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HAEMATOPOIESIS

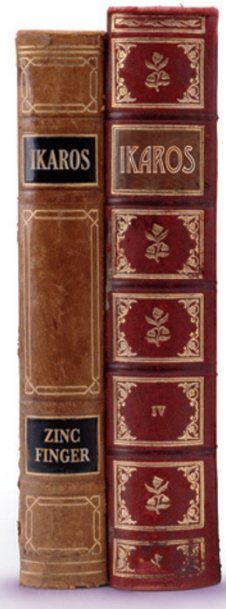
Two versions of the Ikaros tale

Members of the Ikaros protein family are important transcriptional regulators: studies in Ikaros-deficient mice have indicated a role for Ikaros (encoded by *IKZF1*) in lymphopoiesis, and genetic analyses in humans have linked mutations at the *IKZF1* locus with B cell acute lymphoblastic leukaemia (B-ALL). Now, Schjerven *et al.* investigate the involvement of individual zinc finger motifs of Ikaros in its transcriptional activity.

Zinc fingers are conserved DNA-binding motifs. Ikaros family proteins have two carboxy-terminal zinc fingers, which are involved in protein dimerization and multimerization, and four amino-terminal zinc fingers that bind DNA.

Schjerven *et al.* generated transgenic mice that lack *Ikzf1* exon 4, which encodes zinc finger 1 ($Ikzf1^{\Delta F1/\Delta F1}$ mice), or that lack exon 6, which encodes zinc finger 4 ($Ikzf1^{\Delta F4/\Delta F4}$ mice). Analysis of these mice revealed that several functions of Ikaros, including the initiation of B cell development, require only zinc finger 2 and zinc finger 3, whereas other functions also require either zinc finger 1 or zinc finger 4. $Ikzf1^{\Delta F1/\Delta F1}$ mice lacked the full-length Ikaros protein and only expressed an alternatively spliced Ikaros isoform, whereas $Ikzf1^{\Delta F4/\Delta F4}$ mice expressed mutant forms of both isoforms.

> “the tumour suppressor activity of Ikaros depends on zinc finger 4”



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Unlike $Ikzf1^{-/-}$ mice (which lack both Ikaros isoforms), $Ikzf1^{\Delta F1/\Delta F1}$ and $Ikzf1^{\Delta F4/\Delta F4}$ mice showed only a small reduction in the numbers of pre-pro-B cells. However, $Ikzf1^{\Delta F1/\Delta F1}$ mice had substantially fewer large pre-B cells that express IgM on their cell surface compared with wild-type and $Ikzf1^{\Delta F4/\Delta F4}$ mice. Furthermore, low numbers of small pre-B cells and immature B cells were detected in the periphery of $Ikzf1^{\Delta F1/\Delta F1}$ mice, which indicates that zinc finger 1 has a role in the progression of B cell development. By contrast, zinc finger 4 was mainly dispensable for B cell development but was required for the development of natural killer cells and plasmacytoid dendritic cells.

Unlike B cell development, T cell development was mainly dependent on zinc finger 4: $Ikzf1^{\Delta F4/\Delta F4}$ mice had reduced numbers of $CD4^{-}CD8^{-}$ thymocytes compared with wild-type and $Ikzf1^{\Delta F1/\Delta F1}$ mice. Moreover, fetal B cells and T cells were absent from $Ikzf1^{\Delta F4/\Delta F4}$ mice, which indicates that the requirement for zinc finger 4 is different in fetal and adult mice. Importantly, the absence of fetal lymphoid tissue-inducer cells in $Ikzf1^{\Delta F4/\Delta F4}$ mice led to defective development of lymph nodes and Peyer's patches.

These findings, together with chromatin immunoprecipitation (ChIP) sequencing analyses, indicate that zinc finger 1 and zinc finger 4 help Ikaros recognize different DNA sequences. Moreover, mRNA sequencing revealed that the genes that are differentially targeted by Ikaros proteins lacking one of the two zinc finger domains are surprisingly few.

Notably, some of the genes that were selectively upregulated in $Ikzf1^{\Delta F4/\Delta F4}$ mice have previously been implicated in tumour invasion and metastasis. Accordingly, $Ikzf1^{\Delta F4/\Delta F4}$ but not $Ikzf1^{\Delta F1/\Delta F1}$ mice developed aggressive thymic lymphomas, which suggests that the tumour suppressor activity of Ikaros depends on zinc finger 4. This was confirmed using a mouse model of B-ALL, in which irradiated recipients of $Ikzf1^{\Delta F4/\Delta F4}$ bone marrow cells that were transduced with the oncogenic tyrosine kinase BCR–ABL developed more aggressive malignancies than mice that received transduced $Ikzf1^{\Delta F1/\Delta F1}$ bone marrow cells.

On the basis of these observations and preliminary results of mRNA sequencing, the authors propose that their model will help to delineate the gene targets of Ikaros and the mechanisms by which Ikaros contributes to B-ALL progression in humans.

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ORIGINAL RESEARCH PAPER Schjerven, H. *et al.* Selective regulation of lymphopoiesis and leukemogenesis by individual zinc fingers of Ikaros. *Nature Immunol.* **14**, 1073–1083 (2013)