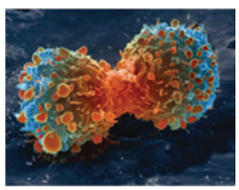
Cancer Research
Breaking Advances
Highlights from Recent Cancer Literature
AACR
American Association for Cancer Research

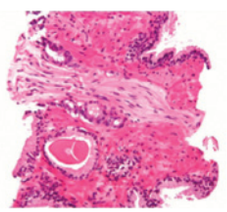
DDX3 Helicase and Lung Cancer



The ATP-dependent RNA helicase, DDX3 (DDX3X), regulates RNA metabolism and is overexpressed and mutated in cancer. Bol and colleagues confirmed high levels of DDX3 expression in lung cancer patients with aggressive disease. Using rational drug design, they generated RK-33, a small molecular inhibitor that blocked ATP binding. This novel tricyclic 5:7:5-fused diimidazodiazepine ring inhibited RNA duplex unwinding mediated by the yeast DDX3 homolog Ded1p. RK-33 blocked growth of lung cancer cell lines in a DDX3-specific manner, and in combination with radiotherapy. These results were confirmed *in vivo* in Ras^{G12D}/*Twist1*-driven and A549 orthotopic xenograft mouse models for lung cancer using RK-33 with fractionated radiotherapy. Finally, in lung cancer cell lines, RK-33 downregulated components of nonhomologous end joining DNA repair, suggesting a mechanism of radiosensitization. (*Image courtesy of Wikimedia Commons.*)

Bol GM, Vesuna F, Xie M, Zeng J, Aziz K, Gandhi N, et al. Targeting DDX3 with a small molecule inhibitor for lung cancer therapy. EMBO Mol Med 2015 Mar 27. [Epub ahead of print].

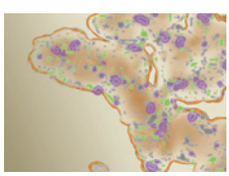
Metastasis Arising from Metastases Drives Lethality



Gundem and colleagues performed whole-genome sequencing of 51 metastases and primary tumors from 10 patients with lethal prostate cancer. While a mother clone contained the majority of the driver mutations, progression apparently involved dissemination of multiple clone variants, many of which arose after metastatic spread. Patterns of metastasis-to-metastasis seeding suggest that metastases may share more similarity to each other than to the primary tumor. Remarkably, polyclonal metastasis resulted from multiple subclones seeding the same site, with interclonal cooperation observed during metastasis. After therapy, several distinct and resistant subclones emerged and gave rise to heterogenic metastases harboring different oncogenic mutations that disrupted androgen receptor signaling. These multiple related tumors evaded therapy through divergent mechanisms and competed for dominance by seeding from one site to another in the patient, driving progression. (*Image by Nephron courtesy of Wikimedia Commons.*)

Gundem G, Van Loo P, Kremeyer B, Alexandrov LB, Tubio JM, Papaemmanuil E, et al. The evolutionary history of lethal metastatic prostate cancer. Nature 2015;520:353–7.

MAPK Pathway Inhibition Is Paramount to Targeting CRC

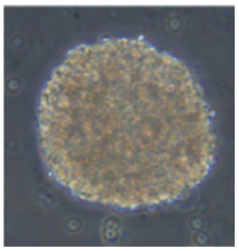


BRAF inhibitor monotherapy is ineffective in the 10% of colorectal cancers (CRC) with $BRAF^{V600E}$ mutations. Results from preclinical and early clinical studies suggest that cotargeting BRAF with MEK or EGFR can improve efficacy in the clinic. Ahronian and colleagues performed whole-exome sequencing on paired pretreatment/post-progression tumors from patients with *BRAF*-mutant colorectal cancer treated with RAF inhibitor combinations. They identified diverse molecular alterations restricted to the MAPK pathway, including *KRAS* mutation/amplification, *BRAF* amplification, and *MEK1* (*MAP2K1*) mutation. Interestingly, ERK inhibition *in vitro* could overcome each of these acquired resistance mechanisms. Reactivation of the MAPK pathway as the common thread highlights the critical dependence of *BRAF*-mutant colorectal cancer on sustained MAPK signaling and positions this pathway as a fundamental therapeutic target in this disease. (*Image from cited article courtesy of publisher.*)

Ahronian LG, Sennott EM, Van Allen EM, Wagle N, Kwak EL, Faris JE, et al. Clinical acquired resistance to RAF inhibitor combinations in BRAF-mutant colorectal cancer through MAPK pathway alterations. Cancer Discov 2015;5:358–67.

