Review Article

Investigating cellular and molecular factors effective in leukemia and analyzing the immune system

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ABSTRACT

Leukemia as one of the common cancers is still studied and needs improvement in diagnosis and treatment. In this study, we examined the activity of hematopoietic stem cells, which can be a precursor to leukemia. Hematopoietic cancer cells, by affecting the bone marrow, preserve the source of stem cells for the development of blood cancers. Also, in this study, various signaling pathways, including Wnt, which regulates the production of blood cells, and the abnormal expression and function of miRNAs in leukemia were investigated. We also analyzed various cellular and molecular factors that play a role in the occurrence of leukemia, as well as further studies in the field of cancer and immunology, which can lead to the discovery of new treatments and improve the function of the body's immune system against cancer cells.

***Keywords*:** Leukemia, signaling pathways, cellular and molecular factors, immune system

INTRODUCTION

Leukemia, as a common type of cancer, still needs to be improved in the field of diagnosis and classification [1]. Leukemia usually starts in the bone marrow, where all blood cells are formed and produced. When a person has leukemia, the white blood cells produced are usually too many and

abnormal, meaning they cannot effectively defend the body against disease, pathogens, or foreign substances. The type of white blood cells affected, whether lymphatic or myeloid, can distinguish the type of leukemia [2].

Leukemia is described as a heterogeneous group of hematologic cancers as a malignant blood disease characterized by uncontrolled proliferation and development of leukocytes in the blood and Bone Marrow (BM), liver, and spleen that accumulate in the blood [3]. Primary mutations may be present for years before causing disease. In some models of cancer progression, early mutations lead to clonal expansion by stem cells or other progenitor cells [4]. Such clonal expansions greatly increase the probability of subsequent mutations occurring in cells that previously harbored the initial mutations [5].

Population dynamics of hematopoietic stem cells may be the precursor of many hematological cancers [5]. A clonally expanded population of stem cells may exist before cancer develops [5]. In this article, we discuss the cellular and molecular factors effective in four common types of leukemia, which are: Chronic Lymphocytic Leukemia (CLL), Chronic Myeloid Leukemia (CML), and Acute Lymphocytic Leukemia (ALL), and Acute Myeloid Leukemia (AML).

Embryonic hematopoiesis in vertebrates takes place in different places and occurs in three consecutive stages. The first two stages occur in the embryonic yolk sac outside the embryo, with the formation of transitional hematopoietic populations (megaloblastic hematopoiesis). The third stage occurs within the embryo in the Aorta-Gonad-Mesonephros (AGM) region and gives rise to adult hematopoiesis (normoblastic hematopoiesis), leading to the formation of Hematopoietic Stem Cells (HSCs) and Mesenchymal Stem Cells (MSCs) that provide the organism with continuous production of blood cells [6].

Fetal BM HSCs was first isolated in 1992 and revealed the characteristic of asymmetric cell division based on functional properties [7]. HSCs differentiate into two daughter cells with similar properties: Long-Term HSCs (LT-HSCs) and Short-Term (ST-HSCs). LT-HSCs are a population of resident cells in the BM that maintain their self-renewal capacity for more than 6 months [7]. However, ST-HSCs are lineage-committed depending on niche-intrinsic and extrinsic signals, and thus cannot maintain their self-renewal property for more than a month [7].

ST-HSCs differentiate into Hematopoietic Progenitor Cells (HPCs), which further differentiate into Common Myeloid Progenitors (CMPs) and Common Lymphoid Progenitors (CLPs). CMPs constitute Granulocyte-Macrophage Precursors (GMPs) and Megakaryocyte-Erythrocyte Precursors (MEPs). GMPs form granulocytes, monocytes, and dendritic cells, while MEPs develop into erythrocytes and megakaryocytes. On the other hand, CLPs induce T, B, NK, and dendritic cells [7,8].

During leukemia progression, secretory factors derived from leukemia cells, including extracellular vesicles (mainly exosomes), involve changes in the niche of normal blood to create a microenvironment supportive of the malignant tumor [9,10]. The most common methods of treating leukemia include chemotherapy, radiation therapy, stem cell transplantation, and immunotherapy with interferon. After years of treatment, many patients overcome the disease and recover and continue to live a normal life. However, these treatments can have disastrous consequences for leukemia victims [2].

Acute Myeloid Leukemia (AML) is an aggressive hematologic malignancy characterized by abnormal proliferation and differentiation of immature myeloid cells. AML is classified according to the World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissue; Classification includes AML with recurrent genetic abnormalities, AML with myelodysplastic changes, treatment-related myeloid neoplasm, and AML not identified except as noted [11]. AML is a heterogeneous group of clonal disorders of the hematopoietic compartment, and although it develops in the hematopoietic stem cells of the bone marrow, it may be seen in other extravascular parts such as lymph nodes, brain, spinal cord, liver, spleen, testes, and other parts of the body [11].

Acute Lymphoblastic Leukemia (ALL) is a malignant disorder (an aggressive hematological tumor) that originates from hematopoietic B cells or T cells and is characterized by marked heterogeneity at the molecular and clinical levels [12]. B-ALL and T-ALL comprise different subtypes defined by their primary chromosomal abnormality (mainly chromosomal translocations causing chimeric gene fusions or extensive aneuploidy [13].

Chronic Myeloid Leukemia (CML) is a Hematopoietic Stem Cell (HSC)

malignancy that accounts for 15–20 % of all leukemia cases in adults [14]. This disease is caused by the clonal expansion of the damaged hematopoietic stem cell [15]. CML is a three-phasic myeloproliferative disorder that begins with a latent phase called the chronic phase (CP) [16]. In general, CML-CP is a Leukemia Stem Cell (LSC)-derived disease in which the overgrowth of LSC-derived Leukemia Progenitor Cells (LPC) leads to disease symptoms [17]. The accelerated phase of the disease (CML-AP) subsequently transforms into its highly aggressive blast crisis phase (CML-BP) [18].

Chronic Lymphocytic Leukemia (CLL) is a B-cell malignancy characterized by clonal expansion of malignant CD5+/CD19+ B cells and exhibits a heterogeneous pathology with chromosomal abnormalities, frequent mutations, and microenvironmental involvement [19]. In peripheral blood, CLL develops in the protective cavities and proliferation centers of the bone marrow, lymph nodes, and spleen, and rarely in the liver [20]. The survival and growth of CLL cells are highly dependent on the support of these surrounding microenvironmental cells, which include T cells, monocytes/macrophages, endothelial and mesenchymal stromal cells, and Natural Killer (NK) cells [20,21]. The complex interactions between CLL cells and these essential microenvironmental components are still poorly defined, but studies have shown how these interactions support disease progression and drug resistance [20,22,23]. Also, specifically, genetic abnormalities can act as prognostic factors in CLL [24]. Clinically, CLL is a heterologous malignancy with a good or poor prognosis, mainly characterized by the presence of specific markers, especially mutated (M-CLL) or unmutated (U-CLL) immunoglobulin heavy chain variable region (IGHV) is determined [25,26].

M-CLL and U-CLL were also characterized by proteome analysis, which showed that U-CLL cells had less migration and more adhesive protein patterns than M-CLL cells. This fact can favor their preservation in lymphoid tissues and the presence of lymphadenopathy [27].

Cellular and molecular factors effective in leukemia

The Warburg effect is a metabolic phenotype of tumor cells that are well produced instead of ATP production through oxidative phosphorylation [28]. Increased glycolysis has been observed in AML cell lines and human primary AML

blasts [29], while both phosphoinositide 3-kinase (PI3K)/ protein kinase serine-threonine B (AKT) and mammalian target of rapamycin appear to (mTOR), apparently contributes to this glycolytic metabolism [30,31].

AML, caused by potent oncogenes, such as Mixed Lineage Leukemia (MLL) fusions, may arise through Committed Myeloid Progenitors (CMP) while AML without any significant cytogenetic abnormalities may arise due to a combination of preleukemic initiating events in the Hematopoietic Stem Cell (HSC) source to be created [32]. Strong oncogenes mainly originate from CMP, followed by a few co-mutations that may enable the development of AML. It may also originate from the HSC compartment, leading to an aggressive and highly resistant phenotype. A large proportion of AML may be generated by the early cooperation of multiple mutations in the HSC compartment, which provides a clonal advantage leading to a preleukemic state, after which additional mutations may lead to AML. Thus, many AML samples show evidence of a cellular origin associated with the hierarchical organization model of leukemia, driven by a small population of stem cells, Leukemia-Initiating Cells (LICs), or Leukemic Stem Cells (LSCs) [33]. The characteristics of LSC include self-renewal, relative quiescence, resistance to apoptosis, and increased drug flow [34]. Single-cell gene expression before genome-wide transcriptional analysis of AML and chronic myeloid leukemia (CML) LSCs has highlighted several cellular markers such as IL1RAP and CD25 that are overexpressed [35]. However, these cell surface constructs of AML and CML LSCs are also expressed in normal HSCs [36]. IL1RAP has been described to enhance multiple oncogenic pathways in AML [37]. Targeting the extracellular portion of IL1RAP with monoclonal antibodies, regulating IL1RAP with short hairpin RNA, and removing Il1rap by genetic deletion inhibit AML growth through induction, differentiation, and apoptosis without affecting healthy hematopoietic cells that have low IL1RAP expression. And the pathogenesis of AML is inhibited *in vivo* (Figure 1) [38]. Inhibition of the canonical IL-1 receptor signaling pathway abrogates IRAK1 expression, which subsequently reduces Myelodysplastic Syndromes (MDS) and AML leukemic colony formation. The IL-1 receptor complex, IL1RAP, MyD88, IL-1R associated with kinases 2 (IRAK2) and [39] IRAK4, activates IRAK1 and TRAF6 and

leads to the activation of the IKK complex, which in turn causes the activation of genes It targets NFκB as well as JNK and p38 [40]. Inhibiting the IL-1 receptor pathway, targeting IL1RAP may also inhibit AML cell signaling and growth that occurs through the FLT3 and c-KIT pathways by reducing the response to the FLT3 ligand, Stem Cell Factor (SCF), and IL-1β [37]. However, FLT3 mutations independently cause constitutive activation of the FLT3-associated IL1RAP pathway, but IL1RAP has been shown to interact with FTL3 and c-KIT, even if FLT3 is mutated. However, IL1RAP overexpression occurs early in LSC pathogenesis [41], while FLT3 and c-KIT activating mutations appear to be a relatively late event in LSC transformation [42]. In addition, chronic inflammation caused by IL-1 exposure disrupts blood homeostasis and limits the relative production of HSC [43]. Chronic exposure to IL-1, in association with IL-6, TNF (tumor necrosis factor), and IFNs (interferons), may cause genomic instability and, through persistent replication, bone marrow dysfunction, and exposure. Exposure to Reactive Oxygen Species (ROS) can cause myeloid malignancies such as AML [44]. IL1RAP is described as a regulator of inflammation and its overexpression in AML may be related to a proinflammatory disease [45].

