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# The Genetics and Mechanisms of T-Cell Acute Lymphoblastic Leukemia

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T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive hematologic malignancy derived from early T-cell progenitors. The recognition of clinical, genetic, transcriptional, and biological heterogeneity in this disease has already translated into new prognostic biomarkers, improved leukemia animal models, and emerging targeted therapies. This work reviews our current understanding of the molecular mechanisms of T-ALL.

T-cell acute lymphoblastic leukemia (T-ALL) is an immature lymphoid tumor characterized by the diffuse infiltration of the bone marrow by malignant hematopoietic cells expressing immature T-cell markers. T-ALL represents 10%–15% of pediatric and 20%–25% of adult ALL cases and is twice more prevalent in males than in females (Dores et al. 2012; Pui et al. 2012). T-ALL patients typically present with elevated white blood cell counts and hematopoietic failure with neutropenia, anemia, and thrombocytopenia and frequently present with mediastinal thymic masses and meningeal infiltration at diagnosis (Greaves et al. 1981; Crist et al. 1988; Garand et al. 1990; Pui et al. 1990; Shuster et al. 1990; Karrman et al. 2009a).

In the early days of combination chemotherapy, T-ALL patients were recognized as a high-risk leukemia group with cure rates of ~10% (Greaves et al. 1981; Thiel 1985). Subsequently, intensified chemotherapy protocols led to a gradual improvement in outcomes with current cure rates in multicenter trials approaching 90% in children (Pui and Evans 2006; Möricke et al. 2008; Pui et al. 2008; Vrooman and Silverman 2009; Hunger et al. 2012; Conter et al. 2014) and 60% in adults (Huguet et al. 2009; Marks et al. 2009; Stock et al. 2013). However, the prognosis remains dismal for patients who fail to obtain a complete hematologic remission or whose disease relapses after initial response (Uderzo et al. 2000; Einsiedel et al. 2005; Parker et al. 2010; Tallen et al. 2010; Hof et al. 2011; Sutton et al. 2015). Although no standard-of-care savage therapy is available in the refractory setting, some drugs have been recently approved for the treatment of relapsed T-ALL. In particular, single agent nelarabine, a deoxyguanosine analog, showed efficacy in several studies conducted in children and adults (Berg et al. 2005; DeAngelo et al. 2007; Gokbuget et al. 2011). In recent years, many research efforts have been per-

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formed to reduce the risk of relapse in T-ALL by improving induction and consolidation therapy. The inclusion of polyethylene glycol–conjugated (PEG) asparaginase and dexamethasone in frontline therapy has been reported to decrease the risk of relapse. Moreover, methotrexate intensification strategies have shown to increase event-free survival (EFS) and overall survival (OS) in T-ALL (Möricke et al. 2016; Winter et al. 2018). In addition, nelarabine is being actively explored in combination with chemotherapy as a frontline treatment in children and adult T-ALL. In the COG trial AALL0434, T-ALL patients receiving nelarabine in addition to the augmented Berlin–Frankfurt–Münster regimen showed a significant improvement in EFS (Dunsmore et al. 2018).

## GENETIC AND BIOLOGIC HETEROGENEITY IN T-ALL

T-ALL is a heterogeneous disease resulting from a multistep transformation process in which accumulating genetic alterations disrupt the normal control of cell growth, proliferation, survival, and differentiation during thymocyte development. A hallmark of T-ALL is the interrelationship between key regulators of early T-cell development and T-ALL oncogenic signals. This is best illustrated by the prominent role of NOTCH1, a key factor driving T-cell fate specification and thymocyte development (Radtke et al. 2013), which is activated by oncogenic gain-of-function mutations in >60% of T-ALL cases (Weng et al. 2004). Activating mutations in *NOTCH1* in T-ALL frequently co-occur with the loss of the *CDKN2A* locus (Hebert et al. 1994) and with chromosomal translocations, resulting in the aberrant expression of a diverse group of T-ALL-specific transcription factor oncogenes including (1) basic helix-loop-helix (bHLH) factors such as *TAL1* (Begley et al. 1989; Bernard et al. 1990; Chen et al. 1990), *TAL2* (Xia et al. 1991), *LYL1* (Mellentin et al. 1989), and *BHLHB1* (Wang et al. 2000); (2) LIM-only domain (LMO) genes such as *LMO1* and *LMO2* (McGuire et al. 1989; Boehm et al. 1991; Royer-Pokora et al. 1991); (3) homeobox genes such as *TLX1* (Dube et al. 1991; Hatano et al. 1991; Kennedy et al. 1991), *TLX3* (Bernard et al. 2001; Ferrando et al. 2002; Su et al. 2006), *NKX2.1* (Homminga et al. 2011), *NKX2.2* (Homminga et al. 2011), *NKX2.5* (Nagel et al. 2003), and *HOXA* (Soulier et al. 2005); and (4) *MYC* (Erikson et al. 1986; Finger et al. 1986; Mathieu-Mahul et al. 1986), *MYB* (Clappier et al. 2007), and *SPI1* (Seki et al. 2017). In addition, somatic mutations disrupt transcription factors tumor suppressor genes (e.g., *ETV6*, *RUNX1, GATA3, BCL11B*) and epigenetic regulators (e.g., *EZH2, SUZ12, PHF6*), leading to the activation of oncogenic signaling pathways (Van Vlierberghe et al. 2011a, 2013; Zhang et al. 2012; Neumann et al. 2013). Numerous studies that have explored the effect of these genetic alterations on T-cell development and transformation are reviewed below.

T-ALL is classified into groups characterized by unique gene expression signatures and immunophenotypic profiles that reflect an arrest at different stages of thymocyte development (Ferrando et al. 2002; Soulier et al. 2005; Seki et al. 2017). Early T-cell precursor (ETP) leukemias show a block at the earliest stages of T-cell differentiation (CD4 CD8 double-negative), aberrant expression of myeloid and stem cell markers, and a transcriptional program related to early T-cell precursor cells, hematopoietic stem cells, and myeloid progenitors (Ferrando et al. 2002; Coustan-Smith et al. 2009; Van Vlierberghe et al. 2011a). Early-immature ETP T-ALLs have a lower prevalence of *NOTCH1* mutations, rarely have *CDKN2A* deletions, and are associated with mutations in signaling factors (e.g., *NRAS*, *FLT3*), epigenetic regulators (e.g., *EZH2*, *IDH1*, *IDH2*, *DNMT3A*), and transcription factors governing hematopoietic and T-cell development (e.g., *RUNX1*, *GATA3*, *ETV6*) (Van Vlierberghe et al. 2011a, 2013; Zhang et al. 2012; Neumann et al. 2013). Although ETP T-ALL accounts for ∼10% of pediatric T-ALL cases (Coustan-Smith et al. 2009; Inukai et al. 2012; Allen et al. 2013), it comprises 40%–50% of adult T-ALLs (Van Vlierberghe et al. 2011a, 2013; Allen et al. 2013). Once described as a high-risk group with dismal outcomes and high rates of chemotherapy resistance (Gutierrez et al. 2010a; Van Vlierberghe

