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Cellular signaling and epigenetic regulation of gene expression in leukemia

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Abstract

Alterations in normal regulation of gene expression is one of the key features of hematopoietic malignancies. In order to gain insight into the mechanisms that regulate gene expression in these diseases, we dissected the role of the Ikaros protein in leukemia. Ikaros is a DNA-binding, zinc finger protein that functions as a transcriptional regulator and a tumor suppressor in leukemia. The use of ChIP-seq, RNA-seq, and ATAC-seq—coupled with functional experiments—revealed that Ikaros regulates both the global epigenomic landscape and epigenetic signature at promoter regions of its target genes. Casein kinase II (CK2), an oncogenic kinase that is overexpressed in leukemia, directly phosphorylates Ikaros at multiple, evolutionarily-conserved residues. Phosphorylation of Ikaros impairs the protein's ability to regulate both the transcription of its target genes and global epigenetic landscape in leukemia. Treatment of leukemia cells with a specific inhibitor of CK2 restores Ikaros function, resulting in cytotoxicity of leukemia cells. Here, we review the mechanisms through which the CK2-Ikaros signaling axis regulates the global epigenomic landscape and expression of genes that control cellular proliferation in leukemia.

Keywords

Ikaros; Tumor suppressor; Casein kinase II (CK2) inhibitor CX-4945; Leukemia; Epigenetic regulation; Gene transcription

1. Introduction

Complex regulatory mechanisms orchestrate development, lineage commitment, and differentiation of hematopoietic cells. Transcription factors play a very important role in regulating expression of genes involved in hematopoiesis. Dysregulation of gene expression is a hallmark of cancer, including leukemia. Recent advances have identified the role of chromatin remodeling and epigenetics as the key mechanisms that regulate gene expression in leukemia. Here, we discuss the role of the Ikaros transcription factor (Georgopoulos et

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al., 1992, 1994; Lo et al., 1991) in regulating gene expression and as a tumor suppressor in acute lymphoblastic leukemia. Ikaros exerts its regulatory effect on gene expression via chromatin remodeling (Brown et al., 1997; Cobb et al., 2000; Ge et al., 2015, 2016a, 2016b, 2016c, 2017, 2018a, 2018b; Kim et al., 1999, 2009; Sridharan and Smale, 2007; Su et al., 2005). Moreover, global influence on the epigenomic landscape in T-cell leukemia underscores the role of Ikaros as a tumor suppressor (Ding et al., 2019). Recently published studies have uncovered several novel functions of Ikaros as an epigenetic regulator using dynamic, global, epigenomic, and gene expression analyses (Ding et al., 2019). Ikaros activity as a regulator of chromatin remodeling and gene expression is controlled via direct phosphorylation at multiple serine/threonine residues (Dovat et al., 2002, 2011; Ge et al., 2015, 2016a, 2016c, 2017, 2018a; Gowda et al., 2016, 2017a, 2017b, 2017c; Gurel et al., 2008; Payne and Dovat, 2011; Song et al., 2011; Uckun et al., 2012; Wang et al., 2014a). Functional inactivation of Ikaros by pro-oncogenic protein Casein Kinase II (CK2) via phosphorylation, has been demonstrated in B-cell acute lymphoblastic leukemia (Han et al., 2019; Popescu et al., 2009; Song et al., 2011; Wang et al., 2014b, 2016). Inhibition of CK2 using specific inhibitors results in an anti-leukemic effect via restoration of Ikaros' functions as a tumor suppressor and regulator of gene expression (Song et al., 2015). In this article, we will focus on the various roles of Ikaros as an epigenetic regulator, specifically in acute lymphoblastic leukemia. We will demonstrate that the Ikaros transcription factor can be indirectly targeted, in order to restore its function, by inhibition of CK2. We will also discuss several important oncogenic signaling pathways regulated by Ikaros. Finally, we will demonstrate Ikaros’ influence in regulating several genes known as global epigenetic regulators in leukemia, such as KBM5B.

2. Ikaros structure and function

Ikaros is a DNA-binding, zinc finger protein encoded by the IKZF1 gene that is located on chromosome 7 (Georgopoulos et al., 1992, 1994; Lo et al., 1991). Alternate splicing of IKZF1 produces a large number of Ikaros isoforms that are functionally diverse (Hahm et al., 1994; Molnár and Georgopoulos, 1994). Isoform Ik-H or Ik1 is the largest with six zinc finger domains, two in the C-terminal end and four in the N-terminal end (Kim et al., 2009; Ronni et al., 2007). Several combinations of zinc fingers in the N-terminus are seen in the various Ikaros isoforms (Li et al., 2011; Molnár et al., 1996; Sun et al., 1996). Dimerization among several isoforms either potentiates or inhibits Ikaros’ DNA binding affinity, which affects the overall transcriptional activity of Ikaros (Fig. 1) (McCarty et al., 2003; Molnár et al., 1996; Sun et al., 1996).

