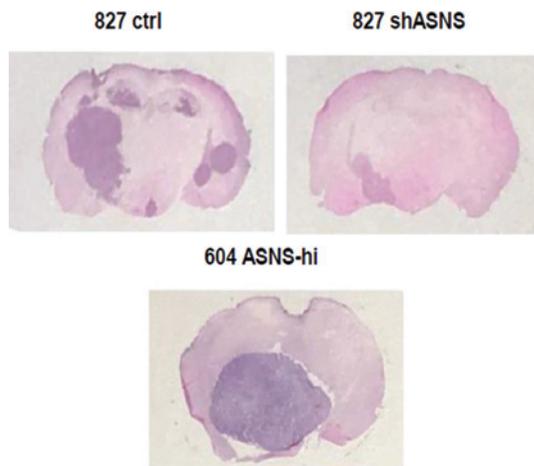


## MOLECULAR CANCER RESEARCH

## HIGHLIGHTS

Selected Articles from This Issue

## Elevated ASNS Drives Glioma Plasticity and Stress Resistance

Thomas *et al.* | Page 1375

Glioblastomas (GBM) are highly invasive brain tumors that can spread rapidly throughout the brain. GBM are marked by a high rate of disease recurrence after therapy by virtue of the self-renewal capacity of glioma stem cells (GSCs), which are highly heterogeneous. Here, Thomas and colleagues identify a subset of GSCs bearing copy number alterations of the ASNS gene, leading to elevated expression of asparagine synthase. ASNS-high GSCs bore distinct metabolic features from other GSCs, including increased capacity for both glycolysis and oxidative phosphorylation and the ability to switch between them as needed in response to environmental cues. This metabolic plasticity allowed for rapid dissemination of ASNS-high GSCs throughout the brain tissue and a marked resistance to oxidative stress, rendering these cells *de novo* resistant to radiation. These findings nominate ASNS as a potential therapeutic target for GBM, which could restrict the pathogenicity of GSCs and enhance the efficacy of standard treatment modalities.

## Preventing Hematological Toxicity from PARP Inhibitors

Xu *et al.* | Page 1350

Inhibitors of poly (ADP-ribose) polymerase (PARPi) are known to be effective in treating a range of tumor types, particularly as a synthetic-lethal approach for tumors with defects in the homologous recombination DNA repair pathway. However, dose-limiting toxicities, particularly hematological toxicities, can cause early cessation of treatment and loss of therapeutic benefit. Here, using a CRISPR/Cas9 screen, Xu and colleagues identify the CHK2-p53 pathway as a key mediator of hematological toxicity in response to the clinically approved PARPi agent, olaparib. CHK2 was required for efficient activation of p53 in response to PARPi in blood cells, and genetic approaches that blocked this connection allowed cells to better tolerate olaparib treatment. Concurrent inhibition of CHK2 alongside olaparib emulated this protective effect, but importantly did not affect PARPi-mediated killing of ovarian cancer cell lines. If this finding extends to people, then these data nominate CHK2 inhibition as a potential target to spare patients from hematological adverse effects in response to PARPi, which could broaden the window of therapeutic benefit for these agents.

m<sup>6</sup>A Targets in Prostate Cancer: Low METTL3 Induces Therapy ResistanceCotter *et al.* | Page 1398

Analogous to epigenetic control of gene expression through histone methylation, epitranscriptomic modifications such as N<sup>6</sup>-methyladenosine (m<sup>6</sup>A) function to modulate RNA stability, processing, and translation. In this study, Cotter and colleagues profile the activity of METTL3, a key constituent of the methyltransferase complex that catalyzes m<sup>6</sup>A modifications, and its role in establishing the pathologic transcriptome observed in metastatic castration-resistant prostate cancer (mCRPC). The authors observe that ablation of METTL3—and by extension, m<sup>6</sup>A modifications—is associated with resistance to androgen receptor signaling inhibitors, a key therapeutic modality in the clinical management of prostate cancer. This effect was shown to be mediated independently of the androgen signaling pathway, and instead relied on activation of a gastrointestinal-specific transcriptional signature driven by the expression of the nuclear receptor NR5A2/LRH-1. Taken together, these observations elucidate a novel mechanism by which epitranscriptomic m<sup>6</sup>A modifications may play a role in establishing the mCRPC transcriptome and in promoting disease progression.

## AXL Drives PDA Progression

Du *et al.* | Page 1412

Pancreatic ductal adenocarcinoma (PDAC) patients often present with metastatic disease and face a dismal prognosis. Because of the high rate of metastasis observed in PDAC tumors, systemic therapies are frequently the only viable option for clinical management; however, PDAC lacks an effective armamentarium of targeted interventions, and tumors quickly develop resistance to standard chemotherapeutic regimens. Using single-cell sequencing of mouse PDAC tumors, Du and colleagues identify the receptor tyrosine kinase AXL as a mediator of PDAC progression and metastatic spread. The authors demonstrate that AXL is overexpressed in PDAC tumor cells with a mesenchymal phenotype, and that its activity promotes and is required for epithelial-mesenchymal transition and metastasis *in vivo*. Concordantly, PDAC tumors that developed in AXL-deficient mice were less aggressive, better differentiated, and more sensitive to gemcitabine chemotherapy than PDAC in mice bearing wild-type AXL. These data suggest that targeting AXL expression and/or activity may present an opportunity to suppress or treat PDAC progression.

# Molecular Cancer Research

## Selected Articles from This Issue

*Mol Cancer Res* 2021;19:1249.

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