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 myeloblation and decrease CAR T cell-mediated normal toxicity, but this strategy would prevent the establishment of long-term immunosurveillance. 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 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.


IMMUNOTHERAPY

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, Fruiaietta 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.


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

Cancer Discov 2018;8:793. Published OnlineFirst June 8, 2018.