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Pieter Van Vlierberghe, Adolfo Ferrando

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Review Series

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The molecular basis of T cell acute lymphoblastic leukemia

Pieter Van Vlierberghe[1] and Adolfo Ferrando[1,2,3]

[1]Institute for Cancer Genetics, [2]Department of Pathology, and [3]Department of Pediatrics, Columbia University Medical Center, New York, New York, USA.

T cell acute lymphoblastic leukemias (T-ALLs) arise from the malignant transformation of hematopoietic progenitors primed toward T cell development, as result of a multistep oncogenic process involving constitutive activation of NOTCH signaling and genetic alterations in transcription factors, signaling oncogenes, and tumor suppressors. Notably, these genetic alterations define distinct molecular groups of T-ALL with specific gene expression signatures and clinicobiological features. This review summarizes recent advances in our understanding of the molecular genetics of T-ALL.

T cell acute lymphoblastic leukemias (T-ALLs) are aggressive hematologic tumors resulting from the malignant transformation of T cell progenitors. T-ALL accounts for 10%–15% of pediatric and 25% of adult ALL cases (1) and is characteristically more frequent in males than females. Clinically, T-ALL patients show diffuse infiltration of the bone marrow by immature T cell lymphoblasts, high white blood cell counts, mediastinal masses with pleural effusions, and frequent infiltration of the central nervous system at diagnosis. Although originally associated with high relapse rates, the prognosis of T-ALL has gradually improved with the Introduction of intensified chemotherapy, with cure rates in modern protocols reaching over 75% in children and about 50% in adults with this disease (2). However, the outcome of T-ALL patients with primary resistant or relapsed leukemia remains poor (3, 4). Therefore, current research efforts are focused on the search for targets for the development of more effective and less toxic antileukemic drugs (5), which will likely require a greater degree of specificity and an improved understanding of the molecular events that lead to the disease.

T cell transformation is a multi-step process in which different genetic alterations cooperate to alter the normal mechanisms that control cell growth, proliferation, survival, and differentiation during thymocyte development. In this context, constitutive activation of *NOTCH1* signaling is the most prominent oncogenic pathway in T cell transformation (6). However, deletions of the *CDKN2A* locus in chromosome band 9p21, which encompasses the *p16/INK4A* and *p14/ARF* suppressor genes, are present in more than 70% of all T-ALL cases (1, 7). Thus, constitutive activation of *NOTCH* signaling cooperates with loss of *p16/INK4A* and *p14/ARF* in T cell transformation and constitutes the core of the oncogenic program in the pathogenesis of T-ALL.

In addition, T-ALLs characteristically show the translocation and aberrant expression of transcription factor oncogenes. These chromosomal rearrangements place T-ALL transcription factor oncogenes under the control of strong T cell–specific enhancers located in the *TCRB* (7q34) or *TCRA–TCRD* (14q11) loci, resulting in their aberrant expression in T cell progenitors. These oncogenic transcription factors include basic helix-loop-helix (bHLH) family members such as *TAL1* (8–10), *TAL2* (11), *LYL1* (12), and *BHLHB1* (13); LIM-only domain (LMO) genes such as *LMO1* and *LMO2* (14–16); the *TLX1/HOX11* (17–19), *TLX3/HOX11L2* (1, 20), *NKX2.1* (21), *NKX2.2* (21), *NKX2.5* (22), and *HOXA* homeobox (HOX) genes (23, 24); *MYC* (25); *MYB* (26); and *TAN1*, a truncated and constitutively activated form of the NOTCH1 receptor (27). In addition, some of these T cell transcription factor oncogenes can be activated as result of alternative genetic rearrangements. Most notably, the *TLX3/HOX11L2* locus is recurrently translocated to T cell regulatory sequences in the proximity of the *BCL11B* locus and only rarely translocated to the TCR loci (20). In addition, small intrachromosomal deletions in chromosome 1p32 result in *TAL1* overexpression (28), and cryptic deletions in chromosome 11p13 can lead to activation of the *LMO2* oncogene (29).

Importantly, gene expression profiling studies have revealed a limited number of well-defined molecular groups of T-ALL (1, 21, 23, 30), which share unique gene expression signatures reflecting distinct stages of arrest during T cell development (1). Early immature T-ALLs show an early block at the double-negative stage of thymocyte development (1, 31, 32). In contrast, early cortical T-ALLs are characteristically CD1a, CD4, and CD8 positive and are typically associated with activation of the *TLX1*, *TLX3*, *NKX2.1*, and *NKX2.2* homeobox genes (1, 21). Finally, late-cortical thymocyte T-ALLs express CD4, CD8, and CD3 and show activation of the *TAL1* transcription factor oncogene (1). Table 1 provides an overview of all main driving genetic lesions that characterize these unique molecular genetic T-ALL subtypes.

