Molecular Targeted Therapies in T-Cell Acute Lymphoblastic Leukemia

Alejandro Gutierrez and A. Thomas Look

Introduction

T cell precursors arise from hematopoietic progenitors in the bone marrow and migrate to the thymus, where they undergo a series of proliferation and differentiation steps that include the somatic recombination of T cell receptor (TCR) gene loci (Market and Papavasiliou 2003). TCR gene rearrangements are followed by positive and negative selection steps that allow the survival of T cells only if their TCR functions appropriately within the context of an individual's immune microenvironment. This highly regulated developmental process results in the generation of a population of T cells with a wide range of somatically acquired T cell receptor variation, which forms the foundation of a fully competent adaptive immune system that can respond to a countless variety of foreign antigens. Genetic alterations involving oncogenes or tumor suppressors can result in the aberrant proliferation, differentiation arrest, and clonal expansion of T cell precursors that is characteristic of T cell acute lymphoblastic leukemia (T-ALL).

T cell lymphoblastic malignancies can be characterized based on the pattern of surface antigen expression in T cell lymphoblasts in relation to the pattern of surface antigen expression that occurs in normal thymocyte development (Reinherz and Schlossman 1980; Rothenberg and Taghon 2005; Staal et al. 2001). The earliest T cell precursors migrate from the bone marrow to the thymus, where they proceed through a series of so-called double-negative (CD4–, CD8–) differentiation stages, during which rearrangements of the T-cell receptor δ, γ and β genes occur. This is

A.T. Look (✉)
Department of Pediatric Oncology, Dana-Farber Cancer Institute and Children's Hospital Boston, 44 Binney Street, Boston, MA 02115, USA
and
Harvard Medical School, Boston, MA, USA
e-mail: thomas_look@dfci.harvard.edu

P.J. Houghton and R.J. Arceci (eds.), *Molecularly Targeted Therapy for Childhood Cancer*, 19
DOI 10.1007/978-0-387-69062-9_2,

followed by the intermediate single-positive (CD4+, CD8−, surface CD3−), and the subsequent double-positive (CD4+, CD8+) stage, during which TCR α rearrangements occur. Intrathymic T cell development ends with the generation of single-positive CD4+ or CD8+ T cells that migrate outside the thymus, although additional differentiation steps occur in T cells upon antigen recognition.

T-ALL accounts for 10 to 15% of acute lymphoblastic leukemias in children, and it is most common in older children and adolescents. This disease typically presents with distinctive clinical features, including very high numbers of lymphoblasts in the peripheral blood, involvement of the central nervous system, and an anterior mediastinal mass. T cell lymphoblastic lymphoma is a closely related malignancy that typically presents with a thymic anterior mediastinal mass and is differentiated from T-ALL based on the degree of bone marrow involvement, with greater than 25% lymphoblasts in the bone marrow defining T-ALL. These diseases exhibit a high degree of similarity in morphology, immunophenotype, and response to therapy, and are generally thought to represent different clinical presentations of the same disease (Cairo et al. 2005). Most of the insights into the molecular pathogenesis of T-cell lymphoblastic malignancies have come through the study of T-ALL rather than T cell lymphoblastic lymphoma, probably due to the greater ease of obtaining primary tumor specimens. This chapter is focused on the key aspects of the molecular pathogenesis of T-ALL that are most relevant to the development of molecular targeted therapies for this disease.

Oncogenic Transcription Factors

Many of the early insight into the pathobiology underlying T-ALL came through the study of genes affected by recurrent chromosomal translocations. In contrast to B-precursor ALL, where recurrent translocations often lead to the expression of a fusion gene product, T-ALL translocations typically lead to the aberrant overexpression of structurally intact transcription factors, due to the placement of these genes under the control of regulatory elements that are highly active in T cell precursors, such as the gene regulatory elements that normally drive the expression of T-cell receptor (TCR) genes. Most often, the transcription factors involved play prominent roles in normal hematopoietic development. Oncogenic transcription factors dysregulated by this mechanism in T-ALL include basic region helix-loop-helix (bHLH) genes such as *TAL1, TAL2, LYL1,* and *MYC*, cysteine-rich genes such as *LMO1* and *LMO2*, and homeodomain genes such as *HOX11* and *HOX11L2*. Furthermore, although chromosomal translocations involving these genes are present in only 25% of cases of T-ALL, gene expression profiling has identified overexpression of these genes in 80% of cases (Ferrando et al. 2004; Ferrando and Look 2003), strongly suggesting that the dysregulated expression of these proto-oncogenic transcription factors plays a fundamental role in the molecular pathogenesis of most cases of T-ALL.

