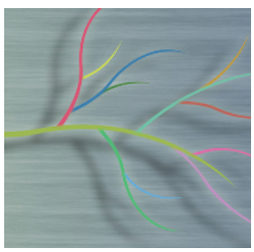
IN THIS ISSUE

Dynamic Mutation Processes Define Esophageal Adenocarcinoma Evolution

- Heterogeneous mutations predict poor neoadjuvant therapy response in esophageal adenocarcinoma.
- The mutation signature in tumors changes over time and in response to platinum chemotherapy.
- Amplification of targetable oncogenes occurs early in tumorigenesis and persists post-chemotherapy.

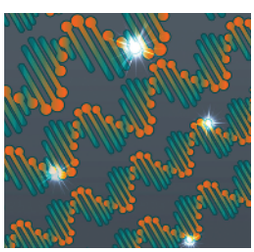


Esophageal adenocarcinoma is an aggressive disease with poor clinical outcome. Treatment involves surgical resection and neoadjuvant chemotherapy; however, frequent resistance remains a challenge. Although past genomic sequencing efforts have identified oncogenic driver mutations, little is known about the acquisition of genetic aberrations over time or the impact of chemotherapy on the mutational landscape of esophageal adenocarcinoma. Murugaesu and colleagues performed multiregion exome sequencing of eight esophageal adenocarcinomas collected at diagnosis and following platinum-containing neoadjuvant chemotherapy. Classification of nonsilent somatic mutations highlighted frequent intratumor heterogeneity and increased mutation burden compared with single-region analysis, and indicated that high intratumor heterogeneity correlated with poor neoadjuvant chemotherapy response. Generation of phylogenetic trees revealed driver mutations in both the trunk and branches, spatial subclonal heterogeneity, and multiple distinct mutations in the same driver genes, suggestive of parallel tumor evolution. All tumors exhibited vast copy-number alterations and evidence of genome doubling; chromosomal amplifications were more likely to be shared across tumor regions, indicating that they may represent early events, and were observed both pre– and post–neoadjuvant chemotherapy. In addition, changes in mutation spectra were detected over time, with a shift from a gastric acid reflux–associated signature to an aging signature and a platinum mutational scar in post-treatment resistant tumors. These data emphasize the dynamic acquisition and impact of platinum therapy on genetic aberrations during esophageal adenocarcinoma progression and highlight the persistent and stable amplification of tractable oncogenes, which may provide potential therapeutic targets. ■

See article, p. 821.

HER2 Activating Mutations in Colorectal Cancer Can Be Targeted

- *HER2* somatic mutations were identified in 4% of patients with colorectal cancer.
- *HER2* activating mutations in colorectal cancer cells confer resistance to anti-EGFR antibodies.
- *HER2* activating mutations confer sensitivity to irreversible tyrosine kinase inhibitors.



HER2 amplification in colorectal cancer confers resistance to anti-EGFR monoclonal antibodies, but it is unclear whether *HER2* somatic mutations, which have been characterized in breast cancer and non–small cell lung cancer (NSCLC), have clinical importance in colorectal cancer. *HER2* somatic mutations and gene amplification were recently identified in 7% of patients with colorectal cancer included in The Cancer Genome Atlas. Of these, four are identical to HER2 kinase domain and extracellular domain mutations found in breast cancer. Kavuri and colleagues found that these *HER2* mutations activate HER2 signaling and induce anchorage-independent growth in colon epithelial cells. Colorectal cancer cell lines with *HER2* activating mutations were resistant to the anti-EGFR monoclonal antibodies cetuximab and panitumumab due to association with increased phosphorylation of MAPK and EGFR. However, treatment of the same lines with the irreversible HER2/EGFR tyrosine kinase inhibitors neratinib and afatinib resulted in growth inhibition with a concomitant decrease in phosphorylation of MAPK, EGFR, AKT, and HER2. As single agents, these small-molecule HER2/EGFR inhibitors had a cytostatic effect on cetuximab-resistant colorectal cancer patient-derived xenografts, whereas regressions were observed when they were used in combination with the anti-HER2 antibody trastuzumab. These results show that *HER2* activating mutations are drivers of colorectal cancer tumorigenesis and provide strong preclinical evidence for the use of dual HER2 targeted therapy in patients with colorectal cancer with activating *HER2* mutations. ■

See article, p. 832.

