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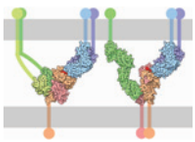
CANCER RESEARCH

BREAKING INSIGHTS

Highlights from Recent Cancer Literature

Universal Anticancer T cells

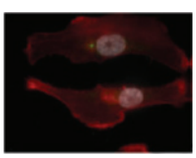


The discovery of a universal receptor that could be engineered into any patient's T cells to make them recognize and kill cancer cells, regardless of the type of malignancy, would revolutionize cancer immunotherapy. Crowther and colleagues discovered MC.7.G5, a T-cell receptor (TCR) that responds to the invariant major histocompatibility (MHC) protein MR-1. Unlike most TCRs that respond to a specific MHC that is highly variable, this MR-1-reactive TCR can respond across individuals. Although MR-1–reactive T cells were thought to be specific to bacterial metabolites, the MC.7.G5 TCR responded to an uncharacterized antigen in complex with MR-1 that appeared to be uniquely present in cancer cells. Importantly, MC.7.G5 T cells never killed normal/healthy cells but killed all cancer lines, and fresh cancer cells were tested. The therapeutic utility of this newly discovered TCR is clear, as transduction of patient-derived T cells imparted the ability to kill cancer cells.

Expert Commentary: A T-cell receptor has been identified that can distinguish cancer cells from healthy cells across multiple cancer types and will likely be effective across all patients. *(Image courtesy of Wikimedia Commons.)*

Crowther MD, Dolton G, Legut M, Caillaud ME, Lloyd A., Attaf M, et al. Genome-wide CRISPR-Cas9 screening reveals ubiquitous T cell cancer targeting via the monomorphic MHC class I-related protein MR1. Nature Immunology 2020;21:178–85.

LIN9/NEK2 Potentiates Taxane Response

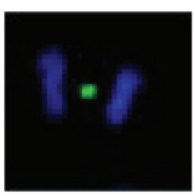


Taxanes such as paclitaxel are a standard-of-care therapy for many malignancies, however, resistance represents a significant therapeutic challenge. Taxanes remain one of the most commonly used cytotoxic therapies for breast cancer. In this study, Roberts and colleagues report a novel, druggable mechanism underlying taxane-resistance in triple-negative breast cancer (TNBC) that involves upregulation of LIN9 and its downstream transcriptional target, NEK2, a centrosomal kinase. Genetically suppressing LIN9 or NEK2 caused profound mitotic defects that synergized with taxanes to induce cell death. Most importantly, therapeutically targeting the LIN9/NEK2 pathway restored taxane-sensitivity in resistant cells and xenografted tumors.

Expert Commentary: Resistance to chemotherapy is a major impediment to cancer therapy. These studies provide a rational therapeutic approach for combating and overcoming the major therapeutic challenge of taxane-resistance in patients with TNBC through the utilization of NEK2 inhibitors. *(Image from cited article courtesy of the publisher.)*

Roberts MS, Sahni JM, Schrock MS, Piemonte KM, Weber-Bonk KL, Seachrist DD, et al. LIN9 and NEK2 are core regulators of mitotic fidelity that can be therapeutically targeted to overcome taxane resistance. Cancer Res 2020;80:1693–707.

Aurora Kinase B Stabilizes MYC

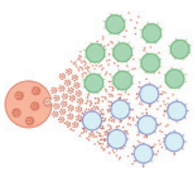


MYC is the most frequently activated oncogene in human cancer and has important functions in T-cell acute lymphoblastic leukemia (T-ALL). Jiang and colleagues identified reciprocal activation of MYC and Aurora kinase B (AURKB). They showed that AURKB directly phosphorylated MYC at serine 67, which in turn prevented phosphorylation of threonine 58 by GSK3β and thus the following FBXW7-mediated proteasomal degradation, promoting MYC stability. Importantly, the stabilized MYC protein together with the T-cell acute lymphoblastic leukemia 1 (TAL1) protein directly activated transcription of *AURKB*. AURKB and MYC then formed a feedforward circuit, promoting T-cell leukemogenesis. The authors further demonstrated that AURKB inhibitors promoted degradation of MYC protein degradation, driving tumor cell death in FBXW7-active T-ALL cells.

