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Damage Mechanism of CK2 and IKAROS in Philadelphia Like Acute Lymphoblastic Leukemia

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Abstract

Acute lymphoblastic leukemia (ALL) is characterized by immature and poorly differentiated B lymphocytes in large numbers in the blood. B cells are distinct from the cell types involved in their development (common lymphoid progenitor cells, pro-B cells, pre-B cells, and mature cells). The process of B cell maturation depends on precise communication within the cell: signals activate specific genes that are essential for proper development. Errors in this intricate signaling network can lead to issues with B cell function and contribute to disease. B-lineage acute lymphoid leukemias, malignancies of precursor-stage B lymphoid cells inhibit lymphoid differentiation, leading to abnormal cell proliferation and survival. The process of developing leukemia (leukemogenesis) can be triggered by an overproduction of both hematopoietic stem cells (the cells that form all blood cells) and the immature versions of white blood cells called lymphoblasts. Acute lymphoblastic leukemia (ALL) with the presence of the Philadelphia chromosome (ALL Ph) is classified as a high-risk manifestation of the disease, this chromosome is the product of the reciprocal translocation, whose product is a BCR-ABL fusion protein. It is a highly active tyrosine kinase that can transform hematopoietic cells into cytokine-independent. Hyperphosphorylation cascades inhibit the differentiating function of IKZF1 as a tumor suppressor gene which leads to an abnormal proliferation of B cells due to the presence of the Philadelphia chromosome; it inhibits the differentiating process, leukemogenesis involving immature B cells in the bloodstream can result from the uncontrolled growth and division of hematopoietic stem cells and immature lymphoblasts (the precursors to B cells).

Keywords

Acute Lymphoblastic Leukemia, IKAROS, Dephosphorylation, Philadelphia

Chromosome, CK2

1. Introduction Lymphoid Progenitor Cells and B Cell Differentiation

Acute lymphoblastic leukemia (ALL) is a condition where a large number of immature B lymphocytes, a type of white blood cell, are found in the blood. These cells originate from stem cells in the bone marrow and normally go through specific stages (pro-B, pre-B, mature B). Signals within the body are responsible for guiding the maturation process, but in ALL, these signals malfunction, leading to abnormal cells. During their maturation, B lymphocytes pass through distinguishable phases, each of which is characterized by distinct cell surface markers and a specific pattern of Ig gene expression. [1]

1) The first cell to be compromised is the pro-B cell that comes from the bone marrow (they express CD19 and CD10).

2) RAG is expressed for the first time and causes the first recombination.

3) Igα and Igβ form the pre-receptor for the antigen of lineage B (pre-RLB).

4) A productive rearrangement is made, that is, bases are added or removed at the junctions in multiples of three. This ensures that the rearranged Ig gene can correctly encode an Ig protein.

5) Once the reorganization is productive, the pro-B lymphocyte is renamed the pre-B lymphocyte.

6) Then each pre-B rearranges the gene for a κ or λ light chain and produces a light chain protein and at the same time, this produces IgM, if it is expressed it ceases to be a pre-B and becomes an immature B lymphocyte.

7) These migrate to the spleen and complete their maturation by two transition phases if they can be committed to becoming marginal zone B lymphocytes or follicular B lymphocytes. [2]

In the case of B-lineage acute lymphoid leukemias, malignancies of precursor-stage B lymphoid cells inhibit lymphoid differentiation, leading to abnormal cell proliferation and survival. The uncontrolled proliferation of hematopoietic stem cells and immature lymphoblastic cells can lead to leukemogenesis. [3] [4] (**Figure 1**)

2. Leukemogenesis

In the case of B-lineage acute lymphoid leukemias, malignancies of precursor-stage B lymphoid cells inhibit lymphoid differentiation, leading to abnormal cell proliferation and survival. The uncontrolled proliferation of hematopoietic stem cells and immature lymphoblastic cells can lead to leukemogenesis. IKZF1 is a lymphocyte differentiation regulator located in chromosome 7p12, and it has tumor suppressor activity in Philadelphia- like leukemia. BCR-ABL and IKZF1 mutations are highly linked; somatic mutations in IKZF1 are present in 80% of Ph-like leukemias. [5] [6]

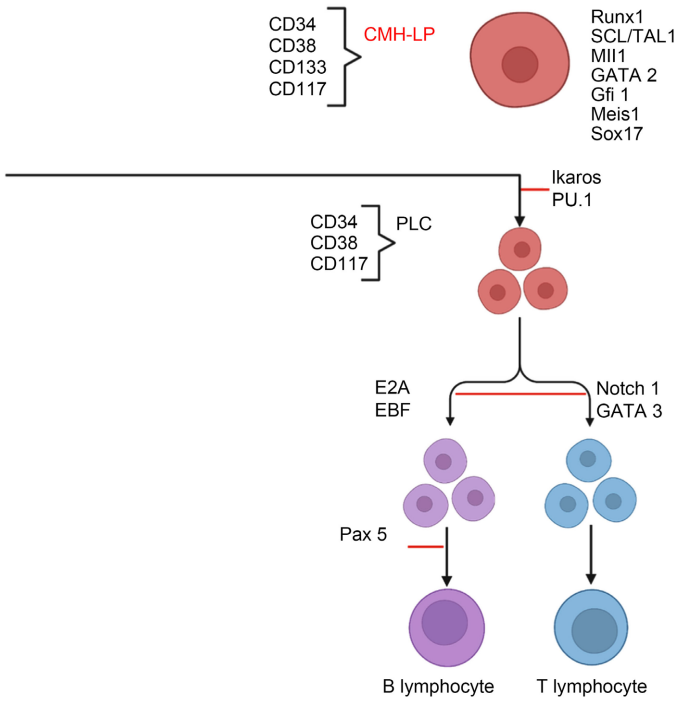

Figure 1. When cells begin to differentiate and develop, specific surface receptors are activated so that they begin a sequential gene expression program so that these cells can become "B" or "T" lymphocytes, progenitor substitution is activated and initiation of the reorganization of tumor receptor genes, these last two points are critical and fundamental for the development of lymphocytes. Virely C, Moulin S, Cobaleda C, *et al.* Haploinsufficiency of the IKZF1 (IKAROS) tumor suppressor gene cooperates with BCR-ABL in a transgenic model of acute lymphoblastic leukemia. Leukemia. 2010; 24(6):1200-4. [4]

3. Epidemiology

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, according to the World Health Organization classification. Sadly, around 15% - 20% of children with ALL succumb to the disease, primarily due to relapse or resistance to treatment.

Leukemias can be categorized based on the cell type they originate from, either lymphoid or myeloid. Among childhood lymphoid leukemias, approximately 85% are B-cell leukemias, while the remaining 15% are T-cell leukemias.

Focusing specifically on ALL in children, it accounts for 75% - 80% of childhood leukemias, with an incidence of 3 - 4 cases per 100,000 children under 15. It is more commonly diagnosed in white males, and in developed countries, the mortality rate is around 1% - 2%.

A specific type of ALL, called Ph-like ALL, exhibits varying prevalence based on factors like age, gender, and ethnicity. It affects roughly 12% of children, 21% of adolescents (16 - 20 years old), and 20% - 24% of adults over 40. Interestingly, young adults (21 - 39 years old) have the highest prevalence (27%). The outlook

(prognosis) for both adults and children with Ph-positive ALL treated with standard chemotherapy is very poor, with a cure rate of less than 5% in adults. [6] [7]

4. Philadelphia Chromosome-Positive (Ph+) Acute Lymphoblastic Leukemia (ALL)

Chromosomes 9 (Abelson) and 22 (Breakpoint Cluster Region)

Acute lymphoblastic leukemia (ALL) has made significant progress in its diagnosis and treatment, however; ALL with the presence of the Philadelphia chromosome (ALL Ph) is classified as a high-risk manifestation of the disease, BCR-ABL leukemic cells are 73 times more resistant to treatment than their counterpart without this alteration. [7] (**Figure 2**)

