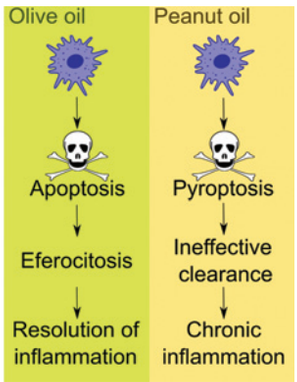
February 1, 2021 | Volume 19 | Number 2

MOLECULAR CANCER RESEARCH

HIGHLIGHTS

Selected Articles from This Issue

Oil Depletes Resident Peritoneal Macrophages



Alsina-Sanchis *et al.* | Page 288

Intraperitoneal (i.p.) injection of experimental therapeutics is a common technique when assessing their bioactivity and efficacy *in vivo*. Many drugs are lipophilic and therefore require lipid carriers, such as mineral or vegetable oil, for delivery. It is known that mineral oil has inflammatory properties, but the specific effects of other carriers are not well understood. In this study, Alsina-Sanchis and colleagues report detailed observations of the differential effects of peanut, corn, olive, and mineral oils on the inflammatory microenvironment of the injection site. While i.p. injection of all oils induced inflammation, there were substantial differences in severity and duration stemming largely from the oils' effects on macrophages. Whereas olive oil primarily induced apoptosis via caspase-3 activation and led to faster resolution of inflammation, peanut and corn oil were associated with caspase-1 activation, pyroptosis, and sustained inflammation. These findings have significant bearing on the reproducibility of data derived from i.p. injection models.

Transcriptome Profiles in Diffuse Intrinsic Pontine Glioma

Surowiec *et al.* | Page 223

Diffuse intrinsic pontine glioma (DIPG) is an intractable brain cancer that displays a high propensity toward developing therapeutic resistance. It is hypothesized that cancer stem cells (CSC) are a major contributor toward this phenotype in DIPG, and thus characterization of CSC populations and their targetable molecular pathways is urgently needed. In this study, Surowiec and colleagues identify one such marker and pathway via transcriptomic analysis: aldehyde dehydrogenase (ALDH)-positive DIPG cells were heterogeneously distributed in patient-derived cells and were shown to harbor CSC characteristics. Specifically, $ALDH^+$ cells displayed increased MYC and E2F expression, increased expression of DNA damage response regulators, and increased glycolytic metabolism. These features were targetable using inhibitors of the PI3K/mTOR pathway, thereby reducing stemness in the $ALDH^+$ subset as well as tumor growth *in vivo*. Taken together, the data highlight key features of CSCs in DIPG patients as well as a potential targeted approach to mitigate their tumorigenic effects.

DLBCL/HGBCL with Dual MYC/TP53 Alterations

Deng *et al.* | Page 249

Co-occurrence of *MYC* and *BCL2* rearrangements in diffuse large B-cell lymphoma (DLBCL), termed "double hit" or DLBCL-DH, comprise a distinct population of high-grade B-cell lymphoma with dismal prognosis. Mutations in p53 are also common in DLBCL, but it has not yet been determined if co-occurrence of p53 mutations with other common DLBCL genetic lesions results in distinct clinicopathological features or disease progression. In this study, Deng and colleagues find that co-occurrence of MYC rearrangement with p53 mutations is associated with distinct molecular and transcriptomic features from those observed in DLBCL, and this combined alteration is correlated with dismal outcomes, similar to those observed in DLBCL-DH. *In vitro* pharmacologic studies using novel inhibitors of MYC signaling, MDM2-p53, and/or BCL-2 were shown to exert synergistic effects in lymphoma cells bearing concurrent *MYC/BCL2* or MYC/p53 abnormalities. Interestingly, the BCL-2 inhibitor venetoclax also synergized with MYC inhibitors in these cells with p53 mutations, even when no *MYC/BCL2* alterations were present. In summary, the study supports the classification of MYC/p53 double-abnormal DLBCL as a distinct clinicopathologic entity of high-grade B-cell lymphomas.

PTK6 Oncogenic Activity Is SH2 Domain-Dependent

Dwyer *et al.* | Page 329

Protein tyrosine kinase 6 (PTK6) is frequently overexpressed across the various subtypes of breast cancer and is associated with poor outcomes. However, the specific signaling events through which PTK6 mediates its protumorigenic effects in triple-negative breast cancer (TNBC) are unknown. Here, Dwyer and colleagues demonstrate that, while PTK6 has little effect on primary breast tumor growth, it acts as an essential mediator of lung metastasis. Employing multiple models of PTK6 expression as well as kinase-dead mutations and deletion of protein-protein interaction domains, the authors show that PTK6 kinase activity is not required to drive TNBC cell migration. Instead, this effect is mediated by the PTK6 SH2 domain, which was shown to interact with RhoA and aryl hydrocarbon receptor (AhR). Disruption of this interaction via deletion of PTK6 SH2 domain or inhibition of RhoA/AhR signaling attenuated TNBC cell migration and primary breast tumor organoid branching and invasive morphology, including in therapy-resistant models of TNBC, thus nominating PTK6/RhoA/AhR as novel therapeutic targets in PTK6-positive breast cancer. This observation bears particular implications for TNBC, which lacks approved targeted therapies.