Cancer Research
Breaking Insights
Highlights from Recent Cancer Literature
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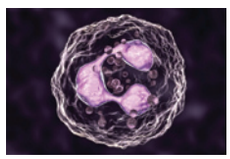
p53-Deficiency Drives Neutrophilic Inflammation and Metastasis

Systemic neutrophilic inflammation is an established driver of metastasis, however, the tumor cell-intrinsic factors that are responsible for this are poorly understood. Wellenstein and colleagues utilized a genetically diverse collection of breast cancer mouse models to elucidate whether distinct genetic subtypes influenced the levels of systemic neutrophilic inflammation. They found that p53-deficiency was associated with increased systemic and tumor neutrophilia and metastasis. This was a p53-dependent process mediated through secretion of WNT ligands, leading to IL1β production in tumor-associated macrophages (TAM). Inhibition of WNT ligand secretion decreased IL1β production in TAMs and tumor metastases.

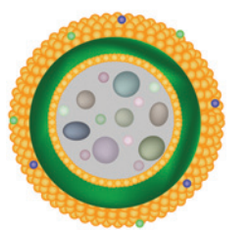


Expert Commentary: This study suggests that inhibition of WNT secretion may be an effective therapeutic strategy in p53-deficient breast cancer to prevent metastases.

Wellenstein MD, Coffelt SB, Duits DEM, van Miltenburg MH, Slagter M, de Rink I, et al. Loss of p53 triggers WNT-dependent systemic inflammation to drive breast cancer metastasis. Nature 2019;572:538–42.

MYC Represses Lysosomal Biogenesis and Autophagy

Lysosomes control the breakdown, processing, or recycling of cell components by biosynthetic, endocytic, and phagocytic pathways. Importantly, these programs are connected to autophagy, because autophagosomes fuse with lysosomes to initiate degradation. Both autophagy and lysosomal trafficking sense nutrients and modulate downstream signaling. This network is regulated transcriptionally by members of the microphthalmia-associated family of transcription factors (MiT/TFE). Annunziata and colleagues identified an epigenetic rheostat controlled by the combined action of c-MYC and histone deacetylases, which together inhibited lysosomal and autophagic biogenesis. This occurred by simultaneously blocking expression of the MiT/TFE and FOXH1 transcription factors, and lysosomal and autophagy genes. The authors further showed that MYC directly downregulated lysosomal and autophagic processes in both pluripotent stem cells and in cancer, potentially contributing to MYC's tumorigenic capacity.

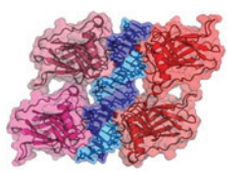


Expert Commentary: One approach for therapeutic intervention of MYC-mediated tumorigenicity could be to activate lysosomal and autophagy processes.

Annunziata I, van de Vlekkert D, Wolf E, Finkelstein D, Neale G, Machado E, et al. MYC competes with MiT/TFE in regulating lysosomal biogenesis and autophagy through an epigenetic rheostat. Nat Commun 2019;10:3623. doi: 10.1038/s41467-019-11568-0.

Dominant-Negative Effects of TP53 Missense Mutations

TP53 is the most commonly mutated gene in human cancer, with most cancers harboring missense mutations in TP53′s DNA-binding domain. It has been widely suggested that such missense mutations are neomorphic, driving a novel gain of function. Using genomic engineering, Boettcher and colleagues generated cells in two distinct acute myeloid leukemia (AML) cell lines, which were $TP53^{+/+}$, $TP53^{+/-(null)}$, $TP53^{-/-}$, *or* $TP53^{+/missense}$, and analyzed functional characteristics in the absence or presence of a chemotherapeutic agent. Using a host of functional and transcriptome analyses, *in vitro* and *in vivo*, they showed that cells harboring $TP53^{+/missense}$ mutations behaved similarly to $TP53^{-/-}$ cells but distinct to $TP53^{+/-}$ cells. Consistent with their experimental results, they also showed that AML patients harboring missense mutations showed similar outcomes with patients harboring large TP53 truncations—inconsistent with such missense mutants harboring neomorphic functions.

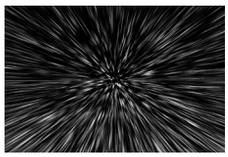


Expert Commentary: TP53 missense mutations function in a dominant-negative fashion to inactivate the WT copy of the TP53 gene. (*Image by Richard Wheeler courtesy of Wikimedia Commons*).

