

RESEARCH WATCH

Immune Evasion

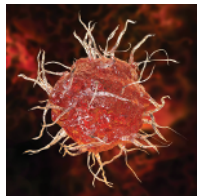
Major finding: Loss of the mRNA m⁶A-binding protein YTHDF1 in dendritic cells enhances antitumor immunity.

Mechanism: YTHDF1 binding promotes translation of lysosomal proteases that suppress cross-priming of CD8⁺ T cells.

Impact: Targeting YTHDF1 may increase the therapeutic efficacy of immune checkpoint blockade.

THE M⁶A-BINDING PROTEIN YTHDF1 MEDIATES IMMUNE EVASION

Effective antitumor immunity is dependent on sufficient priming of T cells against tumor neoantigens. However, the mechanisms by which tumors evade neoantigen recognition remain incompletely understood. Han, Liu, and colleagues found that loss of YTHDF1, a protein that increases mRNA translation efficiency via binding to N⁶-methyladenosine (m⁶A) post-transcriptional modifications in mRNA, attenuated tumor growth in mice. This antitumor effect was mediated by increased T-cell priming against tumor neoantigens and an enhanced antigen-specific CD8⁺ T-cell response. Deletion of *Ythdf1* specifically in classic dendritic cells (DC) augmented the ability of these cells to cross-prime CD8⁺ T cells compared with wild-type DCs and was sufficient to inhibit tumor growth, suggesting that recognition of mRNA m⁶A methylation by YTHDF1 restricts the capacity of DCs to present internalized tumor neoantigens to T cells. Consistent with this idea, YTHDF1-bound mRNAs in DCs were enriched in m⁶A-marked transcripts encoding lysosomal cathepsin proteases, which have



been shown to promote antigen degradation in DCs, and loss of *Ythdf1* reduced the translational efficiency of multiple cathepsin transcripts in classic DCs. Inhibition of lysosomal cathepsins increased the cross-priming of CD8⁺ T cells by wild-type DCs and enhanced the antitumor response in wild-type mice, supporting the notion that YTHDF1 limits immune recognition by promoting the expression of lysosomal proteases that degrade neoantigens in DCs. Furthermore, the increased neoantigen-specific CD8⁺ T-cell response in *Ythdf1*-deficient mice enhanced the antitumor efficacy of anti-PD-L1 antibody, resulting in complete tumor regressions. These findings identify YTHDF1 as a key mediator of tumor immune evasion and a potential therapeutic target to improve the clinical response to immune checkpoint blockade. ■

Han D, Liu J, Chen C, Dong L, Liu Y, Chang R, et al. Anti-tumour immunity controlled through mRNA m⁶A methylation and YTHDF1 in dendritic cells. *Nature* 2019;566:270–4.

Immunotherapy

Major finding: Mutant p53-specific T cells were isolated from patients with metastatic epithelial cancers.

Concept: Patient-derived TILs were screened for responses to neoantigens derived from *TP53* hot spot mutations.

Impact: T cells targeting common p53 neoantigens could be broadly used for adoptive cell therapy.

TP53 MUTATIONS ARE IMMUNOGENIC IN EPITHELIAL CANCER

The adoptive transfer of tumor-infiltrating lymphocytes (TIL) specific to neoantigens derived from mutated genes has been described for several types of cancer. However, this approach to date has been based on private mutations unique to individual patients. Targeting driver mutations that are frequent across many patients has the potential to provide broader applicable adoptive T-cell therapies. Malekzadeh and colleagues conducted a *TP53*-focused screening for neoantigens derived from *TP53* hot spot mutations that elicit a specific T-cell response. Of the patients enrolled in the study, 65% exhibited *TP53* mutations, and 24% of these patients had *TP53* mutations in previously identified hot spots. The screen was conducted by coculturing patient-derived TILs purified from metastases together with autologous antigen-presenting cells (APC) with predicted p53-derived neoepitopes presented either by intracellular expression through electroporation with *TP53*-mutant tandem minigenes or extracellularly by pulsing with mutated peptides. Of 28

evaluable patients, 11 (39%) had mutated *TP53*-reactive T cells restricted to HLA class I or II, and a total of 9 unique T-cell receptors derived from helper (CD4) and cytotoxic (CD8) T cells recognizing 7 different mutant p53-derived neoepitopes were isolated. The isolated TILs and gene-engineered T cells recognized tumor cell lines expressing the HLA and naturally processed mutant p53. These results show that neoepitopes derived from common p53 mutations are able to elicit specific T-cell responses. The ability of the characterized T cells to eliminate metastatic cancer will be evaluated in future clinical trials. This neoantigen screening approach also may serve as a model for targeting other highly mutated genes in cancer. ■

Malekzadeh P, Pasetto A, Robbins PF, Parkhurst MR, Paria BC, Jia L, et al. Neoantigen screening identifies broad *TP53* mutant immunogenicity in patients with epithelial cancers. *J Clin Invest* 2019; 129:1109–14.

CANCER DISCOVERY

The m⁶A-Binding Protein YTHDF1 Mediates Immune Evasion

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