TRKing Down an Old Oncogene in a New Era of Targeted Therapy
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Real-Time Intravital Imaging Establishes Tumor-Associated Macrophages as the Extraskeletal Target of Bisphosphonate Action in Cancer
Précis: Bisphosphonates bind granular microcalcifications and are internalized by tumor-associated macrophages in breast tumors.
See commentary, p. 14

The Vigorous Immune Microenvironment of Microsatellite Instable Colon Cancer Is Balanced by Multiple Counter-Inhibitory Checkpoints
Précis: Mismatch repair-deficient colorectal cancers counteract Th1/CTL immune responses by upregulating immune checkpoint proteins, including PD-1 and PD-L1.
See commentary, p. 16

Mutant KRAS-Induced Expression of ICAM-1 in Pancreatic Aciacer Cells Causes Attraction of Macrophages to Expedite the Formation of Precancerous Lesions
Précis: Crosstalk between pancreatic acinar cells and proinflammatory macrophages promotes initiation of acinar-to-ductal metaplasia via KRASG12D-induced expression of the macrophage chemoattractant ICAM1.
Prospective Blinded Study of $BRAF^{V600E}$ Mutation Detection in Cell-Free DNA of Patients with Systemic Histiocytic Disorders ........................................................................................................... 64


Précis: Cell-free DNA testing using plasma and urine samples may be a reliable, noninvasive method to identify mutations and monitor treatment response in histiocytic disorders.

Induction of Telomere Dysfunction Mediated by the Telomerase Substrate Precursor 6-Thio-2'-Deoxyguanosine ........................................................................................................... 82

I. Mender, S. Gryaznov, Z.G. Dikmen, W.E. Wright, and J.W. Shay

Précis: 6-thio-2'-deoxyguanosine is a precursor of a telomerase substrate that is incorporated into newly synthesized telomeres, leading to telomere dysfunction and death in telomerase-expressing cells.

See commentary, p. 19

Hyman, Diamond, and colleagues carried out a prospective, blinded study to quantitatively detect the $BRAF^{V600E}$ mutation in circulating tumor cell-free DNA (cfDNA) from the urine and plasma of patients with Langerhans cell histiocytosis or Erdheim-Chester disease. Urinary cfDNA analysis defined the $BRAF$ genotype of all 30 patients and was 100% concordant with tissue genotypes among treatment-naïve patients. Furthermore, serial urinary cfDNA analyses in patients treated with a BRAF inhibitor or immunomodulatory therapy showed a progressive decrease in $BRAF^{V600E}$ allele burden, consistent with radiographic evidence of disease improvement. Tissue and cfDNA genotyping also identified a previously unreported somatic $KRAS^{G12S}$ mutation in a $BRAF$ wild-type patient. These data suggest cfDNA testing as a reliable, noninvasive method to detect $BRAF^{V600E}$ mutations and monitor response to therapy in histiocytic disorders. For details, please see the article by Hyman, Diamond, and colleagues on page 64.