The diversity of genetic lesions involved in the pathogenesis of T-ALL is further complicated by a number of recurrent cytogenetic and molecular alterations that are common between all molecular subtypes and cause deregulation in specific cellular processes, including cell cycle signaling, cell growth and proliferation, chromatin remodeling, T cell differentiation, and self-renewal (Table 2).

Recent studies have linked the early immature T-ALL group with the activation of a transcriptional program related to hematopoietic stem cells and myeloid progenitors (32, 33), aberrant expression of the *MEF2C* gene (21), mutations in acute myeloid leukemia oncogenes and tumor suppressors (32, 33) and inactivation of important transcription factors such as *RUNX1*, *GATA3*, and *ETV6* (32, 33). Notably, these tumors frequently show absence of biallelic TCRγ deletions (34) and are associated with a very poor prognosis (31, 34).

Constitutive activation of NOTCH1 signaling in T-ALL

The NOTCH signaling pathway plays a critical role in cell lineage commitment decisions during development (ref. 35 and Figure 1). Aberrant NOTCH1 signaling was originally linked to the patho-

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Table 1
Genetic lesions that define molecular-genetic subtypes in T-ALL

Gene category	Gene target	Genetic rearrangement	Outcome (ref.)	Frequency[A] (ref.)
bHLH family members	*TAL1*	t(1;14)(p32;q11)	Good (66–68)	3% (28)
		t(1;7)(p32;q34)	Good (66–68)	3% (28)
		1p32 deletion	Good (66–68)	16%–30% (61)
	TAL2	t(7;9)(q34;q32)	NA	1% (11, 30)
	LYL1	t(7;19)(q34;p13)	NA	1% (12)
	BHLHB1	t(14;21)(q11.2;q22)	NA	1% (13)
LMO family members	*LMO1*	t(11;14)(p15;q11)	NA	1% (15, 30)
		t(7;11)(q34;p15)	NA	1% (15, 30)
	LMO2	t(11;14)(p13;q11)	NA	6% (126)
		t(7;11)(q34;p13)	NA	6% (126)
		11p13 deletion	NA	3% (29)
	LMO3	t(7;12)(q34;p12)	NA	<1% (21)
Homeobox family members	*TLX1*	t(11;14)(p15;q11)	Good (76)	5%–10% (126)
				30% (76, 88)
	TLX3	t(11;14)(p15;q11)	Poor (83, 88, 126)	20% (20)
			No impact (67)	5% (84)
			Good (127)	5% (84)
	HOXA	Inv(7)(p15q34)	NA	3% (23, 128)
		t(7;7)(p15;q34)	NA	3% (23, 128)
	HOXA (*CALM-AF10*)	t(10;11)(p13;q14)	Poor (87, 126)	5%–10% (87)
	HOXA (*MLL-ENL*)	t(11;19)(q23;p13)	NA	1% (88)
	HOXA (*SET-NUP214*)	9q34 deletion	No impact (33)	3% (30)
		inv(14)(q11.2q13)	NA	
	NKX2.1	inv(14)(q13q32.33)	NA	5% (21)
		t(7;14)(q34;q13)	NA	
	NKX2.2	t(14;20)(q11;p11)	NA	1% (21)
Proto-oncogene	*c-MYB*	t(6;7)(q23;q34)	NA	3% (26)

[A] Frequency refers to the frequency in which each mutation occurs in the patient population.

genesis of T-ALL by the cloning of the t(7;9)(q34;q34.3) chromosomal translocation, which leads to the expression of a truncated and constitutively active form of NOTCH1 (27). However, the central role of NOTCH1 in T cell transformation was only realized upon the identification of activating mutations in the *NOTCH1* gene present in over 50% of T-ALL cases (6). *NOTCH1* mutations typically involve specific domains responsible for controlling the initiation and termination of NOTCH signaling (6, 36). In addition *FBXW7* mutations, present in about 15% of T-ALL cases, contribute to NOTCH activation by impairing the proteasomal degradation of activated NOTCH1 in the nucleus (refs. 37, 38, and Figure 2).

The identification of activating *NOTCH1* mutations, present in nearly 60% of T-ALL patients, has created enormous interest in developing molecularly tailored therapies for T-ALL (6). Most notably, γ-secretase inhibitors (GSIs), which block the proteolytic cleavage of the NOTCH receptors and preclude the release of activated NOTCH1 (ICN1) from the membrane, have been proposed as potential targeted therapy in T-ALL (6, 39–42). More recently, stapled peptides targeting the NOTCH transcriptional complex and NOTCH1-specific inhibitory antibodies have been proposed as alternative anti-NOTCH1 therapies for the treatment of T-ALL (refs. 43, 44, and Figure 1).

