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Addressing the Controversy: Do Bisphosphonates Directly Affect Primary Tumors?
J.A. Sterling
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The Microsatellite Instable Subset of Colorectal Cancer Is a Particularly Good Candidate for Checkpoint Blockade Immunotherapy
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Turning Telomerase into a Jekyll and Hyde Case?
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How Does Multistep Tumorigenesis Really Proceed?
C.L. Chaffer and R.A. Weinberg

MINI REVIEW
TRKing Down an Old Oncogene in a New Era of Targeted Therapy
A. Vaishnavi, A.T. Le, and R.C. Doebele

RESEARCH BRIEFS
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 Acinar 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 \( \text{BRAF}^{V600E} \) 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 \( \text{BRAF}^{V600E} \) 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 \( \text{BRAF} \) 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 \( \text{BRAF}^{V600E} \) allele burden, consistent with radiographic evidence of disease improvement. Tissue and cfDNA genotyping also identified a previously unreported somatic \( \text{KRAS}^{G12S} \) mutation in a \( \text{BRAF} \) wild-type patient. These data suggest cfDNA testing as a reliable, noninvasive method to detect \( \text{BRAF}^{V600E} \) mutations and monitor response to therapy in histiocytic disorders. For details, please see the article by Hyman, Diamond, and colleagues on page 64.