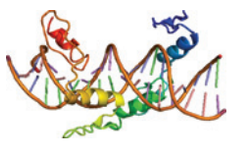
Cancer Research
Breaking Insights
Highlights from Recent Cancer Literature
AACR American Association for Cancer Research

CTCF Is Not Alone

The CTCF DNA-binding protein insulates genes in topologically associated domains (TAD). Through genome-wide chromatin interaction analyses, Weintraub and colleagues (1) show that the ubiquitously expressed zinc finger transcription factor YY1 binds to active enhancers and promoter-proximal elements in functional loops. Similar to CTCF, YYI is capable of dimerization and looping DNA. Perturbation of YY1 binding sites or degradation of YY1 disrupted enhancer-promoter interactions, looping, and gene expression.



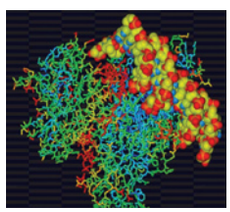
Expert Commentary: This and a prior report by Beagan and colleagues (2) identified YY1 as a mediator of loop interactions between developmentally regulated enhancers and promoters. YYI-mediated interactions also were nested within TADs, arising during transition from pluripotent to neural progenitor cells, suggesting reorganization of these smaller loops during development. *(Image courtesy of Wikimedia Commons.)*

1. Weintraub AS, Li CH, Zamudio AV, Sigova AA, Hannett NM, Day DS, et al. YY1 is a structural regulator of enhancer-promoter loops. Cell 2017:171:1573–88.

2. Beagan JA, Duong MT, Titus KR, Zhou L, Cao Z, Ma J, et al. YY1 and CTCF orchestrate a 3D chromatin looping switch during early neural lineage commitment. Genome Res 2017;27:1139–52.

Mechanical Cues Regulate Mutant p53 Stability

Tumor-associated p53 missense mutants accumulate due to increased stability driven by transformation. Tumors display remarkable spatial heterogeneity of p53 levels, indicating that the local microenvironment regulates p53 stabilization. Ingallina and colleagues found that statins destabilized mutant p53 in breast cancer cells. Mechanistically, statins inhibited geranylgeranylation and RhoA activity, reducing actin polymerization and actomyosin contractility. RhoA silencing reduced mutant p53 levels in cell lines, suggesting a link between cytoskeletal mechanosensing and p53 stability. Accordingly, culturing mutant p53 knockin cells on soft fibronectin destabilized and on stiff fibronectin stabilized p53 mutants. Thus, mechanical inputs in tissue stabilize p53 in a RhoA-dependent manner. Targeting this pathway interferes with mutant p53 stabilization restraining malignancy.



Expert Commentary: Demonstration of mechanosensitive stabilization of p53 provides a new layer of mutant p53 regulation and links extracellular matrix stiffening to oncogenic properties of p53 gain-of-function mutations. *(Image courtesy of Wikimedia Commons.)*

Ingallina E, Sorrentino G, Bertolio R, Lisek K, Zannini A, Azzolin L, et al. Mechanical cues control mutant p53 stability through a mevalonate-RhoA axis. Nat Cell Biol 2018;20:28–35.

Optimizing Cancer Drug Combination Therapies

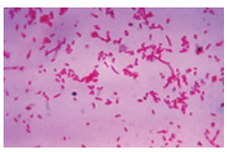
Significant effort has gone into identifying combinations of cancer drugs that act additively or synergistically, with the hope of improving the outcome of cancer patients. Analyzing combination and monotherapy-treated cohorts of patient-derived xenografts and clinical trial data, along with various mathematical modeling, Palmer and colleagues argue that the vast majority of drug combinations tested in clinical trials do not improve patient outcomes via drug addition or synergy. Rather, they suggest that the bulk of cancer drug interactions identified *in vitro* actually work in clinical trials by independently targeting distinct subsets of cancer patients and that the reasons for the lack of such synergy is the high intertumor variability found in cohorts of cancer patients.

Expert Commentary: This work suggests ways to optimize the clinical testing of cancer drug combinations, which does not depend on cooperation *in vitro*. *(Image courtesy of Wikimedia Commons.)*

Palmer AC, Sorger PK. Combination cancer therapy can confer benefit via patient-to-patient variability without drug additivity or synergy. Cell 2017;171:1678–91.

