HIGHLIGHTS

MOLECULAR CANCER RESEARCH

Selected Articles from This Issue

Angiogenic Transcriptional Programs in Angiosarcoma

Kim et al. | Page 847

Angiosarcomas (AS) are rare, aggressive tumors arising from vascular tissues, and harboring extensive genomic events such as driver gene mutations and chromosomal translocations. However, recurrent fusion products and specific genomic events that promote disease progression have thus far proven elusive. In this study, Kim and colleagues employ RNA sequencing data from human angiosarcomas and canine hemangiosarcomas—which closely mirror human AS—and identify 25 novel fusion products among the human and canine samples. Though the fusions were themselves non-recurrent, they co-occurred alongside recurrent mutations in TP53, PIK3CA, PIK3CA, and NRAS, suggesting that genomic instability induced by these mutations may play a role in the genomic complexity of the disease. Further, the novel fusions were uniformly associated with increased angiogenic signaling, indicating that diverse genomic events in AS likely converge on the activation of a specific transcriptional program. Taken together, the data nominate a host of new molecular targets for investigation and clarify a unifying role for diverse genomic events in the pathogenesis of AS.

Extracellular vesicles (EV) have emerged as a key mediator of intercellular signaling and have been linked to the pathogenesis of cancer. EV are loaded with different “cargo” depending on their source, and the characterization of these cargoes is important to understanding and contextualizing their role. Here, Ikeda and colleagues use proteomics to quantitatively probe the differences between EV from cancerous versus normal colon. Employing an ex vivo method for harvesting tissue-exudative EV (Te-EV) from patient samples, the authors find that the amino acid transporter CAT1 is enriched in Te-EV from colorectal cancer (CRC). CAT1-positive EV were found at higher abundance in the plasma of CRC patients—suggestive of CAT1-positive EV as a plasma biomarker for CRC development and progression.

IAPP Is Required for Oncogene-Induced Senescence

Garnett et al. | Page 874

Oncogene signaling is a potent driver of tumorigenesis and progression, but cells inherently resist oncogenic transformation via feedback loops leading to cellular senescence. Understanding how oncogene-induced senescence (OIS) is subverted by tumors is critical to the development of new methods to clinically manage cancers driven by BRAF- and RAS-activating mutations. Here, Garnett and colleagues employ a genetic screen to identify mediators of OIS in the context of BRAF activation. The authors found that Amylin, a 37-amino acid peptide that promotes glycolysis, is a key molecular determinant of the response to oncogene signaling. Amylin-ablated cells underwent a series of metabolic and epigenetic changes that circumvented the onset of senescence in response to BRAF signaling. However, exogenous supplementation of Amylin to the cell growth medium restored the ability of cells to enter a senescent state. These data identify Amylin as a key control node governing the response to oncogene signaling in cancer cells, and suggest that Amylin treatment may hold clinical benefit for patients with oncogene-driven cancers.

ERBB2 and BCL2 Inhibition in MDS and AML Cells

Kam et al. | Page 886

Acute myeloid leukemia (AML) is a genetically diverse cancer with over ten different molecular subtypes characterized by specific genomic events. EGFR pathway signaling has also been described in AML cells, but most AML cells paradoxically do not express any EGFR family members on the cell surface. In this study, Kam and colleagues address this discrepancy and identify intracellular expression of truncated ERBB2 isoforms in AML cells and myelodysplastic syndrome, an AML precursor lesion. These ERBB2 isoforms—which are also known to be pathogenic in breast cancer—mediate active signaling via classical EGFR-related pathways and were sensitive to inhibition with ERBB2 tyrosine kinase inhibitors. While ERBB2 inhibition was effective as a single agent, combination of the ERBB2 inhibitor lapatinib with the BCL-2 inhibitor venetoclax resulted in marked synergism at all tested doses. These observations nominate ERBB2 inhibitors for further investigation to complement the growing arsenal of therapeutic options for AML patients.

CAT1+ EVs Promote Angiogenesis in CRC

Ikeda et al. | Page 834

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