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Pathogenesis of pediatric B-cell acute lymphoblastic leukemia: Molecular pathways and disease treatments (Review)

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Abstract. B-cell acute lymphoblastic lymphoma (B-ALL) is a disease found mainly in children and in young adults. B-ALL is characterized by the rapid proliferation of poorly differentiated lymphoid progenitor cells inside the bone marrow. In the United States, ~4,000 of these patients are diagnosed each year, accounting for ~30% of childhood cancer types. The tumorigenesis of the disease involves a number of abnormal gene expressions (including *TEL-AML1, BCR-ABL-1, RAS* and *PI3K*) leading to dysregulated cell cycle. Risk factors of B-ALL are the history of parvovirus B 19 infection, high birth weight and exposure to environmental toxins. These risk factors can induce abnormal DNA methylation and DNA damages. Treatment procedures are divided into three phases: Induction, consolidation and maintenance. The goal of treatment is complete remission without relapses. Apart from traditional treatments, newly developed approaches include gene targeting therapy, with the aim of wiping out leukemic cells through the inhibition of mitogen-activated protein kinases and via c-Myb inhibition enhancing sensitivity to chemotherapy. To evaluate the efficacy of ongoing treatments, several indicators are currently used. The indicators include the expression levels of microRNAs (miRs) miR-146a, miR-155, miR-181a and miR-195, and soluble interleukin 2 receptor. Multiple drug resistance and levels of glutathione reductase can affect treatment efficacy through the increased efflux of anti-cancer drugs and weakening the effect of chemotherapy through the reduction of intracellular reactive oxygen species. The present review appraised recent studies on B-ALL regarding its pathogenesis, risk factors, treatments, treatment evaluation and causes of disease relapse. Understanding the mechanisms of B-ALL initiation and causes of treatment failure can help physicians improve disease management and reduce relapses.

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Contents

1. Introduction

Leukemia is characterized by the presence of abnormally large numbers of immature, poorly differentiated white blood cells in the blood; the condition often begins with bone marrow abnormalities (1). In children, acute lymphoblastic leukemia (ALL) is the most common type of blood cancer. In the United States, ~4,000 patients are diagnosed each year, accounting for ~30% of childhood cancer types (2,3). Among these ALL cases, >80% result from clonal proliferation of abnormal B cell progenitors (B-ALL) (4). In recent years, cytosolic signal transduction and molecular abnormality have been shown to play important roles in the pathogenesis of B-ALL; the abnormalities include gene mutations, abnormal protein interaction, unarrested cell cycle and increased autophagy (5,6). Knowledge on these abnormalities could help develop gene targeted therapy. In the wake of medical improvements, increasingly more risk factors have been discovered for B-ALL; minimizing these risk factors could therefore lower its prevalence. Over the last few years, the cure rate of B-ALL has

substantially been raised. Despite this improvement, relapse rate maintains at ~15% for patients with B-ALL (7). Such treatment failure could be associated with multiple drug resistance or the abnormal expression of intracellular enzymes.

This present review summarized pediatric B-ALL, its pathogenesis, risk factors, current treatment, and the monitoring of treatment efficacy and treatment failure. Better understanding of the underlying mechanisms of B-ALL could facilitate the development of novel target therapies to reduce the prevalence of B-ALL and the likelihood of relapse.

2. Pathogenesis

Lymphoid cells are initially developed from pluripotent hematopoietic stem cells in the bone marrow. B cells are primarily differentiated from common lymphoid progenitor cells pro-B cells, pre-B cells and mature B cells. The maturation process is normally well managed by cell signal transduction, activated transcription factors and positive/negative selection (8). However, in the case of B-ALL, malignancies of B precursor-stage lymphoid cells inhibit lymphoid differentiation, leading to abnormal cell proliferation and survival (9). The occurrence of B-ALL is known to correlate with a series of gene mutations, which often start at the pluripotent stem cell stage, followed by processes of clonal expansion, differentiation, cell proliferation and dysregulated cell apoptosis; the end result is the replacement of normal lymphoid cells by malignant cells (10). A number of molecular pathways and gene expressions are known to be associated with ALL, which are elaborated below.