Although of great biologic interest due to their central role in the pathobiology of T-ALL, dysregulated transcription factor activity, which relies on intracellular protein–protein and protein–DNA interactions, has been difficult to target with currently available pharmacologic strategies. Small molecules with favorable pharmacologic properties can readily be designed to target intracellular proteins whose activity relies on small hydrophobic pockets, such as enzymes. However, it is estimated that only about 12% of the proteins encoded by the human genome are "druggable" by small molecules with current technology, due to structural and mechanistic considerations (Hopkins and Groom 2002; Hopkins and Groom 2003; Russ and Lampel 2005); most transcription factors are currently considered "undruggable." On the other hand, antibodies can be used as therapeutic agents to inhibit protein–protein interactions and thus have a much broader range of potential targets; however, antibodies generally cannot cross the cell membrane, and are thus poorly suited as targeted modulators of intracellular proteins (Verdine and Walensky 2007). However, recent advances in peptide medicinal chemistry include the development of chemically stabilized alpha-helical peptides that can successfully target intracellular protein–protein interactions and that are taken up *in vivo* by intact cells (Gavathiotis et al. 2008; Walensky et al. 2004). This strategy may allow the development of specific therapies targeting dysregulated oncogenic transcription factor activity in the human leukemias.

NOTCH1

The NOTCH1 Pathway

Notch, which was initially identified by the characterization of a *Drosophila melanogaster* mutant strain with notched wings (Morgan 1917), plays central roles in the development of multicellular organisms, where it acts by regulating cell fate, proliferation, survival, migration, and differentiation (Lai 2004). The first human ortholog of Notch, NOTCH1, was initially identified as a partner gene in a t(7;9) translocation found in very rare cases of T-ALL, in which the expression of a truncated NOTCH1 protein is driven by T cell receptor β gene regulatory elements (Ellisen et al. 1991). NOTCH1 plays central roles in T cell development, where it directs lymphoid progenitors toward a T cell fate at multiple stages of lymphoid development (Grabher et al. 2006; Maillard et al. 2006; Radtke et al. 2004; Rothenberg and Taghon 2005). Additionally, constitutive NOTCH1 signaling transforms T cell precursors in experimental systems (Zweidler-McKay and Pear 2004). Despite the very low frequency of translocations involving NOTCH1, activating mutations in the heterodimerization or PEST domains of the full-length NOTCH receptor have been found in greater than 50% of cases of T-ALL (Weng et al. 2004).

NOTCH1 is a cell surface receptor with an unusual mechanism of action (reviewed in (Bray 2006; Grabher et al. 2006)). After its synthesis, the NOTCH1 protein undergoes cleavage by a furin-like protease into extracellular and transmembrane subunits that remain associated via noncovalent interactions at the cell membrane. The binding of ligand to the extracellular subunit of NOTCH1 triggers two additional cleavage events in the transmembrane subunit, the first catalyzed by ADAM-family metalloproteases and the second by the γ-secretase enzyme complex, which consists of presenilin, nicastrin, PEN2, and APH1. This final γ-secretase-mediated cleavage allows the release of the intracellular domain of NOTCH1, known as ICN, into the cytoplasm. The ICN then translocates to the nucleus, where it binds to the CSL/RBPJ transcription factor, leading to the displacement of transcriptional corepressors and the recruitment of coactivators, thus resulting in the transcriptional upregulation of target genes (Fig. 1).

NOTCH1 activating mutations in T-ALL generally occur in two distinct regions of the protein, and result in the accumulation of nuclear ICN protein via distinct mechanisms. Missense mutations in the heterodimerization domain lead to constitutive proteolytic activation of ICN, whereas truncating mutations in the C-terminal PEST domain impair the degradation of nuclear ICN. Interestingly, mutations in

