Contents lists available at ScienceDirect

Acta Haematologica Polonica

journal homepage: www.elsevier.com/locate/achaem

Review/Praca poglądowa

Functions of the Ikaros transcription factor and the role of *IKZF1* gene defects in hematological malignancies

Funkcje czynnika transkrypcyjnego Ikaros oraz znaczenie defektów genu IKZF1 *w nowotworach hematologicznych*

Anna Gorzkiewicz, Anna Walczewska *

Department of Cell-to-Cell Communication, Medical University of Lodz, Lodz, Poland

ARTICLE INFO

Article history:
Received: 30.06.2014
Accepted: 16.10.2014
Available online: 27.10.2014

Keywords:
- Ikaros
- *IKZF1*
- Acute lymphoblastic leukemia
- ALL

Słowa kluczowe:
- Ikaros
- *IKZF1*
- ostra białaczka limfoblastyczna
- OBL

ABSTRACT

Discovered in the early 1990s, the highly conserved DNA- and protein-binding transcription factor, Ikaros, is now considered one of the most important players in hematopoiesis and the development of certain forms of human malignancies. The Ikaros transcription factor is a multifunctional protein regulating hematopoietic stem cells (HSCs) function, coordinating self-renewal, cell survival processes, cell cycle progression and lymphopoiesis. Ikaros is also considered as one of the most important antileukemic transcription factors. Alterations in the Ikaros gene (*IKZF1*) characterize a subset of acute lymphoblastic leukemia with significant resistance to treatment and increased risk of relapse. Hematological studies highlight shortened and modified dominant negative (DN) Ik-forms, that play an important role in the development and prognosis of hematological malignances. Currently, extensive research in this field is a priority in the battle against leukemia. This paper describes the structural and functional properties of the Ikaros protein and its family members, important interactions with the nuclear proteins, its influence on gene transcriptional profiles, as well as its considerable involvement in the key hematopoietic processes.

Introduction

Interest in Ikaros, the zinc finger-containing transcription factor, has been growing since the early 1990s [1]. Initially, in 1991, a study of erythroid globin switching revealed the existence of a DNA-binding factor with a strong binding activity restricted to hematopoietic tissues. This protein was found to bind to more than 95% of the pyrimidine (PYR)-rich domain on one strand of DNA upstream of the human

* *Corresponding author at*: Zakład Interakcji Międzykomórkowych, Uniwersytetu Medycznego w Łodzi, ul. Mazowiecka 6/8, 92-215 Łódź, Polska. Tel.: +48 42 2725654.
E-mail address: anna.walczewska@umed.lodz.pl (A. Walczewska).

http://dx.doi.org/10.1016/j.achaem.2014.10.001

δ-globin gene [2]. As we know now, it was Ikaros protein associated with the PYR complex. Ikaros, designated as Ik-1, Ik-VI or Lyf-1, is encoded by the *IKZF1* gene (also known as *ZNFN1A1*) located on the short arm of human chromosome 7 and on mouse chromosome 11, next to the epidermal growth factor receptor gene [3, 4]. Ikaros protein is a highly conserved antileukemic transcription factor with a 95% homology between mice and humans at the amino acid level [3].

Ikaros family members comprise two functionally different groups. The members of the first group are the basic form of the proteins, include Ikaros encoded by the *IKZF1* gene, Helios encoded by the *IKZF2* gene, Aiolos encoded by the *IKZF3* gene, Eos encoded by the *IKZF4* gene, and Pegasus encoded by the *IKZF5* gene. These proteins possess both DNA-binding and protein-binding domains. The functional Ik-forms, Ikaros, Helios and Aiolos, together with Ik-H and Ik-X act in concert with the Ikaros protein, partially complementing its function, while Eos can only bind to a palindromic DNA sequence [5].

The second group of the Ikaros family members consists of dominant-negative (DN) Ik-forms encoded by the same genes as functional forms. However, these forms have lost their ability to bind DNA due to the deletion of exon 5 containing two N-terminal zinc fingers (ZF), ZF2 and ZF3 as a result of their alternative splicing. These short, pathological, DNA-nonbinding DN forms inhibit the functional Ik-forms of group one [6–8]. The expression of DNs in normal bone marrow cells is at a very low level [9], but their higher levels are associated with hematopoietic malignancies [10]. Normal infant bone marrow cells and thymocytes produce only Ikaros and Helios localized in the nucleus, whereas the DNs display cytoplasmic localization [11].

It has been demonstrated in mice that the heterozygous deletion of exons 4 and 5, which encode three N-terminal ZFs, cause up-regulation of DN forms such as Ik-6, Ik-7 and Ik-8, and lead to development of a highly aggressive form of lymphoblastic leukemia. However, the same mutation in a homozygous mouse germline completely arrested the development of all lymphoid lineages [11]. It is also interesting to note that Ikaros deletions are found much more frequently in p53KO lymphomas than in wild-type p53 lymphomas: both genes being on the same chromosome [4].

Ikaros and its family members play a crucial role in hematopoiesis, particularly in the lymphoid lineage as a master regulator of early lymphocyte development, their differentiation, homeostasis and function [12–14]. Through the regulation of target gene expression, Ikaros proteins control cell cycle progression and cell survival [6, 15], as well as isotype selection during class-switch DNA recombination of the immunoglobulin [16]. Moreover, this protein is a crucial functional regulator and self-renewal factor of hematopoietic stem cells (HSCs) [13, 17] and a critical tumor suppressor [13, 18, 19]. It has been also demonstrated that during chemotherapy or UV treatment, the Ikaros protein is degraded in the early phase of apoptosis, presumably by the proteasome system, prior to the activation of caspase 3 [20].

The expression profile of Ikaros family members varies depending on cell type [21], and the co-expression of these proteins enables the formation of highly stable homo- and heterodimers, which presumably can associate into multimers [21, 22]. Dimerization of DNA-binding Ikaros isoforms results in their enhanced affinity for DNA and increased transcription activation [22].

The expression of Ikaros is primarily detected in the thymus and spleen, where it is essential for the regulation of T-cell specific gene transcription. Furthermore, Ikaros is expressed in HSCs, myeloid and erythroid precursors, mature T and B cells, natural killer (NK) cells, activated T cells and nucleated erythroid lineage cells [9], as well as in common lymphoid progenitors [17, 23, 24]. Although, Ikaros is upregulated during T cell activation, the protein occurs at a very low level in resting T cells [9, 25, 26]. The highest expression of Ikaros is observed in immature thymocytes, as well as in self-renewing fractions of long term (LT) HSCs. Interestingly, the daughter short term (ST) HSC population displays significantly lower Ikaros levels [17].

