


Review Article

Ikaros (IKZF1): From Normal Hematopoiesis to Hematologic Malignancies

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Abstract

Ikaros zinc finger (IKZF) transcription factors, part of the Krüppel family, have a significant role in the physiological development of immune cells. Ikaros, which is encoded by IKZF1, is a well-researched IKZF transcription factor that specifically impacts the growth and differentiation of lymphocytes. It interacts with various nuclear factors, functioning as either a transcriptional inhibitor or activator; thus, regulates several lymphopoiesis-associated factors like pre-TCR and pre-BCR. Over the years, research has revealed that alterations in IKZF1 as well as Ikaros can cause out-of-control differentiation and proliferation of immune cells, particularly lymphocytes, potentially triggering tumorigenesis in hematologic malignancies such as ALL, AML, CLL, and CML. Recent studies have explored the therapeutic potential of targeting Ikaros or restoring its activities to limit the pathologic differentiation and proliferation of tumor cells. Most of these therapeutic agents are immunomodulatory drugs (IMiDs) that can selectively ubiquitinate and proteasome degrade Ikaros. This study offers a comprehensive overview of Ikaros's physiological roles and highlights the oncogenic characteristics of IKZF1 and Ikaros alterations.

1. INTRODUCTION: A GLANCE INTO IKAROS ZINC FINGER (IKZF)

Ikaros Zinc Finger (IKZF) is a transcription factor family (IKAROS family zinc finger protein family), consisting of five members. They could have several roles in the body; however, their functions in the development of the immune cell population and the regulation of normal lymphopoiesis have been well-studied [1-3]. Among the five members of IKZF family, Ikaros (encoded by IKZF1) has been

demonstrated to exert imperative functions in the development and differentiation of immune cells [4].

IKZFs are known as one of the chief regulators of the hematopoietic system and immune cell development. There are five members in IKZF family, Ikaros (IKZF1 gene), Helios (IKZF2 gene), Aiolos (IKZF3 gene), Eos (IKZF4 gene), and Pegasus (IKZF5 gene) which among them, Ikaros, Helios, and Aiolos are predominantly expressed on lymphoid and hematopoietic cells. By contrast, Eos, and

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Pegasus are ubiquitously expressed in a wide range of organs including the brain, kidney, liver, heart, and skeletal muscle [5].

Ikaros (IKZF1) is a transcription factor capable of influencing the hematopoietic system as this protein is able to act during particular steps of lymphocyte development [6]. According to various studies, Ikaros could play a pivotal role in the development of CD4⁺ T cells. According to evidence, it has been shown that a lack of Ikaros resulted in the elevation of T-bet expression, a chief regulator of Th1 development [7, 8]. Ikaros could also play a role in positive regulation of IL-4 production in Th2 cells [8] as well as Th17 gene program [9]. The generation of IL-4 from naïve CD4⁺ T cells and IL-17 and ROR γ t from Th17 has been shown to be decreased as a result of Ikaros loss [8, 9]. Helios (IKZF2) is one of the important IKZF members as it could perform similar tasks to Ikaros by regulating the functions of the immune cells. Helios is a hallmark of efficient regulatory T cells (Tregs) by playing an imperative role in the differentiation of Tregs [10, 11]. The loss of Helios in Tregs brings about an alteration in the expression of Foxp3 and effector cytokines, leading to the induction of an unstable phenotype [12]. Aiolos (IKZF3) is responsible for trans-differentiation from innate lymphoid cell 3 (ILC3) to ILC1/NK cells as blocking Aiolos and Ikaros can impede this event [13]. It was exhibited that the inhibitory capacity of Tregs is deeply associated with Eos (IKZF4) function [14]. To be precise, Eos could interact with Foxp3 and induce chromatin modifications, leading to gene silencing in Tregs [15]. The exact mechanism of Pegasus (IKZF5) has not been completely identified, yet it was shown that Pegasus can mediate megakaryopoiesis process in human beings [16]. There have been numerous studies evaluating the roles of Ikaros alterations in several diseases including hematologic malignancies, particularly acute lymphoblastic leukemia (ALL) [17]; therefore, the dysregulation of transcription factor could be associated with the development of cancers; as a result, it could be a target for the treatment strategies [18]. The aim of this study is to provide an overview of Ikaros physiologic roles and illustrate how this protein could act as a tumor suppressor as well as the potential therapeutic targeting Ikaros.

2. PHYSIOLOGIC ROLES OF IKZF1

Ikaros is encoded by the IKZF1 gene located on chromosome 7 (7p12.2) and contains eight exons, the last of which at the C-terminal includes the two zinc finger and four N-terminal DNA-binding zinc finger domains [19, 20]. Based on alternative splicing of IKZF1 gene, a minimum of 12 isoforms can be produced from Ik1 to Ik12 [21, 22]. In

addition to various combinations of zinc finger modules, the different dimerization of Ikaros isoforms could influence the intensity of DNA binding [23, 24]. By binding to various nuclear factors defined as epigenetic regulation, Ikaros could serve as either a transcriptional inhibitor or an activator. Providing that Ikaros interact with histone remodeling complexes or ATP-dependent chromatin remodeling complexes such as SW1/SNF, it will bring about tumor suppression or gene activation, respectively [18, 25]. Moreover, it was shown that Ikaros can act as the mediators of nucleosome remodeling and deacetylase complex by catalyzing methyltransferases, acetyltransferases, and deacetylases [26].

As mentioned before, one of the essential functions of Ikaros is its effects on the development of immune cells. In this regard, it has been shown that Ikaros exhibits different influences facing various types of innate or adaptive lymphocytes. Accordingly, the conversion of large and small pre-B stages is derived by Ikaros as a chief mediator. By activating kinase signaling pathways, Ikaros could maintain the proliferation and differentiation of B cells [27]. Ikaros is also one of the notable regulators of ILC3 activities as it could impede the transcriptional function of aryl hydrocarbon receptors, leading to ILC3 inhibition and intestinal immunity regulation [28].

Ikaros also play a role in signal-dependent downregulation of recombination-activating gene 1 (RAG1) and RAG2 gene expression in both CD4⁺ and CD8⁺ T cells, derived from RAG locus chromatin hub disassembly [29]. In addition to the effects of Ikaros on the differentiation of Th1, this transcription factor is able to adversely regulate the expression of Th1-related cytokines such as IFN- γ [8]. Studies showed that loss of Ikaros in Th2 resulted in an elevation of IFN- γ levels and STAT1 and T-bet expression [7, 8]. Furthermore, Ikaros plays a role in the inhibition of IL-2 expression by targeting its promoter, restricting the process of Th1 differentiation (an IL-2/STAT5-dependent phenomenon) [30]. Apart from the function of Ikaros in the generation of IL-4, the Th2 specification could be induced by the negative regulatory role of Ikaros in Th1 differentiation [7]. The findings towards Th17 have been discrepant as some showed that repressing the capacity of Ikaros to interact with DNA negatively and positively affected the IL-17 and IL22 generation, respectively [31], while it was reported that Ikaros deficiency could not reduce the expression of IL-17A, implying that loss of Ikaros might have no effects on the expression of cytokine genes in Th17 [32]. It has been shown that the transcriptional activities of Ikaros and Aiolos could have an association with the upregulation of BCL-6, a key transcriptional mediator of

T follicular helper (TFH) cell differentiation. In this regard, overexpression of Ikaros and Aiolos induced the activity of BCL6 promoter [33]. In addition to the role of Eos in the activity of Tregs [14], it was demonstrated that the lack of Ikaros in CD4⁺ T cells resulted in defects in the upregulation of Foxp3 expression; consequently, the polarization of Tregs could be affected [9, 32, 34]. Indeed, the levels of peripheral Tregs were reduced in animals lack Ikaros [34].

Although myriads of studies have demonstrated the roles of Ikaros in lymphoid lineage differentiation and function, their roles in myeloid lineage are still unclear; however, some investigations have reported the suppressive activities of Ikaros on myeloid differentiation [35]. In this regard, the levels of myelopoiesis and myeloid cells were reduced as a result of the presence of Ikaros mutant form in mouse models. The granulocyte differentiation was impeded in Ikaros null mutants and those models with extremely lower levels of Ikaros [36], implying the functions of Ikaros in myeloid differentiation. Ikaros has been shown to be able to inhibit the differentiation of basophilic granulocyte lineage and stimulate the maturation and survival of neutrophil and granulocyte lineage [36-38]. Moreover, Ikaros could play a role in erythrocyte differentiation; therefore, it could guarantee the survival of the erythrocyte lineage [38]. **Fig.1** is a schematic illustration of the IKZF family and Ikaros target cells.