It is a highly active tyrosine kinase that can transform hematopoietic cells into cytokine-independent. The cause of the molecular predisposition of BCR-ABL1 is not fully understood. Still, there is a substantial multifactorial burden to which its appearance can be attributed, such as environmental factors like ionizing radiation, there are multiple mutations caused by radiation directly on the DNA, since there may be breakage of one or both chains, recombinations, base substitutions, deletions, among others. Infectious factors like Epstein-Barr virus (EBV) and human T-cell lymphotropic virus type 1 (HTLV-1). HTLV-1 infection promotes excessive T-cell activation and transformation into adult T-cell leukemia; HTLV-1 alters cell differentiation, activation, and survival. EBV-positive T-cell leukemia is characterized by monoclonal expansion of T cells with a cytotoxic phenotype. [8] (**Figure 3**)

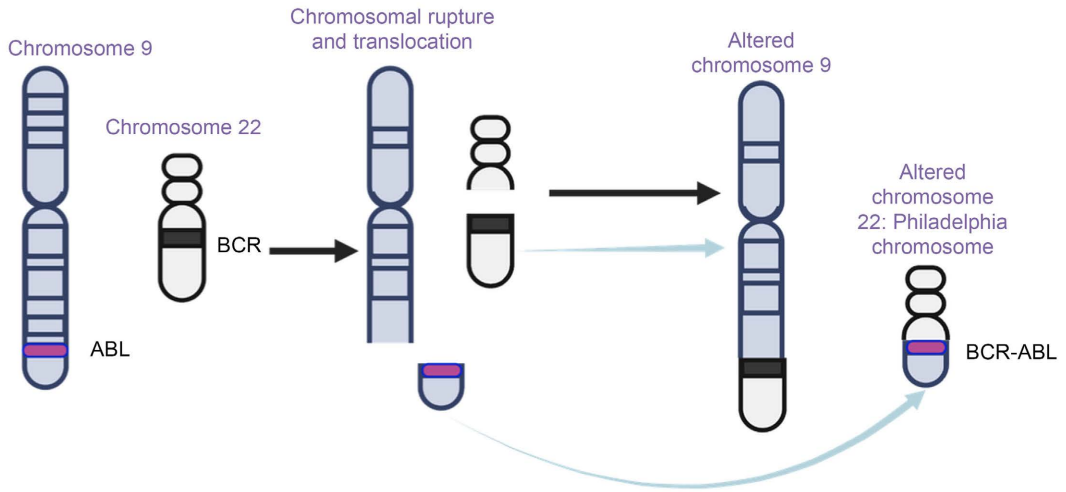

Figure 2. Philadelphia chromosome is the product of the reciprocal translocation between the long arms of chromosomes 9 (Abelson) and 22 (Breakpoint Cluster Region) t (9; 22) (q34; q11), whose product is a BCR-ABL fusion protein. Tan, B. J., Sugata, K., Reda, O., Matsuo, M., Uchiyama, K., Miyazato, P., Hahaut, V., Yamagishi, M., Uchimaru, K., Suzuki, Y., Ueno, T., Suzushima, H., Katsuya, H., Tokunaga, M., Uchiyama, Y., Nakamura, H., Sueoka, E., Utsunomiya, A., Ono, M., & Satou, Y. (12 2021). HTLV-1 infection promotes excessive T cell activation and transformation into adult T cell leukemia/lymphoma. The Journal of Clinical Investigation, 131(24). https://doi.org/10.1172/JCI150472 [7]

