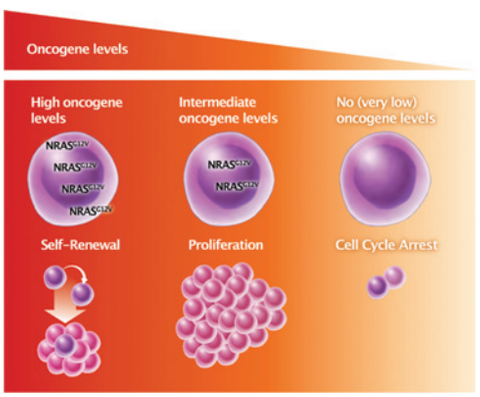
November 1, 2022 | Volume 20 | Number 11

MOLECULAR CANCER RESEARCH
HIGHLIGHTS

Selected Articles from This Issue



NRAS^{G12V} Dose in AML

Kurata *et al.* | Page 1646

Mutant NRAS^{G12V} drives acute myeloid leukemia (AML) cell proliferation and self-renewal in a mutually exclusive manner. Previous studies demonstrated that AML cell proliferation and self-renewal are associated with differential *NRAS*^{G12V} transcript levels, but whether different NRAS^{G12V} protein levels dictate proliferative versus self-renewal phenotypes is not known. To address that knowledge gap, Kurata and colleagues engineered AML cell lines in which tetracycline-inducible *NRAS*^{G12V} expression levels are tunable using various doxycycline doses. The authors found that moderate NRAS^{G12V} protein expression promotes AML cell proliferation, whereas higher NRAS^{G12V} protein expression facilitates AML cell senescence and self-renewal. Using mass cytometry, the authors showed that abundances of several downstream NRAS^{G12V} effectors, including known stemness mediators such as β-catenin, increase in a dose-dependent fashion, whereas others, such as phosphorylated STAT1, are not dose-dependent. Overall, this study demonstrates that differential NRAS^{G12V} protein levels disparately drive AML cell proliferation and self-renewal and illuminates the downstream signaling dynamics underlying each phenotype.

DNMT3B-Mediated Breast Tumor Heterogeneity and Metastasis

So *et al.* | Page 1674

Tumor cell heterogeneity is a major impedance in eliminating cancer, as it promotes therapy-resistant clone selection in response to treatment. Identifying biomarkers indicative of tumor heterogeneity may help quantify it and uncover therapeutic vulnerabilities, but such biomarkers remain elusive. In their study, So and colleagues discovered that DNA methyltransferase 3B (DNMT3B) protein expression displays marked heterogeneity in primary tumors from triple-negative breast cancer (TNBC) patients and TNBC mouse models. By selecting DNMT3B-high and -low clones from 4T1 cells, labeling them with different fluorescent dyes, and quantifying them in circulation and lung metastases after orthotopic injection, the authors found that DNMT3B-high cells are more metastatic than DNMT3B-low cells. Mechanistically, prostaglandin E2 (PGE2) induces DNMT3B expression, and DNMT3B regulates expression of epithelial–mesenchymal transition effectors including vimentin, Twist2, and Snai1. Perioperative treatment with celecoxib, which lowers PGE2 expression, alongside DNMT inhibitor 5-azacytidine and other chemotherapeutic drugs decreases tumor recurrence and metastasis after primary tumor removal. Taken together, this study presents DNMT3B as a therapeutically targetable marker and effector of tumor heterogeneity.

LncRNA A2M-AS1 Promotes Ferroptosis in Pancreatic Cancer

Qiu *et al.* | Page 1636

Therapeutic challenges and poor outcomes in pancreatic cancer make further elucidating its underlying molecular mechanisms and therapeutic vulnerabilities critical. While long non-coding RNA (lncRNA) α-2-macroglobulin-antisense 1 (A2M-AS1) expression positively correlates with overall survival in pancreatic cancer as well as ferroptosis-related genes, how A2M-AS1 might regulate ferroptosis and whether it does so in pancreatic cancer has not been solved. In their study, Qiu and colleagues found that pharmacologically inducing ferroptosis in pancreatic cell lines augments A2M-AS1 expression, and that modulating A2M-AS1 abundance using shRNA and overexpression inhibits and enhances ferroptosis, respectively. Accordingly, A2M-AS1 overexpression limits pancreatic cancer cell growth both *in vitro* and *in vivo*. An RNA pull-down and mass spectrometry revealed that A2M-AS1 interacts with PCBP3. Additional experiments demonstrated that the interaction between A2M-AS1 and PCBP3 abrogates mTOR and AKT activation, while increasing p38 activation and ferroptosis. In sum, this study unveils a novel molecular mechanism by which ferroptosis evasion occurs in pancreatic cancer.

Gln Metabolism and CII Inhibition in AML

Roma *et al.* | Page 1659

Acute myeloid leukemia (AML) cells are dependent on oxidative metabolism. However, electron transport chain complex II (CII) targeting agents and their potential effects on AML cell metabolism and viability have not been assessed. To evaluate CII therapeutic targeting in AML, Roma and colleagues abrogated expression of CII chaperone protein succinate dehydrogenase assembly factor 1 (SDHAF1) using shRNA in AML cell lines. Using an *in silico* screen and HPLC analysis, the authors also identified shikonin as a CII small molecule inhibitor. Both SDHAF1 ablation and shikonin promote AML cell death *in vitro* and *in vivo*, and stable isotope tracing demonstrated concurrent tricarboxylic acid (TCA) cycle truncation. The authors also showed that SDHAF1 ablation and shikonin increase glutamine flux into the TCA cycle via deamination to α-ketoglutarate as well as reductive flux to aspartate. Accordingly, supplementing α-ketoglutarate undermines shikonin effectiveness, and pharmacologically inhibiting glutaminase augments it. Altogether, this study reveals a novel therapeutic target and accompanying therapeutic agent in AML and identifies anaplerotic glutamine metabolism as a compensatory mechanism and therapeutic vulnerability in CII inhibition.

doi: 10.1158/1541-7786.MCR-20-11-HI