et al. 2013), ETP T-ALL can be effectively treated using early-response-based intensification (Patrick et al. 2014; Bond et al. 2017). T-ALLs with a characteristic $CD1a^+$, $CD4^+$, and $CD8^+$ immunophenotype, corresponding to the early stages of cortical thymocyte maturation, show a favorable prognosis (Niehues et al. 1999; Wuchter et al. 2002). These leukemias are associated with activation of the *TLX1, TLX3, NKX2.1*, and *NKX2.2* homeobox genes, have the highest prevalence of *NOTCH1* mutations, and almost universally harbor deletions of the *CDKN2A* locus (Ferrando et al. 2002; Homminga et al. 2011). T-ALLs with a more mature, late-cortical-thymocyte immunophenotype with expression of CD4, CD8, and CD3 show activation of the *TAL1* transcription factor oncogene (Ferrando et al. 2002). Immunophenotypic and biological differences between ETP-ALL and T-ALL may reflect a different cell of origin for these two subsets. The close relationship of ETP-ALL with hematopoietic stem cell transcriptional signatures, the increased incidence with age, and the common presence of mutations associated with clonal hematopoiesis and myeloid leukemia support that these leukemias may originate from early hematopietic progenitors and may have a preleukemic clonal hematopoiesis phase. In the case of T-ALL tumors, the presence of TCR rearrangements to the TCR loci supports that these alterations occur during thymocyte development and point to an intrathymic progenitor as the presumed cell of origin in this case.

Non-cell-autonomous mechanisms are also relevant for the development of T-ALL. In the bone marrow, T-ALL lymphoblasts establish contacts with vascular endothelial niche cells expressing CXCL12 and are dependent on cues from the microenvironment for cell proliferation and survival (Passaro et al. 2015; Pitt et al. 2015). The disruption of leukemia–stroma cell interactions using CXCR4 antagonists suppresses leukemia-initiating cell activity in vivo and induces disease remission in both mouse models of T-ALL and primary-patient-derived T-ALL xenografts (Passaro et al. 2015; Pitt et al. 2015). Moreover, CD44 is required for the engraftment of preleukemic T cells in the bone marrow, for the bone marrow niche interactions supporting leukemia-initiating cells, and for disease progression in human T-ALL xenografts (García-Peydró et al. 2018).

## ONCOGENIC NOTCH1 IN T-ALL

NOTCH1 is a class I transmembrane glycoprotein that functions as a ligand-activated transcription factor. Interaction of NOTCH with delta-like or jagged ligands expressed on the surface of a neighboring cell triggers the cleavage of NOTCH first by the ADAM10 metalloprotease and then by the γ-secretase complex, which releases the active, intracellular portion of NOTCH (ICN) from the membrane. ICN is then translocated to the nucleus where it associates with the RBPJ/CSL DNA-binding protein and activates gene expression via recruitment of mastermind-like coactivators (Bray 2016; Siebel and Lendahl 2017).

Activation of the NOTCH1 receptor in the thymus is required for early T-cell fate specification and thymocyte development (Radtke et al. 1999; Hozumi et al. 2008; Koch et al. 2008; Feyerabend et al. 2009; Germar et al. 2011; Weber et al. 2011). The pathogenic role of NOTCH1 in T-ALL was first identified in rare T-ALLs harboring the t(7;9)(q34;q34.3) chromosomal translocation, which leads to expression of a truncated and constitutively active form of NOTCH1 (Ellisen et al. 1991; Palomero et al. 2006a). An oncogenic role for NOTCH1 in T-ALL was shown by the rapid development of acute leukemia in mice transplanted with hematopoietic progenitors expressing a constitutively active intracellular form of NOTCH1 (Pear et al. 1996). Most commonly, NOTCH1 is activated as a result of somatic mutations that disrupt the negative regulatory region (NRR), an intramolecular lock protecting the extracellular portion of the receptor from cleavage by ADAM10 in the absence of ligand, or from truncation of the NOTCH1 carboxy-terminal PEST domain, which impairs the termination of NOTCH1 signaling through the proteasomal degradation of ICN (Weng et al. 2004; Sulis et al. 2008). In addition, 8%–24% of T-ALLs harbor mutations in the F-box and WD repeat domain containing

7 (*FBXW7*), which is required for the degradation of ICN (Moberg et al. 2001; Malyukova et al. 2007; O'Neil et al. 2007a; Thompson et al. 2007; Liu et al. 2017). Moreover, cyclin C likely functions in NOTCH1 degradation via phosphorylation of the NOTCH1 ICN domain and as a haploinsufficient T-ALL tumor suppressor in mouse and human leukemia (Li et al. 2014). Disruption of multiple regulatory domains of NOTCH1 provides increased signaling and transformative advantage because 20% of T-ALL patients harbor *NOTCH1* NRR mutations co-occurring with either *NOTCH1* PEST or *FBXW7* mutations (Weng et al. 2004; Mansour et al. 2006; Thompson et al. 2007). In addition, expression of the NOTCH1-ligand DLL4 in the microenvironment may provide paracrine signals for human and mouse T-ALL lymphoblasts (Minuzzo et al. 2015), and its aberrant expression in mouse T-cell precursor cells drives T-cell transformation (Xiong et al. 2013).

## Oncogenic Pathways and Effector Mechanisms Controlled by NOTCH1

NOTCH1 promotes leukemic cell growth via direct transcriptional up-regulation of genes that drive anabolic pathways, such as ribosome biosynthesis, protein translation, and nucleotide and amino acid metabolism (Palomero et al. 2006b). NOTCH1 binding in super-enhancers is critical for the dynamic regulation of NOTCH1 target genes (Wang et al. 2014). The *MYC* oncogene, a direct target of NOTCH1 (Palomero et al. 2006b; Herranz et al. 2014; Yashiro-Ohtani et al. 2014), also promotes cell growth and anabolism in leukemia cells (Palomero et al. 2006b; Sharma et al. 2006; Margolin et al. 2009) and shares multiple target genes with NOTCH1 (Palomero et al. 2006b; Margolin et al. 2009). HES1, a transcriptional repressor downstream from NOTCH1 (Jarriault et al. 1995), promotes T-cell development and NOTCH1-induced leukemogenesis (Tomita et al. 1999; Wendorff et al. 2010), favoring activation of PI3K and NF-κB pathways (Palomero et al. 2008; Espinosa et al. 2010; Wong et al. 2012) via negative regulation of glucocorticoid receptor expression (Real et al. 2009) and by suppression of *BBC3* (PUMA)-mediated apoptosis (Schnell et al. 2015). In addition, NOTCH1 promotes a protective stress response in T-ALL via transcriptional up-regulation of heat shock transcription factor 1 (*HSF1*) and downstream heat shock proteins (Kourtis et al. 2018) and regulates the expression of *LUNAR1*, a potentially oncogenic T-ALL long noncoding RNA (Trimarchi et al. 2014).

The PI3K-AKT-mTOR signaling pathway is a critical mediator of cytokine-driven cell growth, proliferation, and survival (Vivanco and Sawyers 2002). NOTCH1 induces PI3K-AKT during thymocyte development to regulate cell size, glucose uptake, and glycolysis (Ciofani and Zuniga-Pflucker 2005). Moreover, PTEN, a strong negative regulator of the PI3K-AKT pathway, is transcriptionally down-regulated by HES1 in T-cell progenitors and T-ALL lymphoblasts (Palomero et al. 2007; Wong et al. 2012). NOTCH1 also induces the expression of pre-TCRα (*PTCRA*) (Reizis and Leder 2002) and other cytokine and growth factor receptors upstream of the PI3K-AKT pathway such as the interleukin 7 receptor α chain (*IL7R*) (González-García et al. 2009) and *IGF1R* (Medyouf et al. 2011). Moreover, NOTCH1 can regulate NF-κB activity in T-ALL (Shin et al. 2006; Thompson et al. 2007) and NF-κB activity is strictly required for the generation and maintenance of NOTCH1-induced tumors (Espinosa et al. 2010; D'Altri et al. 2011).

