Genetic Targets in Pediatric Acute Lymphoblastic Leukemia

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Abstract Acute leukemia represents 31% of all cancers diagnosed in children and 80% of it is of Lymphoblastic type. Multiple genetic lesions in the hematopoietic progenitor cells prior to or during differentiation to B and T cell lead to development of leukemia. There are several subtypes of Acute Leukemia based on chromosome number changes, the presence of certain translocations and gene mutations, each of which has different clinical, biological and prognostic features. High throughput genomic technologies like array-based comparative genomic hybridization (array-CGH) and single nucleotide polymorphism microarrays (SNP arrays), have given us insight through a very detailed look at the genetic changes of leukemia, specifically, ALL. Here, we discuss various genetic mutations identified in Acute Lymphoblastic Leukemia. We also explore various genetic targets and currently available as well as upcoming targeted therapies for ALL.

Keywords Pediatric ALL • B-cell • Immunophenotype • Fanconi anemia • Down's syndrome • Bloom's syndrome • Ataxia telangiectasia • Neurofibromatosis • Leukemia • ALL • Array CGH • SNP • RUNX1 • MLL • BCR-ABL • IKZF1 • CRLF2 • E2A-PBX1 • E2A-HLF • FLT3 • Ras • Gamma sectretase • TKI • ETV6-RUNX1 • Dasatinib • Ikaros • TdT • JAK mutation • STAT • PAX5 • NOTCH • FBXW7 • PTEN • PI3K • Akt • LMO1 • TAL1 • HOX11 • MYB

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Introduction

Acute leukemia is the most common malignancy of childhood. It represents 31% of all cancers diagnosed in children [1]. About 3,250 cases of acute leukemia are diagnosed per year in United States. Approximately 80% of the childhood acute leukemia is lymphoblastic. 80% of Lymphoblastic leukemia in children between ages 2–10 years is of Pre B- cell immunophenotype and the rest are T cell lineage. Adolescents and young adults tend to have myeloid malignancies. There are several subtypes within these broad subgroups based on chromosome number changes, presence of certain translocations and gene mutations. Each of these subtypes have different clinical, biological and prognostic features.

Etiology and Pathogenesis

Exact etiology and pathogenesis of all types of childhood leukemia is still unknown. Only less than 5% cases are explained by inherited, predisposing genetic syndromes, such as Down's syndrome, Neurofibromatosis, Fanconi anemia, Bloom's syndrome, ataxia-telangiectasia, and Nijmegen breakage syndrome, or exposure to ionizing radiation or to specific chemotherapeutic drugs. There is evidence suggesting a prenatal origin for some types of childhood leukemia [2, 3]. Multiple genetic lesions in the hematopoietic progenitor cells prior to or during differentiation to B and T cell lead to development of leukemia. These mutations affect their ability of unlimited self renewal which leads to arrest at that specific developmental stage. Understanding the outcomes of frequently arising genetic lesions and their effects on cell survival, proliferation and differentiation will help researchers then to devise selectively targeted treatments against the altered gene products to which the leukemic clones have become addicted.

Current Treatment and Need for Targeted Therapy

About 60 years back, acute leukemia was universally fatal. Thanks to multicenter, national and international clinical trials, collaborations and basic science research, tremendous progress has been made in this field which has made childhood leukemia a success story of twentieth century. Cure rate for leukemia has increased from 10% to nearly 85% [4].

Current treatment of leukemia is based on intense multiagent chemotherapy and prophylaxis of central nervous system. Risk assessment and treatment allocation is made based on clinical features (age and white cell count at diagnosis), biological features (B or T cell immunophenotype) and response to initial treatment (morphological and minimal residual disease in bone marrow at the end of induction therapy) [5].

Despite high cure rate, nearly one quarter of children with leukemia of certain molecular subtypes, high risk clinical features and those who relapse, have poor outcome. Significant proportions of the children who fall into standard risk category (age 1–10 years and total white count at diagnosis <50,000 and Precursor B cell Immunophenotype) have treatment failure or relapse [6]. Outcome of these children is poor, despite intense chemotherapy and/or allogenic hematopoietic stem cell transplant. Relapsed ALL is a leading cause of cancer related death. There is little room for intensification of already intense chemotherapy due to dose limiting toxicities and related morbidity and mortality. There is need for development of new targeted therapies which can improve outcome in this group of patients and have less side effects [7].

