Cancer Research
Breaking Advances
Highlights from Recent Cancer Literature
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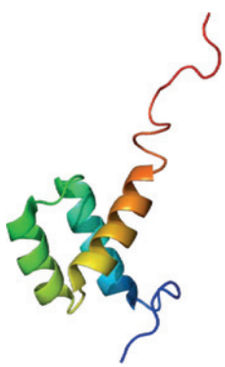
Pan-Cancer Analysis Demonstrates a Cost to Diversity

Andor and colleagues investigated intratumor heterogeneity (ITH) across 12 cancer types. The total number of clones within a tumor and the fraction of the tumor metagenome affected by copy number variation (CNV) were estimated based on somatic single-nucleotide variants and CNVs across 1,165 primary tumor samples. ITH was common with an average of four clones detected per tumor. Fewer than 20% of tumors contained a single clone. Clones with specific mutated driver genes tended to have a similar characteristic size across tumor types. More than two but no more than five clones were associated with poor prognosis across cancer types. Furthermore, using CNV to indicate genomic instability, CNV abundance between 50–75% was associated with poor survival in 11 of 12 tumors types. Thus, diverse cancers show a similar optimal degree of genomic instability. *(Image courtesy of Wikimedia Commons.)*

Andor N, Graham TA, Jansen M, Xia LC, Aktipis CA, Petritsch C, et al. Pan-cancer analysis of the extent and consequences of intratumor heterogeneity. Nat Med 2015 Nov 30. doi: 10.1038/nm.3984. [Epub ahead of print].

HOXA5 Inhibits WNT Signaling in CRC



Ordóñez-Morán and colleagues identified the homeobox transcription factor *Hoxa5* as highly expressed in differentiated cells of intestinal villi relative to WNT-dependent stem cells of the crypt. *Hoxa5* affected expression of WNT target gene *Myc*. Increased expression of *HOXA5* in organoids affected expression of the WNT target gene *Myc*, resulting in decreased $LGR5^{+}$ stem cells/self-renewal and increased differentiation, phenocopying β-catenin (*CTNNB1*) gene deletion. Increased expression of *HOXA5* in patients with colorectal cancer (CRC) enriched for relapse-free survival. While parental CRC cells initiated tumors and metastases in mice, those expressing *HOXA5* showed reduced tumor growth and metastases. Further, *HOXA5* expression in CRC could be reactivated by retinols, reducing the abundance of cancer stem cells and attenuating progression. Thus, retinoid treatment represents a potential new therapeutic agent to treat CRC. *(Image courtesy of Wikimedia Commons.)*

Ordóñez-Morán P, Dafflon C, Imajo M, Nishida E, Huelsken J. HOXA5 counteracts stem cell traits by inhibiting Wnt signaling in colorectal cancer. Cancer Cell 2015;28:815–29.

To Metastasize or Not to Metastasize: EMT Is in Question

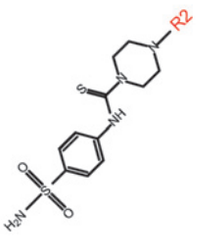
Independent groups using genetically engineered mouse models (GEMM) of breast or pancreatic adenocarcinoma (PDA) report that epithelial-mesenchymal transition (EMT) intermediates *Twist1*, *Snai1*, and *miR-200* were required neither for tumor development nor for metastasis. Using complimentary *in vitro* tumor spheroid assays, *in vivo* experimental metastasis assays, and cell lineage tracing, both groups suggested that PDA and breast cancer cells with epithelial phenotypes were still competent for metastasis. Another concordant finding was that EMT conferred chemoresistance to gemcitabine or cyclophosphamide. EMT-dependent chemoresistance in these GEMMs resulted from suppression of cancer cell proliferation and regulation of chemotherapy transporters and metabolizing gene products. These provocative *in vivo* findings suggest caution in applying anti-EMT therapeutics to prevent metastases, although such agents may have roles in therapy resistance. *(Image courtesy of Wikimedia Commons.)*

Zheng X, Carstens JL, Kim J, Scheible M, Kaye J, Sugimoto H, et al. Epithelial-to-mesenchymal transition is dispensable for metastasis but induces chemoresistance in pancreatic cancer. Nature 2015; 527:525–30.

