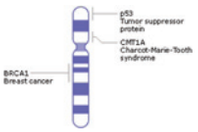
CANCER RESEARCH
BREAKING INSIGHTS

Highlights from Recent Cancer Literature

Predicting Cancer in Li-Fraumeni Syndrome

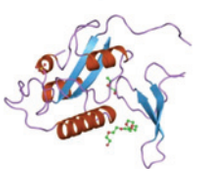


Germline *TP53* mutations are the most frequent cause of Li-Fraumeni syndrome (LFS), which increases the risk of developing cancer. In an attempt to quantify the incidence and features of cancer in individuals with LFS, de Andrade and colleagues analyzed a cohort containing 480 carriers of *TP53* variants. Across the cohort, individuals with LFS had a 24 times higher incidence of developing any cancer compared with the general population. There were also stark differences observed between genders, including females developing breast cancer and males having brain cancer as their first primary malignancies. Careful curation revealed that *TP53* variants with both dominant-negative (DN) and loss-of-function (LOF) effects led to earlier incidence of first and second cancer diagnosis and shortened the interval from first to second cancers compared with non-DN or non-LOF.

Expert Commentary: This study provides extensive data on the natural history of germline *TP53* variants, with the potential to guide personalized surveillance approaches. Incorporating and extending these findings to future studies could guide early detection strategies and improve survival. *(Image courtesy of Wikimedia Commons.)*

de Andrade KC, Khincha PP, Hatton JN, Frone MN, Wegman-Ostrosky T, Mai PL, et al. Cancer incidence, patterns, and genotype-phenotype associations in individuals with pathogenic or likely pathogenic germline TP53 variants: an observational cohort study. Lancet Oncol 2021;22:1787–98.

Endocytic Control of Therapeutic Targets



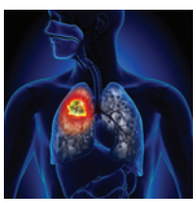
Pancreatic ductal adenocarcinoma (PDAC) remains resistant to current therapies due to intense intratumoral heterogeneity and a highly desmoplastic and immunosuppressive tumor microenvironment (TME). Pin1 is a proline isomerase that is overexpressed both in PDAC cancer cells and cancer-associated fibroblasts and is known to regulate numerous oncoproteins and tumor suppressors. Overexpression of Pin1 correlates positively with the desmoplastic and immunosuppressive TME, and inversely with outcome. Therefore, Koikawa and colleagues explored the concept of inhibiting Pin1 in order to sensitize PDAC tumors to commonly used therapies. Pin1 inhibition using a clinically available combination of all-trans retinoic acid and arsenic trioxide disrupted the desmoplastic and immunosuppressive TME, upregulated PD-L1 and gemcitabine transport, and blocked multiple cancer-related pathways, eradicating aggressive PDAC by synergizing with immuno- and chemotherapy. Mechanistically, Pin1 protected tumor cells by facilitating endocytosis and lysosomal degradation of PD-L1 and the gemcitabine transporter ENT1 through an interaction with Huntingtin-interacting protein 1–related protein (HIP1R).

doi: 10.1158/0008-5472.CAN-82-2-BI

Expert Commentary: This study uncovers a novel function of PIN1 and supports future clinical trials testing Pin1 inhibitors in combination with immunochemotherapy for PDAC patients. *(Image courtesy of Wikimedia Commons.)*

Koikawa K, Kib S, Suizu F, Sekino N, Kim N, Manz TD, et al. Targeting Pin1 renders pancreatic cancer eradicable by synergizing with immunochemotherapy. Cell 2021;184:4753–71.e27.

Prognostic Biomarkers for Immunotherapy in Lung Cancer

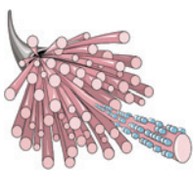


Although immune checkpoint blockade is used commonly in late-stage non-small cell lung cancer (NSCLC), only 15% to 20% of patients show improved overall survival. To identify markers of response, Leader and colleagues performed single-cell analysis of immune cells within newly diagnosed, treatment naïve, early-stage NSCLC using antibody profiling (CITE-seq), single-cell RNA sequencing, and T-cell receptor sequencing. Comparing NSCLC tissue to normal lung tissue, they identified a lung cancer immune activation module (LCAM), which correlated with tumor mutational burden (TMB) and *TP53* mutation status. CITE-seq data identified a panel of antibodies sufficient to identify $LCAM^{hi}$ lesions and further validated $LCAM^{hi}$ enrichment using other cohorts of NSCLC patients. $LCAM^{hi}$ enrichment correlated with TMB but acted independently of it. Thus, stratifying patient data into $LCAM^{hi}$; TMB^{+} allowed for a better predictive response to an immune checkpoint inhibitor.