Molecular Genetics of Acute Lymphoblastic Leukemia (ALL)

It is very important to indentify genetic and epigenetic abrasions of prognostic importance in order to assign the patients to modern classification protocol and offer treatment [8, 9]. About 25% of the primary genetic lesions in ALL cannot be detected by standard genetic analysis. Currently, high throughput genomic technologies like array-based comparative genomic hybridization (array-CGH) and single nucleotide polymorphism microarrays (SNP arrays), have given us insight into very detailed look at the genetic changes of leukemia, specifically, ALL. Multiple novel submicroscopic genetic alterations in ALL samples which are not detectable by cytogenetic analysis have been identified [10]. Highly informative array-CGH using bacterial artificial chromosomes (BACs) typically use probes derived from large (up to 200 kb) fragments of human DNA cloned into BAC vectors [11]. Oligo nucleotide arrays use smaller probes (20–100 bp) for more detailed look at the genomic regions. Oligo CGH array is used for detection of copy number abnormality (CNA) and Single nucleotide polymorphism (SNP) array is used to detect both CNA and copy neutral Loss of Heterozygosity (LOH).

Table 1 shows important genetic alterations seen in B-cell and Table 2 shows important genetic alterations indentified in T cell ALL. Figure 1 shows important intracellular pathways, targets and corresponding therapeutic agents that are under investigation. We will discuss below in detail about some of the most important genetic alterations.

ETV6-RUNX1

ETV6-RUNX1 formerly known as TEL-AML1, is translocation (12; 21) resulting in fusion of the *ETV6* gene from chromosome band 12p13 to the *RUNX1* gene from chromosome band 21q21. It is associated with recruitment of complexes containing

Table 1 Genetic abnormalities identified in B cell ALL

Genetic sub type	Clinical relevance
Hyperdiploidy (>50 chromosomes)	Good prognosis with therapy
ETV6-RUNX1 t(12;21)	Prenatal translocation, good prognosis with chemotherapy
MLL rearrangement t(4,11)(q23;p13); t(11:19); t(9:11)	Eighty percent infant leukemia, poor prognosis, over expression of FLT3
BCR-ABL t(9:22)	Poor prognosis; associated *IKZF1* or *CDKN2A* deletions
IKZF1 deletion/mutation	25 to 30% of B cell ALL and 80% of BCR-ABL + ALL; increased risk of relapse
JAK mutations	Predominantly in High risk leukemia; potential response to JAK 2 inhibitors
CRLF2 overexpression	Poor prognosis; 55% of Down syndrome ALL
PAX 5	Mutations found in 31% of pediatric ALL (43)
E2A-PBX1 t(1:19)	Associated with poor prognosis
MYC t(8,14);t(2,8);t(8,22)	Favorable prognosis
Internal amplification of Chromosome 21	Common in older children, poor outcome
E2A-HLF	Adolescent presentation, hypercalcemia, and disseminated intravascular coagulation

Table 2 Important genetic alterations identified in T cell ALL

Genetic sub type	Clinical relevance
TAL1/SCL t(1;14)	~30% of ALL; Good prognosis
HOX11L2 (5q35)(TLX3)	Poor prognosis in some studies
HOX11(10q24)	Favorable prognosis
NOTCH/FBXW7	Intrageneic gain of function mutation in ~55%; potentially responsive to NOTCH inhibitor
PTEN-P13K-AKT	Resistance to Gamma secretase inhibitor
CDKN2A/2B	?response to DNA methylation inhibitors
LMO1 & LMO2	Good prognosis in some studies, response to HDAC inhibitors
IKAROS	Mutation/deletion in 5–10% T cell ALL

histone deacetylases to AML1 target genes, causing aberrant transcriptional repression [11–15]. It is the most common chromosomal translocation seen in children with 'Common Precursor B cell ALL' (25%) but rarely observed in T cell ALL [12]. It is cryptic by conventional karyotyping but detected by FISH or molecular analysis. Translocation (12;21) [12, 16] was noted in a large number of archived neonatal blood samples suggesting prenatal origin but, only 1% actually developed T cell leukemia indicating that additional mutations later in life are necessary for leukemogenesis [2, 3]. ETV6 -RUNX1 is known to be associated with favorable outcome [12].

