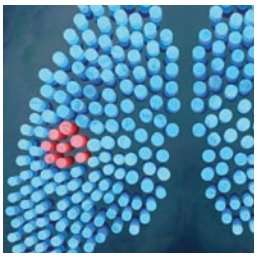
Dual Targeting of PD-1 and C5a Suppresses Lung Cancer Growth

- Inhibiting C5a reduces MDSC frequency and increases CD8$^+$ T-cell frequency to enhance anti–PD-1 efficacy.
- Targeting C5a may relieve MDSC-mediated immunosuppression to promote CD8$^+$ T-cell activation.
- Combined targeting of C5a and PD-1 may be effective against primary and metastatic lung tumors.

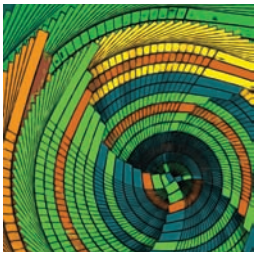


PD-1 blockade is approved to treat patients with metastatic non–small cell lung cancer. However, not all patients respond adequately to anti–PD-1 therapy, and it cannot overcome the effects of immunosuppressive myeloid-derived suppressor cells (MDSC) or regulatory T cells. Thus, combination immunotherapies may enhance the efficacy of PD-1 blockade. Activation of the complement system releases the active proteolytic fragment C5a, which promotes an immunosuppressive microenvironment to support lung cancer progression, prompting Ajona and colleagues to test PD-1 inhibition in combination with inhibition of C5a or its receptor C5aR1. In a mutant *Kras*-driven mouse model of lung adenocarcinoma, C5aR1 depletion reduced tumor size and extended survival. Similarly, C5a inhibition with an L-aptamer (AON-D21) that blocks the interaction with its receptors reduced tumor growth. Combined treatment with AON-D21 and anti–PD-1 suppressed the growth of syngeneic lung tumors more effectively than either therapy alone, resulting in complete tumor rejection in many cases. AON-D21 plus anti–PD-1 also reduced metastases and increased survival in a metastatic tumor model. Combined targeting of C5a and PD-1 increased the frequency of CD8$^+$ T cells, which were required for the antitumor response, and reduced the frequency of MDSCs. Anti–PD-1 therapy plus MDSC depletion had similar effects to anti–PD-1 plus AON-D21, suggesting that C5a inhibition may relieve MDSC-mediated immunosuppression. Moreover, AON-D21 in combination with anti–PD-1 was effective against established tumors and promoted CD8$^+$ T-cell activation. These findings support further investigation of combined immunotherapy targeting PD-1 and C5a in patients with lung cancer. ■

See article, p. 694.

Taselisib Is Safe and Has Antitumor Activity in *PIK3CA*-Mutant Tumors

- A phase I trial tested the PI3K inhibitor taselisib in patients with advanced solid tumors.
- Taselisib achieved partial responses in 36% of patients with *PIK3CA*-mutant tumors.
- Taselisib may be effective in *PIK3CA*-mutant tumors as a single-agent or combination therapy.



Activating mutations or amplifications in *PIK3CA*, which encodes the PI3K catalytic subunit p110α, can promote tumorigenesis and are prevalent in solid tumors. Taselisib, a potent PI3K inhibitor with greater activity against mutant PI3Kα isoforms than wild-type PI3Kα, blocks the ATP-binding pocket of the catalytic PI3K subunit to suppress PI3K signaling. Juric and colleagues evaluated the safety, tolerability, and activity of taselisib in a phase I dose-escalation study in patients with locally advanced or metastatic solid tumors. Treatment of mice with *PIK3CA*-mutant breast cancer xenografts with a range of doses of taselisib resulted in dose-dependent inhibition of tumor growth, and these findings were used to establish the human dose levels for the phase I trial. In total, 34 heavily pretreated patients were enrolled and treated with taselisib. Taselisib was well tolerated; 41% of patients developed adverse events of grade 3 or higher, but these events occurred only at doses higher than the selected dose for future studies. Taselisib achieved PI3K pathway inhibition, consistent with on-target effects. Of the 14 patients with known *PIK3CA*-mutant tumors, 5 (36%) achieved confirmed partial responses including 4 patients with breast cancer and 1 patient with non–small cell lung cancer, whereas no patient without *PIK3CA*-activating mutations responded. These findings suggest that single-agent taselisib is safe and has antitumor activity in patients with *PIK3CA*-mutant tumors, and further studies of taselisib are ongoing both as a single agent and in combination therapies. ■

See article, p. 704.

Downloaded from cancerdiscovery.aacrjournals.org on October 20, 2021. © 2017 American Association for Cancer Research.