Expert Commentary: The $LCAM^{hi}$ profile of immune cell composition provides a useful prognostic signature for response of lung cancer patients to immune checkpoint blockade.

Leader AM, Grout JA, Baier BB, Nabet BY, Park MD, Tabachnikova A, et al. Single-cell analysis of human non-small cell lung cancer lesions refines tumor classification and patient stratification. Cancer Cell 2021;39:1594–1609.e12.

Metabolic Rewiring of Collagen Production

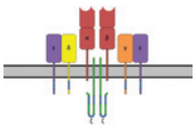


Cancer-associated fibroblasts (CAF) are key components of the tumor microenvironment, responsible for remodeling of the extracellular matrix (ECM) to promote a protumorigenic environment. Schwörer and colleagues were interested in understanding how CAFs are able to produce large amounts of ECM proteins like collagen despite having limited nutrients in the tumor microenvironment. The authors showed that protein translation and collagen production by cancer-associated fibroblasts is dependent on pyruvate carboxylase in nutrient poor environments. The CAFs can utilize extracellular lactate to drive tricarboxylic acid cycle anaplerosis through activation of pyruvate carboxylase, resulting in increased collagen deposition that drives tumor growth in *in vivo* models.

Expert Commentary: The ability of CAFs to rewire their metabolic pathways and adapt to a nutrient poor tumor environment highlights the potential for inhibiting tumor fibrosis by targeting pyruvate carboxylase. *(Image courtesy of Wikimedia Commons.)*

Schwörer S, Pavlova NN, Cimino FV, King B, Cai X, Sizemore GM, et al. Fibroblast pyruvate carboxylase is required for collagen production in the tumour microenvironment. Nat Metab 2021;3(11):1484–99.

Hunting for the Tumor Killers

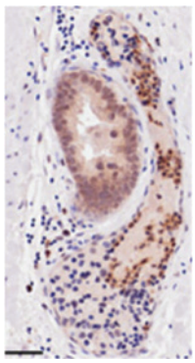


The production of tumor antigens and the engagement of the adaptive immune response, via cells recognizing those antigens, are two important components in cancer immunotherapy. Efficiently identifying tumor antigens, and the corresponding clonal immune cell populations that target them, is an ongoing challenge. To address this issue, Arnaud and colleagues described NeoScreen, a platform that expands tumor-infiltrating lymphocytes *in vitro* while combining them with autologous antigen-presenting B cells carrying libraries of candidate antigens. By applying this technique to previously characterized tumors and then expanding to new cases, the authors showed that NeoScreen identified more tumor epitopes than prior approaches. Testing in a matched patient-derived xenograft model demonstrated that the identified T-cell receptor sequences were tumor-targeting.

Expert Commentary: This report details a new approach with potential to identify a larger number of tumor antigens and their associated T-cell receptor sequences. NeoScreen could improve the success rates of precision medicine approaches in solid tumors—both by identifying tumor-reactive T-cell clones and by revealing tumor-specific mutations. *(Image courtesy of Wikimedia Commons.)*

Arnaud M, Chiffelle J, Genolet P, Navarro Rodrigo B, Perez MAS, Huber F, et al. Sensitive identification of neoantigens and cognate TCRs in human solid tumors. Nature Biotechnology; Published online November 15, 2021; doi: 10.1038/s41587-021-01072-6.

HER3 in Advanced Prostate Cancer



Metastasis in prostate cancer patients significantly worsens prognosis as there is still a lack of effective therapies for this disease. Aberrant HER2 signaling has been studied as a mechanism of endocrine treatment-resistance in prostate cancer, which led to several ultimately unsuccessful clinical trials using ERBB-targeting drugs in metastatic castration-resistant prostate cancer. Gil and colleagues re-investigated ERBB receptors in treatment-resistant prostate cancer and observed that overexpression of HER3 correlated with shorter time to castration resistance and worse overall survival. Additionally, the HER3 ligand NRG1 was expressed by inflammatory myelomonocytic cells within the tumor. Recombinant NRG1 enhanced proliferation and survival of castration-resistant patient-derived xenografted prostate cancer organoids. The authors also assessed the therapeutic potential of targeting HER3 and found that an anti-HER3 antibody-drug conjugate (ADC) with a topoisomerase 1 inhibitor had better efficacy in reducing tumor progression *in vivo* compared with the HER3 antibody alone.

Expert Commentary: This study provides further validation that HER3 is an actionable target in prostate cancer and warrants investigation into the design of ADCs targeting this receptor. *(Image from cited article courtesy of publisher.)*

Gil V, Miranda S, Riisnaes R, Gurel B, D'Ambrosio MA, Vasciaveo A, et al. HER3 is an actionable target in advanced prostate cancer. Cancer Res 2021;81:6207–18.

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.