Cancer Research
Breaking Insights
Highlights from Recent Cancer Literature
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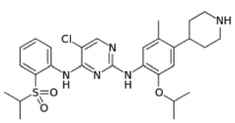
SHP2 Inhibition Restores Sensitivity to ALK Inhibition in NSCLC

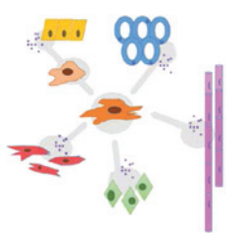


Treatment of non-small cell lung cancer (NSCLC) tumors with second-generation ALK inhibitors results in drug resistance after initial response. Half of resistant tumors harbor *ALK* mutations. Tumors without ALK mutations are not expected to respond to third-generation ALK inhibitors, which can overcome all clinically identified resistant *ALK* mutations. Dardaei and colleagues used an shRNA screen in ALK-inhibitor–resistant patient-derived cells to identify genes that promoted sensitivity to ALK inhibition. SHP2, a nonreceptor protein tyrosine phosphatase, was identified as a resistance-promoting protein, and treatment with SHP099, a small-molecule inhibitor of SHP2, in combination with the ALK inhibitor ceritinib reduced growth of resistant patient-derived cells *in vivo*.

Expert Commentary: This study suggests that combined ALK and SHP2 inhibition overcomes heterogenous *ALK*-independent mechanisms of acquired drug resistance in patients with NSCLC positive for *ALK* rearrangement. (*Image courtesy of Wikimedia Commons.*)

Dardaei L, Wang HQ, Singh M, Fordjour P, Shaw KX, Yoda S, et al. SHP2 inhibition restores sensititivity in ALK-rearranged non-small-cell lung cancer resistant to ALK inhibitors. Nature Medicine; Published online March 5, 2018; doi: 10.1038/nm.4497.

Targeting Specific Cancer-Associated Fibroblast Subtypes

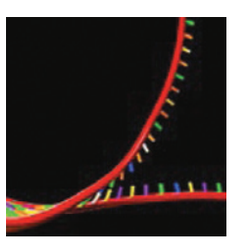


Cancer-associated fibroblasts (CAF) are important components of the tumor microenvironment; however, their role in tumor progression has been controversial, with reports of both pro- and antitumor functions. This reflects the heterogeneity within CAFs. Su and colleagues now identify a subset of CAFs characterized by expression of the cell surface markers CD10 and GPR77 that are associated with chemoresistance and poor survival in breast and lung cancer. The $CD10^{+}/GPR77^{+}$ CAFS provide a supportive environment for cancer stem cells and promote chemoresistance through the secretion of cytokines, including IL6 and IL8. Targeting these CAFS with antibodies against GPR77 effectively blocked tumor growth and restored chemosensitivity in mouse models.

Expert Commentary: These findings identify a subset of CAFs within the tumor microenvironment that support tumor progression and chemoresistance. Unraveling the underlying molecular mechanisms has revealed a potential novel therapeutic strategy whereby targeting cell surface proteins on CAFs can impact progression and response to treatment in both breast and lung cancer models. (*Image courtesy of Wikimedia Commons.*)

Su S, Chen J, Yao H, Liu J, Yu S, Lao L, et al. $CD10^{+}GPR77^{+}$ cancer-associated fibroblasts promote cancer formation and chemoresistance by sustaining cancer stemness. Cell 2018;172:842–56.

Oncogene-Induced Replication Stress and Transcription Conflicts



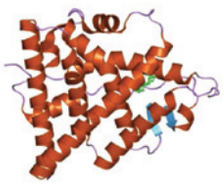
Oncogene-induced replication stress is proposed to produce genomic instability, but mechanisms remain elusive. By monitoring nascent DNA replication in the presence and absence of cyclin E and MYC, Macheret and Halazonetis confirmed that oncogene overexpression led to early S-phase entry. Importantly, early S-phase entry was accompanied by aberrant firing of novel replication origins within protein coding genes, prior to their transcription. Furthermore, the generation of intragenic origins led to fork collapse within highly transcribed genes. These data suggest replication-transcription conflicts as the underlying cause of fork collapse, with resulting DNA damage. Finally, formation of translocations, used as a marker of genomic instability, was enriched at sites of oncogene-induced origins of replication following induction of cyclin E.

Expert Commentary: The mechanism described herein provides novel insights into the function of oncogenes in creating replication-transcription conflicts through the generation of intragenic replication origins. Additionally, this report helps clarify how early S-phase entry results in replication stress.

