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Review Article

CD70-targeted CAR-T/NK therapy: Rationale, advances, and future directions

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ABSTRACT

Chimeric antigen receptor T and natural killer (CAR-T/NK) cells is a rapidly evolving cellular immunotherapy technology that has made great achievements in the treatment of hematologic diseases. CD70, as a surface antigen expressed on tumor cells in a variety of hematologic malignancies, including acute myeloid leukemia, non-Hodgkin lymphoma, multiple myeloma, etc., and solid tumors such as renal cell carcinoma, osteosarcoma, and glioma, is a potential target for CAR-T/NK cells. Several preclinical studies and clinical trials on CAR-T/NK cells targeting CD70 are currently underway, bringing new hope for the treatment of CD70-positive tumors.

Key points

1. CD70 is expressed in a variety of hematologic tumors and solid tumors, and is a possible target for targeted therapy.

2. CAR-T/NK cells targeting CD70 have demonstrated therapeutic potential for the relevant disease.

Abbreviations

AML	acute myeloid leukemia
AZA	azacitidine
BCMA	B cell mature antigen
CAFs	Cancer-associated fibroblasts
CAR	chimeric antigen receptor
CAR-NK	Chimeric antigen receptor natural killer cells
CAR-T	Chimeric antigen receptor T cells
ccRCC	clear cell renal cell carcinoma
CD70	cluster of differentiation 70
CISH	Cytokine induced SH2 protein
CRC	colorectal cancer
CRS	cytokine release syndrome
DLBCL	diffuse large B-cell lymphoma
EGFR	epidermal growth factor receptor
GBM	glioblastoma
GvHD	graft versus host disease
GzmB	granzyme B
HMA	hypomethylating agent
HNSCC	Head and neck squamous cell carcinoma
ICANS	immune effector cell-associated neurotoxicity syndrome
IFN-γ	interferon-gamma.
iPSC	induced pluripotent stem cells
JNK	Jun N-terminal kinase
KAR	killer activation receptor
KIR	killer immunoglobulin-like receptor
MCL	mantle cell lymphoma
MHC	major histocompatibility complex
MM	multiple myeloma
MM	multiple myeloma
NHL	non-Hodgkin lymphoma
NIK	NF-κB-inducing kinase
NK cell	natural killer cell
NKp30	natural killer protein 30
NSCLC	non-small cell lung cancer
OVs	Oncolytic viruses
PARP	Polyadenosine diphosphate-ribose polymerase
PDAC	pancreatic ductal adenocarcinoma
PFN	perforin
PTCL	peripheral T-cell lymphoma
RCC	renal cell carcinoma
RRMM	relapsed/refractory multiple myeloma
ScFv	single-chain variable fragment
TCR	T cell redirected therapy
TKIs	tyrosine kinase inhibitors

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TNFR	tumor necrosis factor receptor
TNFSF7	Tumor Necrosis Factor Ligand Superfamily Member 7
TNF-α	tumor necrosis factor-alpha
TRAC	T cell receptor alpha subunit constant
TRAFs	TNF receptor-associated factors

CD70 as a therapeutic target

CD70 (Tumor Necrosis Factor Ligand Superfamily Member 7, TNFSF7) is a type II transmembrane protein belonging to the tumor necrosis factor (TNF) family [1]. CD70 expression can be induced in activated lymphocytes, including both T and B cells, as well as in terminally differentiated dendritic cells upon immune stimulation [2]. This tightly regulated expression profile suggests CD70 plays a crucial role in both central and peripheral immune regulation.

CD27, the only known receptor for CD70, belongs to the tumor necrosis factor receptor (TNFR) superfamily and plays a central role in immune regulation [3]. Studies have demonstrated that the CD27-CD70 signaling pathway participates in the activation and functional modulation of immune cells through multiple mechanisms. Upon binding to CD70, the intracellular domain of CD27 recruits TNF receptor-associated factors (TRAFs), thereby triggering downstream signaling cascades, including c-Jun N-terminal kinase (JNK) pathway and the canonical NF-κB pathway. CD27 can also bind to the apoptotic mediator Siva-1, thereby expanding its functions in cellular signal transduction. Activation of these signaling pathways significantly enhances the proliferation, differentiation, and functional activation of T cells, B cells, and natural killer (NK) cells. Furthermore, CD27 can activate NF-κB signaling via the NF-κB-inducing kinase (NIK)-dependent pathway, mediating anti-apoptotic effects and promoting immune cell survival [4]. Additionaly, reverse CD70 signaling can activate the phosphoinositide 3-kinase/protein kinase B and mitogen-activated protein kinase signaling pathways, thereby regulating cell proliferation, differentiation, and effector functions [2]. These findings indicate that the CD27-CD70 signaling axis plays a pivotal role in both adaptive and innate immune responses, and its precise regulation is critical for maintaining immune homeostasis (Fig. 1) [1,5,6].

CD70 is also highly expressed in various hematologic malignancies and solid tumors under pathological conditions, including acute myeloid leukemia (AML), non-Hodgkin lymphoma (NHL), multiple myeloma (MM), renal cell carcinoma (RCC), glioma, and colorectal cancer (CRC)/pancreatic ductal adenocarcinoma (PDAC) [2]. High expression of CD70 has been consistently observed in malignant tumors, making CD70-targeted therapies a promising option. In this review, we summarize the current status of Chimeric antigen receptor T/natural killer (CAR-T/NK) cells targeting CD70 for the treatment of malignant tumors.