TEL-AML1. The 'two hits hypothesis' has been proposed to explain the tumorigenesis of childhood ALL (11). Specifically, the TEL-AML1 fusion gene is a mutation that could be present years before any clinical symptom appears, and often the mutation has taken place earlier *in utero* (12). This oncogene can act on the hematopoietic stem cell (HSC) and produces gene lesions; after the second genetic mutation (or environment hit), the multistep pathway is then activated to develop ALL (13,14). TEL-AML1 is therefore the molecular lesion that initiates the disease; here, the leukemic cells stay at the pro-B-cell stage (13,14). Experiments on cord blood samples are in support of the TEL-AML1 gene mutation occurring *in utero* (13,14). TEL-AML1-positive subjects have higher risks in developing ALL. TEL-AML1 potentially induces HSC expansion and accelerates transformation (12). Such series of events is consistent with the 'two hits hypothesis' in that two gene mutations are involved for the subsequent development of the malignancy (15).

BCR-ABL1. The ABL gene on chromosome 9 switches location with the BCR gene on chromosome 22 to form the BCR-ABL fusion gene. Chromosome 22 with the new fusion gene is referred to as the Philadelphia chromosome (Ph) (16). The BCR-ABL1 tyrosine kinase gene, transcribed at the Ph chromosome, is the most common mutation in B-cell ALL. Its worst prognosis is often associated with Ph, BCR-ABL-1 positive gene mutation (17). BCR-ABL can promote complex formation of GRB2, GAB2 and Son-of-Sevenless, with subsequent activation of RAS and recruitment of PI3K (18). The activation of RAS triggers signaling pathways of mitogen-activated protein kinase (MAPK) and stimulates cell proliferation. In mediating cell survival and proliferation, PI3K activates its downstream target, the serine-threonine kinase Akt and suppresses the activity of forkhead O transcriptional factors, degrading p27 and activating mTOR (19,20). To stimulate cell proliferation, BCR-ABL can regulate STAT5 activation, which also enhances cyclin D2 expression through the downregulated expression of miR-93 (21-23).

PAX5. Paired box protein Pax-5 is a B cell activator protein, which encodes nuclear transcriptional factors. It modulates B cell functions, including development, differentiation, migration and proliferation (24). Pax-5 controls B cell development from pro to mature B cells. Abnormal expressions of Pax-5 can lead to leukemic transformation at the early stage of tumorigenesis in B-ALL (25). The development of pro B cells is arrested under downregulated Pax-5 expression, an evidence in support of the critical role of Pax-5 on B cell development. Over 90% pediatric patients with B-ALL have overexpressed Pax-5 (24). Pax-5 can fuse with other proteins, such as Janus kinase (Jak) 2, to create an active kinase domain, leading to B cell proliferation via the Jak-STAT signaling pathways (26).

RAS. Patients with ALL and poor prognosis or relapses often have mutations in the RAS pathways; these mutations frequently occur during chemotherapy and are present in clones of relapsed leukemic cells (27). A recent study sequenced 13 RAS pathway genes derived from 461 initially diagnosed pediatric patients with B cell precursor-ALL and reported that 44.2% of patients displayed mutations in their RAS pathways (28). Such RAS mutations are also present in ~40% of relapsed pediatric patients with ALL (27). The activation of RAS pathways in leukemic cells impairs the efficacy of medical therapy using drugs such as glucocorticoids or anthracycline (29,30). HSC cells with RAS gene mutations show uncontrolled growth (31). Approximately 15% of pediatric patients with ALL have mutations on both NRAS and KRAS genes. These mutations, however, show no correlation with any other clinical symptom (32,33).

PI3K. The PI3K/Akt signaling pathway is involved in cell proliferation and cell survival. PI3K regulates the expression levels of mTOR, Bcl-2, NFκB and other proteins that all promote cell proliferation (34,35). The PI3K/Akt signaling pathway is activated in various types of liquid tumors such as B cell precursor-ALL (36) and hence it serves an important role in pathogenesis (37). In the leukemia microenvironment, marrow stromal cells (MSCs) promote the proliferation of leukemic cells and strengthen their resistance to chemotherapy, through PI3K/Akt signaling pathway (38). MSCs secrete C-X-C motif chemokine 12 that acts on C-X-C chemokine receptor type 4 of the leukemia blast cells and through the PI3K and Wnt pathways exert influences on their survival and proliferation (39). Overactivated PI3K pathway is frequently found in B-ALL and such overactivation is also associated with glucocorticoid resistance (40). Patients with B-ALL bearing negative regulators of the PI3E mutation, such as phosphatase and tensin homolog (PTEN), may have a higher chance of treatment failure and relapse (41).

