Contents lists available at ScienceDirect

Acta Haematologica Polonica

journal homepage: www.elsevier.com/locate/achaem

Review/ Praca poglądowa

Genetic alterations in B-acute lymphoblastic leukemia

Seyedeh Momeneh Mohammadi [1], *Daryosh Mohammad Nejad* [2], *Hojjatollah Nozad Charoudeh* [1,*]

[1] *Stem Cell Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*
[2] *Department of Anatomical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran*

ARTICLE INFO

Article history:
Received: 28.06.2016
Accepted: 26.11.2016
Available online: 06.12.2016

Keywords:
- Genetic alterations
- Leukemia
- Signal transduction
- Review

ABSTRACT

Considerable advances have been made in treatment of acute lymphoblastic leukemia (ALL) with an overall survival rate of 85% in children, and with a great improvement in adults. Despite this improvements and the accessibility of hematopoietic stem cell transplantation, relapsed ALL remains a leading cause of childhood mortality emphasizing the need of new approaches on therapy. Understanding of the pathobiology and genetic alteration of ALL has been enhanced by developing molecular technologies including microarray analysis and genome sequencing. These studies have helped identifying mutations in key signaling pathways and revolutionized the treatment of ALL by drugs which specifically target the genetic defects of leukemia cells, such as tyrosine kinase inhibitors. In this paper, we review the clinically important Genetic Alterations in ALL.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common cancer in children, with top prevalence in the ages of 2–5 years and the important cause of mortality from hematological cancers in adults with second peak after the age of 50 years [1, 2]. Totally children with B linage ALL have a favorable clinical outcome in comparison with those suffering from T linage ALL [3]. Considerable advances have been made in treatment of ALL with an overall survival rate of 85% in children [2]. About adults, the outcome is being improved but it remains poor compared to children with a long- term survival of only 45% [1]. The reasons for these differences are multifactorial and not fully understood, but with increasing age, the frequency of genetic alterations with favorable outcome decreases and alteration with poor outcome like BCR-ABL are more common [2]. Although, all chromosomal translocations is occurred in any age and in both children and adults but there is a significant difference in the incidence of approximately most subgroups based on age (Fig. 1) [4]. For instance ETV6- Ranx1 and hyperdiploidy dominate in young children, with low incidence of this rearrangement in adults (3%,), whereas the incidence of

* *Corresponding author at*: Stem Cell Research Center, Imam Reza Hospital, Tabriz University of Medical Sciences, Daneshgah St., Tabriz 5166614711, Iran. Tel.: +98 41 33373879; fax: +98 41 33373879.
E-mail address: nozadh@tbzmed.ac.ir (H. Nozad Charoudeh).
http://dx.doi.org/10.1016/j.achaem.2016.11.002

