Oncogene (2007) 26, 6838–6849

www.nature.com/onc

REVIEW

Mechanisms of transcription factor deregulation in lymphoid cell transformation

J O'Neil and AT Look

Department of Pediatric Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

The most frequent targets of genetic alterations in human lymphoid leukemias are transcription factor genes with essential functions in blood cell development. TAL1, LYL1, HOX11 and other transcription factors essential for normal hematopoiesis are often misexpressed in the thymus in T-cell acute lymphoblastic leukemia (T-ALL), leading to differentiation arrest and cell transformation. Recent advances in the ability to assess DNA copy number have led to the discovery that the *MYB* transcription factor oncogene is tandemly duplicated in T-ALL. The *NOTCH1* gene, which is essential for key embryonic cell-fate decisions in multicellular organisms, was found to be activated by mutation in a large percentage of T-ALL patients. The gene encoding the FBW7 protein ubiquitin ligase, which regulates the turnover of the intracellular form of NOTCH (ICN), is also mutated in T-ALL, resulting in stabilization of the ICN and activation of the NOTCH signaling pathway. In mature B-lineage ALL and Burkitt lymphoma, the *MYC* transcription factor oncogene is overexpressed due to translocation into the *IG* locus. *PAX5*, a transcription factor essential for B-lineage commitment, is inactivated in 32% of cases of B-progenitor ALL. Translocations resulting in oncogenic fusion transcription factors also occur frequently in this form of ALL. The most frequent transcription factor chimeric fusion, *TEL-AML1*, is an initiating event in B-progenitor ALL that acts by repressing transcription. Therefore, deregulated transcription and its consequent effects on key developmental pathways play a major role in the molecular pathogenesis of lymphoid malignancy. Once the full complement of cooperating mutations in transformed B- and T-progenitor cells is known, and the deregulated downstream pathways have been elucidated, it will be possible to identify vulnerable components and to target them with small-molecule inhibitors.
Oncogene (2007) **26,** 6838–6849; doi:10.1038/sj.onc.1210766

Keywords: TAL1; NOTCH; PAX5; MLL; E2A; TEL-AML1

Correspondence: Dr AT Look, Department of Pediatric Oncology, Dana-Farber Cancer Institute and Professor of Pediatrics, Harvard Medical School, Boston, MA 02115, USA.
E-mail: Thomas_Look@dfci.harvard.edu

Introduction

Uniform structural and numerical chromosomal abnormalities, such as those resulting in identical rearrangements of *IG* or *TCR* genes in patients with acute lymphoblastic leukemia (ALL) (Arnold *et al*., 1983; Waldmann *et al*., 1985), are frequently demonstrated in transformed lymphoblasts, establishing the clonality of this disease. Molecular studies on recurrent chromosomal translocations in ALL have indicated a central role for the aberrant expression of transcription factors in the pathobiology of lymphoid leukemia. Deregulated expression of these transcription factors, which are often functionally normal, leads to abnormal proliferation and differentiation arrest of lymphoid progenitors (Cleary, 1991; Rabbitts, 1994; Look, 1997). Although a substantial fraction of oncogenic transcription factors have essential roles in the development of specific cell lineages, many are not normally expressed in lymphocytes, indicating that transformation by these proteins is a result of misexpression (Armstrong and Look, 2005). In some cases, the chromosomal translocations generate chimeric transcription factors with new functions, enabling them to target genes other than those recognized by the intact factors. Here, we focus on the common mechanisms responsible for the aberrant expression of transcription factor genes in lymphoid leukemias.

Aberrant protein expression in T-cell acute lymphoblastic leukemia

In T-cell acute lymphoblastic leukemia (T-ALL), chromosomal break points often involve the *TCRβ* enhancer (7q34) or the *TCRα/δ* enhancer (14q11), both of which are highly active in committed T-cell progenitors, resulting in the deregulated expression of transcription factor genes located at the break point on the reciprocal chromosome (Ferrando and Look, 2000). The transcription factors affected by these molecular changes include genes encoding basic helix–loop–helix (bHLH) family members, such as TAL1 (Begley *et al*., 1989; Chen *et al*., 1990), TAL2 (Xia *et al*., 1991), LYL1 (Mellentin *et al*., 1989), MYC (Finger *et al*., 1986; McKeithan *et al*., 1986; Shima *et al*., 1986) and BHLHB1 (Wang *et al*., 2000); LIM-only domain (*LMO*) genes,

such as LMO1 and LMO2 (McGuire *et al*., 1992); and the orphan homeobox genes HOX11 and HOX11L2 (Dube *et al*., 1991; Hatano *et al*., 1991; Kennedy *et al*., 1991; Lu *et al*., 1991; Dear *et al*., 1993; Bernard *et al*., 2001; Ferrando and Look, 2003), the major HOXA locus (Soulier *et al*., 2005) and MYB in young children (Clappier *et al*., 2007).

TAL1 is overexpressed in T-ALL as a result of the t(1;14) translocation or by site-specific deletions in approximately one-fourth of childhood T-ALL cases (Brown *et al*., 1990; Aplan *et al*., 1991, 1992; Bernard *et al*., 1991; Breit *et al*., 1993; Bash *et al*., 1995). However, these two mechanisms cannot account for all instances of TAL1 overexpression in this disease, as the gene is aberrantly expressed in the leukemic cells of 60% of children and 45% of adults with T-ALL. An attractive hypothesis, based on observations of biallelic activation of *TAL1*, is that pathways involved in *TAL1* repression during T-cell differentiation are inactivated in T-ALL (Ferrando *et al*., 2004). As a master regulatory protein active during early hematopoietic development, TAL1 is required for the generation of all blood cell lineages (Robb *et al*., 1995; Shivdasani *et al*., 1995), but it is not required for the generation and function of hematopoietic stem cells during adult hematopoiesis (Mikkola *et al*., 2003). This class II bHLH transcription factor binds to DNA by forming heterodimers with class I bHLH factors such as E2A and HEB (Baer, 1993; O'Neil *et al*., 2001). The observation that loss of E2A results in T-cell leukemia in mice (Bain *et al*., 1997; Yan *et al*., 1997), and that the DNA-binding domain of TAL1 is dispensable for transformation in a transgenic mouse model (O'Neil *et al*., 2001), supports the notion that TAL1-mediated inhibition of class I bHLH factors plays a critical role in T-ALL pathogenesis (Figure 1). Further support for this hypothesis comes from a study in which accelerated development of T-cell leukemia was observed in *Tal1* transgenic mice on an *E2A*- or *HEB*-deficient background (O'Neil *et al*., 2004).

The LIM-only domain genes *LMO1*/*RBTN1*/*TTG1* and *LMO2*/*RBTN2*/*TTG2* (McGuire *et al*., 1989, 1992; Boehm *et al*., 1991; Royer-Pokora *et al*., 1991) encode proteins that contain duplicated cysteine-rich LIM domains involved in protein–protein interactions. *LMO1* and *LMO2* can be activated by translocation to the *TCR* enhancer loci, or in the case of *LMO2*, by deletion that removes a negative regulator of *LMO2* expression (McGuire *et al*., 1989; Boehm *et al*., 1991; Royer-Pokora *et al*., 1991; Van Vlierberghe *et al*., 2006). LMO2 interacts with TAL1 in erythroid cells and in T-cell leukemias (Valge-Archer *et al*., 1994; Wadman *et al*., 1994; Larson *et al*., 1996). Moreover, homozygous disruption of *LMO2* in mice causes the same phenotype as described above for *Tal1*-deficient mice, indicating that a multiprotein complex involving LMO2, TAL1 and, potentially, other proteins is required for normal hematopoietic development (Warren *et al*., 1994; Porcher *et al*., 1996). Finally, overexpression of *Lmo1* or *Lmo2* transgenes in mouse thymocytes leads to T-cell lymphomas (Fisch *et al*., 1992; McGuire *et al*., 1992; Larson *et al*., 1994, 1995; Neale *et al*., 1995) and accelerates the onset of leukemia in *Tal1* transgenic mice (Larson *et al*., 1996).

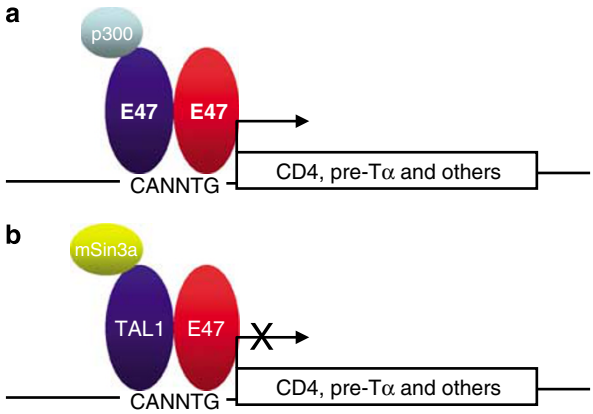

Figure 1 TAL1 acts by inhibiting the function of the class I bHLH proteins E47 and HEB. (**a**) In normal thymocytes, E47 homodimers or E47/HEB heterodimers bind to E-box sequences in DNA, recruit co-activators such as p300, CBP and PCAF, and activate the expression of genes important for T-cell development, including CD4 and pre-Tα. (**b**) When TAL1 is misexpressed in the thymus in T-ALL, it interacts with E47 and HEB and disrupts E47 homodimers or E47/HEB heterodimers. TAL1 can bind to E-box sequences as a heterodimer with class I bHLH proteins; however, TAL1 recruits corepressors such as mSin3a, thereby repressing genes important for T-cell development. The repression of these genes results in differentiation arrest in *Tal1* transgenic mouse models. bHLH, basic helix–loop–helix.