Although Ikaros has been previously described as a lymphoid lineage specific factor, recent studies indicate that it plays a role in other cell types, such as developing striatal mouse neurons [27]. It has been described as inducing both cell cycle arrest of neural progenitors and neurogenesis of late precursors, i.e. ENK-positive striatal neurons [28]. It has also been reported that Ikaros occurs at high levels in progenitor cells of the cerebral cortex in early stages of neurogenesis in mice, after which its expression systematically decreases [29]. Moreover, Ikaros expression has been observed in all early embryonic mouse multipotent retinal progenitor cells which, at later stages, give rise to Ikaros deficient retinal progenitor cells. The studies on the role of Ikaros in neuronal development indicate that this protein is as a mammalian homolog of Hunchback, a temporal zinc finger transcription factor selecting the fate of the first-born neurons in *Drosophila* [29, 30].

Ikaros structure and function

The crucial features of Ikaros that contributed to its discovery were the C2H2 zinc finger (ZF) motifs located in two Krüppel-like zinc finger domains, which are characteristic for both DNA-binding and protein-binding proteins. Four ZF motifs located centrally on the N-terminal domain of the Ikaros protein (ZF1–ZF4) are known to possess DNA-binding affinity, whereas 2 additional zinc fingers (ZF5, ZF6) located on the C-terminal domain, named the dimerization domain, are responsible for protein interaction [10, 31, 32] (Fig. 1). Presumably, the C-terminal zinc fingers are responsible for the pericentromeric targeting of the Ikaros protein within the nucleus [31].

The latest designations of Ikaros family members are different to the original ones. As exon 1 is not translated and has not been initially identified, the first reports describe only seven exons [6, 33]. However, all Ikaros isoforms possess exon 8 with protein-binding ZF5 and ZF6 motifs. Moreover, many of the *IKZF1* family member genes miss the last 30 bases of exon 7 and are designated as *minus* forms [6].

Ikaros interacts with DNA, inserting the DNA-binding domain into the major groove of DNA [32]. As a transcription factor, Ikaros binds to 1 or 2 sites containing the (C/T)GGGA

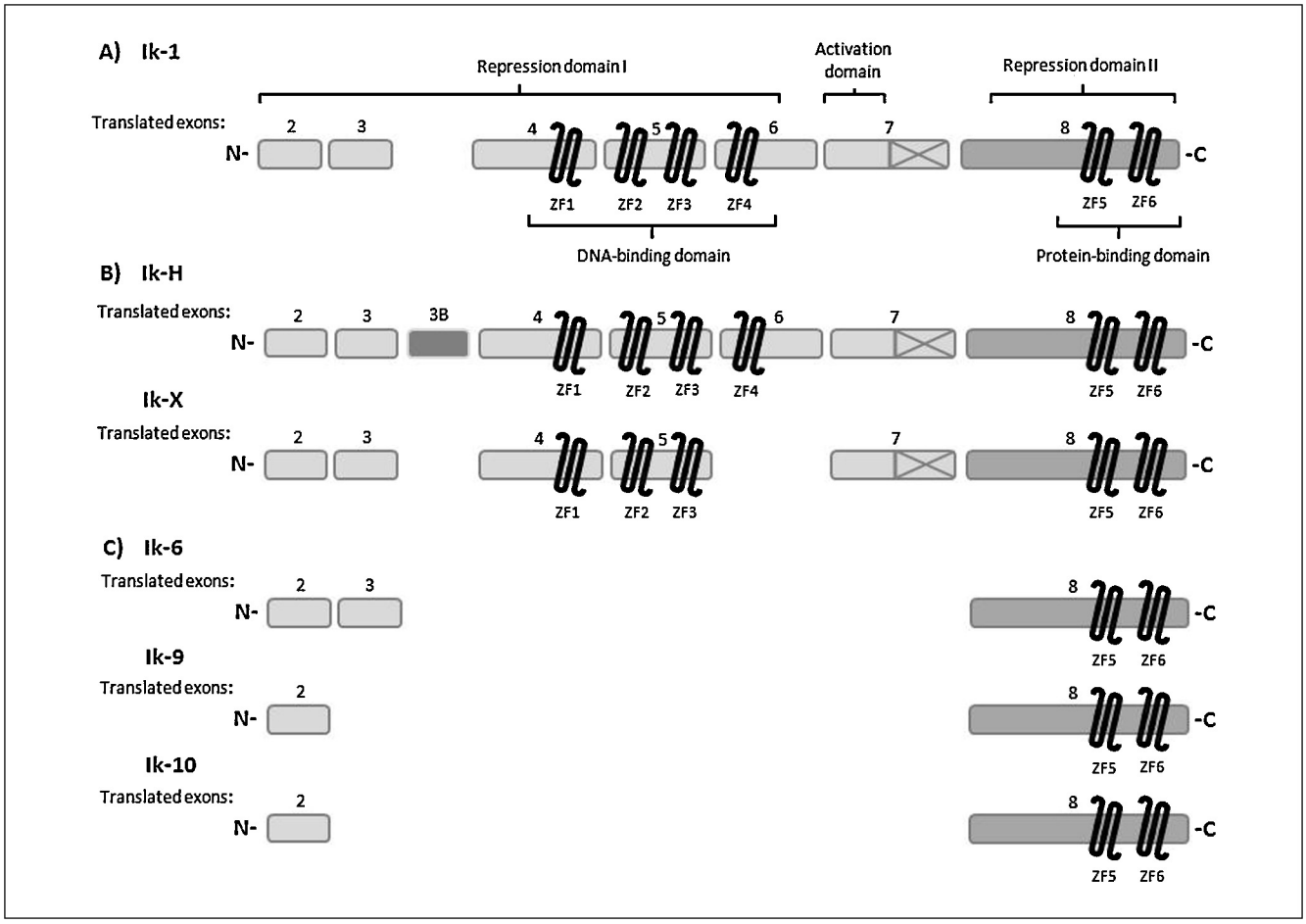

Fig. 1 – Structures of Ikaros family member proteins. Exon 1 is untranslated. Some forms lack translation of the last 30 bases of exon 7 (the part marked with "X") and are designated as "minus" forms. (A) Structure of Ikaros 1 protein. (B) Structures of major functional Ik-forms: Ik-H and Ik-X. (C) Structures of major DN Ik-forms: Ik-6, Ik-9 and Ik-10. ZF: zinc finger; N-: N-terminal end; C-: C-terminal end

Ryc. 1 – Struktury białek z rodziny Ikaros. Ekson 1 nie jest tłumaczony. W niektórych formach ostatnich 30 par zasad eksonu 7 nie jest tłumaczone (fragment przekreślony „X"), a ich nazwy są oznaczane minusem. (A) Struktura białka Ikaros 1. (B) Struktury dwóch głównych białek funkcjonalnych z rodziny Ikaros: Ik-H i Ik-X. (C) Struktury trzech głównych form białek dominujących negatywnych z rodziny Ikaros: Ik-6, Ik-9 i Ik-10. ZF: palec cynkowy; N-: koniec aminowy; C-: koniec karboksylowy

(A/T) sequence in promoters of regulated genes [4, 10, 11, 34–36]. The Ikaros protein possesses 1 activation domain and 2 repression domains [7]. The ability to repress gene transcription does not depend on DNA-binding affinity or dimerization properties but on the cell type and the sequence of gene promoters [37]. The Ikaros-induced repression is mediated by chromatin modification, co-repressor recruitment, as well as competition for DNA sequences [13].

