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Research Brieifs
Somatic HLA Class I Loss Is a Widespread Mechanism of Immune Evasion Which Refines the Use of Tumor Mutational Burden as a Biomarker of Checkpoint Inhibitor Response ............ 282

Précis: Across cancer types, loss of heterozygosity at the locus encoding HLA-I was an independent prognostic factor for response to immune checkpoint blockade, and its predictive power improved when combined with measures of tumor mutation burden.

Lower Airway Dysbiosis Affects Lung Cancer Progression ............ 293

Précis: Lower airway dysbiosis characterized by excessive colonization with oral commensal microbes, particularly Veillonella parvula, was a predictor of poor prognosis in lung cancer, and in vivo experiments supported a role for V. parvula colonization in decreasing survival.

See commentary, p. 224

RESEARCH ARTICLES

Personalized Antibodies for Gastroesophageal Adenocarcinoma (PANGEA): A Phase II Study Evaluating an Individualized Treatment Strategy for Metastatic Disease ......... 308

Précis: In a phase II clinical trial, personalized antibodies plus molecularly targeted chemotheraphy improved median overall survival and the one-year survival rate in patients with gastroesophageal adenocarcinoma relative to historical survival data.

Clinicogenomic Analysis of FGFR2-Rearranged Cholangiocarcinoma Identifies Correlates of Response and Mechanisms of Resistance to Pemigatinib ......................... 326

Précis: In patients with cholangiocarcinoma harboring FGFR fusions or rearrangements, response to the FGFR1–3 inhibitor was equally likely regardless of the type of genomic alteration, and resistance mutations affected the FGFR2 kinase domain.

Selection of Oncogenic Mutant Clones in Normal Human Skin Varies with Body Site .................. 340

Précis: Genetic analyses of healthy aged human epidermal cells revealed skin site–specific mutational signatures, with common skin cancer sites exhibiting more potentially oncogenic mutations and with high variability in mutations under positive selection among sites.

See commentary, p. 227

Genetically Defined, Syngeneic Organoid Platform for Developing Combination Therapies for Ovarian Cancer ....... 362

Précis: Organoids representing high-grade serous ovarian cancer were developed; these organoids exhibited varying sensitivities to chemotheraphy drugs and elicited different immune responses, suggesting they may serve as a novel platform for discovery.

Genetically Defined Syngeneic Mouse Models of Ovarian Cancer as Tools for the Discovery of Combination Immunotherapy .................. 384

Précis: To address the inability of current high-grade serous tubo-ovarian carcinoma models to accurately recapitulate immunotherapy responses, a new mouse model was developed; proof-of-concept experiments uncovered follistatin as a mediator of response.

A TLR3 Ligand Reestablishes Chemotherapeutic Responses in the Context of FRP1 Deficiency .............. 408

Précis: The TLR3 ligand polyinosinic:polycytidylic acid improved the efficacy of chemotherapy observed in the context of FRP1 loss-of-function mutation, which occurs in 30% of individuals and diminishes the antitumor immune response following chemotherapy.
The RNA m6A Reader YTHDF2 Maintains Oncogene Expression and Is a Targetable Dependency in Glioblastoma Stem Cells... 480

Précis: In glioblastoma stem cells, YTHDF2 (which reads mRNA for the modified nucleotide N^6-methyladenosine) stabilized MYC and VEGFA transcripts via an IGFBP3-mediated mechanism, and blocking IGF–IGF1R signaling in vivo hindered glioblastoma growth.

The Hepatic Microenvironment Uniquely Protects Leukemia Cells through Induction of Growth and Survival Pathways Mediated by LIPG ............ 500

Précis: Liver-infiltrating leukemia stem cells in mice acquired a proliferative, chemotherapy-resistant phenotype characterized by over-expression of the gene encoding the lipase LIPG, which was sufficient to induce the same phenotype in non–liver-infiltrating leukemia cells.

Correction: Impact of PD-1 Blockade on Severity of COVID-19 in Patients with Lung Cancers ................. 520

The risk of skin cancers such as basal cell carcinoma and squamous cell carcinoma varies greatly across the body, and it is known that healthy aged skin cells often harbor cancer driver mutations, but whether these observations are connected has not been determined. Fowler and colleagues discovered that the mutation density in healthy human skin differed from location to location across the body. Common sites for skin cancer, such as the forearm, bore more mutations than uncommon sites, and the mutation profile suggested UV radiation as a cause. Interestingly, not only was there selection for cancer-associated mutations in healthy skin, but the DNA repair mechanisms used varied based on site. For more information, see the article by Fowler and colleagues on page 340.

See commentary, p. 230