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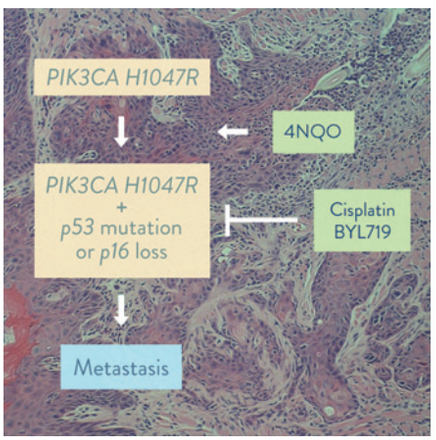
MOLECULAR CANCER RESEARCH

HIGHLIGHTS

Selected Articles from This Issue

Mutant PIK3CA and p53 Synergistically Promote OSCC



García-Carracedo *et al.* | Page 822

Head and neck squamous cell carcinoma (HNSCC) is an intractable disease for which limited progress has been made over the past several decades, and new therapeutic regimens are urgently needed to enhance the standard of care. In this study, García-Carracedo and colleagues generated genetically engineered mouse models with tissue-specific expression of a clinically relevant gain of function mutation in *PIK3CA*, alone or in combination with heterozygous *TP53* R172H mutation. Following tumor induction with the carcinogen 4NQO, *PIK3CA*-mutant mice exhibited progressive loss of the tumor suppressor p16, elevated expression of genes associated with proliferation and cell cycle, and faster tumor growth. Moreover, tumors in mice harboring concurrent *PIK3CA*/*TP53* mutations also grew at a faster rate but were additionally more prone to developing distant metastasis. Finally, the authors demonstrate that HNSCC tumors bearing mutations in *PIK3CA* were exquisitely sensitive to combination therapy with cisplatin and the PI3K inhibitor BYL719, suggesting that this combination may be feasible and effective for clinical management of a subset of HNSCC.

Molecular Foundations of CRISPR Activity in NSCLC

Banas *et al.* | Page 891

The high specificity of CRISPR gene editing technology has made it an attractive candidate for use in clinical gene therapy, particularly in cancer. Here, Banas and colleagues report on the molecular kinetics of CRISPR activity in lung cancer cells for the first time, tracking nuclear entry and site-specific DNA cleavage over time. The authors use *NRF2*, a regulator of chemotherapy resistance, as an archetypal target to demonstrate the cancer specificity of their approach, while also demonstrating efficacy and enhanced chemosensitivity of the CRISPR-edited tumor cells. Specifically, the authors identify a unique protospacer-adjacent motif—a DNA sequence used to target CRISPR/Cas9 activity—that is only present in cancer genomes, and thus forms the molecular basis for the activity of CRISPR DNA cleavage in tumor cells but not normal cells. Taken together, the data provide an empirical basis for the use of CRISPR-directed gene therapy in solid tumor cells and continue to advance the use of this technology closer to clinical implementation.

Cdc42 Mediates Cancer Cell Chemotaxis in Perineural Invasion

Chernichenko *et al.* | Page 913

Perineural invasion (PNI), or cancer cell migration along peripheral nerves, causes motor nerve paralysis and is a marker of dismal prognosis in pancreatic cancer. It is known that glial-derived neurotrophic factor (GDNF) signaling through RET receptors plays a role in PNI, but the intracellular pathways that control the directionality of PNI and its severity are poorly defined. In this study, Chernichenko and colleagues mechanistically link the GTPase Cdc42 to the RET signaling pathway in PNI. Stimulation of pancreatic cancer cells with GDNF caused rapid activation of Cdc42, and ablation of Cdc42 impeded the migration of tumor cells toward neurons. Importantly, Cdc42 disruption only affected the directionality of cell motility but not their speed or viability. By contrast, Rac1—a RHO GTPase responsible for cytoskeletal remodeling—was shown to control the speed of cell migration, but not the directionality. Taken together, the data provide new insight into the molecular underpinnings of PNI in pancreatic cancer and nominate potential targets to mitigate PNI in the clinic.

Stromal-Mdm2 Promotes Lung Cancer Cell Invasion

Kamer *et al.* | Page 926

Cross-talk between tumor cells and their adjacent stromal cells represents a key component of the microenvironment's role in shaping tumor progression. Here, Kamer and colleagues identify a previously unknown tumor-stromal feedback loop functioning through the E3 ubiquitin ligase MDM2 in stromal cells. Specifically, conditioned medium from lung cancer cells was shown to harbor an unknown factor that promoted mTORC1 activation and enhanced translation of MDM2 when applied to stromal cells, which in turn enhanced the invasiveness of the neighboring tumor cells. Interference with AKT/mTOR signaling or ablation of MDM2 from stromal cells negated the effect on tumor cell invasion. Importantly, however, modulation of the MDM2 target p53 did not affect the function of the feedback loop, suggesting that the role of MDM2 in this pathway is p53-independent. Though the soluble factors responsible for activating this pathway remain unidentified, these data form the basis for new insights into lung cancer metastasis and potential avenues to impede it.