Iranian Journal of Blood & Cancer

Iran J Blood Cancer, 2024, 16(1), 21-34
https://ijbc.ir

Review Article

Ikaros (IKZF1): From Normal Hematopoiesis to Hematologic Malignancies

Hamed Baghdadi [1], Mehdi Shakouri Khomartash [2], Nazanin Ahmadi [2], Ali Faridfar [3], Mahdi Ghorbani [1,2*]

[1] Department of Medical Laboratory Sciences, School of Allied Medical Sciences, AJA University of Medical Sciences, Tehran, 1411718541, Iran
[2] Medical Biotechnology Research Center, AJA University of Medical Sciences, Tehran, 1411718541, Iran
[3] AJA Cancer Epidemiology Research and Treatment Center (AJA- CERTC), AJA University of Medical Sciences, Tehran, 1411718541, Iran

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Citation Baghdadi H, Shakouri Khomartash M, Ahmadi N, Faridfar A, Ghorbani M. Ikaros (IKZF1): From normal hematopoiesis to hematologic malignancies. Iran J Blood Cancer. 2024 February 30;16(1): 21-34.

doi 0

Article info:
Received: 17 Nov 2023
Accepted: 26 Jan 2024
Published: 25 Mar 2024

Keywords:
IKZF1
Ikaros
ALL
AML
Immunomodulatory drugs

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

* Corresponding Author:
Mahdi Ghorbani
Affiliation: Department of Medical Laboratory Sciences, School of Allied Medical Sciences, AJA University of Medical Sciences, Tehran, 1411718541, Iran
E-mail: **M.ghorbani@ajaums.ac.ir**

[DOI: 10.61186/ijbc.16.1.21]

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 RORγt 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 approaches 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 IKZF1gene, 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

[DOI: 10.61186/ijbc.16.1.21]

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 ant-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

[DOI: 10.61186/ijbc.16.1.21]

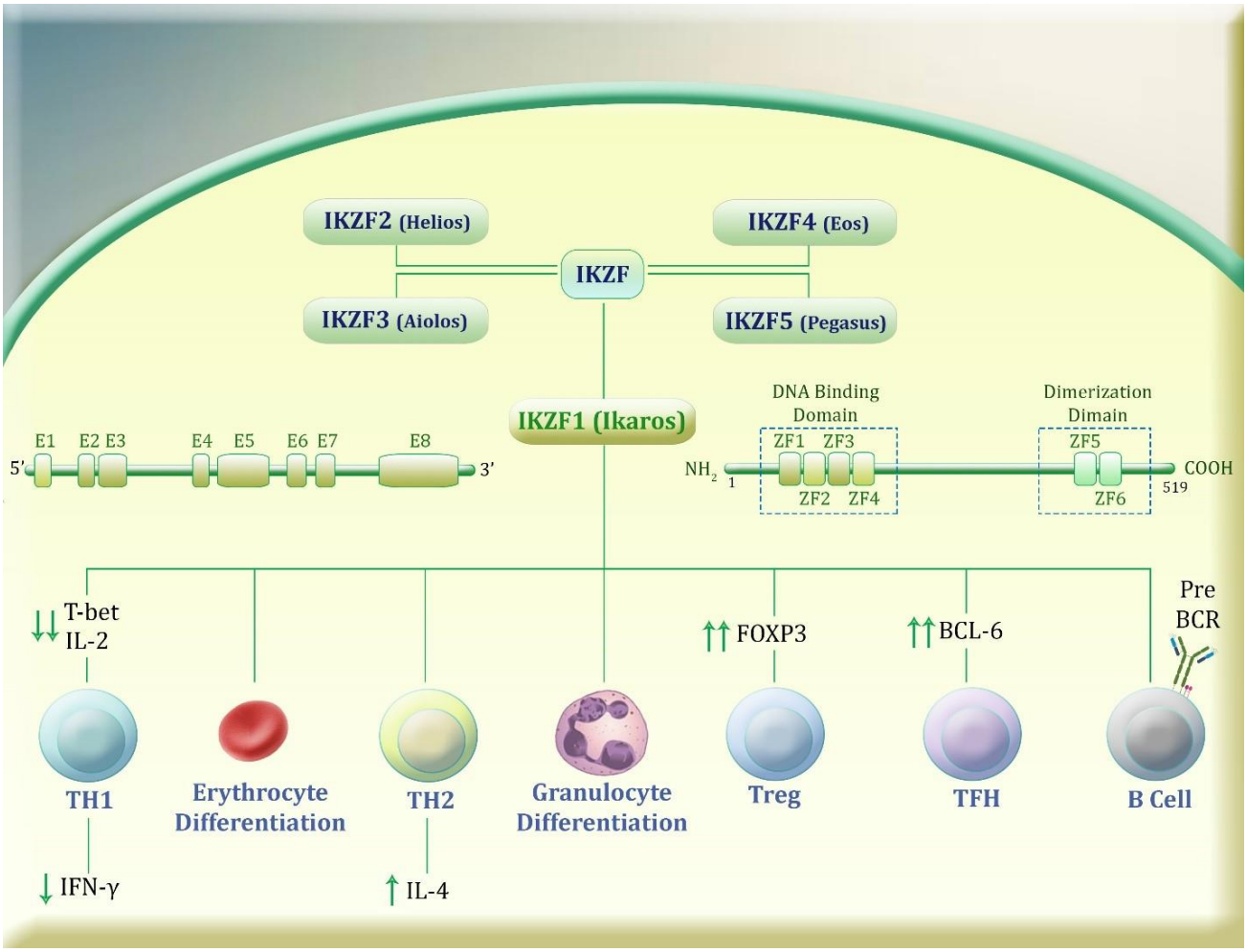

Figure 1. IKZF family, IKZF1 gene, and the functions of Ikaros. The IKZF family consists of five members encoded by IKZF1-5, of which Ikaros is by far the most well-studied transcription factor able to target a range of cells. IKZF1 encodes Ikaros and is located on 7p12.2 and contains eight exons; the 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