Mechanism of CAR-T/NK cells and comparative advantages

CAR-T cell therapy is a rapidly developing cellular immunotherapy technique that has showed promising clinical results in the treatment of hematologic malignancies and has also sparked the interest of researchers working in the field of solid tumor treatment [7,8]. Antigen recognition by CAR-T cells does not depend on the major histocompatibility complex (MHC). These cells can recognize specific antigens on the surface of tumor cells without the need for antigen processing and presentation. CAR-T cells are produced by collecting T cells from the peripheral blood of either the patient or the donor and modifying them *in vitro* using genetic engineering to express CARs. These genetically engineered CAR-T cells are then reintroduced into the patient's body, where they specifically recognize target antigens and rapidly proliferate to exert antitumor effects [9,10]. Currently, CAR-T cells are widely used for the treatment of hematologic malignancies, and the targets of these products are limited to either CD19 or B cell mature antigen (BCMA). However, CD70 has broad prospects for the treatment of these malignancies (Fig. 2).

After specifically recognizing CD70 on the surface of tumor cells, CAR-T cells targeting CD70 directly induce apoptosis of tumor cells by secreting perforin and gramzymes, and can also secrete a variety of cytokines, including TNF-α and IFN-γ to recruit NK cells to kill tumor cells.

Abbreviations: CD70, cluster of differentiation 70; CAR-T cells, chimeric antigen receptor T cells; NK cells, natural killer cells; GzmB, granzyme B; PFN, perforin; TNF-α, tumor necrosis factor-alpha; IFN-γ, interferon-gamma.

NK cells are a type of lymphocytes that can destroy tumor and virus-infected cells without the need for specific antigens [11]. CAR-NK cell therapy is an emerging immunotherapy utilizing genetically engineered natural killer cells equipped with CARs to specifically target and eliminate tumor cells. This approach combines CAR-mediated precision targeting with innate cytotoxic mechanisms of NK cells, including perforin/granzyme release, death receptor signaling, and antibody-dependent cellular cytotoxicity, creating a potent multi-pronged antitumor response while preserving natural immune surveillance functions [12]. These multifaceted mechanisms position CAR-NK cell therapy as a promising strategy for both hematological malignancies and solid tumors. These cells have shown great potential in the field of tumor immunotherapy because of their ability to directly recognize target cells in the absence of MHC as well as their ability to avoid the common adverse effects associated with CAR-T cell therapy, such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS)(Table 1) [13]. CAR-NK cells have shown promising results in preclinical and clinical trials, making them a viable option for cancer treatment [14] (Fig. 3).

CD70 CAR-NK cells eliminate CD70⁺ tumors via (1) perforin/granzyme release, (2) antibody-dependent cell cytotoxicity, (3) stress-ligand sensing, (4) IFN-γ/TNF-α secretion, and (5) FasL/TRAIL-mediated apoptosis.

Abbreviations: KIR, killer immunoglobulin-like receptor; KAR, killer

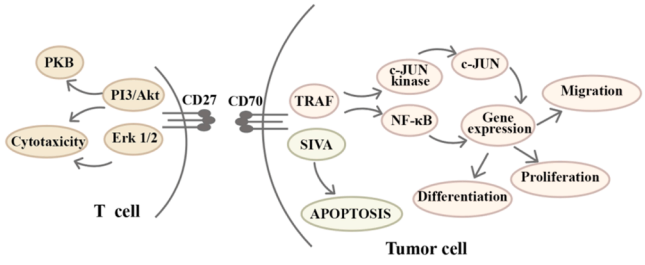

Fig. 1. The interaction between CD70 and CD27 plays a crucial role in modulating the body's immune response.

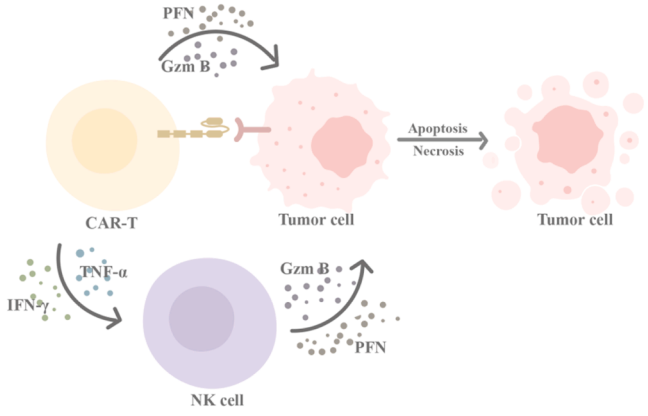

Fig. 2. The mechanism of killing tumor cells by CAR-T cells.

Table 1
Comparison of features between CAR-T cells and CAR-NK cells.

	CAR-T cells	CAR-NK cells
Cell source	Autologous/allogeneic T cells	NK cell lines, peripheral blood, cord blood, or induced pluripotent stem cell-derived NK cells
Targeting mechanism	CAR-dependent single antigen targeting	CAR targeting + innate NK recognition
Killing mechanisms	Primarily perforin/granzyme	Perforin/granzyme + death receptor pathways + antibody-dependent cellular cytotoxicity
Advantages	Durable persistence and proven efficacy	Superior safety profile, multimodal killing, and allogeneic compatibility
Limitations	Manufacturing complexity, high risk of cytokines release syndrome and limited solid tumor efficacy	Transient persistence and limited expansion capacity

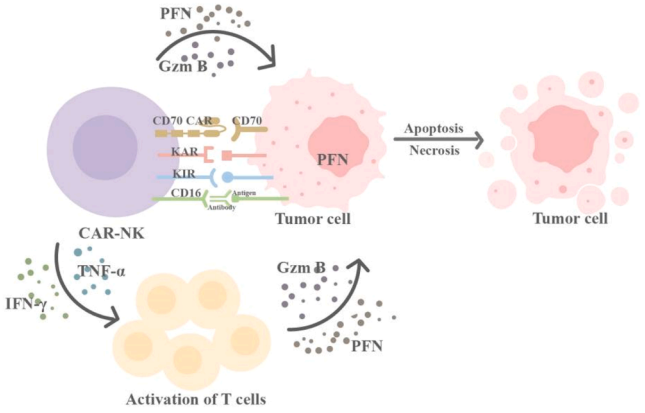

Fig. 3. The mechanism by which CAR-NK kill tumor cells.

activation receptor; CD70, cluster of differentiation 70; CAR-NK, chimeric antigen receptor-natural killer cells; GzmB, granzyme B; PFN, perforin; TNF-α, tumor necrosis factor-alpha; IFN-γ, interferon-gamma.