Cell cycle. Deregulated cell cycles are correlated with the development of B-ALL (42). Uncontrolled proliferation of HSC and immature lymphoblastic cells can lead to leukemogenesis (43). Overexpression of c-MYC protein is associated with accelerated cell cycle progression in B-ALL (44). The dysregulation of c-MYC occurs in aggressive B-ALL cases and is correlated with aggressive course of disease, chemoresistance and poor prognosis (45,46). Autophagy inhibitor is found to inhibit B-ALL proliferation through arrested cell cycle at the G2/M phase (6), which indicates that autophagy in B-ALL potentially expedites cell cycle, and hence autophagy represents a novel therapeutic target for treating B-ALL (6). In addition, an elevated expression of nucleophosmin (NPM) is associated with the pathogenesis of acute leukemia. NPM, which plays an important role on cell proliferation, is commonly found in actively proliferating cells. NPM synthesis begins at G_1 phase and after its phosphorylation at both the Ser10 and Ser70 sites, cell cycle enters G_2/M phase, via the modulations of Cdk1 and Cdc25C (47).

3. Risk factors

Viral infection. One mechanism of leukemogenesis is DNA methylation caused by viral infections (48). The abnormal expression of hematopoietic and proliferation genes persists even after viral clearance. Patients with ALL with an infection history of parvovirus B19 show abnormal DNA methylation (49). Genes associated with cell proliferation and patterns of DNA methylation can be altered by ordinary infections and subsequently lead to altered progression of the ALL disease (50).

High birth weight. The progression of pediatric ALL can start *in utero* or shortly after birth. Rapid growth of the fetus increases the risk of inflicting ALL (51). High birth weight is an important risk factor for pediatric ALL (52,53). Similarly, gene expression of the insulin growth factor (IGF) axis also serves an important role; this abnormal gene expression can start *in utero* or during the early postnatal period when lymphoid stem cells are immature, and therefore increasing the risk of malignant transformation (3). The key regulators of fetal growth are IGF1, IGF2 and their receptors, IGF1R, IGF2R (54). During the postnatal period, IGF1 continues its influence on growth (55). Susceptive genotype of IGF1 is a high risk factor for childhood ALL in both the Hispanic and non-Hispanic populations, while IGF2 expression affects only the Hispanic population (3).

Environmental toxins. Benzene is widely present in the work environment, such as in fumes of paint and cigarette smoke. Benzene is a known carcinogen and parental exposure to benzene increases the risk of childhood ALL (56). In the liver or lung, benzene is metabolized to benzene oxide and hydroquinone, before further converted to benzoquinone in the bone marrow, where cytotoxicity and DNA damages typically occur (57). Prolonged DNA damages in the bone marrow increases the risk of developing ALL (58). A recent study reported that avoiding exposures to occupational and environmental benzene during pregnancy lowers the risk of ALL in the offspring (59).

4. Treatments

Currently, for childhood B-ALL, risk-directed therapy is the standard treatment. The age of the child at diagnosis is taken into account. Other factors considered are the initial white blood cell count, immunophenotypic and cytogenetic characteristics of the blast population, as well as the rapidity of response to early treatment. Standard treatment consists of chemotherapy that lasts 2-3 years. For many patients, complete remission (CR) is achieved at the end of the induction phase (60).

The success of such treatment involves a multidrug regimen that consists of three phases (induction, consolidation and maintenance), during which therapy or prophylaxis directed to the central nervous system (CNS) is delivered in multiple sessions (61).

The primary goal of induction is to reach an initial CR and to restore normal hematopoiesis. Induction therapy involves a weekly medication of vincristine and anthracycline for 3-4 weeks, daily corticosteroids and asparaginase (62).

The routine use of preventive CNS therapy is a major therapeutic advancement in the treatment of childhood ALL. CNS treatment usually begins in the induction phase and lasts until the end of treatment regimen. In some CNS preventive therapy protocols, the craniospinal radiotherapy is replaced by intrathecal chemotherapy (63).