High Oxidative Phosphorylation Promotes AML Chemoresistance

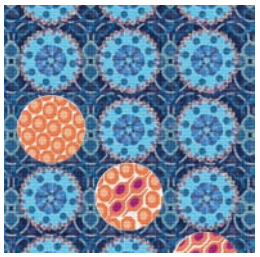
- AraC may induce chemoresistance via selection of high OXPHOS cells rather than leukemic stem cells.
- AraC treatment selected for a pre-existing population of resistance cells with high OXPHOS status.
- Therapeutic targeting of OXPHOS may potentially render AML cells more sensitive to chemotherapy.

The chemotherapeutic cytarabine (AraC) is often used to treat patients with acute myeloid leukemia (AML), but most patients eventually relapse. It has been suggested that a population of quiescent leukemic stem cells (LSC) are responsible for AraC resistance, but the molecular mechanisms underlying AML resistance have not been fully elucidated *in vivo*. Farge and colleagues used 25 naïve AML patient-derived xenografts (PDX) to evaluate the response to AraC. AraC treatment reduced AML disease burden *in vivo*, but unexpectedly reduced the number of LSCs as well as mature AML cells, suggesting that AraC resistance is not mediated by a refractory LSC population. Further, AraC treatment did not enrich for quiescent cells. Instead, AraC induced expression of genes involved in inflammation and stress responses in cells refractory to AraC, including genes involved in the response to reactive oxygen species (ROS). ROS levels were elevated in AraC-resistant cells, and mitochondria exhibited increased activity and mass, consistent with enhanced oxidative phosphorylation (OXPHOS). Indeed, AraC-resistant AML cells displayed high expression of OXPHOS genes compared with chemosensitive cells, and this high OXPHOS phenotype depended on mitochondrial oxidation of fatty acids. *In vivo*, cells with the high OXPHOS gene signature were detected before AraC treatment and enriched after AraC treatment. Resistant cells had increased mitochondrial respiration *in vitro* and *in vivo*, and inhibiting OXPHOS rendered resistant cells more sensitive to AraC. The finding that high OXPHOS activity is associated with chemoresistance in AML suggests that possibility for therapeutic targeting of mitochondrial metabolism to enhance chemosensitivity. ■

See article, p. 716.

Abiraterone Promotes Transdifferentiation to Induce Drug Resistance

- Abiraterone accelerates tumor growth in a subset of mice resembling human neuroendocrine CRPC.
- Abiraterone induces transdifferentiation of luminal prostate adenocarcinoma to neuroendocrine CRPC.
- Neuroendocrine transdifferentiation may promote abiraterone resistance in *PTEN*/*TP53*-mutant CRPC.



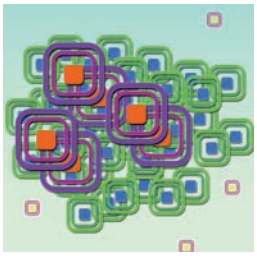
Castration-resistant prostate cancers (CRPC) often exhibit initial responses to therapies that target androgen receptor signaling or synthesis, such as abiraterone, but eventually aggressive resistant disease develops. These resistant tumors often exhibit features of small-cell carcinoma and neuroendocrine (NE) differentiation mixed with adenocarcinoma. This CRPC-NE histopathology is rare in localized prostate cancer, but often occurs in patients who fail to respond to androgen-deprivation therapy. Zou and colleagues evaluated the response to abiraterone in a mouse model of CRPC (NPp53) driven by loss of function of *Pten* and *Trp53*, which are frequently co-mutated in patients with CRPC, in the adult prostate epithelium. Abiraterone treatment failed to suppress CRPC tumor growth and even accelerated tumor growth in a subset of mice. In NPp53 tumors that displayed accelerated growth in response to abiraterone, genes expressed in human CRPC-NE were upregulated, including *Sox11*, a transcription factor previously implicated in neural differentiation. SOX11 depletion downregulated neuroendocrine markers, suggesting that abiraterone treatment–associated neuroendocrine differentiation may be mediated in part by SOX11. Neuroendocrine cells were rare in naïve NPp53 tumors, but became more abundant following castration or abiraterone treatment. *In vivo* lineage tracing showed that the neuroendocrine population arose via transdifferentiation of luminal adenocarcinoma cells. These findings reveal a mechanism by which abiraterone treatment can induce the progression from adenocarcinoma to CRPC-NE to promote drug resistance in CRPC. ■

See article, p. 736.

Downloaded from cancerdiscovery.aacrjournals.org on October 20, 2021. © 2017 American Association for Cancer Research.

The TKI Cabozantinib Provokes an Antitumor Innate Immune Response

- Cabozantinib induces a neutrophil-dependent tumor regression in a mouse model of prostate cancer.
- Cabozantinib promotes tumor cell secretion of CXCL12 and HMGB1 to induce neutrophil infiltration.
- Cabozantinib reprograms the tumor microenvironment, resulting in an antitumor innate immune response.

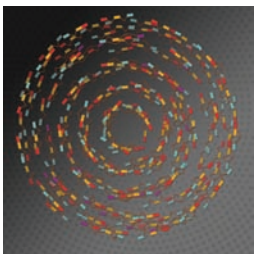


Tyrosine kinase inhibitors (TKI) achieve clinical responses in multiple malignancies, but their effects on the tumor immune microenvironment are not well understood. Cabozantinib is a TKI with activity against multiple tyrosine kinases including RET and c-MET, and has been FDA approved for the treatment of RET-driven medullary thyroid cancer and clear cell renal cell carcinoma. It also showed promising activity in a phase II trial of patients with castration-resistant prostate cancer, but did not extend survival in a phase III trial, suggesting that a better understanding of its mechanism of action is required to identify patients who may respond to cabozantinib. Patnaik and colleagues found that, in a mouse model of *Pten*/*Trp53*-deficient prostate cancer, cabozantinib eradicated tumors via a c-MET independent mechanism. Cabozantinib induced tumor regression, whereas a specific c-MET inhibitor did not. Further, cabozantinib induced activation of neutrophil-mediated antitumor innate immunity, suggesting a mechanism for TKI-mediated tumor clearance. Cabozantinib had only modest effects *in vitro*, further supporting a dominant tumor-cell nonautonomous mechanism for its antitumor activity. Cabozantinib induced tumor cells to release the chemokines CXCL12 and HMGB1 into the tumor microenvironment, resulting in neutrophil infiltration. Neutrophils were required for cabozantinib-mediated tumor clearance, as neutrophil depletion or trafficking to the tumor abrogated the antitumor effects of cabozantinib. Collectively, these findings reveal that cabozantinib promotes prostate tumor clearance via a c-MET–independent neutrophil-mediated innate immune response, and suggest that combining cabozantinib with approaches that activate adaptive immune response warrant further investigation in patients with advanced cancer. ■

See article, p. 750.

DNA Damage Induces Alternative Splicing to Drive Senescence

- A previously unidentified arm of the DDR pathway mediates DNA damage–induced alternative splicing.
- IR-mediated DNA damage induces SRSF7-mediated alternative splicing of *TP53β* to promote senescence.
- Suppression of *TP53β* could abrogate therapeutic irradiation–associated toxicities.



The DNA damage response (DDR) pathway is an integrated signaling pathway that coordinates the numerous responses required for a cell to maintain DNA integrity, including DNA repair and senescence, via proteins such as p53 (encoded by *TP53*), which is a central mediator of cellular damage responses. Having shown that ionizing radiation (IR) promotes the binding of RPL26 to *TP53* mRNA and regulates *TP53* translation, Chen and colleagues characterized the transcriptome bound by RPL26 and found that IR promoted alternative splicing of *TP53* and that the *TP53β* variant was increased in the RPL26 immunocomplex. Pharmacologic inhibition and siRNA-mediated knockdown experiments revealed that IR promotes increased *TP53β* expression via inhibition of the ATM-related kinase SMG1. RPL26 bound to *TP53* pre-mRNA and recruited the splicing factor SRSF7 to induce the alternative splicing of *TP53β*, which promoted markers of a senescent phenotype. IR-induced upregulation of *TP53β* resulted in increased senescence markers, but not apoptosis, of cell lines representing different tumor types, and clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9–mediated knockdown of *TP53β* resulted in a loss of IR-induced cellular senescence markers. Similarly, ablation of *SMG1* or *SRSF7* resulted in, respectively, increased expression of cellular senescence markers or suppression of IR-induced cellular senescence markers. Further, IR was found to induce the alternative splicing of other genes, such as *SMAD3*, via SMG1/RPL26/SRSF7. These results characterize a previously unidentified arm of the DDR pathway that regulates DNA damage–induced alternative splicing in cancer, and demonstrate an apparent role in cellular senescence. ■

See article, p. 766.

In This Issue is written by *Cancer Discovery* editorial staff. Readers are encouraged to consult the original articles for full details.

Downloaded from cancerdiscovery.aacrjournals.org on October 20, 2021. © 2017 American Association for Cancer Research.

AACR American Association for Cancer Research

CANCER DISCOVERY

In This Issue

Cancer Discov 2017;7:653-655.

Updated version Access the most recent version of this article at:
http://cancerdiscovery.aacrjournals.org/content/7/7/653

E-mail alerts Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link
http://cancerdiscovery.aacrjournals.org/content/7/7/653.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC)
Rightslink site.

Downloaded from cancerdiscovery.aacrjournals.org on October 20, 2021. © 2017 American Association for Cancer Research.