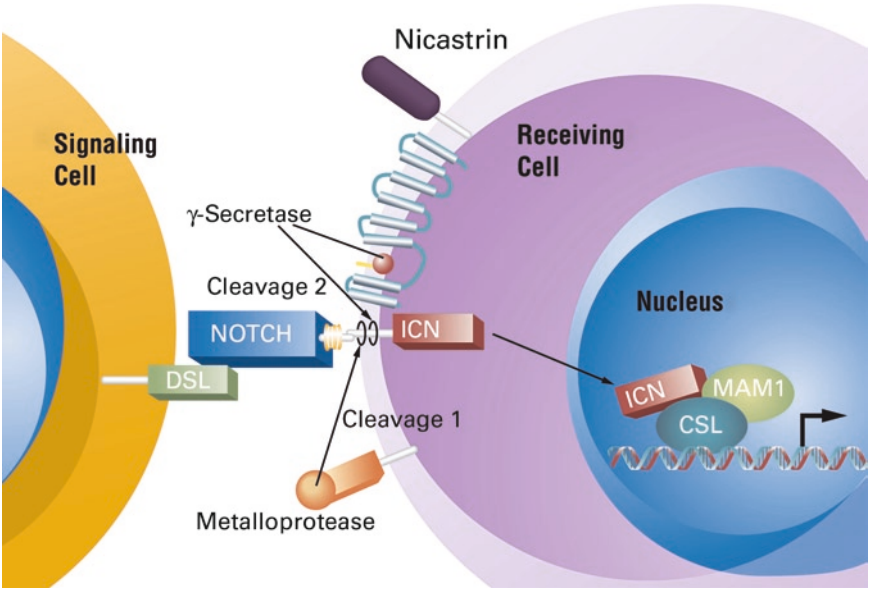

Fig. 1 Activation of NOTCH signaling via proteolytic cleavage and nuclear translocation of the intracellular NOTCH domain (ICN). Interaction with delta serrate ligand (DSL) stimulates proteolytic cleavage of NOTCH by metalloproteases and γ-segretase. This leads to the release of the intracellular ICN domain, which translocates to the nucleus, displaces corepressors and recruits coactivators (MAM1), thereby converting CSL from a repressor to an activator of gene expression. Reprinted with permission from Armstrong and Look (2005)

both regions of the protein frequently occur in *cis* in the same NOTCH1 allele, resulting in the synergistic activation of NOTCH1 signaling (Weng et al. 2004). Prominent transcriptional targets of the NOTCH1 ICN include *MYC,* which has been shown to be critical for the growth-promoting effects of NOTCH1 in T-ALL cell lines (Palomero et al. 2006; Sharma et al. 2006; Weng et al. 2006), while another NOTCH1 target, *HES1,* is a transcriptional repressor that is a critical mediator of the ICN-induced transcriptional repression of the *PTEN* tumor suppressor (Palomero et al. 2007), as discussed in more detail below.

Strategies for NOTCH1 Inhibition

A number of strategies have been devised for the inhibition of NOTCH. Wild-type NOTCH1 signaling can be targeted at the receptor-ligand interaction, but such strategies are unlikely to be effective against T-ALL cells expressing mutant NOTCH1 because the mutant receptor undergoes ligand-independent receptor activation. Other strategies, including the development of monoclonal antibodies that lock NOTCH1 in an inactive conformation, are in preclinical development (reviewed in (Rizzo et al. 2008)).

The identification of a requirement for enzymatic activity of the γ-secretase complex for the proteolytic activation of ICN, both upon ligand binding and in the presence of activating NOTCH1 mutations, generated considerable excitement for the application of γ-secretase inhibitors (GSI) in T-ALL. Small molecule inhibitors of γ-secretase were developed prior to the discovery of NOTCH1 activation in T-ALL because the γ-secretase complex also plays a central role in the proteolytic generation of the insoluble amyloid-β peptide that accumulates in the brain in Alzheimer's disease (reviewed in (Gotz and Ittner 2008). Interestingly, toxicity to normal T cells was found to be a toxicity of GSI during their preclinical development for the treatment of Alzheimer's disease (Wong et al. 2004).

Clinical trials of GSIs have been undertaken in T-ALL; however, the clinical utility of these inhibitors has been hindered by the development of serious gastrointestinal toxicity (DeAngelo et al. 2006; Rizzo et al. 2008). GSI therapy induces apoptosis of intestinal epithelial cells and goblet cell metaplasia (Milano et al. 2004), an on-target toxicity resulting from altered intestinal cell differentiation toward a goblet cell fate in the absence of NOTCH signaling (van Es et al. 2005). Efforts to overcome this toxicity through alterations in drug schedules and doses are the focus of current investigations. It has been reported that patients with breast cancer treated with a combination of tamoxifen and GSI had greatly alleviated intestinal toxicity (Rizzo et al. 2008). Furthermore, another report has demonstrated that the treatment with a combination of dexamethasone and GSI dramatically ameliorates the GSI-mediated intestinal toxicity in an animal model, while GSI therapy could simultaneously reverse NOTCH-mediated glucocorticoid resistance in human T-ALL cell lines (Real et al. 2009). This important finding suggests that combination therapy with dexamethasone and GSIs could

lead to synergistic antileukemic activity while simultaneously abrogating the dose-limiting gastrointestinal toxicity of GSIs, a possibility that should be tested in T-ALL clinical trials in the near future.

