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REVIEW ARTICLE

Mutagenic players in ALL progression and their associated signaling pathways

Saadiya Zia, Ramla Shahid*
Department of Biosciences, COMSATS University, Islamabad, Pakistan

Abstract

An alarming increase in acute lymphoblastic leukemia among children and males has drawn attention of investigators to delve into the genetic causes of ALL and to discover new therapeutic strategies with better prognosis. Although the survival rate in children is much higher than adults, but there's a need to find new potential molecular targets with better treatment outcome. Genomic profiling has made it possible to identify various genetic defects important for driving leukemogenesis. Study of the genetic lesions not only give a better understanding of genes function but also helps to target various signaling pathways involved in disease progression. The current review provides an overview of important genetic defects and dysregulation in their downstream signaling pathways in acute lymphoblastic leukemia.

Keywords Acute lymphoblastic leukemia, Genetic defects, Molecular targets, Signaling pathways.

Introduction

ALL is considered a global burden for adults and children as it represents one third of childhood malignancies. It is estimated that by 2020, the incidence of ALL will increase from 0.4 to 2 per 100,000 population in South America and Asia Pacific [1]. ALL follows bimodal distribution with higher incidence reported in children, decreases with age progression and reaches a hike after 50 years of age [2]. Genetic lesions in hematopoietic progenitors, cell cycle regulators, tumor suppressors, and apoptotic inducers are critical events in leukemogenesis that transforms the normal cellular phenotype into the cancerous one. ALL is characterized by genetic alterations involving deletions, point mutations and chromosomal translocations that form fusion/chimeric proteins due to illegitimate recombination of normal genes [3]. These chimeric proteins in turn trigger tumorigenesis, however, deletion of long arm of chromosome 6 and MLL gene rearrangements are common genetic events identified in acute leukemia [4]. Leukemia initiation is therefore dependent not only on the genetic lesions, but also require oncogenic drivers for full bloom of leukemic phenotype. Down's (trisomy 21) have 20 times more risk of getting ALL than the general population [5]. Based on genetic lesions, use of new treatment strategies has improved the survival rate among ALL patients. Identification of genetic alterations in ALL thus provides an insight into the signaling pathways and has opened new avenues for therapeutic approaches. This review article highlights some crucial genetic lesions responsible for B and T-cell ALL with effect on the downstream signaling pathways.

Genetic lesions in B-cell ALL

B-cell ALL is a common hematological malignancy that accounts for 75–85% of all ALLs and is characterized by the presence of immature B cells [6]. B-cell ALL harbors genetic lesions in (a) transcription factors (BTG1, TBL1XR1); (b) signaling molecules involved in lymphoid development and differentiation (ERG1, EBF1, RUNX1, PAX5, IKZF1/2/3, TCF3, LEF1, RAG1/2); (c) cell cycle regulators and tumor suppressor genes (TP53, RB1, CDKN2A/2B, PTEN) and (d) proteins involved in cell growth (JAK1/2/3, NRAS, KRAS, IL7R, CRLF2, FLT3, PTPN11) [7] (Fig. 1). Hypodiploidy (< 46 chromosomes), hyperdiploidy (51–65 chromosomes), trisomy 4, 6, 10, 14, 18, 21, deletion of 6q arm of chromosome are common cytogenetic abnormalities reported in B-cell ALL

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* Corresponding author.
E-mail address: ramla_shahid@comsats.edu.pk

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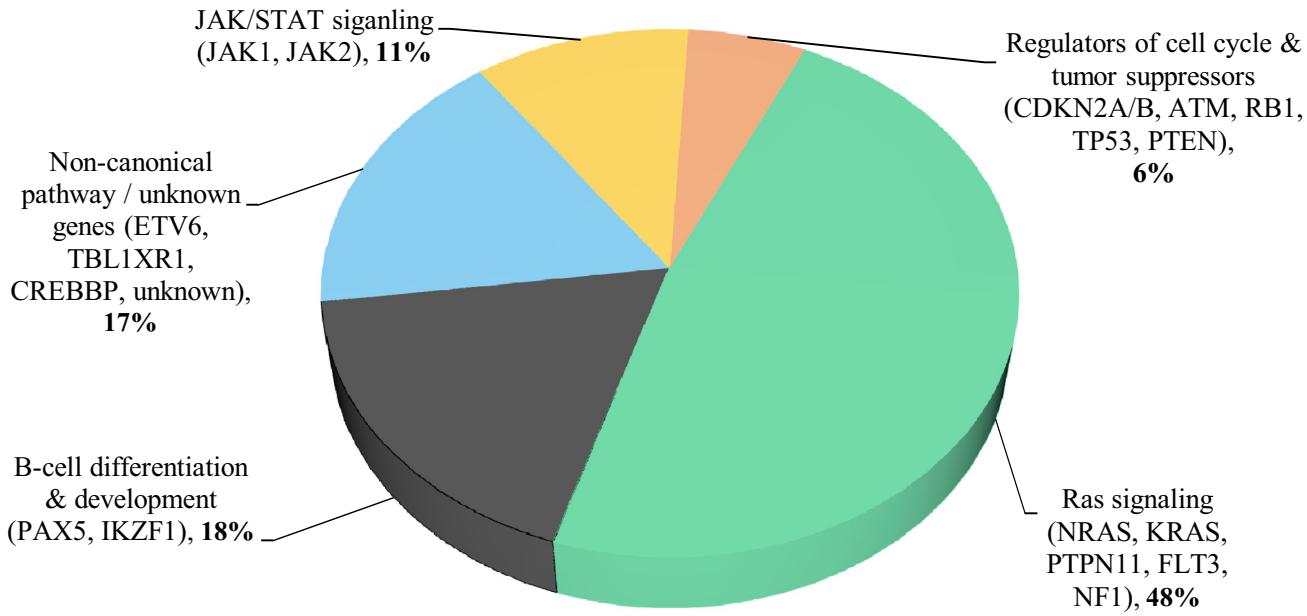

Fig. 1 Common genetic lesions reported in B-cell ALL.

[8–11]. Hypodiploidy constitutes 3% in B-cell ALL and has less favorable outcome than hyperdiploidy which is 30% [12]. Deletion in genes CDKN2A/B, RB1, CREG1, FBXW7, ETV6, SH2B3, INIP, IRF1, PDE4B, CREBBP, VPREB1, BTLA are considered hallmarks of B-cell ALL [13–15]. Development of B cells into mature form is arrested due to deletion in genes (BLNK, TCF3, LEF1 and IKZF1/3) involved in B-cell signaling [16]. In 32% pediatric B-cell ALL, PAX5 is deleted while it undergoes rearrangement with ETV6 and JAK2 in 2.5% cases [17]. TP53 is the most frequently mutated gene and a prognostic biomarker in B-cell ALL [18]. Mutations in genes of Ras signaling pathway (KRAS, NRAS, FLT3, PTPN11) are also common in B-cell ALL. In 2% B-cell ALL, chromosome 21 shows intrachromosomal amplification with the gain of 2 or 3 copies of RUNX1 with loss of subtelomeric region [19]. Mutations in ARID5B affect maturation and differentiation of B-lymphocytes and thus contributes to leukemia initiation. The most frequent chromosomal abnormality identified in adult B-cell ALL is the Philadelphia chromosome which has BCR-ABL1/t(9;22)(q34;q11.2) translocation. It occurs rarely in children and has worse prognosis [20]. MLL gene rearrangements reported in 10% pediatric B-cell ALL are associated with poor treatment outcome due to drug resistance [21]. The most common MLL gene arrangements are MLL-AF4/t(4;11)(q21;q23), MLL-AF6/t(6;11)(q27;q23), MLL-AF9/t(9;11)(p22;q23), MLL-AF10/t(10;11)(p12;q23), and MLL-ENL/t(11;19)(q23;p13.3) [22]. Fusion proteins have different prognostic significance. ETV6-RUNX1/t(12;21)(p13;q22) and Myc rearrangements t(8;14)(q24;q32)/t(2;8)(q12;q24) have favorable prognosis while TCF3-HLF/t(17;19)(q22;p13) (affects genes like LMO2, BCL2 that control cell death in lymphoid progenitors) has poor treatment outcome [23]. The frequency of different fusion proteins along with cytogenetic abnormalities and prognostic significance is shown in Table 1.

Genetic lesions in T-cell ALL

T-cell ALL is an aggressive form of leukemia as compared to B-cell ALL and has poor treatment outcome [24]. An understanding of T-cell ALL pathogenesis is essential for identification of molecular markers for diagnosis. Several oncogenes and tumor suppressor genes have been reported to alter T-cell proliferation and differentiation [25]. The common genetic events in T-cell leukemogenesis involves abnormalities in the expression of (a) transcription factor genes (TAL1/2, LYL1, LMO1/2), (b) HOXA gene clusters, (c) NOTCH signaling (NOTCH, FBXW7), (d) cell cycle regulators (CDKN2A/2B, CCND2, RB1, TP53), (e) genes involved in hematopoietic lineage (Myc, Myb, GATA2/3, WT1, BCL11B), (f) signal transduction pathways (JAK1/2/3, IL7R, FLT3, PTEN, AKT, ABL1, NRAS, NUP98) and (g) chromosomal rearrangements [13,26] (Fig. 2). TLX1 and LMO2 genes are mutated in 5% and 9% pediatric T-cell ALL [27]. Abnormal expression of TLX3 gene increase chances of relapse due to poor prognosis. Deletion of RB1 gene is commonly found in adult T-cell ALL [28]. Activating mutations in NOTCH1, JAK1, IL7R and NRAS have also been reported. NOTCH1 is the most frequently mutated gene identified in T-cell ALL as compared to JAK3, FAT1, FBXW7, NRAS, CREBBP and DNM2 [29]. Missense mutation in GATA3 gene blocks early T-cell development. Overexpression of IL7R prevents apoptosis in leukemia cells and stimulates their growth [30]. PHF6 which is a tumor suppressor gene undergoes missense, nonsense and frameshift mutations in 20–40% T-cell ALL and thereby contributes in leukemogenesis [31]. Deletion in BCL11B, PTEN, CDKN2A/2B, PTPN2 genes, del(6q), del(9)(p21), trisomy 4, are also reported in T-cell ALL [32–34]. Abnormal expression of transcriptional regulators in T-cell ALL affects TCR gene rearrangements by placing them close to enhancers and promoters [35]. In 60% T-cell ALL, TAL1 is up-regulated

Table 1 Frequency and prognostic significance of different fusion proteins identified in B and T-cell ALL.

