January 1, 2022 | Volume 82 | Number 1

CANCER RESEARCH

BREAKING INSIGHTS

Highlights from Recent Cancer Literature

Predicting Response to Immunotherapy

Clear cell renal cell carcinoma (ccRCC) is unique from many other tumor types, as biomarkers of response to immunotherapy, such as tumor mutational burden, do not have predictive value for this disease. Au and colleagues postulated that the failure to identify biomarkers of response to checkpoint blockade immunotherapy was due to high levels of intratumoral heterogeneity found in ccRCC. Thus, they established a phase 2 clinical trial of treatment-naïve metastatic ccRCC patients in which the multiple intratumoral biopsies were sampled at various time periods in order to track disease progression. Patients were divided into two groups, responders and nonresponders, and samples from both were subjected to multiomic and immune microenvironment analyses. Consistent with previous analysis, no correlation was found between various genomic signatures and response to nivolumab (anti-PD1). Importantly, responders exhibited a higher number of expanded T-cell receptor (TCR) clones pretreatment than nonresponders, consistent with some pre-existing immunity. Maintenance of similar TCR clusters during treatment was predictive of outcome.

Expert Commentary: Anti-PD1 agents function by increasing and maintaining clusters of $CD8^+$ T cells that exist prior to treatment.

Au L, Hatipoglu E, de Massy MR, Litchfield K, Beattie B, Rowan A, et al. Determinants of anti-PD-1 response and resistance in clear cell renal cell carcinoma. Cancer Cell 2021;39:1497–1518.e11.

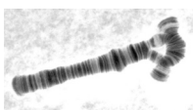
Starving Triple-Negative Breast Cancer

Aggressive triple-negative breast cancer (TNBC) frequently recurs after treatment due to repopulation of cancer stem cells (CSC) or acquired therapy resistance. Salvadori and colleagues demonstrated that a fasting-mimicking diet (FMD) depleted TNBC CSCs. Reduced glucose levels lowered markers of stemness and signaling from protein kinase A (PKA). Consequently, activation of PKA increased TNBC CSC numbers in the setting of FMD. Separate from CSCs, FMD conditions enhanced PI3K-Akt, mTOR, and CDK4/6 signaling pathways in differentiated cells, so the authors explored using small molecule inhibitors of these pathways, which reduced tumor burden in mice. Furthermore, the authors showed that repeated cycles of FMD prevented hyperglycemia as well as toxicity induced by kinase inhibitors. Importantly, metastatic TNBC patients with low levels of glucose lived longer than patients with high levels

Expert Commentary: This study suggests that FMD has potential as a novel therapeutic strategy in combination with targeted cancer drugs.

Salvadori G, Zanardi F, Iannelli F, Lobefaro R, Vernieri C, Longo VD. Fasting-mimicking diet blocks triple-negative breast cancer and cancer stem cell escape. Cell Metab 2021;33:2247–59.e6.

Replication Stress Drives Senescence Escape

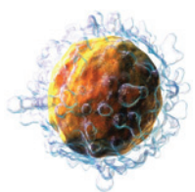


Senescent cells have protumorigenic properties through the release of senescence-associated secretory phenotype (SASP) factors, but less is understood about the impact of senescent cells reentering the cell cycle on tumor formation. Utilizing a CDC6 overexpressing normal human bronchial epithelial model, Zampetidis and colleagues found that senescent cells shifted from replicative stress–induced DNA damage repair to error-prone repair. This shift resulted in recurrent alterations including a frequent inversion in chromosome 3 involving the circadian transcription factor BHLHE40, which led to cell-cycle re-entry. Overexpression and alterations of BHLHE40 were found in human tumors, and BHLHE40 was both sufficient and required for escape from oncogene-induced senescence.

Expert Commentary: The authors present a novel model of escape from oncogene-induced senescence, which suggests a new target for cancer prevention and treatment. *(Image courtesy of Wikimedia Commons.)*

Zampetidis CP, Galanos P, Angelopoulou A, Zhu Y, Polyzou A, Karamitros T, et al. A recurrent chromosomal inversion suffices for driving escape from oncogene-induced senescence via subTAD reorganization. Molecular Cell; Published online November 12, 2021; doi: 10.1016/j.molcel.2021.10.017.

