Dysregulation of mRNA processing has been proposed to generate neoantigens that would be both tumor-specific and shared between patients. Mutations of the SF3B1 splicing factor in tumors had previously been shown to lead to alterations in splicing of particular mRNA junctions. Bigot, Lalanne, and colleagues showed that these splicing aberrations code for additional amino acids or frameshifts in exons and generate neoepitopes presented by HLA molecules. CD8+ T cells specific to these neoepitopes were found in both blood and tumors of patients. Tumor cells were recognized by neoepitope-specific T cells, supporting the use of these neoantigens as therapeutic targets.

See article, p. 1938.

Mutations of a Splicing Factor Generate Shared Tumor-Specific Neoantigens

Drug resistance and toxicity limit the effectiveness of standard-of-care therapies in patients with mismatch repair-deficient (dMMR) colorectal cancer. The viability of dMMR cancer cells depends on Werner syndrome ATP-dependent helicase (WRN). Picco and colleagues demonstrate WRN to be an almost universal vulnerability in a large, heterogeneous collection of dMMR colorectal cancer preclinical models. Specific MMR-pathway gene inactivation was found to be associated with WRN dependency. Moreover, WRN synthetic lethality was observed in dMMR colorectal cancer patient-derived models and cocultures of acquired resistance to standard-of-care therapy, including immunotherapy. These data support the development of WRN-targeted medicines to treat treatment-refractory tumors.

See article, p. 1923.

MHC Class I Expression Marks an Immunogenic Subtype of Small Cell Lung Carcinoma

Small cell lung carcinoma is generally refractory to treatment and lacks biomarkers for effective immune checkpoint blockade (ICB). In this issue, Mahadevan, Knelson, and colleagues report that the majority of small cell lung carcinoma is defective in MHC class I antigen presentation, whereas a distinct subtype with mesenchymal features restores MHC I and STING expression. This MHC I–high subtype was enriched in patients with durable ICB responses and proved to be immunogenic in cell lines and a syngeneic mouse model. Furthermore, transient EZH2 inhibition unveiled this phenotype and primed a durable response to STING agonism in their mouse model.

See article, p. 1952.
Co-targeting LSD1 and TGFβ Breaks Tumor Resistance to Anti–PD-1 Therapy

Perturbation of epigenetic regulators holds promise to overcome tumor resistance to anti–PD-1 therapy, but confounding effects of epigenetic perturbations have to be understood and tackled. Sheng, Liu, and colleagues sought factors limiting the effectiveness of LSD1 depletion in combination with anti–PD-1 treatment and found that immunosuppressive TGFβ cytokines were induced. In the tumor microenvironment, TGFβ suppressed the cytotoxicity of CD8+ T cells whose infiltration was elevated by LSD1 depletion, thereby dampening the combinatorial effect of LSD1 depletion and anti–PD-1 treatment. A triple combination strategy involving LSD1 depletion and dual PD-1/TGFβ blockade led to eradication of previously resistant tumor models.

See article, p. 1970.

Characterization of Immune Responses to SARS-CoV-2 in Patients with Cancer

Despite the increasing knowledge on immune responses to SARS-CoV-2, studies analyzing the particularly vulnerable population of patients with cancer remain scarce. Bilich, Roerden, and colleagues assessed SARS-CoV-2 immune responses in patients with cancer of various tumor entities and observed, in contrast to antibody responses, reduced preexisting and post–COVID-19 T-cell responses and signs of T-cell exhaustion in hematologic malignancies compared with healthy volunteers and patients with solid tumors. Impaired diversity of SARS-CoV-2 T-cell responses in patients with cancer further associated with severe COVID-19, bearing important implications for the development of prophylactic and therapeutic measures.

See article, p. 1982.

Targeting TLR9 in Combination with Ipilimumab to Overcome Anti–PD-1 Resistance

Reinvigorating the antitumor immune response by targeting local antigen presenting cells through intratumoral administration of tilsotolimod, a TLR9 agonist, in combination with systemic ipilimumab is a strategy explored in this phase I/II study to overcome resistance to anti–PD-1 in metastatic melanoma. Haymaker and colleagues found that local tilsotolimod injection resulted in a rapid induction of the type 1 interferon signaling pathway and response was associated with the presence of dendritic cells in the injected lesion. Early on-treatment biopsies revealed immune activation in both injected and uninjected lesions and expansion of tumor-restricted T-cell clones in responding patients.

