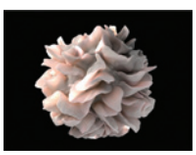
September 15, 2021 | Volume 81 | Number 18

CANCER RESEARCH

BREAKING INSIGHTS

Highlights from Recent Cancer Literature

Targeted Therapy Induces Cross-Resistance to Immunotherapy



Patients with metastatic melanoma are currently treated with both targeted therapy and immunotherapy in an effort to increase response, but it is unclear how first-line treatment with targeted therapy impacts the tumor microenvironment and how this could influence the subsequent response to immunotherapy. Haas and colleagues utilize mouse models and clinical data to demonstrate melanoma tumors that become resistant to MAPK pathway inhibitors and relapse subsequently develop cross-resistance to immunotherapy. Cross-resistance was achieved by reactivation of MAPK signaling in targeted therapy-resistant tumors, which included increased transcription of known MAPK target genes in addition to regulation of new genes by MAPK. Resistance to targeted therapy was associated with decreases in both the number and function of cytotoxic T cells and $CD103^+$ dendritic cells in the tumor microenvironment, and restoration of dendritic cell function and treatment with MAPK inhibitors resensitized tumors to immunotherapy.

Expert Commentary: This study suggests that upfront treatment with targeted therapy in melanoma may jeopardize the future efficacy of immunotherapy and necessitates an understanding of how the tumor microenvironment is altered during treatment to ensure mechanisms of resistance do not develop. *(Image courtesy of Wikimedia Commons.)*

Haas L, Elewaut A, Gerard CL, Umkehrer C, Leiendecker L, Pedersen M, et al. Acquired resistance to anti-MAPK targeted therapy confers an immune-evasive tumor microenvironment and cross-resistance to immunotherapy in melanoma. Nat Cancer 2021;2:693–708.

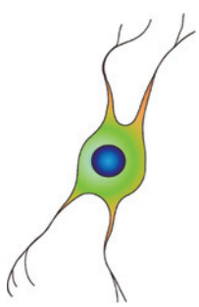
Improving Cancer Immunotherapy by Reducing Immune Toxicity

Checkpoint blockade immunotherapy (CBI) can drive remarkable tumor regressions but is often limited by severe toxicities. Siwicki and colleagues discovered a macrophage-neutrophil axis uniquely responsible for toxic side effects in the liver. Using anti-CD40 treatment as a potent model of cancer immunity and toxicity in mice, they found production of IFNγ and IL12, critical cytokines induced by CBI, to be induced across all tissues. Using antibody blockade, they showed that each cytokine was required for both cancer regression and toxicity. While investigating the source of these cytokines, the authors found that IL12 production from dendritic cells was required for anticancer immunity, while the effects on liver toxicity were driven by tissue resident macrophages in the liver (e.g., Kupffer cells) activated by IFNγ. Immunotherapy activated macrophages to recruit neutrophils to the liver, which mediated a TNF-dependent destruction of healthy tissues. In human patients undergoing CBI, neutrophil responses were associated with toxic side effects.

Expert Commentary: Blocking a macrophage-neutrophil axis induced with immunotherapy eliminates liver toxicity while retaining potent antitumor activity.

Siwicki M, Gort-Freitas NA, Messemaker M, Bill R, Gungabeesoon J, Engblom C, et al. Resident Kupffer cells and neutrophils drive liver toxicity in cancer immunotherapy. Sci Immunol 2021 Jul 2;6:eabi7083. DOI: 10.1126/sciimmunol.abi7083.

GMCSF and Leptomeningeal Spread of Breast Cancer



Leptomeningeal carcinomatosis (LC) is a form of metastatic breast cancer localized to the brain, which is enhanced by factors such as HER2-positivity and is associated with poor outcomes and very few therapeutic strategies. The different environments between the breast and central nervous system (CNS) suggest LC tumors utilize different growth pathways, which could be targeted, so Ansari and colleagues used primary $HER2^+$ LC patient-derived cell lines cocultured with various CNS cell types to identify molecular mechanisms of LC growth. Interestingly, the authors identified that oligodendrocyte progenitor cells (OPC) were able to induce apoptosis of LC cells in coculture. Mechanistically, OPCs were responsible for secretion of the protease TPP1 to degrade the cytokine GMCSF, which was upregulated in LC cells and potently stimulated tumor cell growth. Growth of $HER2^+$ LC cells could be inhibited with neutralizing GMCSF antibodies *in vitro* and *in vivo*, and additionally a chemical screen revealed treatment with a pan-Aurora kinase inhibitor had synergistic effects in reducing tumor growth.

