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Review article

The role of chemokines and interleukins in acute lymphoblastic leukemia: a systematic review

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Abstract
Acute lymphoblastic leukemia (ALL) is the most common childhood hematological malignancy, but it also affects adult patients with worse prognosis and outcomes. Leukemic cells benefit from protective mechanisms, which are mediated by intercellular signaling molecules – cytokines. Through these signals, cytokines modulate the biology of leukemic cells and their surroundings, enhancing the proliferation, survival, and chemoresistance of the disease. This ultimately leads to disease progression, refractoriness, and relapse, decreasing the chances of curability and overall survival of the patients. Targeting and modulating these pathological processes without affecting the healthy physiology is desirable, offering more possibilities for the treatment of ALL patients, which still remains unsatisfactory in certain cases.

In this review, we comprehensively analyze the existing literature and ongoing trials regarding the role of chemokines and interleukins in the biology of ALL. Focusing on the functional pathways, genetic background, and critical checkpoints, we constructed a summary of molecules that are promising for prognostic stratification and mainly therapeutic use.

Targeted therapy, including chemokine and interleukin pathways, is a new and promising approach to the treatment of cancer. With the expansion of our knowledge, we are able to uncover a spectrum of new potential checkpoints in order to modulate the disease biology. Several cytokine-related targets are advancing toward clinical application, offering the hope of higher disease response rates to treatment.

Keywords: Acute lymphoblastic leukemia; Chemokine; Cytokine; Interleukin; Prognostic marker; Targeted therapy

Highlights:
- Cytokines modulate survival, proliferation, and resistance in ALL.
- Targeting cytokine pathways shows promise for overcoming resistance in ALL.
- Emerging therapies aim to combine cytokine inhibition with existing ALL treatments.

Abbreviations:
ADCC – antibody dependent cellular cytotoxicity; AL – acute leukemia; ALL – acute lymphoblastic leukemia; AML – acute myeloid leukemia; APC – antigen presenting cell; BiTE – bi-specific T-cell engager; BM – bone marrow; CAR-T – chimeric antigen receptor cell; CD – cluster of differentiation; CLL – chronic lymphocytic leukemia; CML – chronic myeloid leukemia; CNS – central nervous system; CRS – cytokine release syndrome; CSC – cancer stem cell; CSF – colony stimulating factor; DC – dendritic cell; GvHD – graft versus host disease; HSC – hematopoietic stem cell; (allo – allogeneic, auto – autologous) HSCT – hematopoietic stem cell transplantation; IL – interleukin; IFN – interferon; JAK – Janus kinase; LIC – leukemia initiating cell; LSC – leukemia stem cell; MDS – myelodysplastic syndrome; MoAb – monoclonal antibody; MRD – minimal residual disease; NK – natural killer; PB – peripheral blood; Ph+ – Philadelphia chromosome positive; Ph-like – Philadelphia chromosome like; RAP – receptor accessory protein; STAT – signal transducer and activator of transcription; TIC – tumor initiating cell; TKI – tyrosine kinase inhibitor; TSLP – thymic stromal lymphopoietin

Introduction

Acute lymphoblastic leukemia (ALL) is a hematological malignancy characterized by the clonal expansion of malignant lymphoid hematopoietic precursors. It is the most common malignancy in children, with a second incidence peak in later years of age. According to the affected lineage, ALL is divided into B-ALL and T-ALL.

The treatment of ALL and other hematological malignancies has advanced significantly in the last three decades, introducing new treatment options alongside standard chemother-

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apy, radiotherapy, and allogeneic stem cell transplantation. We can target surface antigens with monoclonal antibodies (MoAbs), bispecific antibodies/bi-specific T-cell engagers (BiTEs), and chimeric antigen T-lymphocytes (CAR-T). Intracellularly acting tyrosine kinase inhibitors (TKI) are a crucial part of the treatment of Ph+ and newly classified Philadelphia chromosome like ALL (Ph-like ALL). Agents designed to target specific genetic mutations in malignant cells are currently in development and progressing through preclinical and clinical trials.

Knowledge of intercellular and intracellular signaling is crucial for understanding the biology of a tumor, which is regulated by various signaling molecules such as cytokines and adhesion molecules in its microenvironment (Malard and Mohty, 2020).

Microenvironment of a tumor

It is not only the tumor itself but also the microenvironment around it that plays an important role in the behavior, biological characteristics, and potentially malignant nature of the disease; particularly its progression despite the effect of systemic chemotherapy and targeted drugs, and ultimately the creation of a specific clone of tumor cells resistant to these therapeutics. Many forms of interaction have been described between tumor cells and their microenvironment at the molecular level, regulating the recruitment, activation, and further implementation of the microenvironment, including interactions with other types of immune cells (Simioni et al., 2021). This phenomenon is clearly not one-way, the microenvironment provides a feedback to the tumor and also influences the surrounding healthy tissues (Moses et al., 2016; Vilchis-Ordoñez et al., 2015).

In leukemia, the bone marrow (BM) microenvironment is the most important element as it serves as the nest of hematopoiesis, healthy and tumorous, the main therapy target, and the most common site of disease relapse. Here, the leukemic cells are mainly influenced by healthy hematopoiesis signals (Moses et al., 2016), and there are several key players among the cell lines that affect these crucial aspects of leukemic behavior.

When describing cells lines in the tumor microenvironment, various terms are used, which often differ from paper to paper, depending on the specific context. The development of a tumor or acute leukemia and its chemoresistance and potential relapse are likely driven by a small pool of tumor/leukemia initiating cells (TICs/LICs), sometimes referred to as cancer/leukemia stem cells (CSCs/LSCs). CSCs/LSCs are a population of cells capable of self-renewal and developing into "clonal daughter cells". The terms "TICs/LICs" are more frequently used in experimental contexts to describe cells with the ability to initiate tumors or leukemia in animal models. Studies on acute leukemias, especially ALL, often interchange the terms of LICs and LSCs. LSCs are believed to possess the fundamental qualities of healthy hematopoietic stem cells (HSCs), including the capability to produce all blood cell lineages. They are mostly in a state of cell cycle arrest, allowing them to evade therapies targeting cycling cells, such as chemotherapeutic drugs and radiation therapy (Babovic and Eaves, 2014; Chiarini et al., 2016; Tan et al., 2017).

HSCs occupy a specific part of the BM microenvironment called the niche, which is defined as a local tissue microenvironment that directly influences a particular type of stem cell or progenitor, regulating HSC quiescence, proliferation, differentiation, and migration. In doing so, it also provides a sanctuary for leukemic populations enabling them to evade chemotherapy or targeted drugs and, consequently, to acquire drug resistance. HSCs interact with the niche through the exchange of various molecular signals. Two distinct types of niches are described in the BM: the osteoblastic (endosteal) and vascular niches (Chiarini et al., 2016; Morrison and Scadden, 2014).

B-ALL blasts are able to hijack the BM microenvironment by producing chemotherapy-induced cytokines, forcing it to form a leukemic niche that protects the residual cells from chemotherapeutics, facilitating chemoresistance, and ultimately, disease relapse (Chen et al., 2019; Ma et al., 2020). In return, the BM microenvironment can modulate ALL cells, altering their metabolism and protein expression, increasing quiescence, and creating a specific cell phenotype with higher chemotherapy resistance (Moses et al., 2016).

Therefore, considering the role of the tumor microenvironment, it is necessary not only to target the tumor cells but also to control the inflammatory microenvironment that contributes to resistance to anti-cancer therapies. In this regard, studies on the interactions between the bone marrow microenvironment and ALL cells have revealed potential therapeutic targets, including cytokines/chemokines and their receptors, adhesion molecules, signal transduction pathways, and hypoxia-related proteins (Clara et al., 2020; Olson and Joyce, 2013). However, while the functions of the BM niches have been well characterized in healthy hematopoiesis and other leukemia types such as acute myeloid leukemia (AML), it remains poorly understood how B-ALL blasts exploit BM microenvironment signaling to develop chemoresistance within the perivascular and endosteal niches, as well as in peripheral blood (PB) (Horacek et al., 2015; Kupsa et al., 2012; Ma et al., 2020). It appears that a possible anti-tumor strategy is to target the inflammatory microenvironment in combination with blocking specific immune checkpoints (Simioni et al., 2021).

