In this issue

HLA-I Loss of Heterozygosity Is Prognostic of Immunotherapy Response

Despite the utility of immune checkpoint blockade (ICB), predicting which patients will respond to ICB is problematic. In data from 83,644 patient samples representing 59 cancer types, Montesion and colleagues found that tumor mutation burden (TMB)—a prognostic factor for ICB response—had a nonlinear relationship with loss of heterozygosity (LOH) at the locus encoding HLA-I. Cancers with moderate TMB had high HLA-I locus LOH, but those with high TMB had low LOH, suggesting that high TMB necessitates alternative mechanisms for immune evasion. Importantly, combining measures of HLA-I locus LOH and TMB enabled better prediction of ICB response than either factor alone.

See article, p. 282.

Lung Colonization by Some Oral Microbes Predicts Lung Cancer Prognosis

Colonization of the lower airways with oral commensal organisms occurs in healthy individuals but is associated with lung inflammation. Tsay and colleagues investigated the role of these organisms in lung cancer, finding that lower airway dysbiosis characterized by an overabundance of oral commensals was associated with greater tumor stage, poorer survival among patients with lower-stage tumors, and increased tumor progression among patients with higher-stage tumors. In particular, colonization by the *Veillonella parvula* was correlated with a cancer-associated transcriptomic signature, and *in vivo* experiments showed that excessive *Veillonella parvula* colonization decreased survival and increased tumor burden.

See article, p. 293.

Personalized Antibodies Show Promise in Gastroesophageal Adenocarcinoma

A major hindrance to the successful treatment of gastroesophageal adenocarcinoma is not only interpatient molecular heterogeneity, but also intrapatient molecular heterogeneity that may evolve over time with treatment. In a phase II clinical trial, Catenacci and colleagues addressed these issues using a combination of molecularly targeted sequential chemotherapy and personalized monoclonal antibodies. In an intention-to-treat analysis including 68 patients, the median overall survival was 15.7 months and the one-year survival rate was 66%; although the study did not include a control group, these values are superior to historical results. Larger, controlled studies of this approach are warranted.

See article, p. 308.

Genomics Sheds Light on Pemigatinib Response in Cholangiocarcinoma

*FGFR* fusions or rearrangements occur in up to 16% of cholangiocarcinomas, and a recent phase II clinical trial revealed that some patients with chemotherapy-pretreated tumors with these genomic alterations responded to the FGFR1–3 inhibitor pemigatinib. Silverman and colleagues further analyzed data from this trial, finding that additional potentially clinically actionable genetic alterations occurred in 44.5% of patients. Response to pemigatinib was equally likely in patients with *FGFR* fusions or alterations, and *FGFR*’s rearrangement partner did not affect response. Notably, all tested patients with acquired pemigatinib resistance had mutations affecting *FGFR2*’s kinase domain. This work provides insight that may refine the clinical use of pemigatinib.

See article, p. 326.
Skin cancers exhibit a predilection for certain sites, and healthy aged skin is characterized by positive selection for some cancer driver mutations, but whether there is a relationship between these facts is unknown. Fowler and colleagues found that mutation density in healthy human skin varied by site, with common skin cancer sites such as the forearm often harboring cancer driver mutations. Interestingly, although most epidermal cells sampled had signatures of UV radiation–induced DNA damage, the DNA repair pathways used varied. Notably, the cancer driver mutations under positive selection varied by site. This study suggests that skin is a patchwork of mutant clones varying by location.

See article, p. 340.

Both genetically engineered mouse models and patient cell–based models such as xenografts and tumoroids fall short of encompassing the full complement of factors in human tumors. In one effort to address these models’ shortcomings, Zhang and colleagues developed a new syngeneic organoid platform to enable the study of treatments for high-grade serous ovarian cancer (HGSC). In this model, mouse fallopian tube epithelial cells were engineered to exhibit genetic characteristics of HGSC. As a proof-of-concept, it was demonstrated that these organoids had various sensitivities to chemotherapy drugs and even elicited different immune responses, potentially enabling them to serve as a platform for discovery of tumor biology and drugs.

See article, p. 362.