Breaking Insights

Microbiome Persistence in Colorectal Cancer Metastases

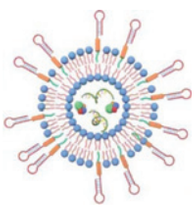


The importance of the tumor microbiome in promoting carcinogenesis has been well established for multiple tumor types, including colorectal cancer, however, its role in metastasis is less well understood. Bullman and colleagues demonstrate that *Fusobacterium* as well as its associated microbiome comigrate with colorectal cancer cells to distant metastases, as they are present at these sites and were almost identical genetically to the primary site microbiome despite temporal and spatial separation. *Fusobacterium*-positive tumors were also associated with a worse outcome in right-sided tumors. Remarkedly, *Fusobacterium* was maintained across multiple passages of patient-derived xenografts (PDX), and antibiotic treatment of PDX-bearing animals decreased tumor growth.

Expert Commentary: These studies not only confirm that the cancer microbiome is maintained during metastases, but suggest antibiotics as a novel therapy for almost half of the colorectal cancers that are *Fusobacterium* positive. *(Image courtesy of Wikimedia Commons.)*

Bullman S, Pedamallu CS, Sicinska E, Clancy TE, Zhang X, Cai D, et al. Analysis of Fusobacterium persistence and antibiotic response in colorectal cancer. Science 2017;358:1443–8.

Aptamer-Conjugated Extracellular Nanovesicles for Drug Delivery

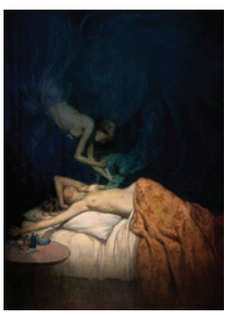


Extracellular nanovesicles (ENV) can deliver therapeutic cargos. Epithelial cancer cell lines used as donor cells for harvesting ENVs have immunogenicity and biosafety concerns that limit *in vivo* application. Wan and colleagues developed ENVs by anchoring a nucleolin-targeting aptamer AS1411 onto mouse dendritic cell membranes. Cells were then manually extruded through microconstrictions to obtain exosome-mimetic ENVs and subsequently loaded with paclitaxel. This novel ENV effectively inhibited cancer both *in vitro* and *in vivo*.

Expert Commentary: This study investigated the biodistribution of ENVs and whether paclitaxel can be more effectively delivered both *in vitro* and *in vivo*. The authors demonstrated that mechanical extrusion of $\sim 10^7$ cells grafted with lipidated ligands can generate cancer cell-targeting ENVs and can be prepared in $\sim$1 hour. This rapid and economic approach along with enhanced *in vivo* therapeutic efficacy and low systemic toxicity improves potential for clinical translation. *(Image from cited article courtesy of the publisher.)*

Wan Y, Wang L, Zhu C, Zheng Q, Wang G, Tong J, et al. Aptamer-conjugated extracellular nanovesicles for targeted drug delivery. Cancer Res 2018;78:798–808.

Live Biobank for Breast Cancer Research



Breast cancer manifests as numerous subtypes with distinct biological features and treatment options. As pioneers of epithelial organoids, the Clevers' laboratory has now established efficient protocols for establishing breast cancer organoid cultures. They bring forward an impressive live-biobank collection of nearly 100 well-characterized breast cancer organoids with tremendous potential for research and drug discovery. The addition of mitogen neuregulin-1 alongside some additional modifications of the existing organoid protocol enabled efficient generation of breast cancer organoids as well as their long-term expansion for >20 passages. Importantly, organoids recapitulate histological and genetic features of original tumors. Proof-of-concept experiments suggest that breast cancer organoids are compatible with CRISPR/CAS9 gene editing and enable high-throughput drug screening, potentially aiding personalized therapy.

Expert Commentary: Such clinically representative breast cancer organoids will dramatically improve the biological relevance of research models in breast cancer research and improve the ability of scientists to investigate fully the heterogeneous aspects and subtype-specific responses of this disease. *(Image courtesy of Wikimedia Commons.)*

Sachs N, de Ligt J, Kopper O, Gogola E, Bounova G, Weeber F, et al. A living biobank of breast cancer organoids captures disease heterogeneity. Cell; Published online December 7, 2017; doi: 10.1016/j.cell.2017.11.010.

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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Cancer Res 2018;78:585-586.