It is not only the BM microenvironment but also the microenvironments of other tissues/organs infiltrated by leukemic cells that can play a critical role in the evolution of the disease process (Chiarini et al., 2016; Gaudichon et al., 2019). For example, the central nervous system (CNS) can protect ALL cells from systemic chemotherapy (Gossai and Gordon, 2017), the hepatic microenvironment can provide a niche for leukemic cells (Kato et al., 2011), and in splenic microenvironment, T-ALL cells could be stimulated to express a higher level of CCL19, a ligand of CCR7, which further stimulates the proliferation and migration of T-ALL cells (Ma et al., 2014).

Role of cytokines in hematopoiesis

Cytokines are small soluble proteins, vital for intercellular signaling, especially in the environment of the immune system. They can be divided based on different criteria, including their structure, cellular origin, receptor types, biological effects, or specific influence on the inflammatory response. It is clear, that a single molecule can be produced by several different cell types and can behave in a completely opposite way in different scenarios. This balance is strictly and comprehensively regulated in a healthy organism, and its disruption can cause severe consequences, such as a cytokine storm, autoimmune disorders, or immune deficiencies.

Basic classification divides cytokines into six groups: chemokines (lymphokines, monokines), interleukins (ILs), growth factors of hematopoiesis (colony stimulating factors – CSFs, poietins), tumor necrosis factors (TNFs), interferons (IFNs), and transforming growth factors (TGFs).

This classification is often based on initial findings during the first discovery of a certain molecule and can be misleading in some cases. Several changes in names and classifications

have occurred in the past. Some members overlap between two groups, such as the IL8/CXCL8 protein (Kupsa et al., 2012; Liu et al., 2021a). Many other molecules that can be classified as cytokines by their function are not included in this classification.

To understand the complexity of tumor microenvironment, we have to analyze not only cytokine-producing cells but also the cells which react to them. Cytokine function is strictly bound to the expression of their specific receptors, therefore most studies performed on their behalf have investigated cells with membrane receptors expressed on the surface, and more rarely the serum levels or the gene expression for certain cytokine in the producing cells. Soluble receptors for cytokines found in the serum/plasma are a specific exception.

In this review, we focus on the role of chemokines and interleukins in ALL biology.

Chemokines

Chemotactic cytokines are a family of small proteins that stimulate the migration of cells, mainly leukocytes, through chemical signal pathways (chemotaxis or leukotaxis, respectively). They therefore participate in the development and maintenance of the immune system homeostasis, including all pro- and anti-inflammatory responses.

As in other cytokine families, some members are redundant to each other, binding the same ligands with different receptors and *vice versa*. Depending on the position of the first two cysteine residues near the N-terminal of the receptor, this family can be divided into four main classes: CC, CXC, XC, and CX3C-chemokines.

In a leukemic microenvironment, chemokines are produced by leukocytes, both healthy and malignant, as well as by stromal cells and other niche cells. In response to these signals, immune cells migrate into the BM and other leukemic microenvironments, further influencing the leukemogenesis, progression, and relapse. Not only immune cells, but also chemokines can target non-immune cells within the leukemic niche. Several main signaling pathways governed by chemokines have been investigated and have shown potential in tumor-targeted therapy (Griffith et al., 2014; Hughes and Nibbs, 2018).

The main ligand-receptor couples participating in the development of ALL are CXCL12/CXCR4, CCL25/CCR9, CXCL10/CXCR3, CCL19/CCR7, and CXCR7/CXCL12. These pathways in ALL are widely described in various recent reviews (Gómez et al., 2015; Hong et al., 2021). For the purpose of this article, we will sum up only the basics of CXCL12/CXCR4 and CCL12/CCR9, with overlapping IL-8/CXC8 mentioned further in the interleukin section.

CXCL12/CXCR4

CXCL12, also known as stromal cell-derived factor-1 (SDF-1), primarily binds with CXCR4 to stimulate the proliferation, survival, differentiation, self-renewal, activation, and migration of healthy and malignant hematopoietic cells (Sahin and Buitenhuis, 2012).

This axis is the most extensively studied chemokine pathway in acute leukemias. Its activation and increased expression of the CXCR4 are associated with a poor prognosis of ALL patients, inducing chemoresistance, mediating dissemination, and enabling the homing of leukemic cells in BM and other tissues (Crazzolara et al., 2001; de Lourdes Perim et al., 2015; Ko et al., 2014; Konoplev et al., 2011; Passaro et al., 2015; Peled et al., 2018). This pathway can be influenced by other chemokines, such as CXCR7, which has been observed to be overexpressed mainly on ALL cells, particularly in T-ALL (Melo et al., 2014). Conversely, in MLL+ ALL, which presents a unique phenotype compared to classic ALL and AML, the CXCR7 versus CXCR4 has shown an opposite effect on the cell chemosensitivity (Ando et al., 2018). Despite documented evidence that ALL employs other mechanisms to create a protective microenvironment without using the CXCL12/CXCR4 axis (de Rooij et al., 2017), it remains one of the main potential targets for future therapeutic strategies (Hong et al., 2021; Passaro et al., 2015; Sugiyama and Nagasawa, 2015). Several molecules have shown promising results in preclinical studies. CXCR4 antagonists are capable of mobilizing leukemic cells from the BM and increase their sensitivity to chemotherapeutic agents (Welschinger et al., 2013; Yu et al., 2011). AMD3100 (Plerixafor) has been used and well tolerated in a group of pediatric patients with AML, ALL, and myelodysplastic syndrome (MDS) in combination with high-dose cytarabine and etoposide. While its desired biological effect of mobilizing leukemic blasts was observed, the actual therapeutic response was not satisfactory (Cooper et al., 2017). However, this study was conducted with only five ALL patients, and the potential of using Plerixafor in different settings remains promising. The ability to mobilize residual leukemic cells has also been utilized to enhance the myeloablative effect within the allogeneic hematopoietic stem cell transplantation (HSCT) (Mori et al., 2021).

CCL25/CCR9

This axis has been described in a variety of malignancies, including ALL. It plays an important role mainly in the T-lymphoid lineage and is expressed in most T-ALL patients samples. CCR9 is mainly found on immature T-lymphocytes and on the surface of intestinal cells. When bound to its specific and only ligand, CCL25, it significantly influences T-lymphocyte development and homing (Qiuping et al., 2003; Skroblyn et al., 2022; Tu et al., 2016). In T-ALL, a line of MOLT4 cells is characterized by high expression of CCR9 and through activation by CCL25 it can infiltrate other tissues (Deng et al., 2017). Interestingly, IL-2 and IL-4 can induce the internalization of CCR9 and therefore dampen this important pro-leukemic mechanism (Tong et al., 2009). This demonstrates the vast complexity of intercellular signaling, where molecules from several different groups can intersect each other's pathways.

There are studies proving the effect of CCL25/CCR9 on MOLT4 cells' resistance to apoptosis and inappropriate proliferation, specifically using the ERM proteins (Qiuping et al., 2004; Zhang et al., 2013b). The Notch1 signaling pathway plays an important role in T-cell development and is highly involved in T-ALL pathophysiology, modulating CXCR4 and CCR9 functions and enhancing leukemia progression (Ma et al., 2014; Mirandola et al., 2012; Tsaouli et al., 2019).

Agents targeting chemokines in preclinical and clinical studies for ALL and related conditions are shown in Table 1.

