Abstract 6

Epitope Editing Enables Targeted Immunotherapies for Acute Myeloid Leukemia

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Despite the striking efficacy observed when targeting a dispensable lineage antigen, such as CD19 in B-ALL1,2, broader applicability of adoptive immunotherapies is hampered by the absence of tumor-restricted antigens. Acute myeloid leukemia (AML) immunotherapies target genes expressed by hematopoietic stem/progenitor cells (HSPC) or differentiated myeloid cells, resulting in intolerable on-target/off-tumor toxicity. Here, we show that epitope-engineering of

donor HSPCs used for bone marrow transplantation endows hematopoietic lineages with selective resistance to CAR-T or monoclonal antibodies (mAb), without affecting protein function or regulation. This strategy allows targeting genes essential for leukemia survival regardless of shared expression on HSPCs, reducing the risk of tumor immune escape. By performing epitope mapping and library screenings, we identified amino-acid changes that abrogate binding of therapeutic mAb targeting FLT3, CD123 and KIT and optimized a base-editing approach to introduce them into CD34+ HSPCs, which retain long-term engraftment and multilineage differentiation capacity. After CAR-T treatment, we confirmed resistance of epitope-edited hematopoiesis and concomitant eradication of patient-derived AML xenografts. Furthermore, we show that multiplex epitope-engineering of HSPCs is feasible and allows more effective immunotherapies against multiple targets without incurring overlapping off-tumor toxicities. We envision that this approach will provide novel opportunities to treat relapsed/refractory AML and allow safer non-genotoxic conditioning.

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