Chapter

Genetic Abnormalities in ALL

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Abstract

Acute lymphoblastic leukemia (ALL), can be defined by a family of genetically heterogeneous lymphoid neoplasms derived from B- and T-lymphoid progenitors. ALL constitutes the most common childhood cancer, due to an overproduction of immature lymphoid hematopoietic cells. Genetic analyzes currently provides important information for classifying patients into prognostic groups, genetic analysis also helps to understand the mechanisms of relapse, pharmacogenetics and the development of new potential therapeutic targets, which should help to further improve the results of leukemia. In fact, the new techniques in molecular cytogenetic permits to identify new cryptic abnormalities, these discoveries have led to the development of new therapeutic protocols. The role of cytogenetic analysis is crucial on ALL patient's management. Karyotyping coupled with FISH analysis identifies recurrent chromosomal abnormalities in ALL, many of these abnormalities have prognostic and treatment impact. This chapter summarizes chromosomal abnormalities that are common and classify ALL according to the World Health Organization (WHO) classifications (2016 revision). We will present the main genetic modifications recently identified as well as the sequence mutations which have helped in the elucidation of the pathogenesis of ALL.

Keywords: Acute lymphoblastic leukemia, World Health Organization classification, cytogenetic analysis, FISH analysis

1. Introduction

Acute lymphoblastic leukemias (ALL) are clonal proliferations of immature cells involved in B (LAL-B) or T (LAL-T) lymphoid differentiation and blocked at an early stage of differentiation. The ALL is the most frequent childhood malignancy. In multiple studies dating back more than 50 years, both B-cell ALL and T-cell ALL are associated with characteristic and recurrent cytogenetic changes [1, 2]. They had a great value for diagnosis, risk stratification, disease monitoring and treatment selection. The conventional cytogenetics techniques have experienced significant advancement into molecular cytogenetics technologies. These recent advancements have largely overcome the limitations of conventional cytogenetics techniques. Fluorescence in situ hybridization (FISH), multiplex ligation-dependent probe amplification (MLPA), array comparative genomic hybridization (aCGH) and next-generation sequencing (NGS) techniques are part of the armory of molecular cytogenetics technologies [3–5].

2. Cytogenetic technics

2.1 Conventional cytogenetic

Conventional banded karyotyping for the detection and prognosis of genetic diagnosis is considered as the gold standard. It has been used to analyze genome modifications that include both genome gains and losses, as well as rearrangements within and between chromosomes [5]. Conventional single cell and metaphase cytogenetics are important in tumor genetics for disease control, tumor staging, and research purposes to recognize chromosomal regions containing genes and proto-oncogeneses of putative tumor suppressors [6].

2.2 Fluorescence in situ hybridization (FISH)

Fluorescence in situ hybridization (FISH) is a technique for determining complex DNA sequences as well as the number and structure of chromosomes. The method is focused on the use of fluorescent probes that can recognize specific DNA sequences. FISH is a technique for detecting genetic defects in embryos that is fast and sensitive. Targeting and denaturing DNA fixed in cells, nuclei, or metaphase chromosomes on the surface of the slide is the basis of the FISH analysis. Next, after its denaturation, a complementary single-stranded DNA sequence probe will precisely re-anneal double-stranded DNA (hybrid) molecules during the hybridization reaction. Probe DNA molecules are labeled enzymatically with modified nucleotides. They are DNA molecules designated hapten-labeled (indirect FISH) and fluorescent-labeled (direct FISH). An antifade solution containing 4′,6-diamidino-2 phenylindole is added to the slide after the removal of unbound single-stranded DNA and nonspecifically bound DNA from the slide by posthybridization washing. Using epifluorescence microscopes with specialized filters for detecting fluorochromes, FISH signals are observed. The signal is captured by a charge-coupled system camera, and the fluorescent signals are then quantified [7, 8].

2.3 Polymerase chain reaction (PCR)

Polymerase chain reaction (PCR) is a fast and cheap technique used to "amplify" small segments of DNA by copying them. Because significant amounts of a sample of DNA are needed for molecular and genetic analysis, without PCR amplification, studies of isolated pieces of DNA are almost impossible. The PCR method is based on a cell's natural processes for replicating a new DNA strand. For PCR, only a few biological ingredients are needed. The template DNA—that is, the DNA that contains the region to be copied, such as a gene—is an essential component. A prototype can be as small as one DNA molecule. The sequence of two short regions of nucleotides (DNA subunits) at either end of the region of interest is all that is needed for this fragment to be replicated. The primers bind to the template at their complementary sites, or anneal, and serve as the starting point for copying. The replication of the desired intervening sequence is achieved when DNA synthesis at one primer is guided toward the other. Free nucleotides and a DNA polymerase, an enzyme that builds new DNA strands by sequentially adding on free nucleotides according to the template's instructions, are also needed.

