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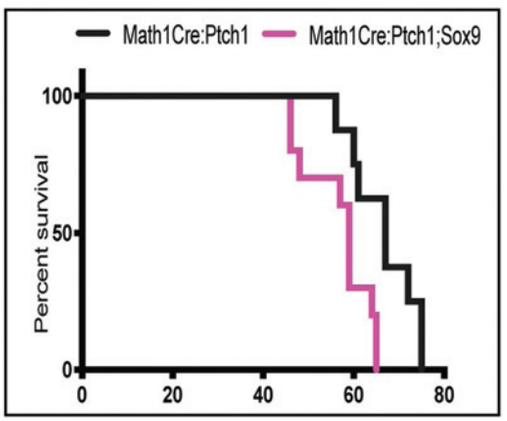
MOLECULAR CANCER RESEARCH

HIGHLIGHTS

Selected Articles from This Issue

SOX9 Is Not Required for Hedgehog Medulloblastoma Formation



Adolphe *et al.* | Page 1831

Medulloblastoma is a common and deadly pediatric malignancy whose lethality is compounded by a lack of targeted therapies, partially owing to the differential biologies of the four major molecular subtypes. The most prevalent subtype, Sonic Hedgehog medulloblastoma (SHH-MB), is driven by hyperactivation of the eponymous SHH pathway within MATH-1-expressing granule cell precursors in the developing brain. Therefore, efforts to develop molecular targeted therapies for SHH-MB have focused largely on downstream targets and effectors of the SHH pathway such as the proto-oncogene SOX9, which has been shown to be specifically overexpressed in SHH-MB but whose functional role in disease progression has yet to be defined. Here, Adolphe and colleagues demonstrate that loss of SOX9 does not significantly impact the course of SHH-MB disease development and progression, indicating a dispensable role for this proto-oncogene in SHH-MB despite its elevated expression in most cases. This finding may have significant implications for ongoing preclinical and translational work aimed at identifying suitable molecular drivers of SHH-MB for therapeutic development.

Lymphangioleiomyomatosis Features and Heterogeneity

Espín *et al.* | Page 1840

Lymphangioleiomyomatosis is a rare neoplastic disease of unknown origin that is nearly exclusive to women, with therapies targeting mTOR as the recognized standard of care. However, there is substantial variability in disease presentation, progression, and therapy response. Here, Espin, Baiges and colleagues perform multi-omics characterization of patient-derived lymphangioleiomyomatosis cells and tissues to identify the molecular features and potential causes of disease heterogeneity. The data suggest that differential expression of certain transcription factors—such as YB1, RUNX1, IRF1, estrogen receptor, and progesterone receptor—as well as certain immunity factors may account for some of these features. Based on the molecular features identified herein, the authors also nominate a breast mesenchymal cell line and certain pleural mesothelioma cell lines as potential surrogate models of lymphangioleiomyomatosis, expanding on the biological basis of the disease. Taken together, the data provide a high-value resource for further exploration of the molecular drivers of lymphangioleiomyomatosis progression.

IDH1 R132H/WT Mediates Gliomagenesis and Drug Resistance

Zhan *et al.* | Page 1878

Glioma patients are frequently treated with temozolomide, a DNA alkylating chemotherapeutic that is known to cross the blood-brain barrier. The isocitrate dehydrogenase (IDH) R132H mutation is a common molecular feature of gliomas and is generally associated with gliomagenesis, but also with a more robust response to temozolomide therapy. However, the molecular underpinnings of this observation are not defined. In this study, Zhan, Ma, and colleagues use a heterozygous knock-in approach to model the effects of IDH R132H/wild-type allele balance on glioma cell biology. They find that the heterozygous IDH genotype in tandem with glioma driver gene alterations in p53, RB, and ATRX predisposes glioma cells to pro-senescent features. This combination of molecular features was associated with increased DNA damage markers and potentiated the effects of temozolomide in this model. However, heterozygous IDH R132H mutation also predisposed astroglial cells toward a senescence-associated secretory phenotype, which is known to exert a pro-tumorigenic effect within a tumor-permissive microenvironment. These data offer a potential mechanistic explanation for how a single mutation within IDH may provide a pro-tumorigenic stimulus while also sensitizing glioma cells to alkylating chemotherapy with temozolomide.

NHEJ Inhibitor Screen Identifies Radio- and Chemosensitizers

Du *et al.* | Page 1889

Potentiating the effects of genotoxic interventions such as chemo- or radiotherapy requires the suppression of DNA damage response pathways, such as non-homologous end joining (NHEJ). Blocking NHEJ with chemical inhibitors is one strategy, but none have been clinically approved for this application. Building upon prior efforts to develop chemical screening strategies for NHEJ inhibitors, Du and colleagues report a miniaturized screening protocol that can be carried out in 96-well plates. By assessing an FDA-approved drug library in this format, the authors identify several potential candidates that function to inhibit NHEJ at concentrations below their cytotoxic dose. One of these drugs, ompalisib, was shown to suppress the phosphorylation of the DNA-dependent protein kinase catalytic subunit (DNA-PKcs) in response to chemo- or radiotherapy, a key step in the initiation of NHEJ to mediate their genotoxic effects. Overall, the authors advance a novel screening strategy to examine the effects of pharmacological interventions on DNA damage responses via NHEJ, and further nominate a candidate FDA-approved drug for development as a chemo- and radiosensitizer.

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