INTRODUCTION

It has been demonstrated that chimeric antigen receptor T-cell (CAR-T) therapy can achieve durable remissions in hematologic malignancies. However, CAR-T therapies have limited efficacy in solid tumors and are often associated with severe toxicity, highlighting the need for safer, more efficacious cell therapies. Natural killer (NK) cells with high-affinity cluster of differentiation 16 (CD16) represent an attractive alternative therapy option to CAR-Ts because of their natural cytotoxic ability and low toxicity. Therefore, we have generated an off-the-shelf, allogeneic, feeder-free, induced pluripotent stem cell (iPSC)-derived NK cell (EDIT-202) for targeting solid tumors.

METHODS

• Flow cytometry was performed to determine expression levels of the indicated markers. Perforin, granzyme b, and T-bet required intracellular staining.

• To determine the IC50, a 3D tumor spheroid-killing assay was used with SKOV-3 target cells. Killer cell immunoglobulin-like receptor (KIR) and perforin levels were correlated using linear regression analysis. Non-linear regression analysis was used to correlate KIR and perforin levels with IC50.

• Flow cytometry was used to determine the expression levels of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) in different cancer cell lines. A biosimilar (trastuzumab or cetuximab) antibody was used to bind the indicated antigen and a conjugated secondary antibody (AF488) was used to bind the biosimilar antibody.

• Cryopreserved EDIT-202 cells were plated with the indicated target cell lines and incubated for 48 hours. A lactate dehydrogenase (LDH) release assay was used to determine EDIT-202-induced cytotoxicity. An AlphaLISA® IFN-γ (human) detection kit was used to detect interferon gamma (IFN-γ) in the supernatant of the LDH assays used in Figure 4.

RESULTS

Figure 1: EDIT-202 cells express high levels of membrane markers and cytokines. Functional, phenotypic, and flow analysis.

Figure 2: Maturation marker levels correlate with increasing potent NK cell activity.

Figure 3: Expression of EGFR and HER2 vary considerably across different cancer cell lines.

Figure 4: Cryopreserved EDIT-202 cells demonstrate activity against multiple solid tumor cell lines.

CONCLUSIONS

EDIT-202 cells:

• Display a mature phenotype, which is correlated with potent killing of tumor cells

• Can be cryopreserved and still maintain their potent killing activity after thawing

• Demonstrate significantly better cytotoxicity and IFN-γ secretion when combined with an ADCC-enabling antibody and target cells that express sufficient levels of antigen

• Showed cytotoxic activity against ten different cancer cell lines from four different tumor types, using two different antibodies

DISCLOSURES

All authors are employees and shareholders of Editas Medicine.

REFERENCES