[DOI: 10.61186/ijbc.16.1.21]

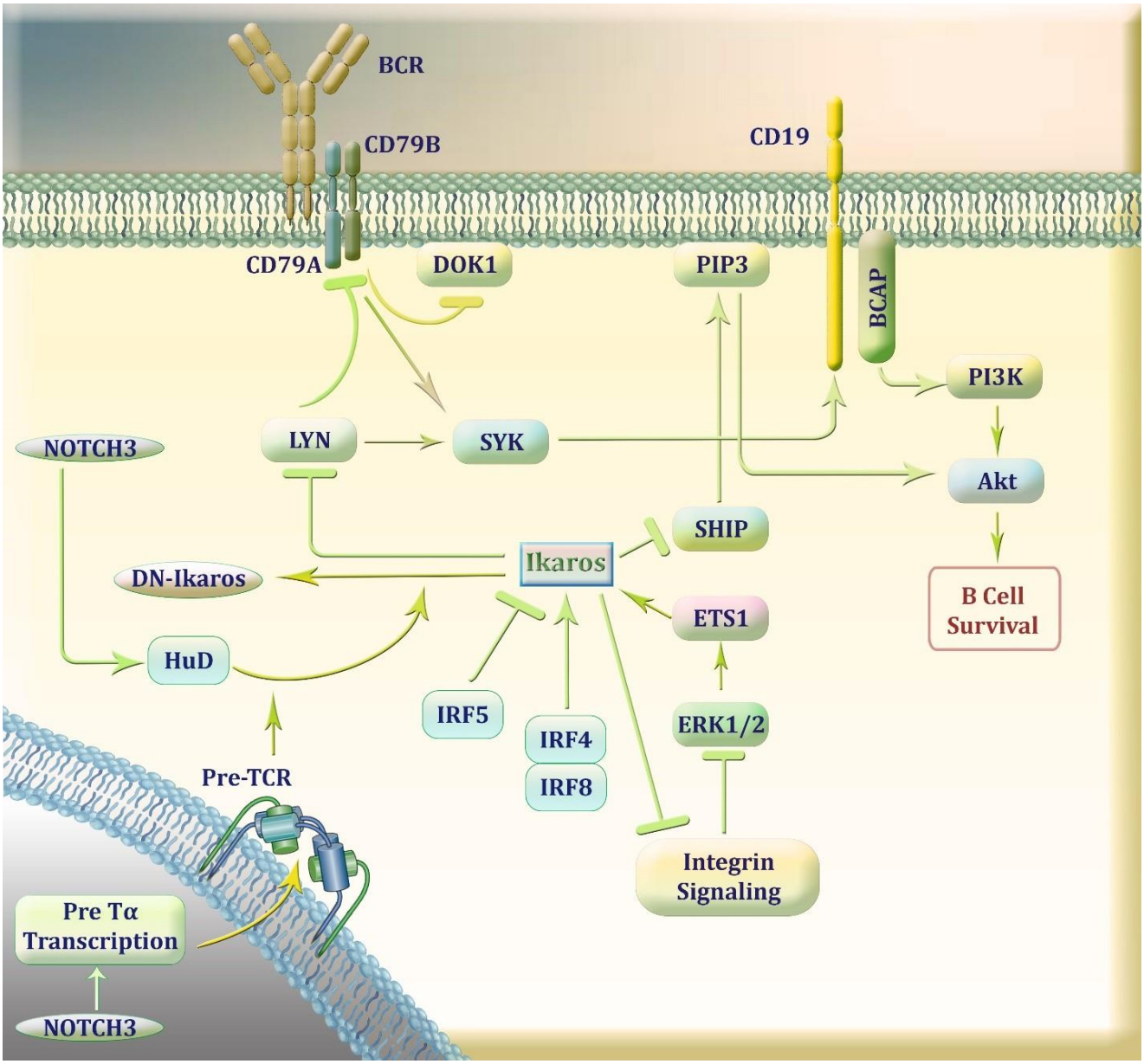

Figure 2. The signaling pathways associated with Ikaros. The activated pre-BCR is able to limit the function of Ikaros; consequently, Ikaros counteracts this event by inhibiting LYN and SHIP. LYN can directly phosphorylate and suppress SYK or indirectly monophosphorylate ITAM CD79A and CD79B, resulting 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.

[DOI: 10.61186/ijbc.16.1.21]

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.

[DOI: 10.61186/ijbc.16.1.21]

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.

[DOI: 10.61186/ijbc.16.1.21]

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.

[DOI: 10.61186/ijbc.16.1.21]

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 indue 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.

[DOI: 10.61186/ijbc.16.1.21]

Acknowledgment

The authors would like to express their gratitude to AJA University of Medical Sciences for supporting this study.

Conflict of interest

The authors declare that they have no conflict of interest.

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[DOI: 10.61186/ijbc.16.1.21]