B-cell ALL Fusion proteins	Cytogenetic abnormality	Frequency	Prognostic significance	References
BCR-ABL1	t(9;22)(q34;q11.2)	20% adults, 2–5% children	Poor	[36]
ETV6-RUNX1	t(12;21)(p13;q22	15–35%	Favorable	[37]
TCF3-PBX1	t(1;19)(q23;p13.3)	2–6%	Excellent	[12,38]
IL3-IGH	t(5;14)(q31;q32)	<1%	Poor	[39,40]
TCF3-HLF	t(17;19)(q22;p13)	1%	Poor	[13]
MLL-AF4	t(4;11)(q21;q23)	5–6% adults	Poor	[41,42]
		1–2% children	Better	
T-cell ALL				
MLL-MLLT1	t(11;19)(q23;p13)	<1%	Unknown	[35]
BCL11B-TLX3	t(5;14)(q35;q32)	13% adults, 20% children	Poor	[12,43]
TLX1-TRD	t(10;14)(q24;q11)	30% adults, 5% children	Favorable	[44,45]
ETV6-JAK2	t(9;12)(p24;p13)	<1%	Poor	[46,47]
CALM-AF10	t(10;11)(p13;q14)	5–10%	Poor	[48,49]
NUP214-ABL1	t(9;9)(q34;q34)	4–8%	Poor	[50]

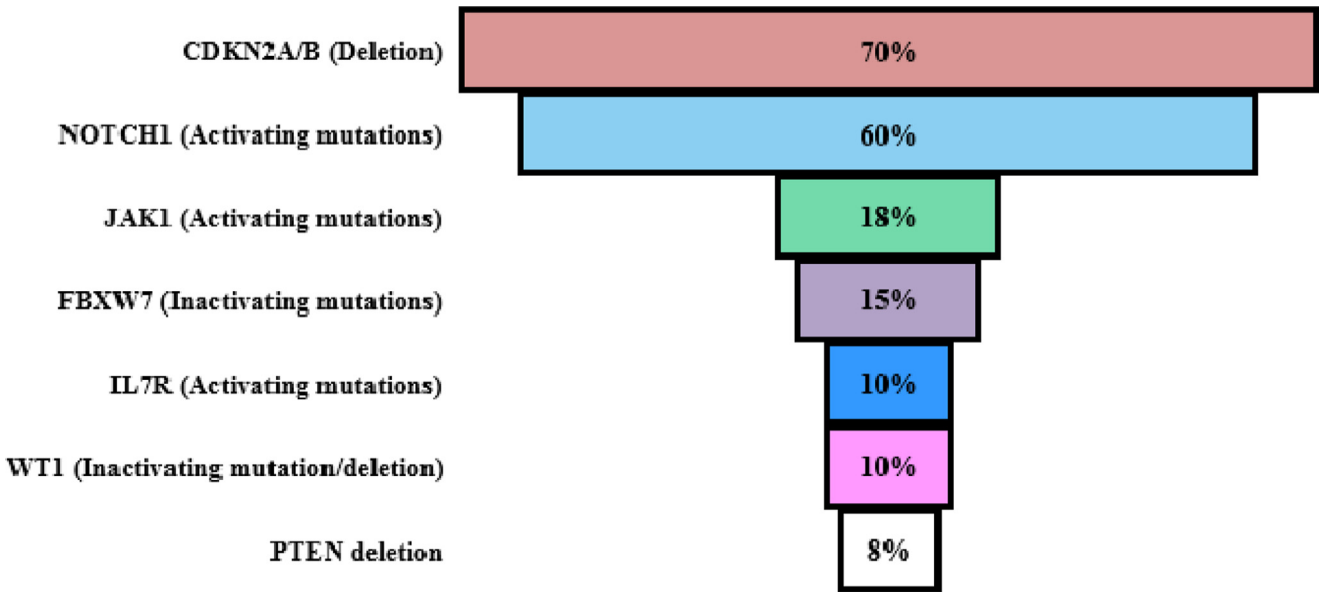

Fig. 2 Frequently mutated genes in T-cell ALL.

and undergoes rearrangement in 25% cases. In STIL-TAL1 rearrangement, TAL1 overexpression is noted as rearrangement moves it closer to STIL promoter. Similarly, in T-cell ALL, HOXA gene overexpression is related to chromosomal inversion inv(7)(p15q35) that relocates HOXA gene cluster close to TCRβ enhancer [35]. In 8% T-cell ALL, ABL1 kinase protein gets activated and produce a weak fusion oncoprotein NUP214-ABL1 that cooperates with other oncoproteins for leukemia development (Table 1). Some pediatric T-cell ALLs with TRB-CCND2/t(7;12)(q34;p13) fusion protein also show CDKN2A deletion and NOTCH1 mutations [35]. Mutation in ribosomal proteins (RPL10, RPL5, CNOT3) and epigenetic regulators (SUZ12, EZH2, KDM6A) are also considered pathogenic for initiation of T-cell ALL [25].

The current review discusses some of the important genetic lesions/mutations reported in B and T-cell signaling pathways (Table 2) (Fig. 3), their effect on downstream signaling and role in ALL initiation and development (Fig. 4). The different genetic lesions are as follows:

IL7R (Interleukin 7 receptor)

IL7R plays an important role in the development and signaling of T-cells. IL7R is a heterodimer of IL7Rα and IL7Rγ subunits. IL7Rα has an extracellular domain with conserved cysteine residues and Trp-Ser-X-Trp-Ser motif, a transmembrane domain and cytoplasmic domain. Upon IL7 ligand binding, association of JAK1 and JAK3 with α and γ subunits activates JAK/STAT, PI3K and MAPK signaling pathways (Fig. 4). The activated pathways inhibit apoptosis in leukemia cells, reduce p27 expression and upregulate BCl-2, SOCS-1, c-Myc and cyclin D1 expression [51]. IL7Rα regulates all stages of T-cell development. It is highly expressed on lymphoid progenitor and pre B-cells, downregulated on pro B-cells and ultimately absent on mature B-cells [52]. <1% B-cell ALL and 9–10% T-cell ALL occurs due to gain of function mutations in IL7Rα resulting in the constitutive activation of IL7 signaling. [53]. Ectopic expression of IL7Rα in hematopoietic stem cells and common lymphoid progenitor cells (CLPs) causes oligoclonal

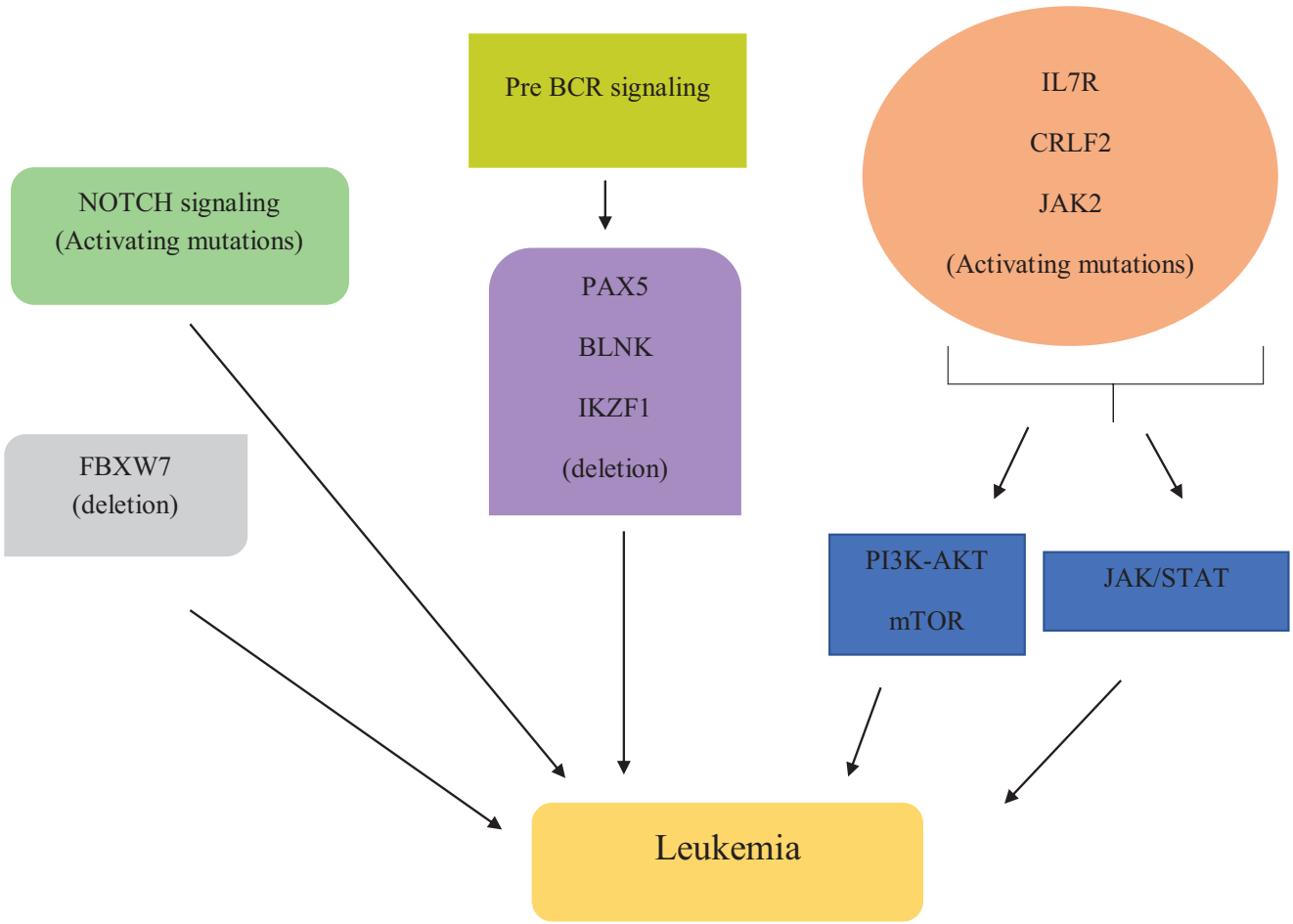

Fig. 3 Schematic representation of genetic lesions responsible for leukemia initiation.

myeloproliferative disorders and B-cell acute lymphoma/leukemia [54,55]. Shochat et al., [56] identified IL7R mutations V253G (c.847T>G), S185C (c.642A>T), 246 Ins KCH (c.828 Ins7 Del T), 244 Ins CHL (c.820 Ins10 Del C), 248 Ins CQ (c.832 Ins 7 GTCAAAG Del 13 TGAGTTTTTTCTC), 254 Ins GEA (c.849 Ins 9 GAGAGGCCG) in B and T-cell ALL patients. In pediatric B and T-cell ALL, non-cysteine mutations in IL7R transmembrane domain activates downstream signaling pathways in ligand independent manner due to receptor homodimerization [57]. Serine-to-cysteine substitutions in extracellular domain are also common in B-cell ALL [58]. High IL7R and low SH2B3 expression in B-cell ALL are associated with poor prognosis [59,60]. IL7Rα mutants Y401F, Y449F and Y456F in which cytosolic tyrosine residues are replaced by phenylalanine fail to undergo IL7 induced cell proliferation [61]. Due to mutations in exon 5 and 6 of IL7R, adult leukemics show resistance to therapy [62,63]. Mutations in exon 2 (197T>C), 4 (254G>A), 6 (755_756ins9) and 8 (1066A>G) of IL7R have also been identified in T-cell ALL patients [64]. Significant correlation between IL7R activation and E2A-PBX1 fusion protein suggests that induced IL7R in pediatric pre B-cell ALL could be used as a prognostic marker for identification of CNS relapse [65]. Studies have shown that treatment of leukemia cells having IL7R mutations with inhibitors of JAK/STAT, MEK and PI3K-AKT pathway helps to reduce leukemia cell proliferation [66,67].