Ikaros is a transcription factor with a critical role in hematopoiesis and development of the immune system (Cobb and Smale, 2005; Georgopoulos, 1997; Georgopoulos et al., 1994, 1997; Papathanasiou et al., 2003; Wang et al., 1996; Winandy et al., 1995). Since its discovery in the early 90's, Ikaros' role as a master regulator of lymphoid development and tumor suppression in leukemia has been extensively studied. The biological function of Ikaros was studied in several Ikaros knockout mice (Nichogiannopoulou et al., 1999; Wang et al., 1996; Wu et al., 1997). Important regulatory functions of Ikaros in hematopoiesis are as follows: First, a pivotal function in early hematopoietic cells called lymphoid-primed multipotent progenitors (LMPPs) where Ikaros regulation of the FLT3-tyrosine kinase

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receptor and upregulation of the interleukin-7 alpha subunit (IL-7α) promote lymphoid differentiation signals (Busslinger, 2004; Yoshida et al., 2006). Second, Ikaros plays a very important role in B-cell differentiation by regulating pre-B cell receptor component Lambda 5—encoded by gene IGLL1—as well as recombinase activating genes (RAGs) (Reynaud et al., 2008). Third, Ikaros regulates expression of several important genes involved in T-cell differentiation, including terminal deoxynucleotide transferase (TdT), CD4, CD8, and IL2 (Avitahl et al., 1999; Ernst et al., 1996; Georgopoulos et al., 1997; Hahm et al., 1994; Harker et al., 2002; Kirstetter et al., 2002; Trinh et al., 2001; Urban and Winandy, 2004). Mice heterozygous for an inactivating *Ikaros* mutation develop T-cells that are hyper-proliferative and develop T-cell leukemia with 100% penetrance (Winandy et al., 1995).

3. Clinical significance of IKZF1 alteration

Genome-wide analysis of genetic alterations in acute lymphoblastic leukemia (ALL) has shown that deletion and mutation of IKZF1 is seen in nearly 15% of pediatric B-cell acute lymphoblastic leukemia (B-ALL) and in more than 80% of BCR-ABL positive (Ph +) ALL (Mullighan and Downing, 2008; Mullighan et al., 2007, 2008). ALL with IKZF1 alteration is associated with high risk features, high relapse rate, and poor outcome (Mullighan et al., 2009a). In T-cell acute lymphoblastic leukemia (T-ALL), IKZF1 alteration is seen in nearly 20% of patients and a specific subgroup—early T-cell precursor (ETP) leukemia—has worse outcome and harbors Ikaros mutations in 11% of patients (Zhang et al., 2012). IKZF1 deletions are also common in cases with CRLF2 genomic alterations and in Ph-like (BCR-ABL1-like) ALL (Harvey et al., 2010; Mullighan et al., 2009b). Several clinical trials are currently looking at risk stratifying B-ALL patients with IKZF1 alteration as high-risk and intensifying therapy (Chen et al., 2012; Hunger et al., 2011; Mullighan, 2011a, b; Roberts and Mullighan, 2011). Ikaros deletion and mutation is seen in 5–7% of acute myeloid leukemia (AML) and myeloid dysplastic syndrome (MDS) (Crescenzi et al., 2004; de Rooij et al., 2015; Lavallee et al., 2015; Yagi et al., 2002). Germline deletion and/or mutation of the IKZF1 gene has been associated with development of leukemia (Churchman et al., 2018; Yoshida et al., 2017).

Ikaros' role in regulating the immune response in humans has been demonstrated in several studies. Point mutations at Ikaros' DNA-binding domain results in severe combined immunodeficiency (SCID) (Goldman et al., 2012). Subsequently, different mutations in the IKZF1 gene were associated with various immunodeficiencies in human (Abdulhay et al., 2016; Berron-Ruiz, 2017; Bigley et al., 2019; Bogaert et al., 2016; Boutboul et al., 2018; Chen et al., 2018; Churchman et al., 2018; Cytlak et al., 2018; Davis et al., 2019; Eskandarian et al., 2019; Hoshino et al., 2017; Kanegane and Hoshino, 2019; Kuehn et al., 2016; Maffucci et al., 2016; Sriaroon et al., 2019). Thus, it has been recognized that germline mutations of Ikaros can cause primary immunodeficiency in humans.

