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

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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 four 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.