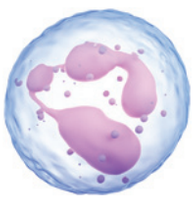
CANCER RESEARCH
BREAKING INSIGHTS

Highlights from Recent Cancer Literature

Lung Fibroblasts Support Breast Cancer Metastasis

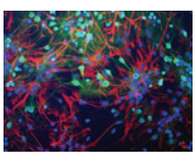


The final and critical step of metastasis is colonization in a secondary tissue, which requires suppression of the immune system to prevent tumor cell clearance. Gong and colleagues used mouse models of breast cancer metastasis to investigate whether an immunosuppressive niche in the lung supports metastasis. They found that in the lung, dendritic cell antigen presentation and T-cell stimulation were reduced compared with other organ tissues, due to a population of fibroblasts that expressed *PTGS2*, the gene encoding cyclooxygenase 2 (COX2), which converts arachidonic acid to prostaglandin E2 (PGE2). Neutrophils, often found at the sites of metastatic cancers, were found to produce high amounts of IL1β that boosted the expression of *PTGS2* in lung fibroblasts. The generation of PGE2 was critical for the immunosuppressive activity of the lung fibroblasts, as receptor antagonists for PGE2 could reverse the immunosuppressive phenotype in the lung. Furthermore, blocking the activity of PGE2 synergized with anti-PD-1 checkpoint blockade immunotherapy in controlling breast cancer metastasis to the lung.

Expert Commentary: A population of lung fibroblasts that generates an immunosuppressive metastatic niche in the lung can be combated using PGE2 antagonists.

Gong Z, Li Q, Shi J, Wei J, Li P, Chang CH, et al. Lung fibroblasts facilitate pre-metastatic niche formation by remodeling the local immune microenvironment. Immunity 2022;55:1483-1500.e9. doi: 10.1016/j.immuni.2022.07.001.

Using Brain Power to Bad Ends

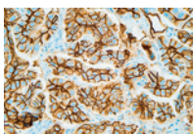


The brain tumor glioblastoma is clinically intractable, in part due to a well-recognized propensity to invade normal brain regions. Glioblastoma cells can also form networks of connections with each other, which is thought to support therapy resistance. Venkataraman and colleagues used labeling with gap junction–permeable agents to separate glioblastoma cells that were or were not part of a tumor cell network, and then examined the genomic and functional features of each population. Strikingly, unconnected glioblastoma cells were more invasive than those participating in functional networks with each other and noncancerous brain cells. These un-networked cells transcriptionally resembled normal neural precursor cells and showed cell movement that was similar to that of precursor cells during development. Finally, though not part of a network of connected cells, these invasive single cells were responsive to stimulation by native neurons, which increased the formation of tumor microtubes and their invasive activity.

Expert Commentary: This work directly couples precursor-like genomic states to functional cancer cell behaviors, including invasion and cooption of neurobiological activity. (*Image courtesy of Wikimedia Commons.*)

Venkataraman V, Yang Y, Schubert MC, Reyhan E, Tetzlaff SK, Wißmann N, et al. Glioblastoma hijacks neuronal mechanisms for brain invasion. Cell 2022;185:2899–917.e31. doi: 10.1016/j.cell.2022.06.054.

Exon 20 Strikes Again

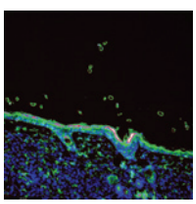


Around 2% of the patients with non-small cell lung cancer (NSCLC) present with oncogenic activation in human epidermal growth factor receptor 2 (HER2). Mutations occur in the tyrosine kinase domain and cluster in exon 20 of *HER2*, increasing kinase activity. Several tyrosine kinase inhibitors (TKI) in clinical use are limited either by poor efficacy against *HER2* exon 20 mutants or by poor selectivity against epidermal growth factor receptor (EGFR). Thus, there is an unmet need for better drugs. Wilding and colleagues identified and optimized novel TKIs selective against *HER2* exon 20 mutants while preserving wildtype EGFR signaling. The novel TKIs led to inhibition of tumor cell growth *in vitro* and resulted in reduced tumor burden in xenograft models of HER2 exon 20 mutant NSCLC in concert with decreased kinase signaling.

Expert Commentary: These results show that clinical translation of selective and potent TKIs is a promising possibility for treatment of HER2 exon 20 insertion–driven tumors.

Wilding B, Scharn D, Böse D, Baum A, Santoro V, Chetta P, et al. Discovery of potent and selective HER2 inhibitors with efficacy against HER2 exon 20 insertion-driven tumors, which preserve wild-type EGFR signaling. Nat Cancer 2022;3:821–36.

