30
49. Wong S, Witte ON. 2004. The BCR-ABL story: bench to bedside and back. *Annu. Rev. Immunol.* 22:247–306
50. Williams RT, Roussel MF, Sherr CJ. 2006. Arf gene loss enhances oncogenicity and limits imatinib response in mouse models of Bcr-Abl-induced acute lymphoblastic leukemia. *Proc. Natl. Acad. Sci. USA* 103:6688–93
51. Wong S, Witte ON. 2001. Modeling Philadelphia chromosome positive leukemias. *Oncogene* 20:5644–59
52. Krivtsov AV, Armstrong SA. 2007. MLL translocations, histone modifications and leukaemia stem-cell development. *Nat. Rev. Cancer* 7:823–33
53. Meyer C, Schneider B, Jakob S, Strehl S, Attarbaschi A, et al. 2006. The MLL recombinome of acute leukemias. *Leukemia* 20:777–84
54. Ernst P, Fisher JK, Avery W, Wade S, Foy D, Korsmeyer SJ. 2004. Definitive hematopoiesis requires the mixed-lineage leukemia gene. *Dev. Cell* 6:437–43
55. Ernst P, Mabon M, Davidson AJ, Zon LI, Korsmeyer SJ. 2004. An Mll-dependent Hox program drives hematopoietic progenitor expansion. *Curr. Biol.* 14:2063–69
56. Attarbaschi A, Mann G, Strehl S, Konig M, Steiner M, et al. 2007. Deletion of 11q23 is a highly specific nonrandom secondary genetic abnormality of ETV6/RUNX1–rearranged childhood acute lymphoblastic leukemia. *Leukemia* 21:584–86
57. Golub TR, Barker GF, Bohlander SK, Hiebert SW, Ward DC, et al. 1995. Fusion of the TEL gene on 12p13 to the AML1 gene on 21q22 in acute lymphoblastic leukemia. *Proc. Natl. Acad. Sci. USA* 92:4917–21
58. Okuda T, van Deursen J, Hiebert SW, Grosveld G, Downing JR. 1996. AML1, the target of multiple chromosomal translocations in human leukemia, is essential for normal fetal liver hematopoiesis. *Cell* 84:321–30

Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org
by University of California - Los Angeles on 02/16/09. For personal use only.