Ikaros is located primary in pericentromeric heterochromatin (PC-HC) in close proximity to transcriptionally silent genes [38]. This is presumably caused by its interaction with histone deacetylase complexes (HDACs) present at hypermethylated DNA fragments [39]. In fact, deacetylation of histones located in inaccessible regions of DNA requires the action of chromatin remodeling complexes. However, since the function of these complexes depends on the cell type, the pattern of gene repression displays high cell specificity [37]. Throughout chromatin remodeling, Ikaros recruits target genes to the pericentromeric heterochromatin, which results in activation or repression of their transcription [10, 12, 18, 40–42]. Ikaros can repress genes in both HDAC-dependent and independent manner, for instance, through its interactions with the co-repressor, the C-terminal binding protein [43].

The differentiation of HSCs into a lymphoid-myeloid lineage requires repression of transcriptional programs affiliated with the fate of megakaryo-erythroid cells. It has been reported that Ikaros modulates lymphoid and myeloid gene expression, but also represses genes responsible for erythroid commitment and the self-renewal ability [44]. Loss of Ikaros function in lymphoid-myeloid restricted progenitors (LMPPs) causes deficiency of tyrosine kinase receptor Flt3 [45] and promotes myeloid lineage by upregulation of specific nuclear factors and cytokine receptors [46]. Loss of Ikaros function in common myeloid progenitors (CMPs) promotes erythro-megakaryocyte formation, however, intermediate levels of Ikaros

were found to generate erythroid and myeloid lineage cells [45]. Ikaros is also a crucial regulator of the self-renewal machinery active in the pool of long term-reconstituting HSCs. A homozygous mutation of Ikaros in mouse fetus results in loss of the (CD150+) long term-HSCs, leaving non-long term self-renewing cellular pools, which causes rapid and fatal anemia, as well as a dysregulation of erythroid cell differentiation and proliferation from reduced progenitors [17].

Moreover, Ikaros plays a crucial role in the regulation of cell cycle and cell differentiation. In the nucleus, specifically in the higher-order chromatin structure, it is colocalized with methyltransferase and Cyclin A, suggesting that it is accessible to both transcription and replication machineries [25]. Cell division, especially during replication or the moment afterwards, provides an opportunity for gene maintenance to occur. This phenomenon may genetically distinguish the daughter from the mother cell, which is the principle of differentiation [25]. Ikaros is known to have the potential to maintain heterochromatic code through cell divisions, as has been described in a study on the role of chromatin remodeling in hematopoietic lineage commitment and differentiation: Ikaros appears to coordinate the correct differentiation of daughter cells from the mother cell, and act as a factor governing the pattern of fate-specific gene expression [47].

Ikaros is also involved in the control of T cell activation in which Ikaros co-localizes with the DNA replication machinery. It has been reported that reduced or abolished Ikaros activity leads to accelerated entry into the S phase by reduction of the activation threshold, reduction of sensitivity to cell cycle inhibitors and hyper-response to IL-2, which is required for G1-S progression [25]. This leads to aberrations in chromosome structures including an oversized chromosome 1. The absence of Ikaros in mice results in rapid development of T-cell neoplasia [25].

Another important function of Ikaros is shaping the course of an immune response which requires the presence of IL-10 for normal direction. Ikaros is known to be a critical activator of *IL-10* gene expression in CD4+ T cells [48]. Ikaros null T cells display aberrant differentiation and low *IL-10* gene expression. Furthermore, recent reports have shown that Ikaros is involved in the repression of the *IL-2* gene in anergic T cells, as well as in the activation of *IL-4*, *IL-5*, and *IL-13* genes in Th2 cells suggesting that Ikaros is a critical factor for T cell effector functions [49].

Ikaros is phosphorylated predominantly by casein kinase II (CKII). As a consequence of this protein phosphorylation, the recruitment of Ikaros to PC-HC, its DNA-binding affinity, the repression of some genes, and the negative regulation of G1-S transition is reduced or abolished [18, 50–52]. Although Ikaros is dephosphorylated by the late G1 phase, Ikaros becomes hyperphosphorylated as it enters the S phase and remains so throughout the M phase [50]. Inappropriate levels of active or inactive proteins regulating G1-S transition, a critical cell cycle checkpoint, induce cell apoptosis or neoplastic state in primary lymphocytes [50].

Moreover, Ikaros has been established as a central regulator of the transition of pre-B or pre-T cells to mature lymphocytes [14]. Lack of Ikaros, in both B and T cells, causes a deficit in antigen-receptor rearrangement [53]. This protein also regulates the transcription of genes, such as Cd4 or Cd8, and has been demonstrated to activate the CD8α gene locus [41, 54]. Lack of Ikaros activity during the progression of double negative T cells ($CD4^-CD8^-$) to double positive ($CD4^+CD8^+$) thymocytes results in inappropriate pre-TCR and TCR signaling [14, 54], nonetheless the T cells progression occurs. However, the rate of differentiation into the double positive stage is increased and the next transition is heavily skewed toward CD4 single-positive T cells, which do not appear in the periphery, presumably because they have not undergone the final selection steps required for their exportation. Moreover, the normal proliferative expansion of T cells does not occur, resulting in a highly hypocellular thymus [14].

Ikaros is also required in mature B cells to ensure the specificity and efficiency of the class-switch recombination. In this process, Ikaros is a regulator of immunoglobulin (Ig) isotype selection. It has been shown that Ikaros deficiency promotes ectopic class-switch recombination toward IgG2b and IgG2a and reduces class-switch recombination into all other types [16].

There are several lines of evidences that Ikaros also promotes the differentiation and survival of human erythroid cells. Furthermore, it is crucial for erythroid maturation and, most importantly, for adult erythroid globin gene expression and globin switch [2, 55, 56]. Ikaros is required for the formation and DNA binding of developmental-stage specific complexes such as chromatin remodeling complexes and the polypyrimidine (PYR) complex, which occur only in adult hematopoietic cells [2, 57–59]. Lack of Ikaros in mice results in no PYR complex formation and delayed globin switching [57, 58, 60].

Ikaros alternations in hematological malignancies

The body of evidence indicating the role of Ikaros in leukemias has accumulated steadily since the mid-1990s [61]. The focal or broad deletions of IKZF1 gene [62] are now known to be the cause or the result of some human hematological diseases, such as acute lymphoblastic leukemia (ALL) [63]. Moreover, Ikaros gene alterations indirectly lead to myeloproliferative neoplasms (MPNs) or its progression to acute myeloid leukemia (AML) [6]. Diverse *IKZF1* mutations are found during blastic progression of chronic myeloid leukemia (CML) [64]. Presumably, activation of the JAK-STAT pathway is responsible for the leukemogenic potential of *IKZF1* gene mutations [65, 66].

