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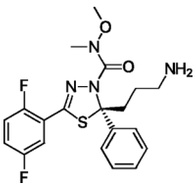
CANCER RESEARCH

BREAKING INSIGHTS

Highlights from Recent Cancer Literature

Targeting KSP in Preclinical Models of High-Risk Neuroblastoma

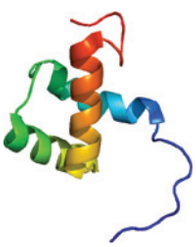


Neuroblastoma is a heterogenous and frequently lethal childhood cancer. Using tumor organoids from *MYCN*-amplified high-risk neuroblastomas, Hansson and colleagues performed a high-throughput screen using approved or emerging cancer drugs. The authors identified several novel compounds specifically affecting neuroblastoma organoids. One of these was ARRY-520, an inhibitor of kinesin spindle protein (KSP). Importantly, Hansson and colleagues found that high expression of *KIF11*, the gene encoding KSP, was correlated with poor outcome in neuroblastoma patients but not in 21 other human cancers. Inhibition of KSP in patient-derived xenografts (PDX) from neuroblastoma caused numerous abnormalities during cell division, leading to tumor cell apoptosis. The authors further showed that inhibition of KSP resulted in decreased tumor burden and enhanced survival mice with *MYCN*-amplified neuroblastoma PDX tumors *in vivo*.

Expert Commentary: These data suggest that inhibition of KSP could be an attractive strategy for treating patients with high-risk neuroblastoma. *(Image courtesy of Wikimedia Commons.)*

Hansson K, Radke K, Aaltonen K, Saarela J, Mañas A, Sjölund J, et al. Therapeutic targeting of KSP in preclinical models of high-risk neuroblastoma. Sci Transl Med 2020;12: eaba4434. DOI: 10.1126/scitranslmed.aba4434.

A Tumor Suppressor Role for the EMT Transcription Factor ZEB1

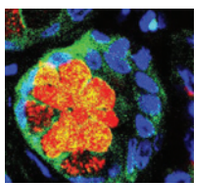


Epithelial-mesenchymal transition transcription factors (EMT-TF) have been implicated in tumorigenesis for multiple solid tumor types. Induction of a cancer stem cell-like phenotype and metastases are two important EMT-TF functions. Almotiri and colleagues examined the role of the EMT-TF ZEB1 in adult hemopoietic stem cells (HSC) and acute myeloid leukemia (AML). Genetic deletion of ZEB1 in HSC resulted in decreased memory T cells secondary to apoptosis, defective cell-autonomous self-renewal, and multilineage hematopoietic differentiation defects. ZEB1 levels were reduced in AML patients and loss of ZEB1 accelerated AML tumorigenesis.

Expert Commentary: This study uncovers an unexpected role for ZEB1 in multilineage hematopoietic differentiation and suppression of AML progression through transcriptional repression. *(Image courtesy of Wikimedia Commons.)*

Almotiri A, Alzahrani HAA, Menendez-Gonzalez JB, Abdelfattah A, Alotaibi B, Saleh L, et al. Zeb1 modulates hematopoietic stem cell fates required for suppressing acute myeloid leukemia. Clinical Investigation; Published October 27, 2020; DOI: 10.1172/JCI129115.

MUC5AC Promotes Pancreatic Cancer Onset and Progression



Secreted mucin 5AC (MUC5AC) is the most abundantly overexpressed member of the mucin family within the early pancreatic intraepithelial neoplasia stage I (PanIN-I) of pancreatic cancer. To evaluate its contributions to initiation and progression of pancreatic cancer, Ganguly and colleagues genetically ablated *Muc5ac* in an autochthonous murine model ($Kras^{G12D}$; Pdx-1cre, KC), which mirrors early stages of disease development. Knockout of *Muc5ac* significantly delayed neoplastic onset and progression of pancreatic cancer precursor lesions, with a reduction in cancer cell stemness. The authors further showed that MUC5AC interacts with integrin β5 in the presence of extracellular matrix proteins, resulting in pSTAT3-mediated upregulation of Klf4, a transcription factor involved in maintaining cancer stem cells.

Expert Commentary: This study documents that *de novo* expression of MUC5AC promotes cancer cell stemness during *Kras*-driven pancreatic tumorigenesis and suggests that drugs targeting MUC5AC could be developed as a novel therapeutic regimen. *(Image from cited article courtesy of publisher.)*

Ganguly K, Kishn SR, Rachagani S, Jahan R, Shah A, Nallasamy P, et al. Secretory mucin 5AC promotes neoplastic progression by augmenting KLF4-mediated pancreatic cancer cell stemness. Cancer Res 2021;81:91–102.