A number of studies have recently addressed the prognostic significance of *NOTCH1* and *FBXW7* mutations in T-ALL (45–51). Overall, these studies show that NOTCH activation is associated with improved early therapeutic response and increased sensitivity to glucocorticoids. However, this early benefit only translates into improved overall survival in some studies (45–48). The association of *NOTCH1* mutations with increased glucocorticoid response is particularly intriguing given that expression of activated NOTCH1 can impair glucocorticoid-induced cell death in thymocytes (52) and that blocking NOTCH1 signaling with GSIs can reverse glucocorticoid resistance in some T-ALLs (53). This last notion was recently tested in a preclinical setting using a combination of PF-03084014, a clinically-relevant GSI, and dexamethasone in glucocorticoid-resistant T-ALL. The study revealed that this glucocorticoid/GSI combination has a synergistic antileukemic effect in human T-ALL cell lines, primary human T-ALL patient samples, and in an in vivo mouse xenograft model of T-ALL (54).

Alterations in cell cycle regulators

The *CDKN2A* locus in the short arm of chromosome 9 contains the *p16INK4A* and *p14ARF* tumor suppressor genes. P16INK4A directly blocks cyclin D–CDK4/6 complexes, whereas p14ARF inhibits MDM2, a negative regulator of the TP53 oncoprotein (55, 56). *CDKN2A* deletions are the most frequent abnormality in T-ALL, present in over 70% of patients (7). In addition, the t(12;14)(p13;q11) and t(7;12)(q34;p13) translocations can induce aberrantly high levels of expression of the *CCND2* cell cycle regulator (57) and chromosomal deletions recurrently inactivate *RB1* and *CDKN1B* in some T-ALL cases (58, 59).

The prognostic implications of loss of heterozygosity at the short arm of chromosome 9 were evaluated in pediatric T-ALL patients treated according to the Berlin-Frankfurt-Munster regimen (60). This study showed that loss of heterozygosity at 9p was associated with a favorable initial treatment response in T-ALL (60).

Table 2
Classification of other recurrent genetic alterations in T-ALL

Category	Gene target	Genetic rearrangement	Outcome (ref.)	Frequency (ref.)
NOTCH1 pathway	*NOTCH1*	t(7;9)(q34;p13)	NA	<1% (27)
		Activating mutation	Good (51, 129) GPR (45, 49, 50) No impact (48)	>60% (6)
	FBXW7	Inactivating mutation	NA	8%–30% (37, 38)
Cell cycle defects	*CDKN2A/2B*	9p21 deletion methylation	Good (60)	70% (7)
	CCND2	t(7;12)(q34;p13) t(12;14)(p13;q11)	NA	1% (57)
	RB1	13q14 deletion	No impact (33)	4% (58)
	CDKN1B	12p13 deletion	NA	2% (59)
Cell growth transcription factor tumor suppressors	*MYC*	t(8;14)(q24;q11)	NA	1% (25)
	WT1	Inactivating mutation/deletion	No impact (80)	10% (80)
	LEF1	Inactivating mutation/deletion	NA	10%–15% (93)
	ETV6	Inactivating mutation/deletion	No impact (33)	13% (32, 33)
	BCL11B	Inactivating mutation/deletion	No impact (33)	10% (98)
	RUNX1	Inactivating mutation/deletion	No impact (33) Poor (101)	10%–20% (100, 101)
	GATA3	Inactivating mutation/deletion	Poor (33)	5% (33)
Signal transduction	PTEN	Inactivating mutation	No impact (106, 130)	10% (33, 106, 130)
		10q23 deletion	Poor (33)	10% (33, 106, 130)
	NUP214-ABL1	Episomal 9q34 amplification	Poor (108) No impact (131)	4% (108)
	EML1-ABL1	t(9;14)(q34;q32)	NA	<1% (109)
	ETV6-ABL1	t(9;12)(q34;p13)	NA	<1% (110)
	BCR-ABL1	t(9;22)(q34;q11)	Poor (132)	<1% (132)
	NRAS	Activating mutation	No impact (33)	5%–10% (32, 113)
	NF1	Inactivating mutation/deletion	No impact (33)	3% (114)
	JAK1	Activating mutation	No impact (33)	4%–18% (118, 119)
	ETV6-JAK2	t(9;12)(p24;p13)	NA	<1% (117)
	JAK3	activating mutation	No impact (33)	5% (33)
	FLT3	activating mutation	No impact (33)	2%–4% (133, 134)
	IL7R	activating mutation	No impact (33)	10% (120, 121)
Chromatin remodeling	*EZH2*	Inactivating mutation/deletion	Poor (33)	10%–15% (33, 135)
	SUZ12	Inactivating mutation/deletion	No impact (33)	10% (33)
	EED	Inactivating mutation/deletion	No impact (33)	10% (33)
	PHF6	Inactivating mutation/deletion	No impact (81)	20%–40% (81)

GPR, good prednisone response.