Homozygous *IKZF1* gene deletions are embryonic lethal and are associated with the defective or abolished development of all lymphoid cells, the earliest lymphoid progenitors, as well as excessive macrophage formation and fully defective erythrocyte and granulocyte differentiation. Heterozygous alterations of the *IKZF1* gene mostly lead to rapid development of aggressive leukemias and lymphomas [7, 61, 67]. Substitution of an amino acid in the DNA-binding ZF domain caused by a point mutation in one allele of the Ikaros gene leads to congenital pancytopenia. Such mutations result in profound B lymphopenia and decimated NK cells, however, the T cell number remains normal, which suggests that other Ikaros family members may compensate for the loss of Ikaros

itself [68]. In addition, Ikaros-dependent changes of lymphopoiesis can also be caused by its abolished expression. It has been revealed that human pituitary gland cells lacking Ikaros mRNA transcripts exhibit significant *IKZF1* promoter DNA hypermethylation [69].

Acute lymphoblastic leukemia

Total or partial deletions of *IKZF1* are very frequent in ALL. Mutations of this gene were found in 20–30% cases of childhood B-cell precursor ALL (BCP-ALL) and in about 50% of adult BCP-ALL and in over 80% of *BCR-ABL1*$^+$ lymphoid leukemia (including de novo ALL and CML transformation to ALL – lymphoid blast crisis), in 58% of *BCR-ABL1*-negative BCP-ALL cases and approximately in 5% of T-cell ALL [18, 62, 64, 70–72]. However, Ikaros deletions are not detected in the accelerated or chronic phase of CML [64]. The frequencies of the various types of *IKZF1* mutations in BCP-ALL was reported as follows: large deletions of chromosome 7 are present in 15% of cases, deletions of exons 2–7 in 15%, deletions of exons 4–7 in 30%, other deletions, including single exon deletions, appear in 30% of cases, and less frequent point mutations are present in 10% of cases [70]. In recent studies, all BCP-ALL cases with *IKZF1* mutations were subdivided into three functional categories characterized by: (1) monoallelic deletions leading to haploinsufficiency (~55% of all BCP-ALL cases), (2) 15–200 kb deletions restricted to the *IKZF1* gene leading to production of DN forms (Δ4–7 account for ~33% of all *IKZF1* mutations), and (3) an Ikaros null phenotype caused by biallelic deletions (~12% of all BCP-ALL cases) [35].

A high risk of childhood ALL development due to a single nucleotide polymorphism (SNP) in *IKZF1* (7p12.2 variant rs4132601) has been reported [73, 74]. Interestingly, another SNP, rs10272724 (T > C), near *IKZF1* (at 7p12.2) has been identified and is associated with a reduced risk of type 1 diabetes [75]. Therefore, it is hypothesized that these SNPs affect the mRNA level interrupting lymphocyte development and leading to reduced impaired immune response, resulting in diabetes-protective and leukemia-susceptible effects.

A strong correlation has been shown between *IKZF1* deletions and a poor outcome in human leukemias arising from the disruption of early B-cell development. For instance, Ikaros restricts the expression of hematopoietic stem cell-specific genes and negatively regulates cell proliferation. As a consequence, Ikaros appears to be a central regulator of the high-risk gene-expression signature [14, 61, 64, 71].

The susceptibility of leukemias to treatment depends on the nature of the mutated transcriptional regulator. A poor prognosis associated with the high-risk BCP-ALL results from two major genetic modifications. The first being overexpression of hematopoietic stem cell genes, giving rise to malignant clones that exhibit such stem cell-like features as self-renewal and drug resistance. The second being the down-regulation of genes responsible for lymphocyte development, which contributes to B-cell developmental arrest at the point of high proliferative potential and, hence, to increased susceptibility to malignant transformation [64, 71].

The presence of *BCR-ABL1* rearrangement is associated with a high risk of leukemia relapse. This type of mutation is found in only 5% of pediatric BCP-ALL and in approximately 40% of adult ALL. In the group of 43 patients with *BCR-ABL1* ALL the *IKZF1* gene deletions were detected in 76.2% of children and 90.9% of adults [64]. Lacobucci et al. examined a group of 106 de novo *BCR-ABL1*$^+$ adult ALL patients for oncogenic lesions that cooperate with *BCR-ABL1* to induce ALL. The most frequent, identified in 75% of patients, was a focal deletion on 7p12 of *IKZF1* gene. Furthermore, patients were examined for two major broad *IKZF1* deletions: exons 4–7 and exons 2–7. Among patients with any *IKZF1* deletion identified, the loss of exons 4–7 was found in 55%, whereas 24% of patients suffered from a lack of exons 2–7 [76]. In another study from 2012, a group of 144 adult B-ALL patients was analyzed for total or partial *IKZF1* deletions. In this cohort, 106 patients were *BCR-ABL1*$^+$ with the frequency of *IKZF1* deletions higher than in the rest of 38 patients negative for known molecular rearrangements (B-NEG patients). The frequencies of *IKZF1* deletions reached 75% and 58%, respectively [34]. In *BCR-ABL1*$^+$ ALL, 59–70% of all examined *IKZF1* mutations were severe Δ4–7 deletions or biallelic mutations [64, 70, 76]. In contrast, 57% of the *IKZF1* mutations in the high-risk BCP-ALL pediatric cases negative for *BCR-ABL1* demonstrated *IKZF1* haploinsufficiency [77]. Loss of Ikaros function due to its gene mutation causes B-lymphoid maturation arrest in *BCR-ABL1*$^+$ ALL by alteration of the earliest lymphoid lineage specification, especially the B-cell development. Moreover, frequent co-deletions of *PAX5* and *CDKN2A* were found together with *IKZF1* deletions in *BCR-ABL1*$^+$ ALL [64, 71]. Although *BCR-ABL1* translocation was considered to appear independently of Ikaros mutations, the Ikaros alterations directly contribute to the pathogenesis of *BCR-ABL1*$^+$ ALL resulting in an increased relapse rate and a greater number of adverse events [64, 71, 77–79]. Moreover, the *IKZF1* gene alterations occur in 40% of ALL with a *BCR-ABL1*-like phenotype and this subset is associated with a high risk of relapse [72]. Another study of *BCR-ABL1*-like ALL subtype showed a high rate of deletions in genes involved in B-cell development (including IKZF1, TCF3, EBF1, PAX5, and VPREB1) occurring in 82% of examined patients [80]. Somatic deletions and mutations of the *IKZF1* gene have also been identified in Philadelphia-like ALL, which is an ALL subtype with a gene expression profile similar to Philadelphia-positive ALL. It was recently found that in 73% of Philadelphia-like ALL cases, a *GATA3* variant (rs3824662) is present together with a *CRLF2* lesion, *JAK* mutation and *IKZF1* deletion [72, 81].