Resistance to NOTCH1 Inhibitors and Therapeutic Strategies to Overcome Resistance

Despite their initial promise, γ-secretase inhibitors are not effective against all T-ALL cell lines harboring activating NOTCH1 mutations. The mechanism mediating the resistance of T-ALL cells to γ-secretase inhibition has been the target of intense investigation, and at least two distinct mechanisms of resistance have been identified. The first of these involves the inactivation of the FBW7 tumor suppressor, which appears to mediate resistance to γ-secretase inhibition by impairing the downregulation of NOTCH1 signaling. FBW7 is an E3 ubiquitin ligase that targets both the ICN and MYC for proteasomal degradation (O'Neil et al. 2007; Thompson et al. 2007). Despite the effective inhibition of NOTCH1 activation at the cell surface by γ-secretase inhibitor therapy, cells harboring inactivation of FBW7 apparently fail to effectively downregulate NOTCH1 signaling because the proteasomal degradation of ICN, and of its prominent target MYC, is impaired by the inactivation of the FBW7 E3 ubiquitin ligase.

The inactivation of PTEN, an important tumor suppressor that negatively regulates PI3K-AKT signaling, has been identified as a second prominent mechanism mediating resistance to γ-secretase inhibitor therapy (Palomero et al. 2007). In contrast to FBW7 mutations, the inactivation of PTEN does not appear to exert its effect by promoting ICN transcriptional activity. Under physiologic conditions, active NOTCH1 signaling leads to the transcriptional upregulation of HES1, which then acts as a transcriptional repressor of PTEN. Thus, in the setting of active NOTCH1 signaling, active PI3K-AKT signaling is promoted due to the transcriptional repression of PTEN (Fig. 2a). Upon inhibition of γ-secretase activity, NOTCH1 signaling is inhibited, the transcriptional repression of PTEN is released, and the resultant upregulation in PTEN expression leads to the inhibition of oncogenic PI3K-AKT signaling. Thus, γ-secretase inhibitor therapy in a cell with intact PTEN results in the inhibition of both NOTCH1 and PI3K-AKT signaling (Fig. 2b). However, deletions and inactivating mutations of *PTEN* have been identified in 36% of primary T-ALL samples, as discussed in more detail below. PTEN-negative T-ALL cells with NOTCH1 activating mutations maintain active signaling through both NOTCH1 and PI3K-AKT pathways (Fig. 2c). Upon effective γ-secretase inhibitor therapy, NOTCH1 signaling is inhibited in PTEN-negative cells. However, PTEN expression cannot be upregulated in these cells despite the downregulation of HES1, and PI3K-AKT signaling remains active in PTEN-negative cells. The failure to downregulate PI3K-AKT signaling thus leads to resistance to GSI treatment in PTEN-negative cells (Fig. 2d). Interestingly, Palomero et al. have shown that, although PTEN loss induces resistance to NOTCH1 inhibition, PTEN-negative

