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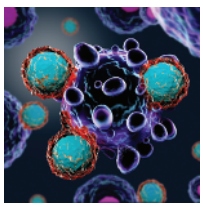
Immunotherapy

Major finding: Autologous T-cell transfer achieves a durable regression in a patient with metastatic breast cancer.

Concept: Autologous T cells targeting four somatic tumor mutation neoantigens were enriched after infusion.

Impact: Engineering autologous T cells to target multiple tumor neoantigens may enhance therapeutic efficacy.

AUTOLOGOUS T CELLS TARGETING FOUR NEOANTIGENS INDUCE TUMOR REGRESSION



Immunotherapy including immune checkpoint blockade or adoptive transfer of autologous tumor-infiltrating lymphocytes (TIL) has demonstrated clinical efficacy in tumors with a high mutation burden but has not been as successful in treating tumors with lower mutation rates. Adoptive transfer of autologous TILs that target the expressed proteins of somatically mutated cancer genes may improve therapeutic efficacy and have induced tumor regression in patients with metastatic bile duct, colon, and cervical cancers. Zacharakis and colleagues assessed autologous TILs from a patient with ER-positive metastatic breast cancer treated with adoptive transfer of mutant protein–specific TILs in combination with IL2 and the anti–PD-1 antibody pembrolizumab. Whole-exome and RNA sequencing identified 62 nonsynonymous somatic mutations in the tumor, and TILs isolated from the patient harbored two mutant tumor antigens—SLC3A2 and KIAA0368. The patient was treated with these mutant SLC3A2 and KIAA0368 TILs and 6 months after cell transfer achieved a 51% reduction in tumor burden. At 22 months after cell transfer all target and nontarget lesions had radiographically resolved. T-cell receptor (TCR)–focused deep sequencing revealed dominant TCR pairs that also recognized the mutant tumor antigens CADPS2 and CTSB. Overall, there were 11 TCR clonotypes that recognized all four neoantigens (SLC3A2, KIAA0368, CADPS2, and CTSB). Only two of these were detectable at low frequency in peripheral blood prior to treatment (0.002%–0.003% of TCRβ variable regions), but 3–12 weeks after cell infusion, the median cumulative frequency was 2.83%. Further, 8 of the 11 neoantigen-reactive TCRs persisted in the peripheral blood, making up 0.81% of the TCR repertoire 17 months after infusion. Altogether, these findings suggest that autologous TILs that target multiple tumor neoantigens may better overcome tumor immune escape mechanisms to induce durable tumor regressions, and these results may aid the engineering of more effective autologous TILS for adoptive transfer to treat patients with cancer. ■

Zacharakis N, Chinnasamy H, Black M, Xu H, Lu YC, Zheng Z, et al. Immune recognition of somatic mutations leading to complete durable regression in metastatic breast cancer. Nat Med 2018;24:724–30.

Genomics

Major finding: Cells with chromosome 1p loss and hemizygous deletion of *MAGOH* are dependent on its paralog, *MAGOHB*.

Mechanism: Inhibition of MAGOHB disrupts alternative splicing and RNA surveillance in MAGOH-deficient cells.

Impact: Direct or indirect MAGOHB inhibition may have activity in a wide range of cancers with chromosome 1p deletion.

PARALOG DEPENDENCY MAY BE EXPLOITABLE IN TUMORS LACKING CHROMOSOME 1p

An emerging concept borne out of synthetic lethality screens is that inactivation of particular genes can confer dependency on their functionally redundant paralogs. Viswanathan and colleagues analyzed such dependencies in genome-wide shRNA and CRISPR synthetic lethal screen datasets and identified the paralogs *MAGOH* and *MAGOHB* as genes for which dependency was significantly correlated with inactivation of its paralog. Of note, *MAGOH* is located on chromosome 1p, which is commonly deleted in human tumors, and hemizygous *MAGOH* loss occurs in 21% of all tumors cataloged in The Cancer Genome Atlas. *MAGOHB* was the top dependency in cells with hemizygous *MAGOH* loss, and chromosome 1p deletion status correlated with *MAGOHB* dependency. *MAGOH* and *MAGOHB* encode core components of the exon–junction complex, a multisubunit complex that acts at exon–exon junctions during splicing and facilitates targeting of transcripts with premature termination codons for nonsense-mediated decay (NMD). In *MAGOH*-deleted cells, decreased viability upon *MAGOHB* knockdown was associated with increased intron retention and expression of transcripts that typically would undergo NMD. MAGOHB does not have domains that are obviously amenable to targeting by small molecules, but delivery of *MAGOHB* siRNA with tumor-penetrating nanocomplexes suppressed growth of tumors with hemizygous deletion of *MAGOH*. A search for potentially more tractable dependencies that correlated with either *MAGOH* or *MAGOHB* dependency identified *IPO13*, a gene also located on chromosome 1p that encodes the karyopherin responsible for importing MAGOH and MAGOHB to the nucleus, as the top correlated gene dependency to both *MAGOH* and *MAGOHB*. Delivery of *IPO13* siRNA also suppressed growth of tumors with hemizygous deletion of *MAGOH*, suggesting that indirect inhibition of MAGOHB may also be effective in the setting of MAGOH loss. Overall, these findings raise the possibility that *MAGOH–MAGOHB* paralog lethality and the *MAGOHB–IPO13* axis may be exploitable vulnerabilities in a substantial subset of human tumors. ■

Viswanathan SR, Nogueira MF, Buss CG, Krill-Burger JM, Wawer MJ, Malolepsza E, et al. Genome-scale analysis identifies paralog lethality as a vulnerability of chromosome 1p loss in cancer. Nat Genet 2018;50:937–43.

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AACR American Association for Cancer Research

CANCER DISCOVERY

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