Cancer Research
Breaking Advances
Highlights from Recent Cancer Literature

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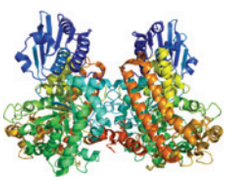
CDK5 Mediates Checkpoint Blockade In Medulloblastoma



Dorand and colleagues knocked down CDK5 in murine medulloblastoma cells, observing reduced tumor growth only in immunocompetent mice, traced to $CD4^+$ T-cell–dependent rejection of CDK5-deficient tumors. IFN-γ induces PD-L1 (CD274) and was highly expressed in CDK5-deficient tumors. *Cdk5* and *PD-L1* mRNA were coexpressed across a wide range of tumor types, with CDK5-deficient tumors showing reduced PD-L1 upon IFN-γ stimulation. IFN-γ stimulation in CDK5-deficient cells led to an increase in the PD-L1 transcriptional repressors IRF2 and IRF2BP2. Finally, intracranial injection of CDK5-deficient medulloblastoma resulted in increased $PD\text{-}L1^+$ immune cells, suggesting that depletion of CDK5 globally activated immunity in response to IFN-γ stimulation. This study suggests that CDK5 modulates immune checkpoints, with depletion of CDK5 enhancing immune checkpoint blockade through downregulation of PD-L1 in the tumor. *(Image courtesy of Wikimedia Commons.)*

Dorand RD, Nthale J, Myers JT, Barkauskas DS, Avril S, Chirieleison SM, et al. Cdk5 disruption attenuates tumor PD-L1 expression and promotes antitumor immunity. Science 2016;353:399–403.

A Landscape of Pharmacogenomic Interactions in Cancer

Analyzing 11,289 primary tumors, Iorio and colleagues identified 1,273 unique cancer functional events (CFE) and mapped these onto ∼1,000 cancer cell lines. The number of CFEs per cell line increased for CFEs occurring in over 5% of primary tumors or when CFEs were compared within the same cancer subtype. They next examined the ability of 265 small-molecule inhibitors to reduce viability of these cancer lines. They identified 688 genomic predictors of sensitivity by comparing the IC_{50} of each drug to cell-type–specific CFEs. Significant drug-CFE pairs were distributed across all lines or in specific cancer subtypes in a mutually exclusive manner. A number of drug-CFE interacting pairs had been described previously, validating their findings. The reliability of these predictions was improved further by associating drug sensitivity with CFE pairs and by logic-based modeling. *(Image courtesy of Wikimedia Commons.)*

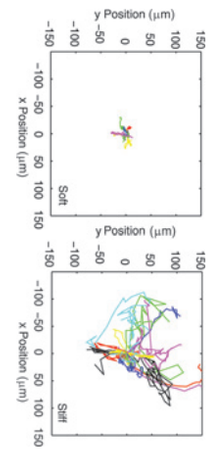
Iorio F, Knijnenburg TA, Vis DJ, Bignell GR, Menden MP, Schubert M, et al. A landscape of pharmacogenomics interactions in Cancer. Cell 2016;166:740–54.

Paradoxical Healing Powers

BRAF inhibitors drive paradoxical activation of the mitogen-activated protein kinase (MAPK) pathway in BRAF wild-type cells, resulting in hyperproliferative skin conditions in patients. Escuin-Ordinas and colleagues investigated the use of topical BRAF inhibitors to promote wound healing in BRAF wild-type skin. In response to the BRAF inhibitor vemurafenib, human epidermal keratinocytes treated with vemurafenib showed MAPK activation, with increased proliferation motility, which was sensitive to the MEK inhibitor trametinib. In two cutaneous wound-healing murine models, vemurafenib activated MAPK, enhanced wound healing, and restored tensile strength by altering the kinetics and the composition of the wound. Vemurafenib-treated wounds closed sooner, and had a more pronounced immune cell infiltrate and enhanced angiogenesis. Importantly, topically applied vemurafenib did not induce epidermal tumors in a two-stage skin carcinogenesis model. *(Image courtesy of Wikimedia Commons.)*

Escuin-Ordinas H, Li S, Xie MW, Sun L, Hugo W, Huang RR, et al. Cutaneous wound healing through paradoxical MAPK activation by BRAF inhibitors. Nat Commun 2016;7:12348. doi: 10.1038/ncomms12348.