A type III receptor tyrosine kinase called KIT helps signal transduction in certain cells such as hematopoietic stem cells, mast cells, and Cajal cells of the gastrointestinal tract [46]. KIT also contributed to signal transduction in many pathways including P13K, JAK/STAT, MAPK, and Src pathways in various cells [46]. KIT mutations have been reported in cases of Acute Myeloid Leukemia (AML), particularly in nuclear binding factor (CBF) leukemia [46,47]. In AML, recent studies of AML genome profiling by Next-Generation Sequencing (NGS) have shown that some mutated genes (such as ASXL1, NPM1, FLT3, TP53, CEBPA, and RUNX1) are prevalent in patients with AML. Ad affects these patients [48].

Both downregulation and upregulation of KIT signaling have been reported in human cancers. In many cancers, such as AML, KIT activation was detected through overexpression or mutation [46]. KIT mutations often occur in the immunoglobulin-like domain proximal to the membrane (exon 8 and exon 9), JMD (exon 11), and tyrosine kinase domain (exon 17) [46].

Heat shock protein 90 (HSP90) is a molecular chaperone that plays an important role in mediating the correct folding and function of proteins in cells [46]. HSP90 is involved in the stabilization of cancer-related proteins necessary for tumor growth, including receptor tyrosine kinases, signal transducers, cell cycle regulators, and transcription factors [49]. One of the mechanisms of HSP90 inhibitors is to block ATP binding, which causes the degradation of target proteins [50]. In AML, it has been reported that HSP90 inhibitors may suppress mutant FLT3 as well as the JAK-STAT and P13K pathways [46]. A study reported that inhibition of Hsp90 disrupts the downstream signaling pathways of mutant KIT in a RUNX1-RUNX1T1 with a KIT-mutant cell line [51].

The PI3K/AKT/mTOR signaling pathway has been identified as a frequently activated switching point in ALL diseases. In particular, monotherapy approaches represent a major problem according cellular resistance. In one study, the PI3K/AKT/mTOR signaling pathway was investigated as a therapeutic target for the treatment of childhood Acute Lymphoblastic Leukemia (ALL) with a novel therapeutic approach to prevent cellular resistance [52]. In the case of BCR-ABL positive B-ALL cells, a combination with the classical inhibitor Imatinib was used, and in the case of MLL-AF4 positive B-ALL cells, a combination with Quizartinib was used to counteract FLT3. In addition, we showed that AKT inhibition alone leads to a feedback mechanism and upregulation of the phosphorylation of several receptor tyrosine kinases [52]. After specific knockdown of the three AKT isoforms in ALL cells, it was found that ErbB2/Her2 is highly phosphorylated in cells with AKT2 knockdown. AKT isoform 1 and 2 knockdown cells, in contrast to AKT isoform 3 knockdown cells, show poor proliferation and are probably maintained by increased ErbB2 receptor-tyrosine-kinase phosphorylation. This work provides the first indications for novel combination therapy of B-ALL cells highly activated against AKT, mTOR, and a kinase [52].

BCR-ABL1 is a constitutively active, multidomain chimeric tyrosine kinase arising from a reciprocal translocation between chromosomes 9 and 22 t(9;22) (q34;q11)-characteristic of Philadelphia chromosome-positive leukemia (Ph1). Depending on the breakpoint on chromosome 22 in the BCR gene, three

major BCR-ABL1 isoforms: 185 kDa, 210 kDa, and 230 kDa proteins are present in acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), and Chronic Neutrophilic Leukemia (CNL) respectively can be generated [53]. In all these conditions, the first exon of c-ABL, the cellular homolog of Abelson's murine leukemia virus (A-MuLV) on chromosome 9 is replaced by one of the BCR sequences. The BCR portion of the protein contributes to several domains responsible for regulating the enzymatic activity of BCR-ABL1 or its interactions [54]. In the N-terminal part of BCR, there is a domain responsible for oligomerization and constitutive activation of the BCR-ABL1 tyrosine kinase. In addition, the BCR sequence contains a Serine/Threonine Kinase (STK) domain, a Ras homolog gene family kinase domain, guanine nucleotide exchange factors (Rho/GEF), and SH2 domains capable of binding adapter molecules such as the receptor-binding protein factor 2 growth (GRB2) [53].

PP2A is a serine-threonine phosphatase tumor suppressor that negatively regulates mitogenic and survival signals mediated by the PI3K/AKT, RAS/MAPK, and MYC pathways [53]. Interestingly, PP2A is downregulated by BCR-ABL1 in CML patients, especially during the blast crisis [53]. BCR-ABL1 inhibition of PP2A is mediated by activation of SET, an endogenous inhibitor of PP2A. Importantly, imatinib treatment, inhibition of SET, or pharmacological activation of PP2A leads to inactivation and degradation of BCR-ABL1, resulting in loss of tumorigenic activity in BCR-ABL1-positive cells, including TKI-resistant CML stem cells [53].

Abnormal miRNA expression and function in acute myeloid leukemia

MicroRNAs are small RNA molecules of approximately 22 nucleotides that bind to the 3′-untranslated region (3′-UTR) of target mRNA and regulate target gene expression at the transcriptional level [55]. miRNAs are mainly involved in the pathogenesis of AML through the following five mechanisms: copy number changes, changes in the proximity of tumorigenic genomic regions due to chromosomal translocations, epigenetic changes, aberrant targeting of miRNA promoter regions by altered transcription factors or oncoproteins, and finally, dysregulated miRNA processing [56].

miR-9 reset reduces leukemia growth and induces single-cell differentiation of t(8;21) AML cell lines in vitro and in vivo.

Functionally, miR-9 exerts its effects by binding to let-7 to suppress the oncogenic LIN28B/HMGA2 axis [57]. In another study, miR-9-1 was observed to be upregulated in t(8;21) AML. In addition, miR-9-1 overexpression induced differentiation and inhibited proliferation in t(8;21) AML cell lines [58]. In AML patients with t(8;21), t(9;11), MiR-10a/b, NPM1 mutation and especially M1, M2 and M3 subtypes were significantly increased. Abnormally high expression in these patients leads to unlimited proliferation of immature blood progenitors and suppressed differentiation and maturation of mature blood cells [59].

Leukemia Stem Cells (LSCs) are believed to be the main source of exosomes. Increased expression of miR-34c-5p can induce LSC senescence through p53-dependent and CKDcyclin/independent pathways. LSC can downregulate miR-34c-5p by actively packaging and transporting miR-34c-5p out of cells in exosomes. Instead, miR-34c-5p can repress exosome-mediated transport through a positive feedback loop with the help of RAB27B, a molecule that promotes exosome degradation. By targeting RAB27B, miR-34c-5p can enrich its intracellular surface and induce LSC senescence [60].

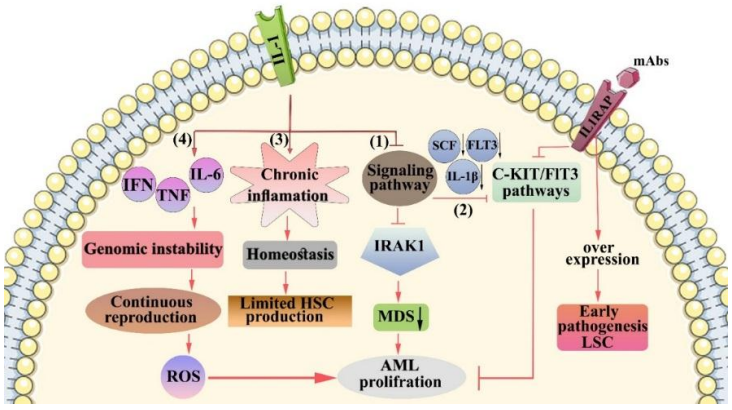

Figure 1. (1) Inhibition of the IL-1 receptor signaling pathway results in deletion of IRAK1 expression, leading to decreased MDS and the formation of AML leukemia colonies. (2) IL-1 signaling pathway inhibition reduces SCF, FLT3, and IL-1B, leading to inhibition of the C-KIT and FLT3 pathways. IL1RAP overexpression occurs early in LSC pathogenesis. (3) Chronic inflammation disrupts blood homeostasis with IL-1 exposure and ultimately limits HSC production. (4) Continuous exposure of IL-1 to IL-6, TNF, and IFN causes genomic instability that, when exposed to ROS, leads to myeloid malignancies such as AML.

FOX family members are known as tumor suppressors and oncogenes depending on the cell type [11]. Mesenchymal Stem Cells (MSCs) are important components of the hematopoietic microenvironment that support hematopoietic stem cells' self-repair and differentiation through interactions, production and secretion of cytokines [11]. Single Nucleotide Polymorphism (SNP) is widely implicated in the pathogenesis of AML. SNPs have been identified as risk factors for AML progression and as prognostic factors in terms of survival outcomes and drug sensitivity/resistance [61,62]. FOXP3 SNPs have recently been identified as prognostic factors in children and adults undergoing HSCT [63].

ALL cells located in the BM migrate through other tissues with a very complex environment consisting of ECM proteins (collagenase, fibronectin, laminin, proteoglycan), soluble molecules (cytokines, chemokines and growth factors) and other types of cells (stromal cells osteoblasts, endothelial cells and macrophages) interact [64]. Selectins have been involved in the early adhesion stages in the migration of blood tumor cells. Selectins are a family of C-type receptors that are divided based on their expression in leukocytes (L-selectin), platelets (P-selectin) or endothelial cells (P/E-selectins) [65,66]. The role of these cell surface receptors and their glycosylated ligands in leukocyte recruitment, granular secretion, and placental growth have been widely investigated [66,67]. Selectins and their ligands are critical in numerous physiological and pathological situations, including those related to cancer and the immune response [65].

