Review Article

From induced pluripotent stem cell (iPSC) to universal immune cells: literature review of advances in a new generation of tumor therapies

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Background and Objective: Tumor therapy is still a tough clinical challenge, and cancer immunotherapy has drawn increasing attention. T cells and natural killer (NK) cells play crucial roles in the immune response. Induced pluripotent stem cell (iPSC) technology opens up a new way to produce functionally improved universal iPSC-derived chimeric antigen receptor (CAR) T (CAR-iT) and iPSC-derived CAR-NK (CAR-iNK) cells. This study aims to comprehensively review the generation and clinical applications of iPSC-derived universal CAR-iT and CAR-iNK cells to explore their potential and future directions in cancer immunotherapy.

Methods: We searched EBSCO, PubMed, and Web of Science databases for relevant literature from 1975 to 2024 on the transformation of iPSCs into universal immune cells.

Key Content and Findings: iPSC technology enables the generation of enhanced CAR-iNK cells. Genetic modifications can boost the antitumor activity of iPSC-derived immune cells. CAR-iT cells have cytotoxicity issues. In contrast, CAR-iNK cells have advantages as they can be sourced from different origins and enhanced via genetic engineering.

Conclusions: This review outlines iPSC technology's application in oncology, iNK cells' properties, and the pros and cons of CAR cells in cancer treatment. It also focuses on the current clinical status and modification strategies of CAR-iT and CAR-iNK therapies, facilitating the development of future effective off-the-shelf blood cell therapies.

Keywords: Induced pluripotent stem cell technology (iPSC technology); chimeric antigen receptor T cells (CAR-T); tumor therapies; chimeric antigen receptor-natural killer (CAR-NK)

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Introduction

It is estimated that ten million people suffer from cancer every year, and one in six patients dies (1). According to the latest incidence projections, the global cancer burden is projected to reach 28.4 million cases by 2040, representing a 47% increase from 2020 levels, posing a major threat to human health worldwide (2). Cancer treatment strategies vary according to the stage of the tumor. In the early stages, surgical resection is often employed to remove the tumor. In the intermediate stages, a combination of radiotherapy and chemotherapy may be utilized to enhance therapeutic efficacy. Advanced-stage treatments are more complex,

incorporating not only traditional methods but also novel techniques such as targeted therapy and immunotherapy. These approaches allow for precise targeting of specific cancer cells and activation of the patient's immune system. The introduction of these innovative therapies has significantly improved patient survival rates and quality of life, offering hope for better prognostic outcomes (3). Immunotherapy is to recognize and destroy cancer cells by activating or enhancing the patient's own immune system, with chimeric antigen receptor (CAR) and immune checkpoint inhibition as the two major emerging therapeutic mechanisms (4,5). To date, CAR T-cell therapy has achieved tangible clinical success in treating patients with hematologic malignancies. However, it continues to present significant challenges in the context of solid tumors (6). CAR-natural killer (NK) cells, which have outstanding advantages over CAR-T cells, such as reducing cytokine release syndrome, neurotoxicity and reduced risk of allogeneic reactivity, are gaining more and more attention (7). Meanwhile, induced pluripotent stem cell (iPSC) technology is becoming a focal point for research, especially in the pathogenesis and development of new drugs. The iPSC-derived NK cells (iNK) have demonstrated a mature immune phenotype, robust cytolytic capabilities, and potent anti-tumor effects, providing a homogenized cell population for CAR-modified NK cells (8). This standardized CAR-iNK cells product holds the potential to become an "off-the-shelf" cancer immunotherapy candidate for clinical application, providing cancer patients with a stable and predictable treatment option (9). We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1087/rc).

Methods

We conducted a comprehensive search of existing literature on the research progress of iPSCs to transform into universal immune cells by searching EBSCO (one of the world's largest multidisciplinary comprehensive databases, providing extensive academic resources), PubMed, and Web of Science databases. In our systematic literature review, we focused on studies published between 1975 and 2024. This period was chosen to ensure that our analysis incorporated the most recent developments and findings related to iPSC technology and its applications in iPSC-derived CAR T cells (CAR-iT) and CAR-iNK cell therapies. Data sources were independently screened by two authors. Data analysis was conducted by two authors. The search strategy is summarized in *Table 1*.

