Molecular Cancer Research

Highlights

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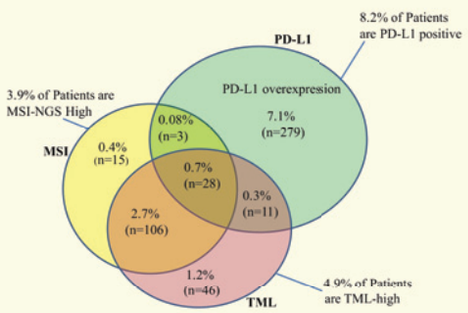
Selected Articles from This Issue



TML, MSI, and PD-L1 Expression in Gastrointestinal Tumors

Salem *et al.* Page 805

The present study characterizes the prevalence of microsatellite instability (MSI), tumor mutation load (TML), and PD-L1 in a large clinical cohort of gastrointestinal tumors. The clinicopathological relationship between these three features offers a more comprehensive understanding of these immune biomarkers, which may enable better patient selection and a more informed therapeutic choice to improve clinical outcome with cancer immunotherapies. These data suggest that TML-high and MSI-high (MSI-H) rates varied widely among gastrointestinal cancers. Although, MSI-H is conceivably the main driver for TML-high tumors other factors (*e.g.*, HPV infection) may be involved.

Regulators of IRE1α-XBP1 Pathway

Yang *et al.* Page 745

Activation of the IRE1α-XBP1 branch of the unfolded protein response (UPR) has been implicated in various human cancers; however, mechanistic understanding of this activation remains elusive. In this Rapid Impact, by Yang and colleagues, a genome-wide, loss-of-function, luciferase reporter-based siRNA screen was performed to identify genes involved in IRE1α-XBP1 signaling regulation. Pathway analysis uncovered a subset of genes implicated in the pathogenesis of breast cancer. Several genes including *BCL10*, *GCLM*, and *IGF1R* correlated with worse relapse-free survival (RFS) for patients with triple-negative breast cancer (TNBC). The novel genes identified as important for XBP1 activation suggest new therapeutic paradigms for cancers in which the UPR is dysregulated.

SWI/SNF Regulates Oncogenic Signaling in AML

Chatterjee *et al.* Page 791

SWI/SNF is an evolutionarily conserved multi-subunit chromatin remodeling complex that regulates epigenetic architecture and cellular identity. Although SWI/SNF genes are frequently altered in human malignancies, the evidence showing their involvement in tumor cell-autonomous chromatin regulation and transcriptional plasticity is limiting. Rac GTPases play a crucial role in leukemia cell engraftment, however the mechanism of Rac activation in acute myeloid leukemia (AML) is incompletely understood. Here, loss of SMARCB1 in AML associates with SWI/SNF$^{\Delta}$ nucleation, which promotes Rac GTPase guanine nucleotide exchange factors expression, Rac activation, migration, and survival of AML cells. Thus, highlighting SWI/SNF$^{\Delta}$ downstream signaling as an important molecular regulator in AML.

Leptin Influences Cancer Stem Cells, EMT, and Mammary Cancer

Bowers *et al.* Page 869

Obesity is associated with poor prognosis in women with triple-negative breast cancer (TNBC). Bowers and colleagues now demonstrate that increased leptin signaling drives obesity-associated TNBC development by promoting cancer stem cell (CSC) enrichment and epithelial-to-mesenchymal transition (EMT). In a transgenic mouse model of TNBC, obesity reduced tumor-free survival and increased CSC/EMT gene expression, aldehyde dehydrogenase activity, and leptin signaling. Leptin receptor knockdown attenuated the obesity-induced CSC/EMT phenotype and *Foxc2*, *Twist2*, *Vim*, *Akt3*, and *Sox2* expression in TNBC cells. Greater understanding of the leptin-related signals regulating CSC and EMT may reveal new strategies for decreasing TNBC burden in obese women.

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