Signaling pathways involved in the development of T-cell acute lymphoblastic leukemia

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doi: 10.3324/haematol.12917

It is generally accepted thatT-cell acute lymphoblastic leukemia (T-ALL) results from the malignant transformation of normal developing T cells in the thymus, the so-called thymocytes[1-4]. T-ALL represent 15% of childhood and 25% of adult ALL. Chromosomal aberrations leading to abnormal fusion proteins, a key characteristic of the majority of precursor B-ALL, are not commonly found in T-ALL, however, signaling pathways that control T-cell development in the thymus or are involved in T-cell activation are important in its development. These pathways are normally strictly regulated, since many of the key molecules in these pathways are considered protooncogenes. These oncogenes can be activated by juxtaposing to one of the T-cell receptor loci, which is in fact the case in at least one-third of T-ALL patients.[5] Therefore, deregulated signaling is considered a major contributing factor in leukemogenesis of T-ALL. This is best illustrated by the fact that activating mutations in the Notch pathways are believed to occur in a large proportion of human T-ALL.[6] In this issue of the journal, two papers from laboratories with a long-standing tradition in T-ALL research illustrate the importance of signaling routes involved in normal T lymphocyte biology for development of T-ALL cells.[7,8] One report deals with the NF-κB and AP-1 pathways, classically associated with T-cell receptor (TCR) and inflammatory cytokine signaling, the other with Notch signaling and therapeutic strategies to combat the constitutive Notch activation found in many T-ALL patients.

Here we will briefly review the early stages of normal T-cell development and the classification of T-ALL. We will then discuss T-ALL oncogenes, focusing on deregulated signaling as key factors in its development. Both the aberrant activation of these pathways that are crucial to normal T-cell development, and the ectopic expression of most T-ALL oncogenes, can be seen as a deregulation of normal gene expression and pathways at stages where their downregulation is required for normal T-cell development.

Normal T lymphocyte development in the thymus

In contrast to all other hematopoietic lineages, development of T cells from pluripotent hematopoietic stem cells takes place in the specialized microenvironment of the thymus. Several recent reviews have given extensive coverage to human T-cell development.[9,10] Recent insights using gene expression profiling and quantitative measurements of the TCR rearrangement status have significantly improved our understanding of human T-cell development and it has been seen that mouse and human T-cell development are much more comparable than usually thought.[11] Our discussion of T-cell development follows these new insights and also classifies T-ALL on the basis of phenotype, TCR rearrangement status and gene expression profiling according to stage of normal thymocyte differentiation.

Several developmental stages of thymocyte differentiation can be distinguished using cell surface markers.[12] Thymocytes are primarily subdivided into double negative (DN), double positive (DP) and single positive (SP) populations relating to the expression of the co-receptors CD4 and CD8. The most immature thymocytes lack expression of both CD4 and CD8 and are therefore called double negative. Unlike mature SP cells, immature SP (ISP) cells arise when thymocytes express a co-receptor in the absence of high levels of CD3. In humans, ISP express CD4, whereas in most strains of mice they express CD8. Subsequently, both CD4 and CD8 are expressed and therefore these cells are referred to as DP. The DP stage represents about 85% of all thymocytes and most of these cells express CD1a. After undergoing positive and negative selection, thymocytes that express a functional TCR commit to either the CD4 or CD8 SP lineage.

In both species, T-cell commitment towards the αβ TCR$^+$ lineage takes place during the DN stages of development at which γδ T cells also split off. This is reflected in the order of rearrangements of the TCR gene loci: *TCRD*, *TCRG* followed by *TCRB* and lastly *TCRA*.[11] The most immature human thymocyte population is characterized by the expression of the stem cell marker CD34.[12] It should be noted that expression of CD34 on human T-ALL does not usually reflect immaturity, since ALL with fully rearranged *TCRB* can express CD34.