The second phase of treatment, or consolidation, is focused on intensive CNS therapy in combination with sustained intensive systemic therapy. This phase of treatment starts shortly after the patient has reached CR. The goal of consolidation chemotherapy is to prevent leukemic regrowth, reduce residual tumor burden and prevent the emergence of drug-resistance in other leukemic cells (64). A combination of several drugs is typically involved with pharmacological mechanisms that are different from those in the induction phase; regimens often include the following drugs: Cytarabine, methotrexate, anthracyclines and alkylating agents (65-67). These drugs are administered according to schedules that would maximize drug synergy and minimize drug resistance.

After completing the consolidation (or intensification) phase of therapy, patients will often receive a less intensive continuation regimen (maintenance chemotherapy) that involves daily oral 6-mercaptopurine, weekly methotrexate with periodic vincristine, corticosteroid and intrathecal therapy. Maintenance phase lasts for another 2-3 years. Extending the maintenance phase thereafter has little benefits (68,69).

Approximately 15% of patients would relapse after treatment and the overall survival of patients with relapse is <10% (70). Thus, it is important to develop new ALL treatment strategies that have higher CR and lower drug toxicity. In recent years, resveratrol has been reported to induce apoptosis, cell cycle arrest or decrease cell proliferation through the enhanced expressions of p21 and p27 (71). The reduced expressions of antiapoptotic proteins, myeloid cell leukemia 1 and Bcl-2 and increased expressions of proapoptotic proteins, Bax, Bcl-2-like protein 11 and Bad, have resulted in upregulating caspase 3 (72). In addition, everolimus is an mTOR inhibitor, which induces autophagy and promotes cell death (73). This drug induces apoptosis through caspase-independent pathways and alters the mitochondrial permeability,

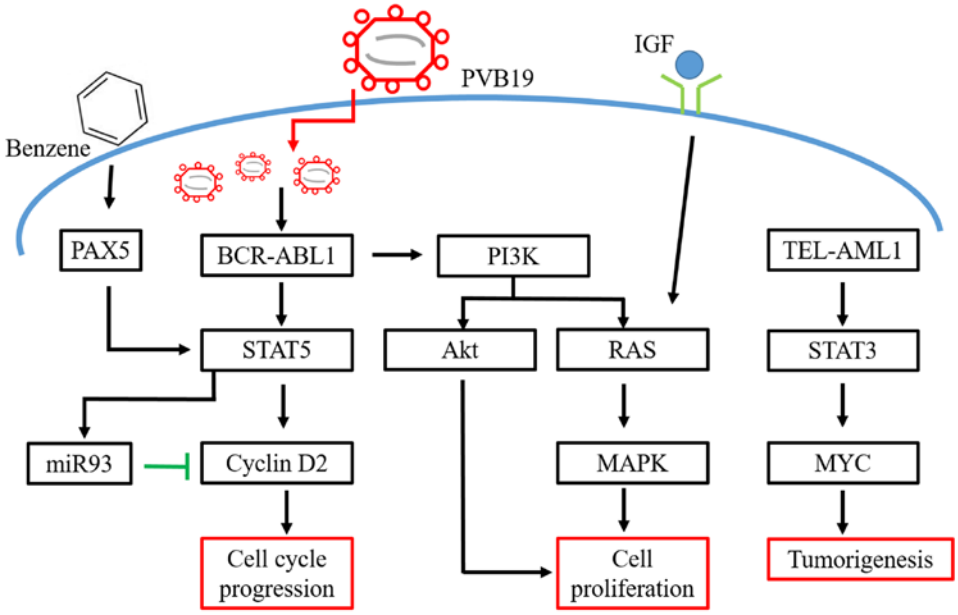

Figure 1. Schematic diagram of pathogenesis and risk factors in acute lymphoblastic leukemia. PVB 19: Parvovirus B19; IGF, insulin growth factor; miR, microRNA.

leading to cell dysfunction (70). Everolimus kills malignant cells through paraptosis (70). A specific inhibitor of mitogen activated protein kinase (MEK), selumetinib, could treat ALL. It acts on MEK1/2 to inhibit ERK-dependent cell proliferation (74). This drug has been used to treat RAS-mutated ALL with good results *in vitro* and *in vivo* (27,75). Besides these aforementioned target therapies, other new strategies to treat ALL are outlined below.