2.1. Signaling pathways in which IKZF1 takes part

One of the most studied signaling pathways of Ikaros is the pre-BCR (B cell receptor) signaling pathway [39]. By suppressing SHIP and LYN, Ikaros can impede several downstream events, leading to the downregulation of pre-BCR activation, Ig light chain recombination, and Igκ germline transcription [40]. Moreover, Ikaros is able to compete with the CSL DNA binding site and suppress the following molecules, resulting in the regulation of pre-TCR [41, 42].

Post-translational phosphorylation, ubiquitination, and SUMOylation (derived by a small ubiquitin-associated mediator) have been exhibited to be the main regulators of Ikaros [43]. In this regard, the association of Ikaros with transcriptional co-repressors Mi-2β, SIN3A, SIN3B, and CtBP could be hindered by SUMOylation, leading to the dysfunction of Ikaros. The SUMOylation was shown to be able to impede the roles of Ikaros in HDAC-dependent and HDAC-independent suppression [44]. Ikaros could be targeted and phosphorylated by casein kinase 2 (CK2), a serine/threonine kinase, and pave the way for self-degradation via ubiquitin-proteasome machinery [45]. Accordingly, studies showed that the blockage of CK2 by

targeting agents could restore the lost DNA binding capacity of Ikaros [46, 47]. Physiologically, the process of Ikaros phosphorylation derived by CK2 can be reversed by protein phosphatase 1 (PP1) functions [48] as blocking this serine/threonine phosphatase can diminish the DNA binding capacity of Ikaros and elevate its degradation [49]. **Fig. 2** represents how Ikaros interact with molecules in signaling pathways.

3. ONCOGENIC ROLES OF IKZF1 AND ITS ALTERATIONS IN HEMATOLOGIC MALIGNANCIES

By interacting with various target sites, Ikaros serves either as a repressor or an activator transcription factor. It has been shown that the presence of mutations in IKZF gene is associated with the induction of numerous disorders such as autoimmune diseases, recurrent infections, reduced number of blood cells, and hematologic malignancies [50]. According to the notable role of Ikaros in the development, proliferation, and apoptosis of lymphocytes [5], the lack of this transcription factor brings about destructive production of B and lymphocytes, NK cells, and dendritic cells [51]. The phosphorylation of Ikaros by CK2 could impede the inhibitory transcriptional function of this protein, whether when it acts on its own or by recruiting HDAC1 to the promoter. For instance, in B cell (B-ALL), the CK2-dependent phosphorylation of Ikaros could elevate the expression of Bcl-xL, an anti-apoptotic agent [52]. In this regard, numerous studies have revealed that IKZF1 alterations are the triggers of ALL and acute myeloid leukemia (AML) induction and poor prognosis [20, 53-55]. Interestingly, the overexpression of Ikaros serves as an anti-tumor agent in some cases. Accordingly, the overexpression of Ikaros is able to suppress the PI3K pathway and stimulate INPP5D which could restrict PI3K per se [47]. The overexpressed Ikaros can limit the phosphorylation of Akt in leukemia cells and this effect is similar to the treatment with imatinib [46].

3.1. IKZF1 and hematologic malignancies

Traces of Ikaros have been investigated in various disorders including immune thrombocytopenia, rheumatoid arthritis, systemic lupus erythematosus, Parkinson's disease, and Crohn's disease [56-60]. This transcription factor is capable of targeting genes in order to regulate events associated with tumorigenesis such as survival and proliferation of cells [61]. In this regard, a sizable number of studies have reported the roles of Ikaros in various malignancies such as breast, liver, ovary, colorectal, and hematologic malignancies as well [61-65]. Having said that, regarding the importance of Ikaros

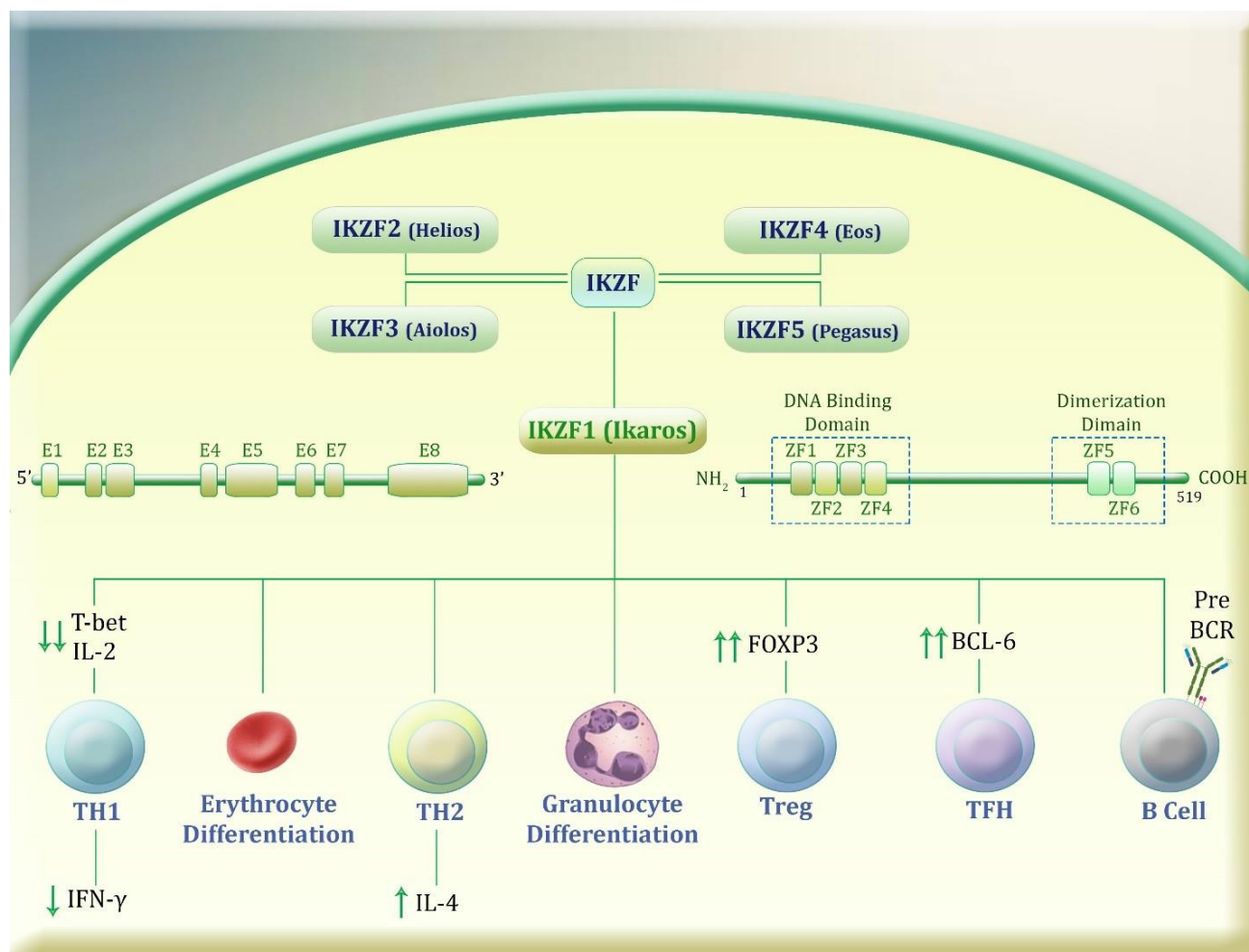


Figure 1. IKZF family, IKZF1 gene, and the functions of Ikaros. The IKZF family consists of five members encoded by IKZF1-5, of which Ikaros is by far the most well-studied transcription factor able to target a range of cells. IKZF1 encodes Ikaros and is located on 7p12.2 and contains eight exons; the one in the C-terminal and the one in the N-terminal comprises two and four DNA-binding zinc finger domains, respectively. Ikaros itself is a transcription factor capable of influencing multiple nuclear factors and exerting either inhibitory or activating roles. Ikaros can suppress T-bet and reduce the expression of IL-2; therefore, it could diminish the differentiation of Th1. Moreover, the expression of Th1-related cytokines like IFN- γ could be hindered by the activity of Ikaros. The regulatory role of Ikaros against Th1 is a trigger for Th2 differentiation. Ikaros is also able to induce Th2-related IL-4 expression. By upregulating Foxp3 and BCL-6 which are chief mediators of T follicular helper (TFH) and regulatory T cell (Treg) differentiation, respectively, Ikaros stimulate the differentiation of T cells towards TFH and Treg. Ikaros is a major mediator of pre-B stage development as it could target pre-BCR, CD79, CD19, and BCAP and positively or negatively regulate the development, differentiation, and survival of B cells. The functions of Ikaros are not limited to lymphoid lineage and this transcription factor could induce the differentiation of neutrophil and granulocyte as well as erythrocyte lineage.

in the development of leukemic cells, the association of Ikaros has been studied considerably in hematologic malignancies.

