Natural Killer Cells with Enhanced Activity (SD 2021-141)

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BACKGROUND

NK cells possess a native ability to kill tumors and virally infected cells without prior antigen priming. Furthermore, NK cells can be administered to patients across HLA allotypes, unlike T cells which require HLA matching to avoid graft-versus-host disease. Many trials utilizing adoptive transfer of allogeneic NK cells demonstrated complete remissions in patients with acute myelogenous leukemia (AML) who are refractory to standard chemotherapy. Another recent clinical study demonstrated effective treatment of lymphoid malignancies using allogeneic CAR-expressing NK cells, with minimal side effects. Thus, NK cells possess a number of advantages over T cells that enables them to be used as safe, effective, “off-the-shelf” adoptive cell therapy product to treat diverse malignancies.

Antibody-dependent cellular cytotoxicity (ADCC) is a key pathway that mediates natural killer (NK) cell cytotoxicity against antibody-opsonized target cells. This process helps mediate the therapeutic efficacy of anti-tumor antibodies. On NK cells, ADCC occurs via engagement of antibody-coated target cells with activating receptor leading to proinflammatory cytokine upregulation, degranulation, and target cell death. Upon cellular activation, the is cleaved from the NK cell surface. Cleavage of the ectodomain prevents further antibody binding and signaling, which dampens NK cell activity. Blocking activation-induced cleavage has been previously demonstrated to augment ADCC activity and provides a novel strategy to improve efficacy of therapeutic antibodies in combination with adoptive transfer of engineered NK cells.

INNOVATION

This invention describes a novel genetic manipulation strategy in iPSCs to produce iPSC-NK cells with enhanced antibody-dependent cellular cytotoxicity (ADCC). To further define the ability to regulate NK cell activity, researchers have generated and characterized knock-out (KO) NK cells derived from CRISPR/Cas9-modified human induced pluripotent stem cells (iPSCs). These KO iPSCs successfully differentiate into hematopoietic progenitor cells, then to NK cells that uniformly express typical NK cell surface markers. KO iPSC-NKs are functional and kill K562 erythroleukemia cells comparable to wildtype iPSC-derived NK cells (WT iPSC-NK cells) and healthy donor-derived peripheral blood NK cells (PB-NK cells) *in vitro*. *In vivo* studies

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OTHER INFORMATION

KEYWORDS
tumors, gene editing

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- Medical
  - Disease: Cancer
  - Gene Therapy

RELATED CASES
2020-001-0

to determine the therapeutic efficacy of KO iPSC-NK cells compared to WT iPSC-NK and PB-NK cells are ongoing. Studies demonstrate KO iPSC-NK cells derived from a renewable source of gene-edited iPSCs possess enhanced ADCC potential, and provide a promising candidate to be used for standardized, off-the-shelf NK cell-based therapies in conjunction with therapeutic antibodies.

APPLICATIONS

ADVANTAGES

STATE OF DEVELOPMENT

Experimental stage

INTELLECTUAL PROPERTY INFO

A patent application has been filed for this technology.

RELATED MATERIALS

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