59. Wang Q, Stacy T, Binder M, Marin-Padilla M, Sharpe AH, Speck NA. 1996. Disruption of the Cbfa2 gene causes necrosis and hemorrhaging in the central nervous system and blocks definitive hematopoiesis. *Proc. Natl. Acad. Sci. USA* 93:3444–49
60. Hock H, Meade E, Medeiros S, Schindler JW, Valk PJ, et al. 2004. Tel/Etv6 is an essential and selective regulator of adult hematopoietic stem cell survival. *Genes Dev.* 18:2336–41
61. Fears S, Gavin M, Zhang DE, Hetherington C, Ben-David Y, et al. 1997. Functional characterization of ETV6 and ETV6/CBFA2 in the regulation of the MCSFR proximal promoter. *Proc. Natl. Acad. Sci. USA* 94:1949–54
62. Hiebert SW, Sun W, Davis JN, Golub T, Shurtleff S, et al. 1996. The t(12;21) translocation converts AML-1B from an activator to a repressor of transcription. *Mol. Cell Biol.* 16:1349–55
63. Rompaey LV, Potter M, Adams C, Grosveld G. 2000. Tel induces a G1 arrest and suppresses Ras-induced transformation. *Oncogene* 19:5244–50
64. Bernardin F, Yang Y, Cleaves R, Zahurak M, Cheng L, et al. 2002. TEL-AML1, expressed from t(12;21) in human acute lymphocytic leukemia, induces acute leukemia in mice. *Cancer Res.* 62:3904–8
65. Quong MW, Romanow WJ, Murre C. 2002. E protein function in lymphocyte development. *Annu. Rev. Immunol.* 20:301–22
66. Nutt SL, Heavey B, Rolink AG, Busslinger M. 1999. Commitment to the B-lymphoid lineage depends on the transcription factor Pax5. *Nature* 401:556–62
67. Rolink AG, Schaniel C, Busslinger M, Nutt SL, Melchers F. 2000. Fidelity and infidelity in commitment to B-lymphocyte lineage development. *Immunol. Rev.* 175:104–11
68. Urbanek P, Wang ZQ, Fetka I, Wagner EF, Busslinger M. 1994. Complete block of early B cell differentiation and altered patterning of the posterior midbrain in mice lacking Pax5/BSAP. *Cell* 79:901–12
69. Mullighan CG, Goorha S, Radtke I, Miller CB, Coustan-Smith E, et al. 2007. Genome-wide analysis of genetic alterations in acute lymphoblastic leukaemia. *Nature* 446:758–64
70. Bousquet M, Broccardo C, Quelen C, Meggetto F, Kuhlein E, et al. 2007. A novel PAX5-ELN fusion protein identified in B cell acute lymphoblastic leukemia acts as a dominant negative on wild-type PAX5. *Blood* 109:3417–23
71. Cortes M, Wong E, Koipally J, Georgopoulos K. 1999. Control of lymphocyte development by the Ikaros gene family. *Curr. Opin. Immunol.* 11:167–71
72. Georgopoulos K. 2002. Haematopoietic cell–fate decisions, chromatin regulation and ikaros. *Nat. Rev. Immunol.* 2:162–74
73. Wang JH, Avitahl N, Cariappa A, Friedrich C, Ikeda T, et al. 1998. Aiolos regulates B cell activation and maturation to effector state. *Immunity* 9:543–53
74. Schmitt C, Tonnelle C, Dalloul A, Chabannon C, Debre P, Rebollo A. 2002. Aiolos and Ikaros: regulators of lymphocyte development, homeostasis and lymphoproliferation. *Apoptosis* 7:277–84
75. O'Neil J, Look AT. 2007. Mechanisms of transcription factor deregulation in lymphoid cell transformation. *Oncogene* 26:6838–49
76. Kamps MP, Murre C, Sun XH, Baltimore D. 1990. A new homeobox gene contributes the DNA binding domain of the t(1;19) translocation protein in pre-B-ALL. *Cell* 60:547–55
77. Aspland SE, Bendall HH, Murre C. 2001. The role of E2A-PBX1 in leukemogenesis. *Oncogene* 20:5708–17
78. Hunger SP, Ohyashiki K, Toyama K, Cleary ML. 1992. Hlf, a novel hepatic bZIP protein, shows altered DNA-binding properties following fusion to E2A in t(17;19) acute lymphoblastic leukemia. *Genes Dev.* 6:1608–20
79. Inaba T, Roberts WM, Shapiro LH, Jolly KW, Raimondi SC, et al. 1992. Fusion of the leucine zipper gene HLF to the E2A gene in human acute B-lineage leukemia. *Science* 257:531–34
80. Seidel MG, Look AT. 2001. E2A-HLF usurps control of evolutionarily conserved survival pathways. *Oncogene* 20:5718–25
81. Hunger SP. 1996. Chromosomal translocations involving the E2A gene in acute lymphoblastic leukemia: clinical features and molecular pathogenesis. *Blood* 87:1211–24
82. Yoshihara T, Inaba T, Shapiro LH, Kato JY, Look AT. 1995. E2A-HLF-mediated cell transformation requires both the transactivation domains of E2A and the leucine zipper dimerization domain of HLF. *Mol. Cell Biol.* 15:3247–55

Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org
by University of California - Los Angeles on 02/16/09. For personal use only.