4. The CK2-Ikaros axis

Multiple signaling pathways involving protein phosphorylation by various kinases regulate cellular proliferation and drug sensitivity in human malignancies (Candido et al., 2018; Choi et al., 2018; Drulis-Fajdasz et al., 2018; Geffken and Spiegel, 2018; Jang et al.,

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2018; Kaushansky and Zhan, 2018; Lee et al., 2018; Pyne et al., 2018; Ramos et al., 2018; Rebello et al., 2018; Saiardi et al., 2018; Sakane et al., 2018; Scarlata et al., 2018). Casein Kinase II (CK2) is a pro-oncogenic kinase that is overexpressed in several cancers, including leukemia. CK2 is a ubiquitous, serine/threonine kinase that is involved in multiple signaling pathways and has over 300 substrates (Ahmad et al., 2005; Gowda et al., 2017a, 2017b; Pinna, 1997; Pinna and Meggio, 1997). CK2 phosphorylates Ikaros at multiple evolutionarily-conserved serine/threonine amino acids (Fig. 1), which impairs Ikaros' ability to bind DNA and localize to peri-centromeric heterochromatin (Gurel et al., 2008; Popescu et al., 2009; Wang et al., 2014b). A fine balance of CK2- and protein phosphatase 1 (PP1)-mediated post-translational modification of Ikaros determines Ikaros' stability and activity (Dovat et al., 2011; Gowda et al., 2017a, 2017c; Popescu et al., 2009; Song et al., 2011; Wang et al., 2014b). In leukemia, as well as other malignancies, the expression and activity of CK2 is increased, which results in functional inactivation of Ikaros and loss of its tumor suppressor function (Barata, 2011; Buontempo et al., 2014; Gomes et al., 2014; Martins et al., 2010, 2011; Silva et al., 2008, 2010). Molecular and pharmacological inhibition of CK2 enhances Ikaros' tumor suppressive function as seen by restored transcriptional regulation of Ikaros target genes (Ge et al., 2015, 2016a, 2016c, 2017, 2018a; Han et al., 2019; Song et al., 2015; Wang et al., 2016). In high risk B-ALL patient derived xenograft (PDX) models, inhibition of CK2 using CX-4945—a small-molecule, ATP-competitive specific inhibitor—results in a strong in vivo anti-leukemic effect that is a result of restored Ikaros function (Song et al., 2015) (Fig. 2). CK2 inhibition was able to restore Ikaros function in vivo even in cases of high-risk B-ALL with a single copy of Ikaros (IKZF1 deletion) (Song et al., 2015). These results led to discovery of the CK2-Ikaros signaling axis where direct phosphorylation of Ikaros by CK2, and a strong relation between CK2 expression and/or activity and Ikaros function, regulates gene expression and tumor suppression in leukemia and hematopoietic cells (Gowda et al., 2016, 2017a, 2017b, 2017c).

5. Epigenetic regulation of gene expression by Ikaros, HDAC1, and Casein Kinase II in leukemia

The mechanism of Ikaros-mediated transcriptional regulation in leukemia is still not well understood. Ikaros directly associates with components of the histone deacetylase complex (NuRD), HDAC1, HDAC2, and Mi-2 in order to bring about chromatin remodeling (Kim et al., 1999; Koipally et al., 2002; O'Neill et al., 2000; Sridharan and Smale, 2007). In order to study the role of Ikaros and Ikaros-HDAC1 complexes in ALL, we used ChiP-seq and analyzed genome-wide occupancy of Ikaros and HDAC1 using B-ALL cells (Nalm-6 cell line). 12,464 distinct binding sites for Ikaros and 9971 for HDAC1 were identified. 6722 and 6182 target genes were associated with Ikaros and HDAC1, respectively. Only 12% overlap noted with both Ikaros and HDAC1 binding. Quantitative chromatin immunoprecipitation (qChIP) analysis of the high- and low-rank ChIP-seq peak values was used to validate the ChIP-seq data. The effect of Ikaros and HDAC1 DNA binding on the surrounding chromatin was determined by analyzing the genome-wide distribution of histone markers including H3 trimethylation at lysine 4 ($H3K4me^3$), lysine 27 ($H3K27me^3$), lysine 36 ($H3K36me^3$), or lysine 9 ($H3K9me^3$); or acetylation at lysine 9 (H3K9ac) using ChiP-seq (Song et al., 2016).