Classification schemes of T-ALL

All classification schemes of T-ALL are essentially based on a comparison with normal development.[13] In clinical practice, the EGIL classification is often used based on membrane expression of CD1a, CD2, CD3, CD4, CD5, CD7 and CD8. Therefore, sCD3$^-$cyCD3$^+$ CD7$^+$ T-ALL is referred to as pro T-ALL, pre-ALL express CD7 together with CD2 or CD5, cortical T-ALL are CD1a$^+$, and mature T-ALL express CD3 but lack CD1a.[14] Recently, other classification schemes which more closely reflect normal development have been proposed using expression of the pre-TCR alpha (pTα) gene and rearrangement status of the TCR loci.[15] This so-called IM classification is biologically quite relevant, but is not often used clinically.

Oncogenes

Many of the oncogenes that are highly expressed in T-ALL are involved in TCR gene translocations, resulting in abnormal expression of developmentally regulated transcription factors and signaling molecules. With the exception of *LCK* and *TAN* (*IC-NOTCH*), all T-ALL oncogenes are down regulated after the first DN stages of development or not expressed at all in the normal thymus.[16] Therefore, *TAL1*, *TAL2*, *TLX1*, and *TLX3* are truly ectopically expressed in T-ALL subtypes. *LYL1*, *LMO1*, and *LMO2* expression are truly oncogenic in the more mature T-ALL subsets, but in the most immature T-ALL subtypes probably reflect a normal thymic developmental program (*WA Dik and AW Langerak, in preparation*). Also, the expression of the entire *HOXA* cluster and of *c-MYC* is often deregulated due to inversion to the *TCRB* locus and translocation to *TCRA/D* respectively (Table 1).[17] While chromosomal translocations resulting in fusion proteins are less common in T-ALL compared to precursor B-ALL, some fusion proteins have been identified, including *MLL*-translocations.[18] These are also found in AML and precursor B-ALL (particularly *MLL-AF10*), *CALM-AF10* fusion proteins, as well as three rare ABL1 fusion proteins (*ETV6-ABL, EML1-ABL* and *NUP214-ABL*).[19] Interestingly, *BCR-ABL* is rarely found in human T-ALL whereas in mice many T-cell lymphomas arise in models for the Bcr-Abl fusion gene. The fairly common *SIL-TAL1* translocation does not result in a fusion protein, but merely puts *TAL1* expression under control of the *SIL* promoter, leading to its aberrant expression (Table 1).

The malignant transformation of developing thymocytes is the result of several genetic alterations in a multistep process that involves arrest in differentiation, changes in cell cycle control and cellular metabolism, and abnormal expression of stem cell self-renewal genes leading to uncontrolled cell growth and clonal expansion. For most T-ALL oncogenes, mouse models have to be used to predict malignant processes. Recent developments in *in vitro* culture systems for human T-cell development allow some of these oncogenes to be assessed. For example, we have recently shown that retroviral overexpression of *LMO2* in human CD34$^+$ stem/progenitor cells, that are subsequently cultured in lineage-specific differentiation systems, is well-tolerated in NK cells, B cells and myeloid cells, but severely hampers T-cell development.[20] The developmental block probably leads to a pre-leukemic condition, as seen in mice transgenically overexpressing *Lmo2*.

A tragic, but interesting role for the *LMO2* oncogene has emerged from gene therapy trials. The oncogenic potential of retrovirus mediated gene therapy has been emphasized by five cases of T-ALL-like disease that emerged from an otherwise successful gene therapy trial for X-linked severe combined immunodeficiency (X-linked SCID).[21] X-linked SCID, a disease caused by inactivating mutations in the IL2Rγ gene, is part of a heterogeneous group of severe combined immunodeficiencies (SCID) characterized by the lack of T cells in conjunction with the absence of B and/or NK cells. Up till now, in 5 patients T-ALL has developed due to insertional mutagenesis activating T-ALL oncogenes. In at least 3 of the 5 cases this involved the *LMO2* oncogene. The consequences of insertional mutagenesis, its role in T-ALL development and implications for gene therapy are extensively discussed elsewhere.[22]

Notch signaling in T-ALL

Until recently, the role of Notch in the leukemogenesis of T-ALL seemed to be limited to the rare t(7,9) translocation that results from translocation of the *TCRB* enhancer to a region of around 100 bp of intron 24 of the *Notch1* gene. These truncated forms of Notch1 (termed TAN1) were shown to act as constitutively active forms of the normal *Notch1* gene (often called IC-NOTCH, abbreviated ICN), which is indispensable for

Table 1. Chromosome aberrations with oncogene overexpression in T-ALL.