HOX11 was originally isolated from the site of the recurrent t(10;14)(q24;q11) translocation in T-ALL (Dube *et al*., 1991; Hatano *et al*., 1991; Kennedy *et al*., 1991; Lu *et al*., 1991; Dear *et al*., 1993) and is aberrantly expressed in 3–5% of pediatric and up to 30% of adult T-ALL cases (Berger *et al*., 2003; Ferrando and Look, 2003; Kees *et al*., 2003). Similar to other *HOX* genes, *HOX11* plays an important role in embryonic development, and functions as a master transcriptional regulator necessary for the genesis of the spleen (Roberts *et al*., 1994; Dear *et al*., 1995). In the mouse embryo, *Hox11* expression can be detected in the branchial arches, restricted areas of the hindbrain and the splenic primordium (Raju *et al*., 1993; Roberts *et al*., 1995), where it is required for the survival of early splenic progenitors (Dear *et al*., 1995). The proposed function of *HOX11* as a transcriptional regulator is supported by the presence of both a 61-amino acid, helix–turn–helix DNA-binding domain (or homeodomain) and by the localization of the HOX11 protein in the cell nucleus (Neale *et al*., 1995). HOX11 can also disrupt the G_2/M cell-cycle checkpoint through a transcription-independent mechanism, which involves its interaction with the PP2A and PP1 phosphatases (Riz and Hawley, 2005; Owens *et al*., 2006).

A second *HOX11* family member, *HOX11L2*, has also been implicated in the pathogenesis of human T-ALL through characterization of the cryptic t(5;14)(q35;q32) chromosomal rearrangement (Bernard *et al*., 2001). This translocation leads to the ectopic expression of *HOX11L2*, possibly by bringing it under the influence of regulatory elements in the *CTIP2*/*BCL11B* gene, which

is highly expressed during T-lymphoid differentiation. Expression of *HOX11L2* can be detected in 20–25% of children but in only 5% of adults with T-ALL (Ballerini *et al*., 2002; Mauvieux *et al*., 2002; Berger *et al*., 2003; Ferrando and Look, 2003). In mice, *Hox11l2* expression is essential for normal development of the ventral medullary respiratory center, supporting its role as a master transcriptional regulator upstream of important pathways involved in cell-fate determination (Shirasawa *et al*., 2000).

Activation of the NOTCH signaling pathway in T-cell acute lymphoblastic leukemia

The mammalian NOTCH proteins are heterodimeric transmembrane receptors that control cell proliferation, apoptosis and cell fate during the development of diverse cellular lineages (Wilson and Radtke, 2006). In adults, NOTCH signaling regulates stem cell maintenance, binary cell-fate decisions such as B- vs T-lineage differentiation and the differentiation of self-renewing organs (Radtke *et al*., 2004). NOTCH is synthesized in the endoplasmic reticulum and is transported to the Golgi network, where it is post-translationally modified. A proteolytic cleavage (S1) separates the extracellular portion of the protein from the intracellular form. These two parts of NOTCH then form a heterodimer that is transported to the cell membrane. Binding of NOTCH ligands, such as DELTA and SERRATE, initiates a series of additional proteolytic cleavages in NOTCH, the last of which is catalysed by γ-secretase, resulting in the release of the intracellular domain of NOTCH (ICN) and its translocation to the nucleus, where it forms part of a multiprotein complex. The ICN interacts with the DNA-binding protein CSL, displaces corepressors and recruits co-activators, thereby converting CSL from a repressor to an activator of gene transcription (Figure 2).

The t(7;9) translocation, which places a truncated form of the *NOTCH1* gene under control of the *TCRβ* locus, is quite rare, occurring in less than 1% of T-ALL cases (Ellisen *et al*., 1991). Deletion of the extracellular, ligand-binding domain of NOTCH1 by this translocation yields a constitutively active ligand-independent allele. Mice transplanted with cells expressing the activated *NOTCH1* allele rapidly develop T-cell leukemia, demonstrating the transforming potential of activated NOTCH signaling (Pear *et al*., 1996).

A recent study has demonstrated a broader role of activated NOTCH signaling in human T-ALL than was originally believed. Activating somatic mutations were found in over 50% of T-ALL patient samples and cell lines (Weng *et al*., 2004; Grabher *et al*., 2006). The mutations were found in all subtypes of T-ALL and in two regions of the NOTCH1 protein. Missense mutations in the heterodimerization domain activate NOTCH signaling by altering the interaction between the transmembrane subunit and the inhibitory extracellular subunit of NOTCH1 (Malecki *et al*., 2006). Frameshift and point mutations in the C-terminal region

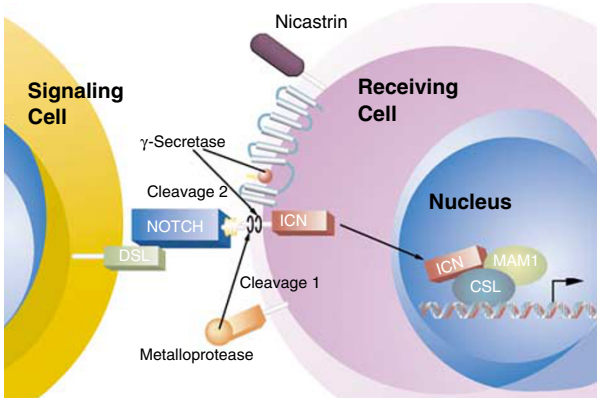

Figure 2 Activation of NOTCH signaling via extracellular and intracellular proteolytic cleavage and nuclear translocation of the intracellular NOTCH domain (ICN). Interaction with delta serrate ligand (DSL) stimulates proteolytic cleavage of NOTCH by metalloproteases and γ-secretase. This leads to the release of the intracellular ICN domain, which translocates to the nucleus where it interacts with the DNA-binding protein CSL, displaces corepressors and recruits co-activators (MAM1), thereby converting CSL from a repressor to an activator of gene expression. Adapted from Armstrong SA, Look AT (2005). Molecular genetics of acute lymphoblastic leukemia. *J Clin Oncol* 23: 6306–6315, with permission from the American Society of Clinical Oncology.

of the *NOTCH1* gene were also observed. These mutations delete the PEST domain, which targets the NOTCH1 protein for degradation by the proteasome, thereby leading to increased ICN stability and increased NOTCH signaling. Similar activating mutations were later found in mouse models of T-ALL, demonstrating the evolutionarily conserved role of NOTCH in T-ALL and providing *in vivo* models in which to test therapeutic agents that target the NOTCH pathway (Lin *et al*., 2006; O'Neil *et al*., 2006). This strategy has considerable appeal, given that T-ALL patients with mutated *NOTCH1* have a poorer prognosis than patients with the wild-type gene (Zhu *et al*., 2006).

The γ-secretase enzyme that cleaves NOTCH to release the ICN also cleaves the amyloid precursor protein, leading to the production of plaques in Alzheimer's patients. As a result, γ-secretase inhibitors have already been developed for use as targeted therapy. Treatment of T-ALL cell lines with γ-secretase inhibitors leads to G_0/G_1 arrest and apoptosis, demonstrating that the cells are dependent on NOTCH signaling for their growth and suggesting that activation of the NOTCH pathway contributes to T-cell transformation by influencing cell-cycle progression and cell survival (Weng *et al*., 2004; Lewis *et al*., 2007). Clinical trials to determine whether γ-secretase inhibitors will be effective in treating T-ALL are underway.

Several recent studies have shed light on the mechanism of NOTCH-induced T-ALL. Studies in both mouse and human T-ALL cells have identified the *MYC* oncogene as a direct transcriptional target of NOTCH (Palomero *et al*., 2006; Sharma *et al*., 2006; Weng *et al*., 2006). Reintroduction of MYC into cells that have been treated with γ-secretase inhibitors rescues their growth, demonstrating the importance of MYC in T-ALL

pathogenesis induced by aberrant NOTCH signaling. A microarray screen for the activation of phosphorylation events downstream of NOTCH in T-ALL identified several phosphorylated components of the mammalian target of rapamycin pathway (Chan *et al*., 2007). Treatment of T-ALL cells with rapamycin, an mammalian target of rapamycin inhibitor, in combination with γ-secretase inhibitors synergistically inhibited cell growth, suggesting a rational drug combination to treat T-ALL patients (Chan *et al*., 2007). Another group has demonstrated activation of the nuclear factor-κB signaling pathway downstream of NOTCH and has shown that the proteasome inhibitor bortezomib can reduce the IC_{50} of γ-secretase inhibitors in T-ALL cell lines (Vilimas *et al*., 2007). These observations underscore an emerging concept in evaluations of pathway-targeted therapeutics; although revision of a single genetic abnormality may be adequate to inhibit tumor growth, eradication of the malignant clone will likely require pathway manipulation at multiple points.

Mutation of *FBW7* in T-cell acute lymphoblastic leukemia

We and others have recently discovered that the FBW7 protein ubiquitin ligase is mutated in human T-ALL cell lines and patient samples (Malyukova *et al*., 2007; Maser *et al*., 2007; O'Neil *et al*., 2007; Thompson *et al*., 2007). The missense mutations occur in arginine residues in the substrate-binding domain of FBW7, whose substrates include NOTCH, MYC and cyclin E. We demonstrate that the mutant forms of FBW7 cannot bind to the ICN, resulting in increased levels of ICN in T-ALL cell lines with mutations in *FBW7*. Mutated FBW7 can bind to MYC but does not promote its degradation. Therefore, *FBW7* mutations likely contribute to T-ALL pathogenesis by increasing the stability of the ICN and MYC. Interestingly, all T-ALL cell lines with mutations in *FBW7* are resistant to γ-secretase inhibitor treatment. We find sustained expression of NOTCH target genes in these cell lines after γ-secretase inhibitor treatment, suggesting that NOTCH signaling is maintained due to decreased turnover of the ICN (O'Neil *et al*., 2007).