Expert Commentary: This study uncovered an AURKB-MYC regulatory circuit that contributes to T-cell leukemia and presents a novel therapeutic approach for targeting MYC via AURKB inhibition. *(Image courtesy of Wikimedia Commons.)*

Jiang J, Wang J, Yue M, Cai X, Wang T, Wu C, et al. Direct phosphorylation and stabilization of MYC by Aurora B kinase promote T-cell leukemogenesis. Cancer Cell 2020;37:200-215.e5.

Mutant KRAS Drives an Immune Paracrine Axis in Pancreatic Cancer



Although the cell intrinsic protumorigenic effects of mutant *KRAS* are well described, the role of KRAS in mediating a protumorigenic immune cell paracrine axis has not been previously defined. Dey and colleagues found that mutant *KRAS* drives type 1 cytokine receptor expression on tumor cells *in vivo* and IL4rα was required for progression. Paracrine IL4 or IL13 increased proliferation through Jak1/Stat6/Myc pathway activation and increased glycolysis. Remarkably, IL4 and IL3 were supplied from T_H2 $CD4^+$ T cells in the tumor microenvironment and were necessary for proliferation of both pancreatic preneoplasias and carcinomas.

Expert Commentary: This study suggests that targeting this paracrine pathway may be an effective therapeutic strategy in pancreatic cancer. *(Image by David Nascari and Alan Syed courtesy of Wikimedia Commons.)*

Dey P, Li J, Zhang J, Chaurasiya S, Strom A, Wang H, et al. Oncogenic Kras-driven metabolic reprogramming in pancreas cancer cells utilizes cytokines from the tumor microenvironment. Cancer Discovery; Published OnlineFirst February 11, 2020; DOI: 10.1158/2159-8290.CD-19-0297.

New Regulators of Osteosarcoma Metastasis

Osteosarcoma is a highly aggressive cancer with few treatment options available for patients with metastatic disease. Wang and colleagues identified a role for chromobox homolog 4 (CBX4) in the metastatic spread of osteosarcoma in a mechanism that involved CBX4-driven transcription of *Runx2*. They also showed that casein kinase 1α (CK1α) regulated expression of CBX4 by phosphorylation. Phosphorylated CBX4 was subsequently degraded by the ubiquitin pathway. Furthermore, an inverse relationship was shown between CBX4 and CK1α expression in human osteosarcoma tumors and was associated with poor survival.

Expert Commentary: This study provides important insight into the regulation of osteosarcoma progression. Further studies will reveal whether this presents a potentially targetable pathway that could be exploited.

Wang X, Qin G, Liang X, Wang W, Wang Z, Liao D, et al. Targeting the CK1α/CBX4 axis for metastasis in osteosarcoma. Nature Commun 2020;11:1141. DOI: 10.1038/s41467-020-14870-4.

E. coli and Colorectal Cancer

Although the link between the gut microbiome and colorectal cancer has been known for years, the exact mechanisms by which gut bacteria contribute to colorectal cancer progression have remained unknown. Various genotoxic *E. coli* strains are enriched in the stool or biopsies of colorectal cancer patients. A number of these strains carry the *pks* pathogenicity island, which expresses the alkylating enzyme colibactin. Pleguezuelos-Manzano and colleagues exposed human colonic organoids to *E. coli* strains expressing or not expressing colibactin for five months and then used whole genome sequencing to identify a DNA mutation signature unique to colibactin-expressing *E. coli*. They subsequently showed that a similar mutation signature could be identified in a significant percentage of colorectal cancer patient samples using two distinct patient cohorts, including in the pivotal colorectal gate-keeper gene *APC*.

Expert Commentary: *E. coli* carrying the *pks* pathogenicity island drive a DNA mutational signature associated with colorectal cancer progression.

Pleguezuelos-Manzano C, Puschhof J, Rosendahl Huber A, van Hoeck A, Wood HM, Nomburg J et al. Mutational signature in colorectal cancer caused by genotoxic E. coli. Nature; Published online February 27, 2020; DOI: 10.1038/s41586-020-2080-8.

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.