Given the high expression of CD70 on the surface of a variety of tumor cells, CD70-targeted CAR-T/NK cell therapies have emerged as highly promising approaches in the cellular immunotherapy of malignant tumors. This review aims to delve into the challenges associated with CD70-targeted CAR-T/NK cell therapies for malignant tumors by examining relevant preclinical studies and clinical trials. It is hoped that the review will guide future research efforts to overcome these obstacles and thereby enhance the therapeutic efficacy and broader applicability of CAR-T/NK cell therapies in the treatment of malignant tumors.

Preclinical exploration and clinical applications

Hematologic malignancies

AML

AML is a malignant clonal disease involving myeloid stem/progenitor cells [15]. CD70 is heterogeneously expressed on AML blasts but remains largely absent from normal hematopoietic stem cells [16,17]. Pre-clinical studies reported that CD27ζ-CAR-T cells targeting CD70 exert cytotoxic activity against CD70+ AML cell lines and primary blasts *in vitro*. In xenograft models these cells reduce tumour burden and prolong survival; nevertheless, complete leukaemia eradication has not yet been achieved [18].

The effectiveness of CAR-T cells targeting CD70 in combating tumors is associated with the level of CD70 on the surface of AML tumor cells, which exhibits heterogeneous expression patterns [17]. Increased CD70 antigen expression can be achieved by using epigenetic regulators. The hypomethylating agent (HMA) azacitidine (AZA) and decitabine (Dacogen) can increase CD70 levels on the surface of tumor cells by inhibiting DNA methyltransferase and decreasing CD70 promoter methylation [19,20]. Early-phase clinical data indicate that relapsed AML patients exhibit increased CD70 expression on leukaemic stem cells following HMA therapy [21,22].

To mitigate antigen-negative escape, a CD70/CLL-1 bispecific CAR-T construct (CLL-1.BiCAR) has been evaluated in pre-clinical AML models; dual targeting improved tumour control and T-cell persistence, extending median survival by approximately 40 % compared with single-antigen CAR-T [23]. Collectively, these findings support continued investigation of CD70-directed therapies for AML, with emphasis on combination strategies to deepen and sustain responses.

NHL

NHL comprises B- and T-cell-derived subtypes. CD70 is expressed on tumour cells in 58 % of cases, including peripheral T-cell lymphoma (PTCL), diffuse large B-cell lymphoma (DLBCL), and mantle cell lymphoma (MCL) [24]. Therefore, CD70 is one of the possible targets of CAR-T cell therapy for NHL.

B cell lymphomas

Pre-clinical work demonstrates that CD70 CAR-T cells eliminate $CD19^{+}/CD70^{+}$ Raji cells more effectively than CD19 CAR-T cells at low effector-to-target ratios, resulting in prolonged tumour-free survival in xenografted mice [25]. CD70 CAR-T cell also retains cytotoxic activity against CD19-negative Raji variants, underscoring its potential for CD19-refractory B-NHL [26]. Therefore, CD70 CAR-T cells represent a potential treatment for CD19-negative B-NHL. Adiditionally, the use of dual-targeting CAR-T cell therapy, shows great potential for treating B-NHL. CAR-T cells co-targeting CD19 and CD70 are available for the treatment of primary central nervous system DLBCL. CAR-T cells co-targeting CD19 and CD70 are available for the treatment of primary central nervous system DLBCL. A single-patient, early-phase study reported complete radiological response one month after sequential infusion of CD19-CAR-T and CD70-CAR-T in a patient with primary CNS DLBCL. CD19 and CD70 CAR-T cells were still detectable 10 months after infusion and the patient maintained disease-free survival for >17 months [27].

Complementing T-cell approaches, CD70 CAR-NK cells have demonstrated potent, antigen-restricted killing of CD70+ malignant B cells *in vitro*, including CD19-negative targets [28]. These data position CD70 as a complementary or alternative target to CD19 for the treatment of B-cell NHL, particularly in the setting of CD19 loss or low expression.

T cell lymphomas

CD70 is widely expressed in most TCL, including angioimmunoblastic T-cell lymphoma, primary cutaneous TCL non-mycosis fungoides; type and peripheral T-cell lymphoma, not otherwise specified [29,30]. CTX130 is an allogeneic CAR-T cells therapy that targets CD70. COBALT-LYM (NCT04502446),an open, multicenter phase I clinical trial designed to evaluate the efficacy of CTX130 in CD70-positive (≥10 %) patients aged ≥ 18 years with relapse/refractory TCL [31]. A total of 39 patients received CTX130 therapy. With a median follow-up of 7.4 months, CRS emerged as the most frequent adverse event, observed in 26 patients (67 %). Grade 1–2 neurotoxicity occurred in four individuals (10 %). Objective responses were documented in 18 of 39 patients. Out of 39 patients, 18 had objective reactions. Among patients treated with grade 3 or higher doses, 16 out of 31 had a response, with 6 showing a complete response and 10 showing a partial response. CTX130 has demonstrated efficacy and safety in relapse/refractory TCL and may be one of the most effective methods for treating relapse/refractory TCL [32,33].

