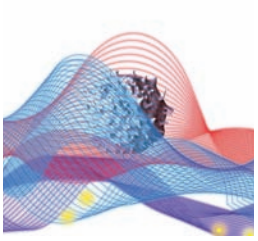
S1P Receptor Potentiates Inflammation-Driven Myeloid Differentiation in Normal and Leukemia Stem Cells

- S1RP3 is highly expressed in CD33$^+$ myeloid cells and promotes myeloid differentiation in HSC and LSC.
- S1RP3 marks a specific subtype of mature LSC subtypes with heightened inflammatory signatures.
- Sphingosine phosphate-mimetic fingolimod disrupts LSC function and decreases leukemia burden *in vivo*.



Inflammatory signaling perturbs hematopoietic stem cell (HSC) differentiation through a process termed emergency hematopoiesis. Whether an equivalent process has a role in regulating leukemia stem cells (LSC) is unclear. Here Xie and colleagues demonstrate that sphingosine-1-phosphate receptor 3 (S1RP3), a receptor for proinflammatory and bioactive lipid sphingosine-1-phosphate (S1P), drives myeloid differentiation in both HSC and LSC. S1RP3 expression is high in CD33$^+$ myeloid cells and low in primitive CD34$^+$ cells. When S1RP3 is upregulated, it promotes myeloid differentiation in synergy with proinflammatory signaling pathways in HSC and LSC. In addition, S1RP3 expression level could be utilized to stratify acute myeloid leukemia (AML) patients into more differentiated and more primitive cases. Moreover, pharmacologic disruption of S1P signaling by the S1P prodrug FTY720 reduces LSC frequency and decreases leukemia burden *in vivo*. The results suggest that S1RP3 could serve as both a biomarker and therapeutic target in human AML. ■

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Preneoplastic CLL DNA Methylome Persists through Disease Progression and Therapy

- CLL cells are profiled at diagnosis and after therapy by bulk and single-cell DNA methylome profiles in comparison with normal and preneoplastic cell counterparts.
- CLL-associated methylome is established in preleukemic cells and is remarkably stable throughout leukemia clonal evolution and therapeutic interventions.
- Methylome reprogramming in preneoplastic cells likely precedes and promotes accumulation of genetic lesions.

Specific alterations in DNA methylation patterns are common in cancer cells across tissue origins and genetic drivers. In this study, Kretzmer and colleagues asked how early cancer-associated methylation patterns emerge during chronic lymphocytic leukemia (CLL) oncogenesis. They have profiled DNA methylomes of single cells and bulk samples across cell types representing key stages of oncogenesis, from normal germinal center B-cell subsets to preneoplastic monoclonal B-cell lymphocytosis (MBL) to serial CLL samples at diagnosis and throughout disease progression and therapy. The authors identify cancer-specific methylation patterns distinguishing normal B-cell subtypes from MBL and CLL. These methylation patterns are shared among all CLL clones in each patient case and are already present in nonmalignant MBL cell state. Persistence of the methylation pattern is particularly remarkable when considered on the backdrop of genetic and transcriptional heterogeneity. These findings shed light on possible CLL cell of origin and provide support to the concept that precancerous methylome may be a prerequisite for oncogenic transformation and maintenance of neoplastic state. ■

See article, p. 54.

An Autochthonous Mouse Model of *Myd88*- and *BCL2*-Driven Diffuse Large B-cell Lymphoma Reveals Actionable Molecular Vulnerabilities

- Myd88/BCL2-driven mouse lymphoma (MBC) model mimics the morphologic and transcriptomic features of human ABC-DLBCL.
- BCL2 inhibitor venetoclax induces apoptosis in MBC tumors and increases overall survival in tumor-bearing mice.
- Combination therapy that blocks both BCL2 and PD-1 further increases overall survival in MBC lymphoma–bearing mice.

Activated B-cell–like diffuse large B-cell lymphoma (ABC-DLBCL) is associated with poor prognosis when compared with germinal center B-cell–like (GCB)-DLBCL, and there is an urgent need to develop a preclinical animal model that closely models human ABC-DLBCL for the development of effective targeting therapies. *MYD88* mutation and gain of *BCL2* copy numbers are two of the most frequent genomic aberrations in ABC-DLBCL. Here Flümann and colleagues characterize the phenotypes of a Myd88/BCL2-driven (MBC) mouse lymphoma model and find that this model closely resembles the morphologic and gene expression signatures of human ABC-DLBCL. Moreover, MBC-derived lymphomas undergo apoptosis in response to venetoclax, revealing their druggable vulnerabilities against BCL2. Furthermore, combined treatment of venetoclax plus anti–PD-1 antibody RMP1-14 extends survival of MBC mice after they develop tumors far longer than either drug alone. These findings validate MBC mice as a tool to study ABC-DLBCL and demonstrate preclinical evidence that targeting both BCL2 and PD-1 could serve as a novel therapy for the treatment of ABC-DLBCL. ■

See article, p. 70.

A Tumor Suppressor Enhancer of PTEN in T-cell Leukemia

- PE (PTEN enhancer), a conserved noncoding genomic region, physically interacts with PTEN promoter and regulates its transcription as a distal enhancer.
- PTEN expression in T cells is decreased, and T-ALL is accelerated in PE-null mice.
- In T-ALL, but not B-ALL, PE deletions are recurrent and correlate with lower PTEN mRNA and proliferative advantage.

PTEN is the second most frequently mutated tumor suppressor gene in cancer. In this study, Tottone and colleagues identified a distal regulatory element enhancing PTEN expression (PE) as a recurrent deletion in human T-ALL. PE displays enhancer-associated chromatin marks in hematopoietic lineage, but not solid tissues. In several human T-ALL cell lines, the PE region is occupied by multiple transcription factors including Notch, is bidirectionally transcribed, and engages in long-range interactions with the PTEN promoter. PE deletion in these cells results in decreased PTEN mRNA and decreased proliferation. PE is conserved across species, and its germline as well as conditional deletion in mice results in dose-dependent diminished PTEN expression in T cells, but not other lineages. Notch1-driven leukemia development is accelerated on PE-null mouse background, providing functional evidence of PE tumor-suppressive role consistent with its deletion profile in human T-ALL. Cancer-associated genetic inactivation of tumor suppressor genes is mostly documented within their promoter or protein-coding regions. This study reveals that distal enhancer deletion is another mechanism by which a classic and ubiquitous tumor suppressor gene can be inactivated in cancer. This work identifies previously uncharacterized PTEN enhancer activity in normal T cells and in T-ALL. It invites exploration of lineage-specific enhancer regulation of PTEN and other classic tumor suppressors in physiology and oncogenesis. ■

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