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Unique Neoantigens Arise from Somatic Mutations in Patients with Gastrointestinal Cancers ...... 1022


Précis: Neoantigens in cancers with low numbers of mutations are similarly recognized by tumor-infiltrating lymphocytes, with implications for improving immunotherapy.

RESEARCH ARTICLES

First-in-Human RNA Polymerase I Transcription Inhibitor CX-5461 in Patients with Advanced Hematologic Cancers: Results of a Phase I Dose-Escalation Study .......... 1036


Précis: A phase I dose-escalation study evaluates the safety and pharmacokinetics of the RNA Polymerase I inhibitor CX-5461 in patients with advanced hematologic cancers.

Clonal Selection with RAS Pathway Activation Mediates Secondary Clinical Resistance to Selective FLT3 Inhibition in Acute Myeloid Leukemia .......... 1050


Précis: Targeted next-generation sequencing of matched pretreatment and progressive samples from patients with AML on gilteritinib identified multiple secondary gilteritinib resistance mechanisms.

See commentary, p. 998
TAS-120 Overcomes Resistance to ATP-Competitive FGFR Inhibitors in Patients with FGFR2 Fusion–Positive Intrahepatic Cholangiocarcinoma


Précis: The irreversible FGFR inhibitor TAS-120 has clinical activity against FGFR2 mutations that confer resistance to FGFR inhibitors in patients with FGFR2-altered intrahepatic cholangiocarcinoma.

Aging Human Hematopoietic Stem Cells Manifest Profound Epigenetic Reprogramming of Enhancers That May Predispose to Leukemia


Précis: Human hematopoietic stem cells undergo age-associated genome-wide epigenomic changes that target developmental and cancer-related pathways and may increase susceptibility to myeloid malignancies.

Cross-Species Single-Cell Analysis of Pancreatic Ductal Adenocarcinoma Reveals Antigen-Presenting Cancer-Associated Fibroblasts

Elyada and colleagues profiled human pancreatic ductal adenocarcinoma tumors and adjacent normal tissue along with mouse pancreatic tumors and discovered a previously unknown class of cancer-associated fibroblasts (CAF) they named antigen-presenting CAFs (apCAF). These CAFs are unique in their expression of MHC class II–related genes, which implies they may interact with CD4+ T cells; supporting this idea, apCAFs activated CD4+ T cells ex vivo in an antigen-dependent fashion. Also unlike other CAFs, apCAFs upregulate MYC targets and antigen presentation, antigen processing, fatty-acid metabolism, and MTORC1 signaling pathways. Hinting that apCAFs may contribute to immune suppression in PDAC, they do not produce costimulatory molecules needed for induction of T-cell proliferation. For details, please see the article by Elyada and colleagues on page 1102.

β-Catenin Activation Promotes Immune Escape and Resistance to Anti–PD-1 Therapy in Hepatocellular Carcinoma


Précis: A mouse model of hepatocellular carcinoma reveals that β-catenin activation leads to anti–PD-1 resistance via faulty immune surveillance.

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Editor’s Note

Editor’s Note: Increased Levels of COX-2 and Prostaglandin E2 Contribute to Elevated Aromatase Expression in Inflamed Breast Tissue of Obese Women

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ON THE COVER Elyada and colleagues profiled human pancreatic ductal adenocarcinoma tumors and adjacent normal tissue along with mouse pancreatic tumors and discovered a previously unknown class of cancer-associated fibroblasts (CAF) they named antigen-presenting CAFs (apCAF). These CAFs are unique in their expression of MHC class II–related genes, which implies they may interact with CD4+ T cells; supporting this idea, apCAFs activated CD4+ T cells ex vivo in an antigen-dependent fashion. Also unlike other CAFs, apCAFs upregulate MYC targets and antigen presentation, antigen processing, fatty-acid metabolism, and MTORC1 signaling pathways. Hinting that apCAFs may contribute to immune suppression in PDAC, they do not produce costimulatory molecules needed for induction of T-cell proliferation. For details, please see the article by Elyada and colleagues on page 1102.