Comment on Faber et al, page 2375

Might as well face it: MLL’s addicted to HOX

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Overexpression of HOX:49 is a hallmark of MLL-rearranged leukemias. In this issue of Blood, Faber and colleagues show that HOX:49 is critical for proliferation and survival of leukemic cells.

Chromosomal rearrangements involving the MLL gene are a characteristic feature of a variety of human leukemias, including acute lymphoid leukemia (ALL) and acute myeloid leukemias (AML) as well as secondary leukemias resulting from treatment with topoisomerase inhibitors. The MEIS1 and HOX:49 genes have been shown to be major downstream targets of MLL fusion proteins. The mammalian HOX genes encode DNA-binding homeobox proteins that have a role in developmental patterns and tissue fate during embryogenesis. MEIS1 is a homeodomain protein that acts as a DNA-binding cofactor of HOX proteins from paralog groups 9 through 13. MEIS1 and HOX:49 genes are normally expressed in hematopoietic progenitor cells and their expression is down-regulated on differentiation. Overexpression of MEIS1 and HOX:49 is seen in a variety of leukemic cell lines and primary AML samples, suggesting roles for these genes in leukemia initiation and maintenance.

In addition, fusion of HOX:49 to NUP98 in some AMLs further supports an important role for HOX:49 in leukemia.

In this issue of Blood, Faber et al ask if HOX:49 expression is required to maintain the leukemic state. The authors investigated the effects of knocking down HOX:49 expression in MLL-rearranged and nonrearranged human leukemia cells. After shRNA-mediated HOX:49 suppression, induction of apoptosis and decreased colony formation were observed in leukemia cell lines. An increase of cells in the G1 phase of the cell cycle and some cellular differentiation was also observed prior to the cells undergoing apoptosis. The apoptotic phenotype was rescued by expression of non-targetable HOX:49. The authors demonstrated that a greater induction of cell death was observed in MLL-rearranged cell lines and primary AML samples compared with MLL germ line cells after shRNA knockdown of HOX:49. In addition, the level of apoptosis positively correlated with levels of HOX:49 expression prior to shRNA knockdown. Gene expression profiling on MLL-rearranged cells after knockdown of HOX:49 expression showed decreased expression of genes, such as MEIS1 and Pbx3, previously shown to play a role in leukemogenesis, suggesting these genes are downstream of HOX:49. Finally, MLL-rearranged cells were subjected to knockdown of HOX:49 and transplanted into mice. These mice showed a significant decrease in leukemia burden, demonstrating that continued HOX:49 expression is required for survival and proliferation of human MLL-rearranged cells in vivo.

The results provided by Faber et al demonstrate that MLL-rearranged cells are addicted to HOX:49 expression to maintain their leukemic state, as shown in the figure. Another major downstream target of MLL fusion proteins is MEIS1. Previous work done by Wong et al and work by Kumar et al used similar strategies to demonstrate that maintenance of the leukemic state in MLL-rearranged cells is also dependent on expression of MEIS1. Knockdown of MEIS1 expression results in decreased proliferation and survival of these cells. Although MEIS1 is important in maintenance of the leukemic state, elevated levels of MEIS1 are not sufficient to induce leukemia. In contrast, elevated levels of HOX:49 are sufficient to induce leukemia with a long latency. Cocexpression of MEIS1 along with HOX:49, however, reduces the latency of HOX-induced leukemia. Taken together, these data suggest a role for both MEIS1 and HOX:49 in leukemia initiation and maintenance.

The data from the gene expression profiling experiment in Faber et al suggest that MEIS1 is downstream of HOX:49. Is continued HOX:49 expression required to maintain high levels of MEIS1 expression in leukemic cells? Knockdown of HOX:49 expression in MLL-rearranged cells and simultaneous ectopic expression of MEIS1 will further elucidate the complex interactions of these transcription factors in leukemia maintenance.

Clarification of this gene partnership will lead to an understanding of gene regulation in MLL-rearranged leukemias. MEIS1 and HOX:49 have been shown to function as a heterodimer and in higher order complexes. Small molecule inhibitors could provide alternate therapeutic strategies by disrupting MEIS1/HOX:49 dimer formation, leading to loss of proliferation and survival in MLL-rearranged leukemic cells.

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REFERENCES


Platelet antigen-induced regulation in ITP

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The immune system has evolved several interactive peripheral regulatory mechanisms to protect against autoimmunity, and it has become increasingly clear that CD4⁺CD25⁺Foxp3⁺ regulatory cells (Tregs) are an important component of this control. Their importance in maintaining peripheral tolerance is exemplified by the observations, for example, that mutation of the nucleoporin gene generates de novo from the patient’s other nonregulatory T cells. This may set the stage for platelet-induced cellular therapy as a treatment for ITP.

Tregs maintain self-tolerance and, although they are significantly deficient in patients with ITP, it now seems that their antigen-specific counterparts can be generated de novo from the patient’s other nonregulatory T cells. This may set the future stage for platelet-induced cellular therapy as a treatment for ITP.

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