



RhoA-NF-κB in CIPN

Zhu *et al.* _____ Page 1910

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and often dose-limiting adverse effect of many chemotherapeutic drugs that negatively impacts both treatment outcomes and patient quality of life. To date, no effective treatment or prevention strategies are available to address CIPN in the clinic. Here, Zhu and colleagues describe novel effects of the ROCK inhibitor Y-27632, which was observed not only to potentiate the effects of cisplatin therapy, but also to prevent loss of nerve function in the footpads of tumor-bearing, immunocompetent mice. Mechanistic analysis of the drug actions revealed that ROCK inhibition suppressed cisplatin-induced NF-κB hyperactivation and reversed the cellular stress effects associated with cisplatin treatment in nerve cells. In sum, the study is the first to identify a rationale for addressing CIPN in the clinic, and has the potential to improve outcomes for patients undergoing chemotherapy.

c-MYC Drives Nab-Paclitaxel Resistance in Pancreatic Cancer

Parasido *et al.* _____ Page 1815

Resistance to chemotherapy undermines the clinical management of pancreatic ductal adenocarcinoma (PDAC), and preclinical models that faithfully recapitulate human disease are needed to assess the underlying mechanisms. Here, Parasido and colleagues employ continuous cultures of conditionally reprogrammed (CR) primary PDAC cells to study resistance to nab-paclitaxel. The CR cells were found to be genetically stable and to self-assemble into well-defined PDACs with lung metastatic potential *in vivo*, thus representing a novel preclinical model useful for both *in vitro* and *in vivo* investigation. Mechanistic investigation revealed that sustained induction of c-MYC was critical for nab-paclitaxel resistance in the CR model. The study showed that while treatment with a MEK inhibitor enhanced the nab-paclitaxel sensitivity, an activator of protein phosphatase 2a entirely restored the drug sensitivity through c-MYC destabilization. The data support CR cells as a novel, easily maintained, and stable platform for PDAC research that supersedes commercial cell lines and complements current *in vitro* and PDX models.

Targetable Recurrent MAP3K8 Rearrangements in Melanoma

Lehmann *et al.* _____ Page 1842

Activating mutations in the MAPK pathway are common in melanoma, and MEK inhibitors have become a cornerstone for the clinical management of BRAF-mutant disease. However, some patients who lack known driver mutations in RAS, RAF, KIT, and other pathway members still respond to MEK inhibitors, indicating that some driver mutations have yet to be defined. Here, Lehmann and colleagues identify a novel recurrent genomic alteration in MAP3K8 that truncates the protein at the COOH-terminal end, rendering it constitutively active. Melanoma cell lines harboring endogenous MAP3K8 rearrangement were *de novo* resistant to BRAF inhibition, but exquisitely sensitive to MEK/ERK inhibition. Taken together, the data define a new oncogenic genomic event that activates the MAPK pathway in melanoma patients, and provide insight into the clinical management of patients harboring these recurrent rearrangements.

Cigarette Smoke Effects on Head and Neck Cancer Metabolism

Domingo-Vidal *et al.* _____ Page 1893

Cigarette smoke (CS) is a known source of oncogenic stimuli in many cancers, including head and neck squamous cell carcinoma (HNSCC), but the metabolic effects of CS on the various cellular compartments that comprise a tumor are unknown. In this study, Domingo-Vidal and colleagues demonstrate that exposure to CS reprograms the mitochondrial metabolism of cancer-associated fibroblasts (CAF), increasing oxidative stress, promoting glycolytic flux and expression of monocarboxylate transporter 4 (MCT4), and inducing a senescent state. These changes were shown to promote metabolic coupling between CAFs and proliferative tumor cells, increasing tumor cell proliferation, survival, and migration both *in vitro* and *in vivo*. Overall, the study demonstrates that CS exposure reprograms stromal cell metabolism toward a glycolytic phenotype, which in turn promotes tumor aggressiveness.

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