Interleukins

Interleukins are signaling molecules produced by various types of body cells, but were first observed to be expressed by leukocytes, hence the name. They are involved in the immune system, playing roles in various diseases, including hematological malignancies.

IL-1 family

This family of cytokines comprises 11 members, of which the most important for this review are the IL-1 isoforms alpha and beta, IL-1RAP, and IL-18.

Table 1. Chemokine-targeting agents for acute lymphoblastic leukemia and related conditions

Chemokines	Agent	Biological effect	Preclinical studies	Clinical studies
CXCL12/CXCR4	AMD3100 (Plerixafor)	Mobilizing, sensitizing ALL cells	Parameswaran et al., 2011, 2012; Sison et al., 2013, 2014; Su et al., 2021; Welschinger et al., 2013; Yu et al., 2011	Cooper et al., 2017; Mori et al., 2021
		Mobilizing healthy CD34+ HSC		Caocci et al., 2014; Gattillo et al., 2015
	AMD11070	Blocking the migration of ALL cells	Parameswaran et al., 2011	
	POL5551	Inhibiting chemotaxis, sensitizing ALL cells	Sison et al., 2015	
	BL-8040	Suppressing growth, mobilizing ALL cells		Uy et al., 2019
CCL25/CCR9	CCL25-PE38	Suppressing growth, inducing apoptosis of ALL cells	Hu et al., 2011	
	91R, 92R	Inducing apoptosis of ALL cells, CDC, ADCC	Chamorro et al., 2014; Somovilla-Crespo et al., 2018	
CCR5	Maraviroc	Suppressing growth and migration, inducing apoptosis of ALL cells	Zi et al., 2017	

Note: ADCC – antibody dependent cellular cytotoxicity; ALL – acute lymphoblastic leukemia; CD – cluster of differentiation; CDC – complement dependent cytotoxicity; HSC – hematopoietic stem cell.

Interleukin 1

IL-1 is a pro-inflammatory cytokine closely linked to innate immunity. It affects a wide spectrum of cells and organs, including local and systemic inflammatory responses, angiogenesis, and hematopoiesis. During many autoimmune, infectious, and degenerative diseases, it mediates the pathological immune response. In sensu stricto, the IL-1 family consists of two agonistic proteins, IL-1α and IL-1β, which have similar properties, but their amino acid sequences and final biological effects are quite distinct. IL-1α is present in healthy cells in the form of a precursor, and when needed, it immediately moves to the surface of the cell and is mainly active in a cell-associated form. IL-1β is one of the most powerful endogenous pyrogens. In contrast to IL-1α, it is not automatically present in healthy cells and requires several intracellular actions to be expressed, but is active in a sole secreted form (Apte and Voronov, 2008; Dinarello et al., 2012; Liu et al., 2021a).

Several older studies have shown that B-ALL precursors express IL-1 receptors, and their binding with IL-1 (IL-1α, respectively) stimulates their proliferation (Mori et al., 1994; Uckun et al., 1989). A propiece IL-1α (an intranuclear form of IL-1α) facilitates proliferation and reduces apoptosis of blasts in T-ALL cell lines (Zhang et al., 2017). IL-1β was observed to be expressed in acute leukemia cell lines as an autocrine growth factor and to be stimulated by activated intracellular pathways through KRAS and NRAS mutated genes, which have grown in importance in recent years (Beaupre et al., 1999).

Interleukin 1 receptor accessory protein

IL-1RAP, a subunit of the IL-1 membrane receptor, is a protein that binds to IL-1, IL-33, and other interleukins and is necessary for their signaling and final inflammatory effect (IL1RAP interleukin 1 receptor accessory protein [Homo sapiens /human/], 2024).

Activated IL-1RAP is overexpressed in AML LSCs and potentiates the proliferation of AML cells (Mitchell et al., 2018).

In chronic myeloid leukemia (CML), TKI-resistant LSCs express IL1-RAP, and its expression levels correlate with clinical phases, increasing with disease progression (Zhao et al., 2014).

In ALL, the levels of IL-1RAP are significantly higher in BCR/ABL-positive (Ph+) and Ph-like B-ALL than in normal B-cell progenitors.

Targeting IL1-RAP in AML and CML xenograft models brought promising results (Ågerstam et al., 2015; Järås et al., 2010; Warda et al., 2019).

The same phenomenon was observed in ETV6/RUNX1 expressing B-ALL cells, where IL-1RAP specific antibodies induced killing of the expressing cells by the antibody-dependent cellular cytotoxicity (ADCC) *in vivo* (Ågerstam et al., 2022).

Interleukin 18

IL-18, historically called interferon-gamma-inducing factor, regulates innate and acquired immune responses. It is a pro-inflammatory cytokine, secreted by hematopoietic and non-hematopoietic cells. It stimulates the secretion of interferon-γ (IFN-γ) from T helper (Th1) cells and, in cooperation with IL-12, participates in host defense against intracellular bacteria, viruses, and fungi, but its range is not limited to type 1 responses only (Esmailbeig and Ghaderi, 2017; Gracie et al., 2003; Yasuda et al., 2019).

Regarding its possible anti-leukemic properties, IL-18 augments the activity of anti-CD20 monoclonal antibodies against B-cell lymphoma by stimulating the production of IFN-γ, increasing the ADCC of natural killer (NK) cells (Srivastava et al., 2013). NK-cell anti-tumor effect, which is suppressed by the leukemic microenvironment, could be restored by IL-18, IL-12, and IL-15 (Boieri et al., 2017).

There are studies investigating the levels of IL-18 in multiple myeloma and B-cell lymphomas (Airoldi et al., 2004; Alexandrakis et al., 2004).

In AML, the expression of IL-18 correlated with the disease status, age, and CD34 expression, variating between the high-risk and intermediate-risk group of patients. IL-18 plays a role in disease aggressiveness by stimulating the production of matrix metalloproteinase 9 (MMP-9) and could be used as a prognostic marker (Zhang et al., 2002, 2004).

In T-ALL, one study found IL-18 PB levels significantly higher in patients than in the control group, correlating with

disease character. Low levels were more frequent in T lymphoblastic lymphoma (T-LBL) with mediastinal effusion, whereas high levels were observed more in a group of T-ALL. No correlation between IL-18 levels and sex, age, CNS infiltration, white blood cell count, or cytogenic abnormalities were found, and disease-free survival was not impacted (Uzan et al., 2014). However, this finding was not confirmed by another study with 40 childhood ALL patients, where the serum levels of IL-18 were not significantly different between the patients and the control group (Solati et al., 2020).

IL-18 production by BM derived mesenchymal stromal cells (MSC) can be enhanced by MEK inhibitors *in vitro* and *in vivo*, resulting in increased T-ALL cell growth. This can be disrupted by adding IL-18 neutralizing antibody (Uzan et al., 2014).

IL-18 is a pro-inflammatory cytokine and certainly has pro-tumor potential, and it is desirable to block this in targeted therapy. However, considering its possible indirect anti-leukemic effect through enhanced NK-cells activity, these strategies will have to take into account these properties, probably dependent on cancer type.

The common γ chain cytokine family

Interleukins in this family bind the γc receptor (CD132) and mainly affect the growth and proliferation of cell progenitors, closely linked to the JAK-STAT signaling pathway. This family comprises several members, of which we discuss IL2, IL-4, IL-7, and IL-15 (Vainchenker and Constantinescu, 2013). The γc cytokines and their receptors are known for stimulating the proliferation and malignant transformation of tumor cells (solid and hematopoietic), as well as for their ability to induce cell cycle arrest and cause tumor regression (Barata et al., 2004; Goh and Hong, 2017; Vigliano et al., 2012).