Results

iPSC technology in tumor immunotherapy

Definition, historical development of iPSC technology

The iPSC technique is reprogrammed into pluripotent stem cells by introducing four specific genes, including *Oct4*, *Sox2*, *Klf4*, and *c-Myc* (10,11), into adult cells (mainly fibroblasts) (12). Their unrestricted self-replicating ability, high degree of gene editing, and potential to differentiate into a wide range of immune cell lineages allow genome-edited clonal seed cell lines to generate useful transplantable anti-tumor immune cells (13-15). Off-the-shelf iPSCs can also be provided by constructing human leukocyte antigen haplotype (HLA-haplotype) libraries for HLA-matching (16,17). Recent research has shown that iT cells, iNKs, iPSC-derived macrophages (iMacs), and iPSC-derived dendritic cells (iDCs) have been used in oncology, and iNK cells in particular are a quite promising means of cancer immunotherapy (9).

NK cells acting on tumors

The primary function of NK cells is to exhibit cytotoxicity, particularly demonstrating potent killing activity against tumor cells, and to produce cytokines (18-20). NK cells have the capability to directly recognize and eliminate tumor and infected cells, particularly those with viral infections, without the need for antigen presentation or prior exposure to specific antigens (21). Their antitumor activity can be substantially enhanced through *ex vivo* activation, expansion, and genetic modification, enabling them to overcome resistance. Recent evidence indicates an increase in NK cell-mediated tumor cell cytotoxicity in the context of molecular targeted therapy (22,23). NK cell-activated receptors, such as NKG2D, play a crucial role in identifying and destroying tumor cells. These receptors recognize specific molecules on infected or transformed cells and can bind to a wide range of ligands (9,24). NK cell-activating receptors such as NKp46, NKp30, and NKp44, known as natural cytotoxicity receptors, recognize specific molecules on target cells. Additionally, the Fc receptor CD16 on NK cells identifies antibody-coated cells, thereby activating NK cell cytotoxicity through antibody-dependent cell-mediated cytotoxicity (ADCC) and directly targeting tumor cells (24). The inhibitory receptors on NK cells include the killer cell immunoglobulin-like receptors (KIR) family and the CD94/

Table 1 The search strategy summary

Items	Specification
Date of search	January 18, 2023 to May 10, 2024
Databases and other sources searched	EBSCO/PubMed/Web of science
Search terms used	iPSC technology; CAR-T; Tumor therapies; CAR-NK; CAR
Timeframe	1975–2024
Inclusion criteria	Restricted to articles published in English
Selection process	J.Z. and Z.J. independently screened data sources. Data analysis was conducted by Q.W., C.Z., J.Z.

iPSC, induced pluripotent stem cells; CAR-T, chimeric antigen receptor T-cells; CAR-NK, chimeric antigen receptor natural killer cells; CAR, chimeric antigen receptor.

NKG2A receptor, which recognize major histocompatibility complex (MHC)-I-like molecules on normal cells and subsequently prevent attacking on these cells by modulating NK cell activity (25). Then, exerting cytotoxic effects, NK cells activate the release of cytotoxic particles (e.g., perforin and granzymes) and/or express death receptor ligands [e.g., Fas ligand (FAS) and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), etc.] to kill the target cells in an apoptosis-inducing pathway (9,26,27). Secondly, the secretion of cytokines such as interleukin (IL)-2, IL-12, IL-15, IL-18, interferon-gamma (IFN-γ) (28) and tumor necrosis factor-alpha (TNF-α) not only enhances anti-tumor effects, but also activates other immune cells, such as T cells and macrophages, which collectively enhances immune responses (29,30). It has been shown that NK cells activated by cytokines (IL-12, IL-15, IL-18) (31-33) under specific conditions show a more rapid and intense response to previously exposed tumor antigens (34-36). The last is to regulate the interaction of NK cells with tumor-associated immune cells, cytokines (XCL1, XCL2), etc., and chemical signals to alter the tumor microenvironment, which together determine the fate of tumor growth, metastasis and immune escape (37). Programmed cell death protein 1 (PD-1) functions as an immune checkpoint receptor located on the cell membrane. It negatively regulates T-cell activation through its immunoreceptor tyrosine-based switch motif (ITSM), and its blockade can significantly enhance the antitumor activity of T cells (38). Recent findings indicate that the phospho-dendrimer macromolecule AK128 promotes NK cell proliferation in peripheral blood mononuclear cells. Additionally, delivering a PD-1 blockade of immune checkpoints (ICBs) restores cytotoxic T cells and NK cells, thereby promoting apoptosis of tumor cells. It also greatly reduces the tumor distribution of regulatory T cells in order to improve immunotherapy for gliomas (39).