Oncogenic NOTCH1 signaling can directly promote proliferation in T-ALL inducing $G_1$/S cell cycle progression (Dohda et al. 2007; Joshi et al. 2009; Rao et al. 2009) via expression of the cell cycle genes *CCND3*, *CDK4*, and *CDK6* (Joshi et al. 2009) and down-regulation of the cyclin-dependent kinase inhibitors *CDKN2D* and *CDKN1B* (Rao et al. 2009). Moreover, NOTCH1 induces transcription of the S-phase kinase-associated protein 2 (*SKP2*), a negative regulator of the CDKN1A and CDKN1B cell cycle inhibitor proteins (Dohda et al. 2007).

## NOTCH as a Therapeutic Target in T-ALL

The prominent role of NOTCH signaling in T-cell transformation has created major interest

in the development of anti-NOTCH1 therapies for T-ALL (Weng et al. 2004). Most notably, γ-secretase inhibitors (GSIs), which block the proteolytic cleavage of NOTCH receptors by the γ-secretase complex precluding the release of intracellular NOTCH1 from the membrane, have been proposed as a potential targeted therapy in T-ALL (Milano et al. 2004; Weng et al. 2004; van Es et al. 2005; Lewis et al. 2007; Paganin and Ferrando 2011). Early on, in vitro studies showed that T-ALL cell lines treated with GSIs show a rapid clearance of intracellular activated NOTCH1 and transcriptional downregulation of NOTCH1 target genes with $G_1$ cell cycle arrest and a decreased cell size in T-ALL cell lines (Weng et al. 2004; Palomero et al. 2006a,b). In addition, GSI-mediated inhibition of NOTCH1 signaling abolishes the engraftment of primary T-ALL cells in mice and induces significant antitumor responses in NOTCH1-induced mouse T-ALLs (Armstrong et al. 2009; Tatarek et al. 2011) and in primary-patient-derived T-ALL xenografts (Herranz et al. 2015). Moreover, pharmacodynamic studies have documented that GSIs induce NOTCH inhibition in the clinical setting (DeAngelo et al. 2006). However, the clinical development of GSIs as anti-NOTCH1 therapy has been hampered by a paucity of therapeutic responses in early clinical trials and dose-limiting toxicities (DeAngelo et al. 2006; Wei et al. 2010; Takebe et al. 2014). The lack of therapeutic efficacy may reflect in some cases the presence of subclonal NOTCH1 mutations. However, it is also possible that even in the presence of a clonal NOTCH1 mutation T-ALL cells show weak oncogene addiction to NOTCH signaling, primary resistance, or rapid tumor adaptation via activation of parallel signaling pathways or adaptive epigenetic responses. In this regard, mutational loss of *PTEN* is associated with GSI resistance in human T-ALL cell lines (Palomero et al. 2007) and *Pten* deletion abrogates the antileukemic response to GSI therapy in mouse models of NOTCH1-induced T-ALL (Herranz et al. 2015). Mechanistically, NOTCH1 inhibition induces suppression of cellular metabolism in *Pten*-positive cells, whereas *Pten* loss and consequent activation of the PI3K-AKT pathway activates glycolysis, uncoupling NOTCH1 signaling and leukemia cell growth (Herranz et al. 2015). Similarly, aberrant expression of *MYC* can overcome the growth suppressing effects of NOTCH inhibition in some tumors (Weng et al. 2006) and mutations in *FBXW7* are highly prevalent in GSI-resistant cell lines (O'Neil et al. 2007a; Thompson et al. 2007). In addition, T-ALL cell lines seem to contain small populations of GSI-tolerant "persister" cells with distinct transcriptional programs and chromatin compaction, supporting an epigenetic mechanism of adaptation to NOTCH1 inhibition (Knoechel et al. 2014).

A second hurdle in the clinical development of GSIs is the development of dose-limiting on-target gastrointestinal toxicity as observed in a phase I clinical trials (DeAngelo et al. 2006; Papayannidis et al. 2015). GSI-induced gastrointestinal toxicity is characterized by secretory goblet cell metaplasia which results in malabsorption syndrome and diarrhea (Milano et al. 2004; van Es et al. 2005; Real et al. 2009; Wei et al. 2010). This phenotype results directly from the inhibition of NOTCH signaling in the intestinal epithelium as shown by genetic inactivation of *Rbpj* (van Es et al. 2005) or dual suppression of *Notch1* and *Notch2* in the gut (Riccio et al. 2008). Four different γ-secretase complexes contain one nicastrin and one presenilin enhancer-2 subunits that combine with a different APH-1 protein (either APH-1A or APH-1B) and a presenilin protein (PSEN, either PSEN1 or PSEN2). It has recently been shown that T-ALL specifically express PSEN1-containing-γ-secretase-complexes. Genetic deletion or pharmacological inhibition of PSEN1 impairs leukemia development and prolongs survival avoiding gut toxicities in vivo (Habets et al. 2019). Alternatively, the use of combination treatments with synergistic antileukemic effects offer the opportunity to obtain strong antitumor responses with lower toxicity. In this regard, metabolomic profiling of T-ALL cells in the context of NOTCH1 inhibition and *Pten* loss has defined a critical role for glutaminolysis in NOTCH1-induced leukemia cell growth, and small-molecule glutaminase inhibitors show strongly synergistic antitumor effects in combi-

nation with GSIs (Herranz et al. 2015). Moreover, genetic suppression of autophagy increases the antitumor effects of NOTCH inhibition in mouse models of NOTCH1-induced T-ALL (Herranz et al. 2015). In addition, GSIs show increased antitumor activity in combination with cyclin-dependent kinase inhibitors (Rao et al. 2009), histone deacetylase inhibitors (Sanda et al. 2010), proteasome inhibitors (Sanda et al. 2010), drugs targeting NF-κB signaling (Thompson et al. 2007), inhibitors of the PI3K-AKT-mTOR pathway (Chan et al. 2007; Palomero et al. 2007; Cullion et al. 2009; Sanda et al. 2010), and in the context of protein phosphatase 2A (PP2A) inhibition with perphenazine (Gutierrez et al. 2014). However, the most direct venue toward the development of a highly active and well-tolerated anti-NOTCH1 therapy in the clinic is the combination of GSIs with glucocorticoids (Real et al. 2009; Samon et al. 2012). Glucocorticoids induce apoptosis in lymphoid progenitor cells and are an essential component of ALL therapy (Inaba and Pui 2010). Early studies suggested an interaction between NOTCH1 signaling and glucocorticoid-induced apoptosis by showing that NOTCH1 activation can impair glucocorticoid-induced cell death in thymocytes (Deftos et al. 1998). Conversely, blocking NOTCH1 signaling with GSIs can reverse glucocorticoid resistance in T-ALLs (Real et al. 2009; Samon et al. 2012). The interaction between GSIs and glucocorticoids is mediated by release of the inhibitory effect of the NOTCH1-HES1 transcriptional axis on glucocorticoid receptor auto up-regulation, a critical amplification loop required for effective glucocorticoid-induced apoptosis (Real et al. 2009). Most notably, the combination of a GSI plus glucocorticoids is not only highly synergistic and active against glucocorticoid resistant leukemia models in vivo, but it also results in abrogation of GSI-induced gut toxicity (Real et al. 2009; Samon et al. 2012).