It has been previously reported that broad exon deletions resulting in DNs expression have been found to originate from gene alterations and non-aberrant post-transcriptional splicing induced by *BCR-ABL1*. Major DN Ik-forms of aberrant *IKZF1* expression are enumerated in Fig. 1. It has been suggested that deletion of exons 4–7 from *IKZF1* arises due to aberrant RAG-mediated recombination [64, 76]. This DN Ik-6 form has been identified in nearly a third of human T-cell acute leukemia cases [69]. Among others, the Ik-6 DN form is the most common product of *IKZF1* mutations (Table I). Overexpression of Ik-6 favors myelopoiesis by simultaneously altering the human globin switch and inhibiting erythroid differentiation [55]. In AML Ik-6 up-regulation enhances Bcl-XL activation in myeloid precursor cells [15]. A high Ik-6 level also causes

Table I – Review of the most common DN products of *IKZF* family genes mutations reported over last 14 years. Initially, researches were based on RT-PCR analysis and after 2007 large-scale comparative genomic hybridization (CGH) technology using high-density microarrays emerged
Tabela I – Przegląd najczęściej występujących form białek dominujących negatywnych powstałych w wyniku mutacji genu IKZF1, opisanych w przeciągu ostatnich 15 lat. Początkowe badania opierały się na technice RT-PCR, a po 2007 roku stosowana była technologia porównawczej hybrydyzacji genomowej z użyciem mikromacierzy o wysokiej gęstości

Publication	Year	Type of disorder	Detected DN Ik-forms	Subgroup with detected spliceforms (%)	Researched group (detected/all)
Sun et al. [11]	1999	ALL	Ik-4, Ik-7, Ik-8	100	7/7 infants
Sun [63]	1999	T-ALL	Ik-4 or Ik-4Δ	80	8/10 infants
			Ik-7 or Ik-7Δ	0	0/10
			Ik-8Δ	60	6/10
		BCP-ALL	Ik-4 or Ik-4Δ	45	5/11 infants
			Ik-7 or Ik-7Δ	18	2/11
			Ik-8Δ	27	3/11
Iacobucci et al. [85]	2000	BCR-ABL1$^+$ ALL	Ik-6	49	23/47 adults
Yagi et al. [15]	2002	AML	Ik-6	29.2	7/24 pediatrics
Ezzat et al. [8]	2003	Pituitary adenomas	Ik-6	36	18/50
			Ik cytoplasmic localization	56	28/50
Mullighan [64]	2008	BCR-ABL1$^+$ ALL	Ik-6, Ik-9, Ik-10	76.2	16/21 pediatrics
				90.9	20/22 adults
Iacobucci et al. [86]	2008	BCR-ABL1$^+$ ALL	Ik-6	41	19/46 adults
Martinelli [79]	2009	BCR-ABL1$^+$ ALL	Ik-6	37	31/83 (all patients)
				59	31/52 (*IKZF1* deleted patients)
			Ik-10	20	17/83 (all patients)
				33	17/52 (*IKZF1* deleted patients)
Mi et al. [87]	2012	BCP-ALL	Ik-6	14.7	56/379 pediatrics
				31.3	64/203 adults

up-regulation of the antiapoptotic signal in 40% of pituitary tumors by Bcl-XL promoter selective acetylation, whereas Ik-1 attenuates Bcl-XL promoter activity [82].

In 2012, an analysis of 422 genes in both B-NEG and *BCR-ABL1*$^+$ adult B-ALL patients revealed that the coexistence of *IKZF1* deletions contributed to up-regulation of 294 genes and down-regulation of 128 genes. The group of up-regulated genes included genes responsible for cell-cycle progression, JAK-STAT signaling, stem cell self-renewal, apoptosis regulation, as well as the production of early primed erythroid factor KLF9 and the late myeloid gene *ID2* [34]. A recent genome-wide analysis revealed that 50% of all genes up-regulated during B-cell lineage specification in vivo are Ikaros targets [83]. The group of down-regulated genes included genes responsible for DNA repair processes (*MSH2*, *MSH6*, *UBE2V2*), the B-cell differentiation pathway (*EBF1*, *BLK*, *BTK*, *IGLL1*, *CD22*, *PLCG2*, *MAP3K1*, *VPREB1*), apoptosis and cell cycle progression, as well as *RAG* gene. Accumulation of DNA damage was confirmed by markedly increased basal phosphorylation of histone H2A.X [34].

Chronic myeloid leukemia

The expression of tyrosine kinase that is constitutively activated due to *BCR-ABL1* translocation underlies chronic myeloid leukemia (CML). This defect can alone induce a CML-like myeloproliferative disease, however, the generation of blastic leukemia requires additional oncogenic lesions. Although CML responds well to therapy in the chronic phase, it acquires resistance to treatment after progressing to blast crisis. Cooperating cytogenetic aberrations and tumor suppressor gene mutations occur in CML progressing to blast crisis. The most frequent events in the transformation of CML to lymphoid blast crisis are *IKZF1* diverse mutations (66%), such as deletions of exons 4–7, 2–7, or even the entire gene [64, 76]. Also the *IKZF1* nonsense mutation has been identified in the C-terminal zinc-finger domain of exon 7 in the non-deleted allele, together with *CDKN2A* deletion and *PAX5* copy number alterations [64].

It is important to note that *IKZF1* deletions are present only in lymphoblast crisis and have not been detected in myeloid blast crisis or the chronic phase of CML. An analysis of 42 newly diagnosed CML Ik-6 positive patients in lymphoblast crisis showed complete remission in only 40%, with a 66.7% rate of relapse after 2–18 months. No expression of Ik-6 was found in healthy controls, nor in chronic or accelerated phase of CML, nor in patients with myeloblast crisis [76, 84].

Myeloproliferative neoplasm and acute myeloid leukemia

The most serious consequence of myeloproliferative neoplasm (MPN) is its transformation to AML. The *JAK2-V617F* gene gain-of-function mutation occurs in more than half of

all MPN patients, however, no significant association exists with post-MPN leukemic transformation, as both *JAK2-V617F*-dependent and *JAK2-V617F*-independent pathways of transformation have been observed. Moreover, a strong association was observed between del7p and leukemic transformation, where the common deleted region contained only the *IKZF1* gene. Six of seven examined patients with del7p progressed to AML whereas only one showed features of advanced phase of primary myelofibrosis with pancytopenia and increased blasts in the peripheral blood. Deletions on the short arm of chromosome 7 (del7p) involve such clinical symptoms as anemia, thrombocytopenia and increased percentage of blasts in the peripheral blood. Ikaros gene alterations do not induce differentiation arrest of myeloid cell types. *IKZF1* deletions, but not point mutations, are acquired late in the disease progression and are strongly associated with *JAK2-V617F* mutation. *IKZF1* haploinsufficiency (including monosomy 7) occurred in 21% of post-MPN leukemia and 0.2% of nonleukemic MPN patients. The *IKZF1* gene haploinsufficiency was found to induce elevated Stat5 phosphorylation and increase cytokine-dependent growth. Monosomy 7 is known to occur in approximately 10% of adult and 5% of childhood AML cases [65]. Another study of childhood AML revealed that 7 of 10 cases of myelomonocytic or monocytic leukemias expressed Ik6. It is likely that Ik-6 plays an exclusive role in monocyte/macrophage differentiation, as it up-regulates the antiapoptotic protein Bcl-XL, which is involved in the differentiation and survival of monocytes/macrophages [15].

