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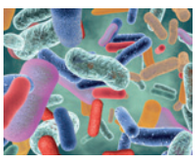
CANCER RESEARCH
BREAKING INSIGHTS

Highlights from Recent Cancer Literature

Microbiota Instructs an Immunosuppressive Response



Only colorectal cancers that exhibit microsatellite instability (MSI high) respond to anti-PD1/PDL1 checkpoint blockade immunotherapy (CBI). The majority of MSI low colorectal cancers are unresponsive to CBI. Investigating the *APC*^{min} mouse and mouse tumor organoid models, Peuker and colleagues discovered additional T-cell checkpoints for immune resistance in colorectal cancer. Previous work identified the importance of the calcineurin-NFAT axis within cancer cells for colorectal cancer progression. This study demonstrated that calcineurin-NFAT enforced immunosuppression of antitumor CD8$^+$ T cells. Myeloid-derived suppressor cells of the polymorphonuclear phenotype responded to microbiota cues (e.g., LPS) to produce IL6 in a calcineurin-NFAT–dependent manner. IL6 acted on tumor cells, inducing coinhibitory molecules B7H3 and B7H4 to block the function of CD8$^+$ T cells. In patients with colorectal cancer, high B7H3 or B7H4 expression correlated with worse overall survival.

Expert Commentary: Microbial sensing by tumor-infiltrating myeloid cells blocks T-cell responses to colorectal cancer by inducing the expression of inhibitory molecules B7H3 and B7H4 on cancer cells.

Peuker K, Strigli A, Tauriello DVF, Hendricks A, von Schönfels W, Burmeister G, et al. Microbiota-dependent activation of the myeloid calcineurin-NFAT pathway inhibits B7H3- and B7H4-dependent anti-tumor immunity in colorectal cancer. Immunity 2022;55:701-17.e7. doi: 10.1016/j.immuni.2022.03.008.

Dependencies of Slow-Cycling Pancreatic Tumor Cells

Cancer cells exist in a heterogenous microenvironment, comprising 'fertile regions' with abundant oxygen and nutrients, and 'arid regions' where nutrients and oxygen are scarce. Most cancer cells reside in 'arid regions,' with slow cycling making them chemoresistant. Sela and colleagues developed an *in vitro* model system that mimicked the nutrient- and oxygen-deprived metabolic environment in pancreatic cancer (PDAC). Using metabolomic profiling, transcriptome analysis, and unbiased genetic screening, they found that metabolic deprivation promoted distinct transcriptional and metabolic reprogramming. Vulnerabilities specific to metabolically deprived slow-cycling cancer cells were identified. Bcl-xL expression was restricted to slow-cycling cancer cells in human PDAC, augmenting the survival of slow-cycling tumor cells following nutrient deprivation. Pharmacological inhibition of Bcl-xL markedly enhanced the activity of standard-of-care gemcitabine/Nab-paclitaxel in PDAC.

Expert Commentary: This study establishes the potential of combining treatments that target the rapid-proliferating cells using conventional chemotherapeutics with a drug that targets the slow-cycling compartments of a tumor, yielding synergistic therapeutic benefits.

Sela Y, Li J, Maheswaran S, Norgard R, Yuan S, Hubbi ME, et al. Bcl-xL enforces a slow-cycling state necessary for survival in the nutrient-deprived microenvironment of pancreatic cancer. Cancer Res 2022;82:1890–908.

Complexity Complicates Single Agent Therapy

The mitogen-activated kinase (MAPK) signaling pathway, which promotes cell proliferation, is abnormally activated in many tumor types, often through mutations upstream of mitogen-activated protein kinase kinase (MEK). Consequently, MEK inhibitors are being widely tested for clinical efficacy. This study from Eckstein and colleagues reported on arm E of the NCI-COG Pediatric MATCH trial, in which pediatric patients with genetic alterations affecting the MAPK pathway were treated with the MEK inhibitor selumetinib. In contrast to successful use of selumetinib in low-grade nervous system tumors, treatment of the 20 patients in this study, who had treatment refractory tumors of which the most common types were high-grade glioma and rhabdomyosarcoma, did not lead to partial or complete remission. The lack of efficacy was potentially due to the presence of additional cancer gene mutations in their higher-grade tumors.

Expert Commentary: This study underscores the challenge of using single targeted agents in genetically complex, aggressive cancers. Moving forward, insights into compensatory signaling or other methods of treatment resistance may help inform the design of multiagent trials.