2.4 Next-generation sequencing (NGS)

NGS requires sequencing of millions of DNA molecules concurrently to produce sequence reads. In order to detect small insertions/deletions (indels) and structural

variants (SVs) of 450 bp, sequence reads are aligned with the reference genome and base variants. Overall, NGS has the potential to generate up to one billion short reads per instrument cycle, an immense amount of data cheaply.

3. Chromosomal and molecular abnormalities associated with ALL-B

60–80% of patients with ALL have abnormalities in chromosome number or structural rearrangements (translocations), whereas the remaining 20–40% have normal karyotype [9, 10]. Besides those with a normal karyotype, t(9;22)(q34,q11); BCR/ABL (BCR-ABL1), t(12;21)(p13;q22);TEL/AML1 (ETV6-RUNX1), t(4;11)(q21;q23); MLL/AF4 (KMT2A/AFF1), t(1;19)(q23;p13); E2A/PBX1 (TCF3-PBX1), are the most common cytogenetic subtypes in ALL [10–12].

3.1 Structural chromosomal abnormalities

3.1.1 The t(9;22)(q34;q11.2)(BCR-ABL1)

The BCR/ABL1 or Philadelphia (Ph) chromosome is a t(9;22) product that fuses the chromosome 9 Abelson kinase gene (ABL1) with the chromosome 22 breakpoint cluster region (BCR) that expresses the fusion protein BCR-ABL1: a constitutively active tyrosine kinase. The breakpoint occurs between exons 1 and 2 (e1 and e2) of the BCR gene in the minor breakpoint cluster region, m-BCR, in the majority of Ph positive ALL patients, and between exons 1 and 2 of the ABL gene in the majority of Ph positive ALL patients (e1a2). This results in the development of a 7-kb mRNA and the expression of the p190 protein [13]. This transcribes an 8.5 kb mRNA that codes for a chimeric p210 protein [14]. The Philadelphia chromosome is the most important cytogenetic abnormality. It is seen in 3% of pediatric patients, and almost 25% of adults, and rises with age, reflecting about half of the cases of patients older than 60 years of age, and although historically associated with poor prognosis, results have been markedly improved with the use of tyrosine kinase inhibitors (TKIs) [15].

3.1.2 The t(12;21)(p13;q22)(ETV6-RUNX1)

The most prevalent translocation in childhood acute lymphoblastic leukemia is TEL-AML1 gene fusion, induced by t(12;21) (p12;q22). However, this anomaly is rare among adults. The translocation of t(12;21) is cryptic by normal G-banding and includes FISH examination for cytogenetic detection [16]. ETV6-RUNX1 patients were thought to have a good prognosis at first, and they were associated with favorable risk factors including female gender, young age, low white cell count, and CD10+ immunophenotype [17]. However, some studies found no gain for ETV6-RUNX1 patients [18], while others found a high incidence of gene fusion in relapse patients and a predilection for late relapse [19, 20]. However, it is now clear that the initial optimism was justified. Almost every major clinical trial group in the world has confirmed that children with the ETV6-RUNX1 fusion have excellent overall survival and very low relapse rates [21, 22], and the presence of added cytogenetic or molecular abnormalities does not modify this good prognosis.

3.1.3 The KMT2A (MLL) Gene Rearrangements (11q23)

A transcriptional coactivator with methyltransferase activity encodes the gene KMT2A. The rearrangements result in the fusion of the 5′ portion of KMT2A, including the methyltransferase domain, to the 3′ region of the partner genes.

KMT2A (MLL) rearrangements, particularly the translocation of t(4;11)(q21;q23), are most common in infants (<1 year of age) and are associated with poor outcomes [23, 24]. The t(4;11)(q21;q23) can be detected by conventional cytogenetics, FISH, RT-PCR, or Southern blot techniques. Overall, ALL with MLL rearrangement have an unfavorable prognosis.

3.1.4 The t(1;19)(q23;P13), TCF3-PBX1

The translocation t(1;19)(q23;p13) is the result of the fusion of the PBX1 gene at 1q23 with the TCF3 (E2A) gene at 19p13.3. This translocation occurs in approximately 5–6% of childhood and adult B-cell precursor (BCP) ALLs [25, 26]. The translocation t(1.19) appears in balanced form (presence of two derived chromosome) or more often in unbalanced form with the derivative chromosome 19: (der (19)t(1.19)(q23;p13)). TCF3-PBX1 patients usually have a pre-B immunophenotype that expresses cytoplasmic μ [27]. It's one of the few genetic disorders that doesn't seem to increase in frequency with age. Originally considered a high-risk subtype of ALL, it is now associated with a favorable outcome with contemporary treatment, although some studies have indicated that it has an independent risk factor for CNS relapse [28].