Duplication of the *MYB* oncogene in T-cell acute lymphoblastic leukemia

The *MYB* transcription factor is the cellular counterpart of the *v-Myb* oncogene of the acutely transforming avian myeloblastosis virus, which causes a fatal monoblastic leukemia in chickens (Klempnauer *et al*., 1982). Mouse knockout studies have demonstrated that *Myb* is essential for normal hematopoiesis, including T-cell development (Mucenski *et al*., 1991; Pearson and Weston, 2000). Overexpression of *v-Myb* in the thymus causes T-ALL (Badiani *et al*., 1996), and retroviral insertion and transcriptional activation of the *Myb* locus represents one of the most frequent accelerating events in several different murine models of T-ALL (http://www.rtcgd.abcc.ncifcrf.gov/). Very recently, *MYB* duplication and translocation were demonstrated in human T-ALL (Clappier *et al*., 2007; Lahortiga *et al*., 2007; J O'Neil *et al*., unpublished data). We have shown that the duplication of *MYB* occurs through homologous recombination mediated by Alu elements flanking the *MYB* locus. We detect the tandem duplication of *MYB* in a low percentage of peripheral blood cells of healthy individuals, suggesting that *MYB* duplication is selected for in the pathogenesis of T-ALL (J O'Neil *et al*., unpublished data). Knockdown of *MYB* in T-ALL cell lines affects T-cell differentiation, and when combined with inhibitors of the NOTCH signaling pathway, inhibits cell proliferation, demonstrating that increased expression of MYB contributes to T-cell transformation (Lahortiga *et al*., 2007).

Activation of *MYC* in mature B-cell T-cell acute lymphoblastic leukemia

In mature B-cell acute leukemia and Burkitt lymphoma, *MYC* is overexpressed due to translocation of one allele into the vicinity of an *IG* gene, either the heavy-chain gene on chromosome 14q32 or the κ- and λ-light-chain genes on chromosomes 2 and 22 (Dalla-Favera *et al*., 1982; Taub *et al*., 1982, 1984; Adams *et al*., 1983; Croce *et al*., 1983; Erikson *et al*., 1983; Emanuel *et al*., 1984; Hollis *et al*., 1984; Rappold *et al*., 1984). MYC is a bHLH protein that binds to canonical E-box DNA sequences (5′-CACGTG-3′) as an MYC:MAX heterodimer and activates transcription (Grandori *et al*., 1996), leading to cell proliferation. MAX can also heterodimerize with other bHLHZip proteins, including MAD (Ayer *et al*., 1993). This interaction inhibits MYC function by competing with MYC for binding to MAX and by directly inhibiting transcription. Deregulated expression of *MYC* due to the t(8;14) results in a higher concentration of MYC:MAX complexes relative to MAX:MAD and hence to transcriptional cell proliferation. MYC has many target genes that are involved in diverse cellular functions including cell-cycle regulation, apoptosis, metabolism and signaling pathways. Chromatin immunoprecipitation experiments have shown that MYC can bind to as much as 15% of all promoter regions (Fernandez *et al*., 2003; Li *et al*., 2003; Orian *et al*., 2003). It is likely that a combination of these targets contributes to the oncogenic function of MYC. A recent study suggests that MYC may also contribute to transformation by controlling DNA replication independent of its transcriptional activity (Dominguez-Sola *et al*., 2007).

PAX5 inactivation in B-progenitor acute lymphoblastic leukemia

The advent of genome-wide technologies to assess gene copy number, such as single-nucleotide polymorphism

arrays and comparative genome hybridization (array CGH), has allowed investigators to identify novel genes involved in the pathogenesis of lymphoid leukemia. A recent search for somatic mutations in 242 cases of pediatric ALL, using DNA microarrays containing probes for approximately 350 000 genetic loci, uncovered deletions, amplifications, point mutations or structural rearrangements in numerous genes that are essential for B-cell development (Mullighan *et al*., 2007). Among these genes, the transcription factor *PAX5* was the most commonly altered, either by deletion or by point mutation. The PAX5-mutant proteins displayed reduced transcriptional activity in a reporter assay, demonstrating that the mutations result in loss of function (Mullighan *et al*., 2007). The *PAX5* gene is also involved in several chromosomal translocations that occur in cases of B-progenitor ALL including *PAX5-ETV6*, *PAX5-EVI3* and *PAX5-ELN* (Cobaleda *et al*., 2007). Although it is not clear as to how all of these translocations contribute to leukemic transformation, it has been shown that the PAX5-ENL protein inhibits the function of the wild-type PAX5 protein (Bousquet *et al*., 2007).

E2A-PBX1 fusion gene in pre-B-cell acute lymphoblastic leukemia

The *E2A-PBX1* fusion gene results from the t(1;19)(q23;p13) chromosomal translocation present in 3–5% of all B-lineage ALLs and in 25% of cases with a pre-B phenotype (Ferrando and Look, 2000). This translocation fuses the *E2A* gene on chromosome 19 to a homeobox gene (*PBX1*) on chromosome 1, leading to the expression of several forms of hybrid E2A-PBX1 oncoproteins. *PBX1* is related to the *Drosophila exd* gene, a homeotic gene that plays a role in segmental development through its ability to heterodimerize with and alter the downstream regulatory programs of the products of the *HOM-C* major homeobox genes. The hybrid proteins resulting from the t(1;19) contain the N-terminal transactivation domains of E2A (AD1 and AD2) (Kamps *et al*., 1990; Mellentin *et al*., 1990; Nourse *et al*., 1990) and the DNA-binding domain of PBX1, enabling the fusion proteins to function as chimeric transcription factors (Van Dijk *et al*., 1993; LeBrun and Cleary, 1994; Lu *et al*., 1994).

Expression of the *E2A-PBX1* fusion gene in the bone marrow of lethally irradiated mice results in acute myeloid leukemia (AML), demonstrating its oncogenic potential (Kamps and Baltimore, 1993). *E2A-PBX* can also transform NIH-3T3 fibroblasts and induce T-cell lymphomas in transgenic mice (Dedera *et al*., 1993; Monica *et al*., 1994). Deletion of one of the E2A activation domains diminishes its transforming activity, while deletion of the PBX1 homeodomain has no effect (Kamps and Baltimore, 1993; Monica *et al*., 1994). However, the homeodomain and flanking sequences are required for interactions with other HOX proteins and for optimal binding of E2A-PBX1 to specific DNA sequences (Chang *et al*., 1995, 1997; Knoepfler and Kamps, 1995; Lu *et al*., 1995; van Dijk *et al*., 1995). Hence, it is likely that interactions between E2A-PBX1 and other HOX proteins target the fusion protein to specific target genes whose activation is critical to lymphoid cell transformation.

E2A-HLF fusion gene in B-progenitor acute lymphoblastic leukemia

The t(17;19) is a rare recurrent chromosomal translocation that fuses the N-terminal transactivation domains of E2A to the C-terminal DNA-binding and dimerization domains of hepatic leukemia factor (HLF) (Hunger *et al*., 1992; Inaba *et al*., 1992), a member of the PAR subfamily of bZIP transcription factors. Although E2A-HLF can bind DNA either as a homodimer or as a heterodimer with HLF and related proteins, no other PAR proteins are expressed at detectable levels in leukemic cells, and the E2A-HLF fusion product appears to bind DNA as a homodimer in cells harboring the t(17;19). Similar to E2A-PBX1, E2A-HLF can transform NIH-3T3 fibroblasts and induce lymphoid tumors in transgenic mice (Yoshihara *et al*., 1995; Hunger, 1996).

Hepatic leukemia factor is the mammalian homologue of the nematode protein cell death specification family member 2 (CES-2), which regulates the death of a specific pair of serotoninergic neurons during *Caenorhabditis elegans* development (Inaba *et al*., 1996; Metzstein *et al*., 1996; Thompson, 1996). CES-2 induces apoptosis by inhibiting the expression of *ces-1*, a pro-survival gene that normally inhibits programmed cell death by antagonizing the activity of the proapoptotic factor EGL-1. In contrast to the proapoptotic role of CES-2 in the worm via repression of *ces-1*, *E2A-HLF* blocks apoptosis by inducing the expression of *SLUG*, a *ces-1* homologue normally responsible for protecting hematopoietic progenitors from DNA-damage-induced apoptosis (Inukai *et al*., 1999; Metzstein and Horvitz, 1999; Inoue *et al*., 2002; Wu *et al*., 2005). Expression of a dominant-negative form of E2A-HLF in t(17;19)-carrying cell lines blocks E2A-HLF function and results in apoptosis (Inaba *et al*., 1996; Figure 3).