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Ikaros loss-of-function or gain-of-function experiments were used to study the transcriptional regulation and epigenetic signature of Ikaros target genes in primary high-risk B-ALL cells. The epigenetic signature at the promoters of Ikaros and Ikaros-HDAC1 target genes in primary high-risk B-ALL (with loss of Ikaros function), and in primary high-risk B-ALL cells following treatment with CK2 inhibitors (TBB, CX-4945) was analyzed.

DNA binding analysis using the qChIP assay showed that Ikaros DNA binding to the promoters of its target genes is impaired in B-ALL. Treatment with CK2 inhibitor, CX-4945, restored Ikaros DNA binding to promoters and induced a distinct epigenetic signature at Ikaros-only and Ikaros-HDAC1 target genes (Song et al., 2016). High-level H3K9me^3, reduced H3K9ac, and the absence of H3K27me^3 was noted at the Ikaros-only target genes (e.g. cell cycle progression gene, CDC7). However, for the Ikaros-HDAC1 target genes (e.g. CDC2), restoration of Ikaros binding following CK2 inhibition results in a high level of H3K27me^3, the loss of H3K9ac, and largely unchanged H3K9me^3. Subsequent studies identified a large number of Ikaros target genes whose expression is regulated at the transcriptional level by Ikaros and/or the CK2-Ikaros signaling axis.

These data led to the conclusion that in B-ALL, chromatin remodeling and target gene expression are regulated by Ikaros alone and in complex with HDAC1 (Song et al., 2016). Ikaros induces the formation of repressive chromatin via direct Ikaros binding resulting in the formation of heterochromatin due to increased H3K9me^3 and reduced H3K9ac. Repressive chromatin formation by Ikaros also occurs following Ikaros recruitment of HDAC1, where the most prominent change is a strong increase in H3K27me^3 along with reduced H3K9ac. Both mechanisms lead to negative regulation of Ikaros target gene expression. These results demonstrate the strong interplay between Ikaros, HDAC1, and CK2 and underscore the importance of the CK2-Ikaros axis in controlling epigenetic regulation of gene expression in leukemia. Thus, both protein-protein interaction with HDAC1 and DNA binding are essential components of Ikaros' function as a regulator of gene expression via chromatin remodeling in leukemia (Song et al., 2016). It is important to emphasize that analyses of gene expression by the CK2-Ikaros axis were limited to epigenetic regulation of transcription of the individual Ikaros target genes, and not the global epigenomic effect of Ikaros.

5.1. Regulation of JARID1B/KDM5B by Ikaros and CK2

The above-described studies identified a large number of Ikaros target genes. Among them, several genes are directly involved in global regulation of the epigenetic signature by encoding proteins that function as epigenetic modifiers. One of them is Lysine-specific histone demethylase 5B (KDM5B) also known as JARID1B, a member of the JmjC domain-containing histone demethylases (Kristensen et al., 2012). This protein functions as an epigenetic eraser, as it can demethylate tri-, di-, and mono-methylated lysine 4 of histone H3. Since H3K4me^3 is the mark of open chromatin and is associated with positive regulation of gene expression (Santos-Rosa et al., 2002), KDM5B is involved in transcriptional repression of its target genes. KDM5B is overexpressed in several types of malignancies, and it has an important role in regulating genome stability and the DNA double-stranded break response (Albert et al., 2013; Bueno and Richard, 2013; Hayami

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et al., 2010; Kristensen et al., 2012; Roesch et al., 2010; Santos-Rosa et al., 2002; Wong et al., 2012; Xiang et al., 2007). KDM5B is upregulated in leukemia and inhibition of KDM5B causes cellular growth arrest (Haferlach et al., 2010). Transcriptional repression of JARID1B is associated with increased global levels of H3K4 trimethylation (Wang et al., 2016). Functional experiments showed that Ikaros represses transcription by directly binding to the promoter of KDM5B (Wang et al., 2016). Ikaros-mediated repression of JARID1B is dependent on the activity of the histone deacetylase, HDAC1, which is recruited to the upstream regulatory element of KDM5B in complex with Ikaros. Repression of KDM5B by the Ikaros-HDAC1 protein complex results in an increased level of H3K4me^3 in the nucleus. Inhibition of CK2 results in increased DNA-binding affinity of the Ikaros-HDAC1 complex to the promoter of JARID1B. This is associated with increased formation of H3K27me^3 and decreased H3K9ac. In high-risk B-ALL that carry deletion of one Ikaros (IKZF1) allele, targeted inhibition of CK2 enhances Ikaros binding and recruitment of HDAC1 to the KDM5B promoter, resulting in repression of KDM5B and increase of global H3K4me^3 in cells (Wang et al., 2016). These results demonstrate that the effect of the CK2-Ikaros axis is not limited only to the regulation of epigenetic signature of Ikaros target genes (such as KDM5B), but that it can affect the global epigenomic signature in leukemia via transcriptional regulation of KDM5B and subsequent increase in H3K4me^3 in cell.