Awakening Quiescent Cancer Cells



Subsets of quiescent cells are critical to maintaining a long-lived stem cell pool in normal tissues. In malignant brain tumors, mathematical modeling, lineage tracing methods, and sequencing data have suggested an analogous slow-cycling or quiescent population is also present and contributes to tumor growth and therapy resistance. Antonica and colleagues mined human tumor single-cell transcript data to identify a subpopulation of malignant cells that express Prominin-1 (CD133) and also lack a cell-cycle signature. In genetically engineered mouse models and human forebrain organoids, they then visualized the spatial distribution of noncycling $CD133^{+}$ cells within the tumor, finding these cells both in the core and infiltrative edge. Inducible ablation of these cells upon tumor initiation resulted in smaller tumors, though a comparable effect was not seen with ablation after the tumor was established. Finally, a subset of pharmacological agents was tested to identify candidate activators of quiescent cells, rendering them more susceptible to antimitotic drugs.

doi: 10.1158/0008-5472.CAN-82-19-BI

Expert Commentary: Collectively, this data detail a new set of tools for further studying this elusive population of quiescent tumor cells and potential strategies to target them therapeutically.

Antonica F, Santomaso L, Pernici D, Petrucci L, Aiello G, Cutarelli A, et al. Nat Comm 2022;13:4767. doi: 10.1038/s41467-022-32448-0.

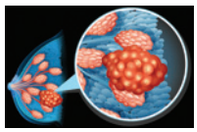
AML Proteomic and Phosphoproteomic Database

In order to build on the genomic and transcriptomic characterization of acute myeloid leukemia (AML), which has previously been described, Kramer and colleagues analyzed bone marrow samples from *de novo* AML patients and healthy bone marrow controls and used label-free quantification to define relative abundance of proteins, as well as tandem mass tag (TMT) to measure absolute abundance. Protein abundance correlated with common AML surface markers, recapitulating known features of AML. Unsupervised hierarchical clustering based on protein abundance on the TMT platform organized samples by clinical features. RNA and protein correlations and anti-correlations, and numerous examples of post-transcriptional regulation were evident. Protein abundance signatures, validated with downstream analysis, were described for AML mutational subgroups. Combining surface protein lists from the Human Protein Atlas and the *in silico* Human Surfaceome and cross-referencing to datasets herein identified potential protein targets for immunologic therapies. Numerous phosphosites were identified on AML-relevant signaling proteins and phospho-signatures associated with AML subgroups.

Expert Commentary: This deep-scale publicly available proteomic and phosphoproteomic database of AML (www.leylab.org/amlproteome) presents a resource of considerable value to the community and provides the missing data layer for part of the LAML TCGA dataset.

Kramer MH, Zhang Q, Sprung R, Day RB, Erdmann-Gilmore P, Li Y, et al. Proteomic and phosphoproteomic landscapes of acute myeloid leukemia. Blood; Published July 27, 2022; doi: 10.1182/blood.2022016033.

Novel Inhibitors of PELP1



Seventy percent of breast cancer is estrogen receptor alpha positive (ER^+). PELP is an ER coregulator and plays a vital role in breast cancer progression. Using a yeast two-hybrid screen, Altwegg and colleagues identified peptide inhibitors of PELP1 that bound to PELP1 and reduced its oncogenic functions. Using the peptidomimetics technology they developed, the authors identified a small-molecule inhibitor of PELP1, SMIP34. SMIP34 inhibited growth of wild-type and mutant ER^+ tumors, as well as therapy-resistant breast cancer cells. This was achieved through downregulated ER signaling and enhanced apoptotic pathways. RNA-seq confirmed decreased activation of ER and cell-cycle pathways. The *ex vivo* and *in vivo* efficacy of SMIP34 was shown in ER^+ breast tumor explants and cell line–derived and patient-derived xenografts from both wild-type and mutant ER^+ breast cancer models.

Expert Commentary: A yeast two-hybrid screen of a peptide library resulted in the discovery and characterization of PELP1 inhibitory peptides leading to a small-molecule first-in-class PELP1 inhibitor, providing potential therapeutic opportunities to treat therapy-resistant, advanced ER^+ breast cancer.

Altwegg KA, Viswanadhapalli S, Mann M, Chakravarty D, Krishnan S, Liu Z, et al. A first-in-class inhibitor of ER coregulator PELP1 targets ER+ breast cancer. Cancer Research; Published online August 11, 2022; doi: 10.1158/0008-5472.CAN-22-0698.

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.