Boettcher S, Miller PG, Sharma R, McConkey M, Leventhal M, Krivtsov AV, et al. A dominant-negative effect drives selection of TP53 missense mutations in myeloid malignancies. Science 2019;365:599-604.

Breaking Insights

RNA Splicing and Arginine Methylation

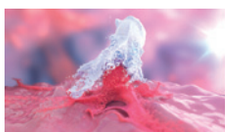


Alterations in RNA splicing have emerged as a potential cancer therapy. Numerous groups are attempting to drug various splicing factors (SF) thought to regulate these processes, especially in tumor cells harboring mutations in SFs. Protein arginine methyltransferases (PRMT) were previously implicated in SF regulation. Fong and colleagues showed that leukemia cells are sensitive to PRMT inhibitors *in vitro* and *in vivo*. Furthermore, leukemia cells harboring mutations in SFs exhibited increased sensitivity to PRMT inhibitors. These effects were synergistic using PRMT1 and PRMT5 inhibitors in combination. Arginine methylation of different subsets of proteins was altered after treatment with PRMT1 or PRMT5 inhibitors, however, both inhibitors preferentially targeted RNA-binding proteins. They concluded that PRMT inhibitors preferentially target cancer cells harboring mutations in SFs by altering arginine methylation.

Expert Commentary: Cancer patients harboring mutations in SFs are likely to get the most benefit from the PRMT inhibitors currently being evaluated in the clinic, especially when they are used in combination.

Fong JY, Pignata L, Goy PA, Kawabata KC, Lee SC, Koh CM, et al. Targeting of RNA splicing catalysis through Inhibition of protein arginine methylation. Cancer Cell 2019;36:194-209.e9. doi: 10.1016/j.ccell.2019.07.003.

Cancers Say 'Don't Eat Me' in a New Way



Cancer evades the immune system by expressing regulatory checkpoint molecules and 'don't eat me' signals. Barkal and colleagues defined a new signaling axis, CD24-Siglec-10, that was utilized by cancers to diminish the capacity for immune cells to engulf tumor cells. They showed that many cancers, particularly ovarian and breast cancers, expressed very high levels of CD24, whereas tumor-infiltrating immune cells, particularly macrophages, expressed high levels of Siglec-10, which bound to CD24 and initiated an inhibitory signaling cascade in immune cells. Using assays both *in vitro* and *in vivo* with both mouse and human cancer cells, they demonstrated that blocking interactions between CD24 and Siglec-10 (by genetic deletion or antibody blockade) enhanced the phagocytosis of tumor cells by immune cells. Most importantly, blocking this axis improved immune control of cancer in mice.

Expert Commentary: A new 'don't eat me' checkpoint is defined that can be disrupted by antibody blockade and used for the immunotherapeutic treatment of cancer.

Barkal AA, Brewer RE, Markovic M, Kowarsky M, Barkal SA, Zaro BW, et al. CD24 signalling through macrophage Siglec-10 is a target for cancer immunotherapy. Nature 2019;572:392–6.

Precision Medicine Uncovers Resistance to NTRK Inhibition

Inhibition of neurotrophin receptor tyrosine kinase (NTRK) is effective across a range of cancers harboring NTRK fusions. However, resistance arises mostly through second mutations in NTRK. To identify NTRK independent mechanisms of resistance, Cocco and colleagues performed targeted sequencing of biopsies pre- and post-treatment. In three patients, mutations in BRAF, KRAS, and MET were identified. Cell-free DNA from an additional 5 patients identified mutations in MEK, KRAS, and ERBB2. Patient-derived xenografts (PDX) were generated from the secondary mutations in $BRAF^{V600E}$ and $KRAS^{G12A}$, with the $BRAF^{V600E}$ mutant tumor showing a durable response to combinatorial therapy and subsequently a robust response in the patient themselves.

Expert Commentary: This study highlights the importance of repeat biopsy post resistance to targeted agents and the power of generating PDX models of oncogene-addicted tumors to model bypass mechanisms to targeted monotherapies. Upfront combinatorial therapies have the potential to overcome bypass mechanisms arising with targeted monotherapies.

Cocco E, Schram AM, Kulick A, Misale S, Won HH, Yaeger R, et al. Resistance to TRK inhibition mediated by convergent MAPK pathway activation. Nature Medicine; Published online August 12, 2019; doi: 10.1038/s41591-019-0542-z.

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.