LKB1 Loss Promotes Progression to Blast-Phase MPN in Mice and Patients

Progression of myeloproliferative neoplasms (MPN) to a severe manifestation of acute myeloid leukemia called blast-phase MPN carries poor prognosis, and although genetic variants correlated with this phenomenon have been identified, the underlying mechanisms remain unclear. Marinaccio, Suraneni, and colleagues performed a CRISPR–Cas9-based screen on murine MPN cells, revealing that loss of Lkb1 (also known as Stk11) led to reduced differentiation and increased self-renewal of MPN cells. Further, Lkb1 deletion reduced life span in murine MPN models and was associated with increased reactive oxygen species and stabilization of cancer-linked HIF1α. Importantly, human MPN progression to blast-phase AML was associated with LKB1 loss.

See article, p. 1398.

Amplification of Protein Kinase TNIK Drives Lung Squamous Cell Carcinoma

Although no targeted therapies have been approved for lung squamous cell carcinoma (LSCC), one hint for a potential target is that the chromosomal amplification 3q26–q29 is common. Torres-Ayuso and colleagues found that this genomic aberration led to amplification of TNIK, encoding the serine/threonine kinase and WNT pathway activator TNIK, in 34% to 44% of cases; a further 46% to 54% of cases had TNIK copy-number gains. Similar results were seen in LSCC cell lines, in which TNIK function was essential for maximal proliferation in 3-D culture, as well as in vivo; these findings may be attributable to TNIK-mediated phosphorylation of the tumor suppressor Merlin (encoded by NF2).

See article, p. 1411.

Genetics Hint at Drug Regimens for Pediatric Patients with Leukemia

Although precision medicine approaches in which genetic aberrations match patients to treatments have been investigated for solid tumors, pediatric blood cancers have lagged behind. Pikman and colleagues explored data from their Leukemia Precision-based Therapy (LEAP) Consortium, a pediatric leukemia clinical genomic consortium aiming to genetically match patients with therapies based on their level of evidence. The analysis revealed that, of 153 patients enrolled, 18% had a strong (tier 1 or 2) treatment recommendation and 14% of patients with relapsed/refractory leukemia received the matched targeted therapy. Ex vivo drug sensitivity testing was also performed in patient samples and combinations of targeted therapies were evaluated in cell line and xenograft models.

See article, p. 1424.

Navitoclax plus Venetoclax Shows Signs of Safety and Efficacy in ALL

The BCL-XL/BCL2 inhibitor and proapoptotic agent navitoclax has shown promise in lymphoid malignancies, but its use is limited by thrombocytopenia. Pullarkat and colleagues conducted a phase I dose-escalation trial of navitoclax at a low dose (to limit thrombocytopenia) with the selective BCL2 inhibitor venetoclax in 47 adult or pediatric patients with relapsed or refractory acute lymphoblastic leukemia or lymphoblastic lymphoma, for whom prognosis is poor, finding that the combination produced complete remission in 60% of patients. The median overall survival was 7.8 months, with longer survival being observed in patients with B-ALL than T-ALL (9.7 months versus 6.6 months, respectively).

See article, p. 1440.
Replication Repair–Deficient Cancers Are Susceptible to MEK Inhibition

Oncogenic mutations affecting proteins in the RAS–MAPK pathway are common in cancer. Campbell, Galati, and colleagues found that hypermutant replication repair–deficient cancers were also enriched with activating mutations affecting the RAS–MAPK pathway. Inhibition of the downstream protein MEK suppressed cancer cell growth in vitro and in vivo in mouse xenograft experiments. These results corresponded to findings in a small number of patients with constitutional mismatch-repair deficiency syndrome, in which patients are prone to developing hypermutant cancers; for example, one patient with diffuse glioma exhibited 80% tumor shrinkage and stable disease for at least three years following MEK inhibitor treatment.

See article, p. 1454.

DLBCL Has Tumor Microenvironment–Based Subtypes That Affect Prognosis

Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous disease, as revealed by genomic and transcriptomic studies. However, less attention has been focused on the possible effects of the tumor microenvironment (TME) in delineating DLBCL subtypes. Kotlov and colleagues performed transcriptomic analyses of the microenvironment of 4,655 DLBCLs, finding evidence for four distinct categories of DLBCL microenvironment (dubbed germinal center–like, mesenchymal, inflammatory, and depleted based on their cellular compositions) with unique biological and clinical properties. Notably, the subtypes represented independent factors affecting prognosis, including drug response and overall survival. Further analyses uncovered specific vulnerabilities of DLBCLs based on their TME subtypes.

See article, p. 1468.