MLL fusion genes

Translocations involving the *MLL* gene on chromosome 11 band q23 occur in approximately 80% of infant ALL cases (Ferrando and Look, 2000). *MLL* encodes a protein that shares significant sequence homology with trithorax, a *Drosophila* regulator of homeotic gene function that is required for normal head, thorax and abdomen development during fly embryogenesis (Zieminvan der Poel *et al*., 1991; Djabali *et al*., 1992; Gu *et al*., 1992; Tkachuk *et al*., 1992). The mixed-lineage leukemia (MLL) protein shares three regions of homology with trithorax, including two central zinc-finger domains and a 210-amino acid C-terminal sur (var) 3-9, enhancer of

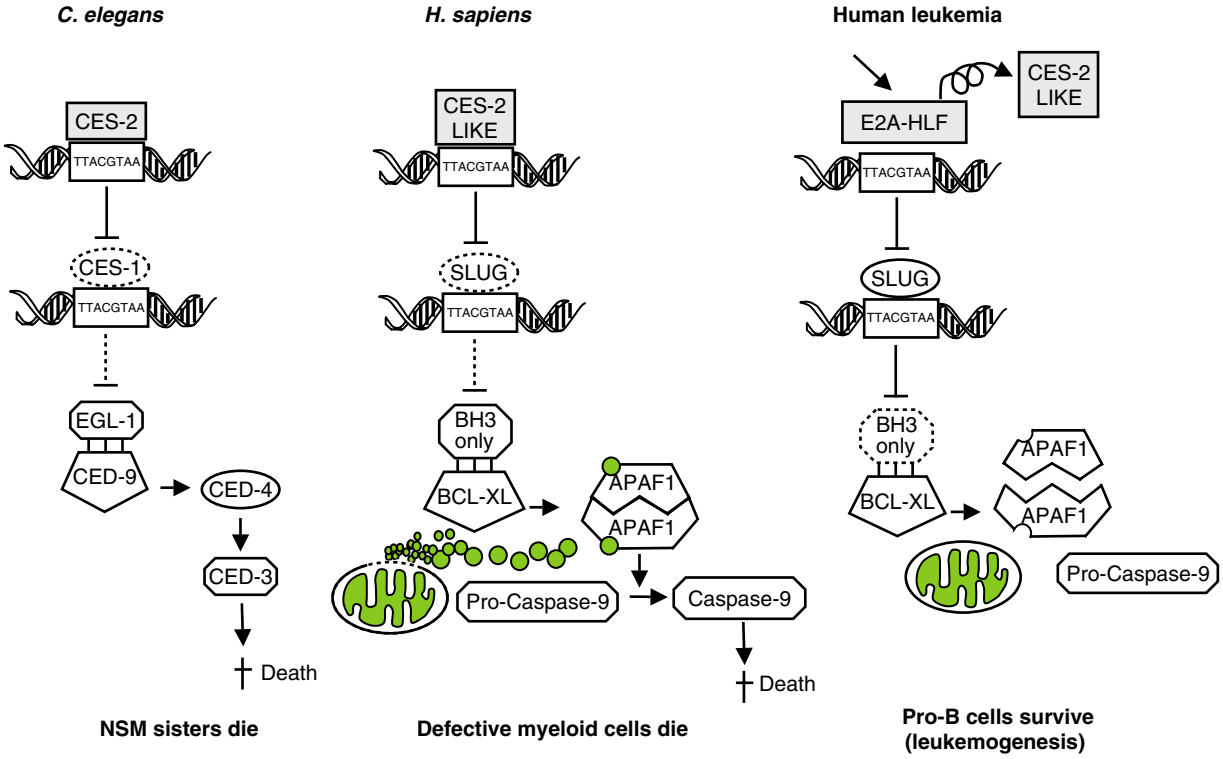

Figure 3 Models of conserved cell-death specification pathways and the role of E2A-HLF in leukemogenesis. In the nematode *C. elegans*, the CES-2 protein negatively regulates *ces-1* to induce the activation of a cell-death pathway that results in the apoptosis of two serotononergic neurons (NSM sisters). This pathway presumably involves the transcriptional activation of *egl1*, whose product is a proapoptotic factor that binds to and inhibits CED-9, preventing it from inhibiting the CED-4 and CED-3 cell-death effectors. In humans, a similar cell-death pathway regulates the survival of myeloid progenitors during hematopoiesis. In this system, a CES-2 homologue negatively controls the expression of *SLUG* (*ces-1* homologue), which presumably downregulates apoptosis by inhibiting a BH3-only family member (*egl1* homologue). In the absence of SLUG, the upregulation of this BH3-only factor blocks the activity of antiapoptotic molecules such as BCL2 and $BCLX_L$, triggering the release of cytochrome *c* from the mitochondria and the activation of downstream apoptotic effector molecules (APAF1, caspase-9). Because E2A-HLF and CES-2 recognize the same DNA sequence, expression of this chimeric oncoprotein with its strong transactivation domains induces expression of *SLUG*, whose activity subsequently inhibits the expression of a BH3-only gene responsible for cell-death activation in pro-B cells. Reprinted from Ferramdo AA, Look AT (2005). Hematology, In: Hoffman (ed). *Pathobiology of Acute Lymphoblastic Leukemia*, 4th edn, chapter 63, with permission from Elsevier.

zeste and tritho-rax (SET) domain. The *MLL* SET domain contains a histone H3/lysine 4 methyl transferase activity that plays a critical role in the regulation of *HOX* gene expression (Milne *et al*., 2002; Yokoyama *et al*., 2004). Other structural features of *MLL* include three A-T hook domains near the N terminus that are thought to bind the minor groove of DNA in AT-rich regions, and a 47-amino acid region of homology with the non-catalytic domains of human DNA methyltransferase (Reeves and Nissen, 1990; Ma *et al*., 1993). *Mll* heterozygous mice exhibit anemia, thrombocytopenia and reduced numbers of B lymphocytes. The mice also display homeotic transformations of the cervical, thoracic and lumbar regions that reflect shifts in the pattern of *Hox* gene expression, establishing a crucial role for *Mll* in *Hox* gene regulation. Mice with homozygous loss of *Mll* die *in utero* and lack *Hox* gene expression, further supporting a key role for *Mll* in *Hox* gene regulation (Yu *et al*., 1998).

The translocation break points cluster in an 8.5-kilobase region of *MLL* between exons 5 and 11, and fuse the N-terminal region of *MLL*, containing the A-T hook and methyltransferase domains, to a variety of partner proteins. Although the role of each partner protein in leukemogenesis has not been fully elucidated, some of them may contribute functional domains to the fusion protein. For example, the t(4;11), t(9;11) and t(11;19)(q23;p13.3) fuse *MLL* to *AF-4*, *AF-9* and *ENL*, respectively. All three of these partners are small serine/proline-rich proteins with nuclear localization signals, suggesting that they may function as transcriptional trans-activators. An RNA polymerase II elongation factor, *ELL*, is fused to *MLL* by the t(11;19)(q23;p13.1) (Thirman *et al*., 1994; Mitani *et al*., 1995; Shilatifard *et al*., 1996). Still other partners have no transcriptional activity but contain a dimerization domain that results in homo-oligomerization of the N-terminal portion of MLL (Hsu and Look, 2003; So *et al*., 2003).

Murine models of *MLL*-induced leukemias have demonstrated the oncogenic role of *MLL* fusions. Chimeric mice harboring aN *MLL-AF9* fusion gene developed leukemias with a latency of 4–12 months (Corral *et al*., 1996). Retroviral transduction of *MLL-ENL*, *MLL-ELL* and *MLL-CBP* fusion genes in hematopoietic precursors induces transformation upon

transplantation into recipient mice (Lavau *et al*., 2000a, b; Zeisig *et al*., 2003). Similar results were obtained with models in which chromosomal translocations involving the *Mll* locus are induced by directed interchromosomal recombination in mice, a strategy that reproduces experimentally the initiating events in the pathogenesis of *MLL*-rearranged leukemias (Forster *et al*., 2003; Drynan *et al*., 2005; Metzler *et al*., 2006). Microarray gene-expression analysis of *MLL*-rearranged B- and T-cell ALLs has uncovered a characteristic gene-expression signature that includes the upregulation of several *HOX* genes including *HOXA9*, *HOXA10*, *HOXC6* and the *HOX* gene regulator *MEIS1* (Armstrong *et al*., 2002; Yeoh *et al*., 2002; Ferrando *et al*., 2003). HOXA9 is required for the transformation of hemopoietic precursors by *MLL* fusion oncogenes in murine leukemia models (Ayton and Cleary, 2003), demonstrating the central role of *HOX* gene deregulation in the pathogenesis of *MLL*-rearranged leukemias.

TEL-AML1 (*ETV6-RUNX1*) fusion gene in B-progenitor acute lymphoblastic leukemia

The t(12;21) translocation that creates the *TEL-AML1* fusion gene is the most common genetic lesion in pediatric ALL, occurring in 20–25% of B-lineage cases, but is much less common in adult ALL (Ferrando and Look, 2000). The chimeric protein contains an HLH domain of TEL fused to nearly all of AML1, including both the transactivation domain and the DNA- and protein-binding Runt homology domain. *TEL-AML1* expression in the mouse does not induce leukemia but does increase the self-renewal of B-cell progenitors (Andreasson *et al*., 2001; Morrow *et al*., 2004; Tsuzuki *et al*., 2004), suggesting that additional hits are necessary to induce leukemia. Supporting this hypothesis, *TEL-AML1* transgenic zebrafish develops B-ALL at a low frequency (3%) and after a long latency (Sabaawy *et al*., 2006). The TEL-AML1 translocation appears to be an initiating event in B-ALL as it can be detected prenatally (Greaves and Wiemels, 2003).

Lack of expression of genes normally upregulated by *AML1* likely plays a role in *TEL-AML1*-induced transformation. Evidence in support of this model includes the interference of AML1-dependent transcriptional transactivation by TEL-AML1 *in vitro* (Hiebert *et al*., 1996), and the interaction of TEL-AML1, but not normal AML1, with N-Cor, a component of the nuclear coreceptor complex with histone deacetylase activity. In fact, *TEL-AML1*-mediated gene repression can be reversed by treatment with histone deacetylase (HDAC) inhibitors, suggesting that these drugs may be useful therapeutic agents for *TEL-AML1* patients (Fenrick *et al*., 1999). The observation that the non-translocated copy of *TEL* is frequently deleted as a secondary event in *TEL-AML1* leukemias suggests that the leukemogenic effect of TEL-AML1 may be mediated, at least in part, by loss of function of the *TEL* gene (McLean *et al*., 1996; Cave *et al*., 1997; Jousset *et al*., 1997; Takeuchi *et al*., 1997). In fact, overexpression of TEL in cell lines reduces proliferation by inducing a G_1 cell-cycle arrest (Rompaey *et al*., 2000). Recent studies in the mouse have demonstrated that several domains of TEL-AML1 from both TEL and AML1 are required for self-renewal of B-cell precursors highlighting the complex function of this fusion gene in B-cell transformation (Morrow *et al*., 2007).