3.1.1. Alterations of Ikaros in ALL

The initial investigation regarding the association of abnormal IKZF1 with ALL was reported by Mullighan et

al. who conducted a genome-wide analysis (GWAS). Accordingly, 83.7% of ALL cases with BCR-ABL1 B-progenitor demonstrated deletion of IKZF1 gene due to aberrant RAG-mediated recombination [55]. The deletion of IKZF1 could involve part of the gene or its entire with a prevalence rate of 40% in the Philadelphia chromosome (when chromosome 9 and chromosome 22 break and

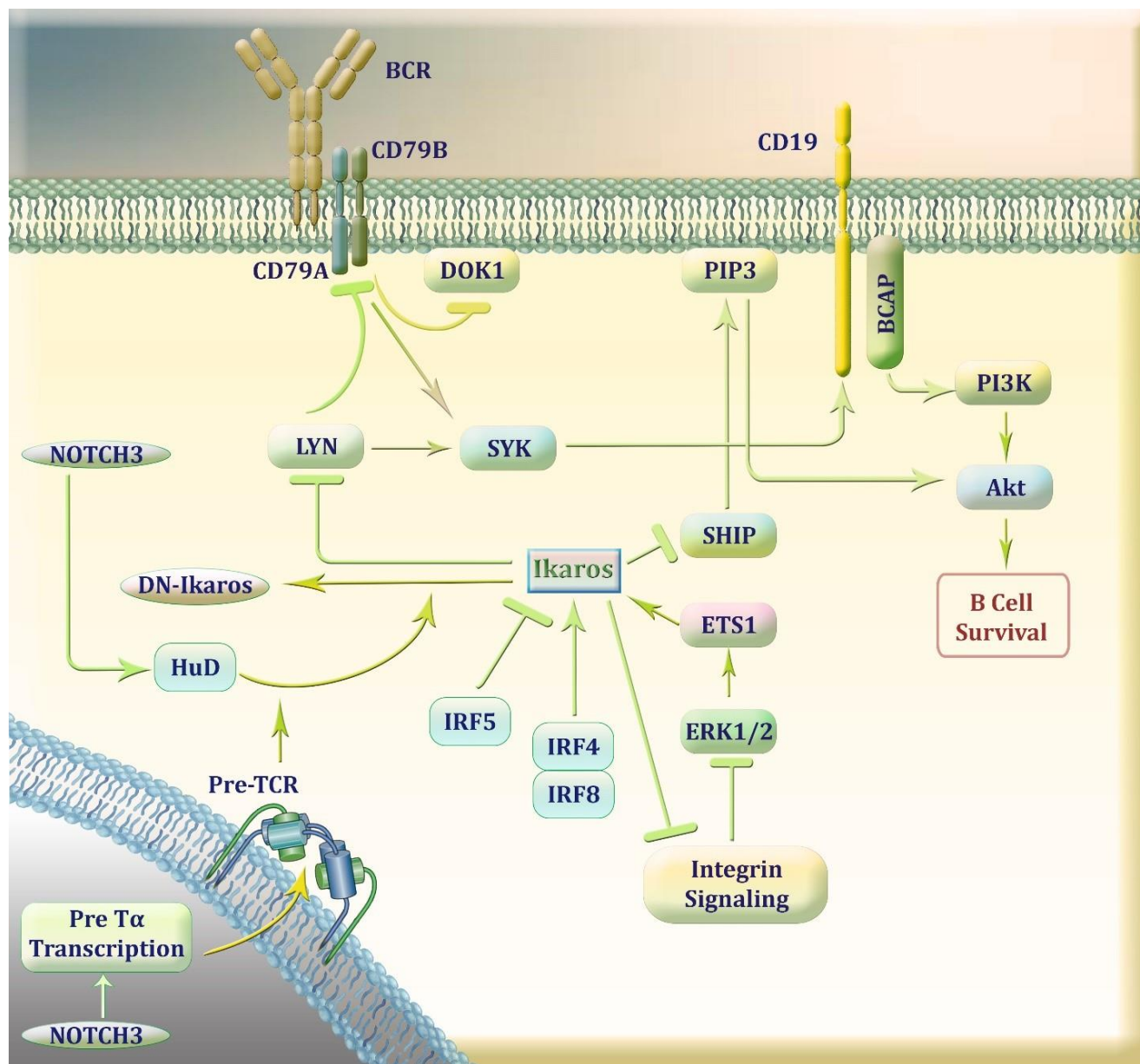


Figure 2. The signaling pathways associated with Ikaros. The activated pre-BCR is able to limit the function of Ikaros; consequently, Ikaros counteracts this event by inhibiting LYN and SHIP. LYN can directly phosphorylate and suppress SYK or indirectly monophosphorylate ITAM CD79A and CD79B, resulting in DOK1 activation (regulator of immunoreceptors) as well as SYK regulation. Therefore, by blocking LYN, Ikaros could stimulate SYK which is able to target CD19 and BCAP and activate the PI3K/Akt signaling pathway, leading to the induction of B cell survival. Furthermore, the Ikaros-mediated suppression of SHIP leads to higher levels of PIP3, a chief mediator of Akt activation. Notch3 can upregulate RNA binding protein HuD and convert the alternative splicing mode of Ikaros to a dominant-negative isoform (DN-Ikaros). Notch3 could induce the transcription of pre-T α and pre-TCR which can stimulate the signaling of HuD upregulation and the conversion of Ikaros to DN-Ikaros as well. Ikaros is able to impede the activated integrin signaling pathway, leading to the restriction of ERK1/2, activation of ETS1, and the upregulation of Ikaros. Interferon regulatory factors (IRFs) have been shown to influence Ikaros. In this regard, IRF4 and IRF8 stimulate the upregulation of Ikaros, while IRF5 could inhibit this event.

exchange parts)-negative B-ALL cases [66, 67]. It has been shown that B-ALL patients can have a poor prognosis and a higher risk of relapse in the presence of IKZF1 alterations [68]. This is while the incidence of loss of Ikaros is 5% in patients with T-ALL [69, 70]. Moreover, the prevalence of IKZF1 abnormalities is higher than 70% in Philadelphia-like ALL, leading to lower 5-year event-free survival and poorer prognosis [71]. The analysis of familial and sporadic pediatric B-ALL cases revealed that 28 germline variants of IKZF1 could be detected across the gene and even outside the known DNA-binding which are able to mediate leukemogenesis processes gene [72].

One of the crucial functions of Ikaros is suppressing the expression of genes associated with cell cycle progression such as ANAPC1, ANAPC7, CDC2, CDC7, CDK2, CDK6, and CCND3, leading to the induction of cell cycle arrest [18, 47]. As a result, loss of function of Ikaros due to alterations of IKZF1 can stimulate the proliferation of cells by downregulating CDKN1A and CDKN2A and upregulating CDK6, BCL-6, and c-MYC [73-75]. In this regard, it has been demonstrated that Ikaros can stimulate and suppress the expression of MYCBP2 and c-MYC, respectively, leading to the regulation of ALL progression; consequently, the loss of function of Ikaros brings about higher c-MYC levels and lower MYCBP2 concentrations, triggers of ALL progression [74].

Another chief activity of Ikaros is its role in regulating pre-BCR checkpoint, leading to the induction of apoptosis and tumor regulation [76, 77]. Regarding the fact that the BCL-6/BACH2 axis plays a pivotal role in the control of pre-BCR checkpoint signaling pathways [78] and its dependency on Ikaros functions [79, 80], it has been exhibited that the deletion of IKZF1 caused the reduction of BACH2; therefore, pediatric ALL patients showed lower disease-free survival [81]. RAG genes, particularly RAG1, are targets of Ikaros; therefore, in B-ALL cases, the lack of Ikaros (and its normal functions) could cause these potential drivers of tumorigenesis to be upregulated. It has been shown that there was a correlation between the upregulation of RAG1, deletion of IKZF1, and poor prognosis of adult ALL [82].