Interleukin 2

Also known as T-cell growth factor (TCGF), IL-2 is an important cytokine, produced mainly by CD4+ T-cells, which stimulates antibody production by B-lymphocytes, proliferation of T-lymphocytes, and cytolytic activity of NK-cells. The IL-2 receptor is expressed highly on immune cells, mainly malignant ones. IL-2 has both inflammation-mediating and anti-tumor effects, but its effect on immune cells is mostly dual, balancing and mediating the immune system in both directions. For example, it has been used as part of renal cell carcinoma and melanoma treatment, but its use in high doses is limited by its toxicity and pleiotropic effect, which cannot guarantee the coveted one-way effect of the therapy (Jiang et al., 2016; Klapper et al., 2008). Several older studies have shown that targeting IL-2 receptors in different ways has potential in oncohematology, autoimmune diseases, and the prevention of graft rejection (Waldmann, 1989). In recent years, several reviews have been published, rethinking the potential of IL-2/IL-2R/sIL-2R targeted anti-cancer therapy, using both the indirect effect of IL-2 on immune cells and direct influence on cancer cells (Ko et al., 2023; Muhammad et al., 2023).

In hematology, experimenting with an immunocytokine, fusion protein of L19-IL2 in a combination with an anti-CD20 antibody rituximab provided a complete eradication of human B-cell lymphoma xenografts (Schliemann et al., 2009).

In AML, a meta-analysis evaluating a significance of IL-2 in maintenance therapy, found no significant beneficial value of IL-2 in monotherapy (Buyse et al., 2011).

In contrast, adult T-cell leukemia displays specific sublines, which are dependent on the IL-2 activating pathways during the development of the disease and can produce IL-2 in an autocrine manner (Maeda et al., 2020; Zhang et al., 2015b).

Using knowledge of T-cell cycle and how it is affected by IL-2, the theory suggests that IL-2 priming could be able to increase a number of malignant T-cells in S phase of their cycle and therefore enhance their sensitivity to cycle specific chemotherapeutics (Zhang et al., 2013a).

Immune modulation in allografted patients using IL-2 to boost CD4+ Treg lymphocytes and prevent allogenic T-lymphocytes expansion in patients with graft versus host disease (GvHD) could be a promising strategy in chronic GvHD; there is already clinical data with promising *in vivo* results in acute GvHD (Ramos et al., 2023; Whangbo et al., 2019; Wobma et al., 2023).

Interleukin 4

IL-4's main function is as a regulator of allergic conditions and protection against parasites. It stimulates type 2 immunity (Th2 cells and B-cell differentiation and production of IgE) and suppresses type 1 responses (Gärtner et al., 2023). IL-4 is considered an anti-tumor cytokine in Hodgkin's lymphoma (HL), Non-Hodgkin's lymphoma (NHL), and chronic lymphocytic leukemia (CLL) in preclinical studies. However, clinical outcomes of its administration were not satisfactory (Kawakami et al., 2005; Kurtz et al., 2007; Wiernik et al., 2010). Recent studies also suggest that it can induce apoptosis of AML cells, and the administration of IL-4 *in vivo* was associated with a lower leukemic burden (Peña-Martínez et al., 2018; Qian et al., 2022).

In ALL, levels of IL-4 at the time of diagnosis were not significantly different from those in the healthy control group (Dai et al., 2023). Several older studies have suggested an anti-leukemic effect on B-ALL cells *in vitro* (Manabe et al., 1994; Okabe et al., 1991), however in T-ALL, IL-4 stimulates the proliferation of leukemic cells through mTOR signaling pathways, making it another attractive target in treating T-cell malignancies, especially those with activated Notch1 signaling (Cardoso et al., 2009; Cuéllar Mendoza et al., 2024).

IL-2 and IL-4 share many features and influence each other's production by the cells; their role in suppressing CCR9 mediated infiltration of T-ALL has already been mentioned (Tong et al., 2009).

Interleukin 15

IL-15 is structurally similar to IL-2, sharing a four α helix bundle and also receptors similar in structure, containing α sections (IL-2Rα and IL-15Rα) binding their ligands, β (IL-2/15Rβ) and γc chains with followed intracellular signaling pathways (e.g., JAK/STAT). Like IL-2, its spectrum of actions is wide and pleiotropic, covering many cell types, but both IL-2 and IL-15 have their distinct purposes. The main effect is regulating the proliferation and activity of T-cells and NK-cells (Goh and Hong, 2017; Ma et al., 2000). Regarding hematological malignancies, the main discoveries were made in the field of mature lymphoproliferative diseases (Epron et al., 2012; Ullrich et al., 2015; Wang et al., 2015a).

In therapy, IL-15 administration can have an indirect anti-tumor effect It stimulates T- and NK-cells, and also boosts the effect of an antibody therapy in treating various malignancies, with several ongoing clinical trials implicating its possible future use (Dubois et al., 2021; Miljkovic et al., 2023; Waldmann et al., 2020; Wrangle et al., 2018; Zhang et al., 2018). On the other hand, inhibiting the IL-15 pathways seems profitable in T-cell related diseases, such as celiac disease and T-lymphoproliferations, taking advantage of IL-2 and IL-15 shared features by using BNZ-1, a multicytokine inhibitor of the common γ chain cytokine family (Frohna et al., 2020; Sestak et al., 2018; Wang et al., 2019).

Regarding ALL, IL-15 gene expression at the time of diagnosis negatively correlates with relapse-free survival (RFS), but no statistically significant correlation was found with overall survival (OS). The gene expression levels were different in various ALL types, depending on the immunophenotype and cytogenetics (Wu et al., 2010a, p. 15). It can also predict CNS involvement in childhood ALL, IL-15 mediates the homing of the blast cells and affects the permeability of the blood-brain barrier due to its pro-inflammatory effect (Cario et al., 2007; Williams et al., 2014). Together with IL-12 and IL-18, IL-15 pre-stimulation of NK-cells slowed down the progression of T-ALL *in vivo* (Boieri et al., 2017).

Interestingly, chimeric IL-15 was used as a membrane-bound signaling antigen for its effect on memory T-cells in a study to find T-memory stem cells (TSCM) among CAR T-lymphocytes, which could help the anti-leukemic memory of CAR-T products to endure even after they disappear from a patient's blood (Hurton et al., 2016).

Regarding its pleiotropic functions and possible antagonistic effects, the potential clinical use of IL-15 will probably be limited.

Interleukin 7

IL-7 is by far the most described interleukin, regarding hematological malignancies. It is considered a pro-tumor cytokine, and its clinical effects are well documented in many nosological units.

IL-7 is produced by stromal cells, primarily in the thymus, bone marrow, and lymphatic tissue, but possibly also in an autocrine manner by T-ALL cells themselves (Buffière et al., 2019).

Its main mechanism of action works through interaction with type I cytokine receptors (IL-7R composed of α and γ chains) and the activation of several pathways (discussed later), stimulating the expansion and survival of thymocytes and various lines of T- and B-lymphocytes (originally called lymphopoietin 1, LP-1). While the expression of IL-7Rα remains through all stages of T-cells, it is decreasing during the maturation of B-cells (Tal et al., 2014).

Higher levels of IL-7 are followed by lymphocytosis and may be associated with autoimmune diseases. Deficiency in IL-7 pathways leads to lymphopenia, its administration is experimentally used in sepsis and immunodeficiencies, widely reviewed by Winer et al. (2022).

As suggested, IL-7 levels are inversely related to an absolute lymphocyte count, confirming its regulated production and lower binding with IL-7R on lymphocytes by negative feedback. This was documented on a group of pediatric patients with ALL, where IL-7 levels dropped after matched unrelated donor or autologous bone marrow transplantation, following total lymphocyte count rise. These results were also different from patients with acute non-lymphoblastic leukemia (Bolotin et al., 1999). IL-7 is one of the key players in the pathobiology of ALL, primarily investigated in T-ALL. It represents a promising target for T-ALL treatment, which still has many weak points. IL-7 shares several properties with thymic stromal lymphopoietin, and their pathological pathways in ALL will be discussed together.