Macheret M, Halazonetis TD. Intragenic origins due to short G1 phases underlie oncogene-induced DNA replication stress. Nature 2018;555:112–6.

Breaking Insights

Overcoming ER Mutant-Driven Endocrine Therapy Resistance

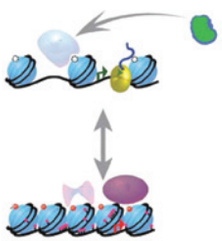


Mutations in the *estrogen receptor (ER)* α gene underlie hormone resistance in patients with metastatic breast cancer. Jeselsohn and colleagues test the hypothesis that cancer-associated ER mutants have neomorphic functions and do not simply act as constitutively active, ligand-independent ER proteins. They analyzed transcriptional networks, chromatin recruitment, and genetic interactions of a series of cell lines engineered to mimic a subset of clinically relevant ER mutants. As expected, a large number of ER mutant-driven signaling networks were similar to those driven by estrogen-activated wild-type ER. However, they also identified a series of allele-specific signaling networks, many of which were prometastatic. Using CRISPR-based genetic screens, they identified ER allele-specific dependencies, against which, they identified a small-molecule inhibitor that they validated *in vivo*.

Expert Commentary: This work identifies novel therapeutic strategies with which to treat patients with advanced ER-mutant breast cancer. (*Image courtesy of Wikimedia Commons.*)

Jeselsohn R, Bergholz JS, Pun M, Cornwell M, Liu W, Nardone A, et al. Allele-specific chromatin recruitment and therapeutic vulnerabilities of ESR1 activating mutations. Cancer Cell 2018;33:173–86.

Reactivation of Oncogene-Induced Senescence in Melanoma

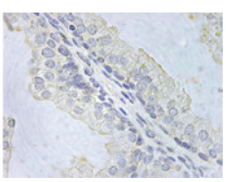


Bypass of oncogene-induced senescence (OIS) is required for RAS/BRAF-driven tumorigenesis. Yu and colleagues investigated whether H3K9 demethylases, which they demonstrated are overexpressed in melanoma, could overcome the OIS checkpoint and if targeting these enzymes would restore OIS. They found that overexpression of the H3K9 demethylases, LSD1 and JMJD2C, could prevent RAS-induced OIS, increase expression of E2F target genes, and allow transformation. Remarkably, loss of H3K9me3 after JMJD2C expression led senescent mouse embryonic fibroblasts to re-enter the cell cycle, suggesting senescence as a potentially reversible process. LSD1 or JMJD2C cooperated with BRAF to drive melanomagenesis. Conversely, treatment with LSD1 or JMJD2C inhibitors restored senescence and inhibited tumor growth.

Expert Commentary: These studies suggest that H3K9 demethylase inhibitors can restore senescence and inhibit growth of melanoma and potentially other tumor types. (*Image courtesy of Wikimedia Commons.*)

Yu Y, Schleich K, Yue B, Ji S, Lohneis P, Kemper K, et al. Targeting the senescence-overriding cooperative activity of structurally unrelated H3K9 demethylases in melanoma. Cancer Cell 2018;33:322–36.e8.

IL30 Drives Prostate Cancer Stem-like Cell Behavior



Prostate cancer stem-like cells (PCSLC) are mediators of treatment resistance, disease recurrence, and metastasis. Sorrentino and colleagues recently found that IL30 is expressed in prostate cancer by both cancer cells and cancer- or lymph node–infiltrating leukocytes. In this study they performed experiments to determine whether IL30 promotes prostate cancer progression by conditioning PCSLCs. IL30 was produced by PCSLCs in human and murine prostatic intraepithelial neoplasia and displayed significant autocrine and paracrine effects. PCSLC-derived IL30 supported PCSLC viability, self-renewal and tumorigenicity, and tumor immune evasion primarily via STAT1/STAT3 signaling. Moreover, IL30 promoted PCSLC dissemination to lymph nodes and bone marrow and these mechanisms were drastically obstructed by IL30 knockdown or knockout in PCSLCs.

Expert Commentary: These results denote IL30 as a key driver of PCSLC behavior and indicate that targeting IL30 signaling could be translated into an effective strategy to hinder prostate cancer progression or recurrence. (*Image from cited article courtesy of the publisher.*)

Sorrentino C, Ciummo SL, Cipollone G, Caputo S, Bellone M, Di Carlo E. Interleukin-30/IL-27p28 shapes prostate cancer stem-like cell behavior and is critical for tumor onset and metastasization. Cancer Research; Published online February 27, 2018; doi: 10.1158/0008-5472.CAN-17-3117.

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;78:1887-1888.