Molecular Cancer Research

Highlights

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Selected Articles from This Issue

Metabolic Profile in FFPE Tissues

Cacciatore *et al.* Page 439

Metabolomics captures the interactions between genetic alterations, enzymatic activity, and metabolic reactions. Here, comparative mass spectrometry-based metabolomics was performed using matched frozen and fixed isogenic prostate cancer cells and clinical specimens. A sufficient number of metabolites were retained in formalin-fixed, paraffin-embedded (FFPE) tissue to allow unsupervised hierarchical clustering of cell populations. This metabolomic profiling approach creates the opportunity, for research and diagnostic purposes, to interrogate annotated tumor banks retrospectively and link metabolomics with clinicopathologic endpoints. Combined, metabolic profiling to discover and validate metabolism-based diagnostic, prognostic or predictive biomarkers in archival diagnostic tissue adds a new, powerful technology for precision medicine.

DREAM Contributes to Cancer Spheroid Dormancy

MacDonald *et al.* Page 371

A critical aspect of metastatic epithelial ovarian cancer (EOC) is tumor cell dormancy, rendering these cells resistant to chemotherapeutics. Employing a systematic approach to analyze the role of negative growth factors, MacDonald and colleagues demonstrate that disruption of the DP, RB family, E2F, and MuvB complex (DREAM) results in death of EOC cells. Specifically, loss of the DREAM assembly factor Dyrk1A, or the DREAM component p130, impairs repression of DREAM target genes, leads to continued DNA synthesis, and is coincident with increased cell death. Importantly, chemical inhibition of Dyrk1A synergizes with conventional chemotherapies to kill EOC cells under dormant conditions.

SN38 Sensitivity is Defined by RIP1

Cabal-Hierro and O'Dwyer Page 395

The basis of resistance or sensitivity to irinotecan in colorectal cancer has still not been clearly established. Strategies to identify susceptible patients and targetable pathways to reverse resistance are urgently needed. Cabal-Hierro and O'Dwyer highlight a role for RIP1 kinase in SN38 sensitivity by mediating cell death/DNA damage signaling in colon adenocarcinoma model systems through the TNF/TNFR pathway. Downregulation of RIP1 protects from SN-38 *in vitro* and *in vivo*, suggesting that RIP1 has potential as a biomarker. Activation of TNF/TNFR signaling potentiates SN38 activity in a RIP1-dependent manner; thus, suggesting a re-evaluation of TNF-based interventions to enhance treatment efficacy.

OSM Drives EMT and Stemness in PDAC

Smigiel *et al.* Page 478

Early metastasis and therapeutic resistance are huge setbacks to patients diagnosed with pancreatic ductal adenocarcinoma (PDAC). Here, Smigiel and colleagues report a unique function of the tumor microenvironment (TME) cytokine oncostatin M (OSM) in inducing epithelial-mesenchymal transition (EMT) and cancer stem cell (CSC) properties in pancreatic cancer cells. Elevated levels of OSM in PDAC induce EMT transcription factors ZEB1 and Snail, and induce $CD44^{+}$ CSC that are more migratory, tumorigenic, highly metastatic and resistant to gemcitabine. As such, targeting OSM or OSM-signaling in PDAC is a potential therapeutic strategy to prevent *de novo* acquisition of CSC properties such as drug resistance and metastasis.

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