Thymic stromal lymphopoietin (TSLP)

TSLP is a cytokine expressed by epithelial cells of the thymus, intestine, lungs, and bronchi. Its physiological function is to mediate innate immune and allergic reactions and to provide protection against parasites (Quentmeier et al., 2001; Siracusa et al., 2011). TSLP promotes helper T-cell activation and cytokine production, their proliferation through the T-cell receptor (TCR), and drives B-cell expansion and maturation. It binds with TSLP receptor (TSLPR) which is comprised of IL-7Rα and TSLPR chain (also known as CRLF2) and activates similar pathways as IL-7 (Al-Shami et al., 2004).

IL-7 and TSLP signaling pathways in ALL

Starting with the receptors themselves, multiple gain-of-function mutations of IL-7Rα were described in T- and B-ALL. Insertions of cysteine or other amino acids in either the extracellular or the transmembrane domain activates the pathways independently of the ligands (Shochat et al., 2011, 2014; Zenatti et al., 2011). These gain-of-function mutations create a high-risk group of pediatric patients (Richter-Pechańska et al., 2017). CRLF2 gene mutations with overexpression of functional TSLPR (Yoda et al., 2010) are prognostically significant in Ph-like ALL (Tasian et al., 2017). It is also described in Down syndrome ALL, and ALL with amplification of a segment on the long arm of chromosome 21 (iAMP21 ALL) (Rand et al., 2011). In Ph+ ALL, IL-7R is expressed more. When treated with TKIs, and by interacting with CXCR4, it prolongs the survival of the cells and creates resistance to the TKIs. This phenomenon can be attenuated by anti-IL-7R antibodies, which delayed leukemia onset *in vivo* (Abdelrasoul et al., 2020). IL-7Rα expression can be found on T-ALL cells and can be upregulated by various mechanisms (Laouar et al., 2004).

Following signaling axes activated by IL-7 can drive a development of lymphoid malignancies in mice models. Also, T-ALL progression was slowed down in IL-7 deficient mice (Silva et al., 2011). IL-7 is crucial for the survival of T-ALL cells in both the thymus and BM microenvironment (Scupoli et al., 2007). In B-ALL, IL-7 is associated with CNS involvement and can predict CNS relapse (Alsadeq et al., 2018).

In the downstream pathways, many other important proteins can be mutated. Naming few, Janus kinases (mainly JAK 1 and 3), Stat proteins, phosphatidylinositol 3 kinase (PI3K), serine/threonine kinase AKT and the kinase inhibitor PTEN. Dynamin2 (DMN2) and Cyclin Dependent Kinase Inhibitor 2 A (CDKN2A) mutations are also linked to IL-7 axis and can promote ALL development (Geron et al., 2022; Tremblay et al., 2016).

Most of the mutations in these pathways have pro-leukemic effects but are not sufficient enough to drive leukemia on their own. Usually, we can observe multiple simultaneous combinations in ALL.

Inhibition of these pathways, either with ruxolitinib, venetoclax, or newly developed TKIs may enhance the effect of the standard ALL therapy (Kołodrubiec et al., 2022; Pemmaraju et al., 2023; Senkevitch et al., 2018; Tran and Tasian, 2022).

Mutated Notch1 is the most common aberration in T-ALL. One of the effects of mutated Notch1 is an upregulated expression of IL-7R on the surface of the cells (González-García et al., 2019, 2009). Several approaches to affect this pathway have been investigated, using antibodies and proteasome inhibitors (Agnusdei et al., 2014; Koyama et al., 2014).

Targeting the IL-7Rα with MoAbs in T-ALL, or using CAR-T products with an anti- IL-7Rα or anti-TSLPR domain could be a potential strategy, probably triggering NK-mediated ADCC and other growth control mechanisms (Akkapeddi et al., 2019; Hixon et al., 2020; Qin et al., 2015). Other drugs for possible intracellular targets along the IL-7 pathways, inhibiting BET bromodomain, STAT5, PI3K, AKT, or mTOR, PIM1, BCL2, CK2, are being investigated (Cramer et al., 2016; Degryse et al., 2018; Melão et al., 2016; Ott et al., 2012). Adding these inhibitors to routine ALL therapy would probably require tar-

geted sequencing of every patient, but with a promise of an individual, more specific, and most effective approach for each clinical case.

As discussed before, IL-7 and its intracellular pathways are investigated and described in many studies exceeding the scope of this article (Oliveira et al., 2019). However, many insights are yet to come to fully understand these mechanisms and our possibilities in order to influence them in a clinically useful therapeutic manner. Clinical studies are currently still missing.

Interleukin 6 family

According to some sources, a total of ten members (seven original and three recently added) belong to the IL-6 family. Some of them overlap with other cytokine groups (IL-27 also belongs to the IL-12 family, discussed later) (Rose-John, 2018; Sun et al., 2015). These cytokines share a four-helix bundle structure, which binds receptor gp130 subunit. Members of the IL-6 family have pleiotropic functions and can be redundant to each other, mainly activating JAK/STAT and other affiliated pathways (Kang et al., 2020). Their main functions lie in the regulation of the immune response to infection, trauma, and other insults, as well as the development of cognitive and behavioral functions. In disease, it is related to multiple immune disorders. Targeted therapies that influence pathways are starting to take a stable place in rheumatology (Jones and Jenkins, 2018). Their role in forming the tumor microenvironment is also highly investigated, indicating their negative prognostic value in various types of cancer (Johnson et al., 2018; Soler et al., 2023).

In this article, we further discuss IL-6 and IL-27, the two members with the highest potential value in the investigation of ALL microenvironments. Another member of this family, leukemia inhibitory factor (LIF), got its name from its pro-differentiation effect on myeloid leukemia cells, but has been mainly examined in solid tumors since then (Gearing et al., 1987; Jorgensen and de la Puente, 2022; Soler et al., 2023; Sun et al., 2012).

Interleukin 6

IL-6 is expressed by monocytes, dendritic cells, macrophages, and solid tissue cells. It signals either through its receptor on the surface of the cell (the classic pathway – IL-6R), or the soluble receptor (trans activation – sIL-6R), which mediates the effect on the malignant niche (Rose-John et al., 2006). Receptor gene mutations lead to various inflammatory and developmental disorders (Rebouissou et al., 2009; Spencer et al., 2019).

Elevated serum levels of IL-6 were observed in multiple cases of cancer, including hematological. However, as discussed above, its functions also lie in an immune response to infection, trauma, irradiation, or surgery, so its elevated levels are not specific in complicated clinical cases and the interpretation could be misleading (Johnson et al., 2018; Ludwig et al., 1991).

The expression of IL-6 genes and plasma levels have been investigated in several small studies, suggesting its significance in AML (Sanchez-Correa et al., 2013). In CML, high plasma levels of IL-6 have been associated with patients who failed to achieve an early molecular response during TKI treatment, as well as with an increased risk of blastic crisis and poorer outcomes in the future (Nievergall et al., 2016). However, high IL-6 plasma levels at the time of withdrawal from TKI treatment were predictive of significantly longer RFS. This phenomenon could be due to LSC exhaustion caused by constant IL-6 stimulation (Pavlovsky et al., 2023).

While activating the JAK/STAT pathways, mutations of these signaling proteins often lead to the development of B- and mainly T-ALL and are desirable targets for a therapeutic approach. However, not many studies have been conducted regarding IL-6 targeting (Casado-García et al., 2022; Govaerts et al., 2019; Reshmi et al., 2017; Waldmann, 2017). Intracellular levels of IL-6 were measured in lymphocytes of pediatric ALL patients and were significantly higher at the time of the diagnosis than in remission (Yin et al., 2006). The gene expression and pathological effect of IL-6 also depends on gene polymorphisms (Liu et al., 2020), and the results were not convincing in the group of B-ALL patients, where mRNA expression levels did not significantly differ from a healthy group. The mRNA expression levels were reduced only in a group of patients with T-ALL (Allahbakhshian Farsani et al., 2020; Inoue et al., 1994; Saadi et al., 2021).