A major difficulty hindering the understanding of high-grade serous tubo-ovarian carcinomas (HGSC) is a lack of models that allow examination of the response of HGSCs to immunotherapies. Iyer, Zhang, and colleagues addressed this by developing new mouse models of homologous recombination–deficient and homologous recombination–proficient HGSC. These models closely mimicked known genotype–drug response relationships, and proof-of-concept analyses revealed that follistatin, which neutralizes TGFβ-superfamily proteins, may mediate resistance to immune checkpoint blockade. Together, the evidence provided in this study demonstrates that this new tumor model recapitulates the immune microenvironment in human tumors and may enable HGSC immunotherapy studies.

See article, p. 384.

Following treatment with cytotoxic chemotherapies, annexin A1 (ANXA1) released by cancer cells is sensed by formyl peptide receptor (FPR1) on myeloid cells such as dendritic cells, an important facet of the anti-tumor immune response. Given that almost one third of individuals worldwide harbor a loss-of-function (LOF) mutation in FPR1, Le Naour, Liu, and colleagues investigated ways to sidestep this issue and discovered that polyinosinic:polycytidylic acid, a ligand of TLR3, enhanced the otherwise low response of FPR1-LOF to chemotherapeutics. Further, polyinosinic:polycytidylic acid treatment was associated with increased dendritic-cell and T-cell activity. This work demonstrates how a common cancer-related genetic variant can be circumvented by treatment.

See article, p. 408.
Although evidence suggests that dissemination of cancer cells through lymphatic vessels to the lymph nodes and subsequently distant sites is an important metastatic pathway, current models do not enable the underlying mechanisms to be assessed. Gengenbacher, Singhal, and colleagues developed a platform to study this phenomenon in which tumors from genetically engineered mouse models (GEMM) are allografted into new hosts, enabling normal tumor lymphatic architecture to be preserved while preventing the need for premetastatic sacrifice common to GEMMs. Proof-of-concept studies identified the Ang2–Tie2 pathway as being essential for lymphogenous metastasis, demonstrating the utility of this new platform.

See article, p. 424.

Cancer-associated fibroblasts (CAF) are critical contributors to tumorigenesis in pancreatic ductal adenocarcinoma (PDAC), but much remains unknown about the mechanisms underlying their multifaceted role. Francescone, Barbosa Vendramini-Costa, and colleagues found that the glutamatergic presynaptic protein Netrin-G1 was an important contributor, with Netrin-G1+ CAFs promoting PDAC tumorigenesis and persistence via effects on glutamate–glutamine metabolism. Further, Netrin-G1+ CAFs suppressed NK-cell function in the tumor microenvironment. In vivo, a Netrin-G1 neutralizing antibody suppressed PDAC tumorigenesis. Collectively, these findings support Netrin-G1 as a potential target, the blockade of which could prevent many of the protumorigenic effects of CAFs in PDAC.

See article, p. 446.

The persistence of glioblastoma stem cells (GSC) underlies the lethality of glioblastoma, and targeting these cells has proved enigmatic. Dixit and colleagues found that, in GSCs, mRNAs containing the modified nucleotide N6-methyladenosine (m6A) were often upregulated, as was the m6A reader YTHDF2. Although YTHDF2 typically destabilizes mRNAs, it stabilized MYC and VEGFA transcripts in GSCs via a mechanism involving the IGF family member IGFBP3. In vivo, targeting IGF–IGF1R signaling using the IGF–IGF1R inhibitor linsitinib suppressed glioblastoma growth without affecting normal neural stem cells. In summary, this work has identified a potentially targetable vulnerability of the cells that make glioblastoma so deadly.

See article, p. 480.

Leukemia cells have access to a variety of sites in the body, and the hepatic microenvironment may be an especially favorable niche. Ye and colleagues found that, in mice, the liver was a reservoir for leukemia stem cells (LSC), which exhibited altered transcriptomic and metabolic signatures compared with LSCs outside the liver. Overexpression of the gene encoding the lipase LIPG was characteristic of liver-resident LSCs and was associated with a proliferative, chemotherapy-resistant phenotype. Hepatic infiltration by LSCs also caused liver damage, resulting in the release of chemotherapy drug–degrading enzymes from liver cells. This work suggests an important role for the liver in leukemia drug resistance.

See article, p. 500.
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