Summary and future directions

Deregulation of transcription factors plays a major role in lymphoid cell transformation. Cloning translocation break points that occur between T-cell receptor loci and transcription factors with essential roles in blood cell development have identified a number of oncogenic T-cell transcription factors, but such rearrangements are relatively rare. Other techniques such as quantitative reverse transcription–PCR and genomic sequencing have revealed that oncogenes are activated or overexpressed in a much higher percentage of ALL patients than previously believed. The application of emerging technologies such as single-nucleotide polymorphism arrays and array comparative genome hybridization to samples of T- and B-cell ALL has expanded the list of candidate oncogenes in these diseases. Detailed study of their activities has begun to generate a more complete picture of the molecular events required for leukemic transformation in a given blast cell. Most exciting, perhaps, is the opportunity to develop new drugs that target the aberrant signaling pathways now being identified in ALL. It is our hope that future therapy for ALL will be tailored to the genetic changes that characterize each patient's leukemia, resulting in more efficient elimination of transformed blast cells and less toxicity to normal tissues.

Acknowledgements

A Thomas Look is supported by the NIH (CA109901). Jennifer O'Neil is supported by a Harvard Medical School Hematology Training Grant.

References

Adams JM, Gerondakis S, Webb E, Corcoran LM, Cory S. (1983). Cellular myc oncogene is altered by chromosome translocation to an immunoglobulin locus in murine plasmacytomas and is rearranged similarly in human Burkitt lymphomas. *Proc Natl Acad Sci USA* **80**: 1982–1986.

Andreasson P, Schwaller J, Anastasiadou E, Aster J, Gilliland DG. (2001). The expression of ETV6/CBFA2 (TEL/AML1) is not sufficient for the transformation of hematopoietic cell lines *in vitro* or the induction of hematologic disease *in vivo*. *Cancer Genet Cytogenet* **130**: 93–104.

Aplan PD, Lombardi DP, Kirsch IR. (1991). Structural characterization of SIL, a gene frequently disrupted in T-cell acute lymphoblastic leukemia. *Mol Cell Biol* **11**: 5462–5469.

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**: 1327–1333.

Armstrong SA, Look AT. (2005). Molecular genetics of acute lymphoblastic leukemia. *J Clin Oncol* **23**: 6306–6315.

Armstrong SA, Staunton JE, Silverman LB, Pieters R, den Boer ML, Minden MD *et al*. (2002). MLL translocations specify a distinct gene expression profile that distinguishes a unique leukemia. *Nat Genet* **30**: 41–47.

Arnold A, Cossman J, Bakhshi A, Jaffe ES, Waldmann TA, Korsmeyer SJ. (1983). Immunoglobulin-gene rearrangements as unique clonal markers in human lymphoid neoplasms. *N Engl J Med* **309**: 1593–1599.

Ayer DE, Kretzner L, Eisenman RN. (1993). Mad: a heterodimeric partner for Max that antagonizes Myc transcriptional activity. *Cell* **72**: 211–222.

Ayton PM, Cleary ML. (2003). Transformation of myeloid progenitors by MLL oncoproteins is dependent on Hoxa7 and Hoxa9. *Genes Dev* **17**: 2298–2307.

Badiani PA, Kioussis D, Swirsky DM, Lampert IA, Weston K. (1996). T-cell lymphomas in v-Myb transgenic mice. *Oncogene* **13**: 2205–2212.

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

Bain G, Engel I, Robanus Maandag EC, te Riele HP, Voland JR, Sharp LL *et al*. (1997). E2A deficiency leads to abnormalities in alphabeta T-cell development and to rapid development of T-cell lymphomas. *Mol Cell Biol* **17**: 4782–4791.

Ballerini P, Blaise A, Busson-Le Coniat M, Su XY, Zucman-Rossi J, Adam M *et al*. (2002). HOX11L2 expression defines a clinical subtype of pediatric T-ALL associated with poor prognosis. *Blood* **100**: 991–997.

Bash RO, Hall S, Timmons CF, Crist WM, Amylon M, Smith RG *et al*. (1995). Does activation of the TAL1 gene occur in a majority of patients with T-cell acute lymphoblastic leukemia? A pediatric oncology group study. *Blood* **86**: 666–676.

Begley CG, Aplan PD, Denning SM, Haynes BF, Waldmann TA, Kirsch IR. (1989). The gene SCL is expressed during early hematopoiesis and encodes a differentiation-related DNA-binding motif. *Proc Natl Acad Sci USA* **86**: 10128–10132.

Berger R, Dastugue N, Busson M, Van Den Akker J, Perot C, Ballerini P *et al*. (2003). t(5;14)/HOX11L2-positive T-cell acute lymphoblastic leukemia. A collaborative study of the Groupe Francais de Cytogenetique Hematologique (GFCH). *Leukemia* **17**: 1851–1857.

Bernard O, Lecointe N, Jonveaux P, Souyri M, Mauchauffe M, Berger R *et al*. (1991). Two site-specific deletions and t(1;14) translocation restricted to human T-cell acute leukemias disrupt the 5′ part of the tal-1 gene. *Oncogene* **6**: 1477–1488.

Bernard OA, Busson-LeConiat M, Ballerini P, Mauchauffe M, Della Valle V, Monni R *et al*. (2001). A new recurrent and specific cryptic translocation, t(5;14)(q35;q32), is associated with expression of the Hox11L2 gene in T acute lymphoblastic leukemia. *Leukemia* **15**: 1495–1504.

Boehm T, Foroni L, Kaneko Y, Perutz MF, Rabbitts TH. (1991). The rhombotin family of cysteine-rich LIM-domain oncogenes: distinct members are involved in T-cell translocations to human chromosomes 11p15 and 11p13. *Proc Natl Acad Sci USA* **88**: 4367–4371.

Bousquet M, Broccardo C, Quelen C, Meggetto F, Kuhlein E, Delsol G *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**: 3417–3423.

Breit TM, Mol EJ, Wolvers-Tettero IL, Ludwig WD, van Wering ER, van Dongen JJ. (1993). Site-specific deletions involving the tal-1 and sil genes are restricted to cells of the T cell receptor alpha/beta lineage: T cell receptor delta gene deletion mechanism affects multiple genes. *J Exp Med* **177**: 965–977.

Brown L, Cheng JT, Chen Q, Siciliano MJ, Crist W, Buchanan G *et al*. (1990). Site-specific recombination of the tal-1 gene is a common occurrence in human T cell leukemia. *EMBO J* **9**: 3343–3351.

Cave H, Cacheux V, Raynaud S, Brunie G, Bakkus M, Cochaux P *et al*. (1997). ETV6 is the target of chromosome 12p deletions in t(12;21) childhood acute lymphocytic leukemia. *Leukemia* **11**: 1459–1464.

Chan SM, Weng AP, Tibshirani R, Aster JC, Utz PJ. (2007). Notch signals positively regulate activity of the mTOR pathway in T cell acute lymphoblastic leukemia. *Blood* **110**: 278–286.

Chang CP, de Vivo I, Cleary ML. (1997). The Hox cooperativity motif of the chimeric oncoprotein E2a-Pbx1 is necessary and sufficient for oncogenesis. *Mol Cell Biol* **17**: 81–88.

Chang CP, Shen WF, Rozenfeld S, Lawrence HJ, Largman C, Cleary ML. (1995). Pbx proteins display hexapeptide-dependent cooperative DNA binding with a subset of Hox proteins. *Genes Dev* **9**: 663–674.

Chen Q, Cheng JT, Tasi LH, Schneider N, Buchanan G, Carroll A *et al*. (1990). The tal gene undergoes chromosome translocation in T cell leukemia and potentially encodes a helix–loop–helix protein. *EMBO J* **9**: 415–424.

Clappier E, Cuccuini W, Kalota A, Crinquette A, Cayuela JM, Dik WA *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**: 1251–1261.

Cleary ML. (1991). Oncogenic conversion of transcription factors by chromosomal translocations. *Cell* **66**: 619–622.

Cobaleda C, Schebesta A, Delogu A, Busslinger M. (2007). Pax5: the guardian of B cell identity and function. *Nat Immunol* **8**: 463–470.

Corral J, Lavenir I, Impey H, Warren AJ, Forster A, Larson TA; *et al*. (1996). An Mll-AF9 fusion gene made by homologous recombination causes acute leukemia in chimeric mice: a method to create fusion oncogenes. *Cell* **85**: 853–861.

Croce CM, Thierfelder W, Erikson J, Nishikura K, Finan J, Lenoir GM *et al*. (1983). Transcriptional activation of an unrearranged and untranslocated c-myc oncogene by translocation of a C lambda locus in Burkitt. *Proc Natl Acad Sci USA* **80**: 6922–6926.

Dalla-Favera R, Bregni M, Erikson J, Patterson D, Gallo RC, Croce CM. (1982). Human c-myc onc gene is located on the region of chromosome 8 that is translocated in Burkitt lymphoma cells. *Proc Natl Acad Sci USA* **79**: 7824–7827.

Dear TN, Colledge WH, Carlton MB, Lavenir I, Larson T, Smith AJ *et al*. (1995). The Hox11 gene is essential for cell survival during spleen development. *Development* **121**: 2909–2915.

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

Dedera DA, Waller EK, LeBrun DP, Sen-Majumdar A, Stevens ME, Barsh GS *et al*. (1993). Chimeric homeobox gene E2A-PBX1 induces proliferation, apoptosis, and malignant lymphomas in transgenic mice. *Cell* **74**: 833–843.