3.1.2. Alterations of Ikaros in AML

There have been studies investigating the roles of Ikaros in myeloid lineage differentiation and function, yet the

precise mechanism of its roles in AML pathogenesis is unclear. Accordingly, several studies have reported the potential role of CK2 in the pathogenesis of AML as this kinase can promote the survival of tumor cells and block the apoptosis process (83, 84). A good case in point is AML leukemia stem cells (CD34⁺CD38⁻) whose high levels of CK2 activity are correlated with a poor prognosis. Indeed, the more CK2 becomes activated, the more Ikaros gets phosphorylated, contributing to the inactivation of Ikaros and the absence of a suppressive process over Bcl-xL in AML cases (84).

Furthermore, studies have shown that deletions of the short arm of chromosome 7 which is a common event in adult de novo and in secondary AML, could bring about loss of IKZF1, particularly in secondary AML cases (85). These results suggest that IKZF1 loss could be the trigger of myeloproliferative neoplasms or myelodysplastic syndrome transformation into AML. In this regard, the loss of IKZF1 variants has been demonstrated in fusion gene-positive AML (86, 87).

3.1.3. Alterations of Ikaros in CLL and CML

The majority of studies have evaluated and reported the roles of Ikaros in acute lymphoma/leukemia; nonetheless, regarding its functions in BCR signaling pathway and its expression in B-1 cells (88), this transcription factor could play roles in chronic lymphoblastic leukemia (CLL) as well. Accordingly, it was exhibited that the levels of Ikaros were reduced in CLL cases and these proteins were localized majorly in cytoplasm of B-CLL cells, which is discrepant as normal B cells show nuclear localization of Ikaros. The knockdown of Ikaros in mouse models resulted in upregulation of Lyn, Blnk, and CD19, necessary elements in BCR signaling pathway. The lack of Ikaros could sensitize B-1 cells to BCR stimulus, leading to elevated cell proliferation and CLL induction (26). A study on chronic-phase chronic myeloid leukemia (CML) showed that Ikaros was absent or reduced in bone marrow samples of CML patients who had shown advanced myeloid disease. By evaluating the forced expression of IK6, a dominant-negative Ikaros isoform, in CD34⁺ cells (CML), it was exhibited that IK6 impeded the functions of Ikaros and induced accelerated phase features including a prolonged augmented output of primitive cells with an enhanced capacity to differentiate into basophils (89). It was demonstrated that the deletions of IKZF1 could play roles in the pathogenesis of CML. The presence of deletions in the IKZF1 gene could bring about the conversion of chronic-phase CML to blast-phase ALL in childhood CML; therefore, there could be an association between IKZF1 deletions and poor prognosis of CML patients (90). All in all, it could be suggested that lack of a Ikaros can accelerate the progression of myeloid disease in CML cases. **Table 1** represents studies regarding the alteration of Ikaros in hematologic malignancies.

Table 1. Studies evaluating the alteration of Ikaros in hematologic malignancies.

Malignancy	Study Population	Specific feature	IKZF1/Ikaros alteration	Finding	Ref
B-ALL	Pediatric	NA	DNA abnormalities	Copy number abnormalities were detected in 28.6% of patients which were correlated with a poor prognosis.	(54)
ALL	Adult	BCR-ABL1	Deletions	75% of patients showed focal deletions and the expression of a dominant-negative isoform with cytoplasmic localization.	(67)
B-ALL	All	Relapsed	Deletions, Nonsense mutations	Deletions had an association with a poor rate of overall and relapse-free survival.	(68)
ALL	Pediatric	NA	Deletions, Point mutation, Structural rearrangement	The presence of alterations in the regulators of B lymphocyte development could result in B-progenitor ALL pathogenesis.	(91)
B-ALL	Adult	Ph	Deletions, Aberrant isoforms expression	The alterations were observed in 52.6% of total population and in 83.3% of Ph-positive cases compared with 38.9% Ph-negative ones.	(92)
BCP-ALL	Pediatric	NA	Deletions	Patients with deletions showed a lower 8-year event-free survival. IKZF1 deletion could be a prognostic hallmark for B-ALL.	(93)
BCP-ALL	Pediatric	NA	Rearrangement	The co-existing of ETV6 and IKZF1 rearrangements which was associated with ETV6-RUNX1-like gene-expression pattern.	(94)
B-ALL	Pediatric	NA	Hypomethylation	96% of cases were unmethylated in IKZF1 promoter, while this was 68% in the control group.	(95)
B-ALL	Adult	Ph	Deletions	The frequency of deletions was high in Ph-positive patients, implying the role of Ikaros in the induction of cell cycle arrest.	(96)
AML	Adult	NA	Hyperphosphorylation (protein)	In patients with higher levels of catalytic subunit of CK2, overall and disease-free survival rates were lower.	(83)
AML	Pediatric	MLL	Homozygosity	Homozygosity for a variant IKZF1 allele was associated with the risk of AML, regardless of the MLL situation.	(35)
AML	Pediatric	NA	Deletions	The Ikaros loss of function led to differentially expressed genes in monosomy 7 patients. The genes were related to myeloid cell cycle and self-renewal.	(53)
AML	Adult	NA	Frameshift, Nonsense mutations, Missense mutations	The mutations were rare but occurred in AML cases along with bi-allele CEBPA or SF3B1 mutation.	(20)
CLL	Adult	NA	Reduced expression, Abnormal cytoplasmic localization	By influencing the BCR signaling, loss of Ikaros induced the proliferation of CLL and B-1 cell.	(26)
CML	Adult	NA	Absence, Reduction (protein)	The absence or reduced levels of Ikaros were recognized in bone marrow blasts of CML patients with advanced myeloid disease.	(89)
CML	Pediatric	NA	Deletions	Deletions of IKZF1 as well as PAX5 and CDKN2A were identified in a 1.6-year-old CML child who were progressing to lymphoid blast phase.	(97)
MM	Adult	NA	Overexpression	The levels of IKZF1 expression were higher in hyperdiploid MM and lower in cases harboring translocation t(11;14).	(98)
MM	Adult	NA	Overexpression	Higher expression levels of Ikaros were associated with a poor prognosis and responsiveness to lenalidomide.	(99)

ALL: Acute lymphoblastic leukemia; Ph: Philadelphia chromosome; AML: Acute myeloid leukemia; MLL: Mixed lineage leukemia; CLL: Chronic lymphocytic leukemia; CML: Chronic myeloid leukemia; MM: Multiple myeloma; NA: Not available.

Table 2. Therapeutic approaches to target dysregulated IKZF1 or Ikaros in hematologic malignancies

Malignancy	Drug	Mechanism	Outcome	Ref
AML, MDS	Pomalidomide	Selective ubiquitination and proteasomal degradation of Ikaros and Aiolos	By inducing the degradation of Ikaros and Aiolos, the proliferation and differentiation of T cells were promoted.	(102)
MM	Lenalidomide, Pomalidomide	Cereblon-dependent ubiquitination and proteasomal degradation of Ikaros and Aiolos	The downregulated Ikaros and Aiolos led to the downregulation of c-Myc and IRF4, causing the suppression of tumor growth and induction of apoptosis.	(110)
MM	Lenalidomide, Daratumumab	Cereblon-dependent ubiquitination and proteasomal degradation of Ikaros and Aiolos, ADCC	The loss of Ikaros and Aiolos caused the activation of interferon-stimulated genes and expression of CD38, leading to NK cell-mediated ADCC of MM tumors.	(104)
MM	Lenalidomide, Pomalidomide	Proteasome-independent calcium-induced calpain degradation of Ikaros	The combination therapy induced the degradation of Ikaros in a novel-identified manner (calcium-induced calpain pathway), leading to the expression of CD38 and ADCC.	(111)
MM	Pomalidomide, pembrolizumab	Selective ubiquitination and proteasomal degradation of Ikaros and Aiolos, Anti-PD-1	Combining to a regimen consisted of pomalidomide and dexamethasone not only reduced the effectiveness of therapy but also increased the rate and severity of adverse events.	(112)
MM	Iberdomide	Cereblon-dependent ubiquitination and proteasomal degradation of Ikaros and Aiolos	Stronger degradation capacity and higher affinity towards Ikaros and Aiolos was shown compared with lenalidomide or pomalidomide.	(113)
NHL	Avadomide	Cereblon-dependent ubiquitination and proteasomal degradation of Ikaros and Aiolos	Favorable safety profile was observed with three out of five NHL patients who exhibited objective responses.	(114)
DLBCL	Avadomide	Cereblon-dependent ubiquitination and proteasomal degradation of Ikaros and Aiolos	The treatment induced the apoptosis of B cells as well as the immunostimulatory responses by stimulating interferons transcription.	(115)
ALL	Rexinoids	Stimulate the expression of Ikaros and its physiologic nucleus localization	Reversed the aberrant adhesion and niche mislocalization while induced cell cycle arrest.	(106)
MCL	DD-03-171	proteasome- and CRBN-dependent degradation of Ikaros and BTK	Showed anti-proliferative functions and overcame the drug resistance associated with ibrutinib.	(109)
AML: Acute myeloid leukemia; MDS: Myelodysplastic syndrome; MM: Multiple myeloma; ADCC: Antibody-dependent cellular cytotoxicity; NHL: Non-Hodgkin lymphoma; DLBCL: Diffuse large B cell lymphoma; ALL: Acute lymphoblastic leukemia; MCL: Mantle cell lymphoma; BTK: Bruton's tyrosine kinase.				