Critical steps in iNK cells

The ability of NK cells to avoid causing major immune rejection makes them an attractive cell type for immunotherapy. Furthermore, the induction of NK cells using iPSC technology offers a new strategy for cancer treatment. The process of iNK cells involves, first, differentiating iPSCs toward $CD34^+$ hematopoietic progenitor cells (HPCs) by means of reprogramming factors (e.g., OCT4) and proliferative and differentiation-blocking small molecules (e.g., Thiazovin), which involves either mixtures of small molecules and cytokines or co-culturing with irradiated stromal cell lines (40). Research shows that the application of the aryl hydrocarbon receptor (AHR) antagonist, StemRegenin-1 (SR-1), significantly enhances the differentiation of iPSCs into $CD34^+CD45^+$ cells, leading to an increased production of iPSC-derived NK cells (41). Subsequently, NK cell initiation factors [IL-3, IL-7, IL-15, stem cell factor (SCF), FLT3L] or a second stromal cell line were initiated to enrich for (41,42) $CD34^+$HPCs and further differentiate them into NK cells. Finally, the obtained iNK cells were co-cultured with irradiated K562 cells for expansion (40,43). In addition, the "spin Embryoid Bodies" (spin EB) method (42) can optimize the production of iNK cells, generate more HPCs, and differentiate into phenotypically mature NK cells (15).

Strategies to enhance iNK cell functions

Although iNK cells have potential in immunotherapy, their immune rejection and functional efficiency limit the scope and effectiveness of their clinical applications and need to be overcome by further research and technological innovation. First, previous studies have shown that

inhibitory receptors can be knocked down, or the expression of activating receptors such as KIR on NK cells can be enhanced, using CRISPR-Cas9 technology. These receptors typically modulate NK cell activity upon binding to MHC-I molecules (44). It was found that iNK cells derived from peripheral blood do not express KIR and therefore exhibit higher anti-tumor cytotoxicity (45). The use of immunomodulators in combination with checkpoint inhibitors, such as PD-1/programmed death-ligand 1 (PD-L1) inhibitors, can then either deregulate the inhibition of NK cell activity, enhance the attack on cancer cells or increase the expression of co-stimulatory molecules to improve NK cell activity and persistence (46,47). Second, the microenvironment of the tumor is altered to change the expression of NK cell receptors (46,48). Finally, the combined use of these strategies may greatly enhance the effectiveness of iNK cells in cancer therapy. However, these approaches are still in the research and clinical trial stage, and further substantiation is needed to determine their safety and efficacy.

iNK cells for tumor therapy (clinical application)

Currently, researchers are exploring the clinical application of iNK cells alone or in combination with monoclonal antibodies. A recent report showed that hnCD16iNK (FT516) and hnCD16/CD19CAR/IL-15RF (FT596) NK cells combined with CD20 antibodies are undergoing clinical trials for the treatment of relapsed/refractory B-cell leukemias and lymphomas (14). Notably, no toxicity or related adverse events were observed in the FT516 trial. In the FT596 trial, out of 11 patients, eight achieved objective remission, with seven reaching complete remission (CR) (15). In another study, no serious adverse events were observed in 12 patients with solid tumors (six with non-cutaneous melanoma, four with cutaneous melanoma, one with non-small-cell lung cancer, and one with triple-negative breast cancer) treated with hncd16 iNK cells in combination with IL-2 and an anti-PD-L1 antibody (avelumab), of the 12 patients had a reduction in tumor load (9). This article displays clinical trials conducted using iPSC cell therapy (14).