CD70.CAR.IL-15 NK cells are cord blood-derived, IL-15-producing

CAR-NK cells designed to target CD70. The CAR construct consists of an anti-CD70 single-chain variable fragment (scFv) coupled with intracellular signaling domains and an IL-15 transgene to enhance NK cell persistence and antitumor activity. Sustained IL-15 expression markedly enhances the *in vivo* persistence and expansion of NK cells while concurrently augmenting their resistance to apoptosis through upregulation of the anti-apoptotic protein BCL-2. The manufacturing process involves isolating NK cells from cord blood, lentiviral transduction with the CD70-targeting CAR construct, and expansion. The resulting CD70. CAR.IL-15 NK cells demonstrate potent cytotoxicity against CD70-positive TCL cell lines, as evidenced by elevated expression of cytotoxicity markers and upregulation of co-receptor/proliferative markers [34]. Accordingly, CD70 has emerged as a promising target for CAR-NK in the treatment of TCL and development of CD70.CAR.IL-15 NK cells are integral to clinical application.

MM

MM is a clonal plasma cell tumor. The current approved CAR-T cells for the treatment of relapsed/refractory MM all target BCMA, and there are no approved products targeting CD70 [35]. In immunohistochemical analysis of patient-derived tumor cells, McEarchern et al. found that CD70 was expressed on the surface of 41.9 % of MM cells [36]. Studies have shown that CD70 is significantly upregulated in patients with high-risk MM, and AZA also increases CD70 expression in MM [37].

CAR-NK may be considered a potential therapy for MM. According to Lin et al., *in vitro* experiments showed that transduced NK cells had a better outcome than untransduced NK cells. CD70-targeted CAR-NK had a stronger killing effect at multiple target ratios and were able to clear MM cells faster. Similar results were observed when the clustered regularly interspaced short palindromic repeats CRISPR/Cas9 system was used to knockout MM cells in the BCMA. In preclinical xenograft models, CD70-targeted CAR-NK cells demonstrated superior tumor control compared to untransduced NK cells [37]. These findings have not yet been tested in humans, and an early-phase trial (Phase I/II, NCT05092451) is currently assessing safety and preliminary efficacy in relapsed/refractory MM.

Solid tumors

Solid tumors also extensively express CD70 on their surface.. Currently, CD70-targeted CAR-T cells are utilized in a variety of solid tumors, with impressive results.

RCC

RCC is the most common renal malignancy, and clear cell (cc) RCC is the most common pathologic type [38]. CD70 is highly expressed on the surfaces of both primary and metastatic ccRCC, making it a promising therapeutic target for ccRCC [39]. Panowski et al. used patient-derived xenografts from metastatic ccRCC patients (clear cell histology confirmed by two pathologists), with CD70 expression validated via IHC ($\geq$2+ intensity in $\geq$50 % cells) [40]. In another preclinical study, Xiong et al. demonstrated that nanoantibody-based CD70-targeting CAR-T cells secreted significantly higher levels of cytokines (IL-2, IFN-γ, and TNF-α) during tumor cell co-culture compared to non-transduced T cells and non-targeting CAR-T controls, while in xenograft mouse models these anti-CD70 CAR-T cells exhibited potent antitumor activity and complete tumor eradication in ccRCC models, outperforming both control groups [41].

Allogeneic CD70 CAR-T cells, which exhibit effectiveness and safety in preclinical studies, have progressed to phase I clinical trials. CTX130 has been used to treat advanced or refractory ccRCC. In preclinical studies, CTX130 demonstrated favorable proliferative and cytotoxic profiles, and completely removed tumors in xenografts. COBALT-RCC is a multicenter phase I trial designed to evaluate the safety and efficacy of CTX130 in patients with unresectable or metastatic ccRCC [42]. Sixteen patients received lymphocyte depleting and CTX130 infusion, of which twelve achieved disease stabilization and one achieved CR. The median progression-free survival and overall survival were 2.6 months and 20.5 months, respectively. One patient has been in complete response for 3 years. The results of this clinical study indicate that CAR-T cell therapy has the potential to achieve complete remission in patients with ccRCC, and suggest that CAR-T cells may have promising applications in the treatment of solid tumors.

ALLO-316, a CAR-T cell therapy targeting CD70, minimizes the risk of graft-versus-host disease (GVHD) by knocking out the T cell receptor alpha subunit constant (TRAC) gene using transcription activator-like effector nucleases gene editing [43]. It is currently in clinical trials for the treatment of advanced or metastatic ccRCC that does not respond to immune checkpoint inhibitors and anti-vascular inhibitors (NCT04696731). In the data published by Srour et al., the study included 18 patients with ccRCC, of whom 17 treated with ALLO-316 had metastatic disease. Three patients achieved partial remission, with an ORR of 12 % and a DCR of 71 %, and nine patients were confirmed to be CD70-positive, with an ORR of 22 % and a DCR of 100 % [44]. ALLO-316 has demonstrated safety and efficacy in advanced ccRCC, and is a possible option for the future treatment of CD70-positive ccRCC.

