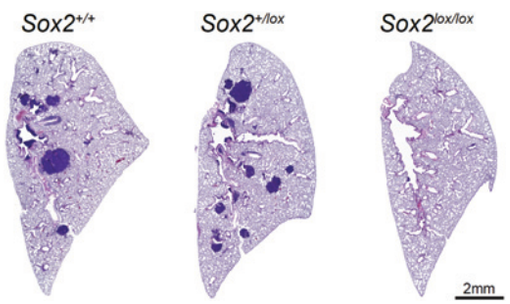
December 1, 2021 | Volume 19 | Number 12

MOLECULAR CANCER RESEARCH

HIGHLIGHTS

Selected Articles from This Issue

Role of SOX2 in Small-Cell Lung Cancer



Voigt *et al.* | Page 2015

Small-cell lung cancer (SCLC) is characterized by mutation of the p53 and Rb tumor suppressors, and patients face a dismal prognosis with few treatment options. SCLC can be classified into four subtypes based on the expression of certain key genetic regulators, such as ASCL1 and NEUROD1, but how these subtypes are established despite common driver events remains to be defined. Here, Voigt, Wallenburg, and colleagues show that upregulation of the pluripotency factor SOX2 following Rb loss of function is a key determinant of SCLC phenotypic diversity. Using a conditional *Sox2* knockout mouse model, the authors demonstrate that SOX2 upregulation is critical for initiation of tumors from pulmonary neuroendocrine cells. Transcriptomic analysis revealed that SOX2 regulated the expression of a broad network of stemness factors, including NEUROD1 and MYC family members. These data indicate that SOX2 may be involved in regulating SCLC tumorigenesis, as well as progression from the ASCL1 subtype to the more aggressive NEUROD1 subtype, through its transcriptional control of stemness factors and MYC family members.

DCLK1-S Promotes ESCC Progression

Ge *et al.* | Page 1980

Cancer-associated splicing alterations represent a key epigenetic mechanism underlying tumor biological changes that drive disease progression. DCLK1-S, a splice variant of the stem cell marker DCLK1, has been shown to promote tumorigenesis in gastrointestinal malignancies. However, the differences in their activities are not well characterized. Here, Ge, Fan, and colleagues characterize the molecular functions of DCLK1-S in esophageal squamous cell carcinoma (ESCC). Ablation of DCLK1-S was shown to inhibit ESCC cell proliferation, migration, and invasion *in vitro*, and overexpression of the shortened isoform was associated with markers of epithelial–mesenchymal transition. These effects were mediated through the MAPK pathway, leading to upregulation of MMP2 and stemness regulators such as Snail and Slug. Critically, these effects were reversible with ERK inhibitors, suggesting a potential therapeutic option for ESCC tumors that are reliant on this splicing event.

MTAP-PRMT5 Axis Regulates Fanconi Anemia Gene Expression

Du *et al.* | Page 2046

Fanconi anemia (FA) family members are key mediators of DNA repair whose activity in tumors can promote resistance to DNA-damaging chemotherapy, and as such represent desirable targets to chemosensitize tumors to genotoxic interventions. In this study, Du and colleagues report that defects in methyladenosine phosphorylase (MTAP) are associated with dysfunctional FA pathway activity and reduced expression of certain FA genes. Mechanistically, genetic alteration of MTAP led to reduced enzymatic activity Protein Arginine Methyltransferase 5 (PRMT5), and subsequently resulted in the inhibited expression of FA family members. This effect could also be achieved via genetic ablation of PRMT5 or pharmacological inhibition of MTAP, both of which enhanced the cytotoxic effects of the DNA crosslinking agent Mitomycin C in cancer cell lines. Taken together, the data suggest that PRMT5-directed therapeutics may hold promise as chemosensitizing agents by virtue of PRMT5's role in regulating the FA pathway.

Inflammation Primes the Premetastatic Niche

Arif *et al.* | Page 2096

Colonization of the metastatic niche depends not only on tumor-intrinsic features that allow for survival in the circulation and metabolic plasticity to support growth in a non-native tissue, but also on conditioning of the niche to accommodate the establishment and growth of tumor cells. In this study, Arif, Huang, and colleagues demonstrate that inflammatory conditions such as asthma, hypersensitivity pneumonitis, and sterile inflammation induced by bleomycin all promote the development of melanoma lung metastases. In all three models, inflammation-induced monocyte-derived macrophages were found to secrete inflammatory cytokines and growth factors, in particular hepatocyte growth factor (HGF), which enhanced melanoma cell survival upon entry to lung tissue without significantly impacting the rate of extravasation. Blockade of HGF signaling with cMET inhibitors eliminated the formation of micrometastases *in vivo*, suggesting that this pathway represents a key node in the metastatic cascade that could be prophylactically targeted to prevent or delay the onset of metastatic disease or reduce metastatic burden.

doi: 10.1158/1541-7786.MCR-19-12-HI