3.1.5 IKZF1(7p12) deletion or mutations

The IKZF1 gene is located on the 7p12.2 chromosome band, consists of 8 exons, and codes for the transcription factor IKAROS with key regulatory functions in lymphopoiesis [29, 30]. IKAROS harbors 6 fingers zinc. Four of these are located in the DNA-binding domain encoded by exons 4 to 6 and are important for the tumor suppressor function of IKAROS to be preserved. Exon 8 encodes the remaining 2 zinc fingers and mediates IKAROS dimerization either as a homodimer or with other transcription factors in its family [29, 31]. The deletions of this gene, are very frequently associated with the BCR-ABL1 fusion in the development of ALL of the B line. These deletions result in haploinsufficiency by partial or total deletion. it seems that these deletions represent an independent risk of relapse.

3.1.6 CRLF2 rearrangement (IGH-CRLF2; P2RY8-CRLF2)

CRLF2 encodes cytokine receptor-like factor 2, also known as the thymic stromal-derived lymphopoietin receptor (TSLPR), wich forms an heterodimeric receptor with the interleukin-7 receptor a chain (IL7Ra) for thymic stromal lymphopoietin (TSLP). CRLF2 is deregulated by translocation into the immunoglobulin heavy chain locus (IGH-CRLF2); focal deletion upstream of CRLF2, resulting in P2RY8-CRLF2 fusion; and less often, CRLF2 point mutations (F232C) [32]. In Ph-like and Down syndrome-related ALL, CRLF2 rearrangements are most common and are age dependent, with P2RY8-CRLF2 associated with young age and IGH-CRLF2 associated with older age and Hispanic ancestry [33, 34]. Most CRLF2-rearranged ALLs have additional JAK–STAT or Ras signaling alterations, particularly activating JAK1 or JAK2 mutations, FLT3 and IL7R sequence mutations, SH2B3 deletions, TSLP rearrangements, and Ras mutations [35–37]. CRLF2 rearrangements have been associated with poor prognosis in most studies, especially in cases of concomitant IKZF1 alteration [38, 39].

3.1.7 Intrachromosomal amplification of chromosome 21 (iAMP21)

Intrachromosomal amplification of chromosome 21 or iAMP21 is defined as the presence of three or more additional copies of *RUNX1* on a structurally

abnormal chromosome 21. The iAMP21 chromosome is often initially detected by *ETV6 - RUNX1* FISH analysis [40, 41]. It affects about 2–5% of B-cell precursor acute lymphoblastic leukemia pediatric patients [42, 43]. Patients with iAMP21 are usually between the ages of 7 and 13, with a median age of 10 [44]. It is particularly uncommon in children under the age of five and in people over the age of twenty. Complex intrachromosomal amplification of chromosome 21 is most common in older children and the poor prognosis is improved by high-risk treatment. Accurate identification of this abnormality is considered to be extremely necessary in determining the best course of treatment.

3.1.8 The Philadelphia Chromosome – like Acute Lymphoblastic Leukemia (Ph-like ALL)

Ph-like, or BCR-ABL1-like ALL is characterized by a leukemic cell transcriptional profile similar to Ph + ALL but lack the BCR-ABL1 fusion gene [45, 46]. Ph-like ALL is vary heterogeneous in the altered genes and the form (rearrangements, mutations, or deletions) of alterations that result in the activated tyrosine kinase or cytokine receptor signaling characteristic of this subtype of ALL [46]. However, these fall into four main groups: (1) Alterations driving JAK–STAT signaling, most commonly rearrangements of CRLF2 (IGH-CRLF2, P2RY8-CRLF2, CRLF2 F232C), and less commonly, rearrangements of JAK2, EPOR, or TYK2, and mutations/deletions of IL7R, SH2B3, JAK1, JAK3, TYK2, IL2RB); (2) fusions involving ABL-class genes (ABL1, ABL2, CSF1R, LYN, PDGFRA, PDGFRB); (3) mutations activating Ras signaling (NRAS, KRAS, PTPN11); and (4) less common fusions (FLT3, FGFR1, NTRK3) [35, 36, 47]. Ph-like is associated with high-risk clinical characteristics, poor response to induction chemotherapy, elevated levels of minimal residual disease (MRD), and/or poor survival [48].

