EDIT-202, a Multiplexed CRISPR-Cas12a Gene-Edited iPSC-Derived NK Cell Therapy, Has Prolonged Persistence, Promotes High Cytotoxicity, and Enhances In Vivo Tumor Killing

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OBJECTIVE

To evaluate the in vitro and in vivo anti-tumor efficacy of EDIT-202, an induced pluripotent stem cell (iPSC)-derived natural killer (NK) cell therapy generated by using Editas’ proprietary engineered, highly active and specific AsCas12a to knock-out growth factor beta receptor 2 (GDFR2) and CD16 and membrane bound interleukin-15 (mIL15-). Enhanced functions of AsCas12a-edited NK cells

INTRODUCTION

• Natural killer (NK) cell-based immunotherapy has emerged as a promising therapeutic approach for solid tumors due to their intrinsic tumor killing capacity, few treatment-related toxicities, and ability to be given to patients as an off-the-shelf therapy.

• NK cell effector function is diminished by the lack of functional persistence, as well as tumor-intrinsic immunosuppressive mechanisms, such as production of transforming growth factor beta (TGFβ), a pleiotropic cytokine that inhibits effector function. Furthermore, NK cells’ ability to exert antibody-dependent cellular cytotoxicity (ADCC) is impaired when CD16 is cleared off after NK cell activation.²

• We established an NK platform where biological limitations can be overcome simultaneously via multiplexed gene editing of iPSCs. Using an engineered AsCas12a and our proprietary selection by essential-gene exon knock-out (SLEEK)™ editing tool, we successfully generated iPSC clones with double knock-out (DKO) of CD16 and GDFR2, and double knock-in (DKI) of CD16 and mIL15.³

• DKO/DKI iPSCs were differentiated into DKO/DKI NK cells, termed EDIT-202, which were characterized in vitro and in vivo to show edited-enhanced NK effector functions.

RESULTS

Figure 1. EDIT-202 cells had increased CD16 and IL-15Rα expression compared with WT NK cells

Figure 2. EDIT-202 cells showed enhanced ADCC-mediated tumor killing and resistance to TGFβ-induced immunosuppression compared with WT NK cells in a 3D ovarian SKOV3 spheroid assay

Figure 3. EDIT-202 showed upregulated and continuous replenishment of CD16 on the cell surface after tumor exposure

Figure 4. mIL-15 induced persistent antigen-specific expansion of EDIT-202 cells in the absence of cytokines

Figure 5. EDIT-202 administered in combination with 3 doses of TRA induced significant tumor reduction to complete clearance in an ovarian SKOV3-luc IP solid tumor model.

Figure 6. EDIT-202 treatment with 3 doses of TRA significantly increased survival over WT NK cells + TRA in an ovarian SKOV3-luc IP solid tumor model.

CONCLUSIONS

• EDIT-202 had significantly higher levels of CD16 and mIL15 compared with WT NK cells indicating that our SLEEK™ method, powered by our proprietary AsCas12a, is a robust method for editing iPSCs (Figure 1).

• EDIT-202 showed significantly higher natural cytotoxicity and augmented ADCC-mediated killing against 3D SKOV3 spheroids compared with WT NK cells. EDIT-202 induced reduction in tumor burden in the absence or presence of TGFβ, indicating that the TGFβ/IRK2 KO makes EDIT-202 resistant to TGFβ-induced immunosuppression (Figure 2). ²

• Due to the CD16, EDIT-202 cells had upregulated and continuous expression of CD16 compared with WT NK cells after tumor exposure (Figure 3).

• In vitro, EDIT-202 had prolonged cytokine independent persistence compared with WT NK cells indicating that the mIL15 KI in EDIT-202 is sufficient for cell survival and maintenance (Figure 4).

• In an in vivo ovarian SKOV3-luc solid tumor model, EDIT-202 treatment with 3 doses of TRA induced significant reduction in tumor burden compared with control + TRA and TRA only, resulting in complete tumor clearance in 40% of mice over the course of the experiment (Figure 5).

• When combined with TRA, EDIT-202 significantly increased mouse survival over WT NK cells in the solid tumor SKOV3 model. At day 120, 100% of EDIT-202-treated mice were alive, compared with 33.3% of WT NK-treated mice (Figure 6).

• These data support the development of EDIT-202 as a potential alloimmune cell-based medicine for treating solid tumors.

DISCLOSURES


REFERENCES

1. NHLBI public database [https://grants.nih.gov/grants/guide/notice-od-2021-001.html]

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