CRLF2 (Cytokine receptor like factor 2)

CRLF2 also known as thymic stromal lymphopoietin receptor (TSLPR) belongs to type I cytokine receptor family. Its ligand thymic stromal lymphopoietin (TSLP) is an epithelial derived cytokine that activates dendritic cells, regulates proliferation and survival of precursor B-cells but gets downregulated in mature B-cells [68]. As cytokine receptors lack intrinsic catalytic activity so they are dependent on tyrosine kinase (Janus kinase) for their activity. Upon ligand (TSLP) binding CRLF2 dimerizes with IL7Rα (Fig. 4). JAK1 and JAK2 which are associated with IL7Rα and CRLF2 undergo phosphorylation and provide docking sites for STAT5, eventually leading to downstream activation of PI3K and mTOR pathways in T-cells and dendritic cells [69,70]. Growth and proliferation of leukemia cells with CRLF2 overexpression is dependent on activation of JAK-STAT pathway [71]. In B-cell ALL, due to gain of function mutation F232C in juxtamembrane domain, CRLF2 undergoes homodimerization and promotes growth of blast cells independent of the cytokine [72]. 50% pre B-cell ALL individuals with Philadelphia chromosome like genetic profile show poor prognosis due to CRLF2 gene rearrangement [73]. In 15% pediatric T-cell ALL, CRLF2 overexpression has been associated with stabilization of intracellular notch domain [74]. Intrachromosomal deletion in

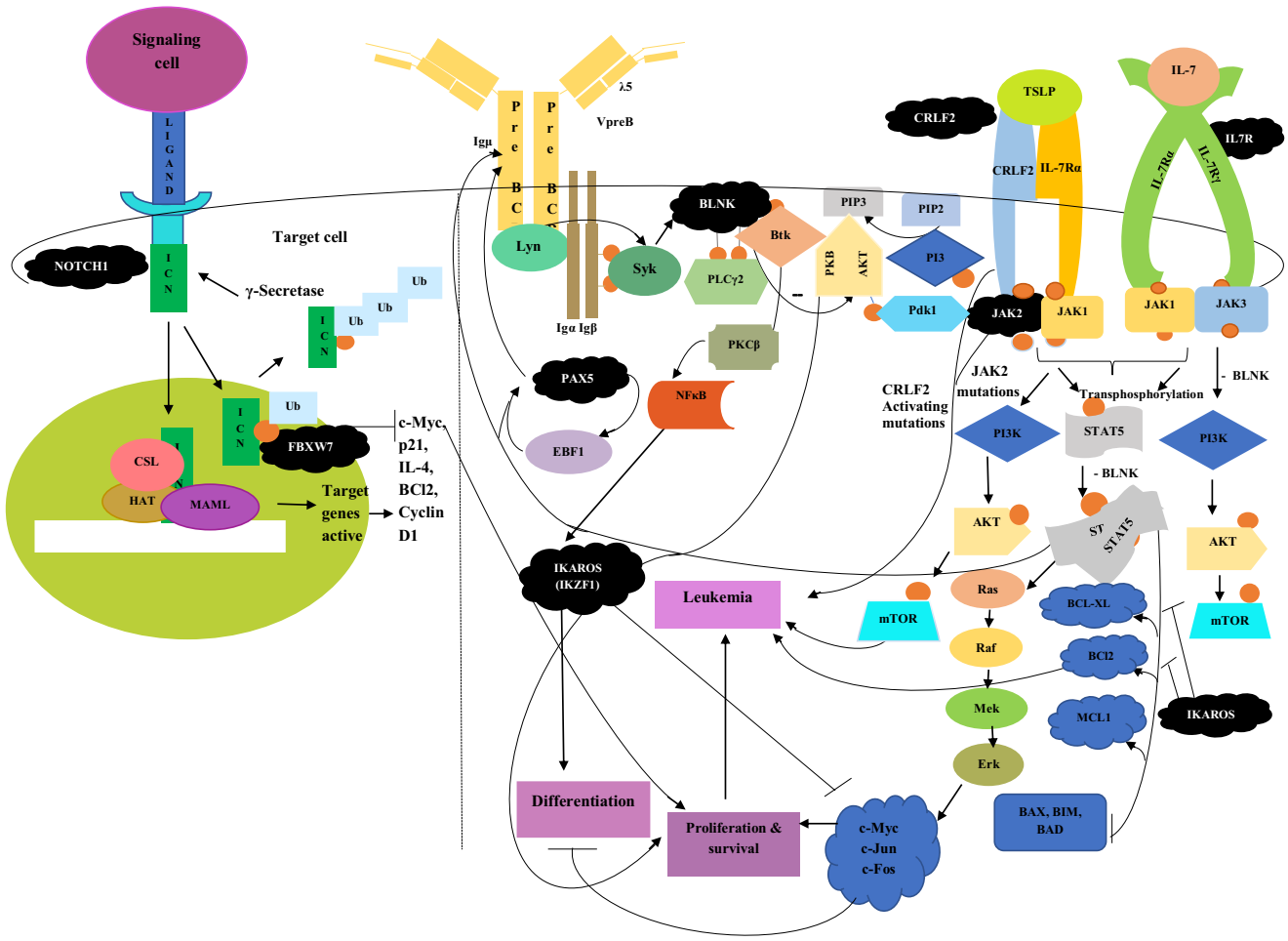

Fig. 4 Integrated B and T-cell ALL signaling pathways. [redacted] represents different molecular targets / signaling molecules with genetic lesions crucial for ALL development (discussed in the review). PAX5 expressed in B-cell lineage commitment is critical for early B-cell development. Both EBF1 and PAX5 co-operate with each other in regulating several components of pre-BCR signaling. In pre-BCR signaling, adapter protein BLNK is important for pro to pre B-cell transition. BLNK induces NFκB which in turn up-regulates Ikaros, ultimately leading to pre B-cell differentiation. BLNK is also a negative regulator of IL7R signaling which is important for leukemia cell proliferation and survival. When IL7R present on pre B-cells is activated, JAK/STAT pathway is stimulated that subsequently leads to proliferation and survival of pre B-cells. In leukemia, activating mutations in IL7R, CRLF2 and JAK2 play critical role in B-cell leukemogenesis. NOTCH signaling is important for T-cell lineage commitment. Ligand binding with the extracellular notch domain mediates cleavage of intracellular notch domain by metalloproteinase and γ-secretase. The intracellular notch domain translocates to the nucleus where it controls c-Myc activation and cell cycle regulation. Binding of FBXW7 with intracellular notch domain mediates proteasomal degradation of NOTCH1 and its target genes. CSL = Citrate Synthase like, MAML = Mastermind Like Transcriptional Coactivator, HAT = histone acetyltransferases, ICN = Intracellular Notch domain, Ub = ubiquitinylated, [redacted] = phosphorylation.

pseudoautosomal region 1 (PAR1) of X and Y chromosomes juxtaposes the first exon of P2RY8 (P2Y purinoceptor 8) gene with the coding region of CRLF2 gene [75]. This juxtaposition cause CRLF2 overexpression due to the formation of CRLF2-P2RY8 fusion protein. In IGHα-CRLF2 fusion protein, CRLF2 gene undergoes translocation with IGHα enhancer [76,77]. This translocation results in poor prognosis due to elevated CRLF2 expression [78]. CRLF2 overexpression is associated with the formation of 48% CRLF2-P2RY8 fusion protein, 18% IGHα-CRLF2, whereas in 20% cases CRLF2 show gain of function mutations [79]. Individuals with CRLF2-P2RY8 and IGHα-CRLF2 fusion proteins often show IKZF1 gene deletion [80]. Ikaros controls CRLF2 regulation as it binds to the CRLF2 promoter. Patients with IKZF1 deletion show significantly higher CRLF2 expression than those with IKZF1 gene. CRLF2 overexpression can be suppressed by casein kinase II (CK2) inhibitors which are known to increase Ikaros activity [81]. In a recent study, inhibition of both JAK/STAT and mTOR pathways has produced robust antileukemic affect in CRLF2 rearranged Ph like B-cell ALL [82]. In BCR-ABL1$^-$ B-cell ALL, CRLF2 overexpression and IKZF1 deletion are associated with poor survival outcome [83]. CSF2RA-CRLF2 is a unique fusion transcript, identified in pediatric ALL, in which CRLF2 shows overexpression (although its promoter

is deleted) due to the presence of CSF2RA enhancer [84]. High expression of CRLF2 makes it an important prognostic marker for identification of high risk leukemia [85].

JAK2 (Janus kinase 2)

JAK2 is an intracellular non-receptor tyrosine kinase that mediates cytokine signaling [86]. Ligand binding with the cytokine receptor activates JAK-STAT pathway that regulates genes like SOCS, CCND1, Myc, BCL-X_L and p21 involved in cell proliferation and survival (Fig. 4). In hematological malignancies, JAK2 either undergo gain of function mutations or chromosomal translocation [87]. Activating mutations in JAK2 stimulates JAK2/STAT5 pathway for leukemia development. JAK2 activating mutations include V617F, R683G, R683S, L611S, H574R, Y613E, Y931C, E864K, I682F, I682T, R867Q, D873N, T875N, P933Q and G935R [88–97]. In B-cell ALL, CRLF2 overexpression has also been noted with JAK2 mutations [72]. 20% DS-ALL with JAK2 mutations mostly die in remission phase while JAK2 mutations in BCP-ALL are associated with poor treatment outcome [98]. JAK2 mutations R683I and R683G have been identified in acute lymphoblastic leukemia cell lines YCUB-5 and KOPN49 in addition to IKZF1 deletion, and KRAS mutations [99]. In acute leukemias and myeloproliferative neoplasms JAK2 undergoes rearrangement with genes like ETV6, SSBP2, PCM1, PAX5, STRN3, and BCR [100]. PAX5-JAK2 translocation in B-cell ALL blocks B-cell differentiation and inhibits apoptosis [101]. When pericentriolar material (PCM1) gene encoding centrosomal protein with multiple coiled-coil domain undergoes t(8;9) translocation with JAK2, PCM1-JAK2 fusion transcript is formed [102]. In T-cell ALL, TEL-JAK2 translocation causes constitutive activation of STAT pathway and promotes leukemia cell growth and survival even in the absence of cytokine [46]. In B-cell ALL, R938Q mutation in JAK2 kinase domain close to ATP loop confers resistance to ATP-competitive JAK2 type I inhibitor ruxolitinib [103]. Studies have shown that JAK2 type II inhibitor CHZ868 not only stabilize the inactive conformation of JAK2 but also kill JAK2 mutant cells [104]. JAK2 signaling is therefore an important target to prevent growth and proliferation of leukemia cells.

BLNK (B-cell linker)

BLNK, also known as SLP65 or BASH, is an adaptor protein involved in BCR signaling. BLNK is homologous to SLP76 protein found in T-lymphocytes [105]. BLNK has SH2 domain, proline rich region, and 13 Tyr phosphorylation sites. In pre B-cells, ligand binding with pre BCR activates phosphorylation of BLNK tyrosine residues that provides docking sites for downstream signaling proteins like Btk, PLCγ, Nck, Grb2 and Vav [106–108] (Fig. 4). BLNK acts as a tumor suppressor protein by inhibiting JAK-STAT pathway and regulates survival and proliferation of normal B cells [109]. Mutation in BLNK gene blocks pro to pre B-cell transition and results in immunodeficiency. In BLNK deficient mice, autocrine production of IL7 promotes leukemogenesis in pre B-cells due to activation of JAK3/STAT5 pathway. [110,111]. Y176 and Y204 tyrosine residues of BLNK are important for its interaction with JAK3. Alteration in these Tyr residues prevents its interaction with JAK3 and downstream signaling molecules [109,112]. BLNK expression is lost in 50% pediatric B-cell ALL due to incorporation of alternative exon in BLNK transcript, leading to premature translation termination and inhibition of pre B-cell differentiation [113]. H431N (c.1291C>A) missense mutation in BLNK gene has been identified in high risk pediatric ALL's [114]. Due to mutations c.435_436delTCInsA p.E145fs25*, c.844C>T p.R282X, c.30C>A p.P10P/c.47+3 A>T and c.367C>T p.R123X in BLNK gene, B cells undergo developmental arrest at pre B1/B2 stage [115,116]. In pre B-cell ALL, BLNK mutations N27S, G30S, L39P, E82K, P165S, W232R, T314A and S436F are associated with RAG1/RAG2 expression and perpetual VDJ recombinase activity [117]. Reduced BLNK activity has been observed in preleukemic clones containing PAX5-PML fusion protein [118]. A chromosomal translocation DNTT-BLNK/ t(10;10)(q24;q24) has also been identified in Ph chromosome like ALL [119].