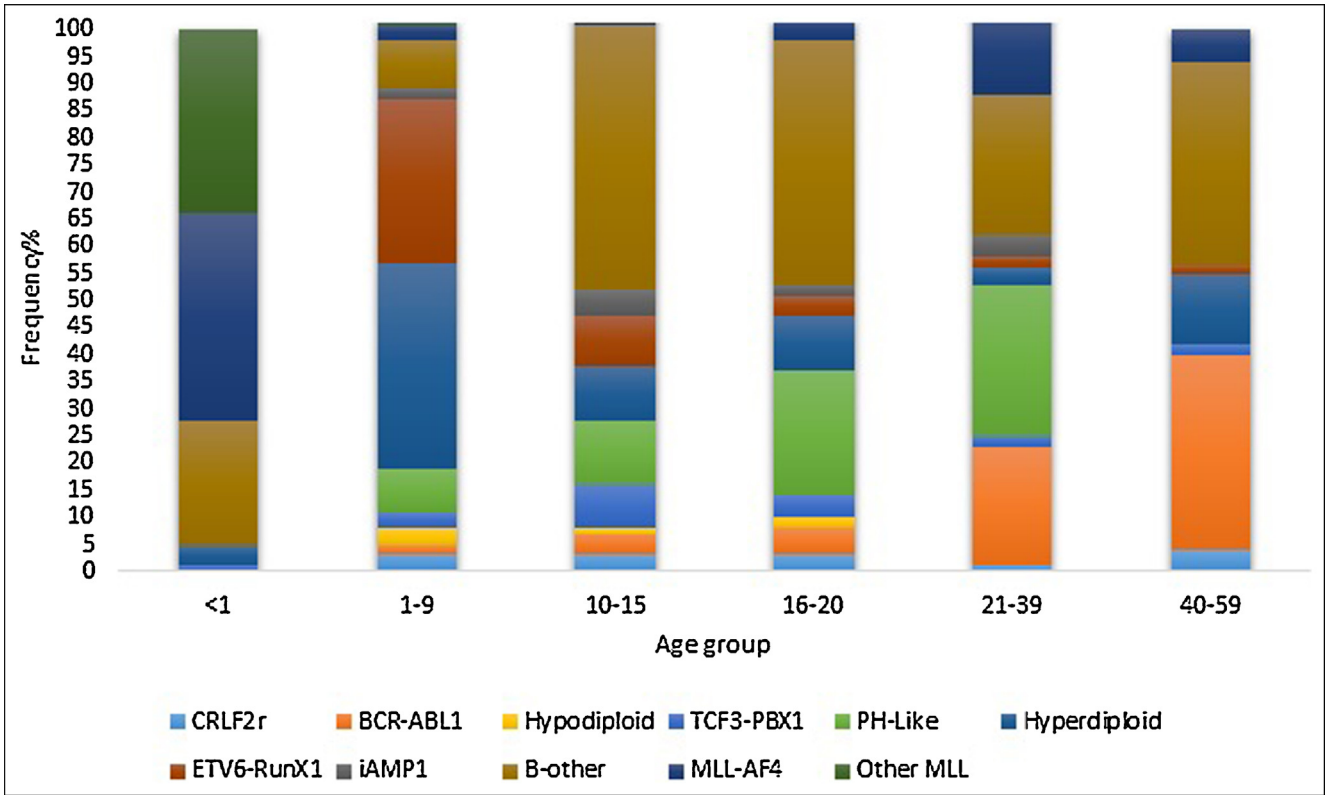

Fig. 1 – Distribution of ALL subtypes according to age groups. The occurrence of ALL. Subtypes varies between age groups. Abbreviations: ALL, acute lymphoblastic leukemia; B-other, B-cell acute lymphoblastic leukemia with other subtypes; CRLF2-r, CRLF-2-rearranged; MLLr, MLL-rearranged; Ph-like, Philadelphia chromosome-like [68, 69]

BCR-AB1 Philadelphia translocation increases considerably with age, 3% in children versus 25% in adult [4]. This biological difference highly likely affects outcome and overall survival in adults which is significantly inferior to children.

Primary genetic subtypes of B-cell precursor ALL

The fundamental mechanisms of leukemia transformation are the same and contain, abnormal expression of proto-ancogen and chromosomal translocation that finally create fusion genes encoding active kinases and transformed transcription factors. Such abnormalities cause ALL by enforcing in lymphoid progenitor cells an unrestricted ability for self-renewal, which typically followed by lacking of control on normal proliferation, a block in cell differentiation and almost resistance to normal apoptosis [5]. The gross chromosomal alterations are hallmark of ALL, and the occurrence of each alteration varies with age (Tab. I). The most common rearrangements observed in B-lineage ALL are the t(12;21) (p13;q22) rearrangement resulting in the expression of *TEL-AML1* fusion, the t(9;22) (q34;q11.2) "Philadelphia" chromosome resulting in the expression of *BCR–ABL1* fusion, the t(1;19) (q23;p13) translocation resulting in the expression of *TCF3–PBX1* fusion; and t(4;11) (q21;q23) translocation encoding *MLL–AF4* fusion. Identification of these rearrangements is important in diagnosis and risk stratification of patients with ALL. Two main genetic subtypes *TEL-AML1* (*ETV6-RUNX1*) positive and hyperdiploidy

Table I – Clinically relevant subgroups of ALL

Chromosomal translocations/gene fusions	Prevalence (%)	Relative prognosis
High hyperdiploidy with more than 50 chromosomes	~30	Excellent
Hypodiploidy with less than 44 chromosomes	2–3	Poor
t(9;22)(q34;q11.2) translocation encoding *BCR–ABL1* fusion	2–4	Poor/ improved with imatinib or other tyrosine kinase inhibitor
t(12;21)(p13;q22) translocation encoding *ETV6–RUNX1* fusion	15–25	Excellent
t(4;11)(q21;q23) translocation encoding *MLL–AF4* fusion	1–2	Poor
t(1;19)(q23;p13) translocation encoding *TCF3–PBX1* fusion	2–6	Excellent
Ph-like ALL	10–15	Multiple cytokine receptor and kinase-activating lesions; amenable to tyrosine-kinase inhibitor therapy

with greater than 50 chromosome compromise the most common abnormalities (approximately 50%) in pediatric precursor B-ALL cases. Both of them have favorable outcome and are classified in good risk cytogenetic abnormalities most likely due to sensitivity of *TEL-AML1* to L-asparaginase and hyperdiploidy to L-asparaginase and antimetabolites such as 6-mercaptopurine and methotrexate [3, 6, 7]. While in adults, the most common genetic abnormalities is Philadelphia chromosome translocation t (9:22) *BCR-ABL1*, which encodes the activated *BCR-ABL1* tyrosine kinase. It is a reciprocal translocation between chromosome 9 and 22 which fuses the *ABL1* oncogene on chromosome 9, to a breakpoint cluster region (*BCR*) from chromosome 22 and is related to a high risk of relapse. Other abnormalities with high risk of relapse and poor outcome are rearrangement of mixed-linage leukemia genes (MLL) in both groups.

The protein with histone methyl transference activity, which is encoded by MLL gene is essential for hematopoietic regulation of *HOX-A* and *MEISI* gene expression. The most common gene rearrangements include t(4;11) encoding *MLL-AFF1*, t(9;11) encoding *MLL-MLLT3*, t(11;19) encoding *MLL-ENL* and t(10;11) encoding *MLL-MLLT10*,between mentioned rearrangements the t(4;11) translocation is the most common with 50% incidence. In general, MLL rearrangements are related with adverse outcome highly likely due to cellular drug resistance [8]. Of note, "*BCR-ABL1-like*" or "Ph.-like" ALL, is a newly described subtype of high risk ALL that is related with poor outcome, and increased in frequency with age (which will be described in more details in the following section) [9].

Submicroscopic genetic aberration in ALL

Primary oncogenic events such as chromosomal rearrangements are not sufficient to cause leukemia by themselves and secondary mutations should accompany this chromosomal translocation. Advances in cytogenetic utilizing array based technology have revealed additional submicroscopic abnormalities in genes that are involved in normal hematopoiesis, apoptosis and tumor suppression (Tab. II).