Polyadenosine diphosphate-ribose polymerase (PARP) inhibitors, which have synthetic lethal effects on mutations in DNA repair genes, have been approved for the treatment of breast cancer susceptibility gene-mutated ovarian and breast cancers. Ji et al. used a xenograft mouse model of ccRCC to evaluate the role and mechanism of PARP inhibitors in CAR-T cell therapy. The results showed that PARP inhibitors could stimulate the chemokine and regulate the tumor microenvironment, thus promoting the infiltration of CAR-T cells [45]. The viability of anti-CD70 CAR-T cells in ccRCC and the interplay between the targeted DNA damage response and antitumor CAR-T cell therapies provides a new strategy for anti-CD70 CAR-T cells treatment of solid tumors.

Glioma

CD70 is not expressed on the surface of normal glial cells and neural stem cells, but is highly expressed on the surface of primary and recurrent low-grade gliomas and glioblastomas (GBM). In particular, the positive rate of CD70 in recurrent GBM is 69 %, so CD70 is one of the possible targets for the treatment of glioma [46]. In a preclinical study by Jinn et al., both human- and mouse-derived CD70 CAR-T cells specifically recognized CD70-positive glioma targets, and both exhibited effective antitumor responses against CD70-positive gliomas in xenografts and syngeneic animal models. These responses result in tumor regression and improved prognosis without causing any observed toxicity. Therefore, CAR-T cells targeting CD70 might be a possible option for the treatment of CD70-positive frontal gliomas [46].

GBM is the most common brain tumor in adults, with high malignancy and very poor prognosis [47]. In vitro studies using CD70 CAR-T cells for the treatment of GBM have demonstrated a stable and persistent immune response against GBM cells expressing CD70. Subsequently, Seyfrid et al. administered an intracranial injection of CD70 CAR-T cells into an *in situ* xenograft mouse model of GBM. The results showed that mice treated with CD70 CAR-T cells had a significantly lower tumor load than the control group, with a marked reduction in tumor volume, demonstrating a significant survival advantage [48]. In preclinical xenograft models, CD70 CAR-T cells induced tumor regression and prolonged survival. These findings are limited to animal studies, and clinical trials are required to assess translational potential.

Oncolytic viruses (OVs) exert their antitumor effects through a dual mechanism involving selective tumor cell killing and induction of systemic antitumor immune effects [49]. Zhu et al. enhanced the efficacy of CD70-specific CAR-T cells by IFN-γ released from GBM cells infected with the oncolytic herpes simplex virus-1 (oHSV-1) for tumor treatment [50]. In their study, CD70-specific CAR-T cells specifically recognized and killed tumor cells *in vitro*. Combination therapy with oHSV-1 promoted tumor degradation by enhancing the pro-inflammatory milieu

and reducing anti-inflammatory factors *in vitro. in vivo* studies, combination therapy increased the proportion of T cells and NK cells in the TME, and decreased the expression of regulatory T cells and transforming growth factor β1 in a GBM *in situ* xenograft animal model. In summary, combining OVs with CD70-specific CAR-T cells has the potential to improve their effectiveness against CD70-positive GBM tumor cells. This approach could pave the way for new CAR-T cell therapy options for GBM, and we anticipate the outcomes of its clinical implementation.

Head and neck squamous cell carcinoma

Head and neck squamous cell carcinoma (HNSCC) is a common malignant tumor. Previous studies have shown that CD70 is expressed on the surface of 69 % of HNSCC tumor cells and is closely related to the differentiation grade of the tumor [51]. Therefore, anti-CD70 CAR-T cell therapy is a promising therapeutic approach. Park et al. developed CD70 CAR-T cells using peripheral blood mononuclear cells from a healthy donor source, and co-cultured them with the HNSCC cell line. This resulted in significant tumor-killing effects [52], suggesting that this approach may be a possible option for HNSCC subgroups that highly express CD70. Further studies are required to confirm it.

Owing to the overexpression of CD70 on the surface of HNSCC cells [51], CAR-NK targeting CD70 may also be an effective treatment option for HNSCC. In vitro studies have shown that radiotherapy can sensitize HNSCC cells expressing CD70 to CAR-NK killing, thereby significantly enhancing the killing effect of CAR-NK on tumor cells [53]. Combining radiation therapy with CD70-targeting CAR-NK may be an effective treatment for HNSCC and warrants further investigation through *in vivo* and clinical trials.

Non-small cell lung cancer

In the treatment of non-small cell lung cancer (NSCLC), a common solid tumor, early clinical activity has been observed with targeted agents, such as tyrosine kinase inhibitors (TKIs) [54]. Treatment options are limited to patients who develop drug resistance, which makes the treatment of drug-resistant patients an urgent issue. CD70 is also expressed on 16.3 % of NSCLC tumor cells [55]. Nilsson et al. showed that resistance to TKIs in patients with epidermal growth factor receptor (EGFR)-mutated NSCLC is achieved through epithelial-to-mesenchymal transition. In these patients, CD70 levels were significantly elevated, and high CD70 expression was strongly associated with poor overall survival. *in vitro* assays using TKI-resistant NSCLC cell lines, CD70 CAR-T cells showed dose-dependent cytotoxicity. No clinical data exist yet, and Phase I trials (e.g., NCT05518253) will determine safety and feasibility [56]. According to Yang et al., CAR-T cells targeting CD70 had a killing effect on drug-resistant cancer cells in patients with EGFR-mutated NSCLC who were treated with ositinib, a TKIs [57]. This approach has the potential to be a promising option for patients with TKI-resistant NSCLC.

CAR-NK cells have been demonstrated to be effective in treating TKI-resistant NSCLC, indicating their potential as a therapeutic option. In a study by Nillson et al., CAR-NK targeting CD70 were able to effectively kill drug-resistant tumor cells, while also demonstrating potent anti-tumor activity in animal studies as well [56]. Yang et al. also confirmed the feasibility of using CD70-targeted CAR-NK for the treatment of TKIs-resistant NSCLC patients [57].