IKZF1 (IKAROS- family zinc finger 1)

IKZF1 encodes a DNA binding protein IKAROS that regulates hematopoiesis and differentiation of lymphoid cells [12]. Ikaros acts as a tumor suppressor gene as it inhibits cell proliferation by down regulating the expression of genes involved in cell cycle and PI3K pathway (Fig. 4). IKZF1 is involved in B-cell receptor signaling and rearrangement of IgH locus. In pre-BCR signaling, upregulation of Ikaros and BLNK inhibits JAK3/STAT5 pathway resulting in cell cycle arrest. When pre-BCR and Ikaros signaling is compromised, activation of JAK3/STAT5 is sufficient to drive leukemogenesis [120]. IKZF1 deletion has been identified in 15% pediatric, 55% adolescent and 45–50% adult B-cell ALLs [6,121]. IKZF1 mutations are categorized as 33% dominant negative deletion (lack of DNA binding domain), 55% haploinsufficiency (loss of C-terminal domain), and 12% null deletions (loss of chromosome 7) [122]. Mutation in N and C-terminal region of IKZF1 gene produce dominant negative effect while haploinsufficiency is associated with defect in the dimerization domain. IKZF1 mutations include p.Glu142Profs*49, p.Arg143Gln, p.Cys150Arg, p.Asn159Ser, p.Leu160Val, p.Arg162Trp, and p.Asp186Thrfs*7 in exon 5, p.Arg274* in exon 7 and p.His421Profs*40, p.Glu465Aspfs*6, p.Cys483Profs*22, p.Phe490Tyrfs*21 in exon 8 respectively [123]. H167R, G158S, L117fs, H224fs, S402fs, E504fs, R111 mutations in IKZF1 allele has also been identified in ALL patients [124,125]. Studies have shown that inactivating mutations in IKZF1 allele produce treatment resistant B-cell leukemia [126]. Resistance to tyrosine kinase inhibitors and other chemotherapeutic drugs has been noted in individuals with IKZF1 deletion [12]. In 70–80% BCR-ABL1 patients, IKZF1 deletion is associated with poor treatment outcome and increase incidence of relapse [121,127,128]. An international study based on transcriptional profile analysis of 1223 B-cell ALL patients has identified hotspot mutations in IKZF1 (p.N159Y), ZEB2 (p.H1038R), and PAX5 (p.P80R) genes [129]. Aoe et al., [130] found IKZF1 mutation p.Q446* (c.1336C>T) in Ph^+ ALL patient at the time of diagnosis. However, during relapse, the patient had increased IKZF1 mutation and an additional ABL1 kinase mutation p.F359C (c.1076T>G). IKZF1 deletion also occurs during transformation of CML to ALL [131]. In pediatric ALL, IKZF1 mutations

p.G337fs (c.1000insC), p.I110fs (c.476_477ins23) and deletion in exon 4–8 are associated with increase chances of relapse [132]. IKZF1 deletion is considered to be a predictor of treatment outcome as it reduces event free survival (EFS) and overall survival (OS) in ALL patients [133].

PAX5 (Paired box gene 5)

PAX5 is a master regulator of B-cell development and is highly expressed in pro B-cells. It activates transcription of genes (CD79a, CD19, CD21, BLNK, CD72) involved in pre BCR signaling and represses transcription of inappropriate genes (NOTCH1, PD1, M-CSFR) of B-cell lineages [134] (Fig. 4). PAX5 somatic gene mutations are among the hallmarks of B-cell ALL. Genome wide analysis has shown that PAX5 mutations occur frequently in pediatric and adult B-cell ALL [135]. PAX5 gene harbors insertion, deletion, point mutations and translocation. Frameshift and missense mutations V319fs, T333fs, V336fs, G24R, D53V, R59G, T75R, I301T, I139T, V151I have also been identified in high risk pediatric ALLs [114]. PAX5 overexpression is associated with high remission rate [136]. In 30% cases, PAX5 undergoes monoallelic deletion that subsequently reduce PAX5 protein [137]. PAX5 deletion arrests B-cell development at an early stage in fetal liver, but it continues up to pre BI stage in adult bone marrow [138]. In 41% pediatric B-cell ALL, PAX5 mutation involves deletion in exon 7, 8 and 9 [139]. Down-regulation of PAX5 initiates B-cell ALL due to activation of STAT5 pathway. However, when PAX5 expression is resumed, leukemia cell growth gets inhibited due to cell cycle arrest [140]. In pre B-cell ALL, mutation p.Gly183Ser (c.547G>A) in octapeptide domain of PAX5 results in the loss of wide type allele [141]. In adult BCR-ABL1$^+$ ALL, PAX5 deletion is associated with loss of IKZF1 [142]. Patients with PAX5 deletion show worse prognosis [143]. DNA-binding and transcriptional activities of PAX5 gene are affected by V26G and P34Q mutations [16]. In 2–3% cases, PAX5 undergoes translocation with variety of genes like ETV6, HIPK1, AUTS2, JAK2, ELN, DACH1, ZNF521 and BRD1 [17,144]. A recurrent chromosomal translocation t(3;9)(p13;p13) between PAX5 and FOXP1 blocks B-cell differentiation into mature form [145]. In lymphoplasmacytoid lymphoma and B-cell non-Hodgkin's lymphoma, PAX5 overexpression has been noted due to chromosomal translocation t(9;14)(p13;q32) that juxtaposes PAX5 close to IGH enhancers [146,147]. A novel PAX5 gene mutation c.239C>G (P80R) has been identified in B-cell ALL which is associated with high event free survival and favorable treatment outcome [148]. Increased PAX5 expression is, therefore, an important prognostic marker in ALL.

NOTCH 1 (Notch Homolog 1, Translocation-Associated)

NOTCH receptor is a transmembrane glycoprotein with an extracellular, transmembrane (juxtamembrane and heterodimerization section) and an intracellular domain (TAD - transcription activation domain and PEST - proline, glutamic acid, serine, threonine rich domain) [149]. Mammalian NOTCH receptor family consists of NOTCH1, NOTCH2, NOTCH3 and NOTCH4 homologues. Dysregulation in NOTCH signaling is associated with lungs, renal, head and neck, pancreatic, hepatocellular, cervical carcinomas and hematological malignancies [150]. NOTCH1 is crucial for differentiation, proliferation and survival of T-cells. It inhibits apoptosis and initiates tumor development [151]. In NOTCH1 signaling, intracellular notch domain (ICN) is cleaved by γ-secretase when extracellular domain of NOTCH1 receptor interacts with jagged / delta ligand present on the neighboring cell. The intracellular domain translocates to the nucleus and regulates transcription of genes responsible for T-cell development [152]. NOTCH1 signaling also activates genes like c-Myc, p21, CCND1, IL7Rα and PI3K/AKT pathway [153,154] (Fig. 4). NOTCH1 gain of function mutations occur in 60% T-cell ALL while in 40% cases NOTCH1 undergoes chromosomal translocation [155]. Due to "gain of function" mutation ligand independent activation of NOTCH1 receptor leads to T-cell ALL. NOTCH1 mutations in heterodimerization domain either involves single amino acid substitutions, or in frame deletions/insertions of few amino acids. However, tandem insertion of 12–15 amino acids at HD-C is rarely found [156]. Mutations in extracellular heterodimerization domain enhances ADAM mediated cleavage and receptor activation independent of ligand while mutations in PEST domain increase stability of ICN [157]. NOTCH1 mutations like L1575P, V1578del, V1578E, P1582dup, L1585R, L1586P, F1593S, L1594P, R1598G, R1599P, N1603 V1604insG, Q1614L, I1616N (in HD-N), L1679P, L1679Q, I1680N, I1681N, A1702P, V1721M, Q1722P (in HD-C), Q2398fs, Q2407X, V2422M, S2423X, S2424X, E2460*, S2486*, Y2491X, , F2509L (in PEST domain) and S2194* and G2345fs (in TAD) have been reported in T-cell ALL [158–160]. 40–45% NOTCH1 mutations L1574P, L1585P, R1598P, L1600P, L1678P and L1709P occur in exon 26 and 27 of heterodimerization domain [161]. In a recent study, Kimura et al., [162] identified frequent NOTCH1 mutations in PEST domain (54.5%) in relapse samples while HD mutations (40%) were commonly found in patients at the time of diagnosis. The identified NOTCH1 chromosomal translocations include NOTCH1-NUP214/t(9;9)(q34;q34), NOTCH1-HNF1B/t(9;17)(q34;q12), and TRA-NOTCH1/t(9;14)(q34;q11). In T-cell ALL chromosomal translocation TRB-NOTCH1/t(7;9)(q34;q34.3) is associated with NOTCH1 overexpression [163]. Activation of NOTCH1 signaling results in poor treatment outcome due to increased metastasis [164]. NOTCH1 mutations are absent in B-cell ALL and occur rarely in AML [165]. Higher frequency of NOTCH1 mutations makes NOTCH signaling an important targetable pathway by gamma secretase inhibitors for ALL treatment [28].

FBXW7 (F-Box and WD40 domain containing protein 7 gene)

FBXW7, an E3 ubiquitin ligase acts as a tumor suppressor gene in numerous cancers by mediating ubiquitin degradation of several oncoproteins like NOTCH1/4, Myc, cyclin E, Jun and mTOR [166] (Fig. 4). FBXW7 deletion or loss of function mutation has been reported in various cancers. FBXW7 gene is mutated in 8–30% T-cell ALL [160]. FBXW7 mutations either occur alone (9%) or in association with NOTCH1 mutations (15%). Inactivating mutations in FBXW7 gene includes Q48*, R222*, R278*, D400D, T410P, G423R,

Table 2 Genetic lesions reported in B and T-cell ALL.

Genes	Mutations	Prognosis	References
IL7R	V253G, S185C, 244 Ins CHL, 197T>C	Poor	[56,64]
Activating mutations	254G>A, 6 (755_756ins9), 1066A>G		
CRLF2			
Activating mutation	F232C	Poor	[72]
Translocation	CRLF2-P2RY8, IGHα-CRLF2, CSF2RA-CRLF2		[75–77,84]
JAK2	V617F, R683G, L611S, H574R, Y613E, Y931C		[46][88–97]
Activating mutations	E864K, I682F, G935R, T875N, D873N, P933Q	Poor	[101,102]
Translocation	PAX5-JAK2, PCM1-JAK2, TEL-JAK2		
BLNK	H431N, N27S, G30S, L39P, E82K, P165S		[114,117]
Inactivating mutations	W232R, T314A, S436F, R282X, R123X	Not defined	
Translocation	DNTT-BLNK		[119]
IKZF1			
Deletion	R111, G158S, N159Y, H167R,	Poor	[123–125]
Frameshift mutations	L117fs, H224fs, S402fs, E504fs, G337fs, I110fs		
PAX5	G24R,D53V, R59G, T75R, I301T	Poor	
Mutations	I139T, V151I, V319fs, T333fs, V336fs		[114]
Translocation	PAX5- BRD1, PAX5-HIPK1, PAX5-DACH1	Intermediate	[17,144]
NOTCH1	L1575P, V1578del, V1578E, P1582dup, L1585R		
Mutations	F1593S, L1594P, R1598G, N1603 V1604insG	Poor	[158–160]
Translocation	NOTCH1-NUP214, TRA-NOTCH1, TRB-NOTCH1	Not defined	[163]
FBXW7	D400D, T410P, G423R, W425C, S462fs, R465C	Poor	[29]
Inactivating mutations	D480A S478fs, R513fs, S558Y, G670E, G654fs		
			[160,167,168]

W425C, S462fs, R465C, R465H, R465L, S478fs, R479G, R479P, R479Q, R479L, D480A, L494fs, G498A, R505C, R505H, R513fs, W526*, S558Y, G670E, G654fs and S665fs [29,160,167,168]. R465C mutation is important for ALL progression while R505C mutation affects FBXW7 and NOTCH1 binding [169]. FBXW7 mutations prevent proteasomal degradation of NOTCH1 protein and thereby increase c-Myc stability and leukemia initiating cells (LIC) [170]. Sustained NOTCH signaling, and resistance to γ-secretase inhibitors (GSI) are commonly observed in FBXW7 mutants [171]. Combined treatment of T-cell ALL with GSI and CDK inhibitors initiates apoptosis in leukemia cells [172]. Huh et al., [161] identified G423V, R505L, and R689W mutations in FBXW7 gene and reported that 75% T-cell ALL patients with both FBXW7 and NOTCH1 mutations have favorable prognosis. In adult T-cell leukemia, FBXW7 mutants D510E and D527G exhibit transforming properties with c-Myc, p53 and Tax oncogenes [173]. Mutational analysis has revealed FBXW7 gene mutations V627A (2029T>C), 715_718delinsGAC, and 2107del in T-cell ALL and T-cell non-Hodgkin's lymphoma [174]. TAL1, an oncogenic transcription factor aberrantly expressed in T-cell ALL down-regulates FBXW7 via miR-223. However, knockdown of TAL1 restores normal FBXW7 expression and reduce NOTCH1, Myc, Myb and cyclin E expression [175]. The mutated FBXW7 therefore acts as an independent prognostic factor for determining the survival rate in T-cell ALL [176].