Development of universal cellular therapy

Features of universal cellular therapy

Universal cell therapy is a method of allogeneic transplantation of immune cells that effectively reduces immunogenicity and rejection and further improves tumor recognition and killing. Even if the iPSC-derived cells are autologous or well-matched, patients may still experience immune rejection in the transplant. The possible reason for this is the accumulation of mitochondrial DNA mutations that occur during reprogramming and differentiation and lead to the generation of neoantigens (49).

Mechanisms of action and status of research

CARs are a cutting-edge branch of the cell therapy field that combine a single-chain variable fragment (scFv), a cell activation domain (50) and a co-stimulatory structural domain. scFvs are derived from monoclonal antibodies that specifically recognize and bind antigens on the surface of tumor cells. The cell activation domain is usually derived from a T cell receptor (TCR) complex, such as the CD3ζ chain, and one or more co-stimulatory domains, such as CD28 or 4-1BB (CD137), which are used to activate the T cells, thereby activating, proliferating and producing cytotoxic effects on the CAR cells and ultimately killing the tumor cells. However, most CAR structures are designed for T cells and are not optimal for NK cell function (14,51), so designing a suitable CAR-NK structure is essential.

CAR-T cell therapy has drawbacks such as limiting the number of autologous T cells, long preparation time, high cost, and severe cytotoxicity [cytokine release syndrome (CRS)] (52,53). However, CAR-NK therapy not only reduces the toxicity of CAR-T cells but also exhibits a proven phenotype and efficient cell lysis capacity (9). In addition, the requirements for HLA matching are less stringent than those for CAR-T therapy, thus reducing the risk of immune rejection. Recently, CAR-NK and CAR-macrophages (CAR-M) have been introduced as complements/alternatives to CAR-T cell therapy for solid tumors (54).

CAR-T cell for immunotherapy

CAR-T cell therapy is considered a very promising cancer immunotherapy (55), in which the CAR gene is introduced into T cells *in vivo* via retroviruses or other vectors *in vitro*, and is mainly used for the treatment of certain refractory or recurrent hematologic cancers, such as acute lymphoblastic leukemia (ALL) and non-Hodgkin's lymphoma (NHL) (12,56,57). The Federal Drug Administration (FDA) has now approved six CAR-T cell therapies for clinical use (55). For example, CAR-T cell therapy targeting CD19 antigen has been shown to be a safe and promising treatment in patients with relapsed/refractory malignant hematologic diseases (5); CAR-T cell therapy targeting B-cell maturation antigen (BCMA) in multiple myeloma (MM), 640 patients

Table 2 The combined therapies of CAR-T cells and vaccine in preclinical trial

NCT number	Study title	Treatments	Phase	Sponsor
NCT05801913	Genetically modified T-cells (CMV-specific CD19-CAR T cells) plus a vaccine (CMV MVA Triplex) for the treatment of intermediate or high grade B-cell non Hodgkin's lymphoma	Intermediate/high grade B-cell non Hodgkin's lymphoma; recurrent B-cell non-Hodgkin's lymphoma; refractory B-cell non-Hodgkin's lymphoma	I	City of Hope Medical Center, Duarte, CA, USA
NCT04745559	Optimizing cellular and humoral immunity by vaccinating with PCV13 before and after CAR-T therapy	Diffuse large-cell lymphoma; PMBCL; TFL; HGBCL; follicular lymphoma	II	Moffitt Cancer Center, Tampa, FL, USA
NCT05432635	Genetically modified T-cells (CMV-specific, CD19-CAR T-cells) plus a vaccine (CMV MVA Triplex) following stem cell therapy for the treatment of intermediate or high grade B-cell non-Hodgkin's lymphoma	B-cell non-Hodgkin's lymphoma; diffuse large B-cell lymphoma; mantle cell lymphoma; recurrent B-cell non-Hodgkin's lymphoma; recurrent diffuse large B-cell lymphoma; recurrent Mantle cell lymphoma; recurrent transformed non Hodgkin's lymphoma; transformed non-Hodgkin's lymphoma	I	City of Hope Medical Center, Duarte, CA, USA
NCT05277753	NGS-MRD assessment of combination immunotherapies targeting T-ALL	T cell acute lymphoblastic leukemia	I	Shenzhen Geno-immune Medical Institute, Shenzhen, Guangdong, China
NCT05262673	NGS-MRD assessment of combination immunotherapies targeting B-ALL	B-cell acute lymphoblastic leukemia	I	Shenzhen Geno-Immune Medical Institute, Shenzhen, Guangdong, China