CRC/PDAC

Cancer-associated fibroblasts (CAFs) play an important role in the proliferation, invasion, metastasis of CRC and PDAC [58]. In patients with CRC, approximately 15 % of cases exhibit CD70-positive expression in tumor tissues, primarily localized to malignant epithelial cells at the invasive margin. In contrast, PDAC demonstrates a higher CD70 prevalence (25 %), with a characteristically diffuse distribution pattern. Notably, within the tumor microenvironment of both malignancies, CD70 displays specific overexpression in α-SMA+ CAFs subsets, accounting for 30–40 % of CAFs in CRC and 50–60 % in PDAC. This selective expression profile positions CD70 as an ideal therapeutic target [59,60]. Researchers have validated the specific killing effect of CD70-CAR-NK on tumor cells with high CD70 expression by co-culturing them with CD70-positive and solid tumors [61]. Additionally, enhanced cytotoxicity of CD70-CAR-NK on tumor cells was demonstrated after IL-15 stimulation. Subsequently, an IL-15 cytokine component was added to the CD70-CAR mRNA construct to generate CD70.CAR.IL-15 NK cells. The results of the *in vivo* experiments demonstrated that the killing activity of these cells in the CD70 positive Raji mouse model exhibited a limited dependence on CD70 density, leading to a marked delay in tumor growth and an extension of the survival period of the mice. This led to a substantial improvement in the survival rate of mice. Finally, researchers have found that in immunodeficient mouse models of CRC/PDAC, CD70.CAR.IL-15 NK cells eliminated CD70+ CAFs and delayed tumor growth [61]. In conclusion, CAR-NK cells targeting CD70 are important in solid tumors characterized by a pro-connective tissue proliferative response. CD70.CAR.IL-15 NK have demonstrated unique advantages, and we look forward to the success of their clinical translation.

Others

CD70 is also a possible target for the treatment of osteosarcoma because it is highly expressed in the lung metastases of osteosarcoma [62]. According to Rav et al., CD70 is expressed on the surface of osteosarcoma cells but not on the surface of normal osteoblast [63]. Their study demonstrated that CAR-NK targeting CD70 have cytolytic activity on osteosarcoma cells *in vitro* and that this activity is influenced by the release of specific cytokines [64]. Therefore, CD70 CAR-NK may also be used for the treatment of osteosarcoma and their clinical transformation is expected.

CD70 and B7-H3 (CD276) are co-expressed in various tumors [65], including kidney, breast, esophageal, liver, colon cancer, glioma as well as melanoma [66]. Yang et al. designed a bivalent tandem CAR (TanCAR) targeting both CD70 and B7-H3, and evaluated its antitumor effects *in vitro* and *in vivo*. TanCAR-T cells demonstrated greater killing of multiple effector cells and possessed greater cytolytic and cytokine-releasing abilities than nonspecific CAR-T cells *in vivo* experiments. Low doses of TanCAR-T cells effectively control lung cancer and melanoma xenografts, thereby improving survival in animals [66]. Therefore, dual-targeting CAR-T cells with CD70 and B7-H3 may be an effective way to improve CD70-targeted CAR-T cells therapy for solid tumors.

Challenges and innovations

At present, CAR-T/NK cell therapies targeting CD70 still face numerous challenges, but several studies are exploring relevant measures, bringing endless possibilities to cell therapies targeting CD70 (Table 2) .

Fratricide

Under normal physiological conditions, the expression of CD70 on the surface of T cells is minimal. However, upon T cell activation, CD70 expression is significantly upregulated. In the context of tumors, this upregulation is further enhanced. Similarly, in resting NK cells, CD70 surface levels are low, but they are markedly elevated upon NK cell activation [67]. The concurrent presence on activated T and NK cells [6] raises the potential for fratricidal elimination in CD70-directed CAR-T/NK therapies [68].

Researchers have used the CRISPR/Cas9 system to knock out the CD70 gene in T cells and have developed a CD70-specific CAR-T cells based on nanoantibodies (nb70CAR-T) to avoid the fratricide of CAR-T cells. In the *in vitro* experiments, nb70CAR-T were specifically activated by CD70-positive tumor cells and had a powerful killing effect. In

Table 2
Challenges and strategies to address the use of CD70 targeting CAR-T/NK cells.

Challenges	Mechanism	Strategies	Research phases
GVHD	Endogenous TCR on donor T cells	Knocking out the TCR gene of T cells	Preclinical and clinical studies
Persistence of CAR-T/NK cells	Exhaustion; cytokine withdrawal	Knocking out CISH of NK cells	Preclinical studies
CRS/ICANS	Systemic cytokine release and neuro-inflammation	Symptomatic and immunosuppressive therapy	Clinical studies
Tumor heterogeneity	Variable CD70 density; spatial distribution	Upregulating the expression of CD70 by demethylating drugs	Preclinical and clinical studies
Resistance and relapse	Antigen loss	Dual-target or multitarget CAR-T/NK cells	Preclinical and clinical studies
	Immunosuppressive tumor microenvironment	IL-15/IL-18-armored CARs; CRISPR knockout of TGFBR2 or CISH	Preclinical studies
	Fratricide: Up-regulation of CD70 on activated T/NK cells	Knocking out the CD70 gene Nano antibodies targeting CD70	Preclinical and clinical studies

Abbreviations: CAR-T/NK cells, chimeric antigen receptor T/natural killer cells; GvHD, graft versus host disease; TCR, T cell receptor; CISH, cytokine inducible SH2-containing protein; CRS, cytokines release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

xenograft mouse models, it has been observed that CD70-expressing tumor cells can be eliminated effectively with good *in vivo* kinetics [20]. Choi et al. confirmed that the introduction of CD70-targeting CAR into activated NK cells resulted in a significant reduction in fratricide-induced NK cell expansion. However, knocking out CD70 via CRISPR/Cas9 editing does not inhibit NK cells expansion or impair the ability to kill target cells [69]. CAT-248 is an allogeneic CAR-NK cells that employs CRISPR/Cas9 technology to knock out CD70, thereby reducing fratricide resulting from endogenous CD70 expression in activated NK cells. Thus, this approach shows promise for the treatment of CD70-positive ccRCC [70]. Therefore, CD70 knockout is a possible method to resolve the fratricide of CAR-T/NK cells.