Because chronic lymphocytic leukemia (CLL) cells are completely dependent on the microenvironment, cross-talk with the surrounding microenvironment has been noted in promoting CLL survival and proliferation [68]. lymph node tissues are the preferred site for CLL cell proliferation, possibly due to bystander cells in the microenvironment that promote proliferation through diverse receptors such as BCR, CD40, and TLR [69].

Tumor cells proliferate primarily in lymph nodes and, to a lesser extent, in the bone marrow [70], where they are in contact

with the extracellular matrix, T cells, follicular dendritic cells, and other stromal cells. Interactions between CLL cells and this complex microenvironment are mediated by a network of adhesion molecules, cell surface ligands, chemokines, cytokines and their respective receptors. CLL cells organize their supportive environment and promote an immunosuppressive environment through various mechanisms such as secretion of soluble factors, cell-cell contact, and release of extracellular vesicles [70]. Environmental antigens and homotypic interactions induce BCR and Toll-Like Receptor (TLR) signaling, increasing the response of CLL cells to other signals from the environment and increasing the activation of anti-apoptotic and proliferative pathways. Genomic studies have identified frequent mutations in genes that regulate tumor cell-microenvironment interactions, which are pre-requisite for tumor cell growth. Therefore, NOTCH1 mutations are dependent on the presence of Notch ligands in the microenvironment and activate processes such as cell migration, invasion and angiogenesis [71].

As miRNAs act as downstream and upstream modulators of important factors such as nuclear factor kappa-B (NF-kB), Signal Transducer and Activator of Transcription 3 (STAT3), Tumor Necrosis Factor (TNF) and transforming growth factor β (TGFβ), which regulate many immune cell functions [72]. However, the mechanism of expression regulation of these miRNAs is still unclear. Over the past decade, many studies have focused attention on the role of miRNAs in cancer especially tumor growth, angiogenesis, invasion, and immune evasion by controlling the expression of target mRNAs [73]. Depending on their expression in tumor cells and their role, miRNAs can be divided into two categories: oncogenic miRNAs and suppressor miRNAs. Onco-miRNAs (onco-miR) are regulated in tumor cells and contribute to carcinogenesis by inhibiting tumor suppressor genes. Suppressive miRNAs are upregulated in tumor cells and normally prevent cancer progression by inhibiting the expression of proto-oncogenes [74].

Signaling pathways involved in blood cancer

One of the important signaling pathways in acute myeloid leukemia is Hedgehog (HH) signaling, which plays a role in the growth of embryonic cells as well as in the proliferation and maintenance of adult

stem cells, including cancer stem cells [75,76]. Also, JAK/STAT, Raf/MEK/ERK, and PI3K/Akt signaling pathways are activated by various cytokines and work to enhance or inhibit hematopoiesis [77].

Dysregulation of the Wnt/β-catenin pathway is a frequent event in the pathogenesis of T-ALL. C-MYC is an oncogene involved in the development and progression of cancer in various tumor types [78,79]. C-MYC represents a target gene of the Wnt/β-catenin and Notch signaling cascades [80,81]. β-catenin overexpression has also been shown to target CD4+, and CD8+ thymocytes, which induce malignancy, leading to c-myc aberrant activation and a Notch-independent form of leukemia (Figure 2) [82,83]. Activation of the Wnt/β-catenin pathway usually activates hypoxia-induced factor α1 (Hif 1α) in leukemic cells. Upregulation of β-catenin and Hif1α may preserve LSCs, while deletion of these proteins strongly decreases the frequency of LSCs without interfering with cancer cell growth [84]. Furthermore, Phosphatase and tensin homolog (PTEN) deletion cooperates with β-catenin in leukemia progression, suggesting that activation of the Wnt/β-catenin pathway is related to the Notch-independent T-ALL subtype characterized by C-MYC rearrangements and PTEN mutations. [85]. LEF1, a member of the LEF/TCF complex, may act as a tumor suppressor or an oncogene in various cellular contexts [86]. Loss of TCF1 as a suppressor of LEF1 leads to increased Wnt activity and may represent an initiating event in lymphoma development [87].

The role of BCR-ABL kinase in destroying important cell signaling pathways

Major cellular events initiated by BCR-ABL include altered adhesion to stromal cells and extracellular matrix, active constitutive mitogenic signaling, reduced apoptosis, and DNA repair mechanisms. However, some factors such as increased levels of Reactive Oxygen Species (ROS) and autophagy seem to play an important role in the development and progression of CML [14]. Neoplastic transformation, which occurs through BCR-ABL, is associated with constitutive activation of the Ras/MAPK signaling pathway. Ras protein activates the serine-threonine Raf kinase, which initiates the signaling cascade through the serine-threonine kinases Mek1/Mek2 and Erk1/Erk2, belonging to MAPK. Kinases migrate to the cell nucleus, where phosphorylation

and activation of transcription factors such as c-Jun, c-Myc, and c-Fos occur, resulting in the expression of genes responsible for proliferation processes [88]. Conversely, active PI3K is required to maintain the proliferative properties of BCR–ABL-positive cells. PI3K is activated by forming complexes with BCR-ABL, Cbl, and adapter molecules such as Crk and Crkl. This leads to the activation of another substrate of the cell signaling cascade such as the serine-threonine kinase Akt [89].

An activated Akt kinase promotes cell survival by phosphorylation of the pro-apoptotic Bad protein at serine 136. Phosphorylated Bad is trapped and retained in the 3-3-14 protein complex. Therefore, it cannot interact with anti-apoptotic proteins such as Bcl-2 and Bcl-xL. In this condition, free Bcl-xL binds to the proapoptotic Bax protein and prevents the formation of proapoptotic Bax homodimers in the mitochondrial outer membrane. Akt kinases may directly phosphorylate caspase-9 on serine 196, thereby preventing Apaf-1/cytochrome c activation of caspase-9. This Akt activity is closely related to BCR-ABL kinase activity. In addition, BCR–ABL increases the expression of antiapoptotic Bcl-2 family members, such as Bcl-2 and Bcl-xL, possibly through direct activation of the transcription factor STAT5, without the involvement of Janus (JAK) kinases [77,90,91]. The action of BCR-ABL kinase on PI3K/AKT, MAPK, and other signaling pathways leads to changes in ROS regulation in HSC (Figure 3). Under physiological conditions, these pathways support HSC residence in the bone marrow/bone niche under hypoxia and low ROS levels. Reregulation of signaling pathways by BCR-ABL constitutive activity leads to increased ROS levels. This results in non-specific oxidative damage to biomolecules such as oxidative DNA damage, DNA single- and Double-Strand Breaks (DSB), as well as DNA repair proteins, leading to increased genomic instability [92].

Analysis of the immune system

Bone marrow (BM) supports the immune system through myelopoiesis and lymphopoiesis, as well as harbors a variety of mature lymphoid cells [93]. A topic of great interest is the function of BM in addition to that of a hematopoietic organ, which plays a key role in maintaining protective immune responses through plasma cell survival and maintenance of immune memory [94,95], and is also a

dynamic entity capable of Do it directly. Sensing and modulating its response to inflammatory signals [96]. Abnormalities in the indentation components of hematopoietic stem cells can induce or maintain myeloid malignancy.

The immune domain of BM is significantly altered by myeloid malignancies. In Myelodysplastic Syndromes (MDS), (a malignancy characterized by myelodysplasia and ineffective hematopoiesis [97]), HSC response to environmental stimuli is detrimental, as chronic inflammatory signaling promotes MDS progression and suppresses normal HSC [98]. Studies show that the difference between low-risk and high-risk diseases also manifests in their different immune microenvironments [99].

Innate and acquired immunity: Classically, host immunity is divided into innate and adaptive immune responses. The former reacts rapidly and nonspecifically to pathogens, while the latter reacts in a slower but specific manner by producing long-term immune memory [100]. Innate immunity is mediated by innate immune cell populations such as myeloid cells, Natural Killer (NK) cells, and innate lymphoid cells (but non-immune cells in certain conditions) as well as by humoral systems. Acquired immunity is a relatively new evolutionary trait based on immunoglobulin family and cells such as B and T lymphocytes in vertebrates [101].

During infection, innate immunity is initially induced (inflammatory response), which takes no more than a few minutes to a few hours to become fully activated [102]. This is very important for host defense in the first phase of a new infection. While innate immunity is generally able to effectively eliminate pathogens, initial clearance of infection can be compromised due to the large number of invading pathogens. In these conditions, lymphocytes and acquired immune mechanisms are activated, which have the ability to specifically identify and eliminate the pathogen. The development of acquired immunity requires 1-2 weeks and is important for host defense in late stages of infection and during secondary infections due to the ability to remember and respond more effectively to stimulation [100].

The innate immune system is the first line of defense and some form of it is present in most cell types of all species. Phagocytosis and cytokine/chemokine

production are two important components of innate immunity. Primary phagocytosis by macrophages or other phagocytes causes the production and secretion of cytokines or chemokines. Pathogen-infected cells can also release cytokines/chemokines. These cytokines or chemokines also recruit more immune cells to effectively eliminate foreign pathogens and infected cells [102]. In the innate immune system, a variety of Pattern Recognition Receptors (PRR) are used to recognize molecules derived from bacteria, viruses, and parasites. Such PRRs include Toll-Like Receptors (TLRs), C-type Lectin Receptors (CLRS), NOD-Like Receptors (NLRs), RIG-Like Receptors (RLRs) and AIM2-Like Receptors (ALRs) [102,103,104].