 CAR, chimeric antigen receptor; CMV, cytomegalovirus; HGBCL, high-grade B-cell lymphoma; MVA, modified vaccinia Ankara; NCT, National Clinical Trial number; NGS-MRD, next generation sequencing-minimal residual disease; PMBCL, primary mediastinal large B-cell lymphoma; T-ALL, T-cell acute lymphoblastic leukemia; TFL, transformed follicular lymphoma.

with 23 different CAR-T cell products, found an overall remission rate of 80.5%, of which 44.8% were CR, but the efficacy and safety of CAR-T cells can be influenced by the types of co-stimulatory molecules and CAR-T antigens used (58,59). In addition, it has potential in the treatment of other diseases, such as anti-gp120 CAR-T cell therapy being tested in patients with targeted human immunodeficiency virus (HIV) (NCT04648046). In advanced sarcoma, human epidermal growth factor receptor 2 (HER2) has been used as a target for CAR-T cells, and the safety of this treatment method has been confirmed (60).

Table 2 shows ongoing clinical trials of CAR-T cell therapy.

CAR-iT cell therapy

Retargeting of iT to tumor antigens with CAR has been described for CD19 (61-64), cd20 (65), gpc3 (66), and LMP-1 (67), or by gene editing iPSC therapy (64,66-68) or transduction at the late stage of differentiation (61-67). The resulting CAR-iT cell therapy demonstrated significant anti-tumor efficacy *in vivo* mouse models (61,64,65). A recent study shows that improving T persistence and antitumor efficacy *in vivo* can be achieved through modulation of epigenetics (64). The targeted integration of CD19-CAR into the T-cell receptor α constant region (TRAC) locus by CRISPR-Cas9 aimed at knocking down the TCR of donor cells and simultaneously introducing specific CAR molecules targeting CD19, enabling transplantation of generalized CAR-T cells to avoid graft-versus-host disease (GvHD), while the expression of CD19-CAR under the natural TCR promoter strengthened the function of CAR-T cells to better control disease progression in pre-B-ALL (69). The first CAR-iT cell therapy was developed in connection with the development of FT819, evaluating the

safety of its anti-tumor activity in patients with relapsed/refractory B-cell lymphomas (BCLs) and leukemias in mid-clinical phase 1 (70). Investigators designed dual antigen-targeted CAR-iT cells to target antigen escape and also target LMP1 and LMP2 antigens, improving cytotoxicity against EB virus-associated lymphomas (67).

CAR-NK cells for immunotherapy

CAR-NK cells preclinically demonstrated significant anti-tumor activity *in vitro* and *in vivo*. Experimental results in xenograft mouse models have shown that CAR-NK cells produce fewer cytokines and exhibit higher survival rates than other cell therapies (71). Currently, clinical trials based on CAR-NK cells from different sources are well underway and are being actively investigated in a variety of hematologic and solid tumors (*Table 3*). In the treatment of recurrent or refractory CD19-positive tumors using anti-CD19 CAR-NK cells derived from umbilical cord blood, HLA mismatched, and co-expressing IL-15 and inducible caspase9, objective remission was seen in eight of 11 subjects, with seven achieving CR accompanied by fewer adverse events (72). CD19 and CD20 of first-generation CAR-NK cells showed moderate therapeutic efficacy in certain refractory or recurrent B-cell malignancies (73,74); CD19-cd28-zeta-2a-ic9-il-15 was subsequently found to have no neurotoxicity, CRS, or GvHD in 8 of 11 patients (seven CRS) with recurrent/refractory $CD19^+$ B-cell malignancies (72). CAR-NK cells can be targeted against