CAR-T cells developed by Lu et al. contained antibodies that targeted CD70. Although CAR-T cells have a high affinity for human CD70, they can be successfully produced and manufactured on a clinical scale without causing significant loss of cell expansion, which can mask CD70 in CAR-T cells and prevent fratricides. Additionally, both *in vivo* and *in vitro* experiments have shown strong antitumor activity [71]. Therefore, CAR-T cells containing CD70-targeted nanoantibodies may also be a solution for CAR-T cells fratricide.

GVHD

Allogeneously derived CAR-T cells also cause GVHD during infusion. Padalia et al. generated CD70-targeted CAR-T cells by CRISPR/Cas9 technology. CD70-targeted CAR-T cells were also edited by knocking out TRAC in T cells from healthy donors [72]. The absence of T cell receptor (TCR) reduces the risk of GVHD, thereby enabling the use of allogeneic CAR-T cells therapy. CAR-T cells have demonstrated strong cytotoxic effects against CD70-positive lymphoma and ccRCC *in vitro* [44]. Therefore, knocking out the TCR gene in CD70-targeting CAR-T cells is an effective way to prevent GVHD.

Persistence of CAR-T/NK cells

Previous studies have shown that IL-15 promotes the expression of CD70-CAR, enhances the activation of CD70-CAR-NK, stimulates NK cell proliferation, and upregulates the expression of activated receptor natural killer protein 30 (NKp30) in NK cells *in vitro* [61,73]. Cytokine induced SH2 protein (CISH) is a checkpoint for IL-15-mediated NK cell survival, proliferation, cytotoxicity, and antitumor immunity [74]. Guo et al. used CRISPR/Cas9 to knock out CISH in peripheral blood NK cells obtained from healthy donors. The results revealed that the CD70-targeting CAR-NK cells knockout of CISH demonstrated extended persistence in culture and potent cytotoxicity against CD70-expressing ccRCC tumor cells [34]. In a recent study, Wang et al. constructed CD70-CAR-NK cells from human induced pluripotent stem cells (iPSC) and, at the iPSC stage, inserted a membrane-bound IL-15/IL-15Rα fusion protein. This modification enables the cells to continuously activate mTOR and STAT5 signaling without exogenous IL-2, supporting stable expansion for 3–4 weeks *in vitro* [75]. CD70-CAR-NK cells engineered either by CISH knockout or membrane-bound IL-15/IL-15Rα fusion protein exhibit superior survival, expansion, and anti-ccRCC activity *in vitro*, offering a highly promising "next-generation" product for clinical adoptive immunotherapy.

CRS and ICANS

CRS and ICANS are the two most common complications of CAR-T cell therapy. CRS is caused by systemic immune activation associated with CAR-T cells amplification and a significant increase in serum inflammatory markers and cytokines. The initial clinical manifestations of CRS include fever, myalgia, and fatigue that can progress to life-threatening vasodilatory shock, capillary leakage, hypoxia, and end-organ dysfunction [76]. ICANS is characterized by a pathological process involving the central nervous system following immunotherapy, resulting in the activation or participation of endogenous or injected T cells and/or other immune effector cells. The signs and symptoms may be progressive, including aphasia, altered levels of consciousness, impaired cognitive ability, motor weakness, seizures, and brain edema [77]. Supportive care remains the primary therapeutic approach, with corticosteroids serving as the most commonly utilized agents for managing both complications. In cases of severe CRS, IL-6 receptor antagonist tocilizumab and IL-1 receptor antagonist anakinra have demonstrated clinical efficacy. However, as tocilizumab shows limited effectiveness in preventing or treating ICANS), further investigation is warranted to identify optimal therapeutic strategies for ICANS management.

Others

Drug resistance and relapse are also problems that must be solved in the process of tumor treatment. The resistance of CD70 targeted CAR-T/NK therapy mainly stems from antigen loss, immunosuppressive tumor microenvironment, and fratricide. To overcome the challenges, combination strategies—such as epigenetic priming to upregulate CD70, dual-target CAR designs to prevent antigen escape, and cytokine armoring or gene editing (e.g., CD70 or CISH knockout) to enhance persistence and reduce fratricide—are being actively explored in preclinical and clinical settings.

Cellular immunotherapy must also address the challenge of tumor heterogeneity. The expression of CD70 on the surface of different tumor cells is different. Consequently, the efficacy of CD70-targeted CAR-T/NK cells varies in different tumors. In AML, epigenetic drugs can increase the expression of CD70 on the surface of AML tumor cells [20–22]. However, the heterogeneity of CD70 on the surface of other tumor cells

requires further exploration. Off-target effects can also arise during CAR-T/NK cells therapy; one possible solution is the use of CAR that can simultaneously target two or more target [23,27].