In addition to GSIs, inhibitors of sarco/endoplasmic reticulum calcium ATPase (SERCA) channels, 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 (Moellering et al. 2009; Wu et al. 2010; Roti et al. 2013; Sharma et al. 2015). SERCA inhibitors abrogate NOTCH signaling by interfering with the maturation and activity of leukemia-associated mutant forms of NOTCH1 and show on-target antileukemic effects in human T-ALL cell lines (Roti et al. 2013). SAHM1, a synthetic, cell-permeable, stabilized α-helical peptide binds to the NOTCH–RBPJ transactivation complex and prevents the recruitment of the MAML1 coactivator, thus blocking NOTCH-mediated transcription (Moellering et al. 2009). Therapeutically, SAHM1 induced strong antileukemic effects in human T-ALL cell lines and NOTCH-induced mouse leukemias without apparent gastrointestinal toxicity (Moellering et al. 2009). Finally, antibodies against the negative regulatory region of NOTCH1 (NRR1) have been shown to specifically block NOTCH1 signaling and inhibit growth in T-ALL cell lines and xenograft models with only minor changes in the intestine, suggesting that antibody-based selective inhibition of NOTCH1 could be effective and devoid of intestinal toxicity (Aste-Amezaga et al. 2010; Wu et al. 2010; Agnusdei et al. 2014; Gordon and Aster 2014; Sharma et al. 2015).

## GENETIC DISRUPTION OF CELL CYCLE CONTROL

The loss of cell cycle control is a hallmark of cancer (Hanahan and Weinberg 2011). Deletions of the *CDKN2A* locus are observed in >70% of T-ALLs (Hebert et al. 1994; Ferrando et al. 2002) and cause the loss of the tumor suppressors *P16/INK4,* which inhibits $G_1$-S cell cycle progression, and of *P14/ARF,* which mediates cell cycle arrest and apoptosis in response to cellular stress (Kamijo et al. 1998; Zhang et al. 1998). Deletions in the cell cycle regulator *RB1*, which encodes a master regulator of cell cycle progression (Mullighan et al. 2007; Van Vlierberghe et al. 2013), and *CDKN1B*, which encodes $p27^{Kip1}$, an inhibitor of cyclin E-CDK2 and cyclin D-CDK4 complexes (Remke et al. 2009), can be found in ∼15% of T-ALL cases (Liu et al. 2017). Moreover, 6% of T-ALLs harbor activating mutations in *CCND3*, which

regulates the $G_1$/S transition (Liu et al. 2017). Finally, the t(12;14)(p13;q11) and t(7;12)(q34;p13) translocations are present in ∼3% of T-ALLs and promote cell cycle progression by driving aberrantly high levels of *CCND2* expression (Clappier et al. 2006).

## T-ALL TRANSCRIPTION FACTOR ONCOGENES

Oncogenic class II bHLH transcription factors, such as *TAL1*, *TAL2*, *LYL1*, and the LIM-only domain factors *LMO1* and *LMO2*, are aberrantly expressed in ∼60% of T-ALLs (Ferrando et al. 2002). *TAL1* up-regulation characterizes 30%–40% of T-ALLs and can be driven by both interchromosomal and intrachromosomal rearrangements that place it under the control of T-cell-specific regulatory sequences in the *TCRA/D* locus (Begley et al. 1989; Bernard et al. 1990; Chen et al. 1990) or the SCL/TAL1 interrupting locus (*STIL*), a TAL1 neighbor gene (Aplan et al. 1990). In addition, precise heterozygous somatic mutations create de novo binding motifs for the MYB transcription factor and result in an active 5′ enhancer driving monoallelic up-regulation of *TAL1* (Mansour et al. 2014; Navarro et al. 2015). More rarely, the *TAL1*-related genes *LYL1*, *TAL2*, and *BHLHB1* are aberrantly expressed when chromosomal translocations reposition them close to TCR-loci enhancers (Mellentin et al. 1989; Xia et al. 1991; Wang et al. 2000; Homminga et al. 2012). Notably, forced expression of *TAL1* in T-cell precursors induces T-ALL in mouse models (Condorelli et al. 1996; Kelliher et al. 1996).

TAL1 transcriptional targets with T-ALL oncogenic potential include *TRIB2* (Tan et al. 2016), *NKX3.1* (Kusy et al. 2010), microRNA 223 (*MIR223*) (Mansour et al. 2013), and GTPase of immunity-associated protein (*GIMAP*) (Liau et al. 2017). Moreover, TAL1 and its binding partners GATA3 and RUNX1 form a positive autoregulatory loop involving activation of MYB that drives the initiation and maintenance of a leukemogenic transcriptional program (Sanda et al. 2012). Furthermore, the TAL1 target gene *ARID5B* encodes an epigenetic regulator that directly up-regulates *MYC*, promotes the TAL1-mediated oncogenic transcriptional program, and induces T-cell tumor formation in zebrafish (Leong et al. 2017).

The LIM-only domain factors *LMO1* and *LMO2* are overexpressed in 10% of T-ALL cases as a result of the t(11;14)(p15;q11) and t(11;14)(p13;q11) chromosomal translocations, respectively (McGuire et al. 1989; Boehm et al. 1991; Royer-Pokora et al. 1991). *LMO1* up-regulation is also driven by a promoter mutation upstream of *LMO1* that creates a new MYB binding site in 2% of T-ALLs (Li et al. 2017). *LMO2* up-regulation is found in 3%–5% of T-ALLs as a result of noncoding mutations in the *LMO2* promoter, which create putative binding sites for MYB, ETS1, or RUNX1 (Rahman et al. 2017) and in up to 5% of T-ALLs because of small chromosomal deletions in the vicinity of the *LMO2* locus (Van Vlierberghe et al. 2006; Van Vlierberghe et al. 2008a). LMO proteins do not interact directly with DNA but form transcriptional complexes with TAL1 and other bHLH factors (Larson et al. 1996), and the oncogenic activity of *Lmo1* or *Lmo2* expression in transgenic mice (Fisch et al. 1992; McGuire et al. 1992) is markedly enhanced by *Tal1* (Larson et al. 1996; Aplan et al. 1997; Tremblay et al. 2010).

Mechanistically, aberrant expression of the *LMO* genes confers properties of self-renewal to T cells. This has been observed in mouse T-cell precursors overexpressing *Lmo2*, and thymocytes from *Tal1-Lmo1* double-transgenic mice, which show up-regulation of a stem cell–like transcriptional program linked with increased self-renewal (McCormack et al. 2013; Gerby et al. 2014). Immature ETP T-ALLs, which characteristically express high levels of *LMO2* and *LYL1*, also show this stem cell–like signature (Ferrando et al. 2002; McCormack et al. 2010). Moreover, genetic suppression of *Lyl1* in *Lmo2*-expressing transgenic mice suppressed LMO2-induced stem cell–like gene expression programs, inhibited self-renewal, and precluded the development of ETP-like T-ALL (McCormack et al. 2013). Aberrant expression of LMO2 by retroviral insertion underlies the accidental development of T-ALL in X-linked severe-combined immunodeficiency patients

undergoing retrovirus-based gene therapy to restore IL-2 receptor γ chain deficiency (Hacein-Bey-Abina et al. 2003, 2008; Howe et al. 2008).