Table II – recently identified genetic alteration in ALL

Gene	Alteration	Frequency	Pathophysiologic and clinical consequences of alteration	References
CRLF2	Rearrangement (as IGH@-CRLF2 or P2RY8-CRLF2)	5–15% pediatric and adult B-ALL, and >50% Down syndrome (DS) ALL, and 50% of Ph-like ALL	Concomitant *JAK1/2* mutations in >50% of cases; associated with *IKZF1* alteration and poor outcome, particularly in non-DS-ALL.	[10, 11, 13]
IKZF1	Focal deletions or sequence mutations	15% of all pediatric patients with B-ALL: 70–80% of *BCR–ABL1*+ patients with ALL and 30% OF high-risk *BCR–ABL1* like B-ALL	Associated with poor outcome in both *BCR-ABL1*–positive and negative ALL cases	[40, 44]
PAX5	Deletions, translocations, sequence mutations	31% of B-ALL	Transcription factor required for B-lymphoid development; mutations impair DNA binding and transcriptional activation but not associated with poor outcomes	[44, 45]
JAK1/2	Pseudokinase and kinase domain mutations	Up to 10% of high-risk BCR ABL1-like B-ALL; 18–35% of DS ALL	concomitant *CRLF2* rearrangement, associated with poor outcome; may be responsive to *JAK* inhibitors	[18, 52]
Kinase rearrangements and mutation	Rearrangements of *ABL1, ABL2, CSF1R, EPOR, PDGFRB*;	10% childhood B-ALL, up to 30% adult ALL; associated with Ph-like gene expression profile	Activation of kinase signaling pathways and associated with increased risk of relapse	
IL7R	Up to 7% of B and T-ALL	Sequence mutations	In B –ALL is associated with the aberrant expression of *CRLF2*, results in receptor dimerization with *CRLF2* and *JAK-STAT* activation, may be responsive to *JAK* inhibitors	[61–64]
NT5C2	Sequence mutations	19% of relapse T cell ALL and 3% of relapse B-precursor ALL	mutants confer resistance to treatment with nucleoside analog therapies	[65]
TP53	Deletions and sequence mutations	Present in 12.4% of relapse B cell ALL and of 6.4% relapse T cell AL	Associated with disease relapse and poor event-free survival and overall survival.	[66]
CREBBP	Deletions and sequence mutations	19% of relapsed B –AL	Mutations result in impaired histone acetylation and transcriptional regulation and associated with glucocorticoid resistance	[67]

Cytokine receptor like factor 2 rearrangements in ALL (*CRLF2*)

CRLF2 rearrangement has been detected in approximately 5–15% of childhood and adult B-cell precursor and also they are more common in Down syndrome ALL (in 50% of cases) [10–12]. *CRLF2* encodes cytokine receptor like factor 2 (also known thymic stromal lymphopoitin receptor/ *TSLPR*) which forms a heterodimeric receptor for thymic stromal lymphopoitin (*TSLP*) with interleukin-7 receptor-alpha (*IL7R*) [13]. Two alterations have been typically recognized in *CRLF2*; a chromosomal translocation which juxtaposes *CRLF2* to the immunoglobin heavy chain locus (*IGHG*) or more commonly a focal deletion upstream of *CRLF2* resulting in fusion of *CRLF2* gene with G protein-coupled puringic receptor *P2Y8* gene (*P2RY8*) [14]. While the *P2RY8-CRLF2* alteration is more common in younger pediatric ALL, but *IGH- CRLF2* is frequently detected in adults with ALL [12, 15]. Both of the rearrangements result in overexpression of *CRLF2* on the cell surface of leukemia lymphoblast which can be detected by flowcytometry [12]. Less commonly alteration of *CRLF2* is a point mutation at codon 232 which replace a phenylalanine with a cysteine. Various groups have tried to describe prognostic value of *CRLF2* alteration and also its association with treatment outcome in patients with ALL. It has been shown that Patients with a high *CRLF2* expression had a high rates of relapse (31% ± 8% vs 11% ± 1%, $P = 0.006$) and a poor event free survival (EFS) (61% ± 8% vs 83% ± 2%, $P = 0.003$) compared to Patients with a low *CRLF2* expression [16]. In a cohort study, it was shown that ALL Patients with overexpression of *CRLF2* have a very poor outcome [17]. Another cohort study of pediatric ALL reported that there is a high occurrence of *CRLF2* genomic lesions in DS-ALL (in more than 50% of cases) [11]. Additionally, shRNA knockdown of *CRLF2* in B-ALL cell lines only partly inhibited cell growth [15], which suggest that *CRLF2* overexpression alone is not sufficient to transform cells and other cooperating mutations and covariates may be involved. The best described of this covariates that accompany *CRLF2* alteration are involving janus kinase1 and januse kinase 2 mutations, *IKZF1* mutations and DS-ALL. Half of patients with *CRLF2* overexpression also harbor *JAK* mutations (*JAK 1* and *JAK 2*) [17]. Mutation in the pseudokinase domain of *JAK2* at *R683* is the most common [18]. *CRLF2* rearrangement together with *JAK2* mutants resulted in constitutive *JAK-STAT* activation and cytokine-independent cell growth [11]. It was revealed that in 41 *CRLF2*-rearranged DS-ALL patients, 34% of them also had JAK2 mutations [11]. In line, in study of 26 high-risk pediatric B-ALL patients with *CRLF2* overexpression, 69% of them had *JAK* mutations [19]. *CRLF2* rearrangements also have revealed to be associated with gain of function mutations of IL7R in patients with ALL [20, 21]. The mutant *IL-7R* proteins forms a functional receptor with *CRLF2* for *TSLP* and resulting in cytokine-independent growth of progenitor lymphoid Cells [20]. Importantly, *CRLF2* rearrangements are surrogates of poor outcome and can be used in risk stratification and targeting therapy.

