May 15, 2020 | Volume 80 | Number 10

CANCER RESEARCH

BREAKING INSIGHTS

Highlights from Recent Cancer Literature

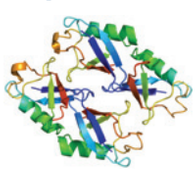
Mechanism of Tumor Formation in ACVR1 Mutant DIPG

Twenty percent of diffuse intrinsic pontine glioma (DIPG) harbor *ACVR1* mutations. Fortin and colleagues expressed Acvr1^{G328V} in the ventral pons through an Olig2-Cre mouse. The resulting *Acvr1*$^{floxG328V/+}$; *Olig2*$^{Cre/+}$ mice died early with neurological signs, hyperactive BMP signaling, proliferation of oligodendrocyte precursor cells (OPC), inhibition of oligodendrocyte differentiation, and upregulation of the OPC marker PDGFRA. Knock-in of an endogenous *Hist1h3b*^{K27M} allele induced BMP target genes through K27me3 hypomethylation but was insufficient to drive tumor formation. Introduction of a *PIK3CA* mutation, observed commonly in DIPG in combination with *ACVR1*^{G328V} and *Hist1h3b*^{K27M}, resulted in high-grade diffuse glioma, with elevated expression of genes seen with Acvr1$^{floxG328V/+}$ alone, specifically ASCL1, SOX11, and ID1/2/3. Treatment with E6201, a dual inhibitor of ACVR1 and MEK1, prolonged survival.

Expert Commentary: The authors show that *ACVR1* mutations inhibit differentiation of OPCs, adding to evidence that OPCs represent cells of origin for DIPG. Characterization of the timing and origin of DIPG suggests driving OPC differentiation as a promising treatment strategy.

Fortin J, Tian R, Zarrabi I, Hill G, Williams E, Sanchez-Duffhues G, et al. Mutant *ACVR1* arrests glial cell differentiation to drive tumorigenesis in pediatric gliomas. Cancer Cell 2020;37:308–23e12.

Neoantigen Processing and Proteasome Dependence



Cancers that exhibit a high mutation burden, such as those characterized by microsatellite instability (MSI), produce numerous neoantigens. Immunotherapy has therefore been successfully utilized for patients having such cancers, with a 40% response rate. To improve this rate of response McGrail and colleagues identified an MSI gene expression signature using cell lines defective for mismatch repair and validated on a panel of cancer cell lines and patient-derived samples. They used this signature to identify small-molecule inhibitors capable of specifically targeting MSI cancers, identifying the Nedd8-activating enzyme E1 inhibitor MLN4924. They went on to show that MSI cancers relied on neddylation to degrade misfolded proteins that resulted from MSI-mutated genes. Inhibiting this process with MLN4924 attenuated cancer growth *in vitro* and *in vivo*. Most importantly, MLN4924 synergized with PD1-based immunotherapy to attenuate the growth of MSI tumors in syngeneic mice.

Expert Commentary: Combining immunotherapy with the neddylation inhibitor MLN4924 could increase its efficacy when treating patients harboring MSI cancers. *(Image courtesy of Wikimedia Commons.)*

McGrail DJ, Garnett J, Yin J, Dai H, Shih DJH, Lam TAN, et al. Proteome instability is a therapeutic vulnerability in mismatch repair-deficient cancer. Cancer Cell 2020;37:371–86.e12.

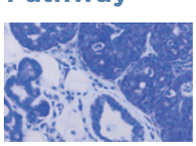
DNA-Dependent Protein Kinase Regulates Translation

The DNA-dependent protein kinase (DNA-PK) complex binds to both DNA and RNA. Shao and colleagues uncovered an RNA-dependent function of DNA-PK in regulating translation. Kinase-dead DNA-PK elicited severe hematopoietic defects independent of defective DNA repair, but instead resulted from compromised global protein translation. DNA-PK resides in the nucleolus bound to the small subunit processome ribonucleoprotein complex, responsible for 18S rRNA processing. Interestingly, the U3 small nucleolar RNA was found to interact with DNA-PK, leading to autophosphorylation and activation of its catalytic subunit (DNA-PKcs). This RNA-dependent autophosphorylation occurred in a region of DNA-PKcs that was dispensable for DNA repair but critical for proper rRNA processing.

Expert Commentary: This report describes a novel, RNA-dependent function of a well-established DNA-binding protein complex and suggest that the binding substrates of a protein complex, whether DNA or RNA, can determine its post-translational status and ultimately, its function. These data demonstrate additional levels of regulation in ribosome biogenesis and may provide novel therapeutic targets for patients with ribosomopathies. *(Image courtesy of Wikimedia Commons.)*

Shao Z, Flynn RA, Crowe JL, Zhu Y, Liang J, Jiang W, et al. DNA-PKcs has KU-dependent function in rRNA processing and haematopoiesis. Nature 2020;579:291–6.