## Homeobox Transcription Factor Oncogenes

Homeobox genes encode for a group of strongly conserved transcription factors involved in cell lineage specification, body patterning, and embryonic organogenesis. Deregulated expression of the *HOXA9* and *HOXA10* genes can be found in ∼3% of T-ALLs harboring chromosomal translocations and inversions that relocate the *HOXA* paralog gene cluster closer to the *TCRB* and *TCRG* loci (Soulier et al. 2005; Speleman et al. 2005). Moreover, aberrant expression of *HOXA* genes is common in early-immature ETP T-ALLs (Ferrando et al. 2002, 2003; Asnafi et al. 2003; Soulier et al. 2005; Van Vlierberghe et al. 2008b) and is characteristic of T-ALLs harboring *KMT2-MLLT1* (*MLL-ENL*) (Tkachuk et al. 1992; Chervinsky et al. 1995; Rubnitz et al. 1996), *PICALM-MLLT10* (Dreyling et al. 1996; Carlson et al. 2000; Asnafi et al. 2003; Soulier et al. 2005), and *SET-NUP214* (Van Vlierberghe et al. 2008b) fusion oncogenes. In mouse models, HOXA9 expression and activating *Jak3* mutations induce accelerated development of leukemia and are linked to enhanced STAT5 transcriptional activity (de Bock et al. 2018).

Chromosomal rearrangements that drive aberrant T-cell expression of the NK-L subclass of HOX transcription factor genes, including *TLX1, TLX2, NKX2-1, NKX2-2*, and *NKX2-5*, are commonly associated with T-ALL. The t(10;14)(q24;q11) rearrangement (Dube et al. 1991; Hatano et al. 1991; Kennedy et al. 1991; Lu et al. 1991; Dear et al. 1993) places *TLX1* under the control of *TCRA/D* gene enhancers and results in *TLX1* overexpression in 5%–10% of pediatric and 30% of adult T-ALLs (Ferrando et al. 2002, 2004). The t(5;14)(q35;q32) translocation places *TLX3* under the control of T-cell regulatory elements near the *BCL11B* locus (Bernard et al. 2001) and is present in 20%–25% of pediatric and 5% of adult T-ALLs (Bernard et al. 2001; Ballerini et al. 2002; Ferrando et al. 2002, 2004; Asnafi et al. 2005). *NKX2-1*- and *NKX2-2*-rearranged leukemias are found in ∼5% of pediatric T-ALLs (Homminga et al. 2011), and chromosomal translocations involving *NKX2-5* have been reported in sporadic T-ALLs (Nagel et al. 2003; Przybylski et al. 2006). TLX1-expressing human T-ALLs are distinguished by arrest at the cortical stage of thymocyte development, which may result from disruption of VDJ recombination by TLX1 binding to *TCRA* enhancer sequences (Dadi et al. 2012). Expression of TLX1 in the mouse thymus leads to T-ALL with *Bcl11b* and *Notch1* mutations (De Keersmaecker et al. 2010; Rakowski et al. 2011). Notably, human and mouse TLX1-expressing T-cell tumors share a transcriptional program and have a defective mitotic checkpoint, and TLX1 can promote aneuploidy during T-cell transformation (Chen et al. 2010; De Keersmaecker et al. 2010).

T-ALLs harboring NK-L homeobox gene rearrangements show unique similarities. Both TLX1 and TLX3 normally down-regulate a large number of overlapping T-ALL tumor suppressor genes including *BCL11B*, *PHF6*, *RUNX1*, and *WT1* (Della Gatta et al. 2012). In addition, *TLX1*- and *TLX3*-rearranged T-ALLs frequently harbor loss-of-function mutations in the *BCL11B*, *WT1*, and *PHF6* tumor suppressor genes and the presence of the *NUP214-ABL1* fusion oncogene (Graux et al. 2004; Tosello et al. 2009; De Keersmaecker et al. 2010; Van Vlierberghe et al. 2010). Similarly, *NKX2-1*- and *NKX2-2*-rearranged leukemias show a TLX-1-like gene expression signature and developmental arrest (Homminga et al. 2011).

## *MYC*

The *MYC* oncogene encodes a basic helix-loop-helix leucine zipper transcription factor that functions as a key master regulator of cell growth and proliferation and is broadly involved in the pathogenesis of human cancer (Dang 2012; Stine et al. 2015). MYC is important for thymocyte development (Dose et al. 2006) and the control of cell growth downstream from NOTCH1 and pre-TCR signaling (Dose et al. 2006). The rare (<1%) T-ALL chromosomal translocation t(8;14)(q24;q11) places the *MYC* locus under the control of *TCRA/D* enhancer

elements (Erikson et al. 1986; Finger et al. 1986; Mathieu-Mahul et al. 1986) and leads to its overexpression in developing T cells. MYC oncogenic activity in T-ALL has been shown in mouse and zebrafish leukemia models in which it drives cell growth and proliferation and confers leukemia-initiating activity (Langenau et al. 2003; King et al. 2013). In addition, NOTCH1 signaling up-regulates *MYC* expression (Palomero et al. 2006b; Sharma et al. 2006), and MYC is a mediator of NOTCH1-induced transformation (Palomero et al. 2006b; Sharma et al. 2006). Mechanistically, NOTCH1 controls *MYC* via N-Me, a T-cell-specific long-range distal *MYC* enhancer (Herranz et al. 2014; Yashiro-Ohtani et al. 2014) essential for T-cell leukemogenesis and targeted by focal chromosomal duplications in ~5% of T-ALL cases (Herranz et al. 2014). Of note, and similar to NOTCH1, the MYC protein is targeted for proteasomal degradation by FBXW7 (Welcker et al. 2004; Yada et al. 2004), and T-ALL-associated *FBXW7* mutations increase both NOTCH1 and MYC protein levels (O'Neil et al. 2007a; Thompson et al. 2007). Ultimately, NOTCH1 and MYC collaborate to activate a common transcriptional program controlling leukemia cell growth and metabolism (Palomero et al. 2006b; Margolin et al. 2009).

### *MYB*

The *MYB* oncogene encodes a leucine zipper transcription factor activated in rare cases of T-ALL harboring the t(6;7)(q23;q32) chromosomal translocation via its translocation to the vicinity of the *TCRB* locus (Clappier et al. 2007). *MYB*-translocated cases are frequently found in children under the age of 2 and show a marked increase in the expression of proliferation and mitosis genes (Clappier et al. 2007). In addition, focal duplications of the *MYB* locus driving increased MYB expression are found in ~10% of T-ALLs in both children and adults (Lahortiga et al. 2007; O'Neil et al. 2007b), and mutations leading to increased MYB activity occur in ~19% of T-ALL cases (Liu et al. 2017). *MYB* can be also up-regulated via direct transcriptional activation by TAL1 (Sanda et al. 2012) and via posttranslational up-regulation by the TAL1/miR-223/FBXW7 regulatory axis (Mansour et al. 2013) or as a result of down-regulation of MYB-targeting microRNAs (Sanghvi et al. 2014; Mets et al. 2015).

