NRG1 rearrangements drive tumorigenesis in a subset of patients with invasive mucinous adenocarcinomas (IMA) of the lung. NRG1 fusions bind to ERBB3, resulting in ERBB3 heterodimerization with ERBB2 and activation of downstream signaling pathways including ERK, PI3K–AKT, and NF-κB, suggesting the potential for therapeutic targeting of ERBB2 or ERBB3 in NRG1-rearranged tumors. Drilon and colleagues identified a patient with NRG1-rearranged IMA who was treated with an anti-ERBB3 monoclonal antibody (GSK2849330) in a phase I trial and achieved an exceptional response. In contrast, ERBB2 inhibition with afatinib did not achieve responses in four patients with NRG1-rearranged lung cancer, suggesting that ERBB3 inhibition may be more effective in this patient population.

In vitro, NRG1-rearranged cell lines exhibited activation of ERBB2/ERBB3 signaling and were sensitive to inhibition of either ERBB2 or ERBB3. However, in vivo, in an NRG1-rearranged patient-derived xenograft model, ERBB3 inhibition produced durable tumor regression, whereas ERBB2 inhibition had less pronounced antitumor activity, consistent with the effects observed in patients. These findings suggest that ERBB3-targeted therapies may be more effective than ERBB2-targeted therapies in patients with NRG1-rearranged tumors. Additionally, analysis of 26,469 tumors from The Cancer Genome Atlas and MSK-IMPACT uncovered NRG1 rearrangements at low frequency in a variety of tumor types including lung, pancreatic, breast, ovarian, and head and neck cancers. The presence of NRG1 fusions in multiple solid tumor types supports a basket trial design for the investigation of ERBB3 targeted therapies in patients with NRG1-rearranged tumors.

See article, p. 686.

EGFR inhibitors have achieved clinical success in multiple EGFR-mutated tumor types. EGFR inhibitors failed to provide clinical benefit in phase III trials of patients with gastroesophageal adenocarcinoma (GEA), but these trials were performed in unselected patients. EGFR amplifications have been reported to occur in approximately 4% of patients with locally advanced GEA, prompting Maron and colleagues to hypothesize that anti-EGFR monoclonal antibody therapy might be effective in EGFR-amplified GEA. Next-generation sequencing of a large cohort of patients with GEA (stage I-IV) revealed EGFR amplifications in 5% (19 of 363 patients), including 6% (8 of 140) of stage IV patients who were prospectively screened with the intention to treat with anti-EGFR therapy. Seven of the 8 prospectively identified patients were treated with EGFR-directed therapy alone or in combination with chemotherapy. Objective responses were achieved in 4 of 7 patients (58%), 3 of which were complete responses, and including 2 of 3 (66.7%) receiving anti-EGFR monotherapy. The overall disease control rate was 100%. The median progression-free survival was 10 months. Sequencing of pre- and post-treatment tumor samples and serial circulating tumor DNA as well as tumor immunohistochemistry and FISH identified potential baseline and acquired mechanisms of resistance including EGFR-negative clones, PTEN deletions, KRAS and GNAS mutations, and KRAS, NRAS, MYC, and HER2 amplifications. Taken together, these findings suggest that EGFR inhibitors may be effective in patients with EGFR-amplified GEA and uncover potential resistance alterations.

See article, p. 696.
Compound ALK Mutations Drive Resistance to Lorlatinib in Lung Cancer

The third-generation ALK inhibitor lorlatinib has exhibited clinical efficacy in patients with ALK-rearranged non-small cell lung cancer (NSCLC) after failure of first- and second-generation ALK inhibitors such as crizotinib and alectinib, respectively. To identify lorlatinib resistance mutations, Yoda and colleagues performed an in vitro ENU mutagenesis assay of EML4–ALK+ Ba/F3 cells. Treatment with either crizotinib or lorlatinib selected single ALK resistance mutations in crizotinib-treated, but not lorlatinib-treated, cells. A second mutagenesis assay performed with EML4–ALK+ Ba/F3 cells harboring single ALK resistance mutations resulted in the emergence of lorlatinib-resistant clones harboring compound ALK mutations. Consistent with these findings, evaluation of repeat biopsies from 20 patients with lorlatinib-resistant NSCLC revealed that of 12 patients with acquired resistance to lorlatinib, 6 patients (50%) harbored compound ALK mutations, including 2 that had been identified in the in vitro mutagenesis screen. In three patients who had relapsed after sequential first-, second-, and third-generation ALK inhibitors, whole-exome sequencing of repeat biopsies after each relapse demonstrated a stepwise accumulation of ALK resistance mutations, culminating in a lorlatinib-resistant compound mutation. Taken together, these findings characterize the lorlatinib-specific spectrum of ALK resistance mutations in resistant ALK-rearranged NSCLC, suggest that compound ALK resistance mutations may emerge after successive ALK inhibitor therapy, and indicate the potential of third-generation ALK inhibitors as front-line therapy for ALK-rearranged NSCLC.