5.2. Regulation of PHF2 by Ikaros and CK2

Analysis of global genomic occupancy showed that Ikaros binds to the promoter of PHD finger protein 2 (PHF2) (Ge et al., 2018a). PHF2 can also function as a demethylase and an eraser of H3K9me^3 epigenetic marks. Since H3K9me^3 is a repressive epigenetic mark, PHF2 can positively regulate transcription of its target genes. PHF2 expression is significantly reduced in subsets of ALL patients, and correlates with leukemia cell proliferation. Ikaros positively regulates PHF2 expression directly (Ge et al., 2018a, 2018b). Molecular CK2 inhibition significantly promotes PHF2 expression in an Ikaros-dependent manner. Pharmacological CK2 inhibition by CX-4945 treatment also results in an increase of PHF2 expression and enrichment of the Ikaros protein at PHF2 promoter in ALL. These results demonstrate that the CK2-Ikaros axis can also act as a positive regulator of gene expression of Ikaros target genes.

6. Ikaros regulates the global epigenetic landscape in T-cell leukemia

Next, we studied the direct role of Ikaros in global regulation of the epigenomic landscape. We used T-cell leukemia cells from Ikaros-deficient mice to determine the role of Ikaros in tumor suppression and in global genome-wide regulation of epigenetic signature. Ikaros haplo-knockout mice develop T-cell leukemia, with arrest in T-cell differentiation at the early (DN3) thymocyte stage (Winandy et al., 1995). During the process of malignant transformation, haplo-knockout Ikaros thymocytes lose the remaining wild-type Ikaros allele; the resulting T-ALL has an Ikaros-null genotype. Re-introduction of Ikaros into Ikaros-null T-ALL induces partial T-cell differentiation, along with cessation of leukemia cell growth and tumor suppression (Kathrein et al., 2005). We used this system to study the dynamics of Ikaros' role in regulating global chromatin rearrangement, epigenetic regulation of gene expression, and tumor suppression. Briefly, T-ALL Ikaros-null cells obtained from

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the spontaneous T-cell leukemia developed in Ikaros knockout mice, were retrovirally transduced with Ikaros. ChIP-seq was used to assess Ikaros' genome-wide DNA occupancy and global epigenomic signature, ATAC-seq was used to determine chromatin accessibility, while microarrays were used to analyze alterations of gene expression following Ikaros reintroduction. In order to study the dynamic changes in the global epigenomic landscape, Ikaros DNA-binding, and gene expression; the above analyses were done on Ikaros-null T-ALL (day #0), and on days #1, #2, and #3 following Ikaros transduction.

Ikaros' interaction with DNA elements were studied in four distinct genomic regions as follows:

- Gene body region with GENCODE annotation
- Promoter region defined as more than or equal to 3 kb upstream or downstream from the transcription start site (TSS) for each annotated gene
- Enhancer defined as 3 kb away from TSS with overlapping H3K4me^1 peak signal regions
- Reminder of the genome without promoter or enhancers, 100 kb apart from the nearest gene, called gene desert.

The total number of Ikaros DNA-binding peaks were noted in all regions, but it was by far the highest in the promoter/enhancer regions on day #1 following Ikaros re-introduction to Ikaros-null T-ALL (Ding et al., 2019). Despite the unchanged Ikaros expression, Ikaros DNA occupancy at promoters, enhancers, and the gene body was severely reduced during subsequent days following Ikaros re-introduction. However, Ikaros occupancy of gene desert regions did not dramatically change. Epigenomic analysis of T-ALL cells following Ikaros re-introduction uncovered several novel Ikaros functions in globally regulating the epigenetic landscape.

6.1. Pioneer activity

Most of the transcription factors are not able to bind DNA if the chromatin is in a compacted, "condensed" structure. These transcriptional factors require chromatin to be in a relaxed, "accessible" state in order to bind to the upstream regulatory elements of their target genes and regulate their transcription (Choukrallah and Matthias, 2014; Mayran and Drouin, 2018). "Pioneer factors" are the small number of transcriptional factors that are capable of binding condensed chromatin and making it accessible for other transcriptional factors and, thus, permissible for transcriptional regulation (Iwafuchi-Doi and Zaret, 2014; Zaret and Carroll, 2011). ATAC-seq analysis showed that Ikaros was able to bind to the chromatin that was condensed in T-ALL in Ikaros-null cells, as evidenced by negative ATAC-seq. Following Ikaros binding, previously condensed chromatin was remodeled into accessible chromatin, as evidenced by positive ATAC-seq. Chromatin remodeling from a condensed into an accessible state was observed at over 3,400 sites. This showed that Ikaros pioneering activity was not restricted to just a few sites, but that it is a global function of Ikaros. Epigenetic analysis showed that a majority of the de novo Ikaros-induced accessible chromatin sites have either promoter (with H3K4me^3 marker), or enhancer (with H3K4me^1) functions (Ding et al., 2019). Enrichment of H3K27ac in some of the de novo accessible

