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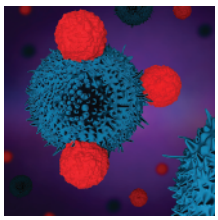
Leukemia

Major finding: Inactivation of CD33 in HSPCs permits CD33-directed CAR T-cell treatment of AML.

Concept: CD33-ablated HSPCs exhibited normal myeloid function and differentiation *in vivo*.

Impact: Gene editing of normal cells is a potential therapeutic approach to generate cancer-specific antigens.

ERASING CD33 IN NORMAL MYELOID CELLS AVERTS CAR T CELL–DRIVEN TOXICITY



The efficacy of target-directed immunotherapies such as CAR T cells depends upon either the cancer-specific expression of surface antigens or a tolerable level of normal tissue–associated toxicity. The CD33 antigen is highly expressed in acute myeloid leukemia (AML) blasts; however, its potential as an immunotherapeutic target for AML is curtailed by the expression of CD33 on normal myeloid progenitors. Currently, efforts have focused on designing transient CAR T cells to limit myeloablation and decrease CAR T cell–mediated normal toxicity, but this strategy would prevent the establishment of long-term immunosurveillence. To alleviate CAR T cell–mediated normal myeloid toxicity, Kim, Yu, and colleagues generated $CD33^{-/-}$ human hematopoietic stem and progenitor cells (HSPC). $CD33^{-/-}$ human HSPCs exhibited similar levels of engraftment, growth, differentiation, and myeloid function as control HSPCs and maintained CD33 loss in immunocompromised mice. Consistent with these findings, $CD33^{-/-}$ nonhuman rhesus macaque HSPCs exhibited similar levels of long-term engraftment, growth, multilineage differentiation, and myeloid trafficking and function as control HSPCs *in vivo*. Further, anti-CD33 CAR T cells eliminated $CD33^{+}$ human AML but not HSPCs in mice engrafted with $CD33^{-/-}$ human HSPCs; in contrast, anti-CD33 CAR T cells eliminated both $CD33^{+}$ human AML and HSPCs in mice engrafted with control human HSPCs. Taken together, these results identify a strategy to generate a leukemia-specific antigen from a shared antigen and show that shared antigens can be selectively eliminated from normal hematopoietic cells to eliminate normal toxicity without significantly affecting normal hematopoietic function. ■

Kim MY, Yu KR, Kenderian SS, Ruella M, Chen S, Shin T-H, et al. Genetic inactivation of CD33 in hematopoietic stem cells to enable CAR T cell immunotherapy for acute myeloid leukemia. Cell 2018;173:1439–53.

Immunotherapy

Major finding: Expansion of a single CAR T-cell clone triggers a complete remission in a patient with CLL.

Concept: CAR T cells with disruption of the *TET2* locus exhibit rapid expansion and enhanced antitumor activity.

Impact: Modifying *TET2* may enhance the efficacy of CAR T-cell therapy in patients with cancer.

TET2 DISRUPTION ENHANCES THE EFFICACY OF CD19 CAR T-CELL THERAPY

Immunotherapy with autologous transfer of chimeric antigen receptor (CAR) T cells targeting CD19 have demonstrated antitumor activity in patients with chronic lymphocytic leukemia (CLL). However, insufficient CAR T-cell expansion and persistence can limit their therapeutic efficacy. To provide insight into determinants of CAR T-cell efficacy and persistence, Fraietta and colleagues evaluated the clinical response in a patient with CLL treated with CD19 CAR T-cell therapy who achieved an exceptional response. After the second adoptive transfer of autologous CD19-targeted CAR T cells, there was a delayed expansion of CAR T cells in the peripheral blood, followed by a contraction, and the patient achieved a complete response that has been sustained for more than five years. Deep sequencing of the T-cell receptor beta repertoire revealed that, at the peak of the response, 94% of the $CD8^{+}$ CAR T cells were derived from a single clone that demonstrated massive *in vivo* expansion. In this clone, the lentiviral vector-mediated insertion of the CAR transgene disrupted the *TET2* gene, and the patient exhibited a hypomorphic mutation in the second *TET2* allele. These *TET2*-disrupted CAR T cells displayed a central memory phenotype at the peak of *in vivo* expansion and had an epigenetic profile that indicated altered T-cell differentiation. Consistent with this case report, *TET2* depletion enhanced the proliferative capacity and cytokine production of CAR T cells. Taken together, these findings suggest that the antitumor response achieved in a patient with CLL was due to expansion of a single CAR T-cell clone with disruption of the *TET2* locus. Further, these results suggest that *TET2* modification may be beneficial to enhance the efficacy of CAR T-cell therapies in patients with cancer. ■

Fraietta JA, Nobles CL, Sammons MA, Lundh S, Carty SA, Reich TJ, et al. Disruption of TET2 promotes the therapeutic efficacy of CD19-targeted T cells. Nature 2018;558:307–12.

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AACR American Association for Cancer Research

CANCER DISCOVERY

Erasing CD33 in Normal Myeloid Cells Averts CAR T Cell–Driven Toxicity

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