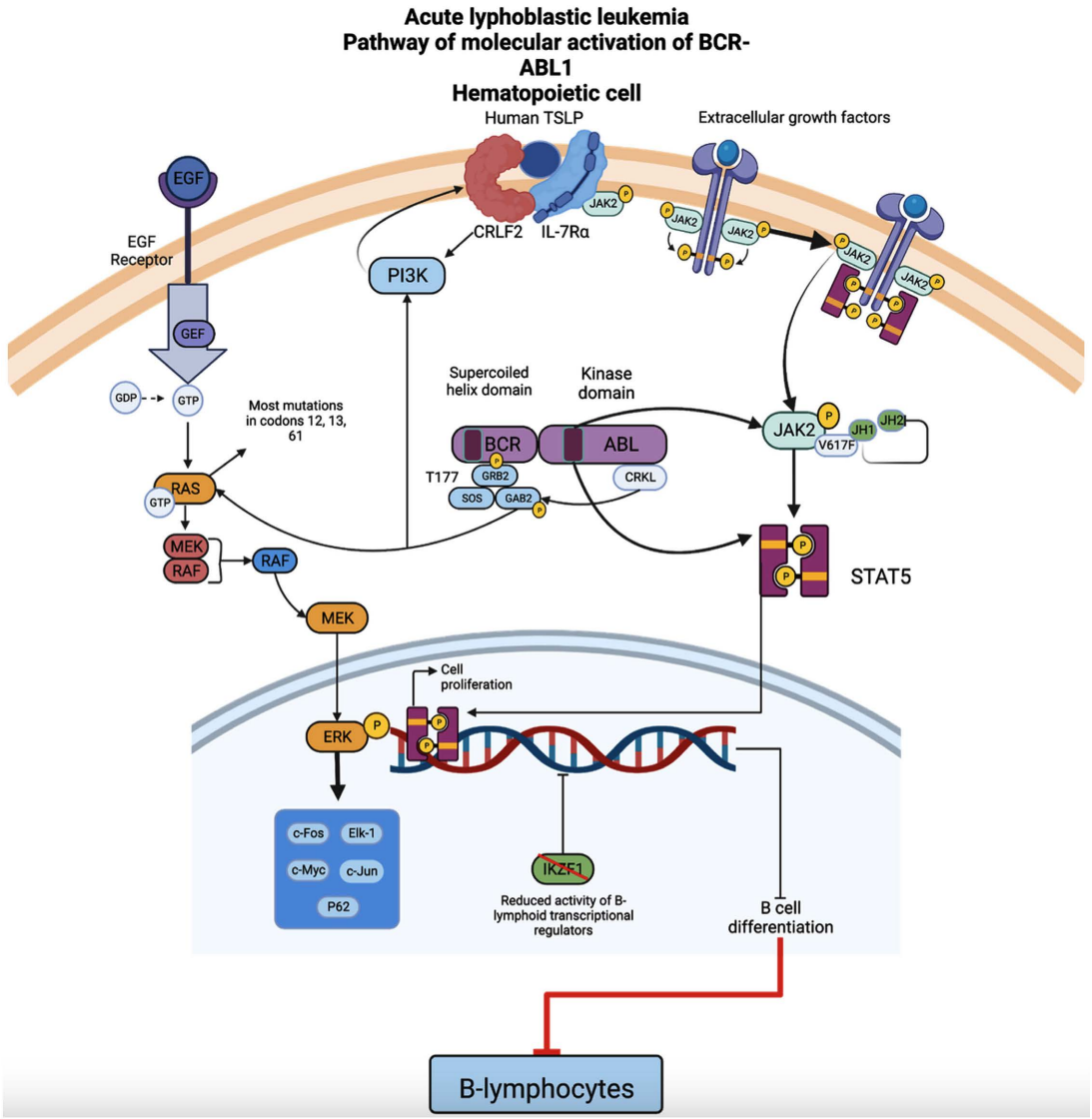

Figure 3. Acute lymphoblastic leukemia (ALL) has made significant progress in its diagnosis and treatment, however; ALL with the presence of the Philadelphia chromosome (LAA Ph) is classified as a high-risk manifestation of the disease, BCR-ABL leukemic cells are 73 times more resistant to treatment than their counterpart without this alteration. This chromosome is the product of the reciprocal translocation between the long arms of chromosomes 9 (Abelson) and 22 (breakpoint cluster region) t (9; 22) (q34; q11), whose product is a BCR-ABL fusion protein. It is a highly active tyrosine kinase that can transform hematopoietic cells to become cytokine-independent. The cause of the molecular predisposition of BCR-ABL1 is not fully understood, but there is a strong multifactorial burden to which its appearance can be attributed. Gowda, C., Soliman, M., Kapadia, M., Ding, Y., Payne, K., & Dovat, S. (2017). Casein Kinase II (CK2), Glycogen Synthase Kinase-3 (GSK-3), and Ikaros mediated regulation of leukemia. Advances in Biological Regulation, 65, 16-25. https://doi.org/10.1016/j.jbior.2017.06.001 [9]