4. THERAPEUTIC VALUES OF IKZF1

As Ikaros play a pivotal role in the development and differentiation of leukocytes, particularly lymphoid lineage, the deletion and mutation in the gene encoding this transcription factor could be associated with poor prognosis and drug resistance [61, 91]; therefore, targeting the event associated with Ikaros could be a potential therapeutic approach. Some well-studied cases in point are multiple myeloma (MM) and myelodysplastic syndrome (MDS) in which Ikaros could play roles in stimulating the proliferation and survival of tumors [92]. It has been demonstrated that immunomodulatory drugs (IMiDs) are able to influence CRL4 E3 ubiquitin ligase and induce ubiquitination and proteasomal degradation of Ikaros and Aiolos in MM and MDS [93, 94]; consequently, the degradation of Ikaros leads to the expression of CD38 in MM tumors, a proper target for NK cell antibody-dependent cellular cytotoxicity (ADCC) [95]. Moreover, the lower levels of Ikaros could reduce the threshold of TCR activation I response to antigens and IL-2, leading to augmented anti-tumor immune responses [96].

The devastating effects of Ikaros alterations could be dampened by using some therapeutic agents such as retinoids which could restore the activity and sensitivity of tyrosine kinase inhibitors (TKIs). Interestingly, retinoids are able to induce the expression of wild-type Ikaros and localize this transcription factor to the nucleus in Ikaros-mutant BCR-ABL1 cells, implying that retinoids and rexinoids could reverse the dysregulated and mislocalized Ikaros [97]. More importantly, CK2 inhibitors such as CX4945 can reverse the dysregulated function of Ikaros and act as anti-tumor agents *in vitro* and in preclinical studies [98, 99]. Furthermore, DD-03-171, a Bruton tyrosine kinase (BTK) inhibitor, was shown to exhibit anti-tumor activities in mantle cell lymphoma (MCL) *in vitro* by targeting BTK as well as Ikaros, and Aiolos [100]. **Table 2** provides data regarding the utilization of therapeutic agents to target Ikaros or IKZF1 alterations.

5. CONCLUSION AND FUTURE PROSPECTS

This IKZF proteins are a family of Zinc Finger transcription factors that play important roles in hematopoiesis, immune system development and function, and tumor suppression. Among them, IKZF1 (encoding Ikaros) is the most widely studied and has been shown to have numerous physiologic and pathologic roles. Ikaros is essential for the differentiation, development, and function of lymphoid and myeloid cells such as B cells and CD4⁺ T cells, and regulates the expression of genes involved in the cell cycle, apoptosis, DNA repair, and chromatin remodeling. This

transcription factor is involved in the signaling pathways associated with pre-BCR and pre-TCR; therefore, it could influence the development of lymphocytes. By interacting with various nuclear factors, Ikaros plays an important role as a transcriptional activator or inhibitor.

Ikaros also acts as a tumor suppressor by preventing the aberrant activation of oncogenes and maintaining genomic stability. Consequently, the mutated and deleted Ikaros have been shown to be associated with the initiation and progression of various hematologic malignancies, such as ALL, AML, CLL, and CML. These alterations impair the normal function of Ikaros and contribute to the initiation, progression, and resistance of these diseases. Studies have shown the presence of Ikaros alterations in hematologic malignancies and demonstrated the association between Ikaros alteration and poor prognosis. The alterations of Ikaros could lead to the induction of proliferation, the inhibition of apoptosis, and the dysregulation of the cell cycle.

Therefore, targeting Ikaros as well as its downstream pathways could be a promising strategy for the treatment of hematologic malignancies. Several approaches have been proposed, such as restoring the expression or activity of Ikaros, inhibiting the interaction of Ikaros with its cofactors or target genes, or modulating the epigenetic or post-translational modifications of Ikaros. In this regard, some well-studied IMiDs exert their anti-tumor functions either by influencing the Ikaros restoration process or the degradation of it. Nonetheless, the clinical application of these strategies faces many challenges, such as the specificity, efficacy, safety, and delivery of therapeutic agents. Further studies are needed to overcome these obstacles and to develop novel and effective therapies based on Ikaros. It seems that understanding the precise role of Ikaros could shed light on the development of novel therapeutic agents able to target dysfunctional Ikaros. Accordingly, there are some ongoing clinical trials evaluating agents able to target Ikaros such as NCT03897036, NCT03904862, and NCT03571438. It could be inferred that combination therapy using multiple drugs including those able to target Ikaros would be a promising therapeutic strategy for hematologic malignancies.

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Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Heizmann B, Kastner P, Chan S. The Ikaros family in lymphocyte development. *Current opinion in immunology*. 2018;51:14-23.
2. Zhao W, Chen TB, Wang H. Ikaros is heterogeneously expressed in lung adenocarcinoma and is involved in its progression. *J Int Med Res*. 2020;48(8):300060520945860.
3. Sigvardsson M. Molecular Regulation of Differentiation in Early B-Lymphocyte Development. *Int J Mol Sci*. 2018;19(7).
4. Read KA, Jones DM, Freud AG, Oestreich KJ. Established and emergent roles for Ikaros transcription factors in lymphoid cell development and function. *Immunol Rev*. 2021;300(1):82-99.
5. Fan Y, Lu D. The Ikaros family of zinc-finger proteins. *Acta Pharm Sin B*. 2016;6(6):513-21.
6. Kastner P, Chan S. Role of Ikaros in T-cell acute lymphoblastic leukemia. *World J Biol Chem*. 2011;2(6):108-14.
7. Thomas RM, Chen C, Chunder N, Ma L, Taylor J, Pearce EJ, et al. Ikaros silences T-bet expression and interferon- γ production during T helper 2 differentiation. *Journal of Biological Chemistry*. 2010;285(4):2545-53.
8. Quirion MR, Gregory GD, Umetsu SE, Winandy S, Brown MA. Cutting edge: Ikaros is a regulator of Th2 cell differentiation. *The Journal of Immunology*. 2009;182(2):741-5.
9. Wong LY, Hatfield JK, Brown MA. Ikaros sets the potential for Th17 lineage gene expression through effects on chromatin state in early T cell development. *Journal of Biological Chemistry*. 2013;288(49):35170-9.
10. Ng MSF, Roth TL, Mendoza VF, Marson A, Burt TD. Helios enhances the preferential differentiation of human fetal CD4(+) naïve T cells into regulatory T cells. *Sci Immunol*. 2019;4(41).
11. Thornton AM, Shevach EM. Helios: still behind the clouds. *Immunology*. 2019;158(3):161-70.
12. Kim HJ, Barnitz RA, Kreslavsky T, Brown FD, Moffett H, Lemieux ME, et al. Stable inhibitory activity of regulatory T cells requires the transcription factor Helios. *Science*. 2015;350(6258):334-9.
13. Mazzurana L, Forkel M, Rao A, Van Acker A, Kokkinou E, Ichiya T, et al. Suppression of Aiolos and Ikaros expression by lenalidomide reduces human ILC3-ILC1/NK cell transdifferentiation. *Eur J Immunol*. 2019;49(9):1344-55.
14. Gokhale AS, Gangaplara A, Lopez-Occasio M, Thornton AM, Shevach EM. Selective deletion of Eos (Ikzf4) in T-regulatory cells leads to loss of suppressive function and development of systemic autoimmunity. *J Autoimmun*. 2019;105:102300.
15. Pan F, Yu H, Dang EV, Barbi J, Pan X, Grosso JF, et al. Eos mediates Foxp3-dependent gene silencing in CD4+ regulatory T cells. *Science*. 2009;325(5944):1142-6.
16. Lentaigne C, Greene D, Sivapalaratnam S, Favier R, Seyres D, Thys C, et al. Germline mutations in the transcription factor IKZF5 cause thrombocytopenia. *Blood*. 2019;134(23):2070-81.
17. Winandy S, Wu P, Georgopoulos K. A dominant mutation in the Ikaros gene leads to rapid development of leukemia and lymphoma. *Cell*. 1995;83(2):289-99.
18. Dhanyamraju PK, Iyer S, Smink G, Bammé Y, Bhadauria P, Payne JL, et al. Transcriptional Regulation of Genes by Ikaros Tumor Suppressor in Acute Lymphoblastic Leukemia. *Int J Mol Sci*. 2020;21(4).
19. Payne MA. Zinc finger structure-function in Ikaros Marvin A Payne. *World J Biol Chem*. 2011;2(6):161-6.
20. Zhang X, Zhang X, Li X, Lv Y, Zhu Y, Wang J, et al. The specific distribution pattern of IKZF1 mutation in acute myeloid leukemia. *J Hematol Oncol*. 2020;13(1):140.
21. Molnár A, Georgopoulos K. The Ikaros gene encodes a family of functionally diverse zinc finger DNA-binding proteins. *Mol Cell Biol*. 1994;14(12):8292-303.
22. Yamamoto E, Ito T, Abe A, Sido F, Ino K, Itakura A, et al. Ikaros is expressed in human extravillous trophoblasts and involved in their migration and invasion. *Mol Hum Reprod*. 2005;11(11):825-31.
23. McCarty AS, Kleiger G, Eisenberg D, Smale ST. Selective dimerization of a C2H2 zinc finger subfamily. *Mol Cell*. 2003;11(2):459-70.
24. Vairy S, Tran TH. IKZF1 alterations in acute lymphoblastic leukemia: The good, the bad and the ugly. *Blood Rev*. 2020;44:100677.
25. Payne JL, Song C, Ding Y, Dhanyamraju PK, Bammé Y, Schramm JW, et al. Regulation of Small GTPase Rab20 by Ikaros in B-Cell Acute Lymphoblastic Leukemia. *Int J Mol Sci*. 2020;21(5).
26. Oliveira VC, Lacerda MP, Moraes BBM, Gomes CP, Maricato JT, Souza OF, et al. Deregulation of Ikaros expression in B-1 cells: New insights in the malignant