Exercise, Cytotoxic T Cells, and Tumor Suppression

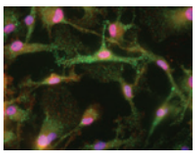
Several studies have revealed the benefits of exercise for cancer patients, although the mechanisms involved are not fully understood. Rundqvist and colleagues showed that exercise-induced reductions in tumor growth in mouse models are dependent on cytotoxic $CD8^+$ T cells. Exercise-induced changes in systemic production of lactate and TCA metabolites were able to alter the activation of $CD8^+$ T cells. Furthermore, exercise also altered the metabolism of T cells, such that adoptive transfer of $CD8^+$ T cells from exercising animals showed enhanced antitumor activity.

Expert Commentary: This study provides important evidence in support of a role for the adaptive immune system in exercise-induced antitumor activity. Further understanding of how these metabolic changes alter the

activity of the immune system in humans is now required. *(Image by Oketch Michael Eriya courtesy of Wikimedia Commons.)*

Rundqvist H, Veliça P, Barbieri L, Gameiro PA, Bargiela D, Gojkovic M, et al. Cytotoxic T-cells mediate exercise-induced reductions in tumor growth. eLife 2020;9:e59996. DOI: 10.7554/eLife.59996.

EGFR, Dickkopf, and Hepatocellular Carcinoma



The secreted glycoprotein Dickkopf-1 (DKK1) is overexpressed in hepatocellular carcinomas (HCC), serving as a negative prognostic indicator. Niu and colleagues showed that xenografts of *DKK1*-expressing HCC cells promoted tumor growth and widespread metastases. Using HCC cell lines, they further showed that EGFR signaling was a pivotal, HCC-relevant activator of *DKK1* expression. Dissecting pathways downstream of EGFR, they identified both the MEK/ERK and PI3K/AKT signaling pathways as drivers of *DKK1* expression. ERK activity resulted in phosphorylation and activation of pyruvate kinase M2 (PKM2), while parallel activation of AKT led to phosphorylation and activation of the acetyl transferase p300. Together, PKM2 and p300 acted synergistically via phosphorylation and acetylation, respectively, on histone H3 at the DKK1 promoter to activate *DKK1*. These findings were validated in a rat HCC model and across a panel of patient-derived HCC samples.

Expert Commentary: Dual inhibition of MEK/ERK and PIK3/AKT signaling could be tested for its effects on HCC metastasis. *(Image courtesy of Wikimedia Commons.)*

Niu J, Li W, Liang C, Wang X, Yao X, Yang RH, et al. EGF promotes DKK1 transcription in hepatocellular carcinoma by enhancing the phosphorylation and acetylation of histone H3. Sci Signal 2020;13:eabb5727. DOI: 10.1126/scisignal.abb5727.

Epigenetic Drugs Awaken Natural Cancer Immunity

Activating expression of endogenous retroelements is a promising strategy to boost immune responses to cancer, but critical elements and mechanisms of action are not clear. Mehdipour and colleagues showed that reversing DNA methylation with the FDA-approved DNA methyltransferase inhibitor 5-aza-2′-deoxycytidine (5-Aza) activated expression of inverted Alu elements (IR-Alus), a type of short-interspersed nuclear element (SINE), to enhance cancer immunity. Cells mount responses to cytosolic dsRNA via recognition by the MDA5 sensor. Using an MDA5-protection assay, the authors detected cellular RNA that bound MDA5, dubbed immunogenic dsRNA. They found that Alu elements, as opposed to other retroelements, interacted predominantly with MDA5. CpG islands upstream of IR-Alus that form RNA stem-loops were also enriched with 5-Aza treatment. Finally, they showed in human colon cancer cells that knockdown of ADAR1 (adenosine deaminase acting on RNA), which can destabilize duplexed RNA, increased Alu association with MDA5, blocking tumor progression in mouse models.

Expert Commentary: Combining DNA methyltransferase inhibitors (DNMTi) with ADAR1 blockade increases Alu element-triggered MDA5 activation and enhances the activity of DNMTi. *(Image courtesy of Wikimedia Commons.)*

Mehdipour P, Marhon SA, Ettayebi I, Chakravarthy A, Hosseini A, Wang Y, et al. Epigenetic therapy induces transcription of inverted SINEs and ADAR1 dependency. Nature 2020;588:169–73.

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.