IKZF1 gene deletions

During recent years, between recurring genetic alterations which cooperate in leukemogenesis, the lymphoid transcription factor gene *IKZF1* has been found to have definite prognostic impact in B-ALL [22, 23]. *IKZF1*, which encodes IKAROS protein member of family of zinc finger, is required for the development of all lymphoid lineages [24] and has been established as one of the most clinically relevant tumor suppressors in high-risk acute lymphoblastic leukemia. *IKZF1* deletions usually result in the expression of dominant-negative IKAROS variants (e.g., *IK6*) that are characterized by loss of N-terminal zinc fingers (which mediate DNA binding) and result in the loss of the tumor suppressor function attributed to wild-type *IKZF1* [25, 26]. The incidence of *IKZF1* deletions in children with Philadelphia chromosome-positive (Ph+) ALL is approximately 70%, whereas its incidence in children with Philadelphia chromosome–negative (Ph-) ALL is 10–15%, and is related with an increased risk of relapse and decreased overall survival in both groups [24, 27–30].

Intrachromosomal amplifications of chromosome 21 (*iAMP21*) in ALL

Intrachromosomal amplification of chromosome 21 (*iAMP21*) is an uncommon high-risk Chromosomal abnormality that occur in approximately 2–5% of pediatric patients with B-cell precursor ALL [31–33]. Fluorescence in situ hybridization (FISH), using *RUNX1*, provides the only reliable detection method (five or more *RUNX1* signals per cell) [34]. Patients with *iAMP21* are older (median 9 years vs 5 years) with a low white cell count (median 3.9 vs 12.4) compared to children without this abnormality [35]. In a study of, 1630 ALL patients were treated on the UK MRC ALL97 protocol, *iAMP21* was recognized as an independent predictor of poor EFS (29% vs 78%) and OS (71% vs 87%) at 5 years [35]. The results of two cohorts of patients with B-cell precursor ALL and iAMP amplification (2%) treated on ALL97 or UKALL2003 showed that iAMP21 patients with ALL benefitted from receiving more intensive therapy in UKALL2003 (event-free survival (29% vs 78%), relapse (70% vs 16%) and overall survival rates (67% vs 89%) at 5 years) [36].

BCR-ABL1-like or “Ph-like” ALL

Ph-like ALL, is a newly described subtype of ALL which exhibit a gene expression profile similar to that of Ph+ ALL but lacks *BCR-ABL1* fusion gene [37–39]. Deletions or mutations of *IKZF1* are hallmark of both *BCR–ABL1*–positive and Ph-like ALL which strikingly is associated with treatment failure and disease relapse in both [7, 30, 38, 40] The incidence of Ph-like ALL increases with age, from 10–15% of childhood B-ALL to over 25% of ALL in young adults (Fig. 1). The prognosis of *BCR-ABL1*–like ALL is poor. In the COG AALL0232 study, the EFS of the *BCR ABL1*–like cases was significantly inferior to that of the non *BCR-ABL1* like cases

Table III – Kinase rearrangements and therapeutic targets in Ph-like ALL [9]

Kinase	Tyrosine kinase inhibitor
ABL1	Dasatinib
ABL2	*Dasatinib*
CSF1R	Dasatinib
PDGFRB	Dasatinib
CRLF 2	JAK2 inhibitor
JAK2	JAK2 inhibitor
EPOR	JAK2 inhibitor
DGKH	Unknown
IL2RB	JAK1/JAK3 inhibitor
NTRK3	Crizotinib
PTK2B	FAK inhibitor
TSLP	JAK2 inhibitor
TYK2	TYK2 inhibitor

(62.6% ± 6.9% vs. 85.8% ± 2.0%) [41]. Rearrangements and sequence mutations in several classes of cytokine receptors and tyrosine kinases are a hallmark of Ph-like ALL [42]. Kinase-activating alterations were identified in 91% of patients with Ph-like ALL; rearrangements involving *ABL1*, *ABL2*, *CRLF2*, *CSF1R*, *EPOR*, *JAK2*, *NTRK3*, *PDGFRB*, *PTK2B*, *TSLP*, or *TYK2* that are responsive to treatment with currently available *TKIs* (Tab. III) [9].

PAX5

The PAX5 gene, belongs to the paired box (*PAX*) gene family of transcription factors, crucial for B lymphoid cell commitment [43]. Somatic alterations of the *PAX5* are a hallmark of B-ALL and occurred in over one – third of this patients [44, 45]. These alterations are heterozygous and comprise focal deletions, translocations, or point mutations that disrupt *PAX5* DNA-binding or transcriptional regulatory functions [46]. Several studies showed that *PAX5* abnormalities were not associated with an unfavorable prognosis and are not associated to outcome [44, 46]. Also in study of 89 patients with ALL, deletions of *PAX5* was observed in 29 patients which had no prognostic significance in ALL [47].

