Cancer Research
Breaking Insights
Highlights from Recent Cancer Literature
AACR
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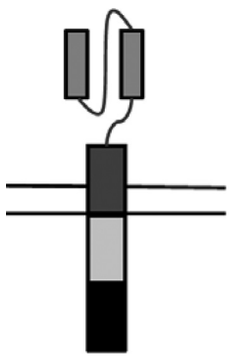
Developing a Universal CAR T-cell Strategy

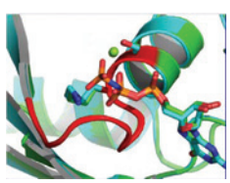


Most solid tumors are comprised of multiple clones that express orthogonal antigens. Lee and colleagues therefore tested the ability of a single antifluorescein CAR T-cell preparation to recognize and destroy multiple antigenically unique human cancer cells upon addition of the appropriate fluorescein-linked tumor-specific ligand. The authors found that both MDA-MB-231 and HEK293 cells transfected with a variety of tumor antigens could be rapidly killed both *in vitro* and *in vivo* upon addition of the correct antigen-matched CAR T-cell adapter molecule.

Expert Commentary: This study demonstrates that a carefully designed cocktail of tumor-targeted bispecific adapters greatly augments CAR T-cell therapies against heterogeneous tumors, highlighting its potential for broader applicability against cancers where standard CAR T-cell therapy. *(Image from cited article courtesy of the publisher.)*

Lee YG, Marks I, Srinivasarao M, Kanduluru AK, Mahalingam SM, Liu X, et al. Use of a single CAR T cell and several bispecific adapters facilitates eradication of multiple antigenically different solid tumors. Cancer Res 2019;79:387–96.

LZTR1 Is Critical for RAS Ubiquitination



LZTR1 mutations have been observed in Noonan Syndrome and multiple tumor types. Two reports demonstrate that LZRT1 is critical for RAS ubiquitination, decreasing its plasma membrane localization and ability to activate the MAPK pathway. Bigenzhan and colleagues initially identified LZTR1 inactivation in a genetic screen as a mediator of BCR-ABL TKI resistance (1). Steklov and colleagues demonstrated that *Lztr1* haploinsufficiency recapitulated the Noonan Syndrome phenotype (2). Both groups found that LZTR1 directly bound to RAS proteins and promoted ubiquitination in a CUL3-dependent manner.

Expert Commentary: These studies demonstrate a novel mechanism regulating RAS localization and activity through ubiquitination. Future studies exploiting this pathway may lead to therapies for RAS-driven cancers. *(Image courtesy of Wikimedia Commons.)*

1. Bigenzahn JW, Collu GM, Kartnig F, Pieraks M, Vladimer GI, Heinz LX, et al. LZTR1 is a regulator of RAS ubiquitination and signaling. Science 2018;362:1171–7.

2. Steklov M, Pandolfi S, Baietti MF, Batiuk A, Carai P, Najm P, et al. Mutations in LZTR1 drive human disease by dysregulating RAS ubiquitination. Science 2018;362:1177–82.

Circulating Glioma Cells Exhibit Stem Cell-like Properties

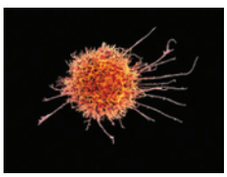
Circulating tumor cells (CTC) are implicated in treatment resistance, tumor recurrence, and ultimately the poor prognosis of patients with cancer via mechanisms that are largely unknown. Using a mouse glioblastoma (GBM) model, Liu and colleagues show that differentially labeled, intravascular-injected CTCs home to and engraft at sites adjacent to the primary GBM. These CTCs express a number of stem cell transcription factors and are resistant to chemotherapy and radiotherapy, consistent with being derived from GBM cancer stem cells. Transcriptome analysis of GBM CTCs implicated Wnt signaling as the pivotal driver of CTC stemness. Consistent with this observation, treatment of CTC-derived sphere cultures with a Wnt inhibitor reduced their growth and sensitized them to chemotherapy. Importantly, a similar high-level expression of Wnt target genes was observed in CTCs derived from patients with GBM.

Expert Commentary: This work suggests that Wnt inhibitors could be used to target the treatment resistance CTCs that drive GBM recurrence. *(Image from cited article courtesy of the publisher.)*

Liu T, Xu H, Huang M, Ma W, Saxena D, Lustig RA, et al. Circulating glioma cells exhibit stem cell-like properties. Cancer Res 2018;78:6632–42.