Table 3 The ongoing clinical trials of CAR-NK therapy

Clinical trial number	NK source	Disease	Phase	Target	Date	Location
NCT05652530	Allogeneic NK	MMC3:C33C3:C32C48C3:C51C3:C31C3:CC3:C51	I	BCMA		
NCT05182073	Allogeneic NK	MM	I	BCMA		
NCT05008536	CB-NK	MM	I	BCMA		
NCT05110742	CB-NK	Hematological malignancy	I	CD5		
NCT05673447	Allogeneic NK	DLBCL	I	CD19		
NCT05645601	Allogeneic NK	B-cell malignancies	I	CD19		
NCT05020678	Allogeneic NK	B-cell malignancies	I	CD19		
NCT04887012	HLA haploidentical NK	NHL	I	CD19		
NCT05472558	CB-NK	NHL	I	CD19		
NCT05570188		B-cell malignancies		CD19		
NCT03056339	CB-NK	BCL, ALL, CLL, NHL	I	CD19	Jun-17	MDACC, USA
NCT04796675	CB-NK	ACL, CLL, NHL	I	CD19		
NCT05410041		B-cell malignancies	I	CD19		
NCT05654038	HPCs	B-cell malignancies	I	CD19		
NCT04639739		NHL	I	CD19		
NCT05842707	CB-NK	BCL	I	CD19/CD70		
NCT05667155	CB-NK	NHL	I	CD19/CD70		
NCT05008575		AML	I	CD33		
NCT03692767	N/A	BCL	I	CD22	Mar-19	China
NCT05194709		AML	I	CD33/CLL1		
NCT05574608	Allogeneic NK	AML	I	CD123		
NCT05410717	PBMCs	Ovarian cancer, testis cancer, endometrial cancer	I	Claudin6		

Table 3 (*continued*)

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Clinical trial number	NK source	Disease	Phase	Target	Date	Location
NCT05507593		SCLC	I	DLL3		
NCT04623944	Allogeneic NK	AML, MDS	I	NKG2D		
NCT05528341	NK-92	solid tumors	I	NKG2D		
NCT05213195		Colorectal cancer	I	NKG2D		
NCT04847466	NK-92	Gastric caner, head and neck cancer	I	PD-L1		
NCT03692663	N/A	Prostate cancer	I	PSMA	Dec-18	China
NCT05703854	CB-NK	RCC, mesothelioma, osteosarcoma	I	CD70		
NCT05092451	CB-NK	BCL, MDS, AML	I	CD70		
NCT05194709		Solid tumors	I	5T4		
NCT03940833	NK/92 cell line	Multiple myeloma	I/II	BCMA	May-19	China
NCT03579927	CB-NK	BCL	I/II	CD19/CD28	Oct-19	MDACC, USA
NCT03690310	N/A	BCL	Early phase I	CD19	Mar-19	China
NCT03824964	N/A	BCL	Early phase I	CD19/CD22	CD19/CD22	China
NCT02892695	NK-92	Leukaemia and lymphoma	I/II	CD19	Sep-16	China
NCT01974479	Haploidentical donor	B-ALL	Phase I	CD19	Sep-13	Singapore
NCT00995137	Donor	B-ALL	I	CD19	Oct-19	St. Jude Children's Research Hospital, USA
NCT02944162	NK-92 cell line	AML	I/II	CD33	Oct-16	China
NCT02742727	NK-92 cell line	Leukemia and lymphoma	I/II	CD7	Mar-16	China
NCT03940820	N/A	Solid tumours	I/II	ROBO1	Mar-19	China
NCT03692637	N/A	Epithelial ovarian cancer	Early phase I	Mesothelin	Mar-19	China
NCT02839954	NK-92	Solid tumours	I/II	MUC1	Jul-16	China
NCT03383978	NK-92	Glioblastoma	I	HER-2	Dec-17	Germany
NCT03415100	N/A	Solid tumours	I	NKG2D	Jan-18	China
NCT05922930	CB-NK	Ovarian cancer, mesonephric-like adenocarcinoma, and pancreatic cancer		TROP2		
NCT03941457	NK92	Pancreatic cancer		ROBO1		
NCT02839954	PBMCs	Solid tumors		MUC1		
NCT06006403	PBMCs	AML and BPDCN		CD123		