T-ALL–specific transcription factor oncogenes

Class II bHLH transcription factors. Overexpression and aberrant activation of a number of bHLH transcription factors activated by chromosomal translocations is a frequent oncogenic event in T-ALL. These proteins are characterized by a basic domain that mediates DNA binding and two α-helices connected by a loop that are involved in the formation of homodimeric and heterodimeric complexes. The *TAL1* gene in chromosome band 1p32 is a key regulator of hematopoietic stem cell development expressed in hematopoietic progenitors, mast cells, and erythroid and megakaryocyte progenitors (5). Abnormal expression of *TAL1* is present in approximately 60% of T-ALL cases as a result of various chromosomal rearrangements (1, 61). Thus, in 3% of childhood T-ALL, the translocation t(1;14)(p32;q11) places *TAL1* gene expression under the control of *TCRA/D* enhancers. In addition, 16%–30% of T-ALLs harbor a small intrachromosomal rearrangement that places *TAL1* under the control of the promoter of the neighbor gene *STIL*, which is highly expressed in T cells (28). T-ALL cases with *TAL1* expression show developmental arrest at the late double-positive stage of thymocyte development (1). In addition, *LYL1*, *TAL2*, and *BHLHB1*, three genes encoding bHLH factors closely related to *TAL1*, are translocated and aberrantly expressed in rare cases of T-ALL (11–13). The oncogenic potential of TAL1 is illustrated by the induction of T-ALL in transgenic mice expressing *TAL1* in developing thymocytes (62, 63). In T-ALL cells, TAL1 forms primarily inactive transcriptional complexes that contain E proteins and the LMO factors, LMO1 and LMO2, resulting in decreased expression of E protein target genes. Thus, although TAL1 may be present in transcriptional complexes activating the expression of some target genes (64), it has been proposed that the oncogenic activity of TAL1 could be mediated primarily by reducing the level of transcriptional activity of promoters normally controlled by E proteins (65). From a clinical point of view, a number of studies have suggested that late-cortical thymocyte T-ALLs showing *TAL1* gene rearrangements have a more favorable outcome (66–68).

LMO proteins. LIM domain proteins were originally linked with T-ALL in cases harboring the t(11;14)(p15;q11) and t(11;14)(p13;q11) chromosomal translocations involving the *LMO1* and

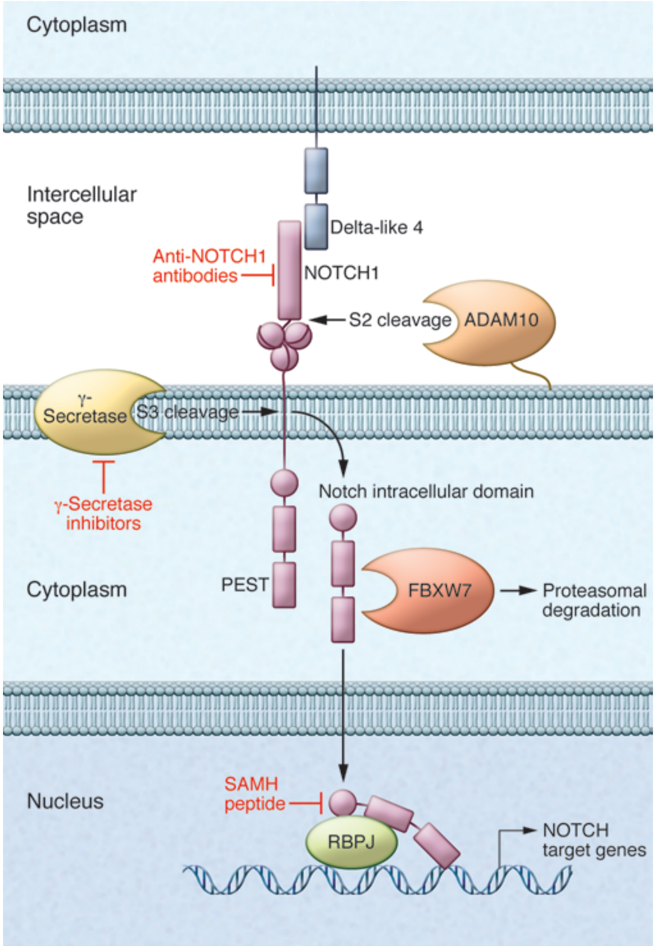

Figure 1
Schematic representation of NOTCH1 signaling in T cell progenitors. Interaction of the NOTCH ligand delta-like 4, expressed on the surface of thymic stroma cells, with NOTCH1 triggers a double proteolytic cleavage of the receptor in T cell progenitors first by the ADAM10 metalloprotease and subsequently by the gamma secretase complex. Release of the intracellular domains of NOTCH1 from the membrane activates the expression of NOTCH target genes in the nucleus. FBXW7 recognizes the PEST domain of activated NOTCH1 and terminates NOTCH signaling in the proteasome. Inhibition of ADAM10 cleavage with anti-NOTCH1 inhibitory antibodies, blockage of γ-secretase activity with small-molecule inhibitors, and disruption of the NOTCH1 nuclear transcriptional complex with small SAMH1 peptides are all approaches to effectively block NOTCH1 signaling in T-ALL.

