Genomic profiling of tumors has become increasingly common across cancer types, but the data are not regularly made available to the entire research community. The American Association for Cancer Research (AACR) launched the Genomics, Evidence, Neoplasia, Information, Exchange (GENIE) project in partnership with eight academic institutions to facilitate large-scale sharing of genomic and clinical data. The AACR Project GENIE Consortium released the first set of data from 19,000 patients in January 2017, and the number of samples included is expected to grow to more than 100,000 within 5 years as more centers join the Consortium. Data from participating centers include matched clinical and genomic data from a variety of tumor types that are harmonized and made accessible in the cBioPortal for Cancer Genomics. Despite the differences in genomic testing at the contributing centers, the genomic data collected so far are largely concordant across the centers, and mutation rates are similar to those reported by The Cancer Genome Atlas. Initial results from Project GENIE suggest that more than 30% of tumors harbor potentially clinically actionable mutations. Advantages of this platform include integration of clinical data from electronic health records and increased statistical power to potentially facilitate understanding of the clinical relevance of somatic mutations and improve patient selection for targeted therapies. The establishment of infrastructure for integrating genomic and clinical data has the potential to aid identification of therapeutic targets and biomarkers of treatment and response in patients with cancer to enhance precision medicine research and improve patient outcomes.

See article, p. 818.

• Project GENIE aims to promote data sharing to enhance precision medicine research.
• Data from Project GENIE may guide identification of drug targets and biomarkers in patients with cancer.

The efficacy of BRAF/MEK inhibitors in BRAF-mutant melanoma is limited by the emergence of resistance, which often occurs via mechanisms that reactivate MAPK signaling. To characterize potential alternative therapeutic targets in BRAF/MEK inhibitor-resistant melanoma, Eskocak and colleagues performed an integrative analysis of a functional genomic screen and copy-number variation in melanoma cell lines and tumors. Among the identified melanoma cell survival genes, addiction to SOX10, assessed by expression of a 5-gene biomarker, distinguished two mechanistic subtypes of melanoma: SOX10-dependent, BRAF/MEK inhibitor–resistant melanoma, and SOX10-independent, BRAF/MEK inhibitor–resistant melanoma. Targeted therapy–resistant melanomas were found to be selectively sensitive to inhibition of the noncanonical IκB kinases TANK-binding kinase 1 (TBK1) and IKKe (encoded by IKBKE), independent of BRAF status. TBK1/Ikke–sensitive melanomas were enriched for innate immune signaling and exhibited TBK1/Ikke–mediated activation of YAP and AKT survival signaling, which may underlie the dependency of this subtype on TBK1/Ikke. In addition, TBK1/Ikke–sensitive melanomas were characterized by increased expression of nicotinamide N-methyltransferase, which has been implicated in epigenetic remodeling and chromatin relaxation. Consistent with this finding, global H3K27 trimethylation was reduced in TBK1/Ikke–sensitive cells, and inhibition of the H3K27 methyltransferase EZH2 was sufficient to confer sensitivity to TBK1/Ikke inhibitors in previously resistant cells. Together, these findings define potential molecular predictors of response to BRAF/MEK inhibition and identify TBK1/Ikke as a candidate therapeutic target for BRAF/MEK inhibitor–resistant melanoma.

See article, p. 832.
Epigenetic drugs including histone deacetylase (HDAC) inhibitors and bromodomain and extraterminal domain (BET) inhibitors have shown promise in a variety of tumor types. Although immunomodulatory effects have been reported, the effects of HDAC and BET inhibitors on the tumor immune microenvironment have not been fully elucidated, prompting Adeegbe and colleagues to investigate the immunoregulatory properties of these drugs in non–small cell lung cancer (NSCLC). In peripheral blood mononuclear cells (PBMC) and tumors from patients with NSCLC, the selective HDAC6 inhibitor ricolinostat reduced the proportion of suppressive CD4+FOXP3+ regulatory T cells (Treg) and increased expression of CD69 on T cells, suggesting T-cell activation. Further, ricolinostat increased surface expression of MHC class II molecules and CD86 on monocytes and tumor-associated macrophages, suggesting that ricolinostat promotes phenotypic changes that support improved antigen presentation and costimulatory capabilities. These changes were recapitulated in vivo in a mouse model of NSCLC, where ricolinostat treatment promoted a more mature tumor-infiltrating macrophage phenotype and increased tumor T-cell activation. The BET inhibitor JQ1 acted on Treg cells within tumors, disrupting their gene expression patterns and diminishing their suppressive activity. Dual inhibition with ricolinostat and JQ1 enhanced the antitumor activity of tumor-infiltrating T cells, suppressed tumor growth, and extended survival in mice with NSCLC. Collectively, these findings uncover immunoregulatory effects of HDAC and BET inhibition, and suggest that dual targeting may enhance the antitumor immune response in NSCLC.

See article, p. 852.