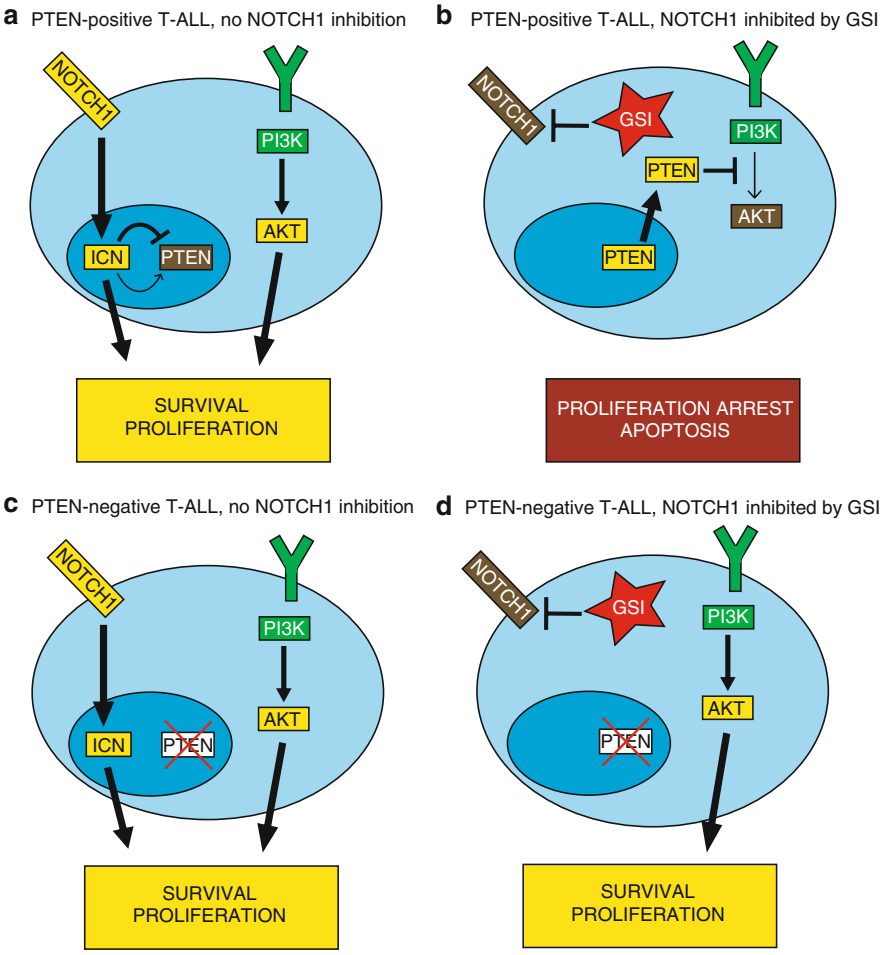

Fig. 2 *PTEN* inactivation leads to resistance to NOTCH1 inhibition but dependence on AKT signaling. (**a**) T-ALL lymphoblasts with activating mutations of *NOTCH1* constitutively generate intracellular NOTCH1 (ICN), whose transcriptional targets include *MYC* and *HES1*. *MYC* appears to be a transcriptional activator of *PTEN*, but *HES1*-mediated repression predominates under ICN signaling conditions. Low expression of *PTEN* leads to incomplete inhibition of the PI3K-AKT pathway. (**b**) Inhibition of proteolytic release of ICN from the NOTCH1 receptor by γ-secretase inhibitors (GSI) blocks ICN-mediated proliferative and survival signals, leading to cell cycle arrest and apoptosis. Additionally, the HES1-mediated repression of *PTEN* expression is relieved, and *PTEN* can therefore inhibit prosurvival signaling mediated by the PI3K-AKT pathway. Thus, *PTEN*-positive T-ALL cells with activating *NOTCH1* mutations depend on NOTCH1 activity for survival and proliferation. (**c** and **d**). In the absence of *PTEN*, uninhibited AKT activation leads to aberrant prosurvival and proliferative signaling independent of NOTCH1 pathway activity, thus leading to resistance to NOTCH1 inhibition. *PTEN*-null T-ALL cells that are resistant to NOTCH1 inhibition appear to be dependent on PI3K-AKT pathway signaling. Reprinted with permission from Gutierrez and Look (2007)

NOTCH1-mutant T-ALL cells are instead dependent on AKT signaling (Palomero et al. 2007). A number of inhibitors of the PI3K-AKT pathway are currently undergoing clinical development, and it seems likely that these will be particularly effective in T-ALL when used in combination with NOTCH1 inhibitors.

PTEN, PI3K-AKT, and mTOR

The role of the PTEN tumor suppressor in T-ALL has been suggested by murine studies demonstrating that T-ALL develops in mice after the conditional deletion of *PTEN* in hematopoietic stem cells (Guo et al. 2008; Yilmaz et al. 2006). The tumor suppressor activity of PTEN is mediated in large part due to its role as a negative regulator of PI3K-AKT signaling (Chow and Baker 2006), an oncogenic signal transduction pathway activated by growth factor signaling and by a variety of oncogenic mutations in human cancer (Brugge et al. 2007). Deletions of *PTEN* have recently been described in approximately 8% of primary T-ALL patient samples (Maser et al. 2007; Mullighan et al. 2007). Additionally, we have recently completed an analysis of *PTEN* as well as *PI3K* and *AKT* genes in primary T-ALL samples, and have identified the presence of genetic lesions in the PTEN-PI3K-AKT pathway in 48% of diagnostic specimens from a series of 44 children with T-ALL (Gutierrez et al. 2009).