83. Inoue A, Seidel MG, Wu W, Kamizono S, Ferrando AA, et al. 2002. Slug, a highly conserved zinc finger transcriptional repressor, protects hematopoietic progenitor cells from radiation-induced apoptosis in vivo. *Cancer Cell* 2:279–88
84. Aster JA, Pear WS, Blacklow SC. 2008. Notch signaling in leukemia. *Annu. Rev. Pathol. Mech. Dis.* 3:587–613
85. Bray SJ. 2006. Notch signalling: a simple pathway becomes complex. *Nat. Rev. Mol. Cell Biol.* 7:678–89
86. Ellisen LW, Bird J, West DC, Soreng AL, Reynolds TC, et al. 1991. TAN-1, the human homolog of the *Drosophila* notch gene, is broken by chromosomal translocations in T lymphoblastic neoplasms. *Cell* 66:649–61
87. Weng AP, Ferrando AA, Lee W, Morris JPt, Silverman LB, et al. 2004. Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. *Science* 306:269–71
88. Palomero T, Lim WK, Odom DT, Sulis ML, Real PJ, et al. 2006. NOTCH1 directly regulates c-MYC and activates a feed-forward-loop transcriptional network promoting leukemic cell growth. *Proc. Natl. Acad. Sci. USA* 103:18261–66
89. Ciofani M, Zuniga-Pflucker JC. 2005. Notch promotes survival of pre–T cells at the β-selection checkpoint by regulating cellular metabolism. *Nat. Immunol.* 6:881–88
90. Palomero T, Sulis ML, Cortina M, Real PJ, Barnes K, et al. 2007. Mutational loss of PTEN induces resistance to NOTCH1 inhibition in T cell leukemia. *Nat. Med.* 13:1203–10
91. Gutierrez A, Look AT. 2007. NOTCH and PI3K-AKT pathways intertwined. *Cancer Cell* 12:411–13
92. Robey E, Chang D, Itano A, Cado D, Alexander H, et al. 1996. An activated form of Notch influences the choice between CD4 and CD8 T cell lineages. *Cell* 87:483–92
93. Beverly LJ, Capobianco AJ. 2003. Perturbation of Ikaros isoform selection by MLV integration is a cooperative event in Notch(IC)-induced T cell leukemogenesis. *Cancer Cell* 3:551–64
94. Winandy S, Wu P, Georgopoulos K. 1995. A dominant mutation in the Ikaros gene leads to rapid development of leukemia and lymphoma. *Cell* 83:289–99
95. Aster JC, Xu L, Karnell FG, Patriub V, Pui JC, Pear WS. 2000. Essential roles for ankyrin repeat and transactivation domains in induction of T cell leukemia by notch1. *Mol. Cell Biol.* 20:7505–15