3.2 ALL with number anomalies

3.2.1 Hyperdiploidy

Hyperdiploidy is the most prevalent recurrent abnormality in childhood B-ALL. In the World Health Organization classification of tumors of hematopoietic and lymphoid tissues, hyperdiploidy in B-lymphoblastic leukemia (B-ALL), characterized by the presence of 51–65 chromosomes, has been identified as a distinct subtype of B-ALL [49]. In hyperdiploidy, numerical chromosomal gains are nonrandom, with additional copies (usually trisomies) of chromosomes 21, X, 14, and 4 most commonly found in pediatric patients [50]. Despite the presence of nonspecific structural abnormalities, the extra chromosomes are still normal copies of chromosomes. There is a poor understanding of the mechanism involved in inducing hyperdiploidy and its role in leukaemogenesis. Hyperdiploid B-ALL comprises approximately 25–30% of pediatric B-ALL cases [51]; and is often associated with a favorable prognosis with a cure rate greater than 90%, especially when hyperdiploidy is associated with trisomies of chromosomes 4 and 10 [52–54].

3.2.2 Hypodiploidy

Hypodiploidy, characterized by less than 44 chromosomes is less frequent than hyperdiploid ALL. Three cytogenetic subgroups of hypodiploidy were defined: near haploidy, with 24–31 chromosomes; low hypodiploid, with 32–39 chromosomes; and high hypodiploid, with 40–43 chromosomes [55]. Near-haploidy patients showed common chromosomal gains, rare structural abnormalities and a

co-incident doubled hyperdiploid population [56–58]. Low hypodiploidy karyotypes are usually monosomic for chromosomes 3, 7, 15, 16, 17, and disomic for chromosomes 1, 6, 11, and 18. In this subgroup, the phenomenon of doubling-up occurs, and sub-clones with near-triploid karyotypes are common. Furthermore, evidence indicates that in near-haploid situations, cytogenetic research is more likely to show only the doubled-up clone. Overall Hypodiploid acute lymphoblastic leukemia (ALL) has been associated with a dismal prognosis [59, 60].

4. Chromosomal and molecular abnormalities associated with ALL-T

T-cell acute lymphoblastic leukemia (T-ALL) is a leukemia that develops when there is an accumulation of genomic lesions that impair T-cell growth. T-ALL is correlated with a lot of genetic diversity. The accumulation of a variety of genetic and epigenetic defects leads to leukemic transformation [61]. As a result of excessive neoplastic cell proliferation, they cause disorders of cell differentiation, apoptosis, oncogene activation, and suppressor inhibition. The first genetic abnormalities in T-ALL patients were chromosome aberrations. Except for tetraploidy, which occurs in around 5% of cases, numerical changes are uncommon and have little prognostic significance.

The identification of chromosomal anomalies, such as 9p deletions that result in CDKN2A (p16) and CDKN2B (p15) inactivation, and translocations affecting T-cell receptor genes, has been crucial in gaining an understanding of the genetic defects present in T-ALL.

The proportion of cytogenetically normal cases at diagnosis is higher in T-ALL than in B-ALL, with about 50 percent of patients with T-ALL possessing a normal karyotype. Approximately one-third of T-ALL patients have a translocation involving one of the T-cell receptor genes (TCR), with a breakpoint at 14q11 (*TCRA/TCRD*) or 7q34 (*TCRB*), juxtaposing the T-cell receptor genes to pivotal transcription factor genes, such as TAL1, TAL2, LYL1, OLIG2, LMO1, LMO2, TLX1 (HOX11), TLX3 (HOX11L2), NKX2–1, NKX2–2, NKX2–5, HOXA genes, MYC, and MYB. In the adult population, the translocation t(10;14)(q24;q11.2), which results in overexpression of the *TLX1 (HOX11)* gene, is the most common and is associated with a favorable outcome [62, 63]. In addition, T-ALLs can contain cryptic rearrangements of ABL1 that may be amenable to TKI therapy. In general, studies of gene expression profiling have helped to classify T-ALL into molecular subgroups characterized by distinct signatures of gene expression and aberrant activation of specific oncogenes of the T-ALL transcription factor, including MEF2C, HOXA, TLX1, NKX2.1, TLX3, TAL1, LMO1, and LMO2 [41, 64].

5. Conclusion

Acute lymphoblastic leukaemia (ALL) is the commonest childhood cancer. However, conventional cytogenetic and molecular analyses fail to identify clonal driver alterations in approximately 25% of ALL in children and the majority of cases in adults but when they are present, they have a crucial role in the management of ALL patients. Recent advancements in gene expression profiling and genome-wide sequencing have revolutionized our understanding of ALL pathogenesis over the last years. As defined in this review, the accumulation of results has restructured ALL genetic classifications. Overall, we expect that research over the next decade can thoroughly define the genomic of ALL across all generations and refine the therapeutic algorithm to be more targeted and individualized.

DOI: http://dx.doi.org/10.5772/intechopen.97429

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