Fig. 1 Cellular pathways and genetic targets with corresponding inhibitors under investigation for targeted therapy of leukemia

BCR-ABL

The Philadelphia chromosome is characterized by the abnormal transposition of the q34 portion of chromosome 9 and the q11 portion of chromosome 22. A reciprocal translocation causes a head to-tail fusion of the breakpoint cluster region (*BCR*) gene on chromosome 22 with the cellular homolog of the Abelson (*c-ABL*) viral oncogene on chromosome 9, thereby placing the *BCR-ABL* oncogene under the control of the ubiquitously expressed *BCR* promoter. *BCR-ABL* encodes two main BCR-ABL fusion oncoproteins of distinct molecular weights, p190 and p210, that arise from different translocation breakpoints in the *BCR* gene. The p210 isoform is expressed in nearly one third of adult Ph+ B-ALL, with the other 2/3rd of adult Ph+ B-ALL expressing the p190 isoform. Approximately 90% of childhood Ph+ B-ALL cases express p190 [17]. BCR-ABL1 positive ALL is highly aggressive and has a poor prognosis [18, 19]. BCR-ABL is seen in 25–40% of adult CML and 3–5% of pediatric B cell -ALL.CML typically responds well to kinase inhibitors. BCR-ABL is a deregulated, constitutively active non receptor tyrosine kinase, and this kinase activity is required for cell transformation. BCR-ABL promotes leukemia mainly through two signal transduction pathways (RAS-MAPK and

PI3K-AKT) that control cell proliferation, size, survival, and activation [20]. The constitutively active BCR-ABL1 cell impedes programmed cell death by keeping pro apoptotic protein in phosphorylated state and impeding it from localizing to mitochondria [21].

Targeted Therapy for BCR-ABL

Prior to use of tyrosine kinase inhibitors, BCR-ABL positive ALL was one of the worst prognostic groups in pediatric ALL [16]. Imatinib Mesylate is a small orally available molecule which acts by binding to the ATP binding site of tyrosine kinase and stabilizing the inactive conformation. Imatinib showed remarkable a result in adults with CML. It is the best available first line therapy for CML in chronic phase [22]. Combination of Imatinib with chemotherapy in adults with Ph+ ALL showed encouraging results but the results were short lived when used as single agent. Children's oncology group (COG) clinical trial COGALL0031 conducted between 2002 and 2006 used Imatinib in children with Ph+ ALL starting after induction chemotherapy. It showed 3 years EFS of 80% which is more than double the EFS of historic control group treated without tyrosine kinase inhibitor (TKI) in the past [23]. The outcome has remained stable in this patient cohort .

Dasatinib is a second generation TKI with potent BCR-ABL kinase inhibitor activity and active against most Imatinib resistant BCR-ABL-mutants (except T3135). Dasatinib also inhibits SRC kinase and is an attractive therapy in Ph+ ALL . Unlike CML, signaling through Src family kinases is required for development of leukemia. COG study AALL0622 is now testing addition of Dasatinib to same intense chemotherapy regimen.

MLL Rearrangement

The *mixed lineage leukemia* (*MLL*) gene encodes a large complex oncoprotein that regulates transcription.MLL methylates histone H3 lysine 4 (H3K4) and regulates gene expression (especially *HOX* family gene expression) to control early hematopoietic progenitor cell development. MLL gene rearrangements are seen in over 80% of Infant leukemia and 10% of childhood ALL cases [24, 25]. More than 40 different balanced chromosomal translocations have been identified as partners for *MLL* in ALL. The five most common *MLL* rearrangements, seen in *MLL*-translocated leukemia are,

t (4; 11)(q21;q23)-encoding MLL-AF4 (seen in 70% cases)
t (11; 19) (q23;p13.3)-encoding MLL-ENL (seen in 13% cases),
t (9; 11)(p22;q23)-encoding MLL-AF9,
t (10; 11) (p12;q23)-encoding MLL-AF10,
t (6;11)(q27;q23)-encoding MLL-AF6.

