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Review article

NK cell-based tumor immunotherapy

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ABSTRACT

Natural killer (NK) cells display a unique inherent ability to identify and eliminate virus-infected cells and tumor cells. They are particularly powerful for elimination of hematological cancers, and have attracted considerable interests for therapy of solid tumors. However, the treatment of solid tumors with NK cells are less effective, which can be attributed to the very complicated immunosuppressive microenvironment that may lead to the inactivation, insufficient expansion, short life, and the poor tumor infiltration of NK cells. Fortunately, the development of advanced nanotechnology has provided potential solutions to these issues, and could improve the immunotherapy efficacy of NK cells. In this review, we summarize the activation and inhibition mechanisms of NK cells in solid tumors, and the recent advances in NK cell-based tumor immunotherapy boosted by diverse nanomaterials. We also propose the challenges and opportunities for the clinical application of NK cell-based tumor immunotherapy.

1. Introduction

Natural killer (NK) cells are innate lymphoid cells with strong cytolytic function to identify and kill tumor cells directly without antigen presentation, which is different to the other adaptive immune cells such as T cells and B cells [1]. In addition, NK cells lack surface T cell receptors (TCRs) and cannot cause cytokine release syndrome (CRS), and graft-versus-host-disease (GVHD) [2], which provides an opportunity to use the autologous (from the patients) or allogeneic (from the healthy donors) sources of NK cells for adoptive cellular therapy [3]. Chimeric antigen receptor (CAR) NK cells have been successfully investigated in clinical studies. The effects of NK cell infusion combined with IL-15 on solid and hematologic tumors, as well as the effects of anti-CD19 CAR-engineered NK cells on leukemia patients were investigated [4,5]. For example, 7/11 patients with relapsed or refractory CD19-positive cancers had a complete remission [5]. CAR-NK cells may have advantages over CAR-T cells, such as less induced side effects. In this context, recent studies have shown that CAR-NK cells did not cause any associated cytokine storm in patients with tumors, which makes the NK cell-based tumor immunotherapy very attractive and promising [6].

NK cell effector function is controlled by the surface activating and inhibiting receptors that can distinguish tumor cells from healthy cells. The most important inhibitory receptors on the surface of NK cells are the members of the killer cell immunoglobulin-like receptor (KIR) family and CD94/NKG2A, which recognize the major histocompatibility complex class I molecules (MHC I; MHC is also known as human leukocyte antigen, HLA). MHC I molecules expressed on the normal healthy cells act as ligands of inhibitory receptors and contribute to the self-tolerance of NK cells [7]. For tumor cells, their expression of MHC I molecules are often downregulated, allowing them escaping from the immune surveillance of $CD8^+$ T cells. In contrast, with the absence of the main ligands of NK cells inhibitory receptors (CD94/NKG2A and KIRs), NK cells are not inhibited and become activated. They can directly kill tumor cells through NK cell-mediated cytotoxicity, or indirectly kill them through secretion of cytotoxic mediators (Granzyme B), pore-forming proteins (perforin), cytokines, and chemokines [8]. Granