Drug Resistance

Major Finding: Elevated JAK/FGFR activity supports lineage plasticity and antiandrogen resistance in prostate cancer.

Concept: Combined JAK/FGFR inhibition reverts cells to a more luminal state and restores antiandrogen sensitivity.

Impact: This study reveals mechanisms of anti-AR sensitivity restoration and the critical nature of therapeutic timing.

SIMULTANEOUS JAK/FGFR INHIBITION RESTORES ANTI-AR SENSITIVITY IN CRPC

Lineage plasticity is well recognized as a method of drug resistance across many unique cancer types but in general remains poorly characterized. In order to fully understand plasticity as a method of therapeutic escape, it is critical to profile identity changes that arise alongside resistance. To thoroughly characterize prostate cancer tumor evolution during anti–androgen receptor (AR) therapy resistance, Chan, Zaidi, and colleagues used genetically engineered mouse models and organoids and found that tumor-intrinsic JAK/STAT inflammatory signaling drives the emergence of a hyperplastic cellular state insensitive to anti-AR therapy. In a mouse model of prostate cancer driven by the deletion of *Pten*, *Rb*, and *Trp53*, single-cell RNA sequencing (scRNA-seq) was performed throughout tumor development to capture progression into two castration-resistant prostate cancer (CRPC) phenotypes—adenocarcinoma (CRPC-adeno) and neuroendocrine prostate cancer (NEPC)—and indicated that CRPC-adeno emerges earlier in tumor development than NEPC and is identified as the most likely source of enhanced plasticity. To determine if this plasticity is cell autonomous or dependent on the tumor microenvironment, organoid cultures were evaluated, with normal prostate epithelial organoids maintaining a luminal identity, but, upon deletion of *Trp53* and *Rb1*, organoids became hyperplastic. This recapitulated early plasticity *in vivo* and suggests that progression into plasticity is a cell-intrinsic phenotype. Identification of gene programs associated with early plasticity that were enriched after anti-AR therapy revealed that the JAK/STAT pathway was strikingly upregulated in plastic cell populations, with particular enrichment for autocrine signaling via the FGF1/FGFR ligand–receptor pair. This signature was also observed using human scRNA-seq data as well as patient-derived CRPC organoids. Functional testing using both genetic and pharmacologic methods to inhibit FGFR and JAK1/2 signaling demonstrated that simultaneously targeting both pathways in hyperplastic cells causes reversion to a more luminal-like state as well as robustly restores sensitivity to anti-AR therapy. Altogether, this work comprehensively profiles the evolution of lineage plasticity that drives castration resistance in prostate cancer and identifies novel therapeutic vulnerabilities for a subset of CRPC. ■

Chan JM, Zaidi S, Love JR, Zhao JL, Setty M, Wadosky KM, et al. Lineage plasticity in prostate cancer depends on JAK/STAT inflammatory signaling. Science 2022;377:1180–91.

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Immunotherapy

Major Finding: *RASA2* ablation increases CAR T-cell cytolytic activity and improves persistent cancer cell killing.

Concept: *RASA2* KO T cells show increased activation, cytokine production, and metabolic activity after chronic antigen exposure.

Impact: Targeting *RASA2* can be a promising genetic approach to improve T-cell therapies in all tumor types.

ABLATION OF *RASA2* IMPROVES T-CELL ACTIVITY IN BOTH SOLID AND LIQUID TUMORS

The poor efficacy of T-cell therapies in solid tumors has, in part, been attributed to the immunosuppressive microenvironment as well as persistent antigen exposure. One strategy that has been used to increase efficacy of these therapies is targeted gene manipulation, but systematic gene manipulation has not yet been conducted. Carnevale, Shifrut, and colleagues performed large-scale CRISPR screens under several immunosuppressive conditions and found that ablation of the *RASA2* gene, which encodes for the RASA2 RAS GTPase activating protein, enhanced the ability of T cells to overcome inhibitory cues under multiple immunosuppressive conditions. Depletion of *RASA2* in T cells boosted their cancer cell killing under immunosuppressive conditions and promoted resistance to numerous mechanisms that suppress adoptive T-cell antitumor activity. Investigation into the effects of RASA2 inactivation on levels of active RAS (RAS-GTP) as well as downstream signaling molecules revealed that loss of *RASA2* expression increased RAS-GTP levels after T-cell receptor (TCR) stimulation as well as increased the downstream RAS effectors MEK and ERK but did not cause unregulated T-cell proliferation, with these T cells still being dependent on TCR stimulation to induce MAPK signaling, proliferation, and activation. Loss of *RASA2* also sensitized T cells to antigen, with *RASA2* knockout (KO) chimeric antigen receptor (CAR) T cells targeting CD19 demonstrating effective killing of leukemia cells with low levels of CD19. Moreover, acute T-cell stimulation reduced *RASA2*, while chronic stimulation led to its upregulation, with reduced *RASA2* expression blocking T-cell dysfunction after chronic cancer antigen exposure and supporting sustained cancer cell killing after multiple stimulations. Furthermore, preclinical models showed that transfer of *RASA2*-deficient CAR T cells reduced tumor growth and improved survival in murine models of sarcoma and leukemia, suggesting clinical relevance. Overall, this study indicates that targeting *RASA2* can contribute to improving T-cell persistence and effector function in cancer immunotherapy. ■

Carnevale J, Shifrut E, Kale N, Nyberg WA, Blaeschke F, Chen YY, et al. RASA2 ablation in T cells boosts antigen sensitivity and long-term function. Nature 2022;609:174–82.

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