ACL, acute lymphocytic leukemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; B-ALL, B-cell acute lymphoblastic leukemia; BCL, B-cell lymphoma; BCMA, B-cell maturation antigen; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CAR, chimeric antigen receptor; CAR-NK, chimeric antigen receptor natural killer cells; CB, cord blood; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; HER-2, human epidermal growth factor receptor 2; HPCs, hematopoietic progenitor cells; MDACC, MD Anderson Cancer Center; MDS, myelodysplastic syndromes; MM, multiple myeloma; MUC1, mucin 1; N/A, not available; NHL, non-Hodgkin's lymphoma; NK, natural killer; NKG2D, NK group 2 member D; PBMCs, peripheral blood mononuclear cells; PD-L1, programmed death-ligand 1; PSMA, prostate-specific membrane antigen; RCC, renal cell carcinoma; ROBO1, roundabout guidance receptor 1; SCLC, small cell lung cancer.

specific tumor antigens in the treatment of NHL; a number of clinical trials are exploring the use of CAR-NK cells targeting BCMA in the treatment of MM.

The remarkable clinical efficacy of CAR-NK cells has attracted extensive attention from researchers around the world, and *Table 3* shows the clinical studies conducted so far. The accumulation of more research data and the optimization of CAR-NK cell therapies herald a possible new era of immune cell therapy.

CAR-iNK cell therapy

The ability of CAR-iNK cells to generate a standardized production process, lower HLA-matching requirements, and a homogeneous population of CAR-NK cells makes them a revolutionary and widely applicable therapeutic option in the field of cancer immunization (3,9). The investigators found that NK-car significantly increased the level of activation of NK cell signaling pathways [phospholipase C-gamma (PLC-γ) and Erk1/2] and elevated NK cell-mediated cytotoxicity against tumor target cells in iNK cells (9). CAR-iNK cells inhibited growth and prolonged survival in an ovarian cancer xenograft model without weight loss, organ damage, or CRS compared to CAR-T cells (71). Cichocki *et al.* created a triple gene-modified CAR-iNK cell showing durable responses in lymphoma and leukemia (75). Their related phase I clinical study is ongoing to further evaluate the safety and efficacy of treating relapsed/refractory BCL or chronic lymphocytic leukemia (CLL) with this cell therapy alone or in combination with an anti-cd20 monoclonal antibody (NCT04245722), with eight out of 11 patients obtaining an objective response of seven CR without dose-limiting toxicity, and with a reduction in GvHD and immune effector cell-associated neurotoxicity syndrome (ICANS) were reduced. Subsequently, four-gene edited CAR-iNK cells were designed, which showed optimal ADCC activity and anti-MM (76) effects when combined with anti-CD38 monoclonal antibody (anti-CD38mAb). Mesothelin-targeted CAR-iNK cells from iPSCs are highly efficacious in killing triple-negative breast cancer cells (77).

Discussion

iPSC challenges

Genetic instability, such as point mutations, copy number variations (CNVs) and chromosomal rearrangements, may be introduced during iPSC reprogramming, which increases the risk of tumor formation (15,78,79); toxicity inducing pluripotent stem cells and undifferentiated cells in teratomas has been observed in autologous animal cells or in immune-deficient animals (80-82). iPSC differentiation towards specific cell lines has variable efficiency and cellular heterogeneity exists, which affects the application in disease models and therapeutics; to address the issue of immune tolerance, it can be solved by knocking out HLA genes or inserting immunosuppressive factors (15).

CAR-immune cell challenges

The most serious challenges for generalized CAR-immune cells, due to GvHD and host-versus-graft reaction (HVGR), are significant (83). The main way to avoid host rejection of allogeneic cells is to prevent the autologous immune cells from recognizing the transplanted cells as foreign cells and thus undergoing killing. The CB011, CB012 series from Caribou Bioscience both inserted B2M-HLA-E by knocking out B2M from donor cells while escaping host T-lymphocyte and NK-cell attacks. In addition, the durability of CAR-immune cells is a major challenge. It was shown that CRISPR/Cas9 could improve CAR gene delivery and CAR-T cell persistence (84-86).

CAR-T cell therapy challenges

Currently, CAR-T has evolved from the first generation to the fifth generation (87). However, the application of CAR-T cell therapy in the treatment of solid tumors is hindered by many limitations (55), for example, immunosuppressive cells and factors within the microenvironment subject them to intense and sustained antigen stimulation, which often leads to exhaustion and apoptosis. The fourth generation CAR-T cell therapies, known as T cells redirected for universal cytokine killing (TRUCKs) recognizing tumor cells can locally release immunomodulators to further activate the immune system and overcome the suppression of the tumor microenvironment (88), but the effect is still limited in the treatment of solid tumors (89,90). In the immunosuppressive microenvironment of solid tumors, immunosuppressive cells and molecules are detrimental to the function of CAR-T cells. For example, adenosine, an important substance that induces tumor immunosuppression, in combination with its receptor A2a (91) impedes immune cell activity and affects the therapeutic efficacy of CAR-T cells (55). CAR-T therapy faces challenges such as the difficulty in identifying

suitable targets and the potential for severe side effects, including CRS and neurotoxicity (3,92); individualized regimens need to be developed for the patients.

By modifying the antibody affinity of CAR-T cells (93), toxicity problems partly caused by targeting non-specificity can be effectively addressed. In addition, Sachdeva *et al.* found that granulocyte-macrophage colony-stimulating factor (GM-CSF) plays a central role in the pathogenesis of CRS, and that knocking down the expression of GM-CSF through gene editing techniques can prevent the onset of CRS while maintaining the tumor-killing efficacy of CAR-T cells (94). Further, CAR-T cells genetically modified to express specific chemokine receptors, such as CXCR2 or CXCR1, have been shown to optimize therapeutic efficacy by enhancing cell migration. In addition, by integrating the PDZ domain (PDZ) binding motif into the internal structural domain of CAR, the "anchoring domain" of CAR is constructed. This innovative design can regulate the formation of immune synapses, so that the extracellular portion of the encoded gene of the CAR gene can more accurately recognize and bind to the corresponding antigens on the surface of the tumor cells to form a stable "immune synapse", which can then enhance the efficacy of the CAR-T cells in the anti-tumor immune response (95). After fine construction by genetic engineering, the researchers successfully designed the alloimmune defense receptor (ADR), which possesses a highly specific recognition ability to accurately recognize the transiently up-regulated 4-1BB cell surface receptor on the surface of activated lymphocytes. CAR-T cells expressing ADR exhibited superior resistance to allogeneic reactive T cells in both *in vivo* and *in vitro* settings. In an in-depth study in hematoma and solid tumor mouse models, we found that the therapeutic strategy of allogeneic CD19-CAR-T cells expressing ADR demonstrated durable tumor elimination (96). This approach may hold good promise for the development of generalized CAR-T in the future.

Review challenges

Despite conducting an extensive literature search, there is potential for subjective bias in the selection of literature, particularly concerning the choice of keywords and databases. Published studies often emphasize positive findings, while studies with negative or non-significant results may remain unpublished, potentially leading to bias in our review outcomes. We primarily searched databases such as EBSCO, PubMed, and Web of Science from 1975 to 2024. Although these databases offer broad coverage, they may still omit some critical studies. Additionally, our search was predominantly focused on English-language literature, which might result in the exclusion of significant information from non-English sources.

Conclusions

CAR-mediated immunotherapy has achieved significant results in the treatment of hematological tumors and some solid tumors, facilitating the exploration of CAR-NK cells in cancer therapy. The iPSCs technology has opened new pathways for the production of functionally enhanced CAR-iNK cells, and researchers have proposed numerous strategies to enhance the efficacy and safety of CAR-iNK cell therapies, but they still need to be validated through more clinical trials. The results of these trials provide key insights into the clinical application of CAR-iNK therapies and are expected to bring new therapeutic hope to a wide range of cancer patients.

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Footnote

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