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Epigenetic regulation of gene expression in leukemia by the Ikaros tumor suppressor

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Statement of the Problem: Acute lymphoblastic leukemia (ALL) is a deadly disease that has limited treatment options. Deregulation of the Ikaros tumor suppressor gene due to deletion or inactivating mutation of a single allele is associated with the development of high-risk ALL, increased the chance of relapse, and overall poor prognosis. The mechanism through which Ikaros regulates gene expression in leukemia is still unknown.

Methodology: Global genome-wide studies using chromatin immunoprecipitation, coupled with next-generation sequencing (ChIP-seq) were used to identify Ikaros target genes and epigenetic signature. Results were confirmed by quantitative chromatin immunoprecipitation (qChIP). We analyzed the epigenetic regulation of gene expression by Ikaros using Ikaros gain- and loss-of-function approaches. Quantitative real-time PCR (qRT-PCR) and western blot were used to assess gene expression.

Findings: Global genome-wide DNA-binding assays identified many genes that are regulated by Ikaros in ALL. Functional experiments followed by scanning qChIP at promoters of Ikaros target genes revealed that Ikaros can repress transcription by inducing the formation of heterochromatin at promoters of several Ikaros target genes. Overexpression of Ikaros in ALL results in an increased repressive epigenetic signature, as evidenced by increased H3K27me3 and H3K9me3 marks at promoters of genes that promote cell cycle progression and the PI3K pathway. In addition, Ikaros regulates the global epigenetic signature by regulating expression of the JARID1B/KDM5B histone demethylase. Increased expression of Ikaros results in transcriptional repression of KDM5B and increased levels of H3K4me3, as evidenced by Western blot.

Conclusion & Significance: Ikaros tumor suppressor activity in high-risk ALL involves epigenetic regulation of its target genes, as well as regulation of H3K4me3 levels via transcriptional repression of the KDM5B gene. These data provide novel insights into the epigenetic regulation of gene expression and the mechanisms of tumor suppression in acute lymphoblastic leukemia.

Recent Publications

1. Song C, Gowda C, Pan X, Ding Y, Tong Y, Tan B H, Wang H, Muthusami S, Ge Z, Sachdev M, Amin S G, Desai D, Gowda K, Gowda R, Robertson G P, Schjerven H, Muschen M, Payne KJ and Dovat S (2015) Targeting casein kinase II restores Ikaros tumor suppressor activity and demonstrates therapeutic efficacy in high-risk leukemia. *Blood* 126(15):1813-22.
2. Song C, Pan X, Ge Z, Gowda C, Ding Y, Li H, Li Z, Yochum G, Muschen M, Li Q, Payne KJ and Dovat S (2016) Epigenetic regulation of gene expression by Ikaros, HDAC1 and Casein Kinase II (CK2) in leukemia. *Leukemia* 30(6):1436-1440.
3. Wang H, Song C, Ding Y, Pan X, Ge Z, Tan BH, Gowda C, Sachdev M, Muthusami S, Ouyang H, Lai L, Francis OL, Morris CL, Abdel-Azim H, Dorsam G, Xiang M, Payne KJ and Dovat S (2016) Transcriptional regulation of JARID1B/KDM5B histone demethylase by Ikaros, Histone deacetylase 1 (HDAC1) and Casein kinase 2 (CK2) in B cell acute lymphoblastic leukemia. *J Biol Chem.* 291(8):4004-18.
4. Ge Z, Zhou X, Gu Y, Han Q, Li J, Chen B, Ge Q, Dovat E, Payne JL, Sun T, Song C and Dovat S (2017) Ikaros regulation of the BCL6/BACH2 axis and its clinical relevance in acute lymphoblastic leukemia. *Oncotarget* 8(5):8022-8034.
5. Gowda C, Soliman M, Kapadia M, Ding Y, Payne K, and Dovat S (2017) Casein Kinase II (CK2), Glycogen Synthase Kinase-3 (GSK-3) and Ikaros mediated regulation of leukemia. *Adv Biol Regul.* 65:16-25.

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Biography

Sinisa Dovat completed his clinical training in Pediatrics at Pennsylvania State University, and in Pediatric Hematology/Oncology at UCLA-Children's Hospital. He received his research training at Cornell University Graduate School of Medical Sciences and at the Howard Hughes Medical Institute at UCLA. As an independent investigator at University of Wisconsin, he focused his work on the regulation of the tumor suppression in childhood leukemia. He is the recipient of The Young Investigator Award by The American Society of Pediatric Hematology/Oncology and has been included in the best doctors in America list. Since September 2010, he has been serving as the Four Diamond Endowed Chair and Director of Translational Research and Developmental Therapeutics in Pediatric Hematology/Oncology at Pennsylvania State University College of Medicine, Hershey, PA. His research interests include epigenomic regulation and transcriptional control of cellular immortalization and senescence in leukemia and experimental therapy of malignant diseases.

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