Molecular Cancer Research

Highlights

March 2018 • Volume 16 • Number 3

Selected Articles from This Issue

Characterization of a Well-differentiated Human NET Model

Benten *et al.* Page 496

Research on new therapies for pancreatic neuroendocrine tumors (pNET) has been hampered by the absence of a clinically relevant tumor model system. Benten and colleagues now provide data on the first well-differentiated and slow-growing human pNET cell line, which is stable and functionally active over many passages. The pNET cell line is also capable of creating a corresponding xenograft model where resulting subcutaneous and intrahepatic tumors resemble the human pNET tumor of origin. Absence of p53 and Ras mutations as well as high expression of somatostatin receptors make this cell line clinically relevant among available pNET cell lines.

Blocking p27 Phosphorylation Potently Arrests Cell Cycle

Patel *et al.* Page 361

Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, such as palbociclib, have shown clinical efficacy, but resistance has emerged as a significant problem. This study demonstrates that CDK2 compensates for loss of CDK4 activity to rescue palbociclib-arrested breast cancer cells, suggesting that inhibition of both kinases is required to achieve durable response. A novel strategy is described to inhibit tyrosine phosphorylation of the cyclin-CDK4 assembly factor, $p27^{Kip1}$ (CDKN1B). Modulating tyrosine phosphorylation of p27 inhibits both proliferative (CDK4) and resistance (CDK2) mechanisms in breast cancer and suggests a role for phospho-p27 as a biomarker for patients that are responsive to CDK4/6 inhibition.

14q32 miRNA Cluster Induces Metastasis in Lung Cancer

González-Vallinas *et al.* Page 390

Metastasis is responsible for most lung cancer deaths; however, the molecular mechanism of tumor cell dissemination is not completely understood. Here, González-Vallinas and colleagues demonstrate overexpression of the chromosome 14q32 miRNA cluster in lung adenocarcinoma patients and its association with genomic DNA hypomethylation using different epigenetic analyses. Simultaneous overexpression of chromosome 14q32 cluster miRNAs, by CRISPR activation technology, revealed that these miRNAs promote cell migration and invasion. Among them, miR-323b, miR-487a and miR-539 strongly contribute to these phenotypes and associate with patient disease-free survival. Thus, chromosome 14q32 cluster miRNAs represent promising anti-tumor targets and prognostic biomarkers in lung adenocarcinoma metastasis.

Metabolism Regulation via BRCA1-Destabilized Oct1

Vázquez-Arreguín *et al.* Page 439

BRCA1 is a prominent tumor suppressor with roles in DNA damage response (DDR) and other incompletely defined functions. In conjunction with another protein, BARD1, BRCA1 has an enzymatic E3 ubiquitin ligase activity. Vázquez-Arreguín and colleagues report that cells lacking this activity have a cancer-associated glycolytic metabolic profile. A new ubiquitination target of BRCA1 was identified, the transcription factor Oct1, and shown to control metabolism downstream of BRCA1. In primary human breast cancer specimens, Oct1 inversely correlates with BRCA1 protein levels and positively correlates with tumor grade. Thus, this study highlights the importance of other activities of BRCA1 apart from DNA repair.

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Mol Cancer Res 2018;16:359.