LMO2 genes, respectively (14–16). Although these translocations only occur in 9% of pediatric T-ALL, aberrant *LMO2* expression can be found in up to 45% of T-ALL cases, suggesting additional mechanisms of activation. Unlike bHLH proteins, LMO1 and LMO2 do not interact directly with DNA; but they form transcriptional complexes with TAL1 and LYL1 (1, 69). Consistently, activation of *LMO1* and *LMO2* is most frequently found in cases with deregulated *TAL1* and/or *LYL1* expression (1). In line with this notion, the oncogenic activity of *Lmo1* or *Lmo2* in transgenic mice (70, 71) was shown to be enhanced in double-transgenic animals expressing *TAL1* in developing thymocytes (69, 72).

Although many of the genetic programs controlled by oncogenic LMO factors remain to be elucidated, a recent report from McCormack and coworkers has shown that forced expression of Lmo2 in mouse T cell progenitor cells confers self-renewal capacity to this normally non–self-renewing population (73). These results suggest a close relationship between the activation of stem cell properties and the oncogenic effects of LMO2 in T cell precursors (73). However, this model does not seem to reflect the late-cortical immunophenotypic arrest observed in primary *LMO2*-rearranged human T-ALL samples. *LMO2* rearrangements predicted poor outcome in a stratified analysis of pediatric T-ALL patients (29). However, given the small number of patients that harbor this specific genetic rearrangement, the significance of these findings needs to be validated in larger and independent T-ALL patient cohorts.

HOX transcription factor oncogenes TLX1, *TLX3,* and *HOXA*. HOX transcription factors play essential roles in body patterning and organogenesis during development. *TLX1* is the founding member of a family of HOX genes that includes *TLX2* and *TLX3* (74). *TLX1* was originally identified as the gene translocated into the *TCRA/D* locus in the recurrent t(10;14)(q24;q11) in T-ALL (17–19, 75). This genetic rearrangement induces aberrant *TLX1* expression and occurs in about 5%–10% of pediatric and 30% of adult T-ALLs (1, 76). Recently, the leukemogenic role of *TLX1* in T cell transformation has been firmly established using a *TLX1* transgenic mouse model that developed clonal T cell leukemias (77). Notably, *TLX1*-induced T-ALLs in mice shared a common transcriptional program with *TLX1*-positive human tumors characterized by the downregulation of TLX1 direct target genes.

TLX3 is overexpressed in 20%–25% of pediatric and 5% of adult T-ALLs harboring the t(5;14)(q35;q32) translocation (20). This rearrangement places the *TLX3* oncogene under the control of strong T cell regulatory elements in the *BCL11B* locus (20). Currently, the in vivo role of aberrant *TLX3* expression in the pathogenesis of T-ALL remains to be established.

TLX1 and TLX3 leukemias share an overlapping mechanism of transformation, have convergent gene expression signatures, and show specific cooperating mutations rarely present in non-TLX–induced leukemias, including the *NUP214-ABL1* fusion oncogene and mutations in the *PTPN2*, Wilms tumor 1 (*WT1*), and *PHF6* tumor suppressors (78–81). In addition, it was recently proposed that the unique cortical thymic maturation arrest in TLX-induced tumors may be related to the binding of TLX1/TLX3-ETS1 complexes to TCRA enhancer sequences, with the consequent downregulation of *TCRA* gene rearrangement and expression (82). *TLX1* expression has been linked with a favorable prognosis and a low risk of relapse in children and adults (1, 76). However, aberrant *TLX3* expression is associated with a less favorable prognosis and a higher incidence of relapse in some studies (83, 84).