5. CK2 and IKAROS Genomic Landscape

CK2, a pro-oncogenic serine/threonine-selective protein kinase, is a widely distributed and highly conserved enzyme that has gained increased attention in cancer research due to its significant impact and crucial role in tumorigenesis. By phosphorylating a range of substrates involved in gene expression, signal

transduction, and other nuclear functions, CK2 exhibits pleiotropic kinase activity. Originally identified for its interaction with casein in test tube experiments, casein is not a relevant target for this protein in living cells. CK2, the protein in question, has a unique structural element: a sequence of more than three basic amino acids in a row, seeing it from other proteins in its family. Importantly, a specific section of six basic amino acids is essential for binding to the CK2b subunit.9.

CK2 is present in humans at 4 different locations in the genome, but only 3 of these locations produce proteins. These 3 locations are found on chromosomes 20, 16, and 6 and produce the A, a0, and b subunits respectively. The roles of the a and catalytic subunits have not been widely studied, but they are very similar to each other with about 75% identical amino acid sequences. CK2 is made up of a tetramer, consisting of two catalytic subunits (a and/or a0) and two regulatory subunits (b). The catalytic subunits are longer (130 kDa) compared to the regulatory subunit (25 kDa). Three different combinations of these subunits can form heterotrimeric complexes: a2b2, aa'b2, and a02b2. CK2 activity does not rely on small molecules involved in second-messenger kinase activation, but it can be inhibited by negatively charged compounds like heparin, and activated by positively charged compounds such as polyamines. [9] [10]

The broad and diverse functions of CK2 in the human body suggest its importance in various physiological processes, particularly in the development and progression of cancer. Researchers have conducted numerous studies to identify potential substrates of CK2 that play crucial roles in disease progression. Previous studies conducted in vitro have confirmed that CK2 substrates regulate gene expression, protein synthesis, and DNA repair. CK2 plays a critical role in regulating cell growth and proliferation by controlling cell cycle progression. Moreover, it phosphorylates specific proteins with anti-apoptotic functions, which in turn, suppress cellular apoptosis. CK2's ability to override apoptotic signaling in cells implies its involvement in tumor formation, and studies have shown that CK2 significantly increases tumor growth in various cancer cells. Consistent with this role in oncogenesis, elevated levels of CK2 have been widely observed in several types of cancers, such as lung, breast, prostate, head and neck, and colon cancers. [9] [10] [11]

6. IKZF1 Mutation

IKAROS belongs to the group of zinc finger proteins that regulate DNA transcription, it is encoded by the IKZF1 gene whose chromosomal location is at (7p12). Its deletion is related to 60% - 80% of positive ALL-Ph. There may be deletion of the entire locus or subsets of exons, this is related to the chemoresistance of leukemic cells. [12]

IKAROS encodes a transcription factor that functions as a tumor suppressor in B-cell acute lymphoblastic leukemia (B-ALL). IKAROS functions as a tumor suppressor, regulating the transition of G1/S and the S phase. [13]

ALL-associated IKZF1 alterations have been linked with the upregulation of

multiple genes involved in cellular proliferation and chemoresistance. One study found that IKZF1-deleted ALL patients benefited from periodic vincristine/steroid pulses during maintenance therapy, prompting the Dutch Childhood Oncology Group to extend maintenance therapy and to include vincristine and steroid pulses for patients with IKZF1 deletions. [14]

7. CK2 Hyperfunction

"Trembley *et al.* discussed that protein kinases are profoundly important for post-translational modification of proteins, which concurs with the rather large portion of the translated human genome devoted to the protein kinase complement." [11]

Related to gene expression, CK2 phosphorylates and interacts with multiple transcription factors. The effects of these events vary from altered localization, stability, activation state, or association with other molecules. [15]

Carcinogenic casein kinase II (CK2) is overexpressed in leukemia (**Figure 1**) [16] (**Figure 4**).