Janus kinase 1 and 2 mutations (*JAK1 or JAK2*) and *JAK-STAT* pathway in ALL

Janus kinase (*JAK*) is a family of intracellular, non-receptor tyrosine kinases that transduce cytokine-mediated signals via the *JAK-STAT* pathway [48, 49]. The JAK family has four members:*JAK1, JAK2, JAK3*, and *TYK2* that functioning as signal transducers to control cellular proliferation, survival, and differentiation [49]. The incidence of *JAK* mutation in ALL has been reported to be about 18 [50, 51] to 35% in DS-ALL [52] and about 10% in high risk *BCR-ABL1* negative ALL and have been associated with poor outcome [18]. Notably, between other family members, *JAK2* mutations are more common (at or near *JAK2 R683*) in B-progenitor ALL [18, 50]. Importantly, *JAK* mutations were shown to be associated with *CRLF2* rearrangements, it has been shown that 70% of *CRLF2*-rearranged cases also harbor *JAK* mutations [19]. Over expression of *CRLF2* with *JAK2* mutants resulted in cytokine-independent cell growth and constitutive activation of *JAK-STAT* signaling pathway, demonstrating that these two genetic lesions together contribute to leukemogenesis in B-progenitor ALL [19]. The signal transducers and activators of transcription (*STAT*) family is one of the best characterized downstream that is activated by *JAK* signaling. It contains a number of latent transcription factors that, when phosphorylated by the *JAKs*, drive the expression of genes involved in proliferation, apoptosis, migration, differentiation [53–55]. Disrupted or dysregulated *JAK-STAT* pathway result in immune deficiency syndromes and cancers [56]. Gain-of-function mutations in *IL7R* is one of the other mutations that activate the *JAK-STAT* signaling pathway and have been identified in patients with ALL. Activating mutations in *IL7R* are commonly found in T and B cell ALL and are frequently placed in the transmembrane domain [20, 57, 58]. *IL7R* is essential for normal lymphoid development [59]. *IL7R* heterodimerizes either with interleukin 2 receptor subunit gamma (*IL2RG*) to form a receptor to *IL-7* or with *CRLF2* to form a receptor to *TSLP* [60, 61]. Activating mutations in *IL7R* lead to dimerization and constitutive activation of the *IL-7* receptor and resulting in cytokine independent activation of the downstream signaling pathways including *JAK–STAT* signaling pathway [57].

Conclusions

Obviously genome sequencing has revolutionized our knowledge of the genomic basis of ALL. These techniques helped us to identify new clinically important ALL subtypes and leukaemogenic alterations, which have led to a better risk stratification and will lead to improvement of patient-directed or individualized therapy for every patient. However, more comprehensively sequenced ALL genome is required to fully understand all somatic genetic alteration of ALL that incorporate to treatment failure and disease relapse.

Authors' contributions/ Wkład autorów

SMM – study design, data collection and interpretation, manuscript preparation, literature search. HNC, DMN – data interpretation, funds collection.

Conflict of interest/ Konflikt interesu

None declared.

Financial support/ Finansowanie

This study was supported by Vice Chancellor for Research (VCR) of Tabriz University of Medical Sciences (Grant No: 54/16960).

Ethics/ Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

REFERENCES/PIŚMIENNICTWO

[1] Larson S, Stock W. Progress in the treatment of adults with acute lymphoblastic leukemia. Curr Opin Hematol 2008;15 (4):400–407.

[2] Pui C-H, Mullighan CG, Evans WE, Relling MV. Pediatric acute lymphoblastic leukemia: where are we going and how do we get there? Blood 2012;120(6):1165–1174.

[3] Meijerink JP, den Boer ML, Pieters R. New genetic abnormalities and treatment response in acute lymphoblastic leukemia. Semin Hematol 2009;46(1):16–23. http://dx.doi.org/10.1053/j.seminhematol.2008.09.006.

[4] Harrison CJ. Targeting signaling pathways in acute lymphoblastic leukemia: new insights. Hematology Am Soc Hematol Educ Program 2013;2013:118–125. http://dx.doi.org/10.1182/asheducation-2013.1.118.

[5] Pui C-H, Relling MV, Downing JR. Acute lymphoblastic leukemia. N Engl J Med 2004;350(15):1535–1548.

[6] Ramakers-van Woerden NL, Pieters R, Loonen AH, Hubeek I, van Drunen E, Beverloo HB, et al. TEL/AML1 gene fusion is related to in vitro drug sensitivity for L-asparaginase in childhood acute lymphoblastic leukemia. Blood 2000;96 (3):1094–1099.

[7] Kaspers GJ, Smets LA, Pieters R, Van Zantwijk CH, Van Wering ER, Veerman AJ. Favorable prognosis of hyperdiploid common acute lymphoblastic leukemia may be explained by sensitivity to antimetabolites and other drugs: results of an in vitro study. Blood 1995;85(3):751–756.

[8] Woo JS, Alberti MO, Tirado CA. Childhood B-acute lymphoblastic leukemia: a genetic update. Exp Hematol Oncol 2014;3:16. http://dx.doi.org/10.1186/2162-3619-3-16.

[9] Roberts KG, Li Y, Payne-Turner D, Harvey RC, Yang YL, Pei D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. N Engl J Med 2014;371 (11):1005–1015. http://dx.doi.org/10.1056/NEJMoa1403088.

[10] Yoda A, Yoda Y, Chiaretti S, Bar-Natan M, Mani K, Rodig SJ, et al. Functional screening identifies CRLF2 in precursor B-cell acute lymphoblastic leukemia. Proc Natl Acad Sci U S A 2010;107(1):252–257. http://dx.doi.org/10.1073/pnas.0911726107.

[11] Mullighan CG, Collins-Underwood JR, Phillips LA, Loudin MG, Liu W, Zhang J, et al. Rearrangement of CRLF2 in B-progenitor- and down syndrome-associated acute lymphoblastic leukemia. Nat Genet 2009;41(11):1243–1246. http://dx.doi.org/10.1038/ng.469.

[12] Russell LJ, De Castro DG, Griffiths M, Telford N, Bernard O, Panzer-Grumayer R, et al. A novel translocation, t(14;19) (q32;p13), involving IGH@ and the cytokine receptor for erythropoietin. Leukemia 2009;23(3):614–617. http://dx.doi.org/10.1038/leu.2008.250.

[13] Pandey A, Ozaki K, Baumann H, Levin SD, Puel A, Farr AG, et al. Cloning of a receptor subunit required for signaling by thymic stromal lymphopoietin. Nat Immunol 2000;1(1):59–64. http://dx.doi.org/10.1038/76923.

[14] Akasaka T, Balasas T, Russell LJ, Sugimoto KJ, Majid A, Walewska R, et al. Five members of the CEBP transcription factor family are targeted by recurrent IGH translocations in B-cell precursor acute lymphoblastic leukemia (BCP-ALL). Blood 2007;109(8):3451–3461. http://dx.doi.org/10.1182/blood-2006-08-041012.

