MIR142 Loss-of-Function Mutations Promote Leukemogenesis via Depression of ASH1L Resulting in Increased HOX Gene Expression

Rahul Ramaswany
Washington University in St. Louis

Follow this and additional works at: https://openscholarship.wustl.edu/wuurd_vol12

Recommended Citation

This Abstracts J-R is brought to you for free and open access by the Washington University Undergraduate Research Digest at Washington University Open Scholarship. It has been accepted for inclusion in Volume 12 by an authorized administrator of Washington University Open Scholarship. For more information, please contact digital@wumail.wustl.edu.
MIR142 Loss-of-Function Mutations Promote Leukemogenesis via Derepression of ASH1L Resulting in Increased HOX Gene Expression

Rahul Ramaswamy

Mentor: Daniel C Link

Mutations of MIR142 have been identified in approximately 2% of de novo AML and in 20% of diffuse large B cell lymphoma. In AML, the mutations in MIR142 disrupt both miRNA-142-3p and miRNA-142-5p function, suggesting that loss of MIR142 plays a role in leukemic transformation. To test this hypothesis, we first characterized hematopoiesis in Mir142−/− mice, and reported that loss of Mir142 results in an expansion of myeloid progenitors with impaired erythropoiesis and lymphopoiesis.

We examined several putative miR-142 target genes, eventually focusing on ASH1L, a histone methyltransferase that has been recently implicated in MLL-associated leukemogenesis. The 3’ UTR of ASH1L contains 4 putative binding sites for miRNA-142-3p, indicating that this miRNA is critical in its post-transcriptional regulation. Indeed, Ash1L protein levels were 3-fold higher in Mir142−/− mice bone marrow compared to control mice. Since ASH1L is a known regulator of HOX gene expression, we examined HoxA9 and HoxA10 expression in Mir142−/− hematopoietic progenitor subsets. While HoxA9 and HoxA10 expression were not different in hematopoietic stem cells, they were markedly upregulated in myeloid progenitors. For example, in granulocyte-macrophage progenitors (GMPs), HoxA9 and HoxA10 expression were increased 2.86-fold and 34.4-fold, respectively in Mir142−/− versus control cells. Likewise, in megakaryocyte-erythroid progenitors (MEPs), HoxA9 and HoxA10 expression were increased 5.3-fold and 21.4-fold. Dysregulated HoxA9 and HoxA10 expression have been implicated in enhanced self-renewal capacity, and HoxA9 overexpression has been shown to cooperate with mutant IDH1 to induce AML in mice. Collectively, these data suggest a model in which MIR142 mutations contribute to leukemogenesis by de-repressing ASH1L expression, which, in turn, increases expression of HoxA9/10 and enhances self-renewal. Inhibitors targeting ASH1L may have therapeutic benefit in AML characterized by increased HOX gene expression.