In This Issue

**CAR T Cells Stimulated by Solid-Tumor Cytokines Show Efficacy In Vivo**

Despite the success of chimeric antigen receptor (CAR) T-cell therapies for some leukemias and lymphomas, CAR T-cell efficacy in most solid tumors has been limited, perhaps in part due to a lack of T cell-supportive cytokines. Because the cytokine GM-CSF is often abundant in solid tumors, Lange, Sand, and colleagues designed CAR T cells expressing a CAR including the α and β chains of the GM-CSF receptor along with the transmembrane and signaling domains of the α and β chains of the IL18 receptor to ensure CAR T-cell stimulation and persistence at tumor sites. These CAR T cells exhibited improved efficacy against solid tumors in vivo.

See article, p. 1661.

**Mobocertinib Selectively Inhibits EGFR with Exon 20 Insertions in NSCLC**

EGFR inhibitors have shown efficacy in many types of EGFR-mutant non–small cell lung cancer (NSCLC) subtypes, but because the ATP binding site of a common type of EGFR mutant harboring insertions in exon 20 resembles that of wild-type EGFR, a more selective inhibitor is needed. Using structure-guided design, Gonzalvez and colleagues developed the EGFR inhibitor mobocertinib, which selectively formed a covalent, irreversible complex with exon 20–mutant EGFR. In genetically engineered and xenograft mouse models, mobocertinib treatment caused dose-dependent reductions in tumor volume, and the drug did not appear to cause toxicity. For more information, see the accompanying article by Riely and colleagues.

See article, p. 1672.

**Mobocertinib Produces Responses in Pretreated Patients with NSCLC**

EGFR mutations are common drivers of non–small cell lung cancer (NSCLC), and mutant-EGFR inhibitors are in clinical use; however, no selective inhibitor of EGFR with insertions in exon 20 is approved. Riely and colleagues conducted a phase I/II dose-escalation and dose-expansion clinical trial of mobocertinib in previously treated patients with NSCLC. Among the 28 patients with EGFR exon 20 insertions who received the recommended phase II dose of mobocertinib, the objective response rate was 43%, with all responses being partial responses. Based on these results, a phase III trial is now enrolling. For more information, see the accompanying article by Gonzalvez and colleagues.

See article, p. 1688.

**Newly Defined “Burned-Out” T Cells Hamper Response to Immunotherapy**

Exhausted CD8+ T cells in the tumor microenvironment (TME) hinder immunotherapy efficacy. In non–small cell lung cancer, Sanmamed, Nie, Desai, Villaruel-Espindola, and colleagues discovered a previously uncharacterized set of CD8+ T cells (dubbed burned-out T cells) similar but not identical to their exhausted counterparts. Like exhausted T cells, burned-out T cells exhibited low IFNγ secretion, expression of coinhibitory receptors (such as PD-1, LAG3, and TIM3), and a terminally differentiated phenotype; both cell types also conferred immunotherapy resistance. However, unlike exhausted T cells, burned-out T cells were highly proliferative and apoptotic, thus representing a newly delineated class of T cells in the TME.

See article, p. 1700.
Inhibitors of oncogenic BRAF\textsuperscript{V600E} may act, at least in part, by disrupting BRAF dimerization, which is thought to be important for the function of this kinase, and mutations that restore dimerization may cause BRAF inhibitor resistance—however, combination monomer–dimer inhibitors have exhibited toxicity at therapeutic doses. To overcome these challenges, Adamopoulos, Ahmed, Tucker, and colleagues used \textit{in silico} experiments and biochemical assays to design a selective inhibitor of dimeric BRAF. In combination with a traditional BRAF\textsuperscript{V600E} inhibitor and a disruptor of interactions between RAF proteins and the downstream kinase MEK, this novel dimeric-BRAF inhibitor showed efficacy and tolerability \textit{in vivo}.

See article, p. 1716.

Activating mutations in \textit{EGFR} or \textit{KRAS} are common drivers of lung adenocarcinoma, in which these mutations commonly co-occur with inactivating mutations in tumor suppressor genes. Foggetti, Li, Cai, and colleagues found, as foreseen, that silencing of the tumor suppressor genes \textit{Apc}, \textit{Rb1}, or \textit{Kbm10} enhanced tumor growth in a mouse model of lung adenocarcinoma driven by \textit{Egfr} and \textit{Trp53} mutations. However, unexpectedly, knockdown of \textit{Lkb1} or \textit{Setd2}—known to increase tumor growth in mouse models of oncogenic \textit{Kras}–driven lung adenocarcinoma—restricted tumor growth in lung tumors driven by mutant \textit{Egfr}. These results were corroborated by patient data and highlight the complex interplay between tumor suppressors and oncogenes.

See article, p. 1736.

