Cancer Research
Breaking Advances
Highlights from Recent Cancer Literature
AACR
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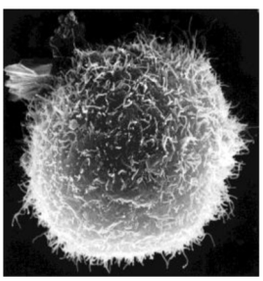
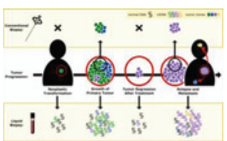
PD-1 Expression by Tumor-Associated Macrophages



T cells have been posited as the primary immune cell target for anti-PD-1/PD-L1 therapies, yet high intratumoral T-cell infiltration does not robustly predict efficacy. Gordon and colleagues show that a subpopulation of M2 tumor-associated macrophages (TAM) from both human and mouse colorectal tumors expresses PD-1. TAMs were derived from circulating bone marrow-derived precursors, and expression of PD-1 in M2 TAMs correlated directly with stage. PD-1 expression on M2 TAMs attenuated antitumor phagocytic ability against mouse and human colorectal cancer cells. Genetic and pharmacologic targeting of PD-1/PD-L1 improved both TAM antitumor activity and tumor responses. These provocative findings suggest that intratumoral PD-L1 shields cancer cells from antitumor immune cells, minimally T-cells and TAMs; that targeting PD-1/PD-L1 may enable a multi-immune cell antitumor response; and that TAMs biomarkers may identify tumors susceptible to PD-1/PD-L1 immune checkpoint therapies. *(Image courtesy of Wikimedia Commons.)*

Gordon SR, Maute RL, Dulken BW, Hutter G, George BM, McCracken MN, et al. PD-1 expression by tumour-associated macrophages inhibits phagocytosis and tumour immunity. Nature 2017;545:495–9.

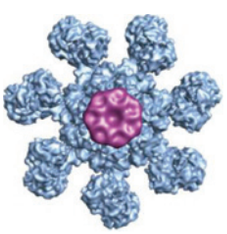
ctDNA Monitoring of Cancer Progression and Relapse



Abbosh and colleagues employed circulating tumor DNA (ctDNA) analysis in a prospective lung cancer clinical trial study, TRACERx. Based on previous sequencing data, Abbosh and colleagues identified rare ctDNA using assays based on single nucleotide variants present specifically in the patient's tumor. The assay allowed them to trace evolutionary patterns of arising tumor subclones by comparing ctDNA in pre- and postsurgery samples. ctDNA detected relapse significantly earlier compared with computed tomography. Detection of ctDNA from liquid-biopsy provided an indication of efficacy for postoperative chemotherapy. In one case, a therapeutically targetable genetic alteration (ERBB2 amplification) arose upon relapse, suggesting that such tests could guide therapy of relapsed patients early on. Sensitivity, however, remains limited with current technologies. In addition, general applicability is restricted by current costs of targeted ctDNA profiling. Nevertheless, with rapidly advancing technology and decreasing costs, precision medicine at this level may see clinical use. *(Image courtesy of Wikimedia Commons.)*

Abbosh C, Birkbak NJ, Wilson GA, Jamal-Hanjani M, Constantin T, Salari R, et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. Nature 2017;545:446–51.

Synergism with PI3KCA Inhibition in Breast Cancer

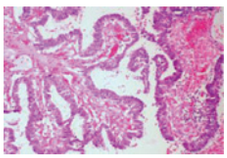


Zwang and colleagues performed an shRNA screen to identify genes whose suppression caused apoptosis in a breast cancer cell line treated with the PI3K inhibitor, GDC0941. Inhibition of *PIM2*, *TACC1*, *ZAK*, *ZFR*, and *ZNF565* caused cell death in GDC0941-treated breast cancer and in cancer models with aberrant PI3KCA signaling. Small-molecule inhibitors of PIM2 and ZAK synergized with GDC0941. Moreover, a microscale implementable device was used to deliver siRNAs or small-molecule inhibitors to validate the role of these genes *in vivo*. The effect of PIM2 loss on PI3K inhibition was mediated through decreased phosphorylation of the BH3-only protein BAD, which increased mitochondrial priming and caused cell death. This study identified novel targets whose inhibition cooperated with that of PI3K to induce cell death in cancers with PI3K activation. *(Image courtesy of Wikimedia Commons.)*

Zwang Y, Jonas O, Chen C, Rinne ML, Doench JG, Piccioni F, et al. Synergistic interactions with PI3K inhibition that induce apoptosis. Elife 2017 May 31;6. [Epub ahead of print]. doi: 10.7554/eLife.24523.