Activation of signaling through the PI3K-AKT pathway, as a result of PTEN loss or the introduction of a constitutively active AKT transgene, has been shown to mediate resistance to NOTCH1 inhibition, but this appears to induce sensitivity to PI3K-AKT pathway inhibitors, as discussed in the section "Resistance to NOTCH1 Inhibitors and Therapeutic Strategies to Overcome Resistance" (Palomero et al. 2007). Additionally, evidence suggests that the mammalian target of rapamycin (mTOR), which is activated by the PI3K-AKT pathway, mediates glucocorticoid resistance in at least some ALL cells, and the inhibition of mTOR effectively reversed glucocorticoid resistance in T-ALL and B-precursor ALL cell lines (Wei et al. 2006). Furthermore, combination therapy with a glucocorticoid and a γ-secretase inhibitor has been shown to both reverse glucocorticoid resistance and to mitigate the serious gastrointestinal toxicity of γ-secretase inhibitors (Real et al. 2009), as discussed in the section "Strategies for NOTCH1 Inhibition." Taken together, these findings suggest that combination therapy with an inhibitor of PI3K-AKT-mTOR signaling, a γ-secretase inhibitor, and a glucocorticoid may represent a particularly effective therapeutic combination in T-ALL, a possibility that will likely be tested by future clinical trials.

Tyrosine Kinase Genes

The *ABL* tyrosine kinase normally plays physiologic roles in the regulation of proliferation, cell adhesion and migration, and apoptosis (Sirvent et al. 2008). Translocations resulting in the expression of a *BCR-ABL* fusion oncoprotein represent the characteristic

genetic lesion in chronic myeloid leukemia (CML) and also occur in B-precursor ALL. Compared to the wild-type *ABL* tyrosine kinase, *BCR-ABL* exhibits aberrant subcellular localization and constitutive kinase activity. The ability of imatinib, a small molecule inhibitor of *BCR-ABL* kinase activity, to provide long-term disease control in CML has revolutionized therapy for this disease, and imatinib also has activity against *BCR-ABL*-positive acute lymphoblastic leukemia.

Despite the rarity of *BCR-ABL* translocations in T-ALL, amplified episomes containing *NUP214-ABL* fusion genes have been described in approximately 6% of adults and children with T-ALL (Graux et al. 2004). The *ABL* breakpoint in these cases occurs in intron 1, the same location as in *BCR-ABL* translocations, and these fusions impart constitutive *ABL* tyrosine kinase activity to the fusion oncoprotein. Therapy with tyrosine kinase inhibitors designed to target *BCR-ABL*, including imatinib, dasatinib, and nilotinib, inhibits proliferation and induces apoptosis in T-ALL cell lines harboring NUP214-*ABL* fusions (Quintas-Cardama et al. 2008). Furthermore, *ABL* amplifications and *EML1-ABL* fusions have also been described in rare cases of T-ALL (Bernasconi et al. 2005; De Keersmaecker et al. 2005). Taken together, these findings suggest that *ABL* kinase inhibitors may have therapeutic utility in a subset of cases of T-ALL, and clinical trials should be initiated to test this possibility.

Mutational activation of JAK1 has recently been reported in 18% of T-ALL cases, and these mutations were associated with poor response to therapy (Flex et al. 2008). The JAK1 gene encodes a nonreceptor tyrosine kinase that associates with cytokine receptors and mediates the activation of STAT proteins upon cytokine receptor activation. JAK1 has been shown to play critical roles in lymphocyte development, and JAK1 knockout mice show a severely hypocellular thymus. JAK1 mutations identified in T-ALL lead to the ligand-independent activation of STAT signaling. A number of inhibitors of JAK/STAT signaling are currently under clinical development, and the determination of their clinical activity against JAK1-mutated T-ALL will be of great interest.

RAS

The RAS proto-oncogenes encode proteins that play central roles in mediating growth factor signaling, and missense mutations at codons 12, 13, or 61 are frequent events in human cancer. Mutant RAS proteins are potently oncogenic and lead to the induction of signaling though the MAP kinase, PI3K-AKT, and RAL-GDS pathways (Schubbert et al. 2007). Mutations activating NRAS or KRAS have been identified in approximately 15% of T-ALL and B-precursor ALL cases (Liang et al. 2006; Perentesis et al. 2004). Due to their role in the pathogenesis of numerous cancers, a number of targeted RAS inhibitors are under development, many of which target the post-translational modifications required for the generation of functional RAS proteins, including farnesylation, palmitoylation and geranylgeranylation. Furthermore, recent studies in *KRAS*-dependent cell lines derived from diverse tumor types revealed inhibition of the *STK33* kinase as effective therapy against *KRAS*-dependent tumors, indicating the need for preclinical studies of *STK33*

inhibitors in *RAS*-dependent T-ALL (Scholl et al. 2009). Targeted inhibitors of RAS, or of signal transduction pathways activated by RAS, including the MAP kinase and the PI3K-AKT pathways, may prove to have a role in the therapy of RAS-mutated T-ALL.