Finally, about 3% of T-ALL patients harbor translocations in the *HOXA* cluster of HOX genes in 7p15 into the *TCRB* and *TCRG* loci, resulting in aberrant expression of the *HOXA10* and *HOXA9* genes (23). In addition, chromosomal translocations that generate fusion transcripts encoding chimeric transcription factor oncogenes can also be found in T-ALL. About 5% of T-ALLs express the *MLL-AFF1* (*MLL-AF4*) and *MLL-MLLT1* (*MLL-ENL*) fusion genes (85). Notably, *MLL* fusion oncogenes are associated with poor prognosis in precursor B cell ALL, although the *MLL-MLLT1* fusion rearrangement seems to confer a favorable progno-

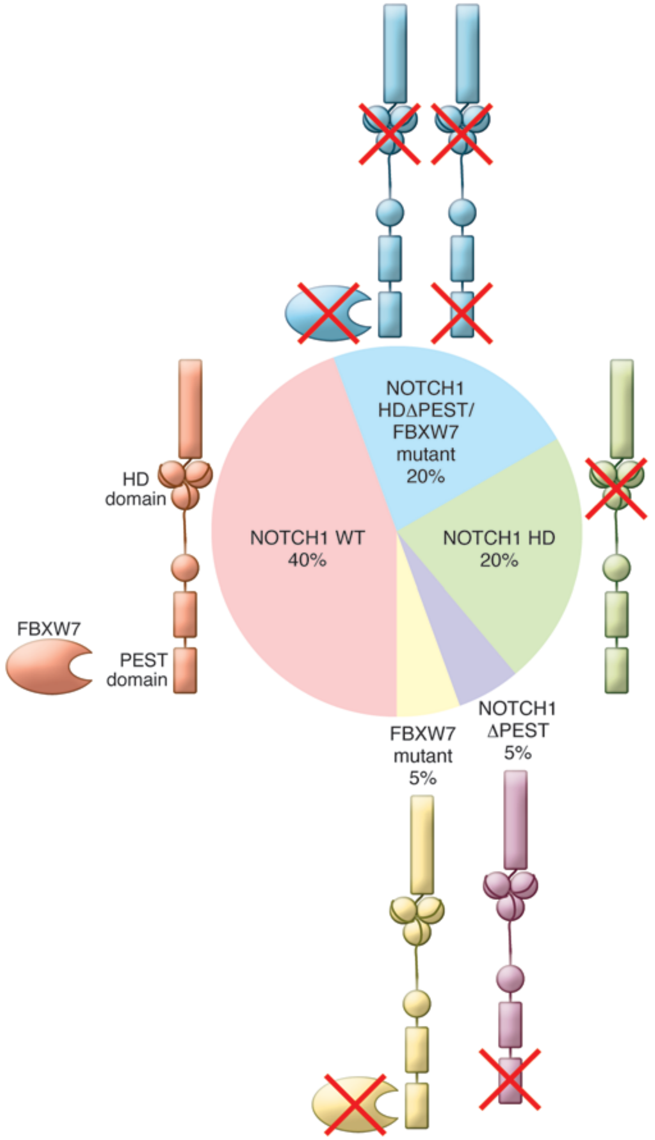

Figure 2

Prevalence and mechanisms of aberrant NOTCH1 signaling in T-ALL (40, 125). Schematic representation of the NOTCH1 receptor structure is shown for each type of NOTCH1 mutation found in T-ALL. The resting, membrane-bound domain structure of the NOTCH1 receptor is shown as depicted and described in Figure 1. Crossed-out domains in NOTCH1 and FBXW7 indicate the targeted areas disrupted in these proteins for each of the *NOTCH1* and *FBXW7* mutant alleles found in T-ALL.

sis in T-ALL (1, 86). In addition, the *PICALM-MLLT10* fusion oncogene is present in 5%–10% of T-ALLs (23, 87), and a rare cryptic del(9)(q34.11q34.13) deletion generating the *SET-NUP214* fusion gene in T-ALL has been described (30). A common feature of leukemias harboring these fusion transcription factor oncogenes is the aberrant expression of *HOXA* genes (1, 23, 30, 87, 88), suggesting a more general pathogenic role of *HOXA* dysregulation in the pathogenesis of T-ALL.

Proto-oncogenes. The *MYC* oncogene is activated in 1% of T-ALLs as result of the t(8;14)(q24;q11) translocation (25). However, *MYC* is broadly activated in T-ALL and functions as a critical NOTCH1 direct target gene, promoting cell growth and proliferation (89, 90).

c-MYB, a leucine zipper transcription factor oncogene, is translocated and overexpressed in T-ALL cases with the t(6;7)(q23;q32). *MYB* translocations are characteristically found in childhood T-ALLs diagnosed before 2 years of age and show a marked increase in the expression of proliferation and mitosis genes (26). In addition, focal duplications of the *MYB* locus are present in about 10% of T-ALLs (91, 92).

Loss of transcription factor tumor suppressor genes

Over the last few years, a wide variety of tumor suppressor genes have been shown to be mutated and deleted in T-ALL. However, the specific role of most of these transcriptional regulators in T cell transformation remains to be elucidated and is an area of active current investigation.

Deletions and mutations in the *WT1* gene are present in about 10% of T-ALLs (78, 80). *WT1* mutations found in T-ALL are predominantly heterozygous frameshift mutations resulting in truncation of the C-terminal zinc finger domains of this transcription factor and are frequently associated with oncogenic expression of the *TLX1*, *TLX3*, or *HOXA* oncogenes (78, 80).