[15] Russell LJ, Capasso M, Vater I, Akasaka T, Bernard OA, Calasanz MJ, et al. Deregulated expression of cytokine receptor gene, CRLF2, is involved in lymphoid transformation in B-cell precursor acute lymphoblastic leukemia. Blood 2009;114(13):2688–2698. http://dx.doi.org/10.1182/blood-2009-03-208397.

[16] Cario G, Zimmermann M, Romey R, Gesk S, Vater I, Harbott J, et al. Presence of the P2RY8-CRLF2 rearrangement is associated with a poor prognosis in non-high-risk precursor B-cell acute lymphoblastic leukemia in children treated according to the ALL-BFM 2000 protocol. Blood 2010;115 (26):5393–5397. http://dx.doi.org/10.1182/blood-2009-11-256131.

[17] Chen IM, Harvey RC, Mullighan CG, Gastier-Foster J, Wharton W, Kang H, et al. Outcome modeling with CRLF2, IKZF1, JAK, and minimal residual disease in pediatric acute lymphoblastic leukemia: a Children's Oncology Group study. Blood 2012;119(15):3512–3522. http://dx.doi.org/10.1182/blood-2011-11-394221.

[18] Mullighan CG, Zhang J, Harvey RC, Collins-Underwood JR, Schulman BA, Phillips LA, et al. JAK mutations in high-risk childhood acute lymphoblastic leukemia. Proc Natl Acad Sci U S A 2009;106(23):9414–9418. http://dx.doi.org/10.1073/pnas.0811761106.

[19] Harvey RC, Mullighan CG, Chen IM, Wharton W, Mikhail FM, Carroll AJ, et al. Rearrangement of CRLF2 is associated with mutation of JAK kinases, alteration of IKZF1, Hispanic/Latino ethnicity, and a poor outcome in pediatric B-progenitor acute lymphoblastic leukemia. Blood 2010;115 (26):5312–5321. http://dx.doi.org/10.1182/blood-2009-09-245944.

[20] Shochat C, Tal N, Bandapalli OR, Palmi C, Ganmore I, te Kronnie G, et al. Gain-of-function mutations in interleukin-7 receptor-alpha (IL7R) in childhood acute lymphoblastic leukemias. J Exp Med 2011;208(5):901–908. http://dx.doi.org/10.1084/jem.20110580.

[21] Zhang J, Ding L, Holmfeldt L, Wu G, Heatley SL, Payne-Turner D, et al. The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. Nature 2012;481(7380):157–163. http://www.nature.com/nature/journal/v481/n7380/abs/nature10725.html#supplementary-information.

[22] Mullighan CG, Su X, Zhang J, Radtke I, Phillips LA, Miller CB, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. N Engl J Med 2009;360(5):470–480. http://dx.doi.org/10.1056/NEJMoa0808253.

[23] Georgopoulos K, Bigby M, Wang JH, Molnar A, Wu P, Winandy S, et al. The Ikaros gene is required for the development of all lymphoid lineages. Cell 1994;79(1):143–156.

[24] Martinelli G, Iacobucci I, Storlazzi CT, Vignetti M, Paoloni F, Cilloni D, et al. 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):5202–5207. http://dx.doi.org/10.1200/jco.2008.21.6408.

[25] Trageser D, Iacobucci I, Nahar R, Duy C, von Levetzow G, Klemm L, et al. Pre-B cell receptor-mediated cell cycle arrest in Philadelphia chromosome-positive acute lymphoblastic leukemia requires IKAROS function. J Exp Med 2009;206 (8):1739–1753. http://dx.doi.org/10.1084/jem.20090004.

[26] Iacobucci I, Lonetti A, Cilloni D, Messa F, Ferrari A, Zuntini R, et al. Identification of different Ikaros cDNA transcripts in