Summary

Ikaros is a multifunctional zinc finger DNA-binding transcription factor encoded by the *IKZF1* gene which is required for the earliest specification of the lymphoid lineage during hematopoiesis. The Ikaros protein and the transcripts of four other genes comprise the basic forms of Ikaros family proteins. In addition, numerous variations of the Ikaros family genes transcripts may occur including defective forms of proteins being involved in a range of hematological disorders such as leukemias. The *IKZF1* gene is subject to such aberrations as point mutations and biallelic deletions, the most common haploinsufficiency, as well as broad deletions of exons 2–7, and 4–7. The last of these mutations causes production of dominant negative Ik-forms, which lack the core of the DNA-binding domain. Overexpression of these dominant negative Ik-forms is detected in about a half of adult BCP-ALL and in most of *BCR-ABL1*$^+$ALL, *BCR-ABL1*-like ALL and *BCR-ABL1*-negative BCP-ALL cases. Dominant negative Ik-forms not only inhibit the functional Ik-forms, but also prevent the basic Ikaros forms from occupying a close proximity to PC-HC and their target genes. However, *IKZF1* mutations can arise as secondary mutations during disease progression, as in CML transformation to *BCR-ABL1*$^+$ ALL, or MPN transformation to AML. Dominant negative Ik-forms occur in CML blast crisis and remain after transformation to *BCR-ABL1*$^+$ ALL. Ikaros deletions are also acquired as a late event in the clonal evolution of myeloid progenitors, and the leukemogenic potential of these mutations is presumably induced via JAK-STAT signaling pathway. Moreover, JAK mutations, particularly JAK2 mutations, are known to be significantly associated with *IKZF1* defects in childhood ALL. The 7p12.2 variation of *IKZF1* increases the risk of childhood ALL, whereas the *BCR-ABL1*-like signature and/or *IKZF1* deletions are associated with high risk of relapse among BCP-ALL patients. The broad research of the Ikaros transcription factor identified this protein as a central regulator of numerous hematopoietic processes and determined Ikaros as a potential therapeutic target of aggressive leukemia treatment.

Authors' contributions/Wkład autorów

Study design was done by AG and AW. AG contributed in data collection and interpretation, manuscript preparation, and literature search.

Conflict of interest/Konflikt interesu

None declared.

Financial support/Finansowanie

There has been no financial support for the conduct of the research and/or preparation of the article.

Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

REFERENCES/PIŚMIENNICTWO

[1] Georgopoulos K, Moore DD, Derfler B. Ikaros, an early lymphoid-specific transcription factor and a putative mediator for T cell commitment. Science 1992;258 (5083):808–812.
[2] O'neill D, Bornschlegel K, Flamm M, Castle M, Bank A. A DNA-binding factor in adult hematopoietic cells interacts with a pyrimidine-rich domain upstream from the human δ-globin gene. Proc Natl Acad Sci U S A 1991;88(20): 8953–8957.
[3] Molnár A, Wu P, Largespada DA, et al. The Ikaros gene encodes a family of lymphocyte-restricted zinc finger DNA binding proteins, highly conserved in human and mouse. J Immunol 1996;156(2):585–592.
[4] Rebollo A, Schmitt C. Ikaros, Aiolos and Helios: transcription regulators and lymphoid malignancies. Immunol Cell Biol 2003;81(3):171–175.
[5] Molnar A, Georgopoulos K. The Ikaros gene encodes a family of functionally diverse zinc finger DNA-binding proteins. Mol Cell Biol 1994;14(12):8292–8303.