Concluding remarks

Use of advance technologies like whole genome and exome sequencing have helped us to uncover the genetic basis of acute lymphoblastic leukemia which is increasing worldwide among children and adult males. The genetic basis of ALL involves chromosomal abnormalities, gene rearrangements, deletion and insertional mutations. Development of gene editing technology has made it possible to study ALL pathogenesis and to eliminate or modify expression of aberrant fusion proteins and point mutations in transcription factors. The current review has highlighted mutations in genes important for lymphoid cell development, differentiation and proliferation. As genes work in a coordinated manner, any defect or unfavorable change in important players of the pathway is likely to change the cell physiology. Genes encoding IL7R, CRLF2, JAK2, and NOTCH1 regulate downstream signaling cascade for blast cell proliferation. Activating mutations in these genes stimulates JAK/STAT, PI3K/AKT/mTOR pathway for leukemia cell growth and survival. BLNK and Ikaros (encoded by IKZF1) have been found to reduce JAK/STAT pathway and formation of antiapoptotic proteins. Loss of function mutations or deletion in BLNK, IKZF1 and PAX5 genes arrests lymphoblast differentiation into mature form. Similarly, alteration in FBXW7 gene disrupts functions like NOTCH1 proteasomal degradation and inhibition of cell cycle and antiapoptotic proteins.

Understanding of molecular mechanisms helps in identifying new oncogenic targets and therapeutic strategies for disease prevention. Targeted therapies specific for mutated genes or pathways have better treatment outcome as compared to multidrug chemotherapy which has more side effects. The prognostic significance of genetic aberrations and chromosomal abnormalities helps to improve treatment options when conventional chemotherapy become unresponsive. PAX5 gene mutation (p.Gly183Ser) detects leukemia susceptibility at an early age so it could be used for early screening of ALL. Further, there's a need to probe details of genetic lesions involved in ALL initiation as it will give a better understanding of disease etiology and will help to design new therapeutic interventions with improved survival rates.

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Supplementary materials

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References

[1] Solomon B, Parihar N, Ayodele L, Hughe M. Global incidence and prevalence of acute lymphoblastic leukemia: a 10-year forecast. J Blood Disord Transfus 2017;8:5.
[2] National Cancer Institute. Surveillance, epidemiology and end results program, https://seer.cancer.gov/statfacts [Assessed 04 May 2018].
[3] Kerketta LS, Rao VB, Ghosh K. Chimeric fusion karyotypes in childhood B-cell acute lymphoblastic leukemia. Indian Pediatr 2014;51(2):152–3.
[4] Hayashi Y, Raimondi SC, Look AT, Behm FG, Kitchingman GR, Pui CH, Williams DL. Abnormalities of the long arm of chromosome 6 in childhood acute lymphoblastic leukemia. Blood 1990;76(8):1626–30.
[5] Nigro LL. Biology of childhood acute lymphoblastic leukemia. J Pediatr Hematol/Oncol 2013;35(4):245–52.
[6] Messina M, Chiaretti S, Wang J, Fedullo AL, Peragine N, Gianfelici V, Holmes AB. Prognostic and therapeutic role of targetable lesions in B-lineage acute lymphoblastic leukemia without recurrent fusion genes. Oncotarget 2016;7(12):13886.
[7] Tijchon E, Havinga J, Van Leeuwen FN, Scheijen B. B-lineage transcription factors and cooperating gene lesions required for leukemia development. Leukemia 2013;27(3):541–52.
[8] Harris M, Shuster J, Carroll A, Look A, Borowitz M, Crist W, Land V. Trisomy of leukemic cell chromosomes 4 and 10 identifies children with B-progenitor cell acute lymphoblastic leukemia with a very low risk of treatment failure: a pediatric oncology group study. Blood 1992;79(12):3316–24.
[9] Raimondi SC, Pui CH, Head D, Behm F, Privitera E, Roberson PK, Williams DL. Trisomy 21 as the sole acquired chromosomal abnormality in children with acute lymphoblastic leukemia. Leukemia 1992;6(3):171–5.
[10] Berger R. Acute lymphoblastic leukemia and chromosome 21. Cancer Genet Cytogenet 1997;94(1):8–12.
[11] Gerard B, Cave H, Guidal C, Dastugue N, Vilmer E, Grandchamp B. Delineation of a 6 cM commonly deleted region in childhood acute lymphoblastic leukemia on the 6q chromosomal arm. Leukemia 1997;11(2):228–32.
[12] Roberts KG, Mullighan CG. Genomics in acute lymphoblastic leukaemia: insights and treatment implications. Nat Rev Clin Oncol 2015;12(6):344.
[13] Harrison CJ. Acute lymphoblastic leukemia. Clin Lab Med 2011;31(4):631–47.
[14] Schwab CJ, Chilton L, Morrison H, Jones L, Al-Shehhi H, Erhorn A, Harrison CJ. Genes commonly deleted in childhood B-cell precursor acute lymphoblastic leukemia: association with cytogenetics and clinical features. Haematologica 2013;98(7):1081–8.
[15] Ivanov Öfverholm I, Tran AN, Olsson L, Zachariadis V, Heyman M, Rudd E, Barbany G. Detailed gene dose analysis reveals recurrent focal gene deletions in pediatric B–cell precursor acute lymphoblastic leukemia. Leuk Lymphoma 2016;57(9):2161–70.
[16] Mullighan CG, Goorha S, Radtke I, Miller CB, Coustan–Smith E, Dalton JD, Su X. Genome-wide analysis of genetic alterations in acute lymphoblastic leukaemia. Nature 2007;446(7137):758–64.
[17] Nebral K, Denk D, Attarbaschi A, König M, Mann G, Haas OA, Strehl S. Incidence and diversity of PAX5 fusion genes in childhood acute lymphoblastic leukemia. Leukemia 2009;23(1):134–43.
[18] Forero-Castro M, Robledo C, Benito R, Bodega-Mayor I, Rapado I, Hernández-Sánchez M, Sala-Valdés M. Mutations in TP53 and JAK2 are independent prognostic biomarkers in B–cell precursor acute lymphoblastic leukaemia. Br J Cancer 2017;117(2):256–65.
[19] Moorman AV, Richards SM, Robinson HM, Strefford JC, Gibson BE, Kinsey SE, Harrison CJ. Prognosis of children with acute lymphoblastic leukemia (ALL) and intrachromosomal amplification of chromosome 21 (iAMP21). Blood 2007;109(6):2327–30.
[20] Mrozek K, Harper DP, Aplan PD. Cytogenetics and molecular genetics of acute lymphoblastic leukemia. Hematol/Oncol Clin 2009;23(5):991–1010.
[21] Ramakers-van Woerden NL, Beverloo HB, Veerman AJP, Camitta BM, Loonen AH, Van Wering ER, Haas OA. In vitro drug-resistance profile in infant acute lymphoblastic leukemia in relation to age, MLL rearrangements and immunophenotype. Leukemia 2004;18(3):521–9.
[22] Teitell MA, Pandolfi PP. Molecular genetics of acute lymphoblastic leukemia. Annu Rev Pathol Mech Dis 2009;4:175–98.
[23] Loghavi S, Kutok JL, Jorgensen JL. B-acute lymphoblastic leukemia/lymphoblastic lymphoma. Am J Clin Pathol 2015;144(3):393–410.
[24] Litzow MR, Ferrando AA. How we treat T-cell acute lymphoblastic leukemia in adults. Blood 2015;126:833–41.
[25] Hefazi M, Litzow MR. Recent advances in the biology and treatment of T cell acute lymphoblastic leukemia. Curr Hematol Malignancy Rep 2018;13(4):265–74.
[26] Van der Meulen J, Van Roy N, Van Vlierberghe P, Speleman F. The epigenetic landscape of T-cell acute lymphoblastic leukemia. Int J Biochem Cell Biol 2014;53:547–57.
[27] Van Vlierberghe P, van Grotel M, Beverloo HB, Lee C, Helgason T, Buijs-Gladdines J, Meijerink JP. The cryptic chromosomal deletion del (11)(p12p13) as a new activation mechanism