Philadelphia-positive adult acute lymphoblastic leukemia by a high-throughput capillary electrophoresis sizing method. Haematologica 2008;93(12):1814–1821. http://dx.doi.org/10.3324/haematol.13260.
[27] Mullighan CG, Su X, Zhang J, Radtke I, Phillips LA, Miller CB, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. N Engl J Med 2009;360(5):470–480.
[28] van der Veer A, Waanders E, Pieters R, Willemse ME, Van Reijmersdal SV, Russell LJ, et al. Independent prognostic value of BCR-ABL1-like signature and IKZF1 deletion, but not high CRLF2 expression, in children with B-cell precursor ALL. Blood 2013;122(15):2622–2629. http://dx.doi.org/10.1182/blood-2012-10-462358.
[29] Kuiper RP, Waanders E, van der Velden VH, van Reijmersdal SV, Venkatachalam R, Scheijen B, et al. IKZF1 deletions predict relapse in uniformly treated pediatric precursor B-ALL. Leukemia 2010;24(7):1258–1264. http://dx.doi.org/10.1038/leu.2010.87.
[30] van der Veer A, Zaliova M, Mottadelli F, De Lorenzo P, Te Kronnie G, Harrison CJ, et al. IKZF1 status as a prognostic feature in BCR-ABL1-positive childhood ALL. Blood 2014;123(11):1691–1698. http://dx.doi.org/10.1182/blood-2013-06-509794.
[31] Ma SK, Wan TS, Cheuk AT, Fung LF, Chan GC, Chan SY, et al. Characterization of additional genetic events in childhood acute lymphoblastic leukemia with TEL/AML1 gene fusion: a molecular cytogenetics study. Leukemia 2001;15(9):1442–1447.
[32] Moorman AV. The clinical relevance of chromosomal and genomic abnormalities in B-cell precursor acute lymphoblastic leukaemia. Blood Rev 2012;26(3):123–135. http://dx.doi.org/10.1016/j.blre.2012.01.001.
[33] Harrison CJ, Moorman AV, Schwab C, Carroll AJ, Raetz EA, Devidas M, et al. An international study of intrachromosomal amplification of chromosome 21 (iAMP21): cytogenetic characterization and outcome. Leukemia 2014;28(5):1015–1021. http://dx.doi.org/10.1038/leu.2013.317.
[34] Harrison CJ. Cytogenetics of paediatric and adolescent acute lymphoblastic leukaemia. Br J Haematol 2009;144(2):147–156. http://dx.doi.org/10.1111/j.1365-2141.2008.07417.x.
[35] Moorman AV, Richards SM, Robinson HM, Strefford JC, Gibson BE, Kinsey SE, et al. Prognosis of children with acute lymphoblastic leukemia (ALL) and intrachromosomal amplification of chromosome 21 (iAMP21). Blood 2007;109(6):2327–2330. http://dx.doi.org/10.1182/blood-2006-08-040436.
[36] Moorman AV, Robinson H, Schwab C, Richards SM, Hancock J, Mitchell CD, et al. Risk-directed treatment intensification significantly reduces the risk of relapse among children and adolescents with acute lymphoblastic leukemia and intrachromosomal amplification of chromosome 21: a comparison of the MRC ALL97/99 and UKALL2003 trials. J Clin Oncol 2013;31(27):3389–3396. http://dx.doi.org/10.1200/jco.2013.48.9377.
[37] Medeiros BC. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. N Engl J Med 2009;360(17):1787. http://dx.doi.org/10.1056/NEJMc090454. author reply 1788.
[38] Den Boer ML, van Slegtenhorst M, De Menezes RX, Cheok MH, Buijs-Gladdines JG, Peters ST, et al. A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study. Lancet Oncol 2009;10(2):125–134. http://dx.doi.org/10.1016/s1470-2045(08)70339-5.
[39] Payne-Turner D, Pei D, Becksfort J, Harvey RC, Li Y, Song G, et al. Integrated genomic and mutational profiling of adolescent and young adult ALL identifies a high frequency of BCR-ABL1-Like all with very poor outcome. Blood 2013;122(21):825.
[40] Mullighan CG, Miller CB, Radtke I, Phillips LA, Dalton J, Ma J, et al. BCR-ABL1 lymphoblastic leukaemia is characterized by the deletion of Ikaros. Nature 2008;453(7191):110–114. http://dx.doi.org/10.1038/nature06866.
[41] Loh ML, Harvey RC, Mullighan CG, Linda SB, Devidas M, Borowitz MJ, et al., editors. A BCR-ABL1-Like. Gene Expression Profile Confers a Poor Prognosis In Patients with High-Risk Acute Lymphoblastic Leukemia (HR-ALL): A Report From Children's Oncology Group (COG) AALL0232. Blood. 1900M STREET, NW SUITE 200, WASHINGTON, DC 20036 USA: AMER SOC HEMATOLOGY; 2011.
[42] Roberts KG, Morin RD, Zhang J, Hirst M, Zhao Y, Su X, et al. Genetic alterations activating kinase and cytokine receptor signaling in high-risk acute lymphoblastic leukemia. Cancer Cell 2012;22(2):153–166. http://dx.doi.org/10.1016/j.ccr.2012.06.005.
[43] Cobaleda C, Schebesta A, Delogu A, Busslinger M. Pax5: the guardian of B cell identity and function. Nat Immunol 2007;8(5):463–470. http://dx.doi.org/10.1038/ni1454.
[44] Mullighan CG, Goorha S, Radtke I, Miller CB, Coustan-Smith E, Dalton JD, et al. Genome-wide analysis of genetic alterations in acute lymphoblastic leukaemia. Nature 2007;446(7137):758–764. http://dx.doi.org/10.1038/nature05690.
[45] Kuiper RP, Schoenmakers EF, van Reijmersdal SV, Hehir-Kwa JY, van Kessel AG, van Leeuwen FN, et al. High-resolution genomic profiling of childhood ALL reveals novel recurrent genetic lesions affecting pathways involved in lymphocyte differentiation and cell cycle progression. Leukemia 2007;21(6):1258–1266. http://dx.doi.org/10.1038/sj.leu.2404691.
[46] Familiades J, Bousquet M, Lafage-Pochitaloff M, Bene MC, Beldjord K, De Vos J, et al. PAX5 mutations occur frequently in adult B-cell progenitor acute lymphoblastic leukemia and PAX5 haploinsufficiency is associated with BCR-ABL1 and TCF3-PBX1 fusion genes: a GRAALL study. Leukemia 2009;23(11):1989–1998. http://dx.doi.org/10.1038/leu.2009.135.
[47] Iacobucci I, Lonetti A, Paoloni F, Papayannidis C, Ferrari A, Storlazzi CT, et al. The PAX5 gene is frequently rearranged in BCR-ABL1-positive acute lymphoblastic leukemia but is not associated with outcome. A report on behalf of the GIMEMA Acute Leukemia Working Party. Haematologica 2010;95(10):1683–1690. http://dx.doi.org/10.3324/haematol.2009.020792.
[48] Yamaoka K, Saharinen P, Pesu M, Holt 3rd V, Silvennoinen O, O'Shea JJ. The janus kinases (Jaks). Genome Biol 2004;5(12):253.
[49] Schindler C, Levy DE, Decker T. JAK-STAT signaling: from interferons to cytokines. J Biol Chem 2007;282(28):20059–20063. http://dx.doi.org/10.1074/jbc.R700016200.
[50] Bercovich D, Ganmore I, Scott LM, Wainreb G, Birger Y, Elimelech A, et al. Mutations of JAK2 in acute lymphoblastic leukaemias associated with Down's syndrome. Lancet 2008;372(9648):1484–1492. http://dx.doi.org/10.1016/s0140-6736(08)61341-0.
[51] Gaikwad A, Rye CL, Devidas M, Heerema NA, Carroll AJ, Izraeli S, et al. Prevalence and clinical correlates of JAK2 mutations in Down syndrome acute lymphoblastic leukaemia. Br J Haematol 2009;144(6):930–932. http://dx.doi.org/10.1111/j.1365-2141.2008.07552.x.
[52] Kearney L, Gonzalez De Castro D, Yeung J, Procter J, Horsley SW, Eguchi-Ishimae M, et al. Specific JAK2 mutation (JAK2R683) and multiple gene deletions in Down syndrome acute lymphoblastic leukemia. Blood 2009;113(3):646–648. http://dx.doi.org/10.1182/blood-2008-08-170928.

