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CANCER RESEARCH

BREAKING INSIGHTS

Highlights from Recent Cancer Literature

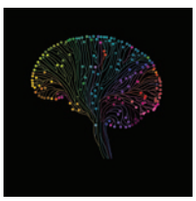
YAP Is a Critical Mediator of Tumor Dormancy after Targeted Therapy

Most EGFR-mutated non-small cell lung cancers are not completely eradicated in response to treatment with EGFR inhibitors, allowing for the eventual development of acquired resistance and cure prevention. Kurppa and colleagues demonstrate that YAP-dependent therapy-induced tumor dormancy plays a key role in subsequent resistance. During dual EGFR and MEK blockade, YAP was required for suppression of apoptosis, which allowed for a drug-tolerant dormant state. YAP suppressed apoptosis through repression of the proapoptotic gene BMF in a TEAD/SLUG-dependent manner. Genetic and pharmacologic inhibition of either YAP or TEAD prevented tumor dormancy *in vitro* and *in vivo*.

Expert Commentary: This study suggests that targeting the YAP/TEAD pathway could prevent tumor dormancy and subsequent acquired resistance in *EGFR*-mutant non-small cell lung cancer. *(Image by Scot Nelson courtesy of Wikimedia Commons.)*

Kurppa KJ, Liu Y, To C, Zhang T, Fan M, Vajdi A, et al. Treatment-induced tumor dormancy through YAP-mediated transcriptional reprogramming of the apoptotic pathway. Cancer Cell 2020;37:104-22.e12.

Adhesive Networks Control Diffuse Infiltration in Glioma



The localized invasion of glioma cells represents a major clinical problem, with no effective treatments. Gritsenko and colleagues identified an adhesion network, orchestrated by the adherens junction regulator p120-catenin, that controls the collective infiltration of glioma cells into the brain parenchyma. In orthotopic mouse models, p120-catenin–dependent cell-cell networks were required for diffuse interstitial and perivascular invasion of human glioma cells. Reduced expression of p120-catenin led to downregulation of genes linked to pathways required for neuronal development and synaptic transmission.

Expert Commentary: The further identification of a p120-catenin gene signature that is associated with survival of glioma patients suggests that targeting the adherens junction may have therapeutic applicability. Understanding the pathways involved will be critical moving forward.

Gritsenko PG, Atlasy N, Dieteren CEJ, Navis AC, Venhuizen JH, Veelken C, et al. p120-catenin-dependent collective brain infiltration by glioma cell networks. Nat Cell Biol 2020;22:97-107.

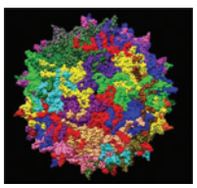
Extrachromosomal DNA in Neuroblastoma

Analyzing whole genome sequencing data from 93 primary neuroblastoma tumors, Koche and colleagues detected circular DNAs comprised mainly of large copy number-amplified extrachromosomal DNAs (ecDNA) that included *MYCN* and smaller extrachromosomal circular DNAs (eccDNA). Characterization using Circle sequencing revealed that the structure of circular DNA varied considerably among tumors. Both types were of monoallelic origin and were enriched in genic regions. *MYCN*-amplified neuroblastomas with ecDNAs contained entire genes, while eccDNAs contained fractions of genes. The authors concluded that ecDNAs contributed to genomic amplification and were exclusively derived from the amplified allele. Allele-specific RNA expression analysis suggested that DNA circularization could drive increased gene expression only with concomitant amplification of the ecDNA, suggesting that most ecDNAs have functions beyond oncogene amplification. Indeed, ecDNAs underwent chromosomal integration, resulting in aberrant gene expression.

Expert Commentary: ecDNA-mediated genomic rearrangements may contribute to the heterogeneity of cancers to confer tumor-specific dependencies. It will be interesting to determine how these structural rearrangements influence the epigenetic landscape and chromatin interactions to drive tumorigenesis.

Koche RP, Rodriguez-Fos E, Helmsauer K, Burkert M, MacArthur IC, Maag J, et al. Extrachromosomal circular DNA drives oncogenic genome remodeling in neuroblastoma. Nat Genet 2020;52:29-34.