IL-1 and IL-6 have their role in the biology of cytokine release syndrome (CRS) and their antagonists are used in the treatment of these complications, mentioned in Table 2.

Interleukin 27

IL-27 is mainly expressed by antigen presenting cells (APCs), activating STAT pathways of various hematopoietic, immune, and epithelial cells through IL-27R. It covers a pleiotropic set of immunomodulating functions as a pro-, anti-inflammatory, and even immunosuppressive cytokine. IL-27 influences a variety of immune cells in different and often conflicting ways (Awasthi et al., 2007; Fabbi et al., 2017; Karakhanova et al., 2011; Schneider et al., 2011). According to many recent studies, IL-27 also displays both pro- and anti-tumor qualities. Its anti-tumor effects prevail to the extent of possible use in cancer, including hematological malignancies (Cocco et al., 2012; Horlad et al., 2016; Zorzoli et al., 2012). IL-27 stimulates the differentiation of hematopoietic cells (Seita et al., 2008). Both normal and ALL B-cells from pediatric patients express IL-27R and its specific subunit WSX1. *In vitro* and *in vivo* models suggest that IL-27 inhibits not only ALL blasts, but also TICs/LICs. Thus, it is a promising agent, reducing ALL proliferation and dissemination, inducing apoptosis, and also inhibiting angiogenesis by upregulating the IFN-γ (Canale et al., 2011). Despite these attractive properties, this study showed a pro-leukemic effect of IL-27. It increased the survival and resistance of AML cells to chemotherapy and reduced apoptosis of leukemic cells, confirming its complicated pleiotropic character that could limit its possible clinical use (Jia et al., 2016).

Interleukin 12 family

The IL-12 family comprises 4 members: IL-12, IL-23, IL-27 (discussed above), and IL-35. These cytokines are structurally and functionally relative to each other, having a specific heterodimer structure (Vignali and Kuchroo, 2012). As described above, IL-27 is a pleiotropic immunomodulatory cytokine. IL-12 and IL-23 possess more pro-inflammatory functions, stimulating a variety of immune cells, mainly helper T-lymphocytes through JAK-STAT pathways. They all have an impact on the growth and development of the cells, but each cytokine of IL-12 family has also its own distinctive roles (Langrish et al., 2004).

Interleukin 12

IL-12 has an anti-leukemic effect *in vivo*, reducing the proliferation and angiogenesis stimuli of AML cells (Ferretti et al., 2010). Its influence on helper T-cells and other intrinsic anti-tumor cell lines has been used in creating genetically en-

forced lymphocyte-based therapies (Chmielewski et al., 2011; Pegram et al., 2012; Zhang et al., 2015a).

The administration of recombinant IL-12 to mice restored the levels of pro-inflammatory cytokines and cells suppressed by ALL in the BM microenvironment (Hunter et al., 2022).

Childhood patients with ALL and higher IL-12A or B gene expression have better EFS and OS, according to TARGET ALL database (Target – Acute Lymphoblastic Leukemia /ALL/ | NCI Genomic Data Commons).

Analysis of the gene expression indicates that calcineurin-deficient leukemia cells express higher levels of pro-inflammatory genes. These cells secrete more cytokines and chemokines than the control leukemia cells, including IL-12, a potent T-cell activator.

In mouse models, the anti-leukemic effect of IL-12 lies in the stimulation of IFN-γ, helper T-lymphocytes, and dendritic cells (DC), prolonging the survival of mice with calcineurin-deficient ALL and reducing the evasion of ALL cells (Rabe et al., 2019).

As mentioned earlier, IL-12, IL-15, and IL-18 could stimulate depressed NK-cells to target ALL blasts (Boieri et al., 2017). The direct anti-tumor effect of IL-12 is questionable, it depends on the presence of a specific receptor on the surface of the leukemic blasts, which tend not to express respective genes due to possible mutations, enabling their evasion (Airoldi et al., 2006).

Interleukin 23

IL-23 is a pro-inflammatory cytokine secreted by macrophages and dendritic cells reacting mainly to microbial stimuli (Toll-like receptors, interferons). It activates a specific line of T-lymphocytes, producing IL-17, called the Th17 line, which has pleiotropic functions in the tumor microenvironment (Aggarwal et al., 2003; Vignali and Kuchroo, 2012; Zou and Restifo, 2010). There are studies suggesting its pro-tumor effect, acting against effector cells activated by IL-12, such as cytotoxic T-cells (Langowski et al., 2006, 2007). Possible anti-tumor properties are also investigated in solid tumors (Lo et al., 2003; Oniki et al., 2006) and hematological malignancies (Cocco et al., 2012). The receptor of IL-23 (IL-23R) is expressed on the surface of ALL cells, making the IL-23 a potential direct influencer of the disease and its gene variants could have a prognostic value (Cocco et al., 2010; Zareinejad et al., 2017). IL-23 peripheral blood (PB) and BM levels have a prognostic value in pediatric ALL and AML. In this study, lower levels corresponded with higher leukemic burden and were decreased after induction therapy in both PB and BM, but the difference between the PB sample levels of all AL patients and the ones from the healthy control group was borderline significant with slight differences regarding AL type (Zampogiannis et al., 2021). IL-23 has the ability to up-regulate IL-23R through an autocrine loop. This can result in an anti-leukemic effect of IL-23 in pediatric ALL via the up-regulation of specific microRNA genes and a reduction of the BCL-2 expression (Cocco et al., 2010).

Interleukin 35

IL-35 is the latest examined interleukin in the IL-12 family and has been vastly investigated over the last 10-15 years. Its receptor shares subunits with other members of this group and activates similar intracellular pathways (mainly JAK-STAT), but its biological effect is slightly different. It is produced by regulatory T-cells, B-cells (T-regs, B-regs respectively), and several other APCs, and has an effect on their function and proliferation (Collison et al., 2007; Wang et al., 2014).

IL-35 mainly has immunosuppressive functions, expanding Tregs, inhibiting effector T-cells, Th17 subset of helper T-cells, and many other lines, resulting in a complex feedback loop that regulates immune responses. This effect is mainly studied in the field of autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease, systemic lupus, and others (Wang et al., 2014; Ye et al., 2021; Zhang et al., 2019). In tumor microenvironment, this disruption of immune mechanisms by IL-35 leads to tumor progression in several *in vitro* and *in vivo* studies (Liu et al., 2021b; Mirlekar et al., 2018; Turnis et al., 2016; Wang et al., 2013). The expansion of Tregs and IL-35 levels were investigated in clinical studies with AML patients, where their levels in PB and BM correlated with stages of the disease, suggesting the strong participance of IL-35 in pro-leukemic mechanisms (Tao et al., 2015; Wang et al., 2015b; Wu et al., 2012; Yang et al., 2022). Regarding ALL, in this only current study with forty childhood ALL patients, the authors found a significant difference in serum levels of IL-35 between ALL patients and the healthy control group. Higher IL-35 serum levels correlated with a higher white blood count and lower platelet count in ALL patients, suggesting its pro-leukemic effect in ALL, but with only a non-significant shortage of the mean overall survival (Solati et al., 2020). Still, regarding the data on solid tumors and AML, IL-35 is a promising molecule to examine in ALL microenvironments for the future trials.

Other relevant interleukins

Various other interleukins, not present in specific families and often overlapping with other cytokine groups, could have potential in acute leukemia. For the purpose of this review, we discuss IL-3, IL-8, IL-13, and IL-10.