See article, p. 1996.

Immune Atlas Revealing Heterogeneity and Contexture of Human Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC) is poorly responsive to therapy. As new immunotherapy combinations are clinically evaluated, deep phenotypic and spatial immune assessment of treated versus untreated PDACs will reveal parameters of immune response and resistance to therapy. Liudahl and colleagues used a single cell multiplex immunohistochemistry imaging platform to quantitatively evaluate lymphoid and myeloid contexture of 135 therapy-naive and neoadjuvant-treated human PDACs. The resulting immune atlas reveals intra- and interpatient leukocyte heterogeneity, and illuminates common features encompassing significant protumoral and T cell–suppressive myeloid infiltrates admixed with PD-1–negative T cells, exposing their diminished activation and effector functionality.

See article, p. 2014.
**CD72 Is an Enriched Immunotherapy Target for MLLr B-cell Leukemia**

B-cell leukemias harboring KMT2A/MLL1 rearrangements (MLLr) remain difficult to treat and relapse more often despite new immunotherapy treatment options. Nix and colleagues performed a mass spectrometry cell surface proteomics screen on MLLr and non-MLLr B-ALL cells and revealed that CD72 is upregulated on the MLLr cell surface and highly targetable by immunotherapy. Fully synthetic nanobodies against CD72 selected via yeast display were incorporated into CAR-Ts. These engineered cells demonstrated robust in vitro and in vivo activity against CD72-bearing malignant B cells. These findings highlight the promise of synthetic nanoCARs targeting CD72 for relapsed/refractory MLLr B-ALL as well as their potential in other B-cell malignancies.

See article, p. 2032.

**Epigenetic Inhibitor with Dual Action on Tumor and Immune Cells**

Many drugs that target cancer cells unfortunately impair antitumor immunity. Kumar and colleagues performed an in vivo genetic screen and discovered that inactivation of CARM1 in T cells enhanced their antitumor function. Inactivation of CARM1 in tumor cells sensitized tumor cells to T-cell attack through induction of a type 1 interferon response. A small-molecule CARM1 inhibitor greatly enhanced tumor infiltration by T cells, natural killer cells, and dendritic cells and showed substantial synergy with immune checkpoint inhibition. Targeting of this epigenetic enzyme thus simultaneously sensitizes tumor cells to immune attack and enhances the cytotoxic function of T cells.

See article, p. 2050.

**A Link between Obesity and Renal Cancer through Adipokine Signaling**

Obesity, which is self-promoting through production of fat-derived adipokines, is a known risk factor for several cancers. In clear cell renal cell carcinoma (ccRCC), the overt lipid storage phenotype suggests that common paracrine mechanisms might drive adipogenesis and support tumor growth, and explain the elevated risk of ccRCC in obese individuals. Chemerin, a fat and tumor derived adipokine, has known adipogenic activity. Here, Tan and colleagues demonstrate chemerin levels spike in patients with ccRCC commensurate with tumor volume and lipid storage levels. Targeting of chemerin molecularly or with a monoclonal antibody prevents lipid storage and induces ferroptotic cell death due to excess lipid oxidation. Thus, chemerin is a bona fide target and biomarker that links obesity to renal cancer.

See article, p. 2072.

**Oncogenic KRAS and Mutant p53 Converge on CREB1 to Drive PDAC Metastasis**

Pancreatic ductal adenocarcinoma (PDAC) is highly metastatic and predominantly characterized by driver mutations in KRAS and TP53. However, prometastatic mechanisms of cooperation between oncogenic KRAS effectors and mutant p53 are not well characterized. Kim and colleagues developed a somatic mutant p53 mouse model to dissect prometastatic mutant p53 gain of function. Oncogenic KRAS effectors were found to activate the transcription factor CREB1, enabling direct interactions with mutant p53 that hyperactivate prometastatic transcriptional networks directed by FOXA1 and β-catenin. Pharmacologic CREB1 inhibition dampened PDAC metastasis and FOXA1 and β-catenin expression/activity, identifying a targetable node between dominant PDAC driver genes.

See article, p. 2094.