Illustrative Use Cases Demonstrate the Utility of the St. Jude Cloud

Large datasets have become the norm in cancer research, but their utility has been limited by factors such as inadequate data sharing—a problem caused in part of the massive sizes of the datasets. Lack of access to computing resources can also be a hindrance. To address this, McLeod, Gout, and colleagues developed the St. Jude Cloud: an online resource that enables sharing, visualization, and analysis of large-scale data on pediatric cancer and other serious illnesses. Use cases reported by this group include pediatric cancer classification using RNA sequencing and analyses of mutation rates and mutational signatures in pediatric cancers.

See article, p. 1082.

PD-1–CTLA4-Targeting Bispecific Antibody Restricts Tumor Growth In Vivo

Combination immune checkpoint blockade using anti–PD-1 or anti–PD-L1 plus anti-CTLA4 has shown signs of synergy, and tumor-infiltrating PD-1+ effector memory T cells enhance response to anti-CTLA4. Dovedi and colleagues investigated the use of the monovalent, PD-1– and CTLA4-targeting bispecific antibody MEDI5752, which was designed to limit the immune-related adverse events associated with combined PD-1–PD-L1 plus CTLA4 blockade. MEDI5752 specifically inhibited CTLA4 activity on PD-1+ activated T cells and, notably, promoted internalization and subsequent degradation of PD-1, leading to cell-surface down-regulation of PD-1. Importantly, MEDI5752 targeted tumors and restricted tumor growth in vivo; as such, the treatment is now being evaluated in a first-in-human trial.

See article, p. 1100.

p300/CBP inhibition Suppresses AR Signaling and Prostate Tumor Growth

The transcription factor activity of the paralogous proteins p300 and CBP is essential to AR-dependent gene expression, making them attractive targets for treating prostate cancer. Welti, Sharp, Brooks, and colleagues found that knockdown of CREBBP (encoding CBP) and EP300 (encoding p300) reduced expression of AR-upregulated genes and inhibited growth of prostate cancer cells. Notably, treatment with the small-molecule p300/CBP inhibitor CCS1477 also inhibited prostate cancer cell growth and reduced expression of genes in prostate cancer-associated pathways, including in castration-resistant cells expressing AR splice variants. Finally, in patient-derived xenograft mouse models (including one resistant to enzalutamide with AR amplification and alternative splicing), CCS1477 diminished tumor growth.

See article, p. 1118.

A Colon Microbe Promotes β-catenin–Notch1-Mediated Breast Tumorigenesis

The nature of microbes colonizing the breast ducts and gut has been proposed to contribute to breast cancer, but little is known about this phenomenon. Parida and colleagues found pervasive colonization of tumor-bearing breasts with Bacteroides fragilis, a colon-dwelling species with a propensity to enter the bloodstream and spread to other sites. Importantly, breast or gut colonization by enterotoxigenic B. fragilis, which produces the toxin BFT, led to mammary epithelial cell hyperplasia in mice. BFT exposure alone promoted an invasive, migratory, stemlike phenotype in breast cancer cells grown in vitro, characteristics that were retained during growth in vivo and mediated by β-catenin and Notch1.

See article, p. 1138.
Mutations Affecting the BAF Complex Hinder Thyroid Cancer Treatments

Although radioiodine treatment can be effective for types of differentiated thyroid cancer, dedifferentiated thyroid cancers are typically unresponsive. Saqcena, Leandro-García, and colleagues investigated the impact of disruptions to the BAF subtype of mammalian SWI/SNF chromatin remodeling complex on thyroid cancer differentiation state, finding that loss of the genes encoding the SWI/SNF components ARID1A, ARID2, or SMARCB1 in Bralf600E-mutant mice promoted thyroid cancer. Mechanistically, functional loss of the BAF complex reduced expression of thyroid differentiation markers, reducing chromatin accessibility at genes encoding thyroid lineage transcription factors. Critically, this loss also abrogated the redifferentiation effects of MAPK inhibition and reduced effectiveness of radioiodide treatment in vivo.

See article, p. 1158.

DNA Polymerase and Mismatch Repair Defects Cause Distinct Genetic Signs

Although constitutional mismatch-repair deficiency syndrome (CMMRD syndrome; caused by defective mismatch-repair genes) shares features with polymerase proofreading deficiency syndrome (PPD syndrome; caused by mutations in POLE or POLD1), Chung and colleagues identified defining genetic features of each syndrome. Notably, microsatellites in tumors from patients with CMMRD syndrome often exhibited deletions spanning multiple base pairs, whereas microsatellites in tumors from patients with PPD syndrome more commonly had single-base pair insertions. Importantly, tumors with mutational signatures more similar to those of patients with PPD syndrome were more likely to respond to immune checkpoint blockade than those of patients with tumors similar to those with CMMRD syndrome.