MET Exon 14 Splice Site Mutations Are Actionable in Lung Adenocarcinoma

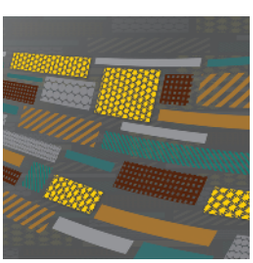
- *MET* exon 14 splice site mutations are found in 4% of lung adenocarcinomas.
- Patients with *MET* exon 14 skipping respond to the MET inhibitors crizotinib and cabozantinib.
- Noncoding mutations affecting splice sites can be actionable targets.

The coding sequence of the *MET* proto-oncogene is mutated in 8% and amplified in 4% of lung adenocarcinomas. Splice site mutations leading to *MET* exon 14 skipping have been observed in 4% of lung adenocarcinomas, and preclinical evidence suggests these mutations also lead to MET activation and promote tumor growth. However, it remains unclear whether *MET* exon 14 alterations are clinically actionable. Paik and colleagues prospectively screened 178 patients with stage IV lung adenocarcinomas for *MET* exon 14 splice site mutations and identified 8 patients (4%), four of whom were then treated with one of two small-molecule tyrosine kinase inhibitors with activity against MET. Three patients received off-label crizotinib, an FDA-approved therapy for non–small cell lung cancer that has been reported to have activity in patients with *MET*-amplified tumors, and 1 patient received cabozantinib as part of a phase II study. The 3 patients treated with crizotinib experienced partial radiographic responses to therapy, and the patient treated with cabozantinib exhibited a complete metabolic response to therapy as measured by positron emission tomography. These results provide clinical validation of splice site mutations as a class of targetable oncogenic driver events and suggest that patients with *MET* exon 14 splice site mutations should be prospectively identified and enrolled in clinical trials of MET inhibitors or treated with crizotinib if no other clinical option exists. ■

See article, p. 842.

MET Exon 14 Splice Variants May Be Targetable in Multiple Tumor Types

- Alterations that cause splicing-based skipping of *MET* exon 14 were identified in a range of tumor types.
- *MET* exon 14 alterations have highly diverse sequences, which poses challenges for diagnostic testing.
- Clinical responses to crizotinib and capmatinib were seen in patients with *MET* exon 14 alterations.



The *MET* proto-oncogene is activated by amplification or point mutation in a number of advanced cancers and can be therapeutically targeted in patients with tumors harboring *MET* alterations. *MET* splice site alterations resulting in exon 14 skipping have been previously reported in primary lung adenocarcinomas and a limited number of cancer cell lines. Frampton and colleagues screened a panel of over 38,000 tumors and identified *MET* exon 14 alterations in several cancer types, particularly lung adenocarcinoma (3%) and glioma. These alterations were highly diverse, with 126 distinct sequence alterations observed in 221 cases with *MET* exon 14 alterations. This makes them particularly challenging to detect accurately. Further analysis of the genomic dataset suggested that *MET* exon 14 splice site mutations are driver events in lung adenocarcinoma oncogenesis. *In vitro* studies further supported the oncogenic nature of *MET* exon 14 alterations: Cell lines harboring *MET* exon 14 deletions exhibited increased MEK–ERK signaling, increased anchorage-independent growth, and sensitivity to the MET inhibitor capmatinib (INC280) and the MEK inhibitor trametinib. The authors demonstrated the clinical relevance of the *in vitro* studies by reporting that 3 patients with tumors harboring *MET* exon 14 alterations exhibited durable partial responses to capmatinib and crizotinib, another MET inhibitor. Taken together, these results support the role of *MET* exon 14 alterations as driver mutations in human cancers and suggest that patients whose tumors harbor these mutations may be candidates for MET-targeted therapy. ■

See article, p. 850.