Fischer KR, Durrans A, Lee S, Sheng J, Li F, Wong ST, et al. Epithelial-to-mesenchymal transition is not required for lung metastasis but contributes to chemoresistance. Nature 2015;527:472–6.

Breaking Advances

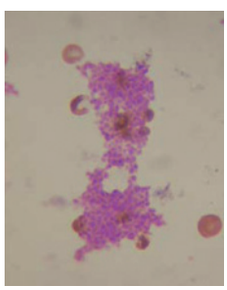
LF3 Has Anticancer Properties



The Wnt/β-catenin signaling contributes to initiation and progression of cancer, and is an attractive target for therapy. Using high-throughput screening, Fang and colleagues assessed small molecules that could disrupt a key step: interaction of β-catenin with the transcription factor TCF4. The authors identified LF3, a 4-thioureido-benzenesulfonamide derivative, as a robust inhibitor, with a core structure essential for activity. LF3 blocked Wnt/β-catenin signaling in cells with high endogenous WNT activity and also suppressed motility, cell cycle progression, and expression of WNT target genes. LF3 did not cause cell death or interfere with cadherin-mediated cell-cell adhesion. Of importance, LF3 could block the self-renewal capacity of cancer stem cells and reduced tumor growth while inducing differentiation *in vivo*. Thus, LF3 is an inhibitor of canonical WNT signaling resulting in anticancer activity. *(Image from cited article courtesy of publisher.)*

Fang L, Zhu Q, Neuenschwander M, Specker E, Wulf-Goldenberg A, Weis WI, et al. A small-molecule antagonist of the β-catenin/TCF4 interaction blocks the self-renewal of cancer stem cells and suppresses tumorigenesis. Cancer Research; Published OnlineFirst December 8, 2015; doi: 10.1158/0008-5472.CAN-15-1519.

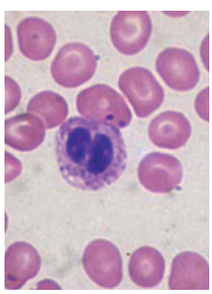
Diagnosing Cancer from Platelet RNA



Noninvasive detection and classification of solid tumors from blood samples, "liquid biopsies," have focused largely on isolating circulating tumor cells and fragments of DNA shed from primary tumors. Best and colleagues profiled platelet RNA from patients with both early ($n = 39$) and late stage ($n = 189$) lung, gastrointestinal, brain, and breast cancer, comparing these to platelet RNA from healthy individuals ($n = 55$). A single drop of blood showed differences in the platelet RNA profiles of cancer-bearing individuals relative to healthy individuals that in cross validation predicted presence of disease with 96% accuracy. Furthermore, specific tumor types were also determined with accuracy from platelet-derived RNAs with further delineation of KRAS and EGFR mutant tumors. Thus, if validated prospectively, platelet-derived RNAs show tremendous potential as predictive biomarkers. *(Image courtesy of Wikimedia Commons.)*

Best MG, Sol N, Kooi I, Tannous J, Westerman BA, Rustenburg F, et al. RNA-Seq of tumor-educated platelets enables blood-based pan-cancer, multiclass, and molecular pathway cancer diagnostics. Cancer Cell 2015;28:666–76.

Neutrophils Drive Breast Cancer



Work from Wculek and Malanchi suggests that neutrophils and neutrophil-secreted leukotrienes facilitate a permissive environment for metastatic breast cancer lung colonization. Using antibody depletion, the group demonstrated that neutrophils were required for initiation of lung metastases in MMTV-PyMT breast cancers. Neutrophils enriched the population of cancer cells at the premetastatic niche. Leukotrienes secreted by neutrophils were necessary for breast cancer lung metastasis as shown by conditioned media and direct leukotriene treatment experiments *in vitro* and later *in vivo* in both immune competent and deficient mouse models. Genetic or small molecule inhibition of the leukotriene synthesis enzyme ALOX5 greatly attenuated metastatic breast cancer colonization. This work shows that inflammatory cell-induced secretion of leukotrienes at the premetastatic niche enriches for tumorigenic cancer cells to colonize and form lung metastases. *(Image by Ed Uthman courtesy of Wikimedia Commons.)*

Wculek SK, Malanchi I. Neutrophils support lung colonization of metastasis-initiating breast cancer cells. Nature 2015;528:413–7.

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.

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Cancer Res 2016;76:507-508.