96. Girard L, Hanna Z, Beaulieu N, Hoemann CD, Simard C, et al. 1996. Frequent provirus insertional mutagenesis of Notch1 in thymomas of MMTVD/myc transgenic mice suggests a collaboration of c-myc and Notch1 for oncogenesis. *Genes Dev.* 10:1930–44
97. Hoemann CD, Beaulieu N, Girard L, Rebai N, Jolicoeur P. 2000. Two distinct Notch1 mutant alleles are involved in the induction of T cell leukemia in c-myc transgenic mice. *Mol. Cell Biol.* 20:3831–42
98. Pear WS, Aster JC, Scott ML, Hasserjian RP, Soffer B, et al. 1996. Exclusive development of T cell neoplasms in mice transplanted with bone marrow expressing activated Notch alleles. *J. Exp. Med.* 183:2283–91
99. Suzuki A, de la Pompa JL, Stambolic V, Elia AJ, Sasaki T, et al. 1998. High cancer susceptibility and embryonic lethality associated with mutation of the PTEN tumor-suppressor gene in mice. *Curr. Biol.* 8:1169–78
100. Di Cristofano A, Pesce B, Cordon-Cardo C, Pandolfi PP. 1998. Pten is essential for embryonic development and tumour suppression. *Nat. Genet.* 19:348–55
101. Welcker M, Clurman BE. 2008. FBW7 ubiquitin ligase: a tumour suppressor at the crossroads of cell division, growth and differentiation. *Nat. Rev. Cancer* 8:83–93
102. Wu G, Lyapina S, Das I, Li J, Gurney M, et al. 2001. SEL-10 is an inhibitor of notch signaling that targets notch for ubiquitin-mediated protein degradation. *Mol. Cell Biol.* 21:7403–15
103. Malyukova A, Dohda T, von der Lehr N, Akhondi S, Corcoran M, et al. 2007. The tumor suppressor gene hCDC4 is frequently mutated in human T cell acute lymphoblastic leukemia with functional consequences for Notch signaling. *Cancer Res.* 67:5611–16
104. Maser RS, Choudhury B, Campbell PJ, Feng B, Wong KK, et al. 2007. Chromosomally unstable mouse tumours have genomic alterations similar to diverse human cancers. *Nature* 447:966–71
105. O'Neil J, Grim J, Strack P, Rao S, Tibbitts D, et al. 2007. FBW7 mutations in leukemic cells mediate NOTCH pathway activation and resistance to γ-secretase inhibitors. *J. Exp. Med.* 204:1813–24
106. Thompson BJ, Buonamici S, Sulis ML, Palomero T, Vilimas T, et al. 2007. The SCFFBW7 ubiquitin ligase complex as a tumor suppressor in T cell leukemia. *J. Exp. Med.* 204:1825–35

Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org
by University of California - Los Angeles on 02/16/09. For personal use only.

107. Onoyama I, Tsunematsu R, Matsumoto A, Kimura T, de Alboran IM, et al. 2007. Conditional inactivation of Fbxw7 impairs cell-cycle exit during T cell differentiation and results in lymphomatogenesis. *J. Exp. Med.* 204:2875–88
108. Soulier J, Clappier E, Cayuela JM, Regnault A, Garcia-Peydro M, et al. 2005. HOXA genes are included in genetic and biologic networks defining human acute T cell leukemia (T-ALL). *Blood* 106:274–86
109. Speleman F, Cauwelier B, Dastugue N, Cools J, Verhasselt B, et al. 2005. A new recurrent inversion, inv(7)(p15q34), leads to transcriptional activation of HOXA10 and HOXA11 in a subset of T cell acute lymphoblastic leukemias. *Leukemia* 19:358–66
110. Dear TN, Colledge WH, Carlton MB, Lavenir I, Larson T, et al. 1995. The Hox11 gene is essential for cell survival during spleen development. *Development* 121:2909–15
111. Roberts CW, Shutter JR, Korsmeyer SJ. 1994. Hox11 controls the genesis of the spleen. *Nature* 368:747–49
112. Hatano M, Roberts CW, Minden M, Crist WM, Korsmeyer SJ. 1991. Deregulation of a homeobox gene, HOX11, by the t(10;14) in T cell leukemia. *Science* 253:79–82
113. Owens BM, Hawley TS, Spain LM, Kerkel KA, Hawley RG. 2006. TLX1/HOX11-mediated disruption of primary thymocyte differentiation prior to the CD4+CD8+ double-positive stage. *Br. J. Haematol.* 132:216–29
114. Riz I, Hawley RG. 2005. G1/S transcriptional networks modulated by the HOX11/TLX1 oncogene of T cell acute lymphoblastic leukemia. *Oncogene* 24:5561–75
115. Hough MR, Reis MD, Singaraja R, Bryce DM, Kamel-Reid S, et al. 1998. A model for spontaneous B-lineage lymphomas in IgHmu-HOX11 transgenic mice. *Proc. Natl. Acad. Sci. USA* 95:13853–58
116. Su XY, Della-Valle V, Andre-Schmutz I, Lemercier C, Radford-Weiss I, et al. 2006. HOX11L2/TLX3 is transcriptionally activated through T cell regulatory elements downstream of BCL11B as a result of the t(5;14)(q35;q32). *Blood* 108:4198–201
117. Mikkola HK, Klintman J, Yang H, Hock H, Schlaeger TM, et al. 2003. Haematopoietic stem cells retain long-term repopulating activity and multipotency in the absence of stem-cell leukaemia SCL/tal-1 gene. *Nature* 421:547–51
118. Aplan PD, Jones CA, Chervinsky DS, Zhao X, Ellsworth M, et al. 1997. 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.* 16:2408–19
119. Aplan PD, Lombardi DP, Reaman GH, Sather HN, Hammond GD, Kirsch IR. 1992. Involvement of the putative hematopoietic transcription factor SCL in T cell acute lymphoblastic leukemia. *Blood* 79:1327–33
120. Xia Y, Brown L, Yang CY, Tsan JT, Siciliano MJ, et al. 1991. TAL2, a helix-loop-helix gene activated by the (7;9)(q34;q32) translocation in human T cell leukemia. *Proc. Natl. Acad. Sci. USA* 88:11416–20
121. Bain G, Engel I, Robanus Maandag EC, te Riele HP, Voland JR, et al. 1997. E2A deficiency leads to abnormalities in αβ T cell development and to rapid development of T cell lymphomas. *Mol. Cell Biol.* 17:4782–91
122. O'Neil J, Billa M, Oikemus S, Kelliher M. 2001. The DNA binding activity of TAL-1 is not required to induce leukemia/lymphoma in mice. *Oncogene* 20:3897–905
123. O'Neil J, Shank J, Cusson N, Murre C, Kelliher M. 2004. TAL1/SCL induces leukemia by inhibiting the transcriptional activity of E47/HEB. *Cancer Cell* 5:587–96
124. Curtis DJ, Robb L, Strasser A, Begley CG. 1997. The CD2-scl transgene alters the phenotype and frequency of T-lymphomas in N-ras transgenic or p53 deficient mice. *Oncogene* 15:2975–83
125. Condorelli GL, Facchiano F, Valtieri M, Proietti E, Vitelli L, et al. 1996. T cell–directed TAL-1 expression induces T cell malignancies in transgenic mice. *Cancer Res.* 56:5113–19
126. Hsu HL, Wadman I, Baer R. 1994. Formation of in vivo complexes between the TAL1 and E2A polypeptides of leukemic T cells. *Proc. Natl. Acad. Sci. USA* 91:3181–85
127. Ferrando AA, Look AT. 2003. Gene expression profiling in T cell acute lymphoblastic leukemia. *Semin. Hematol.* 40:274–80
128. Mellentin JD, Smith SD, Cleary ML. 1989. 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

Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org
by University of California - Los Angeles on 02/16/09. For personal use only.

129. Zhong Y, Jiang L, Hiai H, Toyokuni S, Yamada Y. 2007. Overexpression of a transcription factor LYL1 induces T- and B-cell lymphoma in mice. *Oncogene* 26:6937–47
130. Mucenski ML, McLain K, Kier AB, Swerdlow SH, Schreiner CM, et al. 1991. A functional c-myb gene is required for normal murine fetal hepatic hematopoiesis. *Cell* 65:677–89
131. Pearson R, Weston K. 2000. c-Myb regulates the proliferation of immature thymocytes following β-selection. *EMBO J.* 19:6112–20
132. Clappier E, Cuccuini W, Kalota A, Crinquette A, Cayuela JM, et al. 2007. The C-MYB locus is involved in chromosomal translocation and genomic duplications in human T cell acute leukemia (T-ALL), the translocation defining a new T-ALL subtype in very young children. *Blood* 110:1251–61
133. Lahortiga I, De Keersmaecker K, Van Vlierberghe P, Graux C, Cauwelier B, et al. 2007. Duplication of the MYB oncogene in T cell acute lymphoblastic leukemia. *Nat. Genet.* 39:593–95
134. O'Neil J, Tchinda J, Gutierrez A, Moreau L, Maser RS, et al. 2007. Alu elements mediate MYB gene tandem duplication in human T-ALL. *J. Exp. Med.* 204:3059–66
135. Valge-Archer VE, Osada H, Warren AJ, Forster A, Li J, et al. 1994. The LIM protein RBTN2 and the basic helix-loop-helix protein TAL1 are present in a complex in erythroid cells. *Proc. Natl. Acad. Sci. USA* 91:8617–21
136. McGuire EA, Rintoul CE, Sclar GM, Korsmeyer SJ. 1992. Thymic overexpression of Ttg-1 in transgenic mice results in T cell acute lymphoblastic leukemia/lymphoma. *Mol. Cell Biol.* 12:4186–96
137. Van Vlierberghe P, van Grotel M, Beverloo HB, Lee C, Helgason T, et al. 2006. The cryptic chromosomal deletion del(11)(p12p13) as a new activation mechanism of LMO2 in pediatric T cell acute lymphoblastic leukemia. *Blood* 108:3520–29
138. Yamada Y, Warren AJ, Dobson C, Forster A, Pannell R, Rabbitts TH. 1998. The T cell leukemia LIM protein Lmo2 is necessary for adult mouse hematopoiesis. *Proc. Natl. Acad. Sci. USA* 95:3890–95
139. Neale GA, Rehg JE, Goorha RM. 1995. Ectopic expression of rhombotin-2 causes selective expansion of CD4-CD8 lymphocytes in the thymus and T cell tumors in transgenic mice. *Blood* 86:3060–71
140. Larson RC, Fisch P, Larson TA, Lavenir I, Langford T, et al. 1994. T cell tumours of disparate phenotype in mice transgenic for Rbtn-2. *Oncogene* 9:3675–81
141. Larson RC, Lavenir I, Larson TA, Baer R, Warren AJ, et al. 1996. Protein dimerization between Lmo2 (Rbtn2) and Tal1 alters thymocyte development and potentiates T cell tumorigenesis in transgenic mice. *EMBO J.* 15:1021–27
142. de Wind N, Dekker M, Berns A, Radman M, te Riele H. 1995. Inactivation of the mouse Msh2 gene results in mismatch repair deficiency, methylation tolerance, hyperrecombination, and predisposition to cancer. *Cell* 82:321–30
143. Lowsky R, DeCoteau JF, Reitmair AH, Ichinohasama R, Dong WF, et al. 1997. Defects of the mismatch repair gene MSH2 are implicated in the development of murine and human lymphoblastic lymphomas and are associated with the aberrant expression of rhombotin-2 (Lmo-2) and Tal-1 (SCL). *Blood* 89:2276–82
144. Whiteside D, McLeod R, Graham G, Steckley JL, Booth K, et al. 2002. A homozygous germ-line mutation in the human MSH2 gene predisposes to hematological malignancy and multiple café-au-lait spots. *Cancer Res.* 62:359–62
145. Dreyling MH, Martinez-Climent JA, Zheng M, Mao J, Rowley JD, Bohlander SK. 1996. 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. USA* 93:4804–9
146. Archangelo LF, Glasner J, Krause A, Bohlander SK. 2006. The novel CALM interactor CATS influences the subcellular localization of the leukemogenic fusion protein CALM/AF10. *Oncogene* 25:4099–109
147. Chaplin T, Bernard O, Beverloo HB, Saha V, Hagemeijer A, et al. 1995. The t(10;11) translocation in acute myeloid leukemia (M5) consistently fuses the leucine zipper motif of AF10 onto the HRX gene. *Blood* 86:2073–76
148. Dik WA, Brahim W, Braun C, Asnafi V, Dastugue N, et al. 2005. CALM-AF10+ T-ALL expression profiles are characterized by overexpression of HOXA and BMI1 oncogenes. *Leukemia* 19:1948–57
149. Cayuela JM, Madani A, Sanhes L, Stern MH, Sigaux F. 1996. Multiple tumor-suppressor gene 1 inactivation is the most frequent genetic alteration in T cell acute lymphoblastic leukemia. *Blood* 87:2180–86

Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org
by University of California - Los Angeles on 02/16/09. For personal use only.