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chromatin sites indicated active transcription or active enhancers respectively. Dynamic analysis of Ikaros' pioneering function showed that Ikaros binds transiently to the condensed chromatin; Ikaros binding that was present at Day #1 was not detected on Day #2. However, the accessibility of many of the de novo open chromatin sites remained unchanged for at least 2 days from the initial Ikaros binding. These results confirmed Ikaros' pioneering activity in chromatin remodeling by demonstrating that Ikaros binding to the condensed chromatin produces accessible chromatin, which remains unchanged for a period of time allowing other transcription factors to bind to these sites and regulate transcription of their target genes. This suggests that Ikaros binding to specific silent chromatin sites facilitates initiation of regulatory activities by promoting chromatin accessibility (Ding et al., 2019). This sets up the T-cell differentiation program, as well as growth cessation of leukemia cells, that is further maintained by other transcription factors. A typical pioneer factor often functions as a master regulator of tissue development, or during stem cell differentiation (Boller et al., 2016; Mayran and Drouin, 2018; Mayran et al., 2018; van Oevelen et al., 2015). Since Ikaros is known to act as a master regulator of T- and B-cell differentiation, the pioneering function of Ikaros explains its biological role in hematopoiesis and controlling of gene expression. The pioneering activity as a part of the tumor suppression process in T-cell leukemia is a relatively novel observation, and the role of chromatin accessibility in leukemogenesis and regulation of T-ALL progression should be further studied.

6.2. Regulation of enhancer formation

Ikaros binding to DNA following its re-introduction into Ikaros-null T-ALL cells is associated with the de novo formation of enhancers, as indicated by de novo enrichment of the H3K4me^1 histone modification mark. Despite transient Ikaros DNA-binding, many of the de novo-formed enhancers retained their epigenetic signature during the following days, which indicates that Ikaros binding has a long-lasting effect on determining the enhancer landscape in leukemia and during induction of T-cell differentiation. Ikaros DNA-binding also had opposing effects on the enhancer landscape; it resulted in depletion of the existing enhancers, which was indicated by a loss of the H3K4me^1 histone modification mark. Ikaros-induced enhancer depletion persisted following the loss of Ikaros occupancy in subsequent days, which was consistent with the long-lasting effect of Ikaros on the genome-wide enhancer signature. Overall, these results demonstrate the profound effect of Ikaros in regulating the global enhancer landscape in T-ALL and during induction of T-cell differentiation.

6.3. De novo formation of active enhancers

Enhancer regions that have enrichment in H3K4me^1, but not in H3K27ac histone modification are in a "poised" state (Choukrallah and Matthias, 2014; Cico et al., 2016; Huang et al., 2016). Such enhancers are "primed" for activation, but do not affect the transcription of their target genes. Comparison of the epigenetic signature of Ikaros-null T-ALL and the same cells following Ikaros re-introduction revealed that Ikaros binding induces the de novo formation of active enhancers. This is characterized by the transition of DNA regions with an absence of H3K4me^1 and H3K27ac in Ikaros-null T-ALL, into regions that are enriched with both H3K4me^1 and H3K27ac marks. Thus, Ikaros binding to these regions induces the formation of active enhancers at DNA regions that did not have

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any marks of enhancers in Ikaros-null T-ALL. Overall, 22% of all newly-formed, active enhancers have been occupied by Ikaros, which demonstrates the direct role of Ikaros in chromatin remodeling that results in the formation of active enhancers. Many of the de novo formed activated enhancers remained in active state after the loss of Ikaros occupancy. Formation of de novo activated enhancers resulted in increased expression of nearby genes. These data demonstrated, for the first time, that Ikaros can regulate gene expression not only by binding to their promoters, but also by inducing formation of active enhancers that regulate transcription of their target genes.