Co-occurring Genetic Changes Drive *KRAS*-Mutant Lung Cancer Heterogeneity

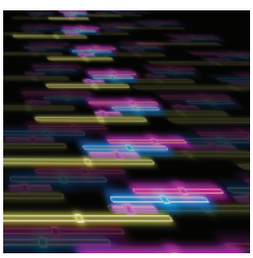
- Alterations in *LKB1* (KL), *TP53* (KP), or *CDKN2A/B* (KC) define three subsets of KRAS-driven lung cancer.
- KP, KL, and KC clusters exhibit biologic differences in tumor histology, signaling, and prognosis.
- Immunotherapy may be relevant for KP tumors, whereas KL cancer cells are sensitive to HSP90 inhibition.

Discovery of efficacious targeted treatments for *KRAS*-mutant lung adenocarcinomas has been hampered by the inherent biologic heterogeneity of these tumors. Utilizing transcriptional, genomic, and proteomic data from early-stage and chemotherapy-resistant *KRAS*-mutant lung tumor cohorts, Skoulidis and colleagues identified three distinct subgroups defined by co-occurring genetic events. The KP (*KRAS–TP53*) cluster was defined by mutations in *TP53* and characterized by a higher overall incidence of somatic mutations, increased inflammation, and elevated expression of immune mediators, including targetable immune checkpoint proteins such as programmed death ligand 1. In addition, KP tumors had significantly improved relapse-free survival compared with non-KP tumors. The KL (*KRAS–LKB1*) subtype was characterized by functional inactivation of LKB1–AMP kinase signaling in both *LKB1* mutation–positive and *LKB1* mutation–negative tumors. Furthermore, KL tumors were distinguished by mutation or loss of kelch-like ECH-associated protein 1 (KEAP1), activation of oxidative and endoplasmic reticulum stress response programs, and lack of immune system engagement. Of note, KL cancer cells displayed enhanced therapeutic sensitivity to HSP90 inhibitors. KC tumors were significantly enriched for biallelic loss of *CDKN2A* and/or *CDKN2B* and displayed low expression of the homeobox transcription factor NKX2.1 (also known as TTF1). KC tumors further exhibited reduced mTOR signaling and increased p53 transcriptional output, and were frequently classified as invasive mucinous carcinomas expressing markers of gastrointestinal differentiation. These findings highlight the biologic and therapeutic relevance of *KRAS*-mutant lung adenocarcinoma subgroups defined by unique genetic, transcriptional, and proteomic attributes. ■

See article, p. 860.

Risk Variants and Ethnic Differences Are Linked to Prostate Cancer

- GWAS analysis identified two previously unreported independent prostate cancer risk variants.
- A polygenic risk score of known SNPs is associated with prostate cancer and shows ethnic variation.
- Variants are enriched in DHSs and account for approximately 33.4% of heritability.



Family history is a risk factor for prostate cancer, which has been the subject of previous genome-wide association studies (GWAS). However, the risk variants identified in these studies are generally associated with modest effects and are not sufficient to fully explain heritability. Hoffmann and colleagues performed a GWAS of a large, ethnically diverse prostate cancer population that was not studied in prior GWAS analyses. They identified two previously unreported genome-wide significant variants, including an independent risk indel (rs4646284), which was associated with decreased expression of *SLC22A1* and *SLC22A3*, and an SNP (rs2659124) in the 5′ untranslated region (UTR) of *KLK3*, which encodes prostate-specific antigen (PSA). In addition, the GWAS replicated a large proportion of the 105 known risk SNPs at various levels across four ethnic groups: non-Hispanic white, African-American, East Asian, and Latino. A combined risk score consisting of the 105 known SNPs was highly significant for all ethnic groups, although it was less predictive for African-Americans and East Asians. Further analysis of the GWAS results suggested that the SNPs associated with prostate cancer are most likely located in coding regions, DNaseI hypersensitivity sites (DHS), and UTRs, and less likely in intronic and intergenic regions. These 105 known SNPs accounted for approximately 35% of heritability explained by the entire GWAS array. Taken together, these results highlight previously unreported genetic risk factors and suggest that the identification of additional risk variants in ethnically diverse populations is necessary to better predict prostate cancer risk. ■

See article, p. 878.

Note: *In This Issue* is written by *Cancer Discovery* Science Writers. Readers are encouraged to consult the original articles for full details.