In this issue

Long-Term COVID-19 Vaccine Efficacy Is Evaluated in Patients with Solid Tumors

The short-term efficacy, immunogenicity, and safety of COVID-19 vaccines in patients with cancer have been reported, but long-term outcomes remain unknown. Waldhorn and colleagues report on the six-month efficacy, immunogenicity, and safety of the BNT162b2 (Pfizer/BioNTech) COVID-19 vaccine in 154 patients with solid tumors on active intravenous treatment and 135 age-matched healthcare workers in Israel, one of the first countries to administer COVID-19 vaccines. Six months post vaccination, 79% of patients were seropositive compared with 84% of control subjects, and serology titer similarly decreased over time in both cohorts. Although further confirmation will be needed, these findings suggest that the long-term outcomes of COVID-19 vaccination in patients with solid tumors undergoing treatment are similar to those of the general population.

See article, p. 2430.

Antigen and Payload Mutations Confer Sacituzumab Govitecan Resistance

Sacituzumab govitecan is an antibody–drug conjugate approved by the FDA for previously treated advanced or metastatic triple-negative breast cancer (mTNBC) that consists of an anti-TROP2 antibody conjugated to a topoisomerase-1 (TOP1) inhibitor payload. To identify potential mechanisms of intrinsic and acquired resistance to sacituzumab govitecan, Coates, Sun, and colleagues performed RNA and whole-exome sequencing of pretreatment and post-progression tumor tissue from patients with mTNBC, and in post-progression metastatic lesions from one patient who had initially responded they observed missense mutations in both TACSTD2 (encoding TROP2) and TOP1 that were not present in pretreatment samples. Future studies will be needed to determine how common parallel alterations of antigen and payload targets are in acquired resistance to sacituzumab govitecan as well as to other antibody–drug conjugates.

See article, p. 2436.

A Colorectal Cancer Mutational Signature Is Linked to Red Meat Intake

Various dietary factors have been associated with an increased risk of colorectal cancer, but direct links to mutational signatures in tumors have been elusive. Gurjao and colleagues leveraged a unique dataset of 900 archival matched primary untreated tumor–normal tissue pairs from participants in three US-wide large prospective cohort studies who had provided longitudinal information on diet, lifestyle, and other factors prior to any cancer diagnosis. Seven distinct mutational signatures across colorectal cancer samples were identified, including one similar to previously characterized DNA alkylating signatures that was specifically associated with prediagnosis intake of red meat and that targeted colorectal cancer–associated KRAS and PIK3CA mutations. This link between a colorectal mutational signature and dietary behavior provides molecular evidence for a role of red meat intake in colorectal cancer initiation.

See article, p. 2446.

APOBEC3 Induction Is an Early Driver of Cancer Evolution

APOBEC3 cytosine deaminases have been implicated in cancer mutational signatures, but exactly when they are activated during tumorigenesis is unclear. Venkatesan and colleagues show that expression of APOBEC3 genes is upregulated in preinvasive breast and lung cancer lesions due to increased cellular proliferation and DNA replication stress and that APOBEC3-driven mutations were early events in the course of evolution from preinvasive to invasive tumors. In a mouse model of lung cancer, induction of APOBEC3B further exacerbated DNA replication stress, chromosome instability, and aneuploidy, and APOBEC3B expression correlated with chromosome instability in preinvasive human tumors. These results suggest that induction of APOBEC3 enzymes is an early event in tumorigenesis that promotes genomic instability and drives tumor evolution.

See article, p. 2456.

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IN THIS ISSUE

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IN THIS ISSUE

HER2 Heterogeneity Is Associated with Response to Anti-HER2 Therapy

Intratumor heterogeneity (ITH) is a potential driver of resistance to targeted therapy. To assess the role of ITH in resistance to HER2-targeted therapy, Metzger Filho, Viale, Stein, and colleagues performed a prospective phase II clinical trial of 164 patients with HER2-positive breast cancer who received trastuzumab emtansine (T-DM1) with pertuzumab and evaluated HER2 heterogeneity in pre- and post-treatment biopsies. They showed that there was a significant association between HER2 heterogeneity, as determined by either protein or copy number level, and pathologic complete response, suggesting that HER2 heterogeneity could potentially improve therapeutic selection of patients with HER2-positive breast cancer.

See article, p. 2474.

FGFR2 Extracellular Domain In-Frame Deletions Drive Cholangiocarcinoma

Patients with cholangiocarcinoma who harbor FGFR-activating fusions or mutations have exhibited mixed responses to FGFR2 inhibitors, depending on the specific FGFR2 alteration. Cleary, Raghavan, Wu, and colleagues performed next-generation sequencing to identify other FGFR2 alterations that might predict sensitivity to FGFR2 inhibitors and identified FGFR2 extracellular domain in-frame deletions (EID) in 5 of 178 patients. FGFR2 EIDs were shown to drive FGFR2 activation, oncogenic transformation, and sensitivity to FGFR2 inhibition, and three patients with FGFR2 EIDs exhibited partial responses to an oral FGFR2 inhibitor. These findings implicate FGFR2 EIDs as an alternative mechanism of FGFR2 activation in cholangiocarcinoma and suggest these alterations should also be considered as biomarkers of sensitivity to FGFR inhibitors.

See article, p. 2488.

Multiregion Single-Cell Sequencing Delineates Lung Adenocarcinoma Evolution

Elucidation of the biology underlying cancer evolution is critical for improving patient outcomes. Sinjab, Han, and colleagues performed multiregion, single-cell analysis of early-stage lung adenocarcinomas (LUAD) and matched adjacent and distal normal lung tissues, after enrichment for epithelial cells. They characterized heterogeneity in LUAD tumor cells at both the cellular and intratumoral level, revealed LUAD-tumor microenvironment cross-talk, and identified normal epithelial populations that exhibit cancer cell transcriptional profiles. Together, these findings provide insights into the development of early-stage LUAD and define potential early intervention strategies.