### *SPI1*

The *SPI1* gene encodes an ETS-family transcription factor and master regulator of hematopoietic development also known as PU.1 (Burda et al. 2010). Recurrent chromosomal rearrangements involving *SPI1* are present in 4% of pediatric T-ALLs with a double-negative or CD8-single-positive immunophenotype (Seki et al. 2017). These rearrangements juxtapose *SPI1* to the *TCF7* (*TCF7-SPI1*) and the *STMN1* (*STMN1-SPI1*) loci causing increased expression of PU.1 (Seki et al. 2017). T-ALLs with SPI1 rearrangements have a distinct gene expression signature and poor prognosis (Seki et al. 2017).

## TRANSCRIPTION FACTOR TUMOR SUPPRESSOR GENES

Mutations and deletions involving transcription factors tumor suppressors are frequently found in T-ALL. Mutations in *ETV6, RUNX1*, and *GATA3* are associated with early immature ETP T-ALLs (Van Vlierberghe et al. 2011a; Zhang et al. 2012), and mutations in *BCL11B, LEF1*, and *WT1* are predominantly found in early cortical T-ALLs, frequently in association with *TLX1* and *TLX3* translocations (De Keersmaecker et al. 2010; Gutierrez et al. 2010b; Della Gatta et al. 2012).

### *ETV6*

The *ETV6* gene encodes an ETS family transcriptional repressor strictly required for the development of hematopoietic stem cells (Wang et al. 1998; Hock et al. 2004). Dominant-negative forms of ETV6 arising from amino- or carboxy-terminal truncating mutations are found in 13% of T-ALLs (Van Vlierberghe et al. 2011a).

### *RUNX1*

The *RUNX1* tumor suppressor gene encodes a master regulator transcription factor with prominent roles in hematopoietic development (Okuda et al. 1996; Cai et al. 2000). Somatic mutations in *RUNX1* are found in ∼5% of T-ALLs, typically in the immature ETP group (Della Gatta et al. 2012; Zhang et al. 2012; Grossmann et al. 2013; Van Vlierberghe et al. 2013). Germline heterozygous mutations in *RUNX1* are found in families affected with FPDMM (platelet disorder, familial, with associated myeloid malignancy; OMIM ID #601399), a leukemia predisposition syndrome characterized by a moderate decrease in platelet numbers and an increased risk of acute myeloid leukemia (Song et al. 1999) and T-ALL (Owen et al. 2008; Preudhomme et al. 2009; Nishimoto et al. 2010).

### *GATA3*

The *GATA3* gene, which encodes an important transcriptional regulator of T-cell development and differentiation (Ting et al. 1996; Ho et al. 2009; Scripture-Adams et al. 2014) shows recurrent mutations in ETP ALL frequently involving R276, which disrupt the zinc finger DNA-binding domain (Zhang et al. 2012).

### *BCL11B*

*BCL11B* encodes a zinc finger transcription factor that is mutated and deleted in mouse thymic lymphomas induced by γ-radiation (Wakabayashi et al. 2003a) and in T-ALL tumors arising in *Atm*-deficient (Ehrlich et al. 2014) and *TLX1* transgenic mice (De Keersmaecker et al. 2010). In human T-ALL, *BCL11B* mutations are present in ∼10% of cases (De Keersmaecker et al. 2010; Gutierrez et al. 2011), frequently in combination with *TLX1* and *TLX3* translocations (Liu et al. 2017). *Bcl11b* inactivation in mouse T-cell progenitors results in early arrest at the DN2-DN3 stage of differentiation (Wakabayashi et al. 2003b; Ikawa et al. 2010; Li et al. 2010a) and promotes aberrant self-renewal activity (Ikawa et al. 2010) and features of natural killer T cells (Li et al. 2010a,b).

### *LEF1*

LEF1 is a member of the lymphoid enhancer factor/T-cell factor (LEF/TCF) family of transcription factors that are critical mediators of WNT signaling (Brantjes et al. 2001). In the absence of WNT activation, LEF/TCFs block the expression of WNT target genes (Brantjes et al. 2001). However, on WNT activation, LEF/TCFs associate with active nuclear β-catenin to induce the expression of WNT target genes (van Noort and Clevers 2002). Mutations and monoallelic or biallelic deletions in the *LEF1* gene are present in ∼15% of T-ALL cases (Gutierrez et al. 2010b). Notably, T-ALLs with *LEF1* inactivation show high levels of *MYC* expression and a characteristic differentiation arrest at the early cortical thymocyte stage of differentiation (Gutierrez et al. 2010b).

### *WT1*

Deletions and mutations in the Wilms Tumor 1 (*WT1*) tumor suppressor gene are present in ∼10% of T-ALLs and also in acute myeloid leukemias (Tosello et al. 2009; Heesch et al. 2010; Renneville et al. 2010; Neumann et al. 2015). T-ALL-associated *WT1* mutations are predominantly heterozygous frameshift mutations resulting in truncation of its carboxy-terminal zinc finger domains and are frequently associated with oncogenic expression of the *TLX1*, *TLX3*, or *HOXA* oncogenes (Tosello et al. 2009; Renneville et al. 2010). In T-ALL, *WT1* mutations are enriched in relapsed series and have been associated with inferior relapse-free survival (Bordin et al. 2018). Moreover, *WT1* loss confers resistance to DNA damaging agents via attenuation of TP53-induced apoptotic factors and up-regulation of the anti-apoptotic factor *XIAP* (Bordin et al. 2018).

## GENETIC ALTERATIONS IN EPIGENETIC REGULATORS

Epigenetic regulators and chromatin modifiers are recurrently mutated in T-ALL. These include *PHF6* (Van Vlierberghe et al. 2010), the PRC2 complex genes *EZH2*, *EED,* and *SUZ12*

(Ntziachristos et al. 2012; Zhang et al. 2012), and the *KDM6A* histone demethylase (Ntziachristos et al. 2014; Van der Meulen et al. 2015). In addition, mutations in *IDH1*, *IDH2*, and *DNMT3A* can be specifically found in the context of ETP T-ALL (Van Vlierberghe et al. 2011a; Zhang et al. 2012).

### *PHF6*

The plant homeodomain (PHD)-like finger 6 (*PHF6*) gene is inactivated by mutations and deletions in ~20% of T-ALL cases (Van Vlierberghe et al. 2010; Van Vlierberghe et al. 2011b), 20%–25% of mixed phenotype acute leukemia with ETP and T/myeloid characteristics (Alexander et al. 2018), and ~3% of acute myeloid leukemias (Van Vlierberghe et al. 2011b; Patel et al. 2012; Welch et al. 2012). Germline *PHF6* mutations are pathogenic in Börjeson–Forssman–Lehmann syndrome (BFLS; OMIM 301900), a rare X-linked disorder associated with intellectual disability, distinctive facial features, truncal obesity, and gynecomastia (Lower et al. 2002; Gecz et al. 2006). Interestingly, somatic mutations in the *PHF6* gene, located on Xq26, are mostly found in male T-ALL patients (Van Vlierberghe et al. 2011b). Moreover, PHF6 may function as a initiating tumor suppressor as suggested by a case of T-ALL arising in a male BFLS patient (Chao et al. 2010) and by the identification of *PHF6* mutations in clonal hemopoiesis (Yoshizato et al. 2015; Abelson et al. 2018). Consistently, in a mouse model of NOTCH1-induced T-ALL, loss of *Phf6* enhances tumor initiation, leukemia-initiating cell activity, represents an early event during T-ALL transformation and leads to increased self-renewal in mouse hematopoietic stem cells (Wendorff et al. 2018). *Phf6*-null hematopoietic stem cells are more quiescent, less prone to stress-induced activation, and confer increased hematopoietic recovery after chemotherapy (Wendorff et al. 2018). Mechanistically, PHF6 is a nucleolar protein and may function in chromatin remodeling and transcriptional regulation via interaction with the NurD nucleosome repositioning and histone deacetylation complex (Todd and Picketts 2012; Liu et al. 2015); however, it is also involved in ribosome biogenesis (Wang et al. 2013; Zhang et al. 2013) via interaction with the PAF1 transcription elongation complex (Zhang et al. 2013) and with UBF, implicated in the control of RNA polymerase I activity and ribosomal DNA (rDNA) transcription.

