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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.
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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.

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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

Research Articles

Poor Survival and Differential Impact of Genetic Features of Black Patients with Acute Myeloid Leukemia .......... 626


Précis: Black patients with AML fared worse than white patients, a trend that held true after adjusting for socioeconomic status and molecular features, and the impact of common prognosticating mutations (e.g., those in NPM1) differed between the two groups.

See commentary, p. 540

Aggressive PDACs Show Hypomethylation of Repetitive Elements and the Execution of an Intrinsic IFN Program Linked to a Ductal Cell of Origin .............. 638


Précis: Transcriptomic and DNA methylation analyses revealed the existence of an aggressive, ductal cell–derived pancreatic ductal adenocarcinoma subgroup defined by low methylation of repetitive elements and expression of an IFN-linked transcriptional program.

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 Transferin 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.

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.

ON THE COVER

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