See article, p. 2506.

Integrated Analysis of Pediatric Liver Tumors Reveals Features of Cisplatin Resistance

Pediatric liver tumors are a diverse set of diseases with heterogeneous responses to chemotherapy. Using multiomic analyses, Hirsch, Pilet, Morcrette, and colleagues revealed the molecular diversity of more than 100 pediatric liver tumors. Hepatocellular carcinomas were characterized by a deleteror phenotype with numerous focal deletions. Among hepatoblastomas, 10% of tumors showed a 11p15 mosaic alteration as the earliest preneoplastic genomic event, and plasticity between molecular subgroups was common. Tracing the mutational footprint of cisplatin adducts in primary and metastatic hepatoblastomas identified cell plasticity and a progenitor phenotype at the origin of cisplatin resistance. In preclinical models, targeting these progenitor cells could overcome cisplatin resistance, suggesting new therapeutic options for patients with refractory disease.

See article, p. 2524.
Drug-Repurposing Screen Reveals Vulnerabilities in Fibrolamellar Carcinoma

Fibrolamellar carcinoma is an often-lethal liver cancer affecting adolescents and young adults. To identify potential therapeutics, Lalazar and colleagues developed patient-derived xenografts and screened a drug-repurposing library. The top hits were then screened against tumors in mice or cells from fresh patient tumor resections. Novel classes of therapeutics and synergistic drug combinations were identified, whereas drugs in clinical use for fibrolamellar carcinoma and agents against overexpressed oncogenes demonstrated no efficacy. This highlights the importance of precision medicine premised on functional screens rather than genomic expression and the value of direct-from-patient screens for solid tumors. ■

See article, p. 2544.

CDK4/6 Inhibition Promotes Immunologic Memory

Heckler, Ali, and colleagues report that CDK4/6 inhibitors promote the formation of memory CD8 T cells, which are important for generating long-term durable remissions in patients with cancer. CD8 T cells cultured with CDK4/6 inhibitors displayed increased persistence upon adoptive transfer and protected mice from tumor challenge. In patients with breast cancer newly starting on palbociclib or abemaciclib, CD8 T-cell memory precursors were increased in peripheral blood. CDK4/6 inhibitors may have broad utility outside of breast cancer, particularly in the neoadjuvant setting when CD8 T-cell priming to tumor antigens may occur or in the setting of adoptive cellular therapy. ■

See article, p. 2564.

Inhibition of CDK4/6 Enhances T-cell Memory and Antitumor Immunity

Inhibitors of CDK4/6 were developed to induce tumor cell cytostasis, but have since demonstrated profound immunomodulatory activity through mechanisms that remain unclear. Using integrated single-cell multiomic analyses, Lelliott and colleagues discovered that CDK4/6 inhibition enhances T-cell memory differentiation, through direct T cell–intrinsic mechanisms. Preconditioning human CAR T cells with CDK4/6 inhibitor enhanced persistence and tumor control, and clinical treatment with CDK4/6 inhibitor promoted expansion of memory T cells, priming a response to immune checkpoint blockade. This study identifies CDK4/6 as a critical regulator of T-cell fate, expanding the potential application of CDK4/6 inhibitors as clinical tools to boost antitumor T-cell immunity. ■

See article, p. 2582.

Anti-Inflammatory Drugs Synergize with Immune Checkpoint Blockade

The protumorigenic effects of inflammation have been well studied; however, less is known about the effect of inflammation on resistance to immunotherapy. Pelly, Moeini, and colleagues demonstrated that targeting the COX2/PGE2/EP2-4 axis with nonsteroidal and steroidal anti-inflammatory drugs reshapes the immune microenvironment toward an antitumor inflammatory state, and in combination with immune checkpoint blockade (ICB) increased the intratumoral accumulation of T cells with improved effector function. These findings identify a mechanism by which anti-inflammatory drugs alter the tumor immune microenvironment and suggest that combining anti-inflammatory drugs with ICB is a promising avenue to increase the efficacy of ICB in patients. ■

See article, p. 2602.
**Dedifferentiation during Tumorigenesis Retraces a Developmental Pathway**

Little is known about the biology of high-grade pancreatic neuroendocrine tumors (PanNET), which are highly lethal. Saghafinia and colleagues characterize dedifferentiation in a mouse model of PanNET, where solid tumors progress to invasive and metastatic islet carcinomas by retracing the developmental pathway of islet β-cells. They identified a regulatory pathway which drives dedifferentiation and includes upregulation of miR-181cd and the transcription factor gene Hmgb3, and increased expression of miR-181cd and HMGB3 correlated with tumor progression and comparatively poor survival in human islet carcinomas. These results provide insights into a mechanism by which dedifferentiation drives pancreatic cancer cell plasticity.

*See article, p. 2638.*

**SS18–SSX Induces CBAF Destruction in Synovial Sarcomagenesis**

Using mouse genetics, molecular biology, and biochemical approaches, Li, Mulvihill, and colleagues define a new conceptual model for synovial sarcomagenesis, based on disruption of the relative abundance of the BAF subfamilies, canonical BAF, PBAF, and GBAF. The authors show that SMARCB1 is required for synovial sarcomagenesis and incorporates into both PBAF and SS18–SSX-containing canonical BAF complexes. SS18–SSX causes the specific degradation of canonical BAF complexes, leading to a relative increase in GBAF and PBAF levels in synovial sarcoma. These results provide a mechanistic explanation for the previously observed reduction in SMARCB1 protein levels and sensitivity to GBAF component degradation.

*See article, p. 2620.*