### *EZH2, EED,* and *SUZ12*

The *EZH2, EED*, and *SUZ12* genes encode members of the Polycomb repressive complex 2 (PRC2), a major epigenetic regulator that mediates transcriptional repression via deposition of the H3K27me3 epigenetic mark (Cao et al. 2002; Czermin et al. 2002). Loss-of-function mutations in these genes are observed in up to 25% of T-ALLs and comprise up to 42% of ETP T-ALLs (Ntziachristos et al. 2012; Zhang et al. 2012). Conditional knockout of *Ezh2* in early hematopoietic progenitors induces γδ T-cell leukemia in mice (Simon et al. 2012), and concomitant deletion of *Runx1* and *Ezh2* induces mouse ETP T-ALL tumors in cooperation with oncogenic FLT3 (Booth et al. 2018). *PRC2* mutations have been proposed to promote T-cell transformation through increased expression and activation of FLT3 (Zhang et al. 2018) and enhanced NOTCH1 transcriptional activity (Ntziachristos et al. 2012) and may be associated with inferior response to chemotherapy (Aries et al. 2018).

### *KDM6A*

The *KDM6A* gene (also known as *UTX*) encodes a H3K27me3 histone demethylase (Agger et al. 2007; Lan et al. 2007) that is mutated in 5%–15% of T-ALLs and functions as a tumor suppressor gene (Ntziachristos et al. 2014; Van der Meulen et al. 2015). T-ALL-associated *KMD6A* mutations are typically located in the catalytic domain, which seems to be critical for leukemia initiation and maintenance (Van der Meulen et al. 2015).

## ONCOGENIC ACTIVATION OF SIGNALING PATHWAYS

In addition to genetic lesions affecting transcription factors and chromatin regulators,

genes encoding critical components of signaling pathways are frequently mutated in T-ALL.

### *PI3K-AKT*

Thymocytes are dependent on the activity of PI3Kγ and PI3Kδ for cell growth, proliferation, and survival (Webb et al. 2005; Swat et al. 2006; Ji et al. 2007), and signaling mutations in T-ALL target and activate the PI3K-AKT-mTOR signaling pathway in ∼30% of cases (Liu et al. 2017). The most frequent alteration in this pathway affects the *PTEN* tumor suppressor gene through loss-of-function mutations and deletions in 10%–15% of T-ALLs (Palomero et al. 2007; Mendes et al. 2014), which could be associated with a poor prognosis (Paganin et al. 2018).

Loss of *PTEN* results in constitutive activation of the AKT-mTOR signaling axis, which directs multiple effectors to promote cell cycle progression, survival, glycolysis and protein biosynthesis (Stambolic et al. 1998; Cully et al. 2006). *Pten* heterozygous knockout mice develop lymphoid hyperplasia, T-ALL, and multiple solid tumors with loss of heterozygosity for the wild-type allele (Di Cristofano et al. 1998; Suzuki et al. 1998; Di Cristofano et al. 1999). Selective inactivation of *Pten* in hematopoietic progenitors (Yilmaz et al. 2006; Zhang et al. 2006) or in early or late thymic populations induces T-ALL (Hagenbeek et al. 2004; Hagenbeek and Spits 2008), similar to activated AKT (Mao et al. 2007). Consistently, inhibition of the PI3K/AKT/mTOR axis induces apoptosis and suppresses the growth of T-ALL in mouse models, cell lines and primary human T-ALL xenografts (Evangelisti et al. 2011; Subramaniam et al. 2012; Piovan et al. 2013; Dail et al. 2014).

In addition, activating mutations in the PI3K–AKT pathway that are detected at a lower frequency in T-ALL are found in *AKT1*, PI3K catalytic and regulatory subunit genes, PIKC3A, and PIK3CD (Gutierrez et al. 2009; Zuurbier et al. 2012; Liu et al. 2017). Moreover, the t(X;7)(q22;q34) and t(X;14)(q22;q11.2) translocations induce overexpression of IRS4 (Karrman et al. 2009b; Kang et al. 2012), a signaling factor that activates AKT (Uchida et al. 2000). Importantly, inhibition of the PI3K/AKT/mTOR axis induces apoptosis and suppresses the growth of T-ALL in mouse models, cell lines and primary human T-ALL xenografts (Evangelisti et al. 2011; Subramaniam et al. 2012; Piovan et al. 2013; Dail et al. 2014) thus representing a potential therapeutic opportunity for T-ALL patients. Notably, PTEN loss and AKT activation can also induce glucocorticoid resistance in mouse models of T-ALL (Piovan et al. 2013), and *PTEN* mutations are associated with primary glucocorticoid resistance in the clinic (Bandapalli et al. 2013). Mechanistically, AKT1 can phosphorylate the glucocorticoid receptor protein thereby blocking glucocorticoid-induced nuclear localization, and mTOR activation increases the expression of MCL1, an anti-apoptotic factor that antagonizes glucocorticoid-induced cell death (Wei et al. 2006). Consequently, PI3K–AKT–mTOR inhibition can effectively reverse glucocorticoid resistance in T-ALL (Wei et al. 2006; Subramaniam et al. 2012; Piovan et al. 2013; Burke et al. 2015).

## IL7 Receptor and JAK-STAT Signaling

Activation of the JAK–STAT pathway by the interleukin-7 receptor (IL7R) supports the growth, proliferation, and survival of early T-cell progenitors (Mazzucchelli and Durum 2007). Aberrant JAK signaling was first linked to T-ALL via the t(9;12)( p24;p13) translocation, a rare rearrangement encoding the constitutively active *ETV6-JAK2* kinase fusion oncoprotein (Lacronique et al. 1997). The JAK–STAT pathway is activated in 25% of T-ALLs, because of mutations in *IL7R*, *JAK1*, *JAK3*, and *STAT5* (Liu et al. 2017), and predominantly in ETP T-ALLs, in which these mutations are found in 47% of cases (Zhang et al. 2012). T-ALL-associated *IL7R* mutations are located in the extracellular juxtamembrane-transmembrane region and lead to increased dimerization and receptor activation (Shochat et al. 2011, 2014; Zenatti et al. 2011). In addition, loss-of-function mutations in dynamin-2 (*DNM2*) impairs clathrin-mediated endocytosis of IL7R, causing increased IL7R surface density and enhanced IL-7 signaling in leukemic stem cells (Tremblay et al. 2016). Expression of mutant *IL7R* in combination with mutant *NOTCH1*

accelerates leukemia development in mice (Yokoyama et al. 2013), and *IL7R* activating mutations generate ETP T-ALL when expressed in thymocytes from *p19/Arf* knockout animals (Treanor et al. 2014). *IL7R* mutations are prevalent in ETP T-ALL cases (Zhang et al. 2012,) and ETP T-ALLs show hyperactivation of STAT5 in response to interleukin-7 (Maude et al. 2015). Moreover, chromosomal rearrangements of ZEB2, which encodes a zinc finger E-box-binding transcription factor (Goossens et al. 2015) are found in ETP-ALL, and *Zeb2* overexpression in mice induces ETP-like leukemia with transcriptional activation of *IL7R* and increased JAK/STAT signaling (Goossens et al. 2015).