See article, p. 1176.

Genetic Screens Provide Hints to Improve CAR T Therapy for Glioblastoma

Despite early hints, chimeric antigen receptor (CAR) T-cell therapies for glioblastoma have largely disappointed in the clinic. To understand why, Wang, Prager, and colleagues performed CRISPR–Cas9-based mutagenesis experiments manipulating both CAR T cells and glioblastoma cells. The CAR T-cell analysis revealed that knockout of the genes encoding the transcriptional regulators TLE4 and IKZF2 enhanced CAR T-cell function and reduced exhaustion. The screen to identify vulnerabilities in glioma stem cells (GSC) showed that knockout of the genes encoding NPLOC4 (involved in the unfolded protein response) and the transcription factor RELA sensitized GSCs to CAR T-cell therapy. These results may enable improved design of CAR T-cell treatments for glioblastoma.

See article, p. 1192.

Tumor Cell ENPP1 Activity Blocks cGAS–STING-Mediated Antitumor Immunity

Cancer cells often harbor rupture-prone double-stranded DNA (dsDNA)-containing micronuclei. Upon release into the cytosol, this dsDNA triggers activation of the cGAS–STING pathway, in which cGAS produces the immunogenic cyclic dinucleotide cGAMP, which is readily released into the cytosol. Li, Duran, and colleagues found that, to circumvent the immunosurveillance extracellular cGAMP would otherwise elicit, cancer cells upregulated the type II transmembrane glycoprotein ENPP1, which hydrolyzes extracellular cGAMP, preventing activation of STING and the consequent type I IFN response. Further, this hydrolysis produced AMP, which was processed into immunosuppressive adenosine. Finally, ENPP1 overexpression increased metastasis, and ENPP1 inhibition increased response to immune checkpoint blockade in vivo.

See article, p. 1212.
Pharmacologic inhibitors of epigenetic enzymes lead to aberrant transcription of genetic elements, such as endogenous retroviruses, which are otherwise normally silenced. Activation of endogenous retroviruses is expected to trigger an IFN-mediated innate immune response, but Fresquet and colleagues also discovered that the released cytosolic double-stranded RNA was sensed by RIG-I and MDA5, RNA helicases that act via ATP hydrolysis. The resulting ATP depletion reversed the Warburg effect such that mitochondrial oxidative phosphorylation increased whereas aerobic glycolysis decreased, but hyperactive mitochondrial succinate dehydrogenase produced reactive oxygen species and consequent caspase-independent tumor necroptosis that could be further promoted by BCL2 inhibitors, suggesting synergy between epigenetic inhibitors and BCL2 inhibitors.

See article, p. 1268.

Gut dysbiosis and defective gut barrier function are associated with cancer-linked liver diseases such as primary sclerosing cholangitis (PSC) and cirrhosis, but whether these factors influence hepatic antitumor immunity is unknown. Zhang and colleagues found that, in mice with PSC or colitis, impaired gut barrier function caused the liver to be exposed to gut microbiota, and Gram-negative bacteria induced hepatic accumulation of tumor-promoting myeloid-derived suppressor cells (MDSC) in a TLR4-dependent manner. Eliminating these bacteria with neomycin reduced cholangiocarcinoma development, as did Tlr4 knockout. Patient data indicated that gut microbial composition influenced liver infiltration by MDSCs, suggesting that these findings may have clinical relevance.

See article, p. 1248.

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See article, p. 1268.

The presence of a small number of quasi-mesenchymal (qM) cancer cells can produce a tumor microenvironment sufficiently immunosuppressive to shelter a majority population of epithelial cancer cells from immunosurveillance. Dongre and colleagues found that qM breast carcinoma cells produced cancer-linked immunomodulatory proteins; CD73 in particular strongly regulated CD8+ T-cell activity. Although tumors grown solely from qM cells did not respond to anti-CTLA4, Cd73 knockout in qM cells restored sensitivity to anti-CTLA4, even in tumors containing 90% epithelial cells and only 10% qM cells. This work reveals a key vulnerability of tumors in which some cells have undergone the epithelial-to-mesenchymal transition.

See article, p. 1286.

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