CANCER DISCOVERY

RESEARCH BRIEFS

Genetic Ancestry Contributes to Somatic Mutations in Lung Cancers from Admixed Latin American Populations …… 591


Précis: Tumor sequencing data from patients with lung cancer from Latin America revealed that Native American ancestry significantly affected tumors’ somatic mutation profiles; the observed disparities arose from germline differences rather than environmental exposures.

See commentary, p. 534

A Critical Role for Fas-Mediated Off-Target Tumor Killing in T-cell Immunotherapy …… 599


Précis: Apoptotic FAS-FASL signaling enabled CD8+ T cells to exert cytotoxic effects on antigen-negative “bystander” tumor cells in vivo, possibly explaining how antigen-specific chimeric antigen receptor T-cell therapies can eliminate tumors with heterogeneous antigen expression.
**A Genetic Mouse Model Recapitulates Immune Checkpoint Inhibitor–Associated Myocarditis and Supports a Mechanism-Based Therapeutic Intervention**  ............... 614

**Précis:** A new mouse model of immune checkpoint inhibitor–induced myocarditis was developed, enabling the discovery that abatacept may be useful for ameliorating this condition; this finding was supported by results from a patient case series.

See commentary, p. 537

**Cell of Origin Influences Pancreatic Cancer Subtype**  .................... 660

**Précis:** Pancreatic ductal adenocarcinomas in adult genetically engineered mice could arise from either ductal or acinar cells, and tumors arising from each cell type had distinct transcriptional profiles that matched those of defined human pancreatic cancer subtypes.

**The Lipogenic Regulator SREBP2 Induces Transferrin in Circulating Melanoma Cells and Suppresses Ferroptosis**  .... 678

**Précis:** Melanoma circulating tumor cells (CTC) prevented ferroptotic death by upregulating SREBP2-mediated lipogenic pathways and iron homeostatic pathways, and blocking this escape mechanism by knocking out the gene encoding transferrin hindered CTC tumor formation.

**An Empirical Antigen Selection Method Identifies Neoantigens That Either Elicit Broad Antitumor T-cell Responses or Drive Tumor Growth**  ... 696

**Précis:** An ex vivo bioassay, ATLAS, was able to identify stimulatory and inhibitory neoantigens for the design of personalized anticancer vaccines; this assay pinpointed anti- and protumorigenic antigens, as demonstrated via in vivo experiments.

**Durable Suppression of Acquired MEK Inhibitor Resistance in Cancer by Sequestering MEK from ERK and Promoting Antitumor T-cell Immunity**  ... 714

**Précis:** Type II RAF inhibitors provided distinct advantages over Type I RAF inhibitors when used in combination with MEK inhibitors in models with MAPK pathway alterations.
Machine-Learning and Chemicogenomics Approach Defines and Predicts Cross-Talk of Hippo and MAPK Pathways ....... 778
Précis: A lineage-independent, unbiased approach to characterize Hippo pathway activity and dependency identified cross-talk between the Hippo and MAPK pathways and suggested a potential therapeutic strategy for Hippo-dependent cancers.

Epigenetic and Transcriptional Control of the Epidermal Growth Factor Receptor Regulates the Tumor Immune Microenvironment in Pancreatic Cancer ................. 736
Précis: A screen for tumor cell–intrinsic suppressors of antitumor immunity identified the histone methyltransferase KDM3A, which activated the expression of EGFR to keep the tumor immune microenvironment in a non–T-cell-inflamed state.

Phenotypic Mapping of Pathologic Cross-Talk between Glioblastoma and Innate Immune Cells by Synthetic Genetic Tracing .................... 754
Précis: A genetic tracing method using synthetic reporters comprised of glioblastoma subtype-specific cis-regulatory elements allowed mapping of cell states and fate transitions.

AC icon indicates AuthorChoice
For more information please visit http://www.aacrjournals.org

ON THE COVER The pattern of somatic mutations in lung cancers varies among populations, including in Latin America, where lung cancer is the primary cause of cancer death. Using tumor-sequencing data from 601 and 552 patients with lung cancer (43% of whom did not smoke) from Mexico and Colombia, respectively, Carrot-Zhang and colleagues identified relationships between Native American ancestry and several important tumor characteristics. For instance, EGFR mutations, particularly oncogenic ones, were more common in those with higher Native American ancestry. The identified differences in somatic mutation profiles arose from germline variation rather than disparate environmental exposures. This work highlights the importance of the finer details of ancestry in cancer genetics. For more information, see the article by Carrot-Zhang and colleagues on page 591.