Breaking Advances



Breast Cancer, Tissue Stiffness, and Oxygen Tension

Pang and colleagues identified integrin-linked kinase (ILK) as promoting development of breast cancer stem-like cells (CSC) in response to tissue mechanics and oxygen tension. Silencing the expression of ILK in stiff and hypoxic microenvironments inhibited CSC marker expression and behavior, while overexpressing ILK in softer or normoxic microenvironments stimulated CSC development. Stiff microenvironments promoted tumor formation and metastasis *in vivo*. However, depleting ILK inhibited the tumorigenic and metastatic potential of invasive breast cancer cells. ILK was regulated by PI3K/Akt in stiff and hypoxic microenvironments. Analyzing human breast cancer specimens, the authors found that ILK and the CSC marker CD44 colocalized in cancer cells in tumor regions predicted to be stiff. Thus, ILK represents a key mechanotransducer that modulates breast CSC development in response to tissue stiffness and hypoxic microenvironments. *(Image from cited article courtesy of the publisher.)*

Pang MF, Siedlik MJ, Han S, Stallings-Mann M, Radisky DC, Nelson CM. Tissue stiffness and hypoxia modulate the integrin-linked kinase ILK to control breast cancer stem-like cells. Cancer Res 2016;76:5277–87.

Defects Identified in Acquired Resistance to Anti-PD-1 Therapy

Zaretsky and colleagues assessed effects of anti-PD-1 checkpoint-blockade in paired baseline and relapse tumors from four patients with melanoma who progressed after initial response. Intratumoral CD8 T-cell infiltration persisted in relapsed tumor margins, suggesting absent cytotoxic activity. Whole-exome sequencing (WES) demonstrated new homozygous loss-of-function mutations in kinases JAK1 and JAK2 in two of four relapsed tumors. Functional studies showed complete loss of JAK2 protein, resulting in lack of response to interferon γ, suggesting a survival advantage in the context of anti-PD1 therapy. WES also identified a frameshift deletion in the β2-microglobulin component of MHC class 1 in patient 3, leading to loss of CD8 T-cell recognition. These data provide insights into the genetic mechanisms of acquired resistance to PD1 blockade therapy and suggest that resistance to interferon γ contributes to immune resistance. (*Image courtesy of Wikimedia Commons.)*

Zaretsky JM, Garcia-Diaz A, Shin DS Escuin-Ordinas H, Hugo W, Hu-Lieskovan S, et al. Mutations associated with acquired resistance to PD-1 blockade in melanoma. N Engl J Med. July 13, 2016. doi: 10.1056/NEJMoa1604958.

Mechanosensitive Regulation of Cancer Cell Proliferation

Kaukonen and colleagues cultured carcinoma cells on cell-derived matrices (CDM) generated from normal or cancer-associated fibroblasts (CAF) from the same patients, observing reduced growth in normal CDMs. The histone demethylase JMJD1A (KDM3A) was downregulated in response to normal CDMs, enhancing proliferation of cancer cells cultured on CAF CDMs and promoting tumor growth *in vivo*. On soft hydrogels or CDMs generated from normal fibroblasts, JMJD1A was predominately cytoplasmic. Conversely, increasing matrix stiffness resulted in JMJD1A nuclear shuttling in a pattern resembling localization of known mechanosensitive transcription factors YAP1/TAZ. In clinical breast cancer samples, JMJD1A expression correlated with both activated α-SMA-positive tumor stroma and YAP1/TAZ expression, and JMJD1A was demonstrated to activate YAP/TAZ transcription. Altogether, the authors identify downregulation of JMJD1A as a novel mechanism, whereby normal healthy stroma prevents epigenetic outgrowth of cancer. *(Image courtesy of Wikimedia Commons.)*

Kaukonen R, Mai A, Georgiadou M, Saari M, De Franceschi N, Betz T, et al. Normal stroma suppresses cancer cell proliferation via mechanosensitive regulation of JMJD1a-mediated transcription. Nat Commun 2016;7:12237. doi: 10.1038/ncomms12237.

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.