Eckstein O, Allen C, Williams P, Roy-Chowdhuri S, Patton D, Coffey B, et al. Phase II study of selumetinib in children and young adults with tumors harboring activating mitogen-activated protein kinase pathway genetic alterations: arm E of the NCI-COG Pediatric MATCH trial. Journal of Clinical Oncology; Published online April 1, 2022; doi: 10.1200/JCO.21.02840.

Overcoming Radioresistance in Brain Metastases

Effective therapeutic options beyond radiation are limited for brain metastases, and the efficacy of whole-brain radiotherapy (WBRT) is limited by toxicity and radioresistance. Monteiro and colleagues have identified the S100A9-RAGE-NFκB-Jun B pathway as a targetable mediator of radioresistance in brain metastases. Targeting multiple components of this pathway affected neither colonization nor growth of brain metastases but sensitized to WBRT even at low radiation doses. Furthermore, low S100A9 brain

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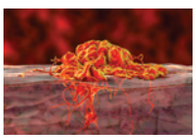
metastases expression and/or low serum S100A9 levels were predictive for WBRT response in patients. Finally, use of a brain penetrant RAGE inhibitor sensitized to WBRT while improving the therapeutic index *in vivo*.

Expert Commentary: This study uncovered a targetable resistance mechanism and possible biomarker of response for patients with brain metastases undergoing whole-brain radiotherapy.

Monteiro C, Miarka L, Perea-García M, Priego N, García-Gómez P, Álvaro-Espinosa L, et al. Stratification of radiosensitive brain metastases based on an actionable S100A9/RAGE resistance mechanism. Nat Med 2022;28:752–65.

Propionate Metabolism and Metastases

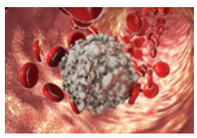


Metabolic reprogramming and alterations are essential hallmarks enabling cancer cells to acquire the ability to generate the energy required for metastasis. Gomes and colleagues showed that propionate metabolism, which is understudied in cancer biology, increased the metastatic potential of lung and breast cancer cells. The authors identified altered metabolites in pulmonary metastases compared with primary tumors in a mouse model of triple-negative breast cancer, with propionate metabolism enriched in metastatic lesions. In subsequent experiments using xenografts of human breast and lung cancer cells, the authors confirmed that metastatic potential increased with downregulation of methylmalonyl coenzyme A epimerase, resulting in the accumulation of methylmalonic acid, an intermediary step in propionate metabolism. Increased methylmalonic acid was observed to promote cancer cell migration and invasion.

Expert Commentary: This study highlights the importance of how propionate metabolism, which is required in lipid biosynthesis, can be co-opted for cancer cell metabolism and invasion. Targeting propionate metabolism may present a novel strategy in inhibiting cancer cell metastasis.

Gomes AP, Iter D, Low V, Drapela S, Schild T, Mullarky E, et al. Altered propionate metabolism contributes to tumour progression and aggressiveness. Nat Metab 2022;4:435–43.

Mutant TP53 in Blood Malignancies



Mutations in *TP53* represent a genetic feature in both myelodysplastic syndrome with excess blast count (MDS-EB) and acute myelogenous leukemia (AML) that is associated with worse survival. In order to understand the relationship of these two disease states, Grob and colleagues performed next-generation sequencing on 2200 AML or MDS-EB samples, of which, roughly 10% had *TP53* mutations. Based on clinical parameters including age, sex, blood counts, treatment, *TP53* mutation number, clone size, survival outcomes, co-occurring mutations, and allelic status, no significant difference was seen between *TP53*-mutant AML and MDS-EB patients. Assessment of molecular minimal residual disease (MRD) is an important prognostic marker in AML, however, deep targeted sequencing of mutant *TP53* did not reveal an association between mutant *TP53* and overall survival, concluding molecular MRD may therefore be of limited benefit prognostically.

Expert Commentary: *TP53*-mutant high risk MDS-EB and AML disease entities have strikingly shared molecular features and clinical outcomes, suggesting these could be considered as a single disease.

Grob T, Al Hinai ASA, Sanders MA, Kavelaars FG, Rijken M, Gradowska PL, et al. Molecular characterization of mutant TP53 acute myeloid leukemia and high-risk myelodysplastic syndrome. Blood 2022;139:2347–54.

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.

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