Conclusions and future directions

CAR-T cell therapy, a rapidly developing cellular immunotherapy technology, has made significant progress with respect to the treatment of hematologic malignancies. Based on the high expression of CD19 and BCMA in B-cell derived malignant tumors and multiple myeloma, currently approved CAR-T cells are limited to CD19 and BCMA.

CD70 is highly expressed in tumor cells in various tumors, making it an important target for CAR-T/NK cell therapy. Numerous clinical trials examining CAR-T cells designed to target CD70 for the treatment of solid tumors and hematologic malignancies (Table 3) support the broad application of CAR-T cells that target CD70. CAR-NK cells play a significant role in the treatment of CD70+ tumors because of their unique advantages, and clinical trials related to these cells are currently ongoing (Table 4).

In contrast, CD70-CAR must still clear three major hurdles: antigen heterogeneity, fratricide of autologous T/NK cells, and the Immunosuppressive tumor microenvironment of solid tumors. In the future, CD70-CAR will move towards dual target or tandem design (such as CD70/CLL-1, CD70/CD19, CD70/B7-H3), and maintain CD70 expression with epigenetic or microenvironmental regulators. To reduce fratricide, CRISPR/Cas9 mediated effector cell CD70 knockout, low affinity CAR based on nanobodies and IL-15/CISH-edited armored constructs are currently being tested for improved persistence and safety. Biomarker-driven patient selection, optimal sequencing of combination regimens, and long-term surveillance for antigen-low escape remain the critical gaps that must be closed before CD70-targeted CAR-T/NK therapy becomes a standard-of-care option across hematologic and solid malignancies (Table 5).

AI declaration

None of the figures or panels were created using AI tools. All figures and panels were generated through traditional methods and software commonly used.

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CRediT authorship contribution statement

Sijia Yan: Methodology, Investigation, Formal analysis, Data curation. **Xiaojian Zhu:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Yi Xiao:** Writing – review & editing, Funding acquisition, Conceptualization.

Table 4
Summary of ongoing clinical trials of CD70-targeted CAR-NK cells.

Indications	Drugs	ClinicalTrials.gov ID	CAR-NK Source	Status
CD19/CD70 in Refractory/ Relapsed B-cell Non-Hodgkin Lymphoma	CB dualCAR-NK19/70	NCT05667155	Cord blood NK cells	Recruiting
CD19/CD70 in Refractory/ Relapsed B-cell Non-Hodgkin Lymphoma	dualCAR-NK19/70 cell	NCT05842707	Cord blood NK cells	Recruiting
Relapse/Refractory Hematological Malignances	CAR.70/IL15-transduced CB-NK cells	NCT05092451	Cord blood NK cells	Recruiting
Advanced Renal Cell Carcinoma, Mesothelioma and Osteosarcoma	CAR.70/IL15-transduced CB-NK cells	NCT05703854	Cord blood NK cells	Recruiting

Table 5
Comparative analysis of CD70 CAR-T and CAR-NK cells.

Features	CD70 CAR-T cells	CD70 CAR-NK cells
Preclinical Efficacy	Demonstrated potent cytotoxicity in AML, NHL, RCC, and gliomas. Dual-targeting (e.g., CD70/ CLL-1, CD70/CD19) enhances tumor control.	Effective against CD70+ tumors, including B-NHL, TCL, and solid tumors (e.g., RCC, CRC/PDAC). Innate recognition mechanisms (e.g., ADCC, stress-ligand sensing) complement CAR targeting.
Toxicity Management	High risk of CRS/ICANS; managed with tocilizumab/ corticosteroids Fratricide mitigated via CD70 knockout or nanobody-based CAR designs.	Lower risk of CRS/ICANS; safer profile due to innate immune compatibility. CD70 knockout reduces fratricide without impairing NK cell function.
Persistence	Durable persistence in hematologic malignancies; limited in solid tumors.	Transient persistence; enhanced by IL-15 engineering or CISH knockout.
Advantages	Proven clinical efficacy in hematologic cancers.	Multimodal killing, allogeneic potential, and reduced toxicity.
Limitations	Manufacturing complexity; GVHD risk in allogeneic settings.	Limited expansion capacity; requires strategies to prolong *in vivo* activity.

Table 3
Summary of ongoing clinical trials of CD70-targeted CAR-T Cells.

Indication	Product	ClinicalTrials.gov ID	Patient	CAR type	Trial Phase	Results
Clear cell renal cell carcinoma	ALLO-316	NCT04696731	Advanced/metastatic clear cell renal cell carcinoma	TCRα-knockout allogeneic CAR-T	Phase I	ORR 12 %; DCR 71 %
Glioblastoma	8R-70CAR T cells	NCT05353530	CD70+ recurrent Glioblastoma	Autologous CAR-T	Phase I	Recruiting
T cell lymphoma	CTX130	NCT04502446	Relapsed/refractory T cell lymhoma	Allogeneic CRISPR-edited CAR-T	Phase I	ORR 70 %, CR 30 %, DCR 90 %
B cell lymphoma	bi-4SCAR19/ 70	NCT05436496	CD19+/CD70+ B-cell malignancies	Dual-target CAR-T (CD19+CD70)	Phase I/ II	Recruiting
non-small cell lung cancer	CD70 CAR-T	NCT05518253	EGFR-tyrosine kinase inhibitors-resistant non-small cell lung cancer	Autologous CAR-T	Phase I	Preclinical efficacy shown
Acute myeloid leukemia	CD70/CLL-1 BiCAR	NCT04662294	Relapsed/refractory acute myeloid leukemia	Dual-target CAR-T (CLL-1+CD70)	Phase I/ II	Preclinical: 40 % survival gain

Declaration of competing interest

The authors declare no competing financial interests.

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