Interleukin 3

IL-3 is a hematopoietic factor produced by T-lymphocytes. IL-3 binds to its receptor, comprised of two subunits, a shared βc (CDw131) and a unique ligand-specific α subunit (CD123) (Ihle, 1992; Sunderland and Roodman, 1991). It stimulates the growth and development of hematopoietic stem cells and their differentiated lines, both myeloid and lymphoid. The loss of the receptor is observed during the differentiation and maturation of the cells, variable from line to line (Huang et al., 1999). In potential clinical use, it was originally meant to be used to treat primary bone marrow deficiency syndromes, such as aplastic anemia and MDS (Ihle, 1992; Sunderland and Roodman, 1991). In hematological malignancies, CD123 expression was investigated mostly in blastic plasmocytoid dendritic cell neoplasm (BPDCN) (Demoulin et al., 2012), hairy-cell leukemia (HCL) (Muñoz et al., 2001), and AL. AML blasts naturally express CD123, making it an attractive minimal residual disease (MRD) marker (Coustan-Smith et al., 2018), and the levels of expression correlate with adverse disease character and prognosis (Jordan et al., 2000; Riccioni et al., 2009; Testa et al., 2002). In ALL, it was originally proven that only B-line blasts and LSCs express CD123 (with an interesting dependence on a genotype – more in hyperdiploid, Ph+ and Ph-like ALL (Bras et al., 2019; Djokic et al., 2009; Lyapichev et al., 2021)), but not T-line blasts or healthy myeloid and lymphoid precursors in BM (Muñoz et al., 2001). Although it was shown in the following years that T-ALL cells also express CD123, the expression decreases with maturity stages of T-ALL and probably has a link to shared AML/T-ALL properties (Du et al., 2016; Khurana et al., 2024). Using *in vitro* and *in vivo* studies, it seems that the pathways of CD123 activation are pro-leukemic, the same as in AML.

EP300-ZNF384 is a pro-leukemic fusion gene that has been investigated in recent years, which stimulates the expression of CD123. The further activation of the STAT5 axis by IL-3 leads to proliferation of EP300-ZNF384 positive cells (Hou et al., 2024). However, two recent, flow-cytometry based studies evaluated CD123 expression in a cohort of B-ALL pediatric (and young adult) patients and found that the high expression of CD123 correlated with a favorable prognosis. This could be questioned to an extent, because high frequency of hyperdiploid ALL associated with higher CD123 expression (as discussed above) leads to more aggressive treatment regiments used due to the genomic-based risk stratification at the time of diagnosis (Boris et al., 2024; Li et al., 2021). Overall, these findings suggest that a proper knowledge of CD123 expression could find a use in prognostic evaluation, MRD monitoring of CD123 positive cells, or even therapeutic targeting (Coustan-Smith et al., 2011; Das et al., 2020). In the therapy area, but mainly in myeloid malignancies, *in vitro* and *in vivo* studies brought interesting findings. The use of fusion diphteria-IL-3 toxin (Cohen et al., 2005; Frankel et al., 2000; Hogge et al., 2006) and a MoAb based therapy options are investigated (Busfield et al., 2012; Kovtun et al., 2018; Nievergall et al., 2014). Using T- and NK-cell mediated cytotoxic effect, BiTEs, trispecific antibodies, dual-affinity retargeting (DART) molecules, or CAR-T lymphocytes could be a promising strategy for days to come, some of them already in clinical trials (Al-Hussaini et al., 2016; Kügler et al., 2010; Mardiros et al., 2013; Slade and Uy, 2020; Stein et al., 2010). Trials involving B-ALL have emerged only in recent years, mainly including ALL samples into studies with anti-CD123 MoAbs. For example with flotezumab (antibody tested in salvage therapy for AML) (City of Hope Medical Center, 2020) and other drugs (Angelova et al., 2019; ImmunoGen, Inc., 2023). Interesting up-regulated expression of CD123 has been observed in CD19+ B-ALL patients after anti-CD19 targeted therapy, associated with target-loss, which could be prevented by dual-antigen targeting (Ruella et al., 2016). The first successful clinical use of CAR-T cells with dual anti-CD19 and anti-CD123 targeting has been reported (Tu et al., 2018).

Serum levels of IL-3 in childhood ALL did not significantly differ, neither at the time of diagnosis, in remission, nor in the comparison samples from the healthy control group. In AML, a significant difference was found, with higher levels of IL-3 at the diagnosis than in remission or in the control group (Elbaz and Shaltout, 2001). However, levels of hematopoietic factors naturally change in the environment of neutropenia and possible infections, which dysregulate hematopoietic stimuli and can be non-specific in these hematological malignancies (Ozbek et al., 2000).

The influence of the IL-3 axis on eosinophiles could have a value in ALL with eosinophilia, where certain suspected gene translocations could induce the promotion of this rare unit (Xu et al., 2024).

Interleukin 8

IL-8 possesses chemotactic capabilities and could be also obtained in the chemokine group (known as CXCL8). It has a close functional link to CXCL12/CXCR4 axis. IL-8 binds to chemokine receptors on the surface of the cells (CXCR1 and CXCR2). Produced by macrophages, endothelial cells and cancer cells, IL-8 attracts neutrophils into the site of inflammation, has an angiogenic effect and a pro-tumor influence on the microenvironment. Its enhanced expression by tumor cells and higher serum levels were observed in cancer patients. Through autocrine pathways, it enhances the proliferation and survival of cancer cells (Baggiolini and Clark-Lewis, 1992; Brat et al., 2005; Holmes et al., 1991; Kim, 2020; Waugh and Wilson, 2008). Interestingly, TKI treatment of lung and renal tumors influences IL-8 expression and plasma levels, which correlate with the malignancy and resistance to this therapy. Additionally, the *in vitro* inhibition of IL-8 has been shown to increase cells' sensitivity to TKI treatment. This should be considered when treating conditions such as CML and Ph+ ALL (Liu et al., 2015; Rizzo et al., 2022).

In hematology, IL-8 levels correspond with other prognostic factors of CLL (Wierda et al., 2003). Malignant B-cells were observed expressing IL-8 and its receptors, but this was not confirmed by *in vitro* studies, suggesting more complex mechanisms of IL-8 production stimuli (di Celle et al., 1994; Risnik et al., 2017). Both AML and ALL cells expressed IL-8 gene and produced IL-8 protein, but only a part of them expressed its receptors on their surface (Tobler et al., 1993). Gene expression of IL-8 was significantly higher in a group of T-ALL patients, than in a healthy control group, and its levels correlated with disease stages (Pandey et al., 2023). In BM of T-ALL patients, IL-8 is produced by stromal cells stimulated through CXCL12/CXCR4 axis (Scupoli et al., 2008), IL-8 in BM is proved to enhance the proliferation, survival, and adhesion of BM stromal cells to ALL cells, but not to directly affect the ALL cells (de Vasconcellos et al., 2011; Magalhães-Gama et al., 2021). The gene expression of IL-8 in relapsed ALL is higher in the isolated BM relapse compared to combined relapse (together with testicular or CNS relapse) (Wu et al., 2006), suggesting the great importance of the BM niche involvement. Higher serum and plasma levels were observed in patients with AML and ALL, corresponding with a higher white blood count and a poorer remission rate (Faderl et al., 2005; Liu et al., 1999). Serum levels of IL-8 were lower in children in CR after a successful chemotherapy and maintenance for ALL compared to a healthy control group (Mazur et al., 2004). Specific genotypes could be significant in prognostic evaluation of newly diagnosed pediatric ALL (Hsu et al., 2023).

Interleukin 13

IL-13 shares some similarities with IL-4. Both of them are included in the Th2 cytokine family, sharing a IL-4Rα receptor subunit, activating similar pathways (JAK/STAT), and influencing various immunity mechanisms (Jiang et al., 2000). Not many studies in the field of cancer biology have been performed; there are studies investigating its influence on the RS cells and the reactive background in Hodgkin's lymphoma (Skinnider et al., 2001, 2002). In ALL, serum levels of IL-13 were lower than in a healthy control group (Wu et al., 2010b). In one *in vitro* study, IL-13 was able to inhibit the cell cycle activity of ALL blasts and their proliferation, suggesting possible anti-leukemic effects of this cytokine (Renard et al., 1994).

