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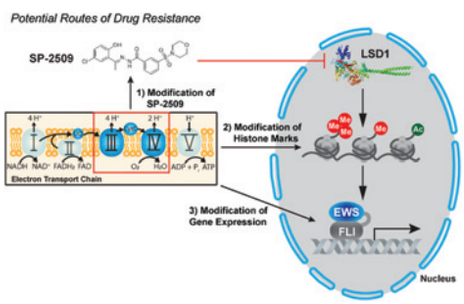
MOLECULAR CANCER RESEARCH
HIGHLIGHTS

Selected Articles from This Issue



Mitochondrial-Driven Drug Resistance in Ewing sarcoma

Tokarsky *et al.* | Page 1035

Ewing sarcoma is characterized by oncogenic gene fusions and elevated lysine-specific demethylase-1 (LSD1) expression. While Theisen and colleagues previously devised a small molecule LSD1 inhibitor that demonstrates therapeutic efficacy against Ewing sarcoma — SP-2509 — treatment with SP-2509 alone potentiates drug resistance. In this study, Tokarsky *et al.*, sought to elucidate molecular mechanisms underlying SP-2509 resistance by using a CRISPR–Cas9 loss-of-function screen in SP-2509–sensitive Ewing sarcoma cell lines. Results from the screen demonstrated that abrogating expression of mitochondrial ribosomal protein L45 (MRPL45) as well as members of electron transport chain complexes III (CIII) and IV (CIV) reduces SP-2509 responsiveness. Accordingly, CIII inhibitors and targeted removal of genes encoding CIII constituents ubiquinone-cytochrome c reductase, Rieske iron-sulfur polypeptide 1 (UQCRFS1) and cytochrome c1 (CYC1) using CRISPR–Cas9 induces SP-2509 resistance in Ewing sarcoma cell lines. Silencing UQCRFS1, CYC1, or MRPL45 expression diminishes transcriptional responses to SP-2509, indicating that mitochondrial function contributes to transcriptional programs underlying SP-2509 cytotoxicity. Overall, this study implicates mitochondrial dysfunction as a mechanism facilitating SP-2509 resistance, providing a target that may augment SP-2509 efficacy.

Templated Insertions as a HRD Genomic Signature

Moore *et al.* | Page 1061

Germline *BRCA1/2* mutations increase the risk of multiple cancers that exhibit homologous recombination deficiency (HRD). *BRCA1/2* mutations and subsequent HRD are associated with a number of genomic mutational signatures that have been previously described and seem to represent use of backup DNA repair pathways. These signatures, such as HRDetect and others, have been quantified and used to inform prognoses and therapeutic strategies. In this study, Moore and colleagues used current pre-clinical knowledge about polymerase theta-mediated end joining (TMEJ) and the genomic scars most typical of this backup repair pathway to determine if TMEJ signatures have prognostic value in advanced ovarian cancer. The authors found that both a TMEJ deletion signature with 4 or more base pair stretches of microhomology (TMEJ4) and TMEJ-associated templated insertions (TINS) are enriched in tumors with *BRCA1/2* mutations. The authors also discovered that patients displaying high HRDetect and TINS signatures survive significantly longer than patients displaying one or neither signature. Taken together, this study highlights the potential utility of TMEJ mutational signatures in advanced ovarian cancer prognosis.

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DNA-PK Inhibition and Radiation Induce Antitumoral Immunity

Wang *et al.* | Page 1137

Immune checkpoint inhibitors (ICI) are ineffective in pancreatic cancer, rendering combination treatments capable of augmenting ICI imperative. Radiation and inhibition of DNA damage response proteins, such as DNA-dependent protein kinase (DNA-PK), can activate antitumor immunity. However, whether and how DNA-PK inhibition mediates antitumor immunity in typically immunology "cold" cancers, including pancreatic cancer, is unknown. In their study, Wang and colleagues used radiation and DNA-PK inhibitor M3814 in mouse pancreatic cancer models to test whether the combination regimen can enhance antitumor immunity. The authors found that radiation-M3814 treatment induces type I interferon (T1IFN) signaling and slows tumor growth uniquely in mice with intact immune systems. The authors demonstrated that radiation and M3814-mediated T1IFN signaling is dependent on RNA polymerase III (POL III)-retinoic acid-inducible gene I (RIG-I)-mitochondrial anti-viral-signaling protein (MAVS) signaling, presumably through production and recognition of double-stranded RNA. Furthermore, T1IFN signaling induces tumor PD-L1 expression, and radiation-M3814 treatment augments anti-PD-L1 efficacy *in vivo*. In sum, this study elucidates a novel mechanism by which ICI efficacy may be enhanced in typically immunologically "cold" pancreatic cancers.

T-cell Dysfunction upon Expression of MYC Mutants

Daniel *et al.* | Page 1151

Increased MYC stabilization is a hallmark of T-cell acute lymphoblastic leukemia (T-ALL), but molecular mechanisms underlying MYC stabilization in T-ALL are incompletely understood. To study effects of two MYC mutations — T58A and S62A — on MYC stabilization and MYC-induced pathophysiology in T-ALL, Daniel and colleagues generated T-cell–specific Myc^{WT}, Myc^{T58A}, and Myc^{S62A} knock-in mouse models in which endogenous wild-type *Myc* can be maintained or eliminated. The authors observed that Myc^{T58A} induces heightened *ex vivo* T-cell proliferation and thymic mass relative to Myc^{S62A}, and that Myc^{T58A} causes T-cell lymphomagenesis more rapidly than does Myc^{S62A}. Nonetheless, Myc^{S62A} does induce clonal T-cell lymphomas that resemble T-ALL and, unlike Myc^{T58A}, causes non-transgene driven, incidental thymic B-cell lymphomas with splenomegaly. Differential phenotypes engendered by Myc^{T58A} and Myc^{S62A} are accompanied by disparate transcriptional programs. Myc^{T58A} is associated with altered expression of genes underlying angiogenesis and inflammation, and Myc^{S62A} displays changes in expression of genes involved in maintaining genomic stability. Altogether, this study demonstrates that Myc^{T58A} and Myc^{S62A} induce unique pathophysiology in T-cell lymphomas, which may inform future research and T-ALL disease management strategies.