Breaking Advances

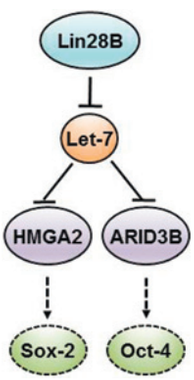
Metabolic Vulnerabilities in Glioma



Kim and colleagues identified glycine decarboxylase (GLDC) as being expressed highly in glioblastoma-derived neurosphere-forming cell lines. Knockdown of GLDC decreased viability and increased intracellular glycine levels. The toxicity was due to conversion of excess glycine by glycine C-acetyltransferase (GCAT) to aminoacetone and methylglyoxal. Knockdown of serine hydroxymethyltransferase (SHMT2), an enzyme upstream of GLDC that converts serine to glycine, reduced intracellular glycine levels and rescued glioma cells from GLDC knockdown. SHMT2 may act to decrease pyruvate kinase activity, decrease carbon flux into the TCA cycle, and limit oxygen consumption. Indeed, forced expression of pyruvate kinase isoform M2 (PKM2) increased oxygen consumption and decreased cell survival under hypoxic conditions similar to levels observed with SHMT2 knockdown. Thus, GLDC may represent a metabolic vulnerability in glioma cells adapted to survive under hypoxic conditions. (*Image from Public Library of Science courtesy of Wikimedia Commons.*)

Kim D, Fiske BP, Birsoy K, Freinkman E, Kami K, Possemato RL, et al. SHMT2 drives glioma cell survival in ischaemia but imposes a dependence on glycine clearance. Nature 2015;520:363–7.

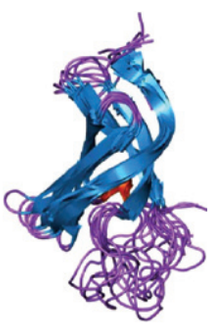
Role of LIN28B/*Let-7* in Oral Squamous Cancer Stem Cells



LIN28B, a miRNA-binding protein, suppresses *let-7* and induces tumorigenesis. Chien and colleagues observed a correlation between high levels of LIN28B, OCT4, and SOX2 and a high percentage of $CD44^{+}ALDH1^{+}$ cancer stem cells (CSC) in oral squamous carcinoma cells (OSCC). Overexpressing LIN28B in $CD44^{-}ALDH1^{-}$ OSCC cells enhanced OCT4/SOX2 expression and CSC properties, whereas coexpression of *let-7* reversed these. *let-7* targeted the 3'UTRs of ARID3B and HMGA2 and inhibited their expression. ARID3B and HMGA2 increased the transcription of OCT4 and SOX2. Furthermore, LIN28B/*let-7* signaling also helped predict the efficiency of normal oral keratinocytes being reprogrammed to induced pluripotent stem cells. In patient samples, $LIN28B^{high}$-$let\text{-}7^{low}$ expression correlated with expression of ARID3B, HMGA2, OCT4, and SOX2. Thus, LIN28B/*let-7* regulates stemness by modulating OCT4/SOX2 expression cancer stem-like properties in OSCC. (*Image from cited article courtesy of publisher.)*

Chien CS, Wang ML, Chu PY, Chang YL, Liu WH, Yu CC, et al. Lin28B/Let-7 regulates expression of Oct4 and Sox2 reprograms oral squamous cell carcinoma cells to a stem-like state. Cancer Res; canres.2215.2014; Published OnlineFirst April 9, 2015; doi:10.1158/0008-5472.CAN-14-2215.

Stressed-out Sarcomas



Stress granules are cytoplasmic ribonucleoprotein complexes that emerge in response to exogenous or endogenous stress and sequester mRNA. They are characterized by stalled translation initiation complexes and represent a mechanism by which cells under stress triage coding RNAs until their fates are determined. Somasekharan and colleagues show that the RNA binding protein YB-1 (YBX1) accumulates in, and is required for the formation of, stress granules in sarcomas cells. G3BP1, of known importance in stress granule assembly, was identified as a key mRNA bound by YB-1. Furthermore, targeting of YB-1 and G3BP1 decreased the number of stress granules *in vivo*, with metastases observed only in tumors that maintained G3BP1, and increased stress granule formation, collectively suggesting a role for stress granules in sarcoma. (*Image courtesy of Wikimedia Commons.*)

Somasekharan SP, El-Naggar A, Leprivier G, Cheng H, Hajee S, Grunewald TG, et al. YB-1 regulates stress granule formation and tumor progression by translationally activating G3BP1. J Cell Biol 2015;208:913–29.

Note: Breaking Advances are written by *Cancer Research* editors. Readers are encouraged to consult the articles referred to in each item for full details on the findings described.

Highlights from Recent Cancer Literature

Cancer Res 2015;75:1923-1924.