[6] Francis OL, Payne JL, Su R, Payne KJ. Regulator of myeloid differentiation and function: the secret life of Ikaros. World J Biol Chem 2011;2(6):19–125.
[7] Sun L, Liu A, Georgopoulos K. Zinc finger-mediated protein interactions modulate Ikaros activity, a molecular control of lymphocyte development. EMBO J 1996;15 (19):5358–5369.
[8] Ezzat S, Yu S, Asa SL. Ikaros isoforms in human pituitary tumors – distinct localization, histone acetylation, and activation of the 5′ fibroblast growth factor receptor-4 promoter. Am J Pathol 2003;163(3):1177–1184.
[9] Payne KJ, Huang G, Sahakian E, et al. Ikaros isoform x is selectively expressed in myeloid differentiation. J Immunol 2003;170(6):3091–3098.
[10] Li Z, Perez-Casellas LA, Savic A, Song C, Dovat S. Ikaros isoforms: the saga continues. World J Biol Chem 2011;2 (6):40–145.
[11] Sun L, Heerema N, Crotty L, et al. Expression of dominant-negative and mutant isoforms of the antileukemic transcription factor Ikaros in infant acute lymphoblastic leukemia. Proc Natl Acad Sci U S A 1999;96(2):680–685.
[12] Payne KJ, Dovat S. Ikaros and tumor suppression in acute lymphoblastic leukemia. Crit Rev Oncog 2011;16(1–2):3–12.
[13] Sellars McL, Kastner P, Chan S. Ikaros in B cell development and function. World J Biol Chem 2011;2(6):32–139.
[14] Winandy S, Wu L, Wang J, Georgopoulos K. Pre-T cell receptor (Tcr) and Tcr-controlled checkpoints in T cell differentiation are set by Ikaros. The Rockefeller University Press. J Exp Med 1999;190(8):1039–1048.
[15] Yagi T, Hibi S, Takanashi M, et al. High frequency of Ikaros isoform 6 expression in acute myelomonocytic and monocytic leukemias: implications for up-regulation of the antiapoptotic protein Bcl-XL in leukemogenesis. Blood 2002;99(4):1350–1355.
[16] Sellars McL, Reina-San-Martin B, Kastner P, Chan S. Ikaros controls isotype selection during immunoglobulin class switch recombination. The Rockefeller University Press. J Exp Med 2009;206(5):1073–1087.
[17] Papathanasiou P, Attema JL, Karsunky H, et al. Self-renewal of the long-term reconstituting subset of hematopoietic stem cells is regulated by Ikaros. Stem Cells 2009;27 (12):3082–3092.
[18] Song C, Li Z, Erbe AK, et al. Regulation of Ikaros function by casein kinase 2 and protein phosphatase 1. World J Biol Chem 2011;2(6):26–131.
[19] Kathrein KL, Lorenz R, Innes AM, Griffiths E, Winandy S. Ikaros induces quiescence and T-cell differentiation in a leukemia cell line. Mol Cell Biol 2005;25 (5):1645–1654.
[20] He LC, Xu HZ, Gu ZM, et al. Ikaros is degraded by proteasome-dependent mechanism in the early phase of apoptosis induction. Biochem Biophys Res Commun 2011;406(3):430–434.
[21] Hahm K, Cobb BS, McCarty AS, et al. Helios, a T cell-restricted Ikaros family member that quantitatively associates with Ikaros at centromeric heterochromatin. Genes Dev 1998;12(6):782–796.
[22] Kelley CM, Ikeda T, Koipally J, et al. Helios, a novel dimerization partner of Ikaros expressed in the earliest hematopoietic progenitors. Curr Biol 1998;8(9): 508–515.
[23] Morgan B, Sun L, Avitahl N, et al. Aiolos, a lymphoid restricted transcription factor that interacts with Ikaros to regulate lymphocyte differentiation. EMBO J 1997;16 (8):2004–2013.
[24] Wang J, Avitahl N, Cariappa A, et al. Aiolos regulates B cell activation and maturation to effector state. Immunity 1998;9(4):543–553.
[25] Avitahl N, Winandy S, Friedrich C, et al. Ikaros sets thresholds for T cell activation and regulates chromosome propagation. Immunity 1999;10(3):333–343.
[26] Ronni T, Payne KJ, Ho S, et al. Human Ikaros function in activated T cells is regulated by coordinated expression of its largest isoforms. J Biol Chem 2007;282(4):2538–2547.
[27] Agoston DV, Szemes M, Dobi A, et al. Ikaros is expressed in developing striatal neurons and involved in enkephalinergic differentiation. J Neurochem 2007;102 (6):1805–1816.
[28] Martín-Ibáñez R, Crespo E, Urbán N, et al. Ikaros-1 couples cell cycle arrest of late striatal precursors with neurogenesis of enkephalinergic neurons. J Comp Neurol 2010;518(3):329–351.
[29] Alsiöa JM, Tarchinib B, Cayouetteb M, Liveseya FJ. Ikaros promotes early-born neuronal fates in the cerebral cortex. PNAS 2013;110(8):E716–E725.
[30] Elliott J, Jolicoeur C, Ramamurthy V, et al. Ikaros confers early temporal competence to mouse retinal progenitor cells. Neuron 2008;60(1):26–39.
[31] Cobb BS, Morales-Alcelay S, Kleiger G, et al. Targeting of Ikaros to pericentromeric heterochromatin by direct DNA binding. Genes Dev 2000;14(17):2146–2160.
[32] Payne MA. Zinc finger structure-function in Ikaros. World J Biol Chem 2011;2(6):61–166.
[33] Hahm K, Ernst P, Lo K, et al. The lymphoid transcription factor LyF-1 is encoded by specific, alternatively spliced mRNAs derived from the Ikaros gene. Mol Cell Biol 1994;14 (11):7111–7123.
[34] Iacobucci I, Iraci N, Messina M, et al. IKAROS deletions dictate a unique gene expression signature in patients with adult B-cell acute lymphoblastic leukemia. PLoS ONE 2012;7 (7):e40934.
[35] Kastner P, Dupuis A, Gaub MP, et al. Function of Ikaros as a tumor suppressor in B cell acute lymphoblastic leukemia. Am J Blood Res 2013;3(1):1–13.
[36] Yap W, Yeoh E, Tay A, et al. STAT4 is a target of the hematopoietic zinc-finger transcription factor Ikaros in T cells. FEBS Lett 2005;579(20):4470–4478.
[37] Koipally J, Renold A, Kim J, et al. Repression by Ikaros and Aiolos is mediated through histone deacetylase complexes. EMBO J 1999;18(11):3090–3100.
[38] Brown KE, Guest SS, Smale ST, et al. Association of transcriptionally silent genes with Ikaros complexes at centromeric heterochromatin. Cell 1997;91(6):845–854.
[39] Nan X, Ng HH, Johnson CA, et al. Transcriptional repression by the methyl-CpG-binding protein MeCP2 involves a histone deacetylase complex. Nature 1998;393(6683): 386–389.
[40] Koipally J, Heller EJ, Seavitt JR, et al. Unconventional potentiation of gene expression by Ikaros. J Biol Chem 2002;277(15):13007–13015.
[41] Harker N, Naito T, Cortes M, et al. The CD8 Gene locus is regulated by the Ikaros family of proteins. Mol Cell 2002;10 (6):1403–1415.
[42] Sabbattini P, Lundgren M, Georgiou A, et al. Binding of Ikaros to the lambda5 promoter silences transcription through a mechanism that does not require heterochromatin formation. EMBO J 2001;20(11): 2812–2822.
[43] Koipally J, Georgopoulos K. Ikaros interactions with CtBP reveal a repression mechanism that is independent of histone deacetylase activity. J Biol Chem 2000;275 (26):19594–19602.
[44] Ng SY, Yoshida T, Zhang J, et al. Genome-wide lineage-specific transcriptional networks underscore Ikaros-dependent lymphoid priming in hematopoietic stem cells. Immunity 2009;30(4):493–507.