Activating mutations in *JAK1* and *JAK3* are found in 10% of T-ALL cases (Flex et al. 2008; Zhang et al. 2012; De Keersmaecker et al. 2013). *Jak3* mutant alleles induce T-ALL in mice albeit with long latency (Degryse et al. 2014), and treatment of these tumors with a selective JAK3 inhibitor reduces white blood cell counts and induces apoptosis in T-ALL lymphoblasts (Degryse et al. 2014). Interestingly, pharmacologic inhibition of JAK1/2 shows therapeutic activity in ETP T-ALL primary patient xenografts in vivo irrespective of JAK/STAT pathway mutations (Maude et al. 2015).

Additional mutations that affect the JAK/STAT signaling pathway are frequently found in T-ALL. Activating mutations in the *STAT5B* gene, which encodes a downstream effector of JAK1 and JAK3, have been reported in 5%–10% of T-ALLs (Bandapalli et al. 2014; Kontro et al. 2014). Genetic inactivation of *PTPN2*, encoding a tyrosine phosphatase that negatively regulates the STAT proteins, is found in ∼6% of T-ALL cases (Kleppe et al. 2011). In addition, loss-of-function mutations in SH2B adaptor protein 3 (*SH2B3*), a gene that encodes a negative regulator of IL-7-mediated JAK/STAT5 signaling, are found in sporadic cases of T-ALL (Zhang et al. 2012; Perez-Garcia et al. 2013). In this context, preclinical studies have shown that JAK-STAT inhibition can induce antitumor effects in T-ALL animal models (Maude et al. 2015; Degryse et al. 2018a). Interestingly, ruxolitinib, a JAK1/2 inhibitor, showed broad antileukemic activity in xenograft models of ETP ALL, suggesting broad addiction to JAK-STAT signaling in these tumors (Maude et al. 2015). In addition, inhibition of ERK, PI3K and BCL2 in *JAK3*-mutant T-ALL cells increased the efficacy of JAK inhibitor treatment in these tumors (Degryse et al. 2018b).

### ABL1-Fusion Oncogenic Kinases

About 6% of T-ALLs show rearrangements of the tyrosine kinase gene *ABL1* resulting in expression of the *NUP214-ABL1* fusion oncogene (Graux et al. 2004, 2009). T-ALL-associated *ABL1* rearrangements also generate the *EML1-ABL1* (De Keersmaecker et al. 2005) and *ETV6-ABL1* (Van Limbergen et al. 2001) fusion genes. *NUP214-ABL1* is almost exclusively found in *TLX1* and *TLX3* T-ALLs (Graux et al. 2004), and NUP214-ABL1 cooperates with TLX1 in a mouse model of T-ALL (Vanden Bempt et al. 2018). Interestingly, this group of leukemias, although not linked with a poor prognosis, shows in vitro sensitivity to different tyrosine kinase inhibitors (TKIs) (Quintas-Cardama et al. 2008). In addition, a few case reports have shown that the use of TKIs in relapsed patients harboring ABL1-fusions can induce complete or partial responses, at least temporarily (Deenik et al. 2009; Clarke et al. 2011; Chen et al. 2017), supporting the relevance of testing the activity of TKI therapy in clinical trials.

### RAS–MAPK Signaling

Activating mutations in the *HRAS* and *KRAS* oncogenes have been described in 10%–15% of T-ALLs and are particularly prevalent in ETP T-ALL (Bar-Eli et al. 1989; Zhang et al. 2012; Van Vlierberghe et al. 2013; Liu et al. 2017). In addition, cryptic deletions and/or mutations in the neurofibromatosis type 1 (*NF1*) gene, which encodes a key negative regulator of Ras signaling, occur in 3% of T-ALL cases (Balgobind et al. 2008).

## RIBOSOMAL PROTEIN MUTATIONS AND THE ROLE OF TRANSLATION IN T-ALL

One of the most intriguing findings of genomic profiling studies in T-ALL is the identification

of recurrent mutations in ribosomal protein genes—in particular, *RPL10, RPS5*, and *RPL11* (De Keersmaecker et al. 2013; Tzoneva et al. 2013). *RPL10* mutations are present in 5%–10% of pediatric T-ALLs, with the recurrent *RPL10* R98S allele accounting for the majority (De Keersmaecker et al. 2013). This alteration up-regulates JAK-STAT signaling components thereby driving hyper-activation of the JAK–STAT pathway following cytokine stimulation (Girardi et al. 2018). *RPL10* mutations may also confer a survival advantage via a specific increase in IRES-mediated translation of the anti-apoptotic factor B-cell lymphoma 2 (*BCL-2*) (Kampen et al. 2019). The *CNOT3* gene, which encodes a component of the CCR4-NOT deadenylase complex, a master regulator of translation and mRNA stability (Bartlam and Yamamoto 2010), is mutated in ~8% of adult T-ALL cases (De Keersmaecker et al. 2013). Finally, the del(6q) chromosomal deletion, found in 30% of *TAL1*-expressing T-ALLs, leads to inactivation of two genes, *SYNCRIP* (encoding hnRNP-Q) and *SNHG5* (small nucleolar RNA host gene 5), which affect ribosomal functions, translation programs, and mitochondrial respiration (Gachet et al. 2018).

## CLOSING REMARKS

The identification and mechanistic dissection of genetic alterations driving malignant transformation in T-ALL illustrates how oncogenic processes hijack the developmental programs that regulate self-renewal, lineage specification, proliferation, survival, and differentiation. Much work is yet needed to fully understand the role of autocrine and paracrine signals, tumor-microenvironment interactions, and the cross talk between different genetic and epigenetic driver alterations in the pathogenesis of T-ALL. Advanced mouse models, in vitro organoid-like culture platforms, and detailed characterization of primary patient sample–derived xenografts are called to close this gap. A thorough understanding of the genetic, transcriptional, developmental, and metabolic programs underlying the development and maintenance of T-ALL will likely offer new opportunities for the rational design of tailored therapies for this disease. Finally, it should not escape our attention that orthogonal therapeutic approaches such as emerging opportunities in immunotherapy may soon transform the treatment of this disease. Thus, chimeric antigen receptor (CAR) T cells targeting CD7 engineered via CRISPR knockout of this T-cell antigen (Cooper et al. 2018) and CAR T cells selectively directed against T-cells expressing a C1 TCRB constant chain (Maciocia et al. 2017) show remarkable activity in preclinical models of T-ALL. Moreover, CD3 activating antibodies elicit strong TCR signals in T-ALLs with surface TCR expression inducing a negative-selection-like programmed cell death mechanism (Trinquand et al. 2016).

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