Chromosome aberration	*Involved genes*	*Presumed effect at protein level*	*Frequency (%)*
t(1;7)(p34;q34)	TCRB, LCK	LCK ↑	1
t(1;14)(p32;q11) / t(1;7)(p32;q34)	TCRD, TCRB, TAL1	TAL1 ↑	3
del(1)(p32p32)	SIL, TAL1	TAL1 ↑	10-15
t(5;14)(q34;q11)	TCRD, TLX3	TLX3 ↑	1
t(5;14)(q35;q32)	BCL11B, TLX3,	TLX3	15-20
t(6;7)(q23;q32-36)	TCRB, MYB	MYB ↑	1
t(7;9)(q34;q32)	TCRB, TAL2	TAL2 ↑	1
t(7;9)(q34;q34)	TCRB, TAN1	IC-Notch-1	1
t(7;12)(q34;p13)	TCRB, CCDN2	CCDN2	1
t(7;19)(q34;p13)	TCRB, LYL1	LYL1 ↑	1
inv(7)(p15q34)	TCRB, HOXA	HOXA ↑	5
t(8;14)(q24;q11)	TCRD/A, MYC	MYC ↑	1
t(10;14)(q24;q11) / t(7;10)(q24;q24)	TCRD, TCRB, TLX1	TLX1 ↑	10-30
t(11;14)(p13q11) / t(7;11)(q34;p13)	TCRD, TCRB LMO2	LMO2 ↑	3
t(11;14)(p15;q11)	TCRD, LMO1	LMO1 ↑	2

normal thymopoiesis. Radtke *et al*. documented the absolute requirement for Notch1 during the earliest stages of T-cell development in the thymus and specification of the T-cell fate.[23] The role of Notch in normal T-cell development is extensively covered elsewhere.[24]

In brief, the Notch family of transmembrane receptors consists of four members, called Notch1 to 4. Signaling is initiated when the extracellular domain of the Notch receptor binds a membrane-bound ligand on a neighboring cell. The five Notch ligands in mammals are Delta-like 1, 3 and 4 and Jagged1 and 2. Interaction of Notch with a ligand induces proteolytic cleavage of Notch, first by metalloproteases and subsequently by γ-secretases, releasing the intracellular part of the protein (ICN). ICN then translocates to the nucleus and binds to the nuclear transcription factor CBF1 (Figure 1). Binding of ICN to CBF1 induces the dislocation of co-repressors such as Mint and recruitment of co-activators, such as Mastermind (Maml), and stimulates the transcription of Notch target genes.

Several reports have shown that transgenic expression of IC-Notch leads to the rapid development of aggressive T-cell lymphomas.[25-27] However, the role of Notch had not been widely documented in human T-ALL, although deregulated Notch signaling without rearrangements, as found in the *TAN1* cases, had been reported in several leukemias. This enigma was solved by an important finding by John Aster and Thomas Look in 2004. They demonstrated that activating mutations in *NOTCH1* occur in more than 50% of human T-ALL.[6] The mutations all center in three introns of the human *NOTCH1* gene. The *TAN1* translocation involves intron 24, truncating most of the extra-cellular part of the protein, and resulting in the constitutively active γ-secretases inhibitor-resistant form (ICN1). The second type of mutations, not involving Notch1 chromosomal aberrations, concern the heterodimerization domain (HD) located in exons 26 and 27. The heterodimerization domain is required for stable association of the extracellular and intracellular portions of the Notch1 receptor and prevents ligand-independent signaling. Therefore, these mutations facilitate ligand-independent, uncontrolled Notch signaling. The third type of mutations is found in the so-called PEST (polypeptide enriched in proline, glutamate, serine and threonine) domain mutations located in exon 34 and affect the half-life of ICN1. The PEST domain normally controls turnover of the ICN protein. These mutations are thought to increase its half-life. Many human T-ALL samples show highly oncogenic mutations in the heterodimerization or PEST domains. Interestingly, activating *NOTCH1* mutations occur in several previously identified T-ALL subsets, either based on specific chromosomal translocations and/or aberrant oncogene expression. Two studies identifying mutations in the FBW7 gene, encoding an ubiquitin ligase implicated in ICN turnover further illustrate the importance of ICN stabilization in human T-ALL leukemogenesis and highlight the role of FBW7 as tumor suppressor.[28-30]

The protooncogene *C-MYC* was recently identified as a direct target of Notch1 in Notch-dependent T-ALL cell lines.[31] *C-MYC* inhibition interfered with the proliferative effects of activated Notch1, and conversely, enforced expression of *C-MYC* rescued T-ALL cell lines from Notch withdrawal by γ-secretases inhibitors. Therefore, *C-MYC* is a direct target of Notch1 that contributes to the growth of T-ALL cells and helps explain why Notch overexpression is oncogenic.

Although Notch2 is expressed in HSC and Notch 3 abundantly in the thymus, only mutations in Notch1 have so far been found in T-ALL. This is remarkable, since ICN2 and ICN3 are equally as oncogenic in model systems as ICN1. Another interesting aspect of Notch induced leukemogenesis is the fact that pre-TCR signaling is required for leukemia induction.[32] Overexpression of ICN did not induce T-cell lymphomas in mice lacking the pre-TCR. In line with this requirement for T-cell specific co-operative signals for Notch to assert its oncogenic effect, is the lack of B-lineage and the small number of myeloid leukemias in which Notch mutations are found.[33]

NF-κB signaling

Recent data by Villimas *et al.* demonstrate that in many T-ALL samples the NF-κB pathway is very active.[34] It was shown that ICN is responsible for activating the NF-κB pathway via the I-κB kinases. Indeed,

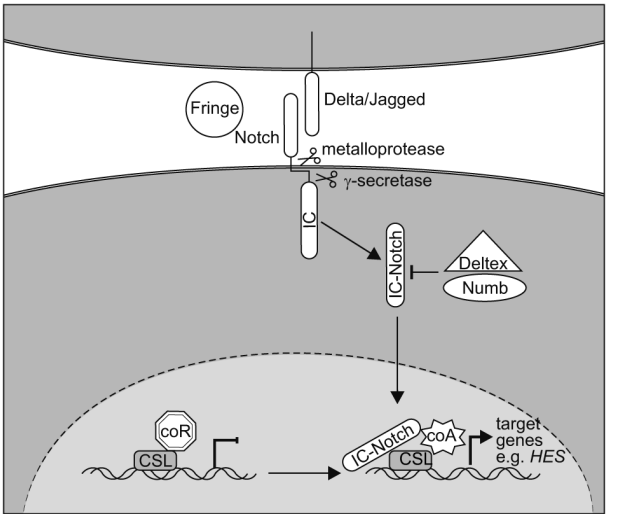

Figure 1. Notch signaling transduction. Depicted is a general scheme in which Notch ligands (either of the Delta or Jagged family) bind to any of four different Notch ligands. This binding leads to activation of proteases, in particular γ-secretases for which specific pharmaceutical inhibitors exits. These proteases cleave the intracellular part of Notch (ICN) which migrates to the nucleus, turning CSL like repressors into transcriptional activators. Activating mutations in the Notch1 receptor lead to constitutive activation of Notch signaling, a causative factor in T-ALL development.

treatment of human T-ALL cells with the NF-κB inhibitor bortezomib severely hampered the growth of the leukemic cells. The deregulated NF-κB activation represents a novel and attractive therapeutic target in T-ALL (see below).

In this issue of the journal, Scupoli *et al.* propose yet another Notch-independent process by which the NF-κB pathway may be involved in T-ALL leukemogenesis.[7] They report on a series of experiments indicating that CXCL12, also known as SDF-1 (stromal derived factor-1) can induce NF-κB and AP-1 (fos/jun) signaling in T-ALL cell lines and, importantly, primary leukemic cells. This is one of the ways in which interleukin-8 (IL-8) can be produced by ALL cells. IL-8 is a known high-risk factor correlating with poor prognosis in leukemias.[35-37] Although definitive proof has not yet been provided, it is likely that stromal cells from bone marrow or thymus, producing CXCL12 binding to the CXCR4 receptor, induce IL-8 production via the NF-κB pathway.

In any case, the NF-κB pathway seems to play an important role in T-ALL cells. As NF-κB signaling is redox regulated,[38] this pathway represents an attractive therapeutic target at several points in its signaling cascade.

Recent observations indicate an intricate connection between Notch, MYC, NF-κB and PI3K/AKT signaling pathways.[34] Interactions with the evolutionary conserved Wnt pathway[39] have also been proposed. Wnt signaling, similar to Notch signaling, is an absolute requirement for the very first stages of T-cell development in the thymus.[40] Data from mouse studies indicate that deregulated Wnt signaling causes T-cell lymphomas,[41] the murine equivalent of human T-ALL. Whether deregulated Wnt signaling is also implicated in human T-ALL leukemogenesis must still be confirmed.

Therapeutic perspectives

The discovery of activating Notch1 mutations in T-ALL has made the Notch pathway an attractive target for small molecule pharmaceutical drugs. Gamma-secretase inhibitors (GSI), originally developed for Alzheimer's disease, are capable of efficiently blocking the proteolysis cleavage of Notch and thereby ICN translocation to the nucleus.[28,42] In this issue of the journal, de Keersmacker *et al*. describe a series of important experiments aimed at determining the efficacy of GSI in combination with other, well-established chemotherapeutic agents, such as imatinib and dexamethasone.[8] Importantly, GSI effects were largely reversible and require long (> 14 days) treatment to induce apoptosis of T-ALL cell lines. It should to be noted that clinical trails have begun using small inhibitor molecules of the γ-secretases complex. So far, a major problem in these trials has been side effects from gastrointestinal problems. Indeed, crypt cells in the small intestine undergo Notch signaling as part of their normal physiology. However, combination therapy such as that described by de Keersmaecker *et al.*[8] may allow for lower dosages of GSI that are still effective for T-ALL treatment. The fact that NF-κB activation occurs in the T-ALL with Notch-1 activating mutations makes combination therapy attractive. Also, the few cases of T-ALL involving the ABL tyrosine kinase can be targeted with imatinib. Combination therapy may, therefore, be more effective and allow lower dosage of a single agent, thereby preventing side effects. Since small molecule inhibitors for Wnt signaling exist (reviewed on the Wnt page: http://www.stanford.edu/~rnusse/assays/ smallmol.html), which inhibit the interaction of β-catenin and Tcf, pharmaceutical intervention in T-ALL with deregulated Wnt signaling is another possibility. The growing knowledge of signaling abnormalities and aberrant transcriptional control in T-ALL is likely to produce novel drug candidates in the future. Current research efforts in human T-ALL should therefore aim to establish the interplay of aberrant signaling pathways in comparison to normal thymocyte development. This should include identification of key components in signaling pathways as well as of the downstream targets of deregulated transcription factors. Once established these could present candidate targets for pharmaceutical agents, eventually leading to inhibition of aberrant signaling or to release of differentiation arrest.

FJTS is supported in part by the Association of International Cancer Research (AICR) and by Fundação para a Ciência e a Tecnologia, Portugal. We would like to thank Dr. Szczepanski for critically reading the manuscript.

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