Djabali M, Selleri L, Parry P, Bower M, Young BD, Evans GA. (1992). A trithorax-like gene is interrupted by chromosome 11q23 translocations in acute leukaemias. *Nat Genet* **2**: 113–118.

Dominguez-Sola D, Ying CY, Grandori C, Ruggiero L, Chen B, Li M *et al*. (2007). Non-transcriptional control of DNA replication by c-Myc. *Nature* **448**: 445–451.

Drynan LF, Pannell R, Forster A, Chan NM, Cano F, Daser A *et al*. (2005). Mll fusions generated by Cre-loxP-mediated *de novo* translocations can induce lineage reassignment in tumorigenesis. *EMBO J* **24**: 3136–3146.

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

Ellisen LW, Bird J, West DC, Soreng AL, Reynolds TC, Smith SD *et al*. (1991). TAN-1, the human homolog of the *Drosophila* notch gene, is broken by chromosomal translocations in T lymphoblastic neoplasms. *Cell* **66**: 649–661.

Emanuel BS, Selden JR, Chaganti RS, Jhanwar S, Nowell PC, Croce CM. (1984). The 2p breakpoint of a 2;8 translocation in

Burkitt lymphoma interrupts the V kappa locus. *Proc Natl Acad Sci USA* **81**: 2444–2446.

Erikson J, Nishikura K, ar-Rushdi A, Finan J, Emanuel B, Lenoir G *et al*. (1983). Translocation of an immunoglobulin kappa locus to a region 3′ of an unrearranged c-myc oncogene enhances c-myc transcription. *Proc Natl Acad Sci USA* **80**: 7581–7585.

Fenrick R, Amann JM, Lutterbach B, Wang L, Westendorf JJ, Downing JR *et al*. (1999). Both TEL and AML-1 contribute repression domains to the t(12;21) fusion protein. *Mol Cell Biol* **19**: 6566–6574.

Fernandez PC, Frank SR, Wang L, Schroeder M, Liu S, Greene J *et al*. (2003). Genomic targets of the human c-Myc protein. *Genes Dev* **17**: 1115–1129.

Ferrando AA, Armstrong SA, Neuberg DS, Sallan SE, Silverman LB, Korsmeyer SJ *et al*. (2003). Gene expression signatures in MLL-rearranged T-lineage and B-precursor acute leukemias: dominance of HOX dysregulation. *Blood* **102**: 262–268.

Ferrando AA, Herblot S, Palomero T, Hansen M, Hoang T, Fox EA *et al*. (2004). Biallelic transcriptional activation of oncogenic transcription factors in T-cell acute lymphoblastic leukemia. *Blood* **103**: 1909–1911.

Ferrando AA, Look AT. (2000). Clinical implications of recurring chromosomal and associated molecular abnormalities in acute lymphoblastic leukemia. *Semin Hematol* **37**: 381–395.

Ferrando AA, Look AT. (2003). Gene expression profiling in T-cell acute lymphoblastic leukemia. *Semin Hematol* **40**: 274–280.

Finger LR, Harvey RC, Moore RC, Showe LC, Croce CM. (1986). A common mechanism of chromosomal translocation in T- and B-cell neoplasia. *Science* **234**: 982–985.

Fisch P, Boehm T, Lavenir I, Larson T, Arno J, Forster A *et al*. (1992). T-cell acute lymphoblastic lymphoma induced in transgenic mice by the RBTN1 and RBTN2 LIM-domain genes. *Oncogene* **7**: 2389–2397.

Forster A, Pannell R, Drynan LF, McCormack M, Collins EC, Daser A *et al*. (2003). Engineering *de novo* reciprocal chromosomal translocations associated with Mll to replicate primary events of human cancer. *Cancer Cell* **3**: 449–458.

Grabher C, von Boehmer H, Look AT. (2006). Notch 1 activation in the molecular pathogenesis of T-cell acute lymphoblastic leukaemia. *Nat Rev Cancer* **6**: 347–359.

Grandori C, Mac J, Siebelt F, Ayer DE, Eisenman RN. (1996). Myc-Max heterodimers activate a DEAD box gene and interact with multiple E box-related sites *in vivo*. *EMBO J* **15**: 4344–4357.

Greaves MF, Wiemels J. (2003). Origins of chromosome translocations in childhood leukaemia. *Nat Rev Cancer* **3**: 639–649.

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

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.

Hiebert SW, Sun W, Davis JN, Golub T, Shurtleff S, Buijs A *et al*. (1996). The t(12;21) translocation converts AML-1B from an activator to a repressor of transcription. *Mol Cell Biol* **16**: 1349–1355.

Hollis GF, Mitchell KF, Battey J, Potter H, Taub R, Lenoir GM *et al*. (1984). A variant translocation places the lambda immunoglobulin genes 3′ to the c-myc oncogene in Burkitt's lymphoma. *Nature* **307**: 752–755.

Hsu K, Look AT. (2003). Turning on a dimer: new insights into MLL chimeras. *Cancer Cell* **4**: 81–83.

Hunger SP. (1996). Chromosomal translocations involving the E2A gene in acute lymphoblastic leukemia: clinical features and molecular pathogenesis. *Blood* **87**: 1211–1224.

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**: 1608–1620.

Inaba T, Inukai T, Yoshihara T, Seyschab H, Ashmun RA, Canman CE *et al*. (1996). Reversal of apoptosis by the leukaemia-associated E2A-HLF chimaeric transcription factor. *Nature* **382**: 541–544.

Inaba T, Roberts WM, Shapiro LH, Jolly KW, Raimondi SC, Smith SD *et al*. (1992). Fusion of the leucine zipper gene HLF to the E2A gene in human acute B-lineage leukemia. *Science* **257**: 531–534.

Inoue A, Seidel MG, Wu W, Kamizono S, Ferrando AA, Bronson RT *et al*. (2002). Slug, a highly conserved zinc finger transcriptional repressor, protects hematopoietic progenitor cells from radiation-induced apoptosis *in vivo*. *Cancer Cell* **2**: 279–288.

Inukai T, Inoue A, Kurosawa H, Goi K, Shinjyo T, Ozawa K *et al*. (1999). SLUG, a ces-1-related zinc finger transcription factor gene with antiapoptotic activity, is a downstream target of the E2A-HLF oncoprotein. *Mol Cell* **4**: 343–352.

Jousset C, Carron C, Boureux A, Quang CT, Oury C, Dusanter-Fourt I *et al*. (1997). A domain of TEL conserved in a subset of ETS proteins defines a specific oligomerization interface essential to the mitogenic properties of the TEL-PDGFR beta oncoprotein. *EMBOJ* **16**: 69–82.

Kamps MP, Baltimore D. (1993). E2A-Pbx1, the t(1;19) translocation protein of human pre-B-cell acute lymphocytic leukemia, causes acute myeloid leukemia in mice. *Mol Cell Biol* **13**: 351–357.

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**: 547–555.

Kees UR, Heerema NA, Kumar R, Watt PM, Baker DL, La MK *et al*. (2003). Expression of HOX11 in childhood T-lineage acute lymphoblastic leukaemia can occur in the absence of cytogenetic aberration at 10q24: a study from the Children's Cancer Group (CCG). *Leukemia* **17**: 887–893.

Kennedy MA, Gonzalez-Sarmiento R, Kees UR, Lampert F, Dear N, Boehm T *et al*. (1991). HOX11, a homeobox-containing T-cell oncogene on human chromosome 10q24. *Proc Natl Acad Sci USA* **88**: 8900–8904.

Klempnauer KH, Gonda TJ, Bishop JM. (1982). Nucleotide sequence of the retroviral leukemia gene v-myb and its cellular progenitor c-myb: the architecture of a transduced oncogene. *Cell* **31**: 453–463.

Knoepfler PS, Kamps MP. (1995). The pentapeptide motif of Hox proteins is required for cooperative DNA binding with Pbx1, physically contacts Pbx1, and enhances DNA binding by Pbx1. *Mol Cell Biol* **15**: 5811–5819.

Lahortiga I, De Keersmaecker K, Van Vlierberghe P, Graux C, Cauwelier B, Lambert F *et al*. (2007). Duplication of the MYB oncogene in T cell acute lymphoblastic leukemia. *Nat Genet* **9**: 593–595.

Larson RC, Fisch P, Larson TA, Lavenir I, Langford T, King G *et al*. (1994). T cell tumours of disparate phenotype in mice transgenic for Rbtn-2. *Oncogene* **9**: 3675–3681.

Larson RC, Lavenir I, Larson TA, Baer R, Warren AJ, Wadman I *et al*. (1996). Protein dimerization between Lmo2 (Rbtn2) and Tal1 alters thymocyte development and potentiates T cell tumorigenesis in transgenic mice. *EMBO J* **15**: 1021–1027.

Larson RC, Osada H, Larson TA, Lavenir I, Rabbitts TH. (1995). The oncogenic LIM protein Rbtn2 causes thymic developmental aberrations that precede malignancy in transgenic mice. *Oncogene* **11**: 853–862.

Lavau C, Du C, Thirman M, Zeleznik-Le N. (2000a). Chromatin-related properties of CBP fused to MLL generate a myelodysplastic-like syndrome that evolves into myeloid leukemia. *EMBO J* **19**: 4655–4664.

Lavau C, Luo RT, Du C, Thirman MJ. (2000b). Retrovirus-mediated gene transfer of *MLL-ELL* transforms primary myeloid progenitors and causes acute myeloid leukemias in mice. *Proc Natl Acad Sci USA* **97**: 10984–10989.

LeBrun DP, Cleary ML. (1994). Fusion with E2A alters the transcriptional properties of the homeodomain protein PBX1 in t(1;19) leukemias. *Oncogene* **9**: 1641–1647.