of LMO2 in pediatric T-cell acute lymphoblastic leukemia. Blood 2006;108(10):3520–9.
[28] Ferrando A. Can one target T-cell ALL? Best Pract Res Clin Haematol 2018;31(4):361–6.
[29] Liu Y, Easton J, Shao Y, Maciaszek J, Wang Z, Wilkinson MR, Zhou X. The genomic landscape of pediatric and young adult T-lineage acute lymphoblastic leukemia. Nat Genet 2017;49(8):1211.
[30] Touw I, Pouwels K, Van Agthoven T, Van Gurp R, Budel L, Hoogerbrugge H, Lowenberg B. Interleukin-7 is a growth factor of precursor B and T acute lymphoblastic leukemia. Blood 1990;75(11):2097–101.
[31] Yoo NJ, Kim YR, Lee SH. Somatic mutation of PHF6 gene in T–cell acute lymphoblatic leukemia, acute myelogenous leukemia and hepatocellular carcinoma. Acta Oncol 2012;51(1):107–11.
[32] Gutierrez A, Kentsis A, Sanda T, Holmfeldt L, Chen SC, Zhang J, Silverman LB. The BCL11B tumor suppressor is mutated across the major molecular subtypes of T-cell acute lymphoblastic leukemia. Blood 2011;118(15):4169–73.
[33] Haydu JE, Ferrando AA. Early T-cell precursor acute lymphoblastic leukemia (ETP T-ALL). Curr Opin Hematol 2013;20(4):369–73.
[34] Girardi T, Vicente C, Cools J, De Keersmaecker K. The genetics and molecular biology of T-ALL. Blood 2017;129(9):1113–23.
[35] Van Vlierberghe P, Pieters R, Beverloo HB, Meijerink JP. Molecular-genetic insights in paediatric T-cell acute lymphoblastic leukaemia. Br J Haematol 2008;143(2):153–68.
[36] Curi DA, Iqbal A, Platanias LC. Pediatric acute lymphoblastic leukemia: the missing pieces in risk and survival. Leuk Lymphoma 2014;55(10):2226–7.
[37] Shurtleff SA, Buijs A, Behm FG, Rubnitz JE, Raimondi SC, Hancock ML, Downing JR. TEL/AML1 fusion resulting from a cryptic t (12; 21) is the most common genetic lesion in pediatric ALL and defines a subgroup of patients with an excellent prognosis. Leukemia 1995;9(12):1985–9.
[38] Knez VM, Carstens BJ, Swisshelm KL, McGranahan AN, Liang X. Heterogeneity of abnormal RUNX1 leading to clinicopathologic variations in childhood B-lymphoblastic leukemia. Am J Clin Pathol 2015;144(2):305–14.
[39] National Cancer Institute. Surveillance, epidemiology and end results program, https://seer.cancer.gov/seertools/hemelymph/51f6cf5ae3e27c3994bd5495 [Accessed 02 June 2018].
[40] Tono-oka T, Sato Y, Matsumoto T, Ueno N, Ohkawa M, Shikano T, Takeda T. Hypereosinophilic syndrome in acute lymphoblastic leukemia with a chromosome translocation (t (5q; 14q)). Med Pediat Oncol 1984;12(1):33–7.
[41] Schoch C, Rieder H, Freund M, Hoelzer D, Riehm H, Fonatsch C. Twenty-three cases of acute lymphoblastic leukemia with translocation t (4; 11)(q21; q23): the implication of additional chromosomal aberrations. Ann Hematol 1995;70(4):195–201.
[42] Pui CH. Acute leukemias with the t (4;11)(q21;q23). Leuk Lymphoma 1992;7(3):173–9.
[43] Bernard OA, Busson-LeConiat M, Ballerini P, Mauchauffe M, Della Valle V, Monni R, Gressin L. A new recurrent and specific cryptic translocation, t (5; 14)(q35; q32), is associated with expression of the Hox11L2 gene in T acute lymphoblastic leukemia. Leukemia 2001;15(10):1495.
[44] Kagan J, Joe YS, Freireich EJ. Joining of recombination signals on the der 14q-chromosome in T-cell acute leukemia with t (10; 14) chromosome translocation. Cancer Res 1994;54(1):226–30.
[45] Kraszewska MD, Dawidowska M, Szczepański T, Witt M. T–cell acute lymphoblastic leukaemia: recent molecular biology findings. Br J Haematol 2012;156(3):303–15.
[46] Lacronique V, Boureux A, Della Valle V, Poirel H, Quang CT, Mauchauffé M, Bernard OA. A TEL-JAK2 fusion protein with constitutive kinase activity in human leukemia. Science 1997;278(5341):1309–12.
[47] Zhou MH, Gao L, Jing Y, Xu YY, Ding Y, Wang N, Wang LL. Detection of ETV6 gene rearrangements in adult acute lymphoblastic leukemia. Ann Hematol 2012;91(8):1235–43.
[48] You MJ, Medeiros LJ, His ED. T-lymphoblastic leukemia/ lymphoma. Am J Clin Pathol 2015;144(3):411–22.
[49] Abdelali RB, Asnafi V, Petit A, Micol JB, Callens C, Villarese P, Guillerm G. The prognosis of CALM-AF10 positive adult T-cell acute lymphoblastic leukemias depends on the stage of maturation arrest. Haematologica 2013;98(11):1711–17.
[50] Burmeister T, Gökbuget N, Reinhardt R, Rieder H, Hoelzer D, Schwartz S. NUP214-ABL1 in adult T-ALL: the GMALL study group experience. Blood 2006;108(10):3556–9.
[51] Barata JT, Cardoso AA, Nadler LM, Boussiotis VA. Interleukin-7 promotes survival and cell cycle progression of T-cell acute lymphoblastic leukemia cells by down-regulating the cyclin-dependent kinase inhibitor p27 kip1. Blood 2001;98(5):1524–31.
[52] Lundström W, Fewkes NM, Mackall CL. IL-7 in human health and disease. In Semin Immunol 2012;24(3):218–24.
[53] Zenatti PP, Ribeiro D, Li W, Zuurbier L, Silva MC, Paganin M, Sarmento LM. Oncogenic IL7R gain-of-function mutations in childhood T-cell acute lymphoblastic leukemia. Nat Genet 2011;43(10):932–9.
[54] Barata JT. IL-7Rα: Mr Hyde's twists and turns. Blood 2011;122(26):4151–2.
[55] Yokoyama K, Yokoyama N, Izawa K, Kotani A, Harashima A, Hozumi K, Tojo A. In vivo leukemogenic potential of an interleukin 7 receptor α chain mutant in hematopoietic stem and progenitor cells. Blood 2013;122(26):4259–63.
[56] Shochat C, Tal N, Bandapalli OR, Palmi C, Ganmore I, te Kronnie G, Schrappe M. Gain-of-function mutations in interleukin-7 receptor-α (IL7R) in childhood acute lymphoblastic leukemias. J Exp Med 2011;208(5):901–8.
[57] Shochat C, Tal N, Gryshkova V, Birger Y, Bandapalli OR, Cazzaniga G, Twizere JC. Novel activating mutations lacking cysteine in type I cytokine receptors in acute lymphoblastic leukemia. Blood 2014;124(1):106–10.
[58] Rozovski U, Li P, Harris D, Ohanian M, Kantarjian H, Estrov Z. Interleukin-7 receptor-α gene mutations are not detected in adult T-cell acute lymphoblastic leukemia. Cancer Med 2014;3(3):550–4.
[59] Ge Z, Gu Y, Xiao L, Han Q, Li J, Chen B, Song C. Co-existence of IL7R high and SH2B3 low expression distinguishes a novel high-risk acute lymphoblastic leukemia with Ikaros dysfunction. Oncotarget 2016;7(29):46014.
[60] Gianfelici V, Messina M, Paoloni F, Peragine N, Lauretti A, Fedullo AL, Chiaretti S. IL7R overexpression in adult acute lymphoblastic leukemia is associated to JAK/STAT pathway mutations and identifies patients who could benefit from targeted therapies. Leuk Lymphoma 2018:1–4. Epub ahead of print.
[61] Zhong J, Pandey A. Site-directed mutagenesis reveals a unique requirement for tyrosine residues in IL-7Rα and TSLPR cytoplasmic domains in TSLP-dependent cell proliferation. BMC Immunol 2010;11(1):5.
[62] Li Y, Buijs-Gladdines JG, Canté-Barrett K, Stubbs AP, Vroegindeweij EM, Smits WK, Buijsman RC. IL-7 receptor mutations and steroid resistance in pediatric t cell acute lymphoblastic leukemia: a genome sequencing study. PLoS Med 2016;13(12):e1002200.
[63] Xiao LC, Li M, Ge Z, Gu Y, Zhou XL, Guo X, Li JY. Mutation of IL-7R in adult patients with T-cell acute lymphoblastic leukemia and its clinical significance. Zhongguo shi yan xue ye xue za zhi 2016;24(4):1014–18.
[64] Zhou X, Gu Y, Han Q, Soliman M, Song C, Ge Z. Coexistence of EZH2, NOTCH1, IL7R, and PHF6 mutations in adult T-cell acute lymphoblastic leukemia. Turk J Hematol 2017;34(4):366.

[65] Alsadeq A, Lenk L, Vadakumchery A, Cousins A, Vokuhl C, Khadour A, Hobeika E. IL7R is associated with CNS infiltration and relapse in pediatric B-cell precursor acute lymphoblastic leukemia. Blood 2018;132(15):1614–17.

[66] Canté-Barrett K, Spijkers-Hagelstein JAP, Buijs-Gladdines JG-CAM, Uitdehaag JC, Smits WK, van der Zwet J, Meijerink JPP. MEK and PI3K-AKT inhibitors synergistically block activated IL7 receptor signaling in T-cell acute lymphoblastic leukemia. Leukemia 2016;30(9):1832.

[67] Richter-Pechańska P, Kunz JB, Hof J, Zimmermann M, Rausch T, Bandapalli OR, Schrappe M. Identification of a genetically defined ultra-high-risk group in relapsed pediatric T–lymphoblastic leukemia. Blood Cancer J 2017;7(2):e523.

[68] Rochman Y, Leonard WJ. Thymic stromal lymphopoietin: a new cytokine in asthma. Curr Opin Pharmacol 2008;8(3):249–54.

[69] Tasian S, Loh ML. Understanding the biology of CRLF2-overexpressing acute lymphoblastic leukemia. Crit Rev™ Oncog 2011;16:1–2.

[70] Tal N, Shochat C, Geron I, Bercovich D, Izraeli S. Interleukin 7 and thymic stromal lymphopoietin: from immunity to leukemia. Cell Mol Life Sci 2014;71(3):365–78.

[71] Levin SD, Koelling RM, Friend SL, Isaksen DE, Ziegler SF, Perlmutter RM, Farr AG. Thymic stromal lymphopoietin: a cytokine that promotes the development of IgM+ B cells in vitro and signals via a novel mechanism. J Immunol 1999;162(2):677–83.

[72] Van Bodegom D, Zhong J, Kopp N, Dutta C, Kim MS, Bird L, Weinstock DM. Differences in signaling through the B-cell leukemia oncoprotein CRLF2 in response to TSLP and through mutant JAK2. Blood 2012;120(14):2853–63.

[73] Bugarin C, Sarno J, Palmi C, Savino AM, te Kronnie G, Dworzak M, Bronzini I. Fine tuning of surface CRLF2 expression and its associated signaling profile in childhood B–cell precursor acute lymphoblastic leukemia. Haematologica 2015;100(6):e229–32.

[74] Maciel ALT, Poubel CP, Noronha EP, Pombo-de-Oliveira MS, Mansur MB, Emerenciano M. CRLF2 expression associates with ICN1 stabilisation in T-cell acute lymphoblastic leukaemia. Genes Chromosomes Cancer 2018. Epub ahead of print.

[75] Mullighan CG, Collins-Underwood JR, Phillips LA, Loudin MG, Liu W, Zhang J, Rabin KR. Rearrangement of CRLF2 in B-progenitor–and down syndrome–associated acute lymphoblastic leukemia. Nat Genet 2009;41(11):1243–6.

[76] Russell LJ, Capasso M, Vater I, Akasaka T, Bernard OA, Calasanz MJ, Guttery DS. Deregulated expression of cytokine receptor gene, CRLF2, is involved in lymphoid transformation in B-cell precursor acute lymphoblastic leukemia. Blood 2009;114(13):2688–98.

[77] Roll JD, Reuther GW. CRLF2 and JAK2 in B-progenitor acute lymphoblastic leukemia: a novel association in oncogenesis. Cancer Res 2010;70(19):7347–52.

[78] Dyer MJ, Akasaka T, Capasso M, Dusanjh P, Lee YF, Karran EL, Siebert R. Immunoglobulin heavy chain locus chromosomal translocations in B-cell precursor acute lymphoblastic leukemia: rare clinical curios or potent genetic drivers? Blood 2010;115(8):1490–9.

[79] Schmäh J, Fedders B, Panzer-Grümayer R, Fischer S, Zimmermann M, Dagdan E, Bleckmann K. Molecular characterization of acute lymphoblastic leukemia with high CRLF2 gene expression in childhood. Pediatr Blood Cancer 2017;64(10):e26539.

[80] Ensor HM, Schwab C, Russell LJ, Richards SM, Morrison H, Masic D, Harrison CJ. Demographic, clinical and outcome features of children with acute lymphoblastic leukemia and CRLF2 deregulation: results from the MRC ALL97 clinical trial. Blood 2010;117(7):2129–36.

[81] Ge Z, Gu Y, Zhao G, Li J, Chen B, Han Q, Olson J. High CRLF2 expression associates with IKZF1 dysfunction in adult acute lymphoblastic leukemia without CRLF2 rearrangement. Oncotarget 2016;7(31):49722.

[82] Zhang Q, Shi C, Han L, Jain N, Roberts KG, Ma H, Mu H. Inhibition of mTORC1/C2 signaling improves anti-leukemia efficacy of JAK/STAT blockade in CRLF2 rearranged and/or JAK driven Philadelphia chromosome–like acute B-cell lymphoblastic leukemia. Oncotarget 2018;9(8):8027.

[83] Yamashita Y, Shimada A, Yamada T, Yamaji K, Hori T, Tsurusawa M, Horibe K. IKZF1 and CRLF2 gene alterations correlate with poor prognosis in Japanese BCR-ABL1-negative high-risk B-cell precursor acute lymphoblastic leukemia. Pediatr Blood Cancer 2013;60(10):1587–92.

[84] Yano M, Imamura T, Asai D, Moriya Saito A, Suenobu SI, Hasegawa D, Kosaka Y. An overall characterization of pediatric acute lymphoblastic leukemia with CRLF2 overexpression. Genes Chromosomes Cancer 2014;53(10):815–23.

[85] Ge Z, Liu J, Zhang R, Guo X, Xu JY, Li M, Li JY. Characteristics and prognostic significance of CRLF2 high expression and the co-existence with JAK1 mutations and ikaros deletion in adult acute lymphoblastic leukemia. Blood 2014;124:3800.