The effects of disrupted DNA methylation patterns in regions outside of promoters and CpG islands are not well understood in acute myeloid leukemia (AML). Glass and colleagues performed enhanced reduced representation bisulfite sequencing (ERRBS) on a panel of 119 primary AMLs to evaluate cytosine methylation changes in nonpromoter gene regulatory elements. This comprehensive methylation sequencing approach more precisely linked genetic lesions to disrupted cytosine methylation patterns than promoter-specific methylation. CpG methylation in “gene neighborhoods” between 2kb and 50kb from the transcription start or end site was best able to capture the epigenetic patterning observed in AML. Active enhancers displayed strong focal changes in methylation whereas promoters exhibited less robust changes in cytosine methylation. AML with dominant hypermethylation was associated with epigenetic disruption of promoters. Conversely, AML with dominant hypomethylation exhibited greater disruption of distal and intronic regions. Co-mutation of IDH2 and DNMT3A, which have opposing effects on DNA methylation, resulted in an epigenetic antagonism, and this subset of AML had the least differential methylation. In preleukemic hematopoietic stem cells, induction of Dnmt3A and Idh2 mutations promoted epigenetic antagonism prior to malignant transformation, indicating it is not a consequence of transformation. Transcriptome analysis in patients with IDH2/DNMT3A-mutant AML revealed upregulation of the Ras signaling signature; accordingly, double-mutant cells exhibited sensitivity to MEK inhibition in ex vivo experiments. Altogether, this comprehensive DNA methylation profiling analysis shows that differential methylation of nonpromoter regulatory elements drives AML epigenetic identity.

See article, p. 868.

HDAC and BET Inhibitors Synergize to Promote Antitumor Immune Responses

- The HDAC6 inhibitor ricolinostat in combination with the BET inhibitor JQ1 promotes T-cell function.
- Ricolinostat promotes T-cell activity and JQ1 reduces Treg activity to suppress tumor growth.
- Dual HDAC6/BET targeting may potentially enhance the antitumor immune response in patients with NSCLC.

Comprehensive Methylation Profiling Reveals Epigenetic Subtypes in AML

- Differential methylation of nonpromoter regulatory elements defines the epigenetic subtype in AML.
- Comprehensive methylome sequencing is superior to promoter-specific analysis for capturing AML biology.
- Co-mutation of IDH2 and DNMT3A results in epigenetic antagonism that may sensitize to MEK inhibitors.
Alveolar rhabdomyosarcoma is a myogenic cancer driven by expression of the oncogenic chimeric transcription factors PAX3–FOXO1 or PAX7–FOXO1. Fusion-positive rhabdomyosarcoma generally affects children and young adults and is associated with a poor survival. PAX3–FOXO1-positive tumors are associated with elevated expression of MYCN and the myogenic transcription factors MYOD1 and MYOG, but the epigenetic mechanisms by which PAX3–FOXO1 dysregulates chromatin have not been described. Gryder and colleagues used chromatin immunoprecipitation sequencing to map the genome-wide landscape of histone modifications in fusion positive rhabdomyosarcoma cell lines to determine how PAX fusions regulate the myogenic program. The large majority of PAX3–FOXO1 was localized at active distal enhancers, where it promoted expression of target genes. Superenhancer analysis revealed a distinct landscape in fusion-positive rhabdomyosarcoma compared with fusion-negative, and identified MYOD, MYOG, and MYCN as master regulators controlled by superenhancers. PAX3–FOXO1 collaborated with these master regulators at superenhancers to promote gene expression, and acted as a pioneering factor, recruiting p300, MED1, and BRD4 to enhance looping and transcription. These findings provide a rationale for the evaluation of BET inhibitors in fusion-positive rhabdomyosarcoma, and treatment with the BET inhibitor JQ1 reduced expression of PAX3–FOXO1 target genes. BRD4 was required for the function and stability of PAX3–FOXO1, and JQ1 inhibited PAX3–FOXO1 activity and suppressed the growth of fusion-positive rhabdomyosarcoma xenografts in vivo. Collectively, these findings demonstrate that PAX3–FOXO1 promotes chromatin remodeling and superenhancer establishment, and support further investigation of BET inhibitors in fusion-positive rhabdomyosarcoma.

See article, p. 884.

VHL is inactivated in the large majority of clear cell renal cell carcinomas (ccRCC), and is frequently accompanied by loss of BAP1 or PBRM1, which also reside on chromosome 3p. PBRM1 is a SWI/SNF chromatin-remodeling complex component mutated in approximately half of ccRCCs, and BAP1 is a deubiquitinating enzyme mutated in approximately 10% to 15% of ccRCCs. BAP1 mutations are associated with aggressive higher-grade tumors and shorter survival than PBRM1 mutations, but it is not clear if PBRM1 and BAP1 mutations drive these differences. Gu and colleagues developed mouse models of Bap1- and Pbrm1-deficient ccRCC recapitulate the human disease. Loss of Vhl and Bap1 induces high-grade ccRCC, whereas loss of Vhl and Pbrm1 induces low-grade ccRCC. ccRCC may arise from Bowman capsule cells, and loss of BAP1 and PBRM1 may determine tumor grade.

See article, p. 900.