Breaking Insights

Obesity Promotes Cancer by Disarming NK Cells

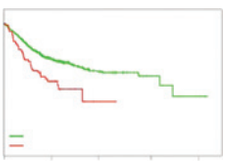


Obesity is associated with an increased risk for many cancers. Michelet and colleagues reveal a direct link between obesity and suppression of antitumor natural killer (NK) cell responses. Using samples from human patients, mice were fed high fat diets and NK cells were treated *in vitro*. They show that circulating free fatty acids (FFA), known to be increased in obese individuals, directly impaired the tumor cell-killing capacity of NK cells. Mechanistically, increased lipid accumulation in NK cells increased the activity of peroxisome proliferator-activated receptors (PPARα and PPARδ) transcription factors, leading to decreased activation of the mTOR pathway and glycolysis. This ultimately decreased expression of genes required for cellular cytotoxicity (perforin and granzymes) and disrupted polarized degranulation of lytic particles required for cell killing. Blocking fatty acid translocation into the mitochondria reversed these effects, restoring NK cell activity in the presence of FFAs.

Expert Commentary: Obesity enforces a metabolic switch toward lipid metabolism in NK cells that directly disables cytolytic activity, relieving tumors from NK cell-mediated control. *(Image courtesy of NIAID.)*

Michelet X, Dyck L, Hogan A, Loftus RM, Duquette D, Wei K, et al. Metabolic reprogramming of natural killer cells in obesity limits antitumor responses. Nat Immunol 2018;19:1330–40.

Targeting CDK8 Suppresses Colon Cancer Hepatic Metastases



In colon cancer, unresectable hepatic metastases are the leading cause of death, as these are resistant to currently available treatments. Cyclin-dependent kinase 8 (CDK8) forms part of the mediator complex that regulates transcription. *CDK8* is frequently amplified in colon cancers. Liang and colleagues show that pharmacological inhibition or knockdown of CDK8 inhibited metastatic growth of colon cancer cells in the liver, without affecting growth of the primary tumor growth. Effects in the liver were mediated through upregulation of the metalloproteinase (MMP) inhibitor TIMP3 via TGFβ/SMAD-mediated expression of miR-181b and downregulation of associated MMPs, dependent on Wnt/β-catenin driven transcription.

Expert Commentary: The site-specific effect of CDK8 inhibition on suppression of established colon cancer hepatic metastases presents an opportunity to treat patients with advanced metastatic colon cancer. These results highlight the importance of understanding context-specific effects of targeting ubiquitous cell signaling pathways. *(Image from cited article courtesy of the publisher.)*

Liang J, Chen M, Hughes D, Chumanevich AA, Altilia S, Kaza V, et al. CDK8 selectively promotes the growth of colon cancer metastases in the liver by regulating gene expression of TIMP3 and matrix metalloproteinases. Cancer Res 2018;78:6594–606.

Overcoming Resistance to ERK Inhibitors in KRAS-Mutant PDAC

Continued MYC expression is required for KRAS tumorigenesis and KRAS has previously been shown to stabilize MYC in part through the MEK/ERK1/2 pathway. A recent study demonstrated that resistance to ERK inhibitors in pancreatic ductal carcinoma (PDAC) correlated with sustained stability of MYC after treatment. In the current study, Vaseva and colleagues utilized three high-throughput screening strategies to identify KRAS-dependent, ERK1/2/FBW7-independent mediators of MYC stability. They identified EGFR-MEK5-ERK5 as a novel compensatory pathway activated in the presence of ERK1/2 inhibition to maintain MYC expression. Combined inhibition of ERK1/2 and ERK5 destabilized MYC protein and was efficacious *in vitro* and *in vivo* against KRAS-mutant PDAC.

Expert Commentary: This study suggests that targeting MYC for degradation through dual inhibition of ERK1/2 and ERK5 may be effective in KRAS-mutant PDAC. *(Image courtesy of Wikimedia Commons.)*

Vaseva AV, Blake DR, Gilbert TSK, Ng S, Hostetter G, Azam SH, et al. KRAS suppression-induced degradation of MYC is antagonized by a MEK5-ERK5 compensatory mechanism. Cancer Cell 2018;34:807–22.e7.

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.