[86] Kong X, Sun H, Pan P, Li D, Zhu F, Chang S, Hou T. How does the L884P mutation confer resistance to type-II inhibitors of JAK2 kinase: a comprehensive molecular modeling study. Sci Rep 2017;7:1–11.

[87] Van Roosbroeck K, Cox L, Tousseyn T, Lahortiga I, Gielen O, Cauwelier B, De Wolf-Peeters C. JAK2 rearrangements, including the novel SEC31A-JAK2 fusion, are recurrent in classical Hodgkin lymphoma. Blood 2011;117(15):4056–64.

[88] Jelinek J, Oki Y, Gharibyan V, Bueso-Ramos C, Prchal JT, Verstovsek S, Issa JPJ. JAK2 mutation 1849G>T is rare in acute leukemias but can be found in CMML, Philadelphia chromosome–negative CML, and megakaryocytic leukemia. Blood 2005;106(10):3370–3.

[89] Kratz CP, Böll S, Kontny U, Schrappe M, Niemeyer CM, Stanulla M. Mutational screen reveals a novel JAK2 mutation, L611S, in a child with acute lymphoblastic leukemia. Leukemia 2006;20(2):381.

[90] Bercovich D, Ganmore I, Scott LM, Wainreb G, Birger Y, Elimelech A, Cario G. Mutations of JAK2 in acute lymphoblastic leukaemias associated with down's syndrome. The Lancet 2008;372(9648):1484–92.

[91] Funakoshi-Tago M, Tago K, Sumi K, Abe M, Aizu-Yokota E, Oshio T, Kasahara T. The acute lymphoblastic leukemia-associated JAK2 L611S mutant induces tumorigenesis in nude mice. J Biol Chem 2009;284(19):12680–90.

[92] Hornakova T, Springuel L, Devreux J, Dusa A, Constantinescu SN, Knoops L, Renauld JC. Oncogenic JAK1 and JAK2-activating mutations resistant to ATP-competitive inhibitors. Haematologica 2011;96(6):845–53.

[93] Weigert O, Lane AA, Bird L, Kopp N, Chapuy B, van Bodegom D, Paranal RM. Genetic resistance to JAK2 enzymatic inhibitors is overcome by HSP90 inhibition. J Exp Med 2012;209(2):259–73.

[94] Li F, Guo HY, Wang M, Geng HL, Bian MR, Cao J, Wu QY. The effects of R683S (G) genetic mutations on the JAK2 activity, structure and stability. Int J Biol Macromol 2013;60:186–95.

[95] Li F, Li W, Liu Y, Tong YX, Zhou P, Wang L, Xu KL. Effects of the I682F mutation on JAK2′s activity, structure and stability. Int J Biol Macromol 2015;79:118–25.

[96] Roncero AM, López-Nieva P, Cobos-Fernández MA, Villa–Morales M, González-Sánchez L, Lopez-Lorenzo JL, Piris MA. Contribution of JAK2 mutations to T-cell lymphoblastic lymphoma development. Leukemia 2016;30(1):94.

[97] Feng J, Gong XY, Jia YJ, Liu KQ, Li Y, Dong XB, Zhao XL. Spectrum of somatic mutations and their prognostic significance in adult patients with B cell acute lymphoblastic leukemia. Zhonghua xue ye xue za zhi= Zhonghua xueyexue zazhi 2018;39(2):98–104.

[98] Mullighan CG, Zhang J, Harvey RC, Collins-Underwood JR, Schulman BA, Phillips LA, Devidas M. JAK mutations in high-

risk childhood acute lymphoblastic leukemia. Proc Natl Acad Sci 2009;106(23):9414–18.
[99] Tomoyasu C, Imamura T, Tomii T, Yano M, Asai D, Goto H, Minegishi M. Copy number abnormality of acute lymphoblastic leukemia cell lines based on their genetic subtypes. Int J Hematol 2018;108(3):1–7.
[100] Ho K, Valdez F, Garcia R, Tirado CA. JAK2 translocations in hematological malignancies: review of the literature. J Assoc Genet Technol 2010;36(3):107–9.
[101] Fazio G, Palmi C, Rolink A, Biondi A, Cazzaniga G. PAX5/TEL acts as a transcriptional repressor causing down-modulation of CD19, enhances migration to CXCL12, and confers survival advantage in pre-BI cells. Cancer Res 2008;68(1):181–9.
[102] Reiter A, Walz C, Watmore A, Schoch C, Blau I, Schlegelberger B, Vanstraelen D. The t (8; 9)(p22; p24) is a recurrent abnormality in chronic and acute leukemia that fuses PCM1 to JAK2. Cancer Res 2005;65(7):2662–7.
[103] Sadras T, Heatley SL, Kok CH, McClure BJ, Yeung D, Hughes TP, White DL. A novel somatic JAK2 kinase-domain mutation in pediatric acute lymphoblastic leukemia with rapid on-treatment development of LOH. Cancer Genet 2017;216:86–90.
[104] Kim SK, Knight DA, Jones LR, Vervoort S, Ng AP, Seymour JF, Johnstone RW. JAK2 is dispensable for maintenance of JAK2 mutant B-cell acute lymphoblastic leukemias. Genes Dev 2018;32:849–64.
[105] Jackman JK, Motto DG, Sun Q, Tanemoto M, Turck CW, Peltz GA, Findell PR. Molecular cloning of SLP-76, a 76-kDa tyrosine phosphoprotein associated with Grb2 in T cells. J Biol Chem 1995;270(13):7029–32.
[106] Fu C, Turck CW, Kurosaki T, Chan AC. BLNK: a central linker protein in B cell activation. Immunity 1998;9(1):93–103.
[107] Kurosaki T, Tsukada S. BLNK: connecting Syk and Btk to calcium signals. Immunity 2000;12(1):1–5.
[108] Hussain A, Faryal R, Nore BF, Mohamed AJ, Smith CE. Phosphatidylinositol-3-kinase-dependent phosphorylation of SLP-76 by the lymphoma-associated ITK-SYK fusion-protein. Biochem Biophys Res Commun 2009;390(3):892–6.
[109] Nakayama J, Yamamoto M, Hayashi K, Satoh H, Bundo K, Kubo M, Kitamura D. BLNK suppresses pre–B-cell leukemogenesis through inhibition of JAK3. Blood 2009;113(7):1483–92.
[110] Minegishi Y, Rohrer J, Coustan-Smith E, Lederman HM, Pappu R, Campana D, Conley ME. An essential role for BLNK in human B cell development. Science 1999;286(5446):1954–7.
[111] Xu LS, Sokalski KM, Hotke K, Christie DA, Zarnett O, Piskorz J, DeKoter RP. Regulation of B cell linker protein transcription by PU. 1 and Spi-B in murine B cell acute lymphoblastic leukemia. J Immunol 2012;189(7):3347–54.
[112] Kabak S, Skaggs BJ, Gold MR, Affolter M, West KL, Foster MS, Clark MR. The direct recruitment of BLNK to immunoglobulin α couples the B-cell antigen receptor to distal signaling pathways. Mol Cell Biol 2002;22(8):2524–35.
[113] Jumaa H, Bossaller L, Portugal K, Storch B, Lotz M, Flemming A, Niemeyer CM. Deficiency of the adaptor SLP-65 in pre-B-cell acute lymphoblastic leukaemia. Nature 2003;423(6938):452–6.
[114] Zhang J, Mullighan CG, Harvey RC, Wu G, Chen X, Edmonson M, Gerhard DS. Key pathways are frequently mutated in high risk childhood acute lymphoblastic leukemia: a report from the children's oncology group. Blood 2011;118(11):3080–7.
[115] Lagresle-Peyrou C, Millili M, Luce S, Boned A, Sadek H, Rouiller J, Schiff C. The BLNK adaptor protein has a nonredundant role in human B-cell differentiation. J Allergy Clin Immunol 2014;134(1):145–54.
[116] NaserEddin A, Shamriz O, Keller B, Alzyoud RM, Unger S, Fisch P, Wahadneh AM. Enteroviral infection in a patient with BLNK adaptor protein deficiency. J Clin Immunol 2015;35(4):356–60.
[117] Sprangers M, Feldhahn N, Liedtke S, Jumaa H, Siebert R, Müschen M. SLP65 deficiency results in perpetual V (D) J recombinase activity in pre-B-lymphoblastic leukemia and B-cell lymphoma cells. Oncogene 2006;25(37):5180.
[118] Imoto N, Hayakawa F, Kurahashi S, Morishita T, Kojima Y, Yasuda T, Kiyoi H. B cell linker protein (BLNK) is a selective target of repression by PAX5-PML protein in the differentiation block that leads to the development of acute lymphoblastic leukemia. J Biol Chem 2016;291(9):4723–31.
[119] Pui CH, Roberts KG, Yang JJ, Mullighan CG. Philadelphia chromosome–like acute lymphoblastic leukemia. Clin Lymphoma Myeloma Leuk 2017;17(8):464–70.
[120] Trageser D, Iacobucci I, Nahar R, Duy C, von Levetzow G, Klemm L, Kim YM. Pre–B cell receptor–mediated cell cycle arrest in Philadelphia chromosome–positive acute lymphoblastic leukemia requires IKAROS function. J Exp Med 2009;206(8):1739–53.
[121] Boer JM, van der Veer A, Rizopoulos D, Fiocco M, Sonneveld E, de Groot-Kruseman HA, Den Boer ML. Prognostic value of rare IKZF1 deletions in childhood B-cell precursor acute lymphoblastic leukemia: an international collaborative study. Blood 2014;124(21) 368–368.
[122] Kastner P, Dupuis A, Gaub MP, Herbrecht R, Lutz P, Chan S. Function of Ikaros as a tumor suppressor in B cell acute lymphoblastic leukemia. Am J Blood Res 2013;3(1):1.
[123] Lana T, de Lorenzo P, Bresolin S, Bronzini I, Den Boer ML, Cavé H, De Groot H. Refinement of IKZF1 status in pediatric Philadelphia-positive acute lymphoblastic leukemia. Leukemia 2015;29(10):2107–11.
[124] Mullighan CG, Su X, Zhang J, Radtke I, Phillips LA, Miller CB, Harvey RC. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. N Engl J Med 2009;360(5):470–80.
[125] Abdulhay N, Fiorini C, Kumánovics A, Sun AA, Hansen-Rejali J, Voelkerding KV, Sankaran VG. Normal hematologic parameters and fetal hemoglobin silencing with heterozygous IKZF1 mutations. Blood 2016;128(16):2100–3.
[126] Olsson L, Johansson B. Ikaros and leukaemia. Br J Haematol 2015;169(4):479–91.
[127] Martinelli G, Iacobucci I, Storlazzi CT, Vignetti M, Paoloni F, Cilloni D, Papayannidis C. IKZF1 (Ikaros) deletions in BCR-ABL1–positive acute lymphoblastic leukemia are associated with short disease-free survival and high rate of cumulative incidence of relapse: a GIMEMA AL WP report. J Clin Oncol 2009;27(31):5202–7.
[128] Zou Y, Liu XM, Zhang L, Chen YM, Guo Y, Chen XJ, Zhu XF. Significance of IKZF1 gene copy number abnormalities in BCR/ABL-negative B-lineage acute lymphoblastic leukemia in children. Chin J Contemp Pediatr 2015;17(11):1154–9.
[129] Li JF, Dai YT, Lilljebjörn H, Shen SH, Cui BW, Bai L, Matsumura I. Transcriptional landscape of B cell precursor acute lymphoblastic leukemia based on an international study of 1223 cases. Proc Natl Acad Sci 2018;115(50):E11711–20.
[130] Aoe M, Ishida H, Matsubara T, Karakawa S, Kawaguchi H, Fujiwara K, Shimada A. Simultaneous detection of ABL 1 mutation and IKZF 1 deletion in Philadelphia chromosome-positive acute lymphoblastic leukemia using a customized target enrichment system panel. Int J Lab Hematol 2018;40(4):427–36.
[131] Mullighan CG, Miller CB, Radtke I, Phillips LA, Dalton J, Ma J, Relling MV. BCR–ABL1 lymphoblastic leukaemia is characterized by the deletion of Ikaros. Nature 2008;453(7191):110–14.
[132] Kuiper RP, Waanders E, Van Der Velden VHJ, Van Reijmersdal SV, Venkatachalam R, Scheijen B, Van Kessel AG. IKZF1 deletions predict relapse in uniformly treated pediatric precursor B-ALL. Leukemia 2010;24(7):1258.
[133] Tang S, Shen H, Qu C, Dai H, Zhu X, Xue S, Tang X. Ikaros family zinc-finger 1 mutation is an independent fac-