FLT3

FLT3 in-frame deletions and internal tandem duplications (ITDs) in the juxtamembrane region and point mutations in the activation loop of the kinase domain results in FLT3 protein over expression and constitutive activation of FLT3 signaling pathways through STAT5, MAP kinase, and AKT. FLT3-ITD mutations are found in approximately 2% of childhood ALL and are associated with poor prognosis. Lestaurtanib is a selective FLT3 inhibitor which has shown promising results in primary infant leukemia and ALL cells with high expression of constitutively activated FLT3. In COG phase three study AALL0631, Lestaurtanib followed by chemotherapy is being tested in infants with MLL rearranged leukemia.

IKZF1

Ikaros encodes a tumor suppressor zinc finger protein that is involved in heritable gene silencing. In hematopoietic cells, Ikaros localizes to pericentromeric heterochromatin (PC-HC) where it recruits its target genes, resulting in their activation or repression via chromatin remodeling [26–28]. The function of Ikaros is controlled by posttranslational modifications. Ikaros is shown to be phosphorylated by CK2 kinase at its C terminus, affecting cell cycle progression [29–31]. Reversible phosphorylation of Ikaros at specific amino acids controls its sub cellular localization as well as its ability to regulate TdT expression during thymocyte differentiation. PP1 regulates thymocyte differentiation by controlling Ikaros' association with chromatin remodeling complexes and its ability to repress the transcription of developmentally regulated genes [32, 33].

Deletion or sequence mutation of the IKZF1 gene, is a hallmark of HR childhood ALL [34, 35]. Deletion of IKZF1 is present in over 80% of cases of BCR-ABL+ lymphoid leukemia, either de novo Ph+ ALL or chronic myeloid leukemia (CML) at progression to lymphoid blast crisis. The deletions either involve entire IKZF1 locus, resulting in loss of function, or delete an internal subset of IKZF1 exons, resulting in the expression of dominant negative IKZF1 alleles. Expression of such dominant negative IKZF1 alleles in hematopoietic progenitors impairs lymphoid development, and loss of IKZF1 accelerates the onset of Ph+ ALL in a retroviral BM transplant and transgenic models of this disease [36]. BCR-ABL negative ALL cases with deletion or sequential mutation of IKZF1 have are shown to have higher chance of treatment failure [37, 38].

JAK Mutations

The Janus kinase (JAK) family of tyrosine kinases is activated by cytokine binding to a Type I cytokine receptor. Activation of JAK leads to phosphorylation of STAT, and subsequent activation of both the RAS/RAF and PI3K/AKT pathways, ultimately

leading to cell proliferation. In ALL cell lines, members of this JAK family are abundantly expressed. JAK2 has been noted to be expressed more frequently than JAK1 or JAK [39, 40]. Constitutively active JAK/STAT results in uncontrolled proliferation of leukemia cells and has been associated with poor prognosis [41]. Activating mutations of JAK also correlate with other gene abnormalities, IKZF1 deletion or mutation and genomic rearrangement involving the Cytokine receptor-like factor 2 gene (CRLF2) which results in its over expression, both of which confer poor prognosis. JAK family of kinases, are mutated in Down syndrome-ALL and High risk non-DS ALL. Inhibitors targeting JAK pathways are currently being tested in clinical trials for adults. INCB018424 is a competitive ATP inhibitor that binds to the catalytic domain of JAK1/2. This agent is known to inhibit both wild-type and mutated JAK proteins. COG trial ADVL1011 is a single-agent phase I trial for children with relapsed/refractory solid tumors, leukemias, and myeloproliferative neoplasms.