Monoallelic or biallelic deletions involving the *LEF1* locus and mutations in the *LEF1* gene are present in about 15% of T-ALL cases (93). Notably, these leukemias show a characteristic differentiation arrest at the early cortical thymocyte stage of differentiation that resembles that of TLX1-positive tumors (93).

ETV6 encodes an ETS family transcriptional repressor strictly required for the development of hematopoietic stem cells (94, 95) and plays a prominent role in precursor B cell ALLs harboring the t(8;21) translocation, which results in the expression of the *ETV6-RUNX1* oncogene (96). *ETV6* mutations encoding truncated proteins with dominant-negative activity are frequently found in early immature T-ALLs (32, 33).

BCL11B encodes a transcription factor critically required for normal T cell development (97). Loss-of-function mutations and heterozygous deletions of the *BCL11B* are recurrently found in T-ALL, suggesting that *BCL11B* haploinsufficiency may be an important pathogenetic event in T cell leukemogenesis (77, 98).

RUNX1 is an important transcription factor tumor suppressor gene involved in the pathogenesis of acute myeloid and precursor B cell leukemias (99). A recent systems biology study that aimed at deciphering the transcriptional regulatory network controlled by *TLX1* and *TLX3* in the pathogenesis T-ALL revealed a prominent role for *RUNX1* in the control of the oncogenic program downstream of the *TLX1* and *TLX3* HOX transcription factor oncogenes (100). Moreover, loss-of-function mutations in *RUNX1* can be found in immature T-ALL samples, suggesting a tumor suppressor role for *RUNX1* in T cell transformation (33, 100, 101).

GATA3 is an important regulator of T cell differentiation and has a crucial role in the development of early T cell progenitors (102). Recurrent somatic *GATA3* mutations have been exclusively identified in the early immature ETP-T-ALL subtype (33). These *GATA3* mutations cluster in the zinc finger DNA-binding protein domain, recurrently involve missense mutations targeting a specific R276 residue critically required for DNA binding (33), and may be responsible for the early block in T cell development of these leukemias.

Genetic alterations in the chromatin remodeling

The polycomb repressive complex 2 (PRC2) is the “writer” of a major repressive chromatin modification, histone H3 lysine 27 trimethylation (H3K27me3). Two recent studies reported loss-of-function mutations and deletions of *EZH2* and *SUZ12* genes, which encode two critical components of the PRC2 complex, in up to 25% of T-ALLs (33, 103). In addition, NOTCH1 activation was shown to specifically induce loss of the repressive H3K27me3 mark by antagonizing PRC2 complex activity during T cell transformation, suggesting a dynamic interplay between oncogenic NOTCH1 activation and loss of PRC2 function in the pathogenesis of T-ALL (103). Importantly, conditional ablation of *Ezh2* in early hematopoietic progenitors using a conditional knockout mouse model revealed a high frequency of spontaneous γδ T cell leukemias, further establishing the PRC2 complex as a bona fide tumor suppressor in the pathogenesis of T-ALL (104).

PHF6, a plant homeodomain–containing (PHD-containing) factor with a proposed role in epigenetic regulation of gene expression, is mutated and deleted about 16% of pediatric and 38% of adult T-ALL cases (81). Notably, *PHF6* is located in Xq26, and *PHF6* mutations are almost exclusively found in male patients with T-ALL (81). Proteins harboring similar PHD domains have been implicated in reading methylation marks present at specific histone tail residues, suggesting that loss of *PHF6* might influence genome-wide chromatin structure.

Genetic alterations in signal transduction pathways

In addition to the above mentioned genetic lesions in transcription factors and chromatin regulators, genes encoding critical components of signaling pathways controlling the growth, proliferation, lineage commitment, and survival of T cell progenitors are frequently mutated in T-ALL.

The *PTEN* tumor suppressor encodes a critical negative regulator of the PI3K-AKT signaling pathway. PTEN specifically dephosphorylates and inactivates PIP3, the lipid second messenger product of the PI3K complex responsible for recruitment and activation of the AKT1 kinase (105). Deletion mutations in *PTEN* occur in 5%–10% of T-ALL cases, and overall 17% of T-ALLs lack PTEN protein expression (106).

ABL1 rearrangements occur in about 8% of T-ALLs (107), and 6% of T-ALL cases show a complex rearrangement resulting in the episomal amplification and expression of the *NUP214-ABL1* fusion oncogene (108). Interestingly, the *NUP214-ABL1* rearrangement is almost exclusively found *TLX1* and *TLX3* T-ALLs (108), which suggests a specific functional interaction between oncogenic ABL1 signaling and TLX1 expression in the pathogenesis of T-ALL. Related *ABL1* rearrangements present in T-ALL include *EML1-ABL1* and *ETV6-ABL1* (109, 110). Notably, preclinical testing of small-molecule tyrosine kinase inhibitors (developed for the treatment of *BCR-ABL1*–positive leukemias) in NUP214-ABL1 tumors support the hypothesis that ABL1 inhibition may be used as a targeted therapy in these patients (111, 112).

