Molecular Cancer Research

Highlights

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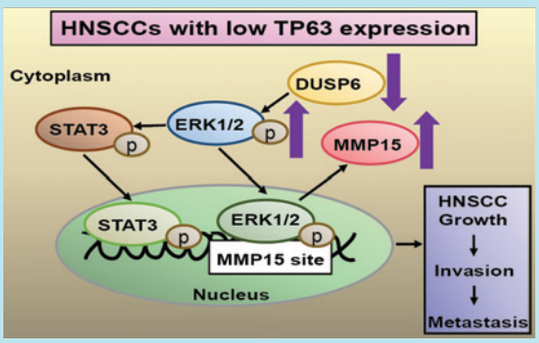
Selected Articles from This Issue



TP63-Dependent Metastasis of HNSCC

Lakshmanachetty *et al.* **Page 1279**

Metastatic head and neck cancer (HNSCC) represents a major clinical challenge, and the molecular underpinnings of HNSCC metastasis are poorly defined. Here, Lakshmanachetty and colleagues demonstrate that TP63, which is overexpressed in some primary HNSCC, is downregulated exclusively in advanced and metastatic disease. Loss of TP63 expression was causative of increased progression and metastasis *in vivo*, and was shown to be acutely reliant on activation of MAPK signaling. This finding is supported by the observation that the MEK inhibitor trametinib significantly reduced metastasis of TP63-deficient HNSCC. Taken together, the data uncover a novel role for TP63 in the progression of HNSCC and highlight a potential avenue to improve patient survival outcomes.

AR-V Dependency on GATA2

Chaytor *et al.* **Page 1264**

Constitutively active androgen receptor splice variants (AR-V) have emerged as a clinically relevant mechanism of disease progression and resistance to hormone therapy in prostate cancer. However, it remains unclear whether AR-V rely on the same chromatin remodeling factors as full-length AR to execute their transcriptional program. In this article, Chaytor and colleagues show that GATA2 regulates AR-V chromatin binding, and that the GATA2/AR-V cistromes overlap considerably with bromodomain and extraterminal (BET) cistromes in castration-resistant prostate cancer cells. BET inhibitors were shown to impede the pioneering role of GATA2 and by extension AR-V activity, thereby exposing a potential weakness in AR-V function which has thus far evaded targeted therapy.

Enhancement of the DNA Damage Response by O-GlcNAcylation

Efimova *et al.* **Page 1338**

Cancer cells extensively rewire their metabolism to meet increased demands on their cellular energetics, but emerging evidence has suggested that altered metabolic states play roles in other aspects of tumor biology as well. Here, Efimova and colleagues expand on their novel observations that the hexosamine biosynthetic pathway can regulate the DNA damage response. Inhibition of O-GlcNAc transferase (OGT) significantly impeded radiation-induced DNA double strand break repair both *in vitro* and *in vivo*, whereas ablation of O-GlcNAcase or supplementation with GlcNAc enhanced the efficiency of the DNA damage response. These observations provide compelling preclinical data to support a novel means of enhancing or restoring sensitivity to ionizing radiation.

Early Detection of Ibrutinib Response in Mantle Cell Lymphoma

Lee *et al.* **Page 1365**

Kinase inhibitors are a cornerstone of clinical cancer management, but current methods of evaluating patient responses present considerable lag time. Here, Lee and colleagues demonstrate metabolic quantification of the cancer cell response, or lack thereof, to ibrutinib, an inhibitor of BTK. Responsive cells experienced marked inhibition of key metabolic pathways, with decreases in lactate and alanine concentrations serving as potential biomarkers of response. Resistant cells maintained their metabolic flux largely through glutaminolysis; accordingly, inhibition of glutamine metabolism potently inhibited cell growth in ibrutinib-resistant cells. Overall, the authors demonstrate precise and expedient evaluation of response to a kinase inhibitor using fluxomic quantification, allowing for early determination of drug sensitivity as well as highlighting potential vulnerabilities in resistant cells that can be exploited therapeutically.

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