6.4. Activation of poised enhancers

During the process of differentiation, a large number of enhancers are in a “poised” state and become activated in order to induce expression of genes that are essential for progression of differentiation (Cico et al., 2016; Heinz et al., 2015; Huang et al., 2016). Since Ikaros-null T-ALL cells are arrested at the DN3 stage of differentiation, many enhancers are in a poised state (with an H3K4me^1+/H3K27ac–signature). Re-introduction of Ikaros induces T-cell differentiation, which is associated with activation of a large number of enhancers. Ikaros binding directly induces activation of over 900 poised enhancers. Importantly, over 40% of Ikaros-induced active enhancers remained activated over at least the next 2 days. This indicates that Ikaros has a critical role in activating poised enhancers and that Ikaros binding sets the stage for long-lasting regulation of gene expression that is associated with T-cell differentiation. Overall, the ability of Ikaros to regulate de novo enhancer formation, enhancer depletion, and activation of poised enhancers shows that Ikaros directly regulates the expression of a much larger number of genes than previously hypothesized. These data revealed an Ikaros-controlled regulatory network that regulates expression of genes involved in cellular proliferation and T-cell differentiation.

6.5. Formation of super-enhancers

DNA domains that contain clusters of enhancers are called super-enhancers (Loven et al., 2013; Whyte et al., 2013). These regulatory regions are often occupied by several transcription factors, span large DNA domains (over 10 kB), and often regulate expression of cell-specific genes. The function of super-enhancers was mostly studied during stem cell differentiation, although they are likely involved in all stages of tissue-specific differentiation (Shin, 2018; Wong et al., 2017, 2018). The epigenomic analysis of Ikaros-null T-ALL cells following re-introduction of Ikaros, revealed that Ikaros binding induces the formation of a very large number of super-enhancers (609 following Ikaros re-introduction vs. 24 in Ikaros-null T-ALL cells). Genes that are regulated by super-enhancers have much higher expression, as compare to the genes regulated by “regular” activated enhancers. Dynamic analysis showed that Ikaros binding to the newly-formed super-enhancers is less transient than its binding to a typical enhancers. Since about 90% of the newly-formed super-enhancers retain Ikaros occupancy 24 h following initial Ikaros binding, while less than 5% of regular enhancers retain Ikaros occupancy over the same time period. Ikaros-induced formation of super-enhancers also has a much longer-lasting effect than the formation of regular enhancers, since over 55% of super-enhancers retain their epigenetic signature 2 days after initial Ikaros binding. These data demonstrate that strong effect of Ikaros on the global epigenomic landscape is accomplished by remodeling large DNA

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domains and inducing the formation of large, potent regulatory elements that control expression of a large number of genes involved in differentiation and regulating cellular proliferation (Ding et al., 2019).

Overall, the studies that analyzed the role of Ikaros re-introduction into Ikaros-null T-ALL using dynamic temporal analysis of the epigenetic landscape following Ikaros re-introduction demonstrated that Ikaros tumor suppressor activity involves complex regulation of the epigenetic signature during T-cell differentiation and in T-ALL (Fig. 3). The complexity of the analysis (dynamic approach involving 4 different time points over 4 days), and specificity of the experimental system (Ikaros-null T-ALL) allowed identification of specific Ikaros functions in epigenomic regulation with minimal background noise. Results of the analysis demonstrated that the major part of Ikaros' tumor suppressor function in leukemia involves global epigenomic control of gene expression. However, whether phosphorylation by CK2 affects Ikaros' role in regulating the global epigenomic landscape remains unknown.

7. Conclusion

Functional analysis of the CK2-Ikaros signaling axis in acute lymphoblastic leukemia revealed the interplay between this signaling pathway and epigenetic regulation of gene expression in leukemia. The CK2-Ikaros axis regulates both the epigenetic signature of Ikaros target genes, as well as the global epigenomic signature by regulating expression of epigenetic modulators, such as KDM5B. Dynamic functional studies into Ikaros' function in tumor suppression in T-ALL and induction of T-cell differentiation showed that Ikaros directly and dramatically regulates the global epigenomic landscape. This is achieved by directly inducing de novo formation and depletion of enhancers, activation of poised enhancers, formation of super-enhancers, and regulation of chromatin accessibility. Future studies will be directed toward further dissecting the role of CK2 and the CK2-Ikaros axis in regulating the epigenomic landscape, cellular differentiation, and leukemia.