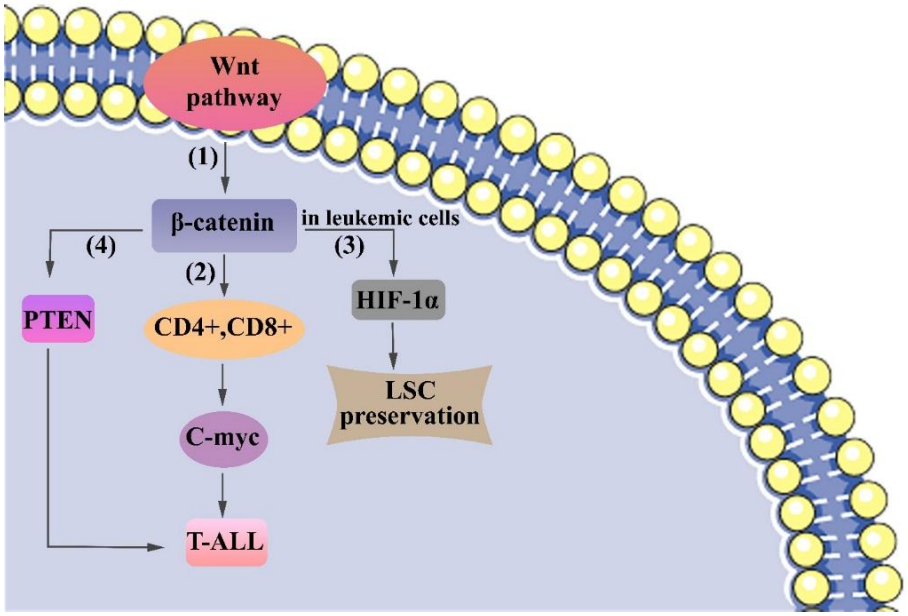

Figure 2. (1) The WNT signaling pathway causes overexpression of β-catenin (2) and targets $CD4^+$ and $CD8^+$ thymocytes, leading to C-MYC activation and Finally, it forms a notch-independent leukemia form (T-ALL). (3) Activation of the Wnt/β-catenin pathway in leukemic cells activates the HIF-1α factor induced by hypoxia. (4) Removal of β-catenin and PTEN contributes to the progression of leukemia.

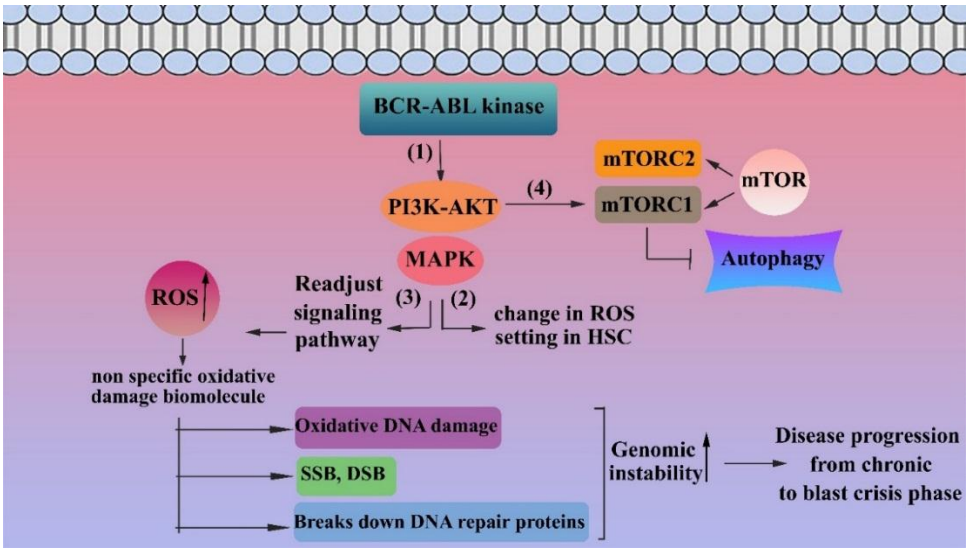

Figure 3. (1) The effect of BCR-ABL kinase on PI3K/AKT and MAPK (2) causes a change in ROS regulation. (3) By resetting the signaling pathway by BCR-ABL, the amount of ROS increases and causes nonspecific oxidative damage to biological molecules, including oxidative DNA damage, single-stranded DNA (SSB), and double-stranded DNA (DSB) and DNA repair proteins. This leads to an increase in genomic instability and ultimately to the progression of the disease from chronic to invasive. (4) mTOR has two distinct forms, mTORC2 and mTORC1. mTORC1 is stimulated by BCR-ABL via the PI3K-AKT pathway and inhibits autophagy.

In myeloid cells, many genes encoding homeostasis are in a repressed position [105]. After initial stimulation, there is a dramatic increase in chromatin accessibility, increased acetylation, and recruitment of RNA polymerase II. These changes are mediated by the recruitment of stimuli-responsive transcription factors (eg, NF-κB, AP-1, and STAT family members) to gene enhancers and promoters, which are usually pre-marked by transcription factors such as PU [106,107]. Transcription factors control coagulation regulators (including acetylated histones and chromatin remodelers) that locally modify chromatin to make it accessible to the transcription machinery. Maintaining such enhanced accessibility underlies more efficient induction of genes after restimulation [108].

Changes in chromatin structure are associated not only with innate immune memory but also with acquired immune memory. The acquired immune system consists of B and T lymphocytes that express highly specific antigen receptors,

the B Cell Receptor (BCR) and the T Cell Receptor (TCR), which appear during somatic gene recombination, a unique feature of these cells [109,110].

In the field of cancer, studies have more extensively investigated the role of macrophages than monocytes. In primary tumors, macrophages are known to induce cancer cell invasion [111]. Macrophages have also been shown to directly help remove cancer cells. Several studies have shown that macrophages contribute to cancer cell survival, engraftment, and cell proliferation once they are established in a new tissue [112]. In some studies, it has been shown that non-classical monocytes reduce metastasis by reducing tumor material and promoting the recruitment and activation of natural killer cells [113]. Inflammatory monocytes facilitate the infiltration of cancer cells and their engraftment by filling the pool of macrophages present at the secondary site of tumor formation [114].

Eosinophil growth and maturation occurs within approximately one week of exposure of myeloid progenitors to IL3, GM-CSF, and IL5 in the bone marrow. IL-5 acts as a stimulus for eosinophil migration into the circulating blood and is a key cytokine in the survival and persistence of circulating and tissue eosinophils, which prevents apoptosis and activates the cell. CD34+ progenitor cells, Innate Lymphoid Cells of group 2 (ILC-2), Th2 lymphocytes, natural killer T cells and mast cells are the main sources of IL5 [115,116]. Furthermore, IL5 can be released by eosinophils in an autocrine/paracrine manner [117,118]. Chemokines such as CCL11, CCL24, and CCL26 eventually promote the recruitment of eosinophils into tissues within 8-12 hours of release from the bone marrow [119]. The chemokine receptor CCR3 plays an important role in this, as it binds inflammatory stimuli such as CCL5, CCL7 and CCL13 [120].

Basophils are members of granulocytes and are of myeloid lineage and are created by the proliferation and differentiation of myeloid progenitors. Basophils in Peripheral Blood (PB) or tissues range in size from 10 to 15 μm and have purple or dark blue nuclei and dark blue to purple cytoplasmic granules seen in PB and Wright's stained Bone Marrow (BM) [121]. In studies, primary Chronic Basophilic Leukemia (CBL) and Chronic Myeloid Leukemia (CML) with the ability to transform into CBL, as a secondary CBL, have been reported [122].

Neutrophils arise from hematopoietic stem cells in the bone marrow, spleen, and possibly lung HSCs that generate Multipotent Progenitors (MPP), which generate Common Myeloid Progenitors (CMP) and then granulocyte monocyte progenitors (GMP) [123]. GMPs commit to becoming monocytes/dendritic cells, mast cells, basophils, or neutrophils/monocytes. During immune stress, immature neutrophils are also found in the peripheral blood. Granulopoiesis is mainly stimulated through the IL-23/IL-17/G-CSF axis and to a lesser extent by GM-CSF and M-CSF [124,125]. Other cytokines such as IL-6 are also involved in granulopoiesis [123]. Neutrophils can mediate a wide range of antitumor activities from direct cancer cell killing to tumor cell proliferation, angiogenesis, metastasis, and regulation of other immune responses.

Natural Killer cells (NK) cells are cytotoxic Innate Lymphoid Cells (ILCs), which can target and kill cancer cells through the secretion of cytolytic granules and induce an immune response through the secretion of immunoregulatory cytokines [126]. Unlike T and B cells, NK cells have a large number of activated membrane receptors and inhibit membrane receptors and therefore do not require antigen specificity [127,128]. Active NK cell receptors include cytotoxic cell receptors (NCR) NKp46, NKp30 and NKp44, CD16, NKG2D, NKG2C, DNAX Accessory Molecule-1 (DNAM-1) and 2B4 [129]. Important inhibitory receptors on NK cells engage MHC-I ligands to dampen the NK cell response, and these include killer cell immunoglobulin-like receptors (KIR) and the CD94/NKG2A heterodimer [130].

Integrins are the most important adhesion receptors that facilitate the migration of neoplastic cells. Integrins are heterodimeric receptors and subunits that mediate cell-cell and cell-ECM interactions and connect the ECM to the actin cytoskeleton [131,132]. In addition, integrin-dependent cell adhesion stimulates intracellular signaling that helps control cell growth and survival [132,133]. Integrins adopt different conformations, which determine their activation state related to their ability to bind ligands with high affinity and induce subsequent intracellular signaling [134].

Chemotaxis: are chemotactic cytokines that increase cell migration and activation under homeostatic and inflammatory conditions and play important roles during hematopoiesis, immune surveillance, inflammation, morphogenesis, and

neovascularization, as well as hematopoietic tumor cell traffic [135].

Also, selectins have been involved in the initial adhesion stages of blood tumor cells. Selectins are a family of C-type receptors that are divided based on their expression in leukocytes (L-selectin), platelets (P-selectin), or endothelial cells (E/P-selectins) [65,66]. Selectins and their ligands are critical in numerous physiological and pathological situations, including those related to cancer and the immune response [65]. Cancer cells exhibit changes in cell surface glycosylation that are recognized by selectins, galectins, and siglecs [136], therefore targeting selectin-ligand interactions has clinical relevance for cancer immunotherapy [25].

In cancer research, success in new immunological methods has inspired an increase in therapies aimed at modulating the immune system to treat cancers, and such advances have resulted in a better overall understanding of the changes in the human immune system and the underlying mechanisms of this change. The idea of personalized therapy or precision medicine comes from the fact that individual patients differ in their disease mechanisms and needs for successful treatment, and better outcomes can be achieved by determining what these needs are for each patient. Understanding when and how a stable immune state is established can help us to promote long-term immune health for all populations through the optimization of modifiable environmental conditions [137].