transformation to chronic lymphocytic leukemia. *J Leukoc Biol.* 2019;106(3):581-94.

27. Ochiai K, Yamaoka M, Swaminathan A, Shima H, Hiura H, Matsumoto M, et al. Chromatin Protein PC4 Orchestrates B Cell Differentiation by Collaborating with IKAROS and IRF4. *Cell Rep.* 2020;33(12):108517.

28. Li S, Heller JJ, Bostick JW, Lee A, Schjerven H, Kastner P, et al. Ikaros Inhibits Group 3 Innate Lymphoid Cell Development and Function by Suppressing the Aryl Hydrocarbon Receptor Pathway. *Immunity.* 2016;45(1):185-97.

29. Naik AK, Byrd AT, Lucander ACK, Krangel MS. Hierarchical assembly and disassembly of a transcriptionally active RAG locus in CD4(+)CD8(+) thymocytes. *J Exp Med.* 2019;216(1):231-43.

30. Quintana FJ, Jin H, Burns EJ, Nadeau M, Yeste A, Kumar D, et al. Aiolos promotes TH17 differentiation by directly silencing Il2 expression. *Nature immunology.* 2012;13(8):770-7.

31. Heller JJ, Schjerven H, Li S, Lee A, Qiu J, Chen Z-ME, et al. Restriction of IL-22-Producing T Cell Responses and Differential Regulation of Regulatory T Cell Compartments by Zinc Finger Transcription Factor Ikaros. *The Journal of Immunology.* 2014;193(8):3934-46.

32. Lyon de Ana C, Arakcheeva K, Agnihotri P, Derosia N, Winandy S. Lack of Ikaros deregulates inflammatory gene programs in T cells. *The Journal of Immunology.* 2019;202(4):1112-23.

33. Read KA, Powell MD, Baker CE, Sreekumar BK, Ringel-Scaia VM, Bachus H, et al. Integrated STAT3 and Ikaros zinc finger transcription factor activities regulate Bcl-6 expression in CD4⁺ Th cells. *The Journal of Immunology.* 2017;199(7):2377-87.

34. Agnihotri P, Robertson NM, Umetsu SE, Arakcheeva K, Winandy S. Lack of Ikaros cripples expression of Foxo1 and its targets in naive T cells. *Immunology.* 2017;152(3):494-506.

35. Ross JA, Linabery AM, Blommer CN, Langer EK, Spector LG, Hilden JM, et al. Genetic variants modify susceptibility to leukemia in infants: a Children's Oncology Group report. *Pediatr Blood Cancer.* 2013;60(1):31-4.

36. Dumortier A, Kirstetter P, Kastner P, Chan S. Ikaros regulates neutrophil differentiation. *Blood.* 2003;101(6):2219-26.

37. Rao KN, Smuda C, Gregory GD, Min B, Brown MA. Ikaros limits basophil development by suppressing C/EBP- α expression. *Blood.* 2013;122(15):2572-81.

38. Dijon M, Bardin F, Murati A, Batoz M, Chabannon C, Tonnelle C. The role of Ikaros in human erythroid differentiation. *Blood.* 2008;111(3):1138-46.

39. Alkhatib A, Werner M, Hug E, Herzog S, Eschbach C, Faraidun H, et al. FoxO1 induces Ikaros splicing to promote immunoglobulin gene recombination. *J Exp Med.* 2012;209(2):395-406.

40. Heizmann B, Kastner P, Chan S. Ikaros is absolutely required for pre-B cell differentiation by attenuating IL-7 signals. *Journal of Experimental Medicine.* 2013;210(13):2823-32.

41. Dumortier A, Jeannet R, Kirstetter P, Kleinmann E, Sellars M, dos Santos NR, et al. Notch activation is an early and critical event during T-Cell leukemogenesis in Ikaros-deficient mice. *Mol Cell Biol.* 2006;26(1):209-20.

42. Collins B, Clambey ET, Scott-Browne J, White J, Marrack P, Hagman J, et al. Ikaros promotes rearrangement of TCR α genes in an Ikaros null thymoma cell line. *Eur J Immunol.* 2013;43(2):521-32.

43. Sridharan R, Smale ST. Predominant interaction of both Ikaros and Helios with the NuRD complex in immature thymocytes. *J Biol Chem.* 2007;282(41):30227-38.

44. Gómez-del Arco P, Koipally J, Georgopoulos K. Ikaros SUMOylation: switching out of repression. *Mol Cell Biol.* 2005;25(7):2688-97.

45. Dovat S, Song C, Payne KJ, Li Z. Ikaros, CK2 kinase, and the road to leukemia. *Mol Cell Biochem.* 2011;356(1-2):201-7.

46. Gowda C, Soliman M, Kapadia M, Ding Y, Payne K, Dovat S. Casein Kinase II (CK2), Glycogen Synthase Kinase-3 (GSK-3) and Ikaros mediated regulation of leukemia. *Adv Biol Regul.* 2017;65:16-25.

47. Song C, Gowda C, Pan X, Ding Y, Tong Y, Tan BH, et al. Targeting casein kinase II restores Ikaros tumor suppressor activity and demonstrates therapeutic efficacy in high-risk leukemia. *Blood.* 2015;126(15):1813-22.

48. Song C, Li Z, Erbe AK, Savic A, Dovat S. Regulation of Ikaros function by casein kinase 2 and protein phosphatase 1. *World J Biol Chem.* 2011;2(6):126-31.

49. Popescu M, Gurel Z, Ronni T, Song C, Hung KY, Payne KJ, et al. Ikaros stability and pericentromeric localization are regulated by protein phosphatase 1. *J Biol Chem.* 2009;284(20):13869-80.

50. Kuehn HS, Niemela JE, Stoddard J, Mannurita SC, Shahin T, Goel S, et al. Germline IKAROS dimerization haploinsufficiency causes hematologic cytopenias and malignancies. *Blood.* 2021;137(3):349-63.

51. Georgopoulos K. Haematopoietic cell-fate decisions, chromatin regulation and ikaros. *Nat Rev Immunol.* 2002;2(3):162-74.