By definition, tumor suppressors restrict the development or progression of cancer, but much remains to be known about their roles at various timepoints. Cai, Chew, Li, and colleagues used somatic CRISPR–Cas9-based genome editing plus tumor barcoding and high-throughput barcode sequencing (Tuba-seq) to evaluate gene function \textit{in vivo} in a mouse model of oncogenic \textit{Kras}–driven lung cancer. These analyses provided multiplexed data revealing previously unknown tumor suppressors and illustrating the roles of several critical tumor suppressors at all cancer stages. Interestingly, inactivation of some such genes accelerated tumor growth, others simply promoted tumorigenesis, and others still promoted development of exceptionally large tumors.

See article, p. 1754.

Little is known about the contributors to metastatic seeding in pancreatic cancer. Pitarresi and colleagues found that \textit{PTHLH}—encoding a multifunctional secreted protein called parathyroid hormone–related protein (PTHrP)—exhibited copy-number gains in patient pancreatic cancer tumors, particularly those that were metastatic. In genetically engineered mice that typically have aggressive pancreatic cancer, loss of one copy of \textit{Pthlh} reduced growth of primary tumors and extended median survival time by 73%, and only 5% of mice with only one copy of \textit{Pthlh} exhibited metastases (compared with 45% of controls). Neutralizing antibodies to PTHrP also reduced primary and metastatic tumor burden, suggesting a possible therapeutic strategy.

See article, p. 1774.
Mutation–Microbiota Interactions Mediate Colorectal Cancer Features

Although colorectal cancer is most commonly associated with inactivating mutations in the tumor suppressor gene APC, activating mutations in BRAF (specifically $BRAF^{V600E}$) are common co-drivers. DeStefano Shields and colleagues found that the substitution of wild-type mouse $Braf$ with human $BRAF^{V600E}$ in an enterotoxigenic $Bacteroides fragilis$–driven model of colorectal cancer led to the development of tumors that more closely recapitulated $BRAF^{V600E}$-mutant human colorectal tumors. Specifically, mice harboring $BRAF^{V600E}$ had tumors in the same location as the corresponding human tumors and had histologic, epigenetic, and immune features comparable to their human tumor counterparts. Finally, these $BRAF^{V600E}$-driven tumors were immunogenic and susceptible to anti–PD-L1 treatment.

See article, p. 1792.

Cancer-Associated Fibroblasts Supply Glutamine to Pancreatic Tumor Cells

The pancreatic ductal adenocarcinoma (PDAC) environment is depleted of nutrients, and the most limiting amino acid is glutamine. To overcome this deficiency, PDAC cells use macropinocytosis to engulf extracellular materials, including proteins. Zhang and colleagues found that cancer-associated fibroblasts (CAFs) in PDAC also use macropinocytosis under glutamine-limiting conditions; however, unlike in PDAC cells, CAFs rely on CaMKK2–AMPK–RAC1 signaling rather than EGFR signaling to activate this process. Macropinocytosis by CAFs not only supports CAF function but also enables CAFs to secrete glutamine into the extracellular space, supplying tumor cells with glutamine as well, providing one explanation for how CAFs support PDAC.

See article, p. 1808.

Optineurin Loss Underlies Immunotherapy Resistance in Colorectal Cancer

Colorectal cancers are frequently resistant to immunotherapy despite the fact that they most often do not appear to harbor mutations in MHC-I or IFNγ pathways. Du, Hua, and colleagues identified optineurin loss, which often occurred early in human colorectal cancer progression, as an alternative underlying mechanism. Optineurin deficiency was associated with poor immunotherapy response in mouse models and patients with colorectal cancer. Mechanistically, optineurin interacted with the lysosome-trafficking protein AP3D1 to prevent lysosomal degradation of palmitoylated IFNγ receptor 1 (IFNGR1); thus, optineurin loss led to increased IFNGR1 degradation. Pharmacologic inhibition of IFNGR1 palmitoylation overcame the effects of optineurin deficiency, increasing immunotherapy sensitivity in mice.

See article, p. 1826.

CD4+ T Cells Mediate ICB Sensitivity in MMR-Deficient B2M-Mutant Tumors

Biallelic loss of $B2M$—encoding β2 microglobulin, a component of MHC-I—is common in colorectal cancer; however, unlike in melanoma and lung cancers, $B2M$ loss does not confer resistance to immune checkpoint blockade (ICB) in mismatch repair (MMR)-deficient colorectal cancer. Germano and colleagues found that $B2m$-knockout MMR-deficient colorectal tumors (but not $B2m$-knockout MMR-proficient tumors) were susceptible to ICB treatment. Interestingly, CD8+ T cells were dispensable for the response of $B2m$-knockout MMR-deficient tumors to ICB. Instead, the observed antitumor efficacy depended on the activity of CD4+ T cells. Correspondingly, B2M-low human tumors treated with anti–PD-1 exhibited elevated levels of tumor-infiltrating CD4+ T cells.

See article, p. 1844.
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