Acute myeloid leukemia is a complex disease characterized not only by significant genetic mutation but also by unfavorable epigenetic differentiation. However, because these epigenetic changes are heritable and highly heterogeneous, acute myeloid leukemia undergoes significant clonal evolution, leading to treatment resistance and eventual relapse [138]. The PI3K/Akt/mTOR pathway is central to a wide range of cellular regulatory processes, such as proliferation, differentiation, and survival. Dysregulation of this pathway is common in AML and is often caused by mutations in membrane-bound proteins especially FLT3-ITD. Activation of PI3K/Akt/mTOR by such activating mutations is associated with chemoresistance. Since the PI3K/Akt/mTOR pathway is considered a possible target for AML, considerable efforts have been made to develop small molecule drugs that have shown promise in clinical settings [139]. AML subtypes

present unique patterns of protein-coding gene and microRNA expression. In addition, a range of newly discovered fusion genes, alternative transcripts, and chimeric RNAs, as well as many non-coding RNAs, contribute to the transcriptional complexity of leukemia. Recent studies on the BM milieu have emphasized its role in the initiation, progression, and relapse of AML. Understanding the molecular interaction between LSCs and the BM niche is not only essential for understanding the biology of AML but also provides new therapeutic strategies for AML [140].

In particular, Mesenchymal Stem Cells (MSC) are important components of the hematopoietic microenvironment that support the renewal and differentiation of stem cells through interactions, production, and secretion of cytokines from hematopoietic stem cells [141,142]. As previously described, FOX family members are known as tumor suppressors and oncogenes depending on the cell type, and their study may provide useful information to inhibit cancer cells [11].

Strategies to analyze molecular genetics and epigenetic aberrations in leukemic cells have led to a more comprehensive understanding of the molecular mechanisms leading to chemotherapy drug resistance and adverse outcomes in ALL. Advances in molecular and cytogenetic profiling have identified a wide range of genetic abnormalities, including gene mutations, chromosomal translocations, and aneuploidy, providing a more comprehensive understanding of the biology and pathogenesis of ALL [143].

T-ALL is a genetically heterogeneous disease that results from a multistep process, which includes cell growth, proliferation, and differentiation of T cells [144]. A better understanding of molecular pathophysiology may refine classification and prognosis [145].

Some miRNAs have been shown to regulate the lymphoid and myeloid cell lineages of the hematopoietic system, and the key role of miRNA-mediated gene regulation in the immune system has been established. Furthermore, the effect of a miRNA on many transcripts of genes often related to function adds complexity to the system [146]. Expression signatures of miRNAs are distinct in the differentiation and maturation of hematopoietic cell lineages, and this may be useful in distinguishing acute lymphoblastic leukemia from acute myeloid leukemia with an accuracy of 97 % [147].

Furthermore, evidence suggests that miRNAs can be used as potential diagnostic and prognostic biomarkers in B-ALL [148].

Chronic Myeloid Leukemia (CML) causes leukemia by affecting BCRABL1 in the cell by biological, intrinsic, or acquired potential. LSC is commonly referred to as CML leukemia stem cell [149]. Initiation and maintenance of clonal bleeding in people with chronic Myelogenous Leukemia (CML) is the responsibility of Leukemia Stem Cells (LSC). These cells persist in the Bone Marrow (BM) despite effective inhibition of BCR-ABL kinase activity by Tyrosine Kinase Inhibitors (TKIs) [16].

Recent molecular studies have provided many insights into the processes governing the development and progression of CLL, including many new mutated genes, clustered in different functional pathways. Analysis of the CLL microenvironment has provided clues to understanding tumor cell viability and resistance to therapy [71]. In this leukemia, genetic mutations in B cells and B Cell Receptors (BCR) are the most important driving factors along with the escape of cytotoxic T lymphocytes and the promotion of regulatory T cells. Moreover, under the influence of various cytokines, dendritic cells are unable to mature and stimulate T cell-mediated antitumor response. The phenotypes of these cells are ultimately controlled by the relevant signaling pathways, among the most famous of them are BCR, Wnt, Notch, and NF-κB, and their activation affects the cytokine profile that controls the pathogenesis of CLL It is challenging to treat.

The function of innate immune components and adaptive immune components are interconnected in blood malignancies, including leukemias, and molecular interactions between innate and acquired immune components are very important for the progress and outcome of treatment [150].

Different signaling pathways effective in leukemia such as Wnt are of great importance. Among these pathways is the Wnt/β-catenin axis, which plays a central role in hematopoiesis and indicates the possible existence of unknown mechanisms through which the Wnt/β-catenin pathway regulates blood cell production. In addition, overexpression of the Wnt/β-catenin signaling axis has been reported in several cancers, including hematological malignancies, and causes resistance to chemotherapy. In this context, the

inhibition of the Wnt/β-catenin pathway provides alternative and interesting possibilities for the therapeutic interventions of blood disorders. Another important step is to elucidate the mutual interactions between Wnt/β-catenin and the BM environment that support the survival of LSCs. These data could have clinical relevance, especially for patients who show high levels of Wnt/β-catenin activation, because Wnt/β-catenin inhibitory drugs may affect healthy HSCs and blood cell production [151].

CONCLUSION

Identifying and investigating mutations and chromosomal aberrations in all types of leukemias can help prevent or treat leukemia. According to the extensive studies that have been conducted in the field of signaling pathways related to the occurrence of cancer, the investigation of molecular factors related to these pathways can play an important role in discovering more and more effective treatment strategies for blood disorders. However, the discovery of treatment methods and prediction of disease factors is dependent on wider and continuous studies in the field of the immune system and cellular and molecular factors related to leukemia.

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REFERENCES

[1]. Labaj W, Papiez A, Polanski A, Polanska J. Comprehensive analysis of MILE gene expression data set advances discovery of leukaemia type and subtype biomarkers. Interdisciplinary Sciences: *Computational Life Sci*. 2017; 9(1): 24-35.

[2]. Cesario A, D'oria M, Bove F, Privitera G, Boškoski I, Pedicino D, Boldrini L, Erra C, Loreti C, Liuzzo G, Crea F. Personalized clinical phenotyping through systems medicine and artificial intelligence. *JPM*. 2021; 11(4): 265.

[3]. Alaswad HA, Mahbub AA, Le Maitre CL, Jordan-Mahy N. Molecular action of polyphenols in leukaemia and their therapeutic potential. *IJMS*. 2021; 22(6): 3085.

[4]. Levine AJ, Jenkins NA, Copeland NG. The roles of initiating truncal mutations in human cancers: the order of

mutations and tumor cell type matters. *Cancer cell.* 2019; 35(1): 10-5.

[5]. Martincorena I. Somatic mutation and clonal expansions in human tissues. *Genome Medicine*. 2019; 11(1): 1-3.

[6]. Belyavsky A, Petinati N, Drize N. Hematopoiesis during ontogenesis, adult life, and aging. *IJMS.* 2021; 22(17): 9231.

[7]. Cheng H, Zheng Z, Cheng T. New paradigms on hematopoietic stem cell differentiation. *Protein cell*. 2020; 11(1): 34-44.

[8]. Raghav PK. Hematopoietic stem cell factors: their functional role in self-renewal and clinical aspects. *Frontiers in Cell Develop Biol*. 2022; 24: 453.

[9]. Jafarzadeh N, Safari Z, Pornour M, Amirizadeh N, Forouzandeh Moghadam M, Sadeghizadeh M. Alteration of cellular and immune-related properties of bone marrow mesenchymal stem cells and macrophages by K562 chronic myeloid leukemia cell derived exosomes. *J cellular physiol.* 2019; 234(4): 3697-3710.

[10]. Kumar B, Garcia M, Weng L, Jung X, Murakami JL, Hu X, McDonald T, Lin A, Kumar AR, DiGiusto DL, Stein AS. Acute myeloid leukemia transforms the bone marrow niche into a leukemia-permissive microenvironment through exosome secretion. *Leukemia.* 2018; 32(3): 575-87.

[11]. Gurnari C, Falconi G, De Bellis E, Voso MT, Fabiani E. The role of forkhead box proteins in acute myeloid leukemia. Cancers. 2019; 21; 11(6): 865.

[12]. Montaño A, Forero-Castro M, Marchena-Mendoza D, Benito R, Hernández-Rivas JM. New challenges in targeting signaling pathways in acute lymphoblastic leukemia by NGS approaches: An update. *Cancers*. 2018; 10(4): 110.

[13]. Mi X, Griffin G, Lee W, Patel S, Ohgami R, Ok CY, Wang S, Geyer JT, Xiao W, Roshal M, Garcia JS. Genomic and clinical characterization of B/T mixed phenotype acute leukemia reveals recurrent features and T-ALL like mutations. *Am J Hematol*. 2018; 93(11): 1358-67.

[14]. Flis S, Chojnacki T. Chronic myelogenous leukemia, a still unsolved problem: pitfalls and new

therapeutic possibilities. *Drug Des. Dev. Ther*. 2019; 13: 825.

[15]. Vatanmakanian M, Tavallaie M, Ghadami S. Imatinib independent aberrant methylation of NOV/CCN3 in chronic myelogenous leukemia patients: a mechanism upstream of BCR-ABL1 function. CCS. 2019; 17(1):1-10.

[16]. Zhang B, Nguyen LX, Li L, Zhao D, Kumar B, Wu H, Lin A, Pellicano F, Hopcroft L, Su YL, Copland M. Bone marrow niche trafficking of miR-126 controls the self-renewal of leukemia stem cells in chronic myelogenous leukemia. Nat Med. 2018; 24(4): 450-62.

[17]. Ruiz MS, Sánchez MB, Bonecker S, Furtado C, Koile D, Yankilevich P, Cranco S, Custidiano MD, Freitas J, Moiraghi B, Pérez MA. miRNome profiling of LSC-enriched CD34+ CD38− CD26+ fraction in Ph+ CML-CP samples from Argentinean patients: A potential new pharmacogenomic tool. Frontiers in pharmacology. 2021; 11: 612573.

[18]. Flis S, Chojnacki T. Chronic myelogenous leukemia, a still unsolved problem: pitfalls and new therapeutic possibilities. Drug Des. Dev. Ther. 2019; 13: 825.

[19]. Hallek M. Chronic lymphocytic leukemia: 2020 update on diagnosis, risk stratification and treatment. American journal of hematology. 2019; 94(11):1266-87.

[20]. Svanberg R, Janum S, Patten PE, Ramsay AG, Niemann CU. Targeting the tumor microenvironment in chronic lymphocytic leukemia. haematologica. 2021; 106(9): 2312.