[45] Yoshida T, Ng SY, Zuniga-Pflucker JC, et al. Early hematopoietic lineage restrictions directed by Ikaros. Nat Immunol 2006;7(4):382–391.
[46] Yoshida T, Ng SY, Georgopoulos K. Awakening lineage potential by Ikaros-mediated transcriptional priming. Immunology 2010;22(2):154–160.
[47] Georgopoulos K. Haematopoietic cell-fate decisions, chromatin regulation and Ikaros. Immunology 2002;2 (3):162–174.
[48] Umetsu SE, Winandy S. Ikaros is a regulator of il10 expression in CD4+ T cells. J Immunol 2009;183(9): 5518–5525.
[49] Quirion MR, Gregory GD, Umetsu SE, et al. Cutting edge: Ikaros is a regulator of Th2 cell differentiation. J Immunol 2009;182(2):741–745.
[50] Gómez-del Arco P, Maki K, Georgopoulos K. Phosphorylation controls Ikaros's ability to negatively regulate the G1-S transition. Mol Cell Biol 2004;24(7): 2797–2807.
[51] Popescu M, Gurel Z, Ronni T, et al. Ikaros stability and pericentromeric localization are regulated by protein phosphatase 1. J Biol Chem 2009;284(20):13869–13880.
[52] Gurel Z, Ronni T, Ho S, et al. Recruitment of Ikaros to pericentromeric heterochromatin is regulated by phosphorylation. J Biol Chem 2008;283(13):8291–8300.
[53] Winandy S. Ikaros to the rescue of TCR-α chain gene rearrangement. Eur J Immunol 2013;43(2):314–317.
[54] Collins B, Clambey ET, Scott-Browne J, et al. Ikaros promotes rearrangement of TCR α genes in an Ikaros null thymoma cell line. Eur J Immunol 2013;43(2):521–532.
[55] Dijon M, Bardin F, Murati A, et al. The role of Ikaros in human erythroid differentiation. Blood 2008;111(3): 1138–1146.
[56] Bottardi S, Ross J, Bourgoin V, et al. Ikaros and GATA-1 combinatorial effect is required for silencing of human γ-globin genes. Mol Cell Biol 2009;29(6):1526–1537.
[57] O'neill DW, Schoetz SS, Lopez RA, et al. An Ikaros-containing chromatin-remodeling complex in adult-type erythroid cells. Mol Cell Biol 2000;20(20):7572–7582.
[58] Lopez RA, Schoetz S, DeAngelis K, O'Neill D, Bank A. Multiple hematopoietic defects and delayed globin switching in Ikaros null mice. PNAS 2002;99(2):602–607.
[59] O'neill D, Yang J, Erdjument-Bromage H, et al. Tissue-specific and developmental stage-specific binding of a SWI/SNF complex associated with human fetal to adult globin. Proc Natl Acad Sci U S A 1999;96(2):349–354.
[60] Keys JR, Tallack MR, Zhan Y, et al. A mechanism for Ikaros regulation of human globin gene switching. Br J Haematol 2008;141(3):398–406.
[61] 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):289–299.
[62] Mullighan CG. The molecular genetic makeup of acute lymphoblastic leukemia. Hematology 2012;2012: 389–396.
[63] Sun L, Goodman PA, Wood CM, et al. Expression of aberrantly spliced oncogenic Ikaros isoforms in childhood acute lymphoblastic leukemia. J Clin Oncol 1999;17 (12):3753–3766.
[64] Mullighan CG. BCR-ABL1 lymphoblastic leukaemia is characterized by the deletion of Ikaros. Nature 2008;453 (7191):110–114.
[65] Jäger R, Gisslinger H, Passamonti F, et al. Deletions of the transcription factor Ikaros in myeloproliferative neoplasms. Leukemia 2010;24(7):1290–1298.
[66] Tefferi A. Novel mutations and their functional and clinical relevance in myeloproliferative neoplasms: JAK2, MPL, TET2, ASXL1, CBL, IDH and IKZF1. Leukemia 2010;24 (6):1128–1138.
[67] Papathanasiou P, Perkins AC, Cobb BS, et al. Widespread failure of hematolymphoid differentiation caused by a recessive niche-filling allele of the Ikaros transcription factor. Immunity 2003;19(1):131–144.
[68] Goldman FD, Gurel Z, Al-Zubeidi D, et al. Congenital pancytopenia and absence of B lymphocytes in a neonate with a mutation in the Ikaros gene. Pediatr Blood Cancer 2012;58(4):591–597.
[69] Zhu X, Asa SL, Ezzat S. Ikaros is regulated through multiple histone modifications and deoxyribonucleic acid methylation in the pituitary. Mol Endocrinol 2007;21 (5):1205–1215.
[70] Dupuis A, Gaub MP, Legrain M, et al. Biclonal and biallelic deletions occur in 20% of B-ALL cases with IKZF1 mutations. Leukemia 2013;27(2):503–507.
[71] Georgopoulos K. Acute lymphoblastic leukemia – on the wings of IKAROS. N Engl J Med 2009;360(5):524–526.
[72] Veer A, Waanders E, Pieters R, et al. Independent prognostic value of BCR-ABL1-like signature and IKZF1 deletion, but not high CRLF2 expression, in children with B-cell precursor ALL. Blood 2013;122(15):2622–2629.
[73] Pastorczak A, Górniak P, Sherborne A, et al. Role of 657del5 NBN mutation and 7p12.2 (IKZF1), 9p21 (CDKN2A), 10q21.2 (ARID5B) and 14q11.2 (CEBPE) variation and risk of childhood ALL in the Polish population. Leuk Res 2011;35 (11):1534–1536.
[74] Papaemmanuil E, Hosking FJ, Vijayakrishnan J, et al. Loci on 7p12.2, 10q21.2 and 14q11.2 are associated with risk of childhood acute lymphoblastic leukemia. Nat Genet 2009;41 (9):1006–1010.
[75] Swafford AD, Howson JM, Davison LJ, et al. An allele of IKZF1 (Ikaros) conferring susceptibility to childhood acute lymphoblastic leukemia protects against type 1 diabetes. Diabetes 2011;60(3):1041–1044.
[76] Iacobucci I, Storlazzi CT, Cilloni D, 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. Blood 2009;114(10):2159–2167.
[77] Mullighan CG, Su X, Zhang J, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. N Engl J Med 2009;360(5):470–480.
[78] Kuiper RP, Waanders E, van der Velden VH, et al. IKZF1 deletions predict relapse in uniformly treated pediatric precursor B-ALL. Leukemia 2010;24(7):1258–1264.
[79] Martinelli G, Iacobucci I, Storlazzi CT, et al. IKZF1 (Ikaros) deletions in BCR-ABL1-positive acute lymphoblastic leukemia are associated with short disease-free survival and high rate of cumulative incidence of relapse: a GIMEMA AL WP report. J Clin Oncol 2009;27(31):5202–5207.
[80] Den Boer ML, van Slegtenhorst M, De Menezes RX, et al. A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study. Lancet Oncol 2009;10(2):125–134.
[81] Perez-Andreu V, Roberts KG, Harvey RC, et al. Inherited GATA3 variants are associated with Ph-like childhood acute lymphoblastic leukemia and risk of relapse. Nat Genet 2013;45(12):1494–1498.
[82] Ezzat S, Zhu X, Loeper S, Fischer S, Asa SL. Tumor derived Ikaros 6 acetylates the Bcl-XL promoter to upregulate a survival signal in pituitary cells. Mol Endocrinol 2006;20 (11):2976–2986.
[83] Ferreirós-Vidal I, Carroll T, Taylor B, et al. Genome-wide identification of Ikaros targets elucidates its contribution to mouse B-cell lineage specification and pre-B-cell differentiation. Blood 2013;121(10):1769–1782.
[84] Xiao M, Wu Y, Yang Y, et al. Analysis of Ikaros 6 expression in 73 patients with chronic myelogenous leukemia. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2011;19(4):907–910.

[85] Iacobucci I, Lonetti A, Messa F, et al. Expression of spliced oncogenic Ikaros isoforms in Philadelphia-positive acute lymphoblastic leukemia patients treated with tyrosine kinase inhibitors – implications for a new mechanism of resistance. Blood 2008;112(9):3847–3855.
[86] Iacobucci I, Lonetti A, Cilloni D, et al. Identification of different Ikaros cDNA transcripts in Philadelphia-positive adult acute lymphoblastic leukemia by a high-throughput capillary electrophoresis sizing method. Haematologica 2008;93(12):1814–1821.
[87] Mi JQ, Wang X, Yao Y, et al. Newly diagnosed acute lymphoblastic leukemia in China (II) – prognosis related to genetic abnormalities in a series of 1091 cases. Leukemia 2012;26(7):1507–1516.