Prognosis-Associated Lung Cancer Features Are Epigenetically Regulated

Lung adenocarcinoma (LUAD) prognosis is associated with relative proportions of histologic features (e.g., lepidic, papillary, acinar, and solid) within tumors. Because little is known about the molecular characteristics of these features, Tavernari and colleagues used a multi-omics approach to probe human LUADs. Examination of histopathologically defined tumor regions using whole-exome sequencing, RNA sequencing, and DNA methylation profiling revealed interpatient and intrapatient histologic pattern differences resulting from gene expression and DNA methylation variation. Molecularly and histologically defined tumor features were associated with specific microenvironment characteristics; for example, solid regions exhibited a highly immune-excluded phenotype, consistent with the poor prognosis for patients with solid-predominant LUAD.

See article, p. 1490.

A GPR20-Targeting Antibody–Drug Conjugate Can Treat GIST In Vivo

The standard-of-care first-line treatments for gastrointestinal stromal tumors (GIST) are tyrosine kinase inhibitors (TKI) that block oncogenic KIT/PDGFRA activity, but a minority of tumors do not harbor mutations in KIT or PDGFRA, and acquired TKI resistance can occur. Because GISTs often highly express the orphan G protein–coupled receptor GPR20, Iida, Ahmed, and colleagues developed the antibody–drug conjugate DS-6157a, in which a humanized antibody to GPR20 is linked to DS-6157a, a cytotoxic topoisomerase I inhibitor. In mouse GIST xenograft models, DS-6157a inhibited growth of GPR20+ GISTs, including those with TKI resistance mutations. Toxicity studies in rats and monkeys suggested a favorable safety profile.

See article, p. 1508.
Pharmacologic Promotion of MHC-I Expression Enhances Immunotherapy

Immune checkpoint blockade (ICB) is efficacious in several cancers; however, ICB resistance mechanisms—such as downregulation of MHC-I—limit its effectiveness for some patients. Gu, Zhang, Wang, Jiang, and colleagues sought modulators of MHC-I, finding that the TRAF3, which inhibits the NFκB pathway, negatively regulated MHC-I expression. In vivo, Traf3 knockout increased T cell–mediated cancer cell killing and improved tumor responsiveness to ICB. The transcriptional profile of Traf3-knockout cells overlapped with the profiles of patient melanomas with higher MHC-I expression and greater CD8+ T-cell infiltration, correlating with better overall survival. A drug screen revealed that the drug birinapant had effects similar to Traf3 knockout.

See article, p. 1524.

Leukemia Cells That Survive Chemotherapy Adopt a Senescent-Like State

Relapse following chemotherapy treatment is common in acute myeloid leukemia (AML), a fact that has often been attributed to the persistence of cancer-perpetuating leukemia stem cells (LSC). However, Duy and colleagues found that chemotherapy treatment promoted the adoption of a senescent-like phenotype among surviving patient-derived AML cells. Ex vivo experiments showed that this senescent-like state was reversible, enabling these surviving cells to reinstate disease, and it appeared that samples from patients whose disease was more resistant to chemotherapy harbored more senescent-like AML cells. Interestingly, LSCs and LSC gene signatures were not enriched in the surviving senescent-like cells.

See article, p. 1542.

Mutation of a SWI/SNF Subunit Confers Sensitivity to BIRC5 Inhibition

Mutations in the tumor-suppressor gene ARID1A, encoding a member of the mammalian SWI/SNF (mSWI/SNF, or BAF) chromatin-remodeling complex, are common in cancers; however, the functional consequences of such mutations are not well characterized. Lo and colleagues found that ARID1A knockout in TP53−/− human gastric organoids—which represent an early stage of gastric cancer development—promoted tumorigenesis and induced transcription of genes associated with microsatellite instability–high and EBV infection–associated gastric cancer, including the gene encoding the apoptosis protein BIRC5 (also known as survivin). In agreement, high-throughput drug screening revealed that these ARID1A-knockout TP53−/− organoids were sensitive to pharmacologic BIRC5 inhibition.

See article, p. 1562.

Serine Dependence Is Targetable in a Subset of Acute Myeloid Leukemias

Internal tandem duplications (ITD) affecting the gene encoding the class III receptor tyrosine kinase FLT3, a key regulator of hematopoiesis, are common in acute myeloid leukemia and associated with poor prognosis. Using a mouse model of MLL-rearranged AML harboring FLT3 ITDs, Bjelosevic and colleagues discovered that leukemia cells harboring FLT3 with ITDs exhibited upregulation of de novo serine biosynthesis and neutral amino acid transport, processes that were regulated by the transcription factor ATF4. Correspondingly, pharmacologic inhibition of PHGDH (the first and rate-limiting enzyme in the de novo serine biosynthesis pathway) reduced AML cell proliferation and conferred cytarabine sensitivity to AML cells with FLT3 ITDs.

See article, p. 1582.
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