[21]. Dubois N, Crompot E, Meuleman N, Bron D, Lagneaux L, Stamatopoulos B. Importance of crosstalk between chronic lymphocytic leukemia cells and the stromal microenvironment: direct contact, soluble factors, and extracellular vesicles. *Frontiers in oncology*. 2020; 19: 1422.

[22]. George B, Mullick Chowdhury S, Hart A, Sircar A, Singh SK, Nath UK, Mamgain M, Singhal NK, Sehgal L, Jain N. Ibrutinib resistance mechanisms and treatment strategies for B-cell lymphomas. *Cancers.* 2020; 12(5): 1328.

[23]. Chen, J. G., Liu, X., Munshi, M., Xu, L., Tsakmaklis, N., Demos,

M. BTKCys481Ser drives ibrutinib resistance via ERK1/2 and protects BTKwild-type MYD88-mutated cells by a paracrine mechanism. *Blood*, 2018 131(18), 2047-59.

[24]. Autore F, Strati P, Laurenti L, Ferrajoli A. Morphological, immunophenotypic, and genetic features of chronic lymphocytic leukemia with trisomy 12: a comprehensive review. *Haematologica*. 2018; 103(6): 931.

[25]. Redondo-Muñoz J, García-Pardo A, Teixidó J. Molecular players in hematologic tumor cell trafficking. *Frontiers in immunology*. 2019; 10: 156.

[26]. Hallek M, Shanafelt TD, Eichhorst B. Chronic lymphocytic leukaemia. *The Lancet*. 2018; 391(10129): 1524-37.

[27]. Chiorazzi N, Stevenson FK. Celebrating 20 years of IGHV mutation analysis in CLL. *Hemasphere*. 2020; 4(1).

[28]. Kumar PR, Moore JA, Bowles KM, Rushworth SA, Moncrieff MD. Mitochondrial oxidative phosphorylation in cutaneous melanoma. *BJC*. 2021; 124(1): 115-23.

[29]. Robinson AJ, Darley RL, Tonks A. Reactive oxygen species in leukemias: maintaining cancer cell proliferation via redox signaling and changing metabolic homeostasis. *Oncotarget*. 2021; 12(10): 952.

[30]. Liu R, Chen Y, Liu G, Li C, Song Y, Cao Z, Li W, Hu J, Lu C, Liu Y. PI3K/AKT pathway as a key link modulates the multidrug resistance of cancers. *CDD*. 2020; 11(9): 1-2.

[31]. Pereira O, Teixeira A, Sampaio-Marques B, Castro I, Girao H, Ludovico P. Signalling mechanisms that regulate metabolic profile and autophagy of acute myeloid leukaemia cells. *JCMM*. 2018; 22(10): 4807-17.

[32]. Fisher JN, Kalleda N, Stavropoulou V, Schwaller J. The impact of the cellular origin in acute myeloid leukemia: learning from mouse models. *Hemasphere*. 2019; 3(1).

[33]. De Grandis M, Mancini SJ, Aurrand-Lions M. In quest for leukemia initiating cells in AML. *Oncoscience*. 2018; 5(1-2): 9.

[34]. Li H, Zhao N, Li Y, Xing H, Chen S, Xu Y, Tang K, Tian Z,

Wang M, Rao Q, Wang J. c-MPL is a candidate surface marker and confers self-renewal, quiescence, chemotherapy resistance, and leukemia initiation potential in leukemia stem cells. *Stem Cells.* 2018; 36(11): 1685-96.

[35]. Roussel X, Daguindau E, Berceanu A, Desbrosses Y, Warda W, Neto da Rocha M, Trad R, Deconinck E, Deschamps M, Ferrand C. Acute Myeloid Leukemia: From Biology to Clinical Practices Through Development and Pre-Clinical Therapeutics. *Frontiers in Oncology*. 2020; 10: 599933.

[36]. Vetrie D, Helgason GV, Copland M. The leukaemia stem cell: similarities, differences and clinical prospects in CML and AML. Nat. Rev. *Cancer*. 2020; 20(3): 158-73.

[37]. Mitchell K, Barreyro L, Todorova TI, Taylor SJ, Antony-Debré I, Narayanagari SR, Carvajal LA, Leite J, Piperdi Z, Pendurti G, Mantzaris I. IL1RAP potentiates multiple oncogenic signaling pathways in AML. *JEM.* 2018; 215(6): 1709-27.

[38]. De Boer B, Sheveleva S, Apelt K, Vellenga E, Mulder AB, Huls G, Schuringa JJ. The IL1-IL1RAP axis plays an important role in the inflammatory leukemic niche that favors acute myeloid leukemia proliferation over normal hematopoiesis. *Haematologica.* 2021; 106(12): 3067.

[39]. Brikos C, Wait R, Begum S, O'Neill LA, Saklatvala J. Mass spectrometric analysis of the endogenous IL-1RI signalling complex formed after IL-1 binding, identifies IL1RAcP, MyD88 and IRAK-4 as the stable components. *MCP*. 2007; 6: 1551-59.

[40]. Barreyro L, Chlon TM, Starczynowski DT. Chronic immune response dysregulation in MDS pathogenesis. *Blood*. 2018; 132(15): 1553-60.

[41]. Mitchell K, Barreyro L, Todorova TI, Taylor SJ, Antony-Debré I, Narayanagari SR, Carvajal LA, Leite J, Piperdi Z, Pendurti G, Mantzaris I. IL1RAP potentiates multiple oncogenic signaling pathways in AML. *JEM*. 2018; 215(6): 1709-27.

[42]. Roussel X, Daguindau E, Berceanu A, Desbrosses Y, Warda

W, Neto da Rocha M, Trad R, Deconinck E, Deschamps M, Ferrand C. Acute Myeloid Leukemia: From biology to clinical practices through development and pre-clinical therapeutics. *Frontiers in Oncology*. 2020; 10: 599933.

[43]. Yamashita M, Dellorusso PV, Olson OC, Passegué E. Dysregulated haematopoietic stem cell behaviour in myeloid leukaemogenesis. *Nat Rev Cancer*. 2020; 20(7): 365-82.

[44]. Pietras EM. Inflammation: a key regulator of hematopoietic stem cell fate in health and disease. *Blood*, 2017; 130(15): 1693-98.

[45]. Dinarello CA. Overview of the IL- 1 family in innate inflammation and acquired immunity. *Immunological reviews.* 2018; 281(1): 8-27.

[46]. Katagiri S, Chi S, Minami Y, Fukushima K, Shibayama H, Hosono N, Yamauchi T, Morishita T, Kondo T, Yanada M, Yamamoto K. Mutated KIT Tyrosine Kinase as a Novel Molecular Target in Acute Myeloid Leukemia. *IJMS*. 2022; 23(9): 4694.

[47]. Kayser S, Levis MJ. Clinical implications of molecular markers in acute myeloid leukemia. *European J haematol.* 2019; 102(1): 20-35.

[48]. Chen X, Zhu H, Qiao C, Zhao S, Liu L, Wang Y, Jin H, Qian S, Wu Y. Next-generation sequencing reveals gene mutations landscape and clonal evolution in patients with acute myeloid leukemia. *Hematology*. 2021; 26(1): 111-22.

[49]. Murugan NJ, Voutsadakis IA. Proteasome regulators in pancreatic cancer. *WJGO*. 2022; 14(1): 38.

[50]. Ikebe E, Shimosaki S, Hasegawa H, Iha H, Tsukamoto Y, Wang Y, Sasaki D, Imaizumi Y, Miyazaki Y, Yanagihara K, Hamaguchi I. TAS-116 (pimitespib), a heat shock protein 90 inhibitor, shows efficacy in preclinical models of adult T-cell leukemia. *Cancer Sci.* 2022; 113(2): 684.

[51]. Yu W, Wang J, Jin J, Qian W, Qian J, Cheng Y, Wang L. Heat shock protein 90 inhibition results in altered downstream signaling of mutant KIT and exerts synergistic effects on Kasumi-1 cells when combining with histone deacetylase inhibitor. *Leuk. Res*. 2011; 35(9): 1212-18.

[52]. Ehm P, Grottke A, Bettin B, Jücker M. Investigation of the function of the PI3-Kinase/AKT signaling pathway for leukemogenesis and therapy of acute childhood lymphoblastic leukemia (ALL). Cellular Signalling. 2022; 93: 110301.

[53]. Amarante-Mendes GP, Rana A, Datoguia TS, Hamerschlak N, Brumatti G. BCR-ABL1 Tyrosine kinase complex signaling transduction: Challenges to overcome resistance in chronic myeloid leukemia. *Pharmaceutics*. 2022; 14(1): 215.

[54]. Peiris MN, Li F, Donoghue DJ. BCR: a promiscuous fusion partner in hematopoietic disorders. *Oncotarget.* 2019; 10(28): 2738.

[55]. Stavast CJ, Erkeland SJ. The non-canonical aspects of microRNAs: many roads to gene regulation. *Cells.* 2019; 8(11): 1465.

[56]. Wallace JA, O'Connell RM. MicroRNAs and acute myeloid leukemia: therapeutic implications and emerging concepts. *Blood,* 2017; 130(11): 1290-301.

[57]. Setijono SR, Kwon HY, Song SJ. MicroRNA, an antisense RNA, in sensing myeloid malignancies. *Frontiers in Oncology*. 2018; 7: 331.

[58]. Fu L, Shi J, Liu A, Zhou L, Jiang M, Fu H, Xu K, Li D, Deng A, Zhang Q, Pang Y. A minicircuitry of microRNA-9-1 and RUNX1-RUNX1T1 contributes to leukemogenesis in t (8; 21) acute myeloid leukemia. *IJC.* 2017; 140(3): 653-61.

[59]. Bi L, Sun L, Jin Z, Zhang S, Shen Z. MicroRNA-10a/b are regulators of myeloid differentiation and acute myeloid leukemia. *Oncol letters*. 2018; 15(4): 5611-19.

[60]. Peng D, Wang H, Li L, Ma X, Chen Y, Zhou H, Luo Y, Xiao Y, Liu L. miR-34c-5p promotes eradication of acute myeloid leukemia stem cells by inducing senescence through selective RAB27B targeting to inhibit exosome shedding. *Leukemia.* 2018; 32(5): 1180-88.