52. Schott CA, Ascoli C, Huang Y, Perkins DL, Finn PW. Declining Pulmonary Function in Interstitial Lung

- Disease Linked to Lymphocyte Dysfunction. *Am J Respir Crit Care Med*. 2020;201(5):610-3.
53. de Rooij JD, Beuling E, van den Heuvel-Eibrink MM, Obulkasim A, Baruchel A, Trka J, et al. Recurrent deletions of IKZF1 in pediatric acute myeloid leukemia. *Haematologica*. 2015;100(9):1151-9.
 54. Mullighan CG, Su X, Zhang J, Radtke I, Phillips LA, Miller CB, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. *N Engl J Med*. 2009;360(5):470-80.
 55. Mullighan CG, Miller CB, Radtke I, Phillips LA, Dalton J, Ma J, et al. BCR-ABL1 lymphoblastic leukaemia is characterized by the deletion of Ikaros. *Nature*. 2008;453(7191):110-4.
 56. Eskandarian Z, Fliegau M, Bulashevskaya A, Proietti M, Hague R, Smulski CR, et al. Assessing the Functional Relevance of Variants in the IKAROS Family Zinc Finger Protein 1 (IKZF1) in a Cohort of Patients With Primary Immunodeficiency. *Front Immunol*. 2019;10:568.
 57. Daneshvar Kakhaki R, Kouchaki E, Dadgostar E, Behnam M, Tamtaji OR, Nikoueinejad H, et al. The correlation of helios and neuropilin-1 frequencies with parkinson disease severity. *Clin Neurol Neurosurg*. 2020;192:105833.
 58. Cunningham Graham DS, Morris DL, Bhargale TR, Criswell LA, Syvänen AC, Rönnblom L, et al. Association of NCF2, IKZF1, IRF8, IFIH1, and TYK2 with systemic lupus erythematosus. *PLoS Genet*. 2011;7(10):e1002341.
 59. Yang M, Liu Y, Mo B, Xue Y, Ye C, Jiang Y, et al. Helios but not CD226, TIGIT and Foxp3 is a Potential Marker for CD4(+) Treg Cells in Patients with Rheumatoid Arthritis. *Cell Physiol Biochem*. 2019;52(5):1178-92.
 60. Sriaroon P, Chang Y, Ujhazi B, Csomos K, Joshi HR, Zhou Q, et al. Familial Immune Thrombocytopenia Associated With a Novel Variant in IKZF1. *Front Pediatr*. 2019;7:139.
 61. Xia R, Cheng Y, Han X, Wei Y, Wei X. Ikaros Proteins in Tumor: Current Perspectives and New Developments. *Front Mol Biosci*. 2021;8:788440.
 62. Javierre BM, Rodriguez-Ubreva J, Al-Shahrour F, Corominas M, Graña O, Ciudad L, et al. Long-range epigenetic silencing associates with deregulation of Ikaros targets in colorectal cancer cells. *Mol Cancer Res*. 2011;9(8):1139-51.
 63. He LC, Gao FH, Xu HZ, Zhao S, Ma CM, Li J, et al. Ikaros inhibits proliferation and, through upregulation of Slug, increases metastatic ability of ovarian serous adenocarcinoma cells. *Oncol Rep*. 2012;28(4):1399-405.
 64. Liu YY, Ge C, Tian H, Jiang JY, Zhao FY, Li H, et al. The transcription factor Ikaros inhibits cell proliferation by downregulating ANXA4 expression in hepatocellular carcinoma. *Am J Cancer Res*. 2017;7(6):1285-97.
 65. Edgren H, Murumagi A, Kangaspeka S, Nicorici D, Hongisto V, Kleivi K, et al. Identification of fusion genes in breast cancer by paired-end RNA-sequencing. *Genome Biol*. 2011;12(1):R6.
 66. Iacobucci I, Mullighan CG. Genetic Basis of Acute Lymphoblastic Leukemia. *J Clin Oncol*. 2017;35(9):975-83.
 67. Iacobucci I, Storlazzi CT, Cilloni D, Lonetti A, Ottaviani E, Soverini S, et al. Identification and molecular characterization of recurrent genomic deletions on 7p12 in the IKZF1 gene in a large cohort of BCR-ABL1-positive acute lymphoblastic leukemia patients: on behalf of Gruppo Italiano Malattie Ematologiche dell'Adulto Acute Leukemia Working Party (GIMEMA AL WP). *Blood*. 2009;114(10):2159-67.
 68. Kuiper RP, Waanders E, van der Velden VH, van Reijmersdal SV, Venkatachalam R, Scheijen B, et al. IKZF1 deletions predict relapse in uniformly treated pediatric precursor B-ALL. *Leukemia*. 2010;24(7):1258-64.
 69. Mullighan CG, Downing JR. Global genomic characterization of acute lymphoblastic leukemia. *Semin Hematol*. 2009;46(1):3-15.
 70. Zhang J, Ding L, Holmfeldt L, Wu G, Heatley SL, Payne-Turner D, et al. The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. *Nature*. 2012;481(7380):157-63.
 71. Roberts KG, Gu Z, Payne-Turner D, McCastlain K, Harvey RC, Chen IM, et al. High Frequency and Poor Outcome of Philadelphia Chromosome-Like Acute Lymphoblastic Leukemia in Adults. *J Clin Oncol*. 2017;35(4):394-401.
 72. Churchman ML, Qian M, Te Kronnie G, Zhang R, Yang W, Zhang H, et al. Germline Genetic IKZF1 Variation and Predisposition to Childhood Acute Lymphoblastic Leukemia. *Cancer Cell*. 2018;33(5):937-48.e8.
 73. Ge Z, Zhou X, Gu Y, Han Q, Li J, Chen B, et al. Ikaros regulation of the BCL6/BACH2 axis and its clinical relevance in acute lymphoblastic leukemia. *Oncotarget*. 2017;8(5):8022-34.
 74. Ge Z, Guo X, Li J, Hartman M, Kawasaki YI, Dovat S, et al. Clinical significance of high c-MYC and low MYCBP2 expression and their association with Ikaros dysfunction in adult acute lymphoblastic leukemia. *Oncotarget*. 2015;6(39):42300-11.