Lewis HD, Leveridge M, Strack PR, Haldon CD, O'Neil J, Kim H *et al*. (2007). Apoptosis in T cell acute lymphoblastic leukemia cells after cell cycle arrest induced by pharmacological inhibition of notch signaling. *Chem Biol* **14**: 209–219.

Li Z, Van Calcar S, Qu C, Cavenee WK, Zhang MQ, Ren B. (2003). A global transcriptional regulatory role for c-Myc in Burkitt's lymphoma cells. *Proc Natl Acad Sci USA* **100**: 8164–8169.

Lin YW, Nichols RA, Letterio JJ, Aplan PD. (2006). Notch1 mutations are important for leukemic transformation in murine models of precursor-T leukemia/lymphoma. *Blood* **107**: 2540–2543.

Look AT. (1997). Oncogenic transcription factors in the human acute leukemias. *Science* **278**: 1059–1064.

Lu M, Gong ZY, Shen WF, Ho AD. (1991). The tcl-3 proto-oncogene altered by chromosomal translocation in T-cell leukemia codes for a homeobox protein. *EMBO J* **10**: 2905–2910.

Lu Q, Knoepfler PS, Scheele J, Wright DD, Kamps MP. (1995). Both Pbx1 and E2A-Pbx1 bind the DNA motif ATCAATCAA cooperatively with the products of multiple murine Hox genes, some of which are themselves oncogenes. *Mol Cell Biol* **15**: 3786–3795.

Lu Q, Wright DD, Kamps MP. (1994). Fusion with E2A converts the Pbx1 homeodomain protein into a constitutive transcriptional activator in human leukemias carrying the t(1;19) translocation. *Mol Cell Biol* **14**: 3938–3948.

Ma Q, Alder H, Nelson KK, Chatterjee D, Gu Y, Nakamura T *et al*. (1993). Analysis of the murine All-1 gene reveals conserved domains with human ALL-1 and identifies a motif shared with DNA methyltransferases. *Proc Natl Acad Sci USA* **90**: 6350–6354.

Malecki MJ, Sanchez-Irizarry C, Mitchell JL, Histen G, Xu ML, Aster JC *et al*. (2006). Leukemia-associated mutations within the NOTCH1 heterodimerization domain fall into at least two distinct mechanistic classes. *Mol Cell Biol* **26**: 4642–4651.

Malyukova A, Dohda T, von der Lehr N, Akhondi S, Corcoran M, Heyman 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**: 5611–5616.

Maser RS, Choudhury B, Campbell PJ, Feng B, Wong KK, Protopopov A *et al*. (2007). Chromosomally unstable mouse tumours have genomic alterations similar to diverse human cancers. *Nature* **447**: 966–971.

Mauvieux L, Leymarie V, Helias C, Perrusson N, Falkenrodt A, Lioure B *et al*. (2002). High incidence of Hox11L2 expression in children with T-ALL. *Leukemia* **16**: 2417–2422.

McGuire EA, Hockett RD, Pollock KM, Bartholdi MF, O'Brien SJ, Korsmeyer SJ. (1989). The t(11;14)(p15;q11) in a T-cell acute lymphoblastic leukemia cell line activates multiple transcripts, including Ttg-1, a gene encoding a potential zinc finger protein. *Mol Cell Biol* **9**: 2124–2132.

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**: 4186–4196.

McKeithan TW, Shima EA, Le Beau MM, Minowada J, Rowley JD, Diaz MO. (1986). Molecular cloning of the breakpoint junction of a human chromosomal 8;14 translocation involving the T-cell receptor alpha-chain gene and sequences on the 3′ side of MYC. *Proc Natl Acad Sci USA* **83**: 6636–6640.

McLean TW, Ringold S, Neuberg D, Stegmaier K, Tantravahi R, Ritz J *et al*. (1996). TEL/AML-1 dimerizes and is associated with a favorable outcome in childhood acute lymphoblastic leukemia. *Blood* **88**: 4252–4258.

Mellentin JD, Nourse J, Hunger SP, Smith SD, Cleary ML. (1990). Molecular analysis of the t(1;19) breakpoint cluster region in pre-B cell acute lymphoblastic leukemias. *Genes Chromosomes Cancer* **2**: 239–247.

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.

Metzler M, Forster A, Pannell R, Arends MJ, Daser A, Lobato MN *et al*. (2006). A conditional model of MLL-AF4 B-cell tumourigenesis using invertor technology. *Oncogene* **25**: 3093–3103.

Metzstein MM, Hengartner MO, Tsung N, Ellis RE, Horvitz HR. (1996). Transcriptional regulator of programmed cell death encoded by *Caenorhabditis elegans* gene ces-2. *Nature* **382**: 545–547.

Metzstein MM, Horvitz HR. (1999). The *C. elegans* cell death specification gene ces-1 encodes a snail family zinc finger protein. *Mol Cell* **4**: 309–319.

Mikkola HK, Klintman J, Yang H, Hock H, Schlaeger TM, Fujiwara Y *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**: 547–551.

Milne TA, Briggs SD, Brock HW, Martin ME, Gibbs D, Allis CD *et al*. (2002). MLL targets SET domain methyltransferase activity to Hox gene promoters. *Mol Cell* **10**: 1107–1117.

Mitani K, Kanda Y, Ogawa S, Tanaka T, Inazawa J, Yazaki Y *et al*. (1995). Cloning of several species of MLL/MEN chimeric cDNAs in myeloid leukemia with t(11;19)(q23;p13.1) translocation. *Blood* **85**: 2017–2024.

Monica K, LeBrun DP, Dedera DA, Brown R, Cleary ML. (1994). Transformation properties of the E2a-Pbx1 chimeric oncoprotein: fusion with E2a is essential, but the Pbx1 homeodomain is dispensable. *Mol Cell Biol* **14**: 8304–8314.

Morrow M, Horton S, Kioussis D, Brady HJ, Williams O. (2004). TEL-AML1 promotes development of specific hematopoietic lineages consistent with preleukemic activity. *Blood* **103**: 3890–3896.

Morrow M, Samanta A, Kioussis D, Brady HJ, Williams O. (2007). TEL-AML1 preleukemic activity requires the DNA binding domain of AML1 and the dimerization and corepressor binding domains of TEL. *Oncogene* **26**: 4404–4414.

Mucenski ML, McLain K, Kier AB, Swerdlow SH, Schreiner CM, Miller TA *et al*. (1991). A functional c-myb gene is required for normal murine fetal hepatic hematopoiesis. *Cell* **65**: 677–689.

Mullighan CG, Goorha S, Radtke I, Miller CB, Coustan-Smith E, Dalton JD *et al*. (2007). Genome-wide analysis of genetic alterations in acute lymphoblastic leukaemia. *Nature* **446**: 758–764.

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**: 3060–3071.

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

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**: 3897–3905.

O'Neil J, Calvo J, McKenna K, Krishnamoorthy V, Aster JC, Bassing CH *et al*. (2006). Activating Notch1 mutations in mouse models of T-ALL. *Blood* **107**: 781–785.

O'Neil J, Grim J, Strack P, Rao S, Tibbitts D, Winter C *et al*. (2007). FBW7 mutations in leukemic cells mediate NOTCH pathway activation and resistance to gamma-secretase inhibitors. *J Exp Med* **204**: 1813–1824.

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**: 587–596.

Orian A, van Steensel B, Delrow J, Bussemaker HJ, Li L, Sawado T *et al*. (2003). Genomic binding by the *Drosophila* Myc, Max, Mad/Mnt transcription factor network. *Genes Dev* **17**: 1101–1114.

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**: 216–229.

Palomero T, Lim WK, Odom DT, Sulis ML, Real PJ, Margolin A *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**: 18261–18266.

Pear WS, Aster JC, Scott ML, Hasserjian RP, Soffer B, Sklar J *et al*. (1996). Exclusive development of T cell neoplasms in mice transplanted with bone marrow expressing activated Notch alleles. *J Exp Med* **183**: 2283–2291.

Pearson R, Weston K. (2000). c-Myb regulates the proliferation of immature thymocytes following beta-selection. *EMBO J* **19**: 6112–6120.

Porcher C, Swat W, Rockwell K, Fujiwara Y, Alt FW, Orkin SH. (1996). The T cell leukemia oncoprotein SCL/tal-1 is essential for development of all hematopoietic lineages. *Cell* **86**: 47–57.

Rabbitts TH. (1994). Chromosomal translocations in human cancer. *Nature* **372**: 143–149.

Radtke F, Wilson A, Mancini SJ, MacDonald HR. (2004). Notch regulation of lymphocyte development and function. *Nat Immunol* **5**: 247–253.

Raju K, Tang S, Dube ID, Kamel-Reid S, Bryce DM, Breitman ML. (1993). Characterization and developmental expression of Tlx-1, the murine homolog of HOX11. *Mech Dev* **44**: 51–64.

Rappold GA, Hameister H, Cremer T, Adolph S, Henglein B, Freese UK *et al*. (1984). c-myc and immunoglobulin kappa light chain constant genes are on the 8q+ chromosome of three Burkitt lymphoma lines with t(2;8) translocations. *EMBO J* **3**: 2951–2955.

Reeves R, Nissen MS. (1990). The A.T-DNA-binding domain of mammalian high mobility group I chromosomal proteins. A novel peptide motif for recognizing DNA structure. *J Biol Chem* **265**: 8573–8582.

Riz I, Hawley RG. (2005). G1/S transcriptional networks modulated by the HOX11/TLX1 oncogene of T-cell acute lymphoblastic leukemia. *Oncogene* **24**: 5561–5575.