[61]. Bargal SA, Rafiee R, Crews KR, Wu H, Cao X, Rubnitz JE, Ribeiro RC, Downing JR, Pounds SB, Lamba JK. Genome-wide association analysis identifies SNPs predictive of in vitro leukemic cell

sensitivity to cytarabine in pediatric AML. *Oncotarget*. 2018; 9(79): 34859.

[62]. Wang X, Chen X, Yang Z, Dou H, Lu L, Bi J, Zou L, Yu J, Bao L. Correlation of TET2 SNP rs2454206 with improved survival in children with acute myeloid leukemia featuring intermediate-risk cytogenetics. Genes, *Chromosomes and Cancer*. 2018; 57(8): 379-86.

[63]. Nam M, Shin S, Park KU, Kim I, Yoon SS, Kwon TK, Song EY. Association of FOXP3 single nucleotide polymorphisms with clinical outcomes after allogenic hematopoietic stem cell transplantation. Annals of laboratory medicine. 2018; 38(6): 591.

[64]. Vadillo E, Dorantes-Acosta E, Pelayo R, Schnoor M. T cell acute lymphoblastic leukemia (T-ALL): New insights into the cellular origins and infiltration mechanisms common and unique among hematologic malignancies. *Blood reviews.* 2018; 32(1): 36-51.

[65]. Borsig L. Selectins in cancer immunity. *Glycobiology.* 2018; 28(9): 648-55.

[66]. Zarbock A, Ley K, McEver RP, Hidalgo A. Leukocyte ligands for endothelial selectins: specialized glycoconjugates.

[67]. Ley K, Kansas GS. Selectins in T-cell recruitment to non-lymphoid tissues and sites of inflammation. *Nat. Rev. Immunol.* 2004; 4(5): 325-36.

[68]. Haselager MV, Kater AP, Eldering E. Proliferative signals in chronic lymphocytic leukemia; what are we missing? *Frontiers in Oncol.* 2020; 8: 592205.

[69]. Dadashian EL, McAuley EM, Liu D, Shaffer III AL, Young RM, Iyer JR, Kruhlak MJ, Staudt LM, Wiestner A, Herman SE. TLR signaling is activated in lymph node–resident CLL cells and is only partially inhibited by ibrutinib. *Cancer Res.* 2019; 79(2): 360-71.

[70]. Wu R, Roy AM, Tokumaru Y, Gandhi S, Asaoka M, Oshi M, Yan L, Ishikawa T, Takabe K. NR2F1, a Tumor Dormancy Marker, Is Expressed Predominantly in Cancer-Associated Fibroblasts and Is Associated with Suppressed Breast Cancer Cell Proliferation. *Cancers.* 2022; 14(12): 2962.

[71]. Delgado J, Nadeu F, Colomer D, Campo E. Chronic lymphocytic leukemia: From molecular pathogenesis to novel therapeutic strategies. *Haematologica*. 2020; 105(9): 2205.

[72]. Jia Y, Wei Y. Modulators of MicroRNA function in the immune system. *IJMS*. 2020; 21(7): 2357.

[73]. Segal M, Slack FJ. Challenges identifying efficacious miRNA therapeutics for cancer. *Expert Opin. Drug Discov*. 2020; 15(9): 987-91.

[74]. Del Gaizo M, Sergio I, Lazzari S, Cialfi S, Pelullo M, Screpanti I, Felli MP. MicroRNAs as modulators of the immune response in T-Cell acute lymphoblastic leukemia. *IJMS*. 2022; 23(2): 829.

[75]. Cortes, J. E., Heidel, F. H., Hellmann, A., Fiedler, W., Smith, B. D., Robak, Heuser, M. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. Leukemia, 2019; 33(2), 379-89.

[76]. Sari IN, Phi LT, Jun N, Wijaya YT, Lee S, Kwon HY. Hedgehog signaling in cancer: a prospective therapeutic target for eradicating cancer stem cells. *Cells*. 2018; 7(11): 208.

[77]. Song Y, Zhao M, Zhang H, Yu B. Double-edged roles of protein tyrosine phosphatase SHP2 in cancer and its inhibitors in clinical trials. Pharmacology & therapeutics. 2021; 14: 107966.

[78]. Elbadawy M, Usui T, Yamawaki H, Sasaki K. Emerging roles of C-Myc in cancer stem cell-related signaling and resistance to cancer chemotherapy: a potential therapeutic target against colorectal cancer. *IJMS*. 2019; 20(9): 2340.

[79]. Wang Y, Hou Z, Li D. Long noncoding RNA UCA1 promotes anaplastic thyroid cancer cell proliferation via miR‐135a mediated c‐myc activation. *Mol Med Reports*. 2018; 18(3): 3068-76.

[80]. Evangelisti C, Chiarini F, McCubrey JA, Martelli AM. Therapeutic targeting of mTOR in T-cell acute lymphoblastic leukemia: an update. *IJMS*. 2018; 19(7): 1878.

[81]. Bocchicchio S, Tesone M, Irusta G. Convergence of Wnt and Notch signaling controls ovarian

cancer cell survival. *J. Cell. Physiol*. 2019; 234(12): 22130-43.

[82]. Yi S, Jin X, Liu B, Wu P, Xiao W, Chen W. Portulaca oleracea extract reduces gut microbiota imbalance and inhibits colorectal cancer progression via inactivation of the Wnt/β-catenin signaling pathway. *Phytomedicine*. 2022; 16: 154279.

[83]. Bigas A, Guillén Y, Schoch L, Arambilet D. Revisiting β-catenin signaling in t-cell development and t-cell acute lymphoblastic leukemia. *BioEssays.* 2020; 42(2): 1900099.

[84]. Hajizadeh F, Okoye I, Esmaily M, Chaleshtari MG, Masjedi A, Azizi G, Irandoust M, Ghalamfarsa G, Jadidi-Niaragh F. Hypoxia inducible factors in the tumor microenvironment as therapeutic targets of cancer stem cells. *Life Sci.* 2019; 237: 116952.

[85]. Chiarini F, Paganelli F, Martelli AM, Evangelisti C. The role played by Wnt/β-catenin signaling pathway in acute lymphoblastic leukemia. *IJMS.* 2020; 21(3): 1098.

[86]. Chiarini F, Paganelli F, Martelli AM, Evangelisti C. The role played by Wnt/β-catenin signaling pathway in acute lymphoblastic leukemia. *IJMS.* 2020; 21(3): 1098.

[87]. Wang F, Qi Z, Yao Y, Yu G, Feng T, Zhao T, Xue HH, Zhao Y, Jiang P, Bao L, Yu S. Exploring the stage-specific roles of Tcf-1 in T cell development and malignancy at single-cell resolution. *Cell Mol Immunol.* 2021; 18(3): 644-59.

[88]. Medda N, De SK, Maiti S. Different mechanisms of arsenic related signaling in cellular proliferation, apoptosis and neo-plastic transformation. *Ecotoxicol Environ Safety*. 2021; 208: 111752.

[89]. Simioni C, Martelli AM, Zauli G, Vitale M, McCubrey JA, Capitani S, Neri LM. Targeting the phosphatidylinositol 3-kinase/Akt/mechanistic target of rapamycin signaling pathway in B-lineage acute lymphoblastic leukemia: *J. Cell. Physiol*. 2018; 233(10): 6440-54.

[90]. Battle TE, Frank DA. The role of STATs in apoptosis. *Curr. Mol. Med.* 2002; 2(4): 381-92.

[91]. Catlett-Falcone R, Landowski TH, Oshiro MM, Turkson J, Levitzki A, Savino R, Ciliberto G,

Moscinski L, Fernández-Luna JL, Nuñez G, Dalton WS. Constitutive activation of Stat3 signaling confers resistance to apoptosis in human U266 myeloma cells. *Immunity*. 1999; 10(1): 105-15.

[92]. Mannan A, Germon ZP, Chamberlain J, Sillar JR, Nixon B, Dun MD. Reactive oxygen species in acute lymphoblastic leukaemia: reducing radicals to refine responses. *Antioxidants*. 2021; 10(10): 1616.

[93]. Barakos GP, Hatzimichael E. Microenvironmental features driving immune evasion in myelodysplastic syndromes and acute myeloid leukemia. *Diseases.* 2022; 10(2): 33.

[94]. Slamanig SA, Nolte MA. The bone marrow as sanctuary for plasma cells and memory T-cells: Implications for adaptive immunity and vaccinology. *Cells*. 2021; 10(6): 1508.

[95]. Chang HD, Tokoyoda K, Radbruch A. Immunological memories of the bone marrow. *Immunological Rev.* 2018; 283(1): 86-98.

[96]. Sezaki M, Hayashi Y, Wang Y, Johansson A, Umemoto T, Takizawa H. Immuno-modulation of hematopoietic stem and progenitor cells in inflammation. *Frontiers in Immunol.* 2020; 24; 11: 585367.

[97]. Cazzola M. Myelodysplastic syndromes. *NEJM*. 2020; 383(14): 1358-74.

[98]. Sezaki M, Hayashi Y, Wang Y, Johansson A, Umemoto T, Takizawa H. Immuno-modulation of hematopoietic stem and progenitor cells in inflammation. *Frontiers in Immunol*. 2020; 24; 11: 585367.

[99]. Winter S, Shoaie S, Kordasti S, Platzbecker U. Integrating the immunome in the stratification of myelodysplastic syndromes and future clinical trial design: *Systems Immunol;* 2020; 20; 38(15): 1723-35.

[100]. Netea MG, Schlitzer A, Placek K, Joosten LA, Schultze JL. Innate and adaptive immune memory: an evolutionary continuum in the host's response to pathogens. *Cell host microbe.* 2019; 9; 25(1): 13-26.

[101]. Netea MG, Schlitzer A, Placek K, Joosten LA, Schultze JL. Innate and adaptive immune

memory: an evolutionary continuum in the host's response to pathogens. *Cell host microbe*. 2019; 9; 25(1):13-26.

[102]. Fitzgerald KA, Kagan JC. Toll-like receptors and the control of immunity. *Cell*. 2020; 19; 180(6): 1044-66.

[103]. Kim CH. Innate immunity via glycan-binding lectin receptors. *InGlycobiol Innate Immunol*. 2022; 261-309.