Autophagy-targeting treatment. Autophagy is the process of breaking down intracellular organelles for energy transfer to maintain homeostasis compatible with cell viability. The process of autophagy is switched on when cells are stressed or damaged to a certain degree. Leukemic cells resistant to chemotherapy are found to have activated autophagy (76). Thus, targeting autophagy is a promising new therapeutic approach to treat B-ALL. In models of ALL cell line, newly developed drugs produce autophagy, cell cycle arrest and apoptosis. However, after combined treatment with autophagy inhibitor, cell viability is often downregulated. Results indicate that autophagy protects leukemic cells against cytotoxicity caused by anti-cancer drugs (77,78). This approach of autophagy manipulation might be an alternative for ALL treatment.

c-Myb-targeted therapy. c-Myb is the protein product of a proto-oncogene. It has three domains: N-terminal DNA binding domain, central transcriptional activation domain and C-terminal domain (79). The gene is carried by the avian myeloblastosis virus and the E26 retrovirus (80). During proliferation, especially of immature cells, the c-Myb transcription factor is overexpressed (81). In leukemia animal models and *in vitro* systems, c-Myb inhibitors delay disease onset (2). Inhibition of c-Myb downregulates leukemic cell proliferation, increases G0/G1 arrest and increases sensitivity of pre-B-ALL cells to cytotoxic agents (82,83). Experimental evidence is in support of c-Myb being a potential target for immunotherapy of ALL (83). Furthermore, other tumor cells also express c-Myb, making c-Myb-targeting therapy promising in clinical practice (84).

5. Monitoring treatment efficacy

It is important to evaluate treatment efficacy of any ALL therapy. Apart from the traditional blood test, the levels of microRNA and soluble interleukin receptors are used to monitor the treatment efficacy (85,86). In a whole genome microRNA analysis on patients with ALL, dysregulated expression of miR-128, miR-146a, miR-155, miR-181a and miR-195 were found (87). Treatments lasting for 6 months resulted in downregulated expressions of miR-146a, miR-155, miR-181a and miR-195 (87). Soluble interleukin 2 receptor (sIL-2R) has been identified as a biomarker of the disease activity of non-Hodgkin's lymphoma and it also reflects the tumor volume (88). Increased expression of sIL-2R are present in other lymphoproliferative disorders such as chronic lymphocytic leukemia and ALL. Immature blast cells release sIL-2R before entering the blood stream (89). Therefore, sIL-2R is useful for monitoring the treatment efficacy of ALL.

6. Treatment failure

For B-ALL patients, the frequency of relapse is associated with multiple drug resistance (MDR) (90). The overexpression of drug efflux pumps on leukemic cells under drug treatment is the most common condition for MDR and consequently the intracellular drug concentration is lowered (91). ATP-binding cassette (ABC) transporters actively pump drugs out of cells and their expression level is regulated by a number of intracellular signaling pathways, including MAPK, ERK and JNK (92,93). The ABC transporter pump is encoded by genes including ABCB1, ABCC1 and ABCG2.

Higher expression of ABCB1 gene has been reported in ALL cell lines and higher expression of ABCB1 is known to associate with poorer prognosis and shorter disease-free survival rates (94,95). Another mechanism of MDR concerns glutathione (GSH) and its associated enzymes, which are a part of the cell defense system against chemodrug-induced reactive oxygen species stress (96,97). Glutathione reductase is the key enzyme of the GSH redox cycle and it reduces the sensitivity to chemodrugs in leukemic cells by modulating redox homeostasis (98).

7. Conclusion

B-ALL is the most prevalent cancer in children. Despite better cure rates in recent years, the disease will still relapse for some patients. Therefore, understanding the molecular pathways for the pathophysiology of B-ALL and its relapse mechanisms are important (Fig. 1). Not all patients with B-ALL have satisfactory outcomes under the current treatments. Newly developed immune-targeting therapy would probably enhance the efficacy of chemotherapy and improve prognosis. Biomarkers can be used to monitor treatment course and to provide information for drug and dose adjustments. Well-designed clinical trials should be conducted to gain insights for constructing more effective immune targeting therapies and treatment protocols.

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Authors' contributions

FLH, CYY and SJY drafted the manuscript. ECL and CLL were involved in literature review and revising the manuscript. CYY and SJY edited the manuscript and were involved in the conception and design of this review article. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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