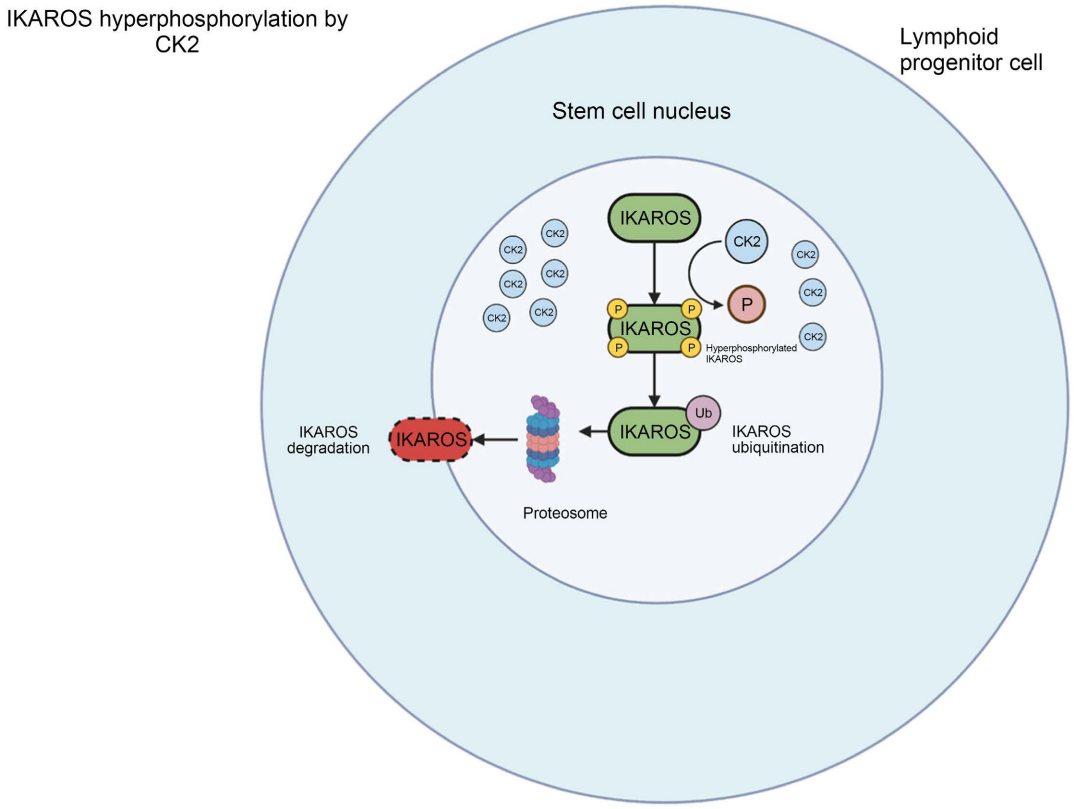

Figure 4. Carcinogenic casein kinase II (CK2) is overexpressed in hematopoietic stem cells. CK2 phosphorylates IKAROS amino acids, resulting in hyperphosphorylation, and inducing its degradation by ubiquitin-proteaseEl sistema de ubiquitinas y la eliminación de proteínas. (s/f). Uah.es. Recuperado el 28 de marzo de 2023, de http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S1729-519X2013000100004 Zamudio-Arroyo, J. M., Peña-Rangel, M. T., & Riesgo-Escovar, J. R. (2012). La ubiquitinación: un sistema de regulación dinámico de los organismos. Tip revista especializada en ciencias químico-biológicas, 15(2), 133–141. https://www.medigraphic.com/cgi-bin/new/resumen.cgi?IDARTICULO=42723. [16] [17]