Colorectal Tumors Have Evolutionary Mechanisms to Evade Immune Attack

Colorectal tumors exhibit diverse genetic events and immune responses. In patients with microsatellite instability–high (MSI-high) tumors, the high somatic mutational load may increase neoantigens, resulting in effective immunotherapy, whereas microsatellite stable (MSS) tumors have a lower mutation burden and do not respond to immune checkpoint blockade. However, increased selection pressure may result in immunoediting and immune evasion in MSI-high tumors. To better understand the genetic drivers of immune recognition and evasion, Grasso and colleagues analyzed 1,211 primary colorectal tumors, including 179 MSI-high. In total, 62 significantly mutated genes were identified, with 53 genes significantly mutated across MSI-high tumors, including 27 not previously linked to MSI-high colorectal cancer. Forty mutated genes were specific to MSI-high tumors, 9 were identified only in MSS tumors, and 13 were detected in both. WNT signaling genes were frequently mutated in both MSI-high and MSS tumors, and immune-related gene mutations were enriched in MSI-high tumors. Biallelic losses occurred in 26 of the 62 significantly mutated genes, including 13 WNT signaling genes (disrupted across all colorectal tumors) and 8 immune-related genes (disrupted in MSI-high tumors). The mutated immune-related genes included components of the antigen presentation machinery that disrupted antigen processing and presentation to promote immunoediting and immune escape. Further, increased WNT signaling in MSI-high and MSS tumors was associated with reduced T-cell infiltration. Together, these multi-omic analyses suggest that colorectal tumors evolve to escape immune detection through immunoediting, which facilitates immune evasion despite a high mutational burden, or suppression of T-cell infiltration.

See article, p. 714.

See article, p. 730.
The success of autologous CAR T-cell therapy has been partially mitigated by the development of severe side effects, such as neurotoxicity and cytokine release syndrome (CRS), in a subset of patients. Although recent studies have identified potential biomarkers for the development of these significant toxicities, currently there is a dearth of clinically relevant animal models to interrogate the pathophysiology of, and potential therapeutic strategies against, neurotoxicity and CRS. To identify therapies that may ameliorate CRS and neurotoxicity, Taraseviciute and colleagues developed and characterized a rhesus macaque model for assessing CD20 CAR T cell–mediated neurotoxicity that recapitulates patient CD19 CAR T cell–mediated CRS and neurotoxicity. They showed that neurotoxicity and CRS are associated with increased levels of proinflammatory cytokines during peak CD20 CAR T-cell expansion concurrently with the development of encephalitis, which is driven by the accumulation of both CD20 CAR and non–CD20 CAR T cells in the brain parenchyma and cerebrospinal fluid, suggesting that CD19 CAR T cell–mediated neurotoxicity is neither CAR-specific nor tumor-dependent. Together, these findings describe the establishment of a clinically relevant nonhuman primate model of CAR T cell–mediated neurotoxicity that can be used to further elucidate the mechanisms underlying neurotoxicity and identify therapeutic strategies to ameliorate potentially fatal immune-related adverse events.

See article, p. 750.

### PIK3CA Mutation and PTEN Loss Cooperate to Promote Prostate Cancer

- PTEN loss frequently co-occurs with PIK3CA mutation or amplification in patients with prostate cancer.
- PIK3CA mutation and PTEN loss cooperate to accelerate tumorigenesis and castration resistance.
- PIK3CA mutations are linked to a poor prognosis in patients and induce prostate tumors in mice.

The PI3K signaling pathway is frequently hyperactivated in prostate cancer, suggesting the potential for therapeutic targeting. Loss of the tumor suppressor PTEN, a negative regulator of the PI3K pathway, can promote prostate tumorigenesis, but how other PI3K genetic drivers contribute to prostate cancer remains unclear. Pearson and colleagues sought to identify other genetic drivers of PI3K signaling during prostate tumorigenesis. Analysis of prostate cancer datasets revealed PIK3CA mutations in up to 4% of patients and PIK3CA copy-number gain in up to 62% of cases. Further, PIK3CA mutation or amplification correlate with poorer outcomes in patients with prostate cancer. In mice, prostate specific expression of a p110α-activating mutation (Pik3ca<sup>H1047R</sup>) induced locally invasive prostate cancer. Similarly, Pten deletion induced invasive prostate carcinoma, but tumor growth was accelerated relative to Pik3ca mutant prostate cancer, reflecting the involvement of both p110α and p110β in contributing to elevated mTORC1/2 signaling and AKT hyperactivation. Concomitant PTEN loss and PIK3CA mutation resulted in accelerated prostate tumor growth in mice, with augmented mTORC1/2 signaling compared with single mutants. Moreover, compound mutants exhibited innate resistance to castration, whereas single mutants slowly acquired castration-resistant disease. Collectively, these data provide evidence that Pik3ca mutation and Pten deletion coordinate independent oncogenic signaling events to facilitate prostate cancer initiation and progression, and indicate that the coexistence of PIK3CA mutation and PTEN loss may serve as a prognostic indicator of rapid prostate cancer progression and de novo resistance to androgen deprivation therapy.

See article, p. 764.
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