Mast Cells Stimulate the Estrogen Receptor Pathway



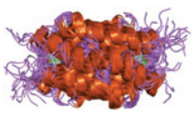
There is growing interest in the interaction between cancer and immune cells, because tumors develop a multitude of mechanisms to escape immune system surveillance, even hijacking the immune system, to grow and disseminate. Mast cells are bone marrow-derived c-Kit-expressing immune cells with established roles in allergy. Mast cells affect cancer cells by direct interaction or through modulating extracellular matrix and immune infiltrates. Majorini and colleagues showed that mast

cells activate the estrogen receptor to promote breast cancer growth, preventing development of basal CK5-positive areas in favor of a luminal gene program. In mice engrafted with HER2-positive breast cancers, coinjection of mast cells increased engraftment and outgrowth, supporting the link between mast cells and relapse in patients.

Expert Commentary: This study demonstrates that mast cells impact tumor aggressiveness by modulating cancer cell phenotype. Mast cells influence breast cancer outcome by directly stimulating the estrogen receptor pathway. *(Image from cited article courtesy of the publisher.)*

Majorini MT, Cancila V, Rigoni A, Botti L, Dugo M, Triulzi T, et al. Infiltrating mast cell-mediated stimulation of estrogen receptor activity in breast cancer cells promotes the luminal phenotype. Cancer Research; Published OnlineFirst March 16, 2020; DOI: 10.1158/0008-5472.CAN-19-3596.

Improving the Specificity of BET Inhibitors

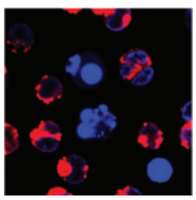


BET inhibitors (BETi) have clinical activity in malignancy and inflammatory conditions. BETis bind to bromodomains BD1 and BD2 in BET proteins, however, whether inhibition of both domains is necessary is not well understood. Gilan and colleagues synthesized highly selective BD1 and BD2 BETis and characterized them *in vitro* and *in vivo*. The BD1 domain was required for steady-state gene expression and tumorigenesis, while both domains were required for cytokine-induced transcription. BD2-specific inhibitors were effective against multiple models of autoimmune and inflammatory disorders.

Expert Commentary: This study suggests that BD1- and BD2-specific BETis may be better tolerated and efficacious than pan-BET inhibitors. *(Image courtesy of Wikimedia Commons.)*

Gilan O, Rioja I, Knezevic K, Bell MJ, Yeung MM, Harker NR, et al. Selective targeting of BD1 and BD2 of the BET proteins in cancer and immuno-inflammation. Science. 2020: eaaz8455. DOI: 10.1126/science.aaz8455.

Fish Oil Uncouples Obesity and Mammary Tumor Growth



Obesity is associated with increased cancer risk and mortality. It remains unknown whether fatty acid composition in different high-fat diets influences obesity-associated tumor development. Liu and colleagues established obese mouse models with different high-fat diets rich in either saturated fatty acids (cocoa butter) or n-3 fatty acids (fish oil: omega-3, docosapentaenoic acid, eicosapentaenoic acid, EPA). Both high-fat diets induced murine obesity. However, obesity-associated mammary tumor growth in these high-fat diet-induced obese mice was dramatically different. While the cocoa butter high-fat diet-induced obesity promoted mammary tumor growth, the fish oil high-fat diet uncoupled obesity from accelerated tumor growth. Mechanistically, they found that n-3 fatty acid treatment enhanced protumor macrophage cell death through an adipose/macrophage fatty acid-binding protein ROS-dependent axis.

Expert Commentary: This study provides mechanistic insight into dietary supplementation with fish oil for breast cancer prevention and advances a new concept that not all high-fat diets leading to obesity are tumorigenic. *(Image from cited article courtesy of the publisher.)*

Liu L, Jin R, Hao J, Zeng J, Yin D, Yi Y, et al. Consumption of the fish oil high-fat diet uncoupled obesity and mammary tumor growth through induction of reactive oxygen species in pro-tumor macrophages. Cancer Research; Published OnlineFirst March 25, 2020; DOI: 10.1158/0008-5472.CAN-19-3184.

Note: Breaking Insights 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.

Cancer Research
The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

AACR American Association for Cancer Research

Highlights from Recent Cancer Literature

Cancer Res 2020;80:1903-1904.