CRLF2 is a subunit of the type I cytokine receptor, which forms a heterodimer with interleukin seven receptor (IL7R). Cytokine binds to the receptor and stimulates B-cell proliferation. Rearrangements involving CRLF2 have causes constitutive dimerization with IL7R, resulting in cytokine-independent activation of JAK2 and STAT5. This leads to subsequent B-cell proliferation, and possibly cell transformation, especially in the presence of a constitutively activated JAK mutation [41]. Targeting cells with activated JAK mutations may help to improve prognosis for patients with IKAROS mutations and CRLF-2 over expression because of the known high-frequency association of these abnormalities. 30% of childhood 'BCR-ABL1-like' ALL cases harbor rearrangements of the lymphoid cytokine receptor gene CRLF2, either alone or with concomitant mutation of the Janus kinase genes JAK1 and JAK2 [40–42].

PAX 5 Mutations

PAX5 encodes a gene required for B lymphoid lineage maturation. Recent SNP array and genomic DNA sequencing on B cell ALL samples have shown deletion and point mutation in 32% of cases [43]. Altered PAX5 may cause differentiation blockade in B cell development by targeting transcription factor genes known to be involved in B and T cell differentiation (IKAROS -IKZF1, and AIOLOS -IKZF3) [44–46].

E2A-PBX1

Translocation (1;19) is found in 3–5% of B-ALL cases. *E2A* encodes class I b Helix-loop -Helix (HLH) E47 and E12 E-box transcription factors that regulate the common lymphoid progenitor (CLP) to pre-pro-B cell transition in early B cell development. At (1; 19) (q23; p13) fuses the *PBX1* class II divergent *HOX* gene to *E2A* which encodes a chimeric transcription factor that binds and sequesters normal

PBX partners leading to repression of E2A target genes. This leads to uncontrolled cell-cycle progression [47]. This translocation is mostly seen in cytoplasmic Immunoglobulin positive (cIg+) Pre B ALL rather than cIg negative B -ALL and is associated with poor prognosis in those cases.

E2A-HLF

Translocation (17; 19) *E2A* variant translocation occurs in 1% of cases of childhood B-cell precursor ALL, which creates an *E2A-HLF* (hepatic leukemia factor) fusion gene. The novel chimeric transcription factor E2A-HLF promotes aggressive, treatment-resistant pro–B cell stage ALL that shows unique clinical associations including adolescent presentation, hypercalcemia, and disseminated intravascular coagulation [48].

TAL1/SCL

TAL1 (SCL) gene at Chromosome band 1p34 encodes a class II basic Helix loop helix (bHLH) transcription factor that is a master regulator of hematopoietic lineage commitment. *SCL* is a target for translocation or mutation in nearly 25–30% of childhood T-ALL cases. Translocation t(1;14)(p34;q11), and deletions aberrantly activating *SCL* during thymocyte maturation causes leukemia by promoting transformation.

Homeobox (HOX) Genes

Homeobox genes regulate axial patterning and cellular differentiation during embryonic development. HOX A cluster which belongs to Class I HOX is implicated in T cell leukemia.

HOX11 (also known as *T cell leukemia*, *homeobox 1* and *TLX1*) is a class II orphan *HOX* gene that is normally required for survival of splenic precursors during organogenesis. Translocation t(10;14)(q24;q11) or t(7;10)(q34;q24), causes juxtaposition of HOX11 to *TCR* α/δ- or *TCR* β-loci regulatory elements leading to increased expression of HOX11. Over expression of HOX11 is found in about 5% of pediatric T cell-ALL. Loss of negative regulatory elements with cytogenetic rearrangements or by loss of silencing DNA methylation also causes aberrant HOX expression. HOX11-containing T-ALL has a better prognosis than other T-ALL subtypes [17, 49–51].

HOX11L2 (*TLX3*) is another well-studied class II orphan *HOX* gene that undergoes a t(5;14)(q35;q32), bringing it under the influence of *TCR*α-/δ-regulatory elements downstream of *BCL11B* (a gene expressed throughout T cell development) in ~20% of children with T-ALL and these cases have less favorable prognosis compared to HOX11 positive T cell ALL [16–52].