Robb L, Lyons I, Li R, Hartley L, Kontgen F, Harvey RP *et al*. (1995). Absence of yolk sac hematopoiesis from mice with a targeted disruption of the scl gene. *Proc Natl Acad Sci USA* **92**: 7075–7079.

Roberts CW, Shutter JR, Korsmeyer SJ. (1994). Hox11 controls the genesis of the spleen. *Nature* **368**: 747–749.

Roberts CW, Sonder AM, Lumsden A, Korsmeyer SJ. (1995). Development expression of Hox11 and specification of splenic cell fate. *Am J Pathol* **146**: 1089–1101.

Rompaey LV, Potter M, Adams C, Grosveld G. (2000). Tel induces a G1 arrest and suppresses Ras-induced transformation. *Oncogene* **19**: 5244–5250.

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

Sabaawy HE, Azuma M, Embree LJ, Tsai HJ, Starost MF, Hickstein DD. (2006). TEL-AML1 transgenic zebrafish model of precursor B cell acute lymphoblastic leukemia. *Proc Natl Acad Sci USA* **103**: 15166–15171.

Sharma VM, Calvo JA, Draheim KM, Cunningham LA, Hermance N, Beverly L *et al*. (2006). Notch1 contributes to mouse T-cell leukemia by directly inducing the expression of c-myc. *Mol Cell Biol* **26**: 8022–8031.

Shilatifard A, Lane WS, Jackson KW, Conaway RC, Conaway JW. (1996). An RNA polymerase II elongation factor encoded by the human ELL gene. *Science* **271**: 1873–1876.

Shima EA, Le Beau MM, McKeithan TW, Minowada J, Showe LC, Mak TW *et al*. (1986). Gene encoding the alpha chain of the T-cell receptor is moved immediately downstream of c-myc in a chromosomal 8;14 translocation in a cell line from a human T-cell leukemia. *Proc Natl Acad Sci USA* **83**: 3439–3443.

Shirasawa S, Arata A, Onimaru H, Roth KA, Brown GA, Horning S *et al*. (2000). Rnx deficiency results in congenital central hypoventilation. *Nat Genet* **24**: 287–290.

Shivdasani RA, Mayer EL, Orkin SH. (1995). Absence of blood formation in mice lacking the T-cell leukaemia oncoprotein tal-1/SCL. *Nature* **373**: 432–434.

So CW, Lin M, Ayton PM, Chen EH, Cleary ML. (2003). Dimerization contributes to oncogenic activation of MLL chimeras in acute leukemias. *Cancer Cell* **4**: 99–110.

Soulier J, Clappier E, Cayuela JM, Regnault A, Garcia-Peydro M, Dombret H *et al*. (2005). HOXA genes are included in genetic and biologic networks defining human acute T-cell leukemia (T-ALL). *Blood* **106**: 274–286.

Takeuchi S, Seriu T, Bartram CR, Golub TR, Reiter A, Miyoshi I *et al*. (1997). TEL is one of the targets for deletion on 12p in many cases of childhood B-lineage acute lymphoblastic leukemia. *Leukemia* **11**: 1220–1223.

Taub R, Kelly K, Battey J, Latt S, Lenoir GM, Tantravahi U *et al*. (1984). A novel alteration in the structure of an activated c-myc gene in a variant t(2;8) Burkitt lymphoma. *Cell* **37**: 511–520.

Taub R, Kirsch I, Morton C, Lenoir G, Swan D, Tronick S *et al*. (1982). Translocation of the c-myc gene into the immunoglobulin heavy chain locus in human Burkitt lymphoma and murine plasmacytoma cells. *Proc Natl Acad Sci USA* **79**: 7837–7841.

Thirman MJ, Levitan DA, Kobayashi H, Simon MC, Rowley JD. (1994). Cloning of ELL, a gene that fuses to MLL in a t(11;19)(q23;p13.1) in acute myeloid leukemia. *Proc Natl Acad Sci USA* **91**: 12110–12114.

Thompson BJ, Buonamici S, Sulis ML, Palomero T, Vilimas T, Basso G *et al*. (2007). The SCFFBW7 ubiquitin ligase complex as a tumor suppressor in T cell leukemia. *J Exp Med* **204**: 1825–1835.

Thompson CB. (1996). Transcription. A fate worse than death. *Nature* **382**: 492–493.

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

Tsuzuki S, Seto M, Greaves M, Enver T. (2004). Modeling first-hit functions of the t(12;21) TEL-AML1 translocation in mice. *Proc Natl Acad Sci USA* **101**: 8443–8448.

Valge-Archer VE, Osada H, Warren AJ, Forster A, Li J, Baer R *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**: 8617–8621.

van Dijk MA, Peltenburg LT, Murre C. (1995). Hox gene products modulate the DNA binding activity of Pbx1 and Pbx2. *Mech Dev* **52**: 99–108.

Van Dijk MA, Voorhoeve PM, Murre C. (1993). Pbx1 is converted into a transcriptional activator upon acquiring the N-terminal region of E2A in pre-B-cell acute lymphoblastoid leukemia. *Proc Natl Acad Sci USA* **90**: 6061–6065.

Van Vlierberghe P, van Grotel M, Beverloo HB, Lee C, Helgason T, Buijs-Gladdines J *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**: 3520–3529.

Vilimas T, Mascarenhas J, Palomero T, Mandal M, Buonamici S, Meng F *et al*. (2007). Targeting the NF-kappaB signaling pathway in Notch1-induced T-cell leukemia. *Nat Med* **13**: 70–77.

Wadman I, Li J, Bash RO, Forster A, Osada H, Rabbitts TH *et al*. (1994). Specific *in vivo* association between the bHLH and LIM proteins implicated in human T cell leukemia. *EMBO J* **13**: 4831–4839.

Waldmann TA, Davis MM, Bongiovanni KF, Korsmeyer SJ. (1985). Rearrangements of genes for the antigen receptor on T cells as markers of lineage and clonality in human lymphoid neoplasms. *N Engl J Med* **313**: 776–783.

Wang J, Jani-Sait SN, Escalon EA, Carroll AJ, de Jong PJ, Kirsch IR *et al*. (2000). The t(14;21)(q11.2;q22) chromosomal translocation associated with T-cell acute lymphoblastic leukemia activates the BHLHB1 gene. *Proc Natl Acad Sci USA* **97**: 3497–3502.

Warren AJ, Colledge WH, Carlton MB, Evans MJ, Smith AJ, Rabbitts TH. (1994). The oncogenic cysteine-rich LIM domain protein rbtn2 is essential for erythroid development. *Cell* **78**: 45–57.

Weng AP, Ferrando AA, Lee W, Morris JPt, Silverman LB, Sanchez-Irizarry C *et al*. (2004). Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. *Science* **306**: 269–271.

Weng AP, Millholland JM, Yashiro-Ohtani Y, Arcangeli ML, Lau A, Wai C *et al*. (2006). c-Myc is an important direct target of Notch1 in T-cell acute lymphoblastic leukemia/lymphoma. *Genes Dev* **20**: 2096–2109.

Wilson A, Radtke F. (2006). Multiple functions of Notch signaling in self-renewing organs and cancer. *FEBS Lett* **580**: 2860–2868.

Wu WS, Heinrichs S, Xu D, Garrison SP, Zambetti GP, Adams JM *et al*. (2005). Slug antagonizes p53-mediated apoptosis of hematopoietic progenitors by repressing puma. *Cell* **123**: 641–653.

Xia Y, Brown L, Yang CY, Tsan JT, Siciliano MJ, Espinosa III R *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**: 11416–11420.

Yan W, Young AZ, Soares VC, Kelley R, Benezra R, Zhuang Y. (1997). High incidence of T-cell tumors in E2A-null mice and E2A/Id1 double-knockout mice. *Mol Cell Biol* **17**: 7317–7327.

Yeoh EJ, Ross ME, Shurtleff SA, Williams WK, Patel D, Mahfouz R *et al*. (2002). Classification, subtype discovery, and prediction of outcome in pediatric acute lymphoblastic leukemia by gene expression profiling. *Cancer Cell* **1**: 133–143.

Yokoyama A, Wang Z, Wysocka J, Sanyal M, Aufiero DJ, Kitabayashi I *et al*. (2004). Leukemia proto-oncoprotein MLL forms a SET1-like histone methyltransferase complex with menin to regulate Hox gene expression. *Mol Cell Biol* **24**: 5639–5649.

Yoshihara T, Inaba T, Shapiro LH, Kato JY, Look AT. (1995). E2A-HLF-mediated cell transformation requires both the trans-activation domains of E2A and the leucine zipper dimerization domain of HLF. *Mol Cell Biol* **15**: 3247–3255.

Yu BD, Hanson RD, Hess JL, Horning SE, Korsmeyer SJ. (1998). MLL, a mammalian trithorax-group gene, functions as a transcriptional maintenance factor in morphogenesis. *Proc Natl Acad Sci USA* **95**: 10632–10636.

Zeisig BB, Garcia-Cuellar MP, Winkler TH, Slany RK. (2003). The oncoprotein MLL-ENL disturbs hematopoietic lineage determination and transforms a biphenotypic lymphoid/myeloid cell. *Oncogene* **22**: 1629–1637.

Zhu YM, Zhao WL, Fu JF, Shi JY, Pan Q, Hu J *et al*. (2006). NOTCH1 mutations in T-cell acute lymphoblastic leukemia: prognostic significance and implication in multifactorial leukemogenesis. *Clin Cancer Res* **12**: 3043–3049.

Ziemin-van der Poel S, McCabe NR, Gill HJ, Espinosa III R, Patel Y, Harden A *et al*. (1991). Identification of a gene, MLL, that spans the breakpoint in 11q23 translocations associated with human leukemias. *Proc Natl Acad Sci USA* **88**: 10735–10739.