[53] Shuai K, Liu B. Regulation of JAK-STAT signalling in the immune system. Nat Rev Immunol 2003;3(11):900–911. http://dx.doi.org/10.1038/nri1226.
[54] O'Shea JJ, Pesu M, Borie DC, Changelian PS. A new modality for immunosuppression: targeting the JAK/STAT pathway. Nat Rev Drug Discov 2004;3(7):555–564. http://dx.doi.org/10.1038/nrd1441.
[55] Fridman JS, Scherle PA, Collins R, Burn T, Neilan CL, Hertel D, et al. Preclinical evaluation of local JAK1 and JAK2 inhibition in cutaneous inflammation. J Invest Dermatol 2011;131(9):1838–1844. http://dx.doi.org/10.1038/jid.2011.140.
[56] Aaronson DS, Horvath CM. A road map for those who don't know JAK-STAT. Science 2002;296(5573):1653–1655. http://dx.doi.org/10.1126/science.1071545.
[57] Zhang J, Ding L, Holmfeldt L, Wu G, Heatley SL, Payne-Turner D, et al. The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. Nature 2012;481(7380):157–163. http://dx.doi.org/10.1038/nature10725.
[58] Zenatti PP, Ribeiro D, Li W, Zuurbier L, Silva MC, Paganin M, et al. Oncogenic IL7R gain-of-function mutations in childhood T-cell acute lymphoblastic leukemia. Nat Genet 2011;43(10):932–939. http://dx.doi.org/10.1038/ng.924.
[59] Peschon JJ, Morrissey PJ, Grabstein KH, Ramsdell FJ, Maraskovsky E, Gliniak BC, et al. Early lymphocyte expansion is severely impaired in interleukin 7 receptor-deficient mice. J Exp Med 1994;180(5):1955–1960.
[60] Noguchi M, Nakamura Y, Russell SM, Ziegler SF, Tsang M, Cao X, et al. Interleukin-2 receptor gamma chain: a functional component of the interleukin-7 receptor. Science 1993;262(5141):1877–1880.
[61] Liu YJ, Soumelis V, Watanabe N, Ito T, Wang YH, Malefyt Rde W, et al. TSLP: an epithelial cell cytokine that regulates T cell differentiation by conditioning dendritic cell maturation. Annu Rev Immunol 2007;25:193–219. http://dx.doi.org/10.1146/annurev.immunol.25.022106.141718.
[62] Rochman Y, Kashyap M, Robinson GW, Sakamoto K, Gomez-Rodriguez J, Wagner KU, et al. Thymic stromal lymphopoietin-mediated STAT5 phosphorylation via kinases JAK1 and JAK2 reveals a key difference from IL-7-induced signaling. Proc Natl Acad Sci U S A 2010;107(45):19455–19460. http://dx.doi.org/10.1073/pnas.1008271107.
[63] Shochat C, Tal N, Bandapalli OR, Palmi C, Ganmore I, te Kronnie G, et al. Gain-of-function mutations in interleukin-7 receptor-α (IL7R) in childhood acute lymphoblastic leukemias. J Exp Med 2011;208(5):901–908.
[64] Zenatti PP, Ribeiro D, Li W, Zuurbier L, Silva MC, Paganin M, et al. Oncogenic IL7R gain-of-function mutations in childhood T-cell acute lymphoblastic leukemia. Nat Genet 2011;43(10):932–939. http://www.nature.com/ng/journal/v43/n10/abs/ng.924.html#supplementary-information.
[65] Tzoneva G, Perez-Garcia A, Carpenter Z, Khiabanian H, Tosello V, Allegretta M, et al. Activating mutations in the NT5C2 nucleotidase gene drive chemotherapy resistance in relapsed ALL. Nat Med 2013;19(3):368–371. http://dx.doi.org/10.1038/nm.3078.
[66] Hof J, Krentz S, van Schewick C, Korner G, Shalapour S, Rhein P, et al. Mutations and deletions of the TP53 gene predict nonresponse to treatment and poor outcome in first relapse of childhood acute lymphoblastic leukemia. J Clin Oncol 2011;29(23):3185–3193. http://dx.doi.org/10.1200/jco.2011.34.8144.
[67] Mullighan CG, Zhang J, Kasper LH, Lerach S, Payne-Turner D, Phillips LA, et al. CREBBP mutations in relapsed acute lymphoblastic leukaemia. Nature 2011;471(7337):235–239. http://dx.doi.org/10.1038/nature09727.
[68] Roberts KG, Mullighan CG. Genomics in acute lymphoblastic leukaemia: insights and treatment implications. Nat Rev Clin Oncol 2015;12(6):344–357.
[69] Harrison CJ. Targeting signaling pathways in acute lymphoblastic leukemia: new insights. ASH Edu Prog Book 2013;2013(1):118–125.