Breaking Advances

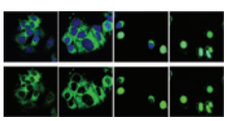
Brain Microenvironment Drives PI3K Drug-Resistance



Half of HER2-positive breast cancers manifest brain metastases, against which the efficacy of HER2 targeting agents is poor. Using HER2 and/or PI3KCA-mutant breast cancer cell lines implanted in the mammary fat pad (MFP) or intracranially, Kodack and colleagues found that despite full blood brain barrier penetration and equivalent drug levels in both tumor sites, the small-molecule inhibitor of the PI3K pathway lacked efficacy in brain metastasis while driving significant regression in MFP tumors. Mechanistically, the brain microenvironment upregulates HER3 protein and mRNA both in mouse xenografts and in paired human primary tumors and brain metastases. HER3 upregulation and heterodimerization activated PI3K-Akt and facilitated resistance to PI3K pathway and HER2 inhibition. Importantly, both could be overcome by HER3 blocking antibody. While mechanisms of how the brain microenvironment induces HER3 expression remains uncertain, these data identify a translatable therapeutic strategy for HER2 brain metastasis. *(Image by Ed Uthman courtesy of Wikimedia Commons.)*

Kodack DP, Askoxylakis V, Ferraro GB, Sheng Q, Badeaux M, Goel S, et al. The brain microenvironment mediates resistance in luminal breast cancer to PI3K inhibition through HER3 activation. Sci Transl Med 2017;9. doi: 10.1126/scitranslmed.aal4682.

EBV-Induced Inflammation and Nasopharyngeal Carcinoma



Huang and colleagues investigated how Epstein-Barr virus (EBV)–induced inflammation promotes nasopharyngeal carcinoma. They identified a correlation between tumor infiltration of tumor-associated macrophages (TAM) and a cytokine preferentially secreted by TAMs, CCL18, with serum EBV titers and tumor progression in patients. Using *in vitro* assays, the authors showed that EBV^+ nasopharyngeal carcinoma cell lines could better attract monocytes and manipulate them to differentiate into a TAM-like phenotype. The authors further performed cytokine profiling analysis and demonstrated that nasopharyngeal carcinoma cells with active EBV replication utilized VEGF to recruit monocytes and GM-CSF to induce TAMs in an NF-κB-dependent manner. Further, TAMs, through CCL18, induced epithelial-mesenchymal transition and NF-κB activation in tumor cells. Finally, using humanized mice, the authors showed that nasopharyngeal carcinoma cells with active EBV replication had increased metastasis and that neutralization of CCL18, GM-CSF, and VEGF reduced metastasis. In summary, the authors have identified a feed-forward loop between tumor cells and macrophages in nasopharyngeal carcinoma that highlights the relevance of virus-induced chronic inflammation in aiding metastasis. *(Image from cited article courtesy of publisher.)*

Huang D, Song S, Wu ZZ, Wu W, Cui X, Chen JN, et al. Epstein-Barr virus-induced VEGF and GM-CSF drive nasopharyngeal carcinoma metastasis via recruitment and activation of macrophages. Cancer Res 2017;77:3591–604.

Mutational Landscape across All Human Cancers

Zehir and colleagues from Memorial Sloan Kettering (MSK) performed prospective targeted sequencing of 341-410 genes on >10,000 patients covering 62 cancers with MSK-IMPACT, their CLIA-certified panel. DNA from normal tumors and, in 98% of cases, matched peripheral blood was analyzed to detect somatic mutations, small indels, copy number alterations, and chromosomal rearrangements. All were manually reviewed and reported in the medical record within 3 weeks. Eleven percent of patients were enrolled in genomically matched clinical trials. The majority of samples profiled represented metastatic sites from previously treated patients, whereas The Cancer Genome Atlas (TCGA) tumors are mainly primary, treatment naïve. Many significant genes in TCGA studies were even more frequently mutated in MSK-IMPACT, with *TP53* significantly enriched following treatment. Somatic mutations in the *TERT* promoter were found in bladder cancer, glioma, thyroid cancer, and melanoma. Finally, MSK-IMPACT results were representative of genome-wide mutational processes, such as microsatellite instability, and mutational burden, predictive for checkpoint blockade therapy. *(Image courtesy of Wikimedia Commons.)*

Zehir A, Benayed R, Shah RH, Syed A, Middha S, Kim HR, et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med 2017;23:703–13.

Note: Breaking Advances 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.