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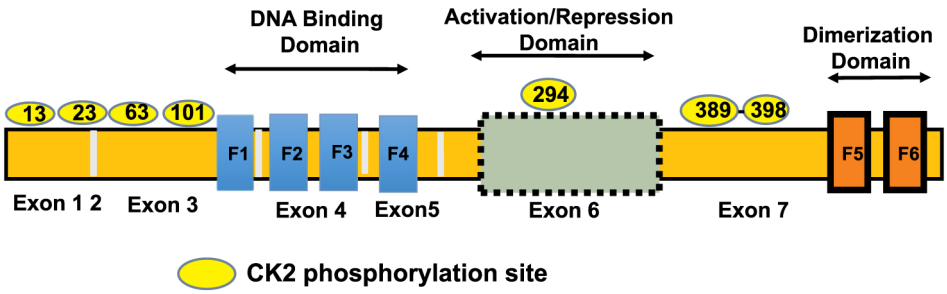

Fig. 1.
Structure of Ikaros and CK2 phosphorylation sites.

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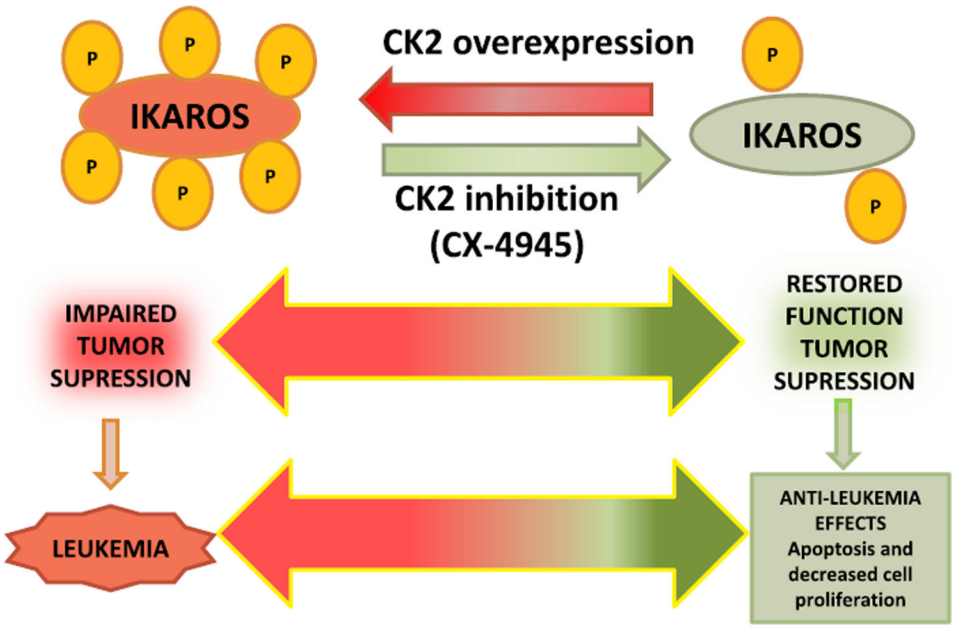

Fig. 2.
Mechanism of action of CK2 inhibitor via Ikaros.

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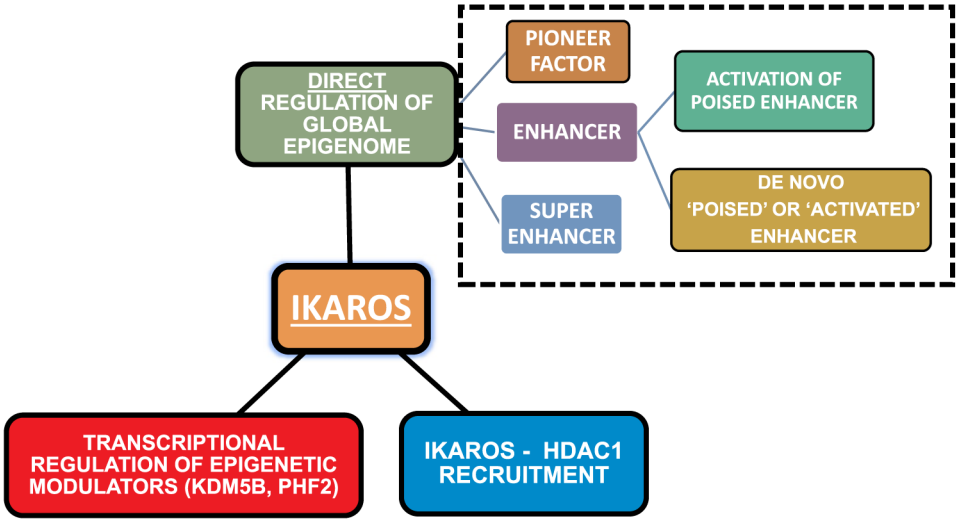

Fig. 3.
Multifaceted functions of Ikaros in leukemia epigenetic regulation.