Combating Antigen Loss Variants



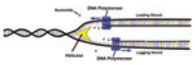
Adoptive transfer of T cells specific to cancer (CAR-T therapies) succeed via cytolytic $CD8^+$ T cells killing cancer cells. Selection for antigen loss variants (ALV) renders cancer cells invisible to T cells. Xue and colleagues revealed that IL9-producing tumor-specific helper T cells (Th9 cells) were superior to alternatively differentiated T helper cells (Th1/Th17) in controlling ALV cancers. Th9-cell therapy recruited and activated monocytes ($CD11b^+Ly6c^+$) in tumors. Unlike other T-cell types, Th9 cells did not express the extracellular ATPase CD39, generating a sink of extracellular ATP. This enabled Th9 cells to recruit monocytes and induced endogenous retroviral elements, triggering dsRNA sensors to produce type I IFN in monocytes. All events coalesced to control ALV cancers in mice, revealing a unique capacity for Th9 cells to recruit and activate innate immune cells to control cancer.

doi: 10.1158/0008-5472.CAN-82-1-BI

Expert Commentary: Adoptive transfer therapy for cancer with Th9 cells uniquely mobilized antitumor monocyte responses to cancers that lost expression of the targeted T-cell antigen. *(Image courtesy of Wikimedia Commons.)*

Xue G, Zheng N, Fang J, Jin G, Li X, Dotti G, et al. Adoptive cell therapy with tumor-specific Th9 cells induces viral mimicry to eliminate antigen-loss-variant tumor cells. Cancer Cell; Published online October 5, 2021; doi: 10.1016/j.ccell.2021.09.011.

Searching for a Response Signature

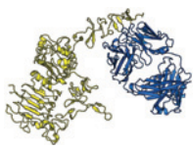


Most cancers lack robust predictors for response to immune checkpoint blockade (ICB). Here, leveraging a gene expression signature that represents a defective replication stress response (RSR), the authors examined cell lines, murine breast cancer models, and cancer patients with multiple tumor types to demonstrate that a high RSR signature corresponds to replication fork stalling, the accumulation of immunogenic single-stranded cytosolic DNA, and immunogenic cytokine/chemokine production. Small molecules can be used to modulate the RSR response and thus response to ICB. The authors showed that this signature is predictive of response to ICB in multiple solid tumor types using data from several prior clinical trials.

Expert Commentary: This study tests a defective RSR transcriptional signature and shows that it outperforms other proposed classifiers in predicting ICB response. This work reveals potential for refined prospective trial designs in "nonhypermutator" solid tumors, using the RSR signature to identify patients most likely to benefit from ICB as well as those who may require a combinatorial approach to make their cancer cells more immunogenic. *(Image courtesy of Wikimedia Commons.)*

McGrail DJ, Pilie PG, Dai H, Lan TNA, Liang Y, Voorwerk L, et al. Replication stress response defects are associated with response to immune checkpoint blockade in non-hypermutated cancers. Sci Transl Med 2021;13:eabe6201. doi: 10.1126/scitranslmed.abe6201.

Pathway Dependency Switching Drives Resistance to HER2-Targeted Therapies



HER2 therapies were one of the first targeted therapies. Since development in the 1990s, they have provided significant benefit to breast cancer patients. However, resistance, particularly in the metastatic setting, remains a major clinical problem. Smith and colleagues performed genomic profiling of metastatic tumors and identified that alterations that promote MEK/ERK signaling were associated with shortened progression-free survival. Preclinical studies identified a switch from AKT dependency to MEK/ERK pathway dependency in HER2^{+}-resistant models that was mediated via CDK2 driven cell-cycle progression.

Expert Commentary: This study highlights the power of analyzing pre- and post-treatment clinical samples to identify targetable vulnerabilities in resistant disease. Follow-up studies will determine whether patients with genetic alterations in the MAPK/ERK pathway that have progressed on HER2 therapies will benefit from treatments that target this pathway. *(Image by Simon Caulton courtesy of Wikimedia Commons.)*

Smith AE, Ferraro E, Safonov A, Morales CB, Lahuerta EJA, Li Q, et al. HER2+ breast cancers evade anti-HER2 therapy via a switch in driver pathway. Nat Commun 2021;12:6667. doi: 10.1038/s41467-021-27093-y.

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.