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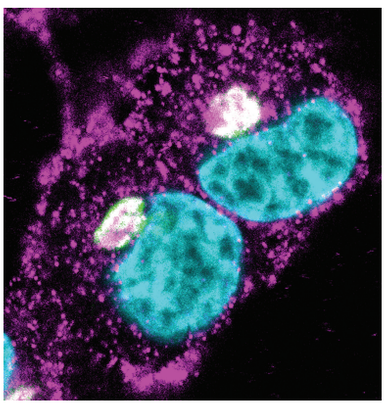
MOLECULAR CANCER RESEARCH
HIGHLIGHTS

Selected Articles from This Issue

Elongin BC Complex Negatively Regulates AXL in Melanoma



Schieven *et al.* | Page 428

AXL, a receptor tyrosine kinase, contributes to tumor cell invasion, dedifferentiation, and drug resistance. Mechanisms governing AXL protein abundance are incompletely understood, and identifying AXL regulators could elucidate novel therapeutic targets. To that end, Schieven and colleagues performed a whole-genome CRISPR-Cas9 screen in a melanoma cell line and measured subsequent AXL protein expression using flow cytometry. Single-guide RNA (sgRNA) sequencing in cells sorted based on high and low AXL expression revealed that 5 members of the Elongin BC ubiquitin ligase complex—ELOB, ELOC, SOCS5, UBE2F and RNF7—negatively regulate AXL abundance. Pharmacologic inhibition of neddylation and proteosomal degradation increases AXL expression significantly more in control cells than cells expressing *ELOB*-targeting sgRNA, demonstrating that a functional Elongin BC complex promotes AXL degradation. Transcriptional and IHC analyses show that Elongin B/C expression positively correlates with melanoma differentiation status. Lastly, pharmacologic BRAF or MEK inhibition suppress *Elongin C* expression while augmenting *AXL* expression. Taken together, this study presents the Elongin BC complex as a negative regulator of oncogenic AXL in melanoma.

JAK/STAT Pathway Activation in Refractory ATC

Limberg *et al.* | Page 397

BRAF^{V600E} is a common oncogenic driver in thyroid cancer, but small molecule inhibitors targeting BRAF^{V600E} (BRAFi) have exhibited poorer efficacy in thyroid cancer than in other cancer types. To query mechanisms underlying BRAFi resistance and identify putative therapeutic vulnerabilities therein, Limberg and colleagues treated *BRAF*^{V600E}-expressing thyroid cancer cells with BRAFi vemurafenib and performed transcriptomic analysis. Both initial and resistance-inducing long-term BRAFi treatment increase JAK/STAT signaling in *BRAF*^{V600E}-expressing thyroid cancer cells. Correspondingly, the authors showed that protein expression of downstream JAK/STAT targets is enhanced after BRAFi treatment. Pharmacologic JAK/STAT disruption and CRISPR-Cas9-mediated *STAT1* deletion each augment BRAFi sensitivity, functionally demonstrating that JAK/STAT signaling underlies BRAFi resistance in thyroid cancer. Transcriptomic data from this study and The Cancer Genome Atlas show that *IRF1* expression positively correlates with that of JAK/STAT, suggesting *IRF1* may mediate JAK/STAT-driven BRAFi resistance. Overall, this study presents JAK/STAT signaling as a facilitator of BRAFi resistance and provides evidence that targeting the JAK/STAT pathway may bolster BRAFi efficacy in thyroid cancer.

BAP1-deficient MPM Elevates ASS1 Expression

Barnett *et al.* | Page 411

BRCA1-associated protein 1 (BAP1), a nuclear deubiquitylase, is a tumor suppressor that is often inactivated in malignant pleural mesothelioma (MPM). Mechanisms by which BAP1 inactivation potentiates MPM are poorly understood and elucidating them may identify novel therapeutic targets and/or biomarkers. To investigate global cellular consequences of BAP1 inactivation, Barnett and colleagues sequentially mutated and removed *BAP1* alleles via homologous recombination in a normal mesothelial cell line and performed mass spectrometry- and nuclear magnetic resonance-based proteomic and metabolomic analyses. The authors found that BAP1 inactivation enhances argininosuccinate synthase 1 (ASS1) expression and validated that finding using MPM patient sample immunohistochemical stains. The authors also demonstrated that MPM cell lines with inactivated BAP1 and high ASS1 expression are resistant to arginine depletion by pegylated arginine deiminase (ADI-PEG20), a logical finding given ASS1 synthesizes arginine, and that cells expressing wild-type BAP1 are sensitive to ADI-PEG20. All together, this study suggests that arginine metabolism is a compensatory mechanism for BAP1 inactivation, and that BAP1 status may be a biomarker capable of informing responsiveness to therapeutic arginine deprivation.

Targeting MYC/Glutamine to Overcome Gemcitabine Resistance

Dash *et al.* | Page 444

While deoxycytidine analog gemcitabine often provides efficacy against pancreatic ductal adenocarcinoma (PDAC) upon initial treatment, gemcitabine resistance often develops, facilitating disease progression. Several mechanisms underlying gemcitabine resistance have been described, but to date none of those pathways have been therapeutically leveraged to enhance gemcitabine responsiveness. To search for targetable gemcitabine resistance mediators, Dash and colleagues performed whole-genome CRISPR-Cas9 knockout library screening and found that deoxycytidine kinase (DCK) loss promotes gemcitabine resistance. RNA-sequencing using DCK#10 cells—in which *DCK* was removed via CRISPR-Cas9—revealed that expression of MYC transcriptional targets as well as one-carbon and glutamine metabolism genes is augmented upon *DCK* loss. Correspondingly, the authors showed that MYC expression increases upon gemcitabine treatment in PDAC cells, as do intracellular glutamine levels. The authors also demonstrated that DCK#10 cells are sensitive to pharmacologic inhibitors of MYC, one-carbon metabolism, and glutamine metabolism. In sum, this study unveils novel therapeutic vulnerabilities in gemcitabine-resistant PDAC cells with diminished DCK expression.

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