### The Genetic Basis of Hepatosplenic T-cell Lymphoma


Précis: In-depth genetic characterization of the genomic landscape of hepatosplenic T-cell lymphoma identifies SETD2 as a tumor suppressor and STAT5B and PIK3CD as drivers of hepatosplenic T-cell lymphoma. See commentary, p. 352

### PTEN Regulates Glutamine Flux to Pyrimidine Synthesis and Sensitivity to Dihydroorotate Dehydrogenase Inhibition


Précis: PTEN-mutant tumor cells require glutamine-dependent de novo pyrimidine synthesis for their enhanced proliferation and survival, creating a vulnerability that may be targeted with DHODH inhibitors to induce DNA damage and cell death. See related article, p. 380

### Adaptive Reprogramming of De Novo Pyrimidine Synthesis Is a Metabolic Vulnerability in Triple-Negative Breast Cancer

K.K. Brown, J.B. Spinelli, J.M. Asara, and A. Toker

Précis: Chemotherapy activates the de novo pyrimidine synthesis pathway to elevate pyrimidine nucleotide levels in TNBC, suggesting that targeting de novo pyrimidine synthesis may enhance chemotherapeutic efficacy. See related article, p. 390
RESEARCH ARTICLES

Safety and Antitumor Activity of the Multitargeted Pan-TRK, ROS1, and ALK Inhibitor Entrectinib: Combined Results from Two Phase I Trials (ALKA-372-001 and STARTRK-1) ........................................... 400

Précis: The multikinase inhibitor entrectinib is well tolerated and has antitumor activity in patients with TKI-naïve NTRK1/2/3, ROS1, or ALK-rearranged tumors, including those with CNS disease.

Interaction Landscape of Inherited Polymorphisms with Somatic Events in Cancer ................................. 410

Précis: A pan-cancer genome-wide association study of data from The Cancer Genome Atlas identifies genetic risk variants that affect cancer-specific somatic alterations and influence tumor site of origin.

See commentary, p. 354

The APC/C E3 Ligase Complex Activator FZR1 Restricts BRAF Oncogenic Function .......................... 424

Précis: The putative tumor suppressor FZR1 negatively regulates BRAF kinase activity via APC/C-dependent ubiquitination and subsequent proteolysis in nontransformed cells and APC/C-independent disruption of BRAF dimerization in cancer cells.

See commentary, p. 356

ON THE COVER

To discover interactions between germline variants and somatic events in cancer, Carter and colleagues performed a genome-wide association study, evaluating genomic data from The Cancer Genome Atlas (TCGA) including more than 5,900 tumors and 22 cancer types. Association studies that compared tumor-specific SNPs identified loci that were significantly associated with specific tumor types, while association testing of SNPs in TCGA samples and the alteration status of 138 cancer driver genes identified 35 associations between 28 germline loci and 20 cancer driver genes. Analysis of mutational heterogeneity based on germline loci identified 20 candidate cancer driver genes, 15 of which had not previously been shown to be frequently mutated. In addition to providing a resource of germline–somatic interactions in cancer, these findings demonstrate that inherited risk variants can alter the somatic evolution of cancer. For details, please see the article by Carter and colleagues on page 410.
**CANCER DISCOVERY**

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*Cancer Discov 2017;7:OF3-441.*

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