[104]. Chen CY, Shih YC, Hung YF, Hsueh YP. Beyond defense: regulation of neuronal morphogenesis and brain functions via Toll-like receptors. *JBS*. 2019; 26(1): 1-3.

[105]. Delogu A, Schebesta A, Sun Q, Aschenbrenner K, Perlot T, Busslinger M. Gene repression by Pax5 in B cells is essential for blood cell homeostasis and is reversed in plasma cells. Immunity. 2006;1;24(3):269-81.

[106]. Schönheit J, Leutz A, Rosenbauer F. Chromatin dynamics during differentiation of myeloid cells. JMB. 2015;13;427(3):670-87.

[107]. Hall DD, Spitler KM, Grueter CE. Disruption of cardiac Med1 inhibits RNA polymerase II promoter occupancy and promotes chromatin remodeling. AJP-Heart. 2019;1;316(2):H314-25.

[108]. Netea MG, Schlitzer A, Placek K, Joosten LA, Schultze JL. Innate and adaptive immune memory: an evolutionary continuum in the host's response to pathogens. *Cell Host Microbe*. 2019; 25(1): 13-26.

[109]. Jameson SC, Masopust D. Understanding subset diversity in T cell memory. *Immunity*. 2018; 48(2): 214-26.

[110]. Kumar BV, Connors TJ, Farber DL. Human T cell development, localization, and function throughout life. *Immunity*. 2018; 48(2): 202-13.

[111]. Li C, Xu X, Wei S, Jiang P, Xue L, Wang J. Tumor-associated macrophages: potential therapeutic strategies and future prospects in cancer. *JITC*. 2021; 9(1).

[112]. Li J, Jiang X, Li H, Gelinsky M, Gu Z. Tailoring materials for modulation of macrophage fate. *Advanced Materials*. 2021; 33(12): 2004172.

[113]. Delprat V, Michiels C. A bi-directional dialog between vascular cells and monocytes/macrophages

regulates tumor progression. *Cancer Metastasis Rev*. 2021; 40(2): 477-500.

[114]. Butler KL, Clancy-Thompson E, Mullins DW. CXCR3+ monocytes/macrophages are required for establishment of pulmonary metastases. *Sci Reports*. 2017; 7(1): 1-9.

[115]. Boussommier-Calleja A, Atiyas Y, Haase K, Headley M, Lewis C, Kamm RD. The effects of monocytes on tumor cell extravasation in a 3D vascularized microfluidic model. *Biomaterials.* 2019; 198: 180-93.

[116]. Symowski C, Voehringer D. Interactions between innate lymphoid cells and cells of the innate and adaptive immune system. *Frontiers in Immunol*. 2017; 8: 1422.

[117]. Diny NL, Rose NR, Čihákova D. Eosinophils in autoimmune diseases. *Frontiers in Immunol*. 2017; 27; 8: 484.

[118]. Bagnasco D, Ferrando M, Varricchi G, Puggioni F, Passalacqua G, Canonica GW. Anti-interleukin 5 (IL-5) and IL-5Ra biological drugs: efficacy, safety, and future perspectives in severe eosinophilic asthma. *Frontiers in Med*. 2017; 31; 4: 135.

[119]. Amorim NR, Luna-Gomes T, Gama-Almeida M, Souza-Almeida G, Canetti C, Diaz BL, Weller PF, Torres Bozza P, Maya-Monteiro CM, Bandeira-Melo C. Leptin elicits LTC4 synthesis by eosinophils mediated by sequential two-step autocrine activation of CCR3 and PGD2 receptors. *Frontiers in Immunol*. 2018; 20; 9: 2139.

[120]. Ramirez GA, Yacoub MR, Ripa M, Mannina D, Cariddi A, Saporiti N, Ciceri F, Castagna A, Colombo G, Dagna L. Eosinophils from physiology to disease: a comprehensive review. *Bio Med Res. Int.* 2018.

[121]. Li H, Wu M, Zhao X. Role of chemokine systems in cancer and inflammatory diseases. *Med Comm.* 2022; 3(2): 147.

[122]. Çehreli C. Diagnostic problems in chronic basophilic leukemia. *Turkish J Hematol*. 2018; 35(4): 283.

[123]. Grieshaber-Bouyer R, Nigrovic PA. Neutrophil heterogeneity as therapeutic opportunity in immune-mediated

disease. *Frontiers in Immunol.* 2019; 4; 10: 346.

[124]. Sioud M. Microbial sensing by haematopoietic stem and progenitor cells: Vigilance against infections and immune education of myeloid cells. *Scandinavian J Immunol*. 2020; 92(5): 12957.

[125]. Grieshaber-Bouyer R, Nigrovic PA. Neutrophil heterogeneity as therapeutic opportunity in immune-mediated disease. *Frontiers in Immunol*. 2019; 4; 10: 346.

[126]. Oguro H. The roles of cholesterol and its metabolites in normal and malignant hematopoiesis. *Frontiers in Endocrinol*. 2019; 2; 10: 204.

[127]. Wolf NK, Kissiov DU, Raulet DH. Roles of natural killer cells in immunity to cancer, and applications to immunotherapy. *Nature Rev Immunol*. 2022; 30: 1-6.

[128]. Chu J, Gao F, Yan M, Zhao S, Yan Z, Shi B, Liu Y. Natural killer cells: a promising immunotherapy for cancer. *J Translational Med*. 2022; 20(1): 1-9.

[129]. Yilmaz A, Cui H, Caligiuri MA, Yu J. Chimeric antigen receptor-engineered natural killer cells for cancer immunotherapy. *J Hematol Oncol*. 2020; 13(1): 1-22.

[130]. Wolf NK, Kissiov DU, Raulet DH. Roles of natural killer cells in immunity to cancer, and applications to immunotherapy. *Nat. Rev. Immunol.* 2022; 30: 1-6.

[131]. Hamidi H, Ivaska J. Every step of the way: integrins in cancer progression and metastasis. *Nat. Rev. Cancer*. 2018; 18(9): 533-48.

[132]. Jain M, Chauhan AK. Role of integrins in modulating smooth muscle cell plasticity and vascular remodeling: from expression to therapeutic implications. *Cells.* 2022; 11(4): 646.

[133]. Moreno-Layseca P, Icha J, Hamidi H, Ivaska J. Integrin trafficking in cells and tissues. *Nat. Rev. Cancer*. 2019; 21(2): 122-32.

[134]. Sun Z, Costell M, Fässler R. Integrin activation by talin, kindlin and mechanical forces. *Nat. Cell Biol*. 2019; 21(1): 25-31.

[135]. David BA, Kubes P. Exploring the complex role of chemokines and chemoattractants in vivo on leukocyte dynamics. *Immunol Rev.* 2019; 289(1): 9-30.

[136]. Teixido J, Martinez-Moreno M, Diaz-Martinez M, Sevilla-Movilla S. The good and bad faces of the CXCR4 chemokine receptor. *IJBCB*. 2018; 1; 95: 121-31.

[137]. Brodin P, Davis MM. Human immune system variation. Nat. Rev. Immunol. 2017; 17(1): 21-29.

[138]. Goldman SL, Hassan C, Khunte M, Soldatenko A, Jong Y, Afshinnekoo E, Mason CE. Epigenetic modifications in acute myeloid leukemia: prognosis, treatment, and heterogeneity. *Frontiers in Genetics*. 2019; 1; 133.

[139]. Darici S, Alkhaldi H, Horne G, Jørgensen HG, Marmiroli S, Huang X. Targeting PI3K/Akt/mTOR in AML: rationale and clinical evidence. *JCM*. 2020; 11; 9(9): 2934.

[140]. Handschuh L. Not only mutations matter: molecular picture of acute myeloid leukemia emerging from transcriptome studies. *J. Clin. Oncol.* 2019.

[141]. Yu L, Wei J, Liu P. Attacking the PI3K/Akt/mTOR signaling pathway for targeted therapeutic treatment in human cancer. *Seminars in Cancer Biol* 2021; 25.

[142]. Zhang K, Jiang Y, Wang B, Li T, Shang D, Zhang X. Mesenchymal Stem Cell Therapy: A potential treatment targeting pathological manifestations of traumatic brain injury. *Oxidative Med Cellular Longevity*. 2022; 15; 2022.

[143]. Mohseni M, Uludag H, Brandwein JM. Advances in biology of acute lymphoblastic leukemia (ALL) and therapeutic implications. *Am J Blood Res*. 2018; 8(4): 29.

[144]. Ho YH, Méndez-Ferrer S. Microenvironmental contributions to hematopoietic stem cell aging. *Haematologica*. 2020; 105(1): 38.

[145]. Fattizzo B, Rosa J, Giannotta JA, Baldini L, Fracchiolla NS. The physiopathology of T-cell acute lymphoblastic leukemia: focus on molecular aspects. *Frontiers in Oncol.* 2020; 28; 10: 273.

[146]. Del Gaizo M, Sergio I, Lazzari S, Cialfi S, Pelullo M, Screpanti I, Felli MP. MicroRNAs as modulators of the immune response in T-Cell acute lymphoblastic leukemia. *IJMS.* 2022; 23(2): 829.

[147]. Nair RA, Verma VK, Beevi SS, Rawoof A, Alexander LE, Prasad ER, Kumari PK, Kumar P, Kumar LD. MicroRNA signatures in blood or bone marrow distinguish subtypes of pediatric acute lymphoblastic leukemia. *Translational Oncol*. 2020; 13(9): 100800.

[148]. Lv M, Zhu S, Peng H, Cheng Z, Zhang G, Wang Z. B-cell acute lymphoblastic leukemia-related microRNAs: uncovering their diverse and special roles. *Am J Cancer Res*. 2021; 11(4): 1104.

[149]. Houshmand M, Simonetti G, Circosta P, Gaidano V, Cignetti A, Martinelli G, Saglio G, Gale RP. Chronic myeloid leukemia stem cells. *Leukemia*. 2019; 33(7): 1543-56.

[150]. Haseeb M, Anwar MA, Choi S. Molecular interactions between innate and adaptive immune cells in chronic lymphocytic leukemia and their therapeutic implications. *Frontiers in Immunol*. 2018; 26; 9: 2720.

[151]. Chiarini F, Paganelli F, Martelli AM, Evangelisti C. The role played by Wnt/β-catenin signaling pathway in acute lymphoblastic leukemia. *IJMS*. 2020; 21(3): 1098.