NOTCH1

NOTCH is a transmembrane heterodimeric receptor. Sequentially cleavage of NOTCH by an ADAM metalloproteinase and then c-secretase, releases the intracellular domain Notch1 (ICN1). There it forms a transcription complex which functions as a transcription activator that regulates T-cell development in normal cells, and has been shown to activate transcription of genes such as MYC and NFKB1. Translocation t (7; 9) (q34; q34.3), fuses *TCRB* to the gene encoding the NOTCH1 and is extremely uncommon. It is found in less than 1% of T cell ALL. Gain-of-function intrageneic mutation in NOTCH1 were recently discovered in ~55% of translocation negative T-ALL cases, which results in ligand-independent cleavage of Notch1 [53, 54]. This process still needs gamma secretase proteolysis to release active ICN1 which makes Gamma secretase Inhibitors (GSI) attractive therapy for NOTCH1 altered T cell ALL. GSIs are under development, and being tested in phase I trials [55–57].

PTEN

PTEN is a tumor suppressor with lipid and protein phosphatase activity that opposes the receptor tyrosine kinase–PI3K-induced activation of AKT. *PTEN* is mutated and is the most consistently down regulated gene in GSI-resistant T-ALL cell lines. Gain-of-function *NOTCH1* mutations and mutational loss of *PTEN* are associated with resistance to GSIs in T-ALL. This is because the malignant clone transfers its oncogene addiction from constitutive NOTCH1 signaling to constitutive PI3K-AKT signaling.

FBXW7

FBW7 (F-box- and WD repeat domain–containing 7) is a protein substrate recognition subunit of the SCF-type E3 ubiquitin ligases. It is mutated in a wide range of human cancers, where it functions as a tumor suppressor. FBW7 mutation block FBW7-mediated ICN1 and possibly MYC degradation, leading to excessive NOTCH pathway signaling [58, 59]. FBW7 mutations make T-ALL cell lines and relapsed T-ALL insensitive to GSIs. Mechanism for drug resistance that is potentially related to stabilization of MYC expression. FBW7 mutations may also coexist with NOTCH1 heterodimerization–domain mutations to further augment NOTCH pathway signaling [59].

LYL1

LYL1 encodes another class II basic helix loop helix transcription factor that forms heterodimers with class I bHLH proteins, such as E2A (E47 and E12) and HEB. *LYL1* was identified from a t(7;19)(q35;p13) in a T cell leukemia line and is aberrantly expressed in only a few T-ALL cases [17, 59, 60]. LYL1 has an unknown cellular function, but it has an overlapping expression pattern with TAL1.

MYB

MYB is the cellular homolog of the *v-Myb* oncogene which is essential for T cell development in mouse. Translocation and duplication involving MYB is detected in 8–15% of T cell ALL cases leading to *MYB* over expression and a blockade in T cell differentiation. Translocation t(6; 7)(q23;q34), juxtaposes the *C-MYB* gene at chromosome band 6q23 with the *TCRB* locus. Interestingly, translocation t(6; 7) is noted in younger children with T cell ALL. These cases also contain NOTCH1 mutations and CDNK2A p16 ARF deletions. This translocation is readily detectable by FISH but not by conventional karyotyping due to subtelomeric location of C-MYB and TCRB.

LMO1 and LMO2

LMO1 and LMO2 are oncogenic transcription factors, when fused to different TCR loci lead to unscheduled expression of the respective transcription protein. *LMO1* (e.g., *RBTN1, TTG1*) and *LMO2* (e.g., *RBTN2, TTG2*) genes encode cysteine-rich tandem LIM–only domain-containing proteins that interact with a variety of nuclear factors, including TAL1 in erythroid cells. LMO 2 translocations occur in 10–20% T cell ALL cases.

Conclusion

Detailed information about genetic alterations in Leukemia is being generated as a result of high throughput genomic analysis tools and many potential targets for therapy have been identified. Ideal 'target' is a protein or pathway which is specific to the tumor cell, not shared by normal cells, essential for tumor cell maintenance and/or proliferation and is easily accessible by therapeutic agent. Understanding these targets will help us identify and develop best targeted therapies for childhood leukemia.

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