Interleukin 10

IL-10 was originally described only as an anti-inflammatory/immunosuppressive cytokine, although its effect seems to be more pleiotropic in certain situations. Produced by various cells, depending on the site of the insult, IL-10 directly affects monocytes/macrophages and indirectly regulates T- and NK-cells, inhibiting the Th1 response (Moore et al., 2001). In cancer microenvironment, it contributes to cancer escape from immunity. However, it may also have some immunomodulating effects, creating an anti-tumor memory (Mocellin et al., 2004). The bluntness of the anti-tumor immune cells, caused by IL-10, can be overcome by cyclophosphamide or anti-IL-10 antibodies (Jovasevic et al., 2004; Vicari et al., 2002).

In hematology, the pro-tumor loop effect was described and can be inhibited, resulting in sensitizing the tumor to the native anti-tumor immunity (Alas et al., 2001; Alhakeem et al., 2018; Sredni et al., 2004). Higher levels of IL-10 in plasma were observed in AML patients, with a correlation to a higher white blood count and neutrophil count (Wu et al., 2012).

In ALL, IL-10 affect the leukemogenesis, supports the resistance and the escape of leukemic blasts. However, in pediatric ALL, an "infection hypothesis" arises. With IL-10 as a potential modulator of infectious imbalance, its deficiency can supposedly lead to the development of ALL (Chang et al., 2011; Fitch et al., 2022). BM plasma, peripheral blood, and intracellular levels of IL-10 were investigated in ALL. Some were elevated at the time of diagnosis, with a significant drop after successful induction therapy and with persistent levels in refractory cases. This could find a potential use in risk stratification and MRD monitoring (Bien et al., 2009; Brix et al., 2023; Inagaki et al., 2006; Magalhães-Gama et al., 2021; Zhang et al., 2021), although some studies indicated no clear significance (Mazur et al., 2004; Park et al., 2006). According to several studies, gene polymorphisms of IL-10 potentially have prognostic relevance in ALL (Abdalhabib et al., 2022; Ghufran et al., 2019; Hiroki et al., 2015; Liu et al., 2020). Clinical use of IL-10 is yet to be a reality and it would be certainly weighted down by potential adverse inflammatory and immunosuppressive effects (Naing et al., 2018). Overexpression of the receptor, IL-10R, has been observed in AML and targeted by using CAR-T lymphocytes *in vivo* (Chen et al., 2021a).

Agents targeting interleukins in preclinical and clinical studies for ALL and related conditions are shown in Table 2.

Table 2. Interleukin-targeting agents for acute lymphoblastic leukemia and related conditions

Interleukins	Agent	Biological effect	Preclinical studies	Clinical studies
IL-1	IL1RAP mAb81.2	Inducing ADCC	Ågerstam et al., 2022	
	Anakinra	Blocking IL-1 mediated CRS and ICANS		Dreyzin et al., 2022; Gazeau et al., 2023
	anti-hIL1β-IgG	Blocking endothelial activation in CRS	Chen et al., 2021b	
IL-18	mIL-18Ab	Suppressing T-ALL cells growth	Uzan et al., 2014	
	IL-18, IL-12, IL-15	Activating NK-cells	Boieri et al., 2017	
IL-2	orthogonal IL-2	Expanding regulatory T cells, reducing aGvHD	Ramos et al., 2023	
	LD IL-2	Expanding regulatory T cells, reducing cGvHD		Koreth et al., 2016; Wobma et al., 2023
IL-15	IL-18, IL-12, IL-15	Activating NK-cells	Boieri et al., 2017	
	CAR-T cells with mbIL15	Persisting anti-leukemic memory of CAR-T cells	Hurton et al., 2016	
IL-7	IL-7R MoAb	Prolonging survival of mice with Ph+ ALL	Abdelrasoul et al., 2020	
	chimeric anti-IL-7Rα 4A10 MoAb	Inhibiting R/R T-ALL *in vivo*	Hixon et al., 2020	
	human anti-IL-7Rα B12 MoAb	Delayed T-ALL development *in vivo*	Akkapeddi et al., 2019	
TSLP	TSLPR-targeted CAR-T cells	B-ALL regression *in vivo*	Qin et al., 2015	
IL-6	Tocilizumab	Blocking IL-6 mediated CRS and ICANS		Jain et al., 2023
IL-27	human rIL-27	Inducing apoptosis, reducing dissemination of ALL cells, reducing angiogenesis	Canale et al., 2011	
	mouse and human rIL-27	Stimulating differentiation of HSCs	Seita et al., 2008	
IL-12	rIL-12	Restoring anti-tumor microenvironment	Hunter et al., 2022	
	IL-18, IL-12, IL-15	Activating NK-cells	Boieri et al., 2017	
	rIL-12	Prolonging survival of mice with B-ALL	Rabe et al., 2019	
IL-23	human rIL-23	Inhibiting proliferation, inducing apoptosis of ALL cells	Cocco et al., 2010	
IL-13	human rIL-13	Inhibiting proliferation of ALL cells	Renard et al., 1994	
IL-3	antiCD123 CAR-T	Targeting LICs, preventing antigen loss	Ruella et al., 2016	Tu et al., 2018

Note: ADCC – antibody dependent cellular cytotoxicity; ALL – acute lymphoblastic leukemia; CAR-T – chimeric antigen receptor cell; CD – cluster of differentiation; CRS – cytokine release syndrome; (a – acute; c – chronic) GvHD – graft versus host disease; h – human; HSC – hematopoietic stem cell; ICANS – immune effector cell-associated neurotoxicity syndrome; Ig – immunoglobulin; IL(R) – interleukin (receptor); LD – low dose; LIC – leukemia initiating cell; m – mouse; mb – membrane bound; MoAb – monoclonal antibody; NK – natural killer; Ph+ – Philadelphia chromosome positive; r – recombinant; RAP – receptor accessory protein; R/R – relapsed/refractory; TSLP(R) – thymic stromal lymphopoietin (receptor).

Conclusion

Several major steps were made in the treatment of ALL during the last decade of the 20th century and in the 21st century, putting chemotherapy, immunotherapy, and HSCT into routine clinical use and improving the clinical outcome of our patients. However, especially in specific subgroups like T-ALL or Ph-like B-ALL, the results remain poor in great numbers until this day. Many cytokine pathways discovered in the late nineties went unnoticed for a long time and have been investigated in recent years; some underwent arduous research – with a clinical use already in process or knocking on the door.

The greatest leap forward in therapy targeting of ALL happened in the field of chemokine pathways (e.g., CXC4 antagonists). Regarding interleukins, IL-7 and TSLP play distinctive roles in the pathology of T-ALL. As a hematopoietic factor, IL-3 has been shown to play an important part, mainly in Ph+ and Ph-like ALL biology. Its receptor, CD123, could be a promising target in B-ALL. The pathways of IL-23, IL-27, and IL-35 have only been studied more in recent years but are already bringing promising results.

Indirect anti-tumor effect, modulating native immunity, is also a possible approach in ALL treatment, with IL-12, IL-15, and IL-18 currently being investigated.

Several cytokine pathways without direct anti-tumor effects may also offer benefits in the treatment of ALL. We can either profit from established agents such as IL-1 and IL-6 antagonists in treating CRS, or by using IL-2 to suppress acute and chronic GvHD.

Targeted therapy is a new and promising approach to the treatment of cancer. With possibilities such as routine next-generation sequencing, fluorescent in-situ hybridization, flow cytometry, and others, we are allowed to reveal pathological alterations in a disease's biology, leading to its progression and refractoriness. The expansion of our knowledge reveals a spectrum of new potential checkpoints to target and modulate, hopefully bringing with it the promise of a higher response rate of diseases to the treatment.

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Ethical aspects and conflict of interest
The authors have no conflict of interest to declare.

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