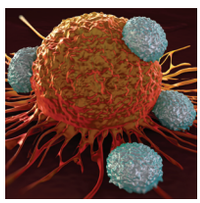
Immunotherapy

Major finding: Tumors with elevated neoantigen-specific TILs lose expression of T cell–specific neoantigens.

Approach: Neoantigen-specific TIL reactivity and neoantigen expression were assessed in longitudinal samples.

Impact: Induction of a broad neoantigen-specific T-cell response may prevent tumor resistance.

MELANOMA–T CELL INTERACTIONS AFFECT THE NEOANTIGEN REPERTOIRE



Cancer immunotherapies, such as adoptive T-cell transfer (ACT), are predicated on the ability of lymphocytes to recognize tumor neoantigens, which arise from tumor-specific somatic mutations. However, T cell–dependent immunoselection drives cancer immunoediting in animal models and induces the loss of defined neoantigens, which results in the outgrowth of nonimmunogenic clones and may lead to therapeutic resistance. To ascertain the stability of T cell–recognized neoantigens in patients, Verdegaal and colleagues characterized the expression and T-cell recognition of neoantigens in two patients with melanoma treated with ACT. For both patients, melanoma cell lines were generated from metastatic and recurrent lesions and tumor-infiltrating lymphocyte (TIL) cell lines were generated either independently or concurrently with the melanoma cell lines. In the first patient, T-cell reactivity to the neoepitopes KIA0020^{P451L} and RPL28^{S76F} was detectable in peripheral blood before ACT, increased after ACT, and decreased after tumor regression. TILs isolated from the brain metastasis exhibited reactivity for KIA0020^{P451L}, but not RPL28^{S76F}, in the primary tumor. Consistent with this finding, KIA0020^{P451L}, but not RPL28^{S76F}, was clonally present in the cell line and archived tissue from the brain metastasis. In the second patient, tumor-reactive T cells obtained by repeated stimulation of peripheral blood mononuclear cells with pre-ACT melanoma cells reacted to three different neoantigens that were lost or showed reduced expression in tumor cells from a recurrent lesion. Post-ACT TILs exhibited reactivity to an additional neoantigen that was expressed in the pre-ACT cell line and expression was increased in the post-ACT cell line, suggesting that changes in the tumor neoantigen repertoire may induce novel neoantigen-specific T-cell responses. These findings provide evidence that T cell–mediated immunoselection drives cancer immunoediting in patients with melanoma and suggest that broadening neoantigen-specific T-cell responses may overcome immunoediting-induced therapeutic resistance. ■

Verdegaal EM, de Miranda NF, Visser M, Harryvan T, van Buuren MM, Andersen RS, et al. Neoantigen landscape dynamics during human melanoma–T cell interactions. Nature 2016 Jun 27 [Epub ahead of print].

Glioblastoma

Major finding: RBPJ is required for GBM tumor–initiating cell self-renewal and tumor growth.

Concept: RBPJ activates a distinct transcriptional program from NOTCH, enhancing elongation via CDK9.

Impact: RBPJ may be a potential therapeutic target in GBM, even where NOTCH inhibition fails.

RBPJ MAY BE A MORE EFFECTIVE THERAPEUTIC TARGET THAN NOTCH IN GBM

Activation of stem cell pathways maintains brain tumor–initiating cells (BTIC) and contributes to glioblastoma (GBM) initiation and resistance. The NOTCH pathway is an attractive target in BTICs given its known role in maintaining stemness, but NOTCH inhibition has achieved only transient effects in glioma clinical trials. NOTCH activity is largely mediated by a central transcriptional mediator, recombining binding protein suppressor of hairless (RBPJ), prompting Xie and colleagues to investigate the role of RBPJ in BTICs. Unexpectedly, BTICs exhibited elevated expression and activation of RBPJ compared with differentiated cells, but NOTCH was not differentially activated. Consistent with these findings, NOTCH inhibition did not significantly affect BTIC proliferation, whereas RBPJ knockdown suppressed BTIC growth and self-renewal and inhibited tumor growth *in vivo*, altogether indicating the RBPJ is specifically required for BTIC maintenance. Targeting RBPJ had little effect on the expression of canonical NOTCH target genes, but reduced expression of genes regulating BTIC stemness and cell-cycle progression. The majority of RBPJ binding sites in the genome were within active promoters or enhancers, supporting a role for RBPJ as a transcriptional enhancer. Proteomic analysis of RBPJ binding proteins to identify downstream effectors identified cyclin-dependent kinase 9 (CDK9), a core component of the P-TEFb transcriptional elongation complex, which was also shown to promote BTIC growth and self-renewal. A high level of RBPJ/CDK9 co-occupancy was observed at gene promoters, and RBPJ knockdown reduced CDK9 occupancy at co-occupied sites and reduced RNA polymerase II binding at 3′ ends of genes, indicating a role for RBPJ in transcriptional elongation. The finding that RBPJ has NOTCH-independent functions in maintaining BTICs suggests that targeting RBPJ may be beneficial even when NOTCH inhibitors are ineffective. ■

Xie Q, Wu Q, Kim L, Miller TE, Liau BB, Mack SC, et al. RBPJ maintains brain tumor-initiating cells through CDK9-mediated transcriptional elongation. J Clin Invest 2016;126:2757–72.

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