tor for the poor prognosis of adult B-cell acute lymphoblastic leukemia, and allogeneic hematopoietic stem cell transplantation can improve clinical outcomes. Bone Marrow Transplant 2018;54(2):236–43.
[134] Holmes ML, Pridans C, Nutt SL. The regulation of the B–cell gene expression programme by Pax5. Immunol Cell Biol 2008;86(1):47–53.
[135] Ou Z, Sherer M, Casey J, Bakos HA, Vitullo K, Hu J, Yatsenko SA. The genomic landscape of PAX5, IKZF1, and CDKN2A/B alterations in B-cell precursor acute lymphoblastic leukemia. Cytogenet Genome Res 2016;150(3–4):242–52.
[136] Lin ZK, Zhang R, Ge Z, Xu JY, Liu J, Guo X, Zhang JF. Mutation and expression of PAX5 gene in adult acute lymphoblastic leukemia. Zhongguo shi yan xue ye xue za zhi 2014;22(5):1206–11.
[137] Wachtel M, Schäfer BW. Unpeaceful roles of mutant PAX proteins in cancer. Seminars in cell & developmental biology, 44. Academic Press; 2015. p. 126–34.
[138] Urbánek P, Wang ZQ, Fetka I, Wagner EF, Busslinger M. Complete block of early B cell differentiation and altered patterning of the posterior midbrain in mice lacking Pax5BSAP. Cell 1994;79(5):901–12.
[139] Firtina S, Sayitoglu M, Hatirnaz O, Erbilgin Y, Oztunc C, Cinar S, Devecioglu O. Evaluation of PAX5 gene in the early stages of leukemic B cells in the childhood B cell acute lymphoblastic leukemia. Leukemia Res 2012;36(1): 87–92.
[140] Liu GJ, Cimmino L, Jude JG, Hu Y, Witkowski MT, McKenzie MD, Shi W. Pax5 loss imposes a reversible differentiation block in B-progenitor acute lymphoblastic leukemia. Genes Dev 2014;28(12):1337–50.
[141] Shah S, Schrader KA, Waanders E, Timms AE, Vijai J, Miething C, Zhang J. A recurrent germline PAX5 mutation confers susceptibility to pre-B cell acute lymphoblastic leukemia. Nat Genet 2013;45(10):1226.
[142] Iacobucci I, Lonetti A, Paoloni F, Papayannidis C, Ferrari A, Storlazzi CT, Paolini S. The PAX5 gene is frequently rearranged in BCR-ABL1-positive acute lymphoblastic leukemia but is not associated with outcome. Haematologica 2010;95(10):1683–90.
[143] Moafi A, Zojaji A, Salehi R, Najafi SD, Rahgozar S. The correlation between Pax5 deletion and patients survival in Iranian children with precursor B-cell acute lymphocytic leukemia. Cellular and molecular biology, 63. France: Noisy-le-Grand; 2017. p. 19–22.
[144] Cazzaniga G, Daniotti M, Tosi S, Giudici G, Aloisi A, Pogliani E, Biondi A. The paired box domain gene PAX5 is fused to ETV6/TEL in an acute lymphoblastic leukemia case. Cancer Res. 2001;61(12):4666–70.
[145] Put N, Deeren D, Michaux L, Vandenberghe P. FOXP1 and PAX5 are rare but recurrent translocations partners in acute lymphoblastic leukemia. Cancer Genet 2011;204(8):462–4.
[146] Morrison AM, Jäger U, Chott A, Schebesta M, Haas OA, Busslinger M. Deregulated PAX-5 transcription from a translocated IgH promoter in marginal zone lymphoma. Blood 1998;92(10):3865–78.
[147] Poppe B, De Paepe P, Michaux L, Dastugue N, Bastard C, Herens C, De Paepe A. PAX5/IGH rearrangement is a recurrent finding in a subset of aggressive B-NHL with complex chromosomal rearrangements. Genes Chromosomes Cancer 2005;44(2):218–23.
[148] Passet M, Boissel N, Sigaux F, Saillard C, Bargetzi M, Ba I, Lengliné E. PAX5 P80R mutation identifies a novel subtype of B-cell precursor acute lymphoblastic leukemia with favorable outcome. Blood 2018;133(3):280–4.
[149] Olsauskas-Kuprys R, Zlobin A, Osipo C. Gamma secretase inhibitors of notch signaling. OncoTargets Ther 2013;6:943.
[150] Espinoza I, Pochampally R, Xing F, Watabe K, Miele L. Notch signaling: targeting cancer stem cells and epithelial-to-mesenchymal transition. OncoTargets Ther 2013;6:1249.
[151] Yuan L, Lu L, Yang Y, Sun H, Chen X, Huang Y, Bao L. Genetic mutational profiling analysis of T cell acute lymphoblastic leukemia reveal mutant FBXW7 as a prognostic indicator for inferior survival. Ann Hematol 2015;94(11):1817–28.
[152] Ahrenhoerster LS, Leuthner TC, Tate ER, Lakatos PA, Laiosa MD. Developmental exposure to 2, 3, 7, 8 tetrachlorodibenzo-p-dioxin attenuates later-life Notch1-mediated T cell development and leukemogenesis. Toxicol Appl Pharmacol 2015;283(2):99–108.
[153] Mungamuri SK, Yang X, Thor AD, Somasundaram K. Survival signaling by notch1: mammalian target of rapamycin (mTOR)–dependent inhibition of p53. Cancer Res 2006;66(9):4715–24.
[154] Yap LF, Lee D, Khairuddin ANM, Pairan MF, Puspita B, Siar CH, Paterson IC. The opposing roles of NOTCH signaling in head and neck cancer: a mini review. Oral Dis 2015;21(7):850–7.
[155] Tosello V, Ferrando AA. The NOTCH signaling pathway: role in the pathogenesis of T-cell acute lymphoblastic leukemia and implication for therapy. Ther Adv Hematol 2013;4(3):199–210.
[156] Aster JC, Pear WS, Blacklow SC. Notch signaling in leukemia. Annu Rev Pathol 2008;3:587–613.
[157] González-García S, García-Peydró M, Alcain J, Toribio ML. Notch1 and IL-7 receptor signalling in early T-cell development and leukaemia. Curr Top Microbiol Immunol 2012;360:47–73.
[158] Mansour MR, Linch DC, Foroni L, Goldstone AH, Gale RE. High incidence of Notch-1 mutations in adult patients with T-cell acute lymphoblastic leukemia. Leukemia 2006;20(3):537.
[159] Zhu YM, Zhao WL, Fu JF, Shi JY, Pan Q, Hu J, Gu LJ. NOTCH1 mutations in T-cell acute lymphoblastic leukemia: prognostic significance and implication in multifactorial leukemogenesis. Clin Cancer Res 2006;12(10):3043–9.
[160] Jang W, Park J, Kwon A, Choi H, Kim J, Lee GD, Yoon JH. CDKN2B downregulation and other genetic characteristics in T-acute lymphoblastic leukemia. Exp Mol Med 2019;51(1):4.
[161] Huh HJ, Lee SH, Yoo KH, Sung KW, Koo HH, Jang JH, Lee KO. Gene mutation profiles and prognostic implications in Korean patients with T-lymphoblastic leukemia. Ann Hematol 2013;92(5):635–44.
[162] Kimura S, Seki M, Yoshida K, Shiraishi Y, Akiyama M, Koh K, Oka A. Notch 1 pathway activating mutations and clonal evolution in pediatric T-cell acute lymphoblastic leukemia (T-ALL). Cancer Sci 2018.
[163] Ellisen LW, Bird J, West DC, Soreng AL, Reynolds TC, Smith SD, Sklar J. TAN-1, the human homolog of the drosophila notch gene, is broken by chromosomal translocations in T lymphoblastic neoplasms. Cell 1991;66(4):649–61.
[164] Rodriguez-Vita J, Fischer A. Notch1 induces endothelial senescence and promotes tumor progression. Cell Cycle 2017;16(10):911.
[165] Palomero T, McKenna KJON, Galinsky I, Stone R, Suzukawa K, Stiakaki E, Look AT. Activating mutations in NOTCH1 in acute myeloid leukemia and lineage switch leukemias. Leukemia 2006;20(11):1963–6.
[166] Fujii Y, Yada M, Nishiyama M, Kamura T, Takahashi H, Tsunematsu R, Nakayama KI. Fbxw7 contributes to tumor suppression by targeting multiple proteins for ubiquitin-dependent degradation. Cancer Sci 2006;97(8):729–36.
[167] Malyukova A, Dohda T, von der Lehr N, Akhondi S, Corcoran M, Heyman M, Sangfelt O. The tumor suppressor gene hCDC4 is frequently mutated in human T-cell acute lymphoblastic leukemia with functional consequences for Notch signaling. Cancer Res 2007;67(12):5611–16.
[168] Erbilgin Y, Sayitoglu M, Hatirnaz O, Dogru O, Akcay A, Tuysuz G, Yuksel-Soycan L. Prognostic significance of NOTCH1 and FBXW7 mutations in pediatric T-ALL. Dis Markers 2010;28(6):353–60.

[169] Moharram SA, Shah K, Kazi JU. T-cell acute lymphoblastic leukemia cells display activation of different survival pathways. J Cancer 2017;8(19):4124.
[170] King B, Trimarchi T, Reavie L, Xu L, Mullenders J, Ntziachristos P, Sandy P. Regulation of leukemia-initiating cell activity by the ubiquitin ligase FBXW7. Cell 2013;153(7):1552.
[171] O'Neil J, Grim J, Strack P, Rao S, Tibbitts D, Winter C, Draetta G. FBW7 mutations in leukemic cells mediate NOTCH pathway activation and resistance to γ-secretase inhibitors. J Exp Med 2007;204(8):1813–24.
[172] Valliyammai N, Nancy NK, Sagar TG, Rajkumar T. Study of NOTCH1 and FBXW7 mutations and its prognostic significance in South Indian T-cell acute lymphoblastic leukemia. J Pediatr Hematol/Oncol 2018;40(1):e1–8.
[173] Yeh CH, Bellon M, Pancewicz-Wojtkiewicz J, Nicot C. Oncogenic mutations in the FBXW7 gene of adult T-cell leukemia patients. Proc Natl Acad Sci 2016;113(24):6731–6.
[174] Park MJ, Taki T, Oda M, Watanabe T, Yumura-Yagi K, Kobayashi R, Hayashi Y. FBXW7 and NOTCH1 mutations in childhood T cell acute lymphoblastic leukaemia and T cell non-Hodgkin lymphoma. Br J Haematol 2009;145(2):198–206.
[175] Mansour MR, Sanda T, Lawton LN, Li X, Kreslavsky T, Novina CD, von Boehmer H. The TAL1 complex targets the FBXW7 tumor suppressor by activating miR-223 in human T cell acute lymphoblastic leukemia. J Exp Med 2013;210(8):1545–57.
[176] Liu RB, Guo JG, Liu TZ, Guo CC, Fan XX, Zhang X, Cai XY. Meta-analysis of the clinical characteristics and prognostic relevance of NOTCH1 and FBXW7 mutation in T-cell acute lymphoblastic leukemia. Oncotarget 2017;8(39):66360.