Cellular homeostasis is carried out largely through phosphorylation, a clear example is protein kinase II (CK2), responsible for 25% of the phosphoproteome. Although oncogenic cases of CK2 have never been reported, its overexpression and hyperactivation are intrinsically associated with pathologies, such as positive Philadelphia-type acute lymphoblastic leukemia (Ph-ALL). [18] [19]

8. IKAROS Hyperphosphorylation and Ubiquitination

CK2 phosphorylates IKAROS amino acids, and when it is hyperphosphorylated its degradation by ubiquitin-protease is facilitated. The loss of regulation that IKAROS makes in the precursors of B cells contributes to the block in the differentiation of these cells, thus provoking the proliferation of immature B lymphocytes. [20] [21]

CK2 phosphorylates at multiple sites during post-translational modification and as a result, IKAROS loses its regulatory effect on cellular proliferation and differentiation. Phosphorylated IKAROS binds deficiently to its target genes and cannot localize to subcellular regions in the nucleus. This contributes to poor regulation of cell cycle progression and cell differentiation, resulting in malignant transformation and the development of leukemia. [22] [23]

The ubiquitination system is made up of three enzymes: E1 (activation), E2 (conjugation), and E3 (ligation). E1 (ubiquitin activase), is the enzyme responsible for activating ubiquitin since it binds to the C-terminus of a cysteine residue, this link requires ATP. After the binding of ubiquitin and the E1 enzyme, the E1-Ub complex is formed, this will interact with a cysteine residue of the E2 enzyme to form the E2-Ub complex. Finally, E3 (ubiquitin ligase) will bind to the E2-Ub complex to take the ubiquitin from it and transfer it to the target protein. [24] [25]

9. Conclusions

Acute lymphoblastic leukemia (ALL) is a type of blood cancer that arises from the abnormal proliferation of immature B lymphocytes in the bone marrow. A hallmark of this disease is an abundance of abnormal cells in the blood. These cells disrupt the normal development of immune cells (lymphoid differentiation). This disruption leads to uncontrolled cell growth and prolonged survival of the abnormal cells. When this uncontrolled growth involves blood-forming stem cells and immature white blood cells (lymphoblasts), it can result in leukemia. The prevalence of ALL is highest among children, with a higher incidence in white males. The prognosis of patients with Ph-positive ALL treated with standard chemotherapy is very poor, with less than 5% of adults being cured.

The presence of the Philadelphia chromosome (ALL Ph) is a high-risk manifestation of acute lymphoblastic leukemia (ALL), as BCR-ABL leukemic cells with this alteration are 73 times more resistant to treatment. As a tyrosine kinase with abnormally high activity, the BCR-ABL protein has the potential to alter the behavior of hematopoietic cells, rendering them capable of proliferation without

the need for cytokine stimulation. The molecular predisposition of BCR-ABL1 is not fully understood. Still, environmental factors like ionizing radiation and infectious factors like Epstein-Barr virus (EBV) and human T-cell lymphotropic virus type 1 (HTLV-1) contributed to its appearance. HTLV-1 infection promotes excessive T-cell activation and transformation into adult T-cell leukemia, while EBV-positive T-cell leukemia is characterized by monoclonal expansion of T cells with a cytotoxic phenotype.

CK2 is a widely distributed and highly conserved enzyme that is crucial in tumorigenesis due to its significant impact as a pro-oncogenic serine/threonine-selective protein kinase. By phosphorylating a diverse array of substrates, this kinase exhibits wide-ranging effects on cellular functions. These substrates play key roles in the regulation of genes, signal transmission pathways, and other critical processes within the nucleus. CK2 plays a critical role in regulating cell growth and proliferation by controlling the cell cycle.

The protein kinase CK2 plays a crucial role in regulating the degradation of IKAROS, a transcription factor essential for the differentiation of B cells. CK2-mediated phosphorylation of IKAROS amino acids facilitates its degradation by ubiquitin-protease, leading to the loss of regulation in the B cell precursors. This disruption in the normal differentiation process ultimately leads to the proliferation of immature B lymphocytes, which can have significant implications for the immune system's overall functioning.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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