150. Deshpande AJ, Cusan M, Rawat VP, Reuter H, Krause A, et al. 2006. Acute myeloid leukemia is propagated by a leukemic stem cell with lymphoid characteristics in a mouse model of CALM/AF10-positive leukemia. *Cancer Cell* 10:363–74
151. Caudell D, Zhang Z, Chung YJ, Aplan PD. 2007. Expression of a CALM-AF10 fusion gene leads to Hoxa cluster overexpression and acute leukemia in transgenic mice. *Cancer Res.* 67:8022–31
152. Mikkola HK, Orkin SH. 2006. The journey of developing hematopoietic stem cells. *Development* 133:3733–44
153. Vivanco I, Sawyers CL. 2002. The phosphatidylinositol 3–kinase AKT pathway in human cancer. *Nat. Rev. Cancer* 2:489–501

Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org
by University of California - Los Angeles on 02/16/09. For personal use only.

Annual Review of Pathology: Mechanisms of Disease

Volume 4, 2009

Contents

Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org by University of California - Los Angeles on 02/16/09. For personal use only.

The First Fifty Years in Research
Peter A. Ward 1

Graft Vascular Disease: Immune Response Meets the Vessel Wall
Richard N. Mitchell 19

Molecular Pathology of Head and Neck Cancer: Implications for Diagnosis, Prognosis, and Treatment
Sara I. Pai and William H. Westra 49

Mechanisms of Endothelial Dysfunction, Injury, and Death
Jordan S. Pober, Wang Min, and John R. Bradley 71

The Pathogenesis of Pituitary Tumors
Sylvia L. Asa and Shereen Ezzat 97

PTEN and the PI3-Kinase Pathway in Cancer
Nader Chalhoub and Suzanne J. Baker 127

Pathogenesis of Classical and Lymphocyte-Predominant Hodgkin Lymphoma
Roland Schmitz, Jens Stanelle, Martin-Leo Hansmann, and Ralf Küppers 151

Molecular Genetics of Acute Lymphoblastic Leukemia
Michael A. Teitell and Pier Paolo Pandolfi 175

MicroRNAs in Cancer
Yong Sun Lee and Anindya Dutta 199

Epigenetic Changes in Cancer
Christine A. Iacobuzio-Donahue 229

Molecular Pathogenesis and Diagnostics of Bladder Cancer
Anirban P. Mitra and Richard J. Cote 251

Ovarian Cancer
Kathleen R. Cho and Ie-Ming Shih 287

Drosophila Models of Neurodegenerative Diseases
Bingwei Lu and Hannes Vogel 315

Serrated Polyps and Colorectal Cancer: New Pathway to Malignancy
Amy E. Noffsinger 343

Nod-Like Receptors: Role in Innate Immunity and Inflammatory Disease
Grace Chen, Michael H. Shaw, Yun-Gi Kim, and Gabriel Nuñez 365

Tumor Suppressors, Chromosomal Instability, and Hepatitis C Virus–Associated Liver Cancer
David R. McGivern and Stanley M. Lemon 399

The Immunopathogenesis of Rheumatoid Arthritis
John B. Imboden 417

The Pathology of Chronic Obstructive Pulmonary Disease
James C. Hogg and Wim Timens 435

Linking the Cellular Functions of *BRCA* Genes to Cancer Pathogenesis and Treatment
Ashok R. Venkitaraman 461

Regulation of Hepcidin and Iron-Overload Disease
Pauline L. Lee and Ernest Beutler 489

The Brainstem and Serotonin in the Sudden Infant Death Syndrome
Hannah C. Kinney, George B. Richerson, Susan M. Dymecki, Robert A. Darnall, and Eugene E. Nattie 517

Molecular Pathogenesis of Cutaneous Melanocytic Neoplasms
Nageatte Ibrahim and Frank G. Haluska 551

Indexes

Cumulative Index of Contributing Authors, Volumes 1–4 581

Cumulative Index of Chapter Titles, Volumes 1–4 583

Errata

An online log of corrections to *Annual Review of Pathology, Mechanisms of Disease* articles may be found at http://pathol.annualreviews.org

Annu. Rev. Pathol. Mech. Dis. 2009.4:175-198. Downloaded from arjournals.annualreviews.org
by University of California - Los Angeles on 02/16/09. For personal use only.