Prototypical *RAS*-activating mutations that result in the accumulation of Ras in its active, GTP-bound conformation have been described in 5%–10% of T-ALLs, particularly in the early immature group (32, 33, 113). In addition, cryptic deletions and/or mutations in the neurofibromatosis type 1 (*NF1*) gene, which encodes a negative regulator of the Ras pathway, occur in 3% of T-ALL (114). Importantly, a conditional K-Ras^{G12D} murine knockin model, in which oncogenic K-Ras was expressed from its endogenous promoter, resulted in a highly penetrant, aggressive T cell leukemia/lymphoma, further confirming an important role for RAS signaling in T cell transformation (115).

The IL-7 receptor signals through the JAK/STAT pathway and is strictly required to support the growth, proliferation, and survival of early T cell progenitor cells (116). Aberrant JAK signaling was first linked with T-ALL in the context of the t(9;12)(p24;p13) translocation, a rare rearrangement encoding the constitutively active *ETV6-JAK2* kinase fusion oncoprotein (117). More recently, activating mutations in *JAK1* and *JAK3* have been reported in T-ALLs (33, 118, 119). Moreover, somatic gain-of-function mutations in the *IL7R* gene, encoding the IL-7 receptor and resulting in constitutive activation of JAK/STAT signaling, have recently been identified in approximately 10% of T-ALLs (120, 121).

The challenge ahead: predicting prognosis and developing molecularly targeted drugs

In conclusion, T-ALL is an aggressive hematologic cancer for which limited therapeutic options are available for patients with primary resistant or relapsed disease, underscoring the need for better treatment stratification protocols and for identifying more effective antileukemic drugs (2). This imperative is further supported by studies of the long-term effects of intensified chemotherapy in T-ALL survivors, which show that gains in leukemia-free survival have been achieved in parallel with significant increases in rates of acute and chronic life-threatening and debilitating toxicities (122).

The identification of activating *NOTCH1* mutations that are present in over 60% of T-ALL patients (6) created enormous interest in developing molecularly tailored therapies for T-ALL and prompted the initiation of clinical trials to test the effectiveness of blocking NOTCH1 signaling with GSIs. The combination of GSIs and glucocorticoids may have increased efficacy and decreased toxicity in the treatment of T-ALL (123). In addition, the presence of activated kinase oncoproteins in a subset of T-ALLs may offer an additional opportunity for molecularly tailored therapies. Given the efficacy of ABL1 kinase inhibitors for the treatment of BCR-ABL1–positive leukemias and the sensitivity of NUP214-ABL1 to these inhibitors (108, 111, 124), NUP214-ABL1–positive T-ALL patients may benefit from the inclusion of ABL1 inhibitors in their treatment schemes. Similarly, patients with activating *JAK1* (119), *JAK3* (33), or *IL7R* mutations (120, 121) might benefit from the JAK/STAT inhibitors currently under development for the treatment of myeloproliferative disorders.

Finally, understanding the pathogenesis of T-ALL is critical for the development of prognostic markers that may identify patients at increased risk of relapse. In light of this, recent studies have shown that early immature T-ALLs in children (31) and those with an absence of biallelic *TCRG* deletion (34) have a very poor prognosis. Intensive genetic characterization of these early immature leukemias has revealed great heterogeneity among these tumors (33). Nevertheless, these early immature leukemias share a gene expression signature closely related to hematopoietic stem cells and show overlapping myeloid and T-lymphoid immunophenotypic features and genetic alterations, suggesting that they may be more adequately treated with myeloid-based chemotherapy (32, 33).

Overall, the identification and molecular characterization of new oncogenes and tumor suppressors has uncovered much of the mechanisms involved in the pathogenesis of T-ALL. The development of representative and well-characterized xenograft and genetic animal models of T-ALL for preclinical testing, the identification of solid biomarkers of treatment response to standard therapies, and the development of a dynamic framework of clinical trials that facilitates testing new and emerging drugs and drug combinations in the clinic are essential to ensure the effective translation of this information to the clinic in the form of molecularly tailored therapies for the treatment of T-ALL.

Address correspondence to: Adolfo Ferrando, Institute for Cancer Genetics, Columbia University, Irving Cancer Research Center 4-402A, 1130 St. Nicholas Ave., New York, New York 10032, USA. Phone: 212.851.4611; Fax: 212.851.5256; E-mail: af2196@columbia.edu.

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