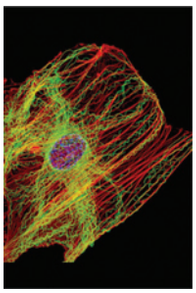
Expert Commentary: Identification of mechanisms by which CNS-resident cells restrain metastatic tumor cell growth may provide new therapeutic targets for the treatment of breast cancer. *(Image courtesy of Wikimedia Commons.)*

Ansari KI, Bhan A, Saotome M, Tyagi A, Kimar BD, Chen C, et al. Autocrine GMCSF signaling contributes to growth of $HER2^+$ breast leptomeningeal carcinomatosis. Cancer Res 2021;81:4723–35.

doi: 10.1158/0008-5472.CAN-81-18-BI

BREAKING INSIGHTS

Interactions between Immune and Mesenchymal Cells Inhibit Tumor Growth

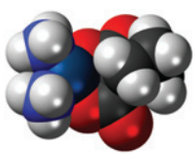


Cancer-associated fibroblasts (CAF) are now appreciated as important regulators of tumorigenesis, however, heterogeneity among this group of cells enables distinct fibroblast lineages to have either pro- or antitumorigenic functions and has complicated the use of therapies targeting CAFs. Hutton and colleagues employed mass cytometry on 18 normal mouse tissues and 39 tumors from multiple mouse cancer models and typed 14 million cells. They found extensive stromal heterogeneity within and between normal and cancer tissues and identified harmonized links between subsets of mesenchymal and immune cells in pancreatic ductal adenocarcinoma. Expression of CD105 defined two distinct fibroblast lineages in most normal tissues and tumors. CD105-positive pancreatic fibroblasts were supportive for tumor growth *in vivo*, while CD105-negative fibroblasts robustly restricted tumorigenesis by supporting adaptive immunity. These data demonstrate two separate pancreatic fibroblast populations and reveal functional interactions between immune and mesenchymal cells in inhibiting tumor growth.

Expert Commentary: This study suggests that further functional analysis on the mesenchyme could result in stromal-targeting approaches to treat cancer. *(Image courtesy of Wikimedia Commons.)*

Hutton H, Heider F, Blanco-Gomez A, Banyard A, Kononov A, Zhang X, et al. Single-cell analysis defines a pancreatic fibroblast lineage that supports anti-tumor immunity. Cancer Cell; Published online July 14, 2021; DOI: 10.1016/j.ccell.2021.06.017.

Subgroup Specific Outcomes for Chemotherapy in Medulloblastoma

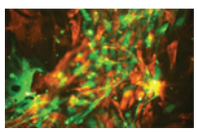


Medulloblastoma is the most common primary malignant brain tumor in children, but treatment of this disease is currently limited by a lack of effective therapeutic interventions. In order to identify combination therapies with increased effectiveness, Leary and colleagues reported a randomized clinical trial of 261 patients aged 3 to 21 with newly diagnosed high-risk medulloblastoma. Patients with group 3 high-risk medulloblastoma who received the radiosensitizing agent carboplatin, along with radiation therapy and vincristine, showed improved survival from 54% to 73%, including patients with metastases. The authors also reported that the use of the proapoptotic agent isotretinoin during maintenance chemotherapy showed no benefit. These findings suggest the inclusion of carboplatin for group 3 high-risk medulloblastoma but not for the other subgroups.

Expert Commentary: The results from this phase 3 clinical trial substantiate the importance of a combined molecular and clinical stratification for therapy strategy in medulloblastoma. *(Image courtesy of Wikimedia Commons.)*

Leary SES, Packer RJ, Li Y, Billups CA, Smith KS, Jaju A, et al. Efficacy of carboplatin and isotretinoin in children with high-risk medulloblastoma, a randomized clinical trial from the Children's Oncology Group. JAMA Oncology; Published online July 22, 2021; DOI:10.1001/jamaoncol.2021.2224.

CD93: A New Player in Vascular Normalization



Abnormal tumor vasculature creates an unfavorable hypoxic tumor microenvironment that limits immune cell infiltration, restricting the efficacy of immunotherapies. In an effort to identify molecular targets to enhance vessel normalization, Sun and colleagues showed that CD93, a C-type lectin transmembrane protein, was selectively upregulated in tumor vasculature and together with its binding partner insulin-like growth factor binding protein 7 (IGFBP7) was a key contributor to disorganization of the tumor vasculature. Antibodies directed against CD93 increased tumor perfusion and reduced hypoxia, and importantly had very little effect on normal tissue vessels. Normalization of blood flow in the tumor with CD93 blockade increased immune cell infiltration, which was essential for sensitizing tumors to immunotherapy and ultimately reduced tumor growth.

Expert Commentary: Although targeting the vascular endothelial growth factor can help generate a functional vascular network within tumors, toxic side effects on normal tissue vasculature present a problem for cancer treatment. This study supports blockade of CD93 as a safer approach and warrants further study. *(Image courtesy of Wikimedia Commons.)*

Sun Y, Chen W, Torphy RJ, Yao S, Zhu G, Lin R, et al. Blockade of the CD93 pathway normalizes tumor vasculature to facilitate drug delivery and immunotherapy. Sci Transl Med 2021;13:eabc8922. DOI: 10.1126/scitranslmed.abc8922.

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.