75. Schjerven H, Ayongaba EF, Aghajani-refah A, McLaughlin J, Cheng D, Geng H, et al. Genetic analysis of Ikaros target genes and tumor suppressor function in BCR-ABL1(+) pre-B ALL. *J Exp Med*. 2017;214(3):793-814.
76. Casolari DA, Makri M, Yoshida C, Muto A, Igarashi K, Melo JV. Transcriptional suppression of BACH2 by the Bcr-Abl oncoprotein is mediated by PAX5. *Leukemia*. 2013;27(2):409-15.
77. Muto A, Hoshino H, Madisen L, Yanai N, Obinata M, Karasuyama H, et al. Identification of Bach2 as a B-cell-specific partner for small maf proteins that negatively regulate the immunoglobulin heavy chain gene 3' enhancer. *Embo j*. 1998;17(19):5734-43.
78. Swaminathan S, Duy C, Müschen M. BACH2-BCL6 balance regulates selection at the pre-B cell receptor checkpoint. *Trends Immunol*. 2014;35(3):131-7.
79. Ye BH, Mai Y. A Bach2 link between pre-B cell receptor checkpoint and pre-B cell ALL. *Cancer Cell*. 2013;24(3):282-4.
80. Muto A, Tashiro S, Nakajima O, Hoshino H, Takahashi S, Sakoda E, et al. The transcriptional programme of antibody class switching involves the repressor Bach2. *Nature*. 2004;429(6991):566-71.
81. Liu J, Sørensen AB, Wang B, Wabl M, Nielsen AL, Pedersen FS. Identification of novel Bach2 transcripts and protein isoforms through tagging analysis of retroviral integrations in B-cell lymphomas. *BMC Mol Biol*. 2009;10:2.
82. Han Q, Ma J, Gu Y, Song H, Kapadia M, Kawasaki YI, et al. RAG1 high expression associated with IKZF1 dysfunction in adult B-cell acute lymphoblastic leukemia. *J Cancer*. 2019;10(16):3842-50.
83. Kim JS, Eom JI, Cheong JW, Choi AJ, Lee JK, Yang WI, et al. Protein kinase CK2alpha as an unfavorable prognostic marker and novel therapeutic target in acute myeloid leukemia. *Clin Cancer Res*. 2007;13(3):1019-28.
84. Gowda C, Song C, Ding Y, Iyer S, Dhanyamraju PK, McGrath M, et al. Cellular signaling and epigenetic regulation of gene expression in leukemia. *Adv Biol Regul*. 2020;75:100665.
85. Klampfl T, Harutyunyan A, Berg T, Gisslinger B, Schalling M, Bagicnski K, et al. Genome integrity of myeloproliferative neoplasms in chronic phase and during disease progression. *Blood*. 2011;118(1):167-76.
86. Bolouri H, Farrar JE, Triche T, Jr., Ries RE, Lim EL, Alonzo TA, et al. The molecular landscape of pediatric acute myeloid leukemia reveals recurrent structural alterations and age-specific mutational interactions. *Nat Med*. 2018;24(1):103-12.
87. Tyner JW, Tognon CE, Bottomly D, Wilmot B, Kurtz SE, Savage SL, et al. Functional genomic landscape of acute myeloid leukaemia. *Nature*. 2018;562(7728):526-31.
88. Oliveira VC, Moretti NS, Augusto Lda S, Schenkman S, Mariano M, Popi AF. Ikaros could be a key factor in the maintenance of "B-side" of B-1 cells. *Immunobiology*. 2015;220(11):1232-9.
89. Beer PA, Knapp DJ, Miller PH, Kannan N, Sloma I, Heel K, et al. Disruption of IKAROS activity in primitive chronic-phase CML cells mimics myeloid disease progression. *Blood*. 2015;125(3):504-15.
90. Moschovi M, Adamaki M, Athanasiadou A, Divane A, Karytianiou A, Tourkanton N. Possible implication of IKAROS gene deletion and BCR-ABL1 variants in progression of chronic myeloid leukemia to lymphoid blast crisis in childhood: a single-institution experience. *Leukemia & Lymphoma*. 2015;56(8):2460-2.
91. Mullighan CG, Goorha S, Radtke I, Miller CB, Coustan-Smith E, Dalton JD, et al. Genome-wide analysis of genetic alterations in acute lymphoblastic leukaemia. *Nature*. 2007;446(7137):758-64.
92. Tokunaga K, Yamaguchi S, Iwanaga E, Nanri T, Shimomura T, Suzushima H, et al. High frequency of IKZF1 genetic alterations in adult patients with B-cell acute lymphoblastic leukemia. *Eur J Haematol*. 2013;91(3):201-8.
93. Clappier E, Grardel N, Bakkus M, Rapon J, De Moerloose B, Kastner P, et al. IKZF1 deletion is an independent prognostic marker in childhood B-cell precursor acute lymphoblastic leukemia, and distinguishes patients benefiting from pulses during maintenance therapy: results of the EORTC Children's Leukemia Group study 58951. *Leukemia*. 2015;29(11):2154-61.
94. Lilljebjörn H, Henningsson R, Hyrenius-Wittsten A, Olsson L, Orsmark-Pietras C, von Palfy S, et al. Identification of ETV6-RUNX1-like and DUX4-rearranged subtypes in paediatric B-cell precursor acute lymphoblastic leukaemia. *Nat Commun*. 2016;7:11790.
95. Rahmani M, Fardi M, Farshdousti Hagh M, Hosseinpour Feizi AA, Talebi M, Solali S. An investigation of methylation pattern changes in the IKZF1 promoter in patients with childhood B-cell acute lymphoblastic leukemia. *Blood Res*. 2019;54(2):144-8.
96. Trageser D, Iacobucci I, Nahar R, Duy C, von Levetzow G, Klemm L, et al. Pre-B cell receptor-mediated cell cycle arrest in Philadelphia chromosome-positive acute lymphoblastic leukemia requires IKAROS function. *J Exp Med*. 2009;206(8):1739-53.

97. Klumb CE, Barbosa TDC, Nestal de Moraes G, Schramm MT, Emerenciano M, Maia RC. IKZF1 deletion and co-occurrence with other aberrations in a child with chronic myeloid leukemia progressing to acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2019;66(4):e27570.
98. Kriegsmann K, Baertsch MA, Awwad MHS, Merz M, Hose D, Seckinger A, et al. Cereblon-binding proteins expression levels correlate with hyperdiploidy in newly diagnosed multiple myeloma patients. *Blood Cancer J*. 2019;9(2):13.
99. Tachita T, Kinoshita S, Ri M, Aoki S, Asano A, Kanamori T, et al. Expression, mutation, and methylation of cereblon-pathway genes at pre- and post-lenalidomide treatment in multiple myeloma. *Cancer Sci*. 2020;111(4):1333-43.
100. Conserva MR, Redavid I, Anelli L, Zagaria A, Tarantini F, Cumbo C, et al. IKAROS in Acute Leukemia: A Positive Influencer or a Mean Hater? *Int J Mol Sci*. 2023;24(4).
101. Cippitelli M, Stabile H, Kosta A, Petillo S, Gismondi A, Santoni A, et al. Role of Aiolos and Ikaros in the Antitumor and Immunomodulatory Activity of IMiDs in Multiple Myeloma: Better to Lose Than to Find Them. *Int J Mol Sci*. 2021;22(3).
102. Zeidner JF, Knaus HA, Zeidan AM, Blackford AL, Montiel-Esparza R, Hackl H, et al. Immunomodulation with pomalidomide at early lymphocyte recovery after induction chemotherapy in newly diagnosed AML and high-risk MDS. *Leukemia*. 2020;34(6):1563-76.
103. Lu G, Middleton RE, Sun H, Naniong M, Ott CJ, Mitsiades CS, et al. The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins. *Science*. 2014;343(6168):305-9.
104. Fedele PL, Willis SN, Liao Y, Low MS, Rautela J, Segal DH, et al. IMiDs prime myeloma cells for daratumumab-mediated cytotoxicity through loss of Ikaros and Aiolos. *Blood*. 2018;132(20):2166-78.
105. Avitahl N, Winandy S, Friedrich C, Jones B, Ge Y, Georgopoulos K. Ikaros sets thresholds for T cell activation and regulates chromosome propagation. *Immunity*. 1999;10(3):333-43.
106. Churchman ML, Mullighan CG. Ikaros: Exploiting and targeting the hematopoietic stem cell niche in B-progenitor acute lymphoblastic leukemia. *Exp Hematol*. 2017;46:1-8.
107. Borgo C, D'Amore C, Sarno S, Salvi M, Ruzzene M. Protein kinase CK2: a potential therapeutic target for diverse human diseases. *Signal Transduct Target Ther*. 2021;6(1):183.
108. Gowda C, Sachdev M, Muthusami S, Kapadia M, Petrovic-Dovat L, Hartman M, et al. Casein Kinase II (CK2) as a Therapeutic Target for Hematological Malignancies. *Curr Pharm Des*. 2017;23(1):95-107.
109. Dobrovolsky D, Wang ES, Morrow S, Leahy C, Faust T, Nowak RP, et al. Bruton tyrosine kinase degradation as a therapeutic strategy for cancer. *Blood*. 2019;133(9):952-61.
110. Bjorklund CC, Lu L, Kang J, Hagner PR, Havens CG, Amatangelo M, et al. Rate of CRL4(CRBN) substrate Ikaros and Aiolos degradation underlies differential activity of lenalidomide and pomalidomide in multiple myeloma cells by regulation of c-Myc and IRF4. *Blood Cancer J*. 2015;5(10):e354.
111. Ganesan S, Palani HK, Balasundaram N, David S, Devasia AJ, George B, et al. Combination Lenalidomide/Bortezomib Treatment Synergistically Induces Calpain-Dependent Ikaros Cleavage and Apoptosis in Myeloma Cells. *Mol Cancer Res*. 2020;18(4):529-36.
112. Mateos MV, Blacklock H, Schjesvold F, Oriol A, Simpson D, George A, et al. Pembrolizumab plus pomalidomide and dexamethasone for patients with relapsed or refractory multiple myeloma (KEYNOTE-183): a randomised, open-label, phase 3 trial. *Lancet Haematol*. 2019;6(9):e459-e69.
113. Matyskiela ME, Zhang W, Man HW, Muller G, Khambatta G, Baculi F, et al. A Cereblon Modulator (CC-220) with Improved Degradation of Ikaros and Aiolos. *J Med Chem*. 2018;61(2):535-42.
114. Rasco DW, Papadopoulos KP, Pourdehnad M, Gandhi AK, Hagner PR, Li Y, et al. A First-in-Human Study of Novel Cereblon Modulator Avadomide (CC-122) in Advanced Malignancies. *Clin Cancer Res*. 2019;25(1):90-8.
115. Hagner PR, Man HW, Fontanillo C, Wang M, Couto S, Breider M, et al. CC-122, a pleiotropic pathway modifier, mimics an interferon response and has antitumor activity in DLBCL. *Blood*. 2015;126(6):779,