Heating Up Tumor Immunogenicity with CRISPR



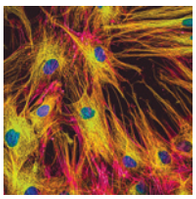
Many potential neoantigens are not expressed, or underexpressed, in tumor cells. Wang and colleagues used CRISPR-directed gene activation (CRISPRa) to increase the expression of neoantigens in tumors and to enhance antitumor immune responses. Whole genome-targeted CRISPRa led to near complete rejection of a transplanted triple-negative breast cancer cell line that was dependent on the presence of T cells. Next, they converted this CRISPRa-transduced tumor line into a vaccine that could block the development of the parental (nontransduced) tumor line. An adeno-associated virus (AAV)–based targeting strategy to deliver CRISPRa to tumor cells in living animals slowed and even eliminated tumors that were directly injected with AAV. The enhanced immune response acted systemically, also blocking growth of distant tumors not directly injected with AAV. Finally, they designed the CRISPRa to target only tumor-specific mutated genes in their tumor line and demonstrated superior control of tumor growth.

Expert Commentary: AAV-based CRISPR activation of tumor-specific neoantigens boosts CD8 T-cell responses within tumors and can control tumor development. *(Image courtesy of Wikimedia Commons.)*

Wang G, Chow RD, Bai Z, Zhu L, Errami Y, Dai X, et al. Multiplexed activation of endogenous genes by CRISPRa elicits potent antitumor immunity. Nat Immunol 2019;20:1494–1505.

BREAKING INSIGHTS

Cancer-Associated Fibroblast Heterogeneity Governs Metastatic Spread

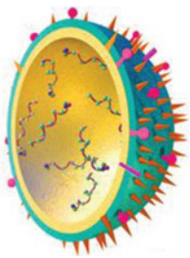


The recognized importance of cancer-associated fibroblasts (CAF) in driving tumor progression and response to therapy is well established. More recently, distinct CAF subpopulations have been identified in different tumor types, including breast cancer. Analysis of breast primary tumors and matched axillary lymph nodes revealed two CAF subsets that were enriched within metastatic lymph nodes and were independent prognostic factors. These subsets were distinguished by differential expression of CAF markers and gene expression signatures. Functional analysis showed that they could promote tumor spread by distinct mechanisms through utilization of different signaling pathways.

Expert Commentary: The association of specific CAF subsets in lymph nodes with presence of distant metastases at diagnosis and survival highlights the potential importance of CAF subset analysis as a prognostic indicator.

Pelon F, Bourachot B, Kieffer Y, Magagna I, Mermet-Meillon F, Bonnet I, et al. Cancer-associated fibroblast heterogeneity in axillary lymph nodes drives metastases in breast cancer through complementary mechanisms. Nat Commun 2020;11:404. DOI: 10.1038/s41467-019-14134-w.

Flu Shots That Also Treat Cancer



Newman and colleagues show that vaccination with influenza directly into the tumor bed enhanced immune cell infiltration and anticancer immunity. Infecting the lungs of tumor-bearing mice with active influenza virus, they observed reductions in tumor burden. Furthermore, retrospective analysis revealed that lung cancer patients hospitalized with influenza showed better long-term survival. Next, the authors show that intratumoral injection of heat-inactivated influenza also reduced subcutaneous tumor growth. Tumors exhibited increased percentages of cross-presenting dendritic cells and $CD8^+$ T cells. Finally, they tested intratumoral injection of the seasonal flu vaccine, observing synergy with checkpoint blockade and protection from influenza infection. Interestingly, the adjuvant Adda-Vax blocked the effectiveness of the flu vaccine. This adjuvant, while equally increasing intratumoral dendritic cells, supported regulatory B cells that produced IL10 at the expense of the $CD8^+$ T-cell response.

Expert Commentary: Adjuvant-free seasonal influenza vaccine injected directly into tumors promotes tumor clearance while still providing effective immunity against the flu. *(Image courtesy of Wikimedia Commons.)*

Newman JH, Chessona CB, Herzoga NL, Bommareddya PK, Aspromonte SM, Pepe R, et al. Intratumoral injection of the seasonal flu shot converts immunologically cold tumors to hot and serves as an immunotherapy for cancer. Proc Natl Acad 2020;117:1119–28.

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.