Vaccines

Major Finding: Years after receiving Neo Vax, patients with melanoma remained alive with persistent T-cell responses.

Concept: In this phase I trial, the vaccine was given to eight patients with stage IIIB/C or IVM1b melanoma.

Impact: This work shows that personalized neoantigen vaccines can create lasting, beneficial immune responses.

IMMUNE RESPONSES TO PERSONALIZED NEOANTIGEN VACCINES ARE DURABLE

The development of anticancer vaccines that induce immune responses to tumor-specific antigens has long been hindered by a lack of ideal target antigens; however, in recent years, advances in sequencing have enabled the development of personalized vaccines based on patients' individual neoantigens. Recently, promising results have been seen with a personalized anticancer vaccine called NeoVax, which consists of long peptides encompassing up to 20 target neoantigens along with the TLR3 and MDA5 agonist poly-ICLC, which is included as an immunostimulant. In a phase I clinical trial, Hu, Leet, Allesøe, and colleagues investigated the use of NeoVax in eight patients with high-risk surgically resected stage IIIB/C or IVM1b melanoma, specifically focusing on the long-term immunologic effects of the vaccine, which had not been investigated previously. Additional treatments, such as immunotherapy with anti–PD-1, were allowed upon disease recurrence following vaccination. After a median follow-up period of nearly four years, all eight patients remained alive, and six (75%) had no evidence of active disease. Transcriptional profiling revealed that $CD4^+$ T cells exhibited a naïve-like phenotype prior to vaccination, whereas after vaccination $CD4^+$ T cells clustered into groups characterized by either memory-like or cytotoxic gene signatures, with the proportion of memory-like $CD4^+$ T cells increasing over time. The clonal composition of neoantigen-specific $CD4^+$ T cells also evolved with time, diversifying to include multiple additional T-cell receptor clonotypes. Importantly, the neoantigen-specific T-cell responses that occurred after vaccination were persistent, lasting years after treatment with NeoVax. Additionally, epitope spreading was observed following vaccination, implying release of tumor-associated antigens or tumor neoantigens not included in the vaccine formulation and thus suggesting that the vaccine had on-target cytolytic effects on tumor cells. In summary, this work provides evidence not only that a neoantigen vaccine–induced antitumor immune responses can be durable but also that treatment with such a vaccine can promote epitope spreading, possibly further enhancing its potential efficacy. ■

Hu Z, Leet DE, Allesøe RL, Oliveira G, Li S, Luoma AM, et al. Personal neoantigen vaccines induce persistent memory T cell responses and epitope spreading in patients with melanoma. Nat Med 2021 Jan 21 [Epub ahead of print].

Epigenetics

Major Finding: FBXO44 bound H3K9me3 at replication forks, recruiting a complex to repress repetitive elements.

Concept: FBXO44 silenced repetitive elements, preventing replication stress and antiviral signaling *in vitro*.

Impact: This study suggests FBXO44 inhibition as a novel strategy that may be effective across many cancers.

FBXO44 SILENCES REPETITIVE ELEMENTS DURING DNA REPLICATION IN CANCER

Transcriptional silencing of repetitive elements (RE) in the genome prevents accumulation of double-stranded RNA and DNA, which may otherwise trigger antipathogen immune responses, trigger MAVS- and cGAS-mediated IFN signaling, and cause DNA replication stress. Recent evidence suggests that antitumor therapies may be augmented by inducing RE transcription, and epigenetic modifications including trimethylation of histone 3 at lysine residue 9 (H3K9me3) contribute to RE silencing. To further elucidate this mechanism, Shen, Qiu, and colleagues performed an RNAi screen in human cancer cell lines to identify regulators of H3K9me3. The screen identified F-box only protein 44 (FBXO44) as a top hit, as knockdown of *FBXO44* significantly decreased H3K9me3 and increased pRPA32T21, a readout of replication stress. Chromatin immunoprecipitation and qRT-PCR experiments revealed that FBXO44 colocalized with H3K9me3 at REs and that *FBXO44* knockdown activated expression of these REs. Proteomic analysis of FBXO44 interactors followed by immunoprecipitation experiments uncovered that FBXO44 recruited SUV39H1, CRL4, and components of Mi-2/NuRD to the replication fork and that this complex cooperated to silence REs. Inhibiting complex members phenocopied *FBXO44* knockdown and activated MAVS- and cGAS-mediated IFN signaling. *In vitro, FBXO44* knockdown decreased cancer cell proliferation, migration, and invasion, reduced cell-cycle progression through S phase, and increased apoptosis. Notably, neither genetic inhibition of FBXO44 nor pharmacologic inhibition of SUV39H1 had a significant effect on normal cells, suggesting a potential therapeutic window. *In vivo*, inhibition of FBXO44 or SUV39H1 slowed mammary tumor growth in mice and increased tumor infiltration of CD8+ T and natural killer cells. Consistent with this increased antitumor immunity phenotype, *Fbxo44* or *Suv39h1* knockdown sensitized mice to immune checkpoint blockade using anti–PD-1. Patient data revealed that high FBXO44 expression correlated with poor clinical outcome across many cancers and that *FBXO44* expression inversely correlated with IFN signaling, antigen processing and presentation, and DNA replication stress. In summary, these findings uncover a mechanism by which cancer cells silence REs and implicate the FBXO44 complex as a therapeutic target that may be important across different cancer types. ■

Shen JZ, Qiu Z, Wu Q, Finlay D, Garcia G, Sun D, et al. FBXO44 promotes DNA replication-coupled repetitive element silencing in cancer cells. Cell 2020;184:352–69.E23.