BLOOD CANCER DISCOVERY

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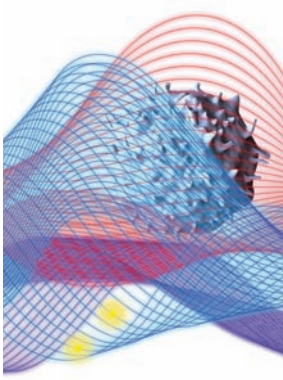
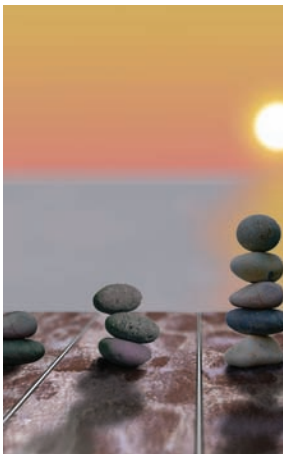
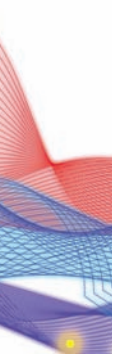
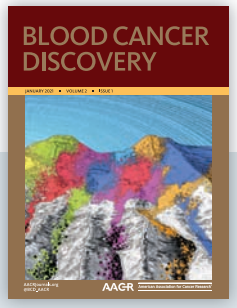




Précis: Noncoding genetic region PE is a conserved hematopoietic-specific PTEN long-distance enhancer. Its deletion accelerates Notch-driven leukemia in mice and is recurrent in human T-ALL.





ON THE COVER Leukemia stem cell (LSC) plasticity in acute myeloid leukemia (AML) presents a major therapeutic challenge. In this issue, Stephanie Xie, John Dick, and colleagues characterize sphingosine-1-phosphate receptor 3 (S1PR3) as a plausible target in AML. Through extensive gene profiling in large AML patient datasets, the authors identify two AML subsets with different sphingolipid gene signature, responsiveness to the S1P prodrug fingolimod, and responsiveness to chemotherapy. S1PR3 expression on human HSC and LSC is induced by inflammatory cytokines and drives their myeloid differentiation in synergy with NF-κB signaling. Genetic and pharmacologic interrogation demonstrates how S1PR3 activation can drive AML cells into a differentiated state. This study offers detailed mechanistic insights into interconnections between metabolic, inflammatory, and myeloid differentiation circuits in HSC and LSC, and identifies two AML patient subgroups with distinct chemosensitivity. For details, please see the article on page 32 and the accompanying commentary by Toshio Suda and colleagues on page 3.

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