CANCER DISCOVERY

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A. Reuben, R. Gittelman, J. Gao, J. Zhang, E.C. Yusko, C.-J. Wu, R. Emerson, J. Zhang,

Précis: T-cell receptor sequencing of 45 tumor regions from 11 patients with NSCLC found T-cell repertoire intratumor heterogeneity that was associated with disease relapse and reduced disease-free survival.

Immune Escape in Breast Cancer During In Situ to Invasive Carcinoma Transition .......... 1098

Précis: Progression from ductal carcinoma in situ to invasive ductal carcinoma is characterized by a switch to a more suppressive immune microenvironment.

See commentary, p. 1062

Whole-Genome and Epigenomic Landscapes of Etiologically Distinct Subtypes of Cholangiocarcinoma ............. 1116

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**Précis:** In-depth genetic characterization defines cholangiocarcinoma subtypes and identifies previously undescribed drivers, noncoding promoter mutations, and structural variants.

**Superenhancer Analysis Defines Novel Epigenomic Subtypes of Non-APL AML, Including an RARα Dependency Targetable by SY-1425, a Potent and Selective RARα Agonist**


**Précis:** Characterization of enhancer landscapes in patients with AML identified a subset of non-APL AML with an RARA superenhancer that confers sensitivity to treatment with the selective RARα agonist SY-1425.

See commentary, p. 1065

**Overcoming the Immunosuppressive Tumor Microenvironment of Hodgkin Lymphoma Using Chimeric Antigen Receptor T Cells**


**Précis:** Anti-CD123 chimeric antigen receptor T cells overcome the immunosuppressive tumor microenvironment in Hodgkin lymphoma by targeting both malignant cells and tumor-associated macrophages.

**Loss of MutL Disrupts CHK2-Dependent Cell-Cycle Control through CDK4/6 to Promote Intrinsic Endocrine Therapy Resistance in Primary Breast Cancer**


**Précis:** Dysregulation of the mismatch repair complex MutL promotes intrinsic resistance to endocrine therapy in ER+ breast cancer model systems and patients and may confer sensitivity to CDK4/6 inhibitors.

**BLIMP1 Induces Transient Metastatic Heterogeneity in Pancreatic Cancer**


**Précis:** Pancreatic ductal adenocarcinoma metastasis is promoted by hypoxia and HIF–driven upregulation of the prometastatic transcription factor BLIMP1.

See commentary, p. 1067

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**ON THE COVER**

To determine how intratumor heterogeneity in the T-cell landscape correlates with the genomic landscape and with patient outcome in non–small cell lung cancer (NSCLC), Reuben and colleagues characterized the T-cell repertoire in a cohort of 11 patients with NSCLC who had previously been subject to whole-exome sequencing. T-cell receptor (TCR) sequencing profiled 45 tumor regions across the 11 tumors and revealed a high level of intratumor heterogeneity, with differences in T-cell density, clonality, and repertoire. TCR intratumor heterogeneity was linked to neoantigen heterogeneity and was correlated with disease relapse and reduced disease-free survival in patients with NSCLC. These findings link T-cell repertoire heterogeneity to genomic intratumor heterogeneity and relapse in NSCLC. For details, please see the article by Reuben and colleagues on page 1088.