Conclusions

Recent advances in our understanding of the molecular pathogenesis of T-ALL have uncovered a number of therapeutic targets in this disease, including proteins in the NOTCH and PI3K-AKT pathways. Despite initial challenges, and the early difficulties with gastrointestinal toxicity with the use of NOTCH inhibitors, remarkable recent advances have suggested rational combination therapies that may lead to both synergistic antileukemic activity and reduced toxicity. Our understanding of T-ALL oncogenic pathways almost certainly remains incomplete, and new advances should lead to the successful clinical application of molecularly targeted agents in T-ALL.

References

Armstrong SA, Look AT (2005) Molecular genetics of acute lymphoblastic leukemia. Journal of Clinical Oncology 23:6306–6315.

Bernasconi P et al. (2005) *ABL*1 amplification in T-cell acute lymphoblastic leukemia. Cancer Genet Cytogenet 162:146–50.

Bray SJ (2006) Notch signalling: a simple pathway becomes complex. Nat Rev Mol Cell Biol 7:678–89.

Brugge J et al. (2007) A new mutational AKTivation in the PI3K pathway. Cancer Cell 12:104–7.

Cairo MS et al. (2005) Childhood and adolescent non-Hodgkin lymphoma: new insights in biology and critical challenges for the future. Pediatr Blood Cancer 45:753–69.

Chow LM, Baker SJ (2006) PTEN function in normal and neoplastic growth. Cancer Lett 241:184–96.

De Keersmaecker K et al. (2005) Fusion of EML1 to *ABL*1 in T-cell acute lymphoblastic leukemia with cryptic t(9;14)(q34;q32). Blood 105:4849–52.

DeAngelo DJ et al. (2006). A phase I clinical trial of the notch inhibitor MK-0752 in patients with T-cell acute lymphoblastic leukemia/lymphoma (T-ALL) and other leukemias. Abstract, American Society of Clinical Oncology 2006 Annual Meeting.

Ellisen LW et al. (1991) TAN-1, the human homolog of the Drosophila notch gene, is broken by chromosomal translocations in T lymphoblastic neoplasms. Cell 66:649–61.

Ferrando AA et al. (2004) Biallelic transcriptional activation of oncogenic transcription factors in T-cell acute lymphoblastic leukemia. Blood 103:1909–11.

Ferrando AA, Look AT (2003) Gene expression profiling in T-cell acute lymphoblastic leukemia. Semin Hematol 40:274–80.

Flex E et al. (2008) Somatically acquired JAK1 mutations in adult acute lymphoblastic leukemia. J Exp Med 205:751–8.

Gavathiotis E et al. (2008) BAX activation is initiated at a novel interaction site. Nature 455:1076–81.

Gotz J, Ittner LM (2008) Animal models of Alzheimer's disease and frontotemporal dementia. Nat Rev Neurosci 9:532–44.
Grabher C et al. (2006) Notch 1 activation in the molecular pathogenesis of T-cell acute lymphoblastic leukaemia. Nat Rev Cancer 6:347–59.
Graux C et al. (2004) Fusion of NUP214 to *ABL*1 on amplified episomes in T-cell acute lymphoblastic leukemia. Nat Genet 36:1084–9.
Guo W et al. (2008) Multi-genetic events collaboratively contribute to Pten-null leukaemia stem-cell formation. Nature 453:529–33.
Gutierrez A, Look AT (2007) NOTCH and PI3K-AKT pathways intertwined. Cancer Cell 12:411–413.
Gutierrez A et al. (2009) High frequency of PTEN, PI3K and AKT abnormalities in T cell acute lymphoblastic leukemia. Blood 114:647–50.
Hopkins AL, Groom CR (2002) The druggable genome. Nat Rev Drug Discov 1:727–30.
Hopkins AL, Groom CR (2003) Target analysis: a priori assessment of druggability. Ernst Schering Res Found Workshop:11–7.
Lai EC (2004) Notch signaling: control of cell communication and cell fate. Development 131:965–73.
Liang DC et al. (2006) K-Ras mutations and N-Ras mutations in childhood acute leukemias with or without mixed-lineage leukemia gene rearrangements. Cancer 106:950–6.
Maillard I et al. (2006) Notch-dependent T-lineage commitment occurs at extrathymic sites following bone marrow transplantation. Blood 107:3511–9.
Market E, Papavasiliou FN (2003) V(D)J recombination and the evolution of the adaptive immune system. PLoS Biol 1:E16.
Maser RS et al. (2007) Chromosomally unstable mouse tumours have genomic alterations similar to diverse human cancers. Nature 447:966–71.
Milano J et al. (2004) Modulation of notch processing by gamma-secretase inhibitors causes intestinal goblet cell metaplasia and induction of genes known to specify gut secretory lineage differentiation. Toxicol Sci 82:341–58.
Morgan TH (1917) The Theory of the Gene. The American Naturalist 51:513.
Mullighan CG et al. (2007) Genome-wide analysis of genetic alterations in acute lymphoblastic leukaemia. Nature 446:758–64.
O'Neil J et al. (2007) FBW7 mutations in leukemic cells mediate NOTCH pathway activation and resistance to gamma-secretase inhibitors. J Exp Med 204:1813–24.
Palomero T et al. (2006) NOTCH1 directly regulates c-MYC and activates a feed-forward-loop transcriptional network promoting leukemic cell growth. Proc Natl Acad Sci U S A 103:18261–6.
Palomero T et al. (2007) Mutational loss of PTEN induces resistance to NOTCH1 inhibition in T-cell leukemia. Nat Med 13:1203–10.
Perentesis JP et al. (2004) RAS oncogene mutations and outcome of therapy for childhood acute lymphoblastic leukemia. Leukemia 18:685–92.
Quintas-Cardama A et al. (2008) Activity of tyrosine kinase inhibitors against human NUP214-*ABL*1-positive T cell malignancies. Leukemia 22:1117–24.
Radtke F et al. (2004) Notch regulation of lymphocyte development and function. Nat Immunol 5:247–53.
Real PJ et al. (2009) Gamma-secretase inhibitors reverse glucocorticoid resistance in T cell acute lymphoblastic leukemia. Nat Med 15:50–8.
Reinherz EL, Schlossman SF (1980) Current concepts in immunology: Regulation of the immune response--inducer and suppressor T-lymphocyte subsets in human beings. N Engl J Med 303:370–3.
Rizzo P et al. (2008) Rational targeting of Notch signaling in cancer. Oncogene 27:5124–31.
Rothenberg EV, Taghon T (2005) Molecular genetics of T cell development. Annu Rev Immunol 23:601–49.
Russ AP, Lampel S (2005) The druggable genome: an update. Drug Discov Today 10:1607–10.
Scholl C et al. (2009) Synthetic lethal interaction between oncogenic KRAS dependency and STK33 suppression in human cancer cells. Cell 137:821–34.
Schubbert S et al. (2007) Hyperactive Ras in developmental disorders and cancer. Nat Rev Cancer 7:295–308.

Sharma VM et al. (2006) Notch1 contributes to mouse T-cell leukemia by directly inducing the expression of c-myc. Mol Cell Biol 26:8022–31.
Sirvent A et al. (2008) Cytoplasmic signalling by the c-Abl tyrosine kinase in normal and cancer cells. Biol Cell 100:617–31.
Staal FJ et al. (2001) Transcriptional control of T-lymphocyte differentiation. Stem Cells 19:165–79.
Thompson BJ et al. (2007) The SCFFBW7 ubiquitin ligase complex as a tumor suppressor in T cell leukemia. J Exp Med 204:1825–35.
van Es JH et al. (2005) Notch/gamma-secretase inhibition turns proliferative cells in intestinal crypts and adenomas into goblet cells. Nature 435:959–63.
Verdine GL, Walensky LD (2007) The challenge of drugging undruggable targets in cancer: lessons learned from targeting BCL-2 family members. Clin Cancer Res 13:7264–70.
Walensky LD et al. (2004) Activation of apoptosis in vivo by a hydrocarbon-stapled BH3 helix. Science 305:1466–70.
Wei G et al. (2006) Gene expression-based chemical genomics identifies rapamycin as a modulator of MCL1 and glucocorticoid resistance. Cancer Cell 10:331–42.
Weng AP et al. (2004) Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. Science 306:269–71.
Weng AP et al. (2006) c-Myc is an important direct target of Notch1 in T-cell acute lymphoblastic leukemia/lymphoma. Genes Dev 20:2096–109.
Wong GT et al. (2004) Chronic treatment with the gamma-secretase inhibitor LY-411,575 inhibits beta-amyloid peptide production and alters lymphopoiesis and intestinal cell differentiation. J Biol Chem 279:12876–82.
Yilmaz OH et al. (2006) Pten dependence distinguishes haematopoietic stem cells from leukaemia-initiating cells. Nature 441:475–82.
Zweidler-McKay PA, Pear WS (2004) Notch and T cell malignancy. Semin Cancer Biol 14:329–40.

http://www.springer.com/978-0-387-69060-5

Molecularly Targeted Therapy for Childhood Cancer
Houghton, P.J.; Arceci, R.J. (Eds.)
2010, XVIII, 536 p., Hardcover
ISBN: 978-0-387-69060-5