Genetic ablation of CD33 in human stem/progenitor cells enables immunotherapy against leukemia

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Researchers from Columbia University Medical Center recently showed that **genetic ablation of CD33 in human stem/progenitor cells (HSPCs) using CRISPR/Cas9 technology enables anti-CD33 immunotherapy** against acute myeloid leukemia (AML). Current antigen-directed immunotherapies, such as chimeric antigen receptor T cells (CAR-Ts) or antibody-drug conjugates (ADCs), are not specific for leukemic cells, causing severe toxicity. This novel approach to treat AML targets the lineage-specific myeloid antigen CD33 --through targeted CAR-T cells or the ADC **gemtuzumab ozogamicin**-- with the transplantation of hematopoietic stem cells engineered to ablate CD33 expression using genomic engineering methods. The results confirmed the highly efficient genetic ablation of CD33 in HSPCs without impairment in the ability to engraft and to repopulate a functional multilineage hematopoietic system in vivo. Moreover, the analysis confirmed no detectable off-target mutagenesis and no loss of functional p53 pathways. By modeling a postremission human marrow with minimal residual leukemic disease in mice, researchers showed that the transplantation of CD33-ablated HSPCs with CD33-targeted immunotherapy led to effective leukemia clearance without myelosuppression, as demonstrated by the reconstitution of the CD33-deleted human graft. This targeted immunotherapy approach showed promising results for the treatment of myeloid leukemias and could be potentially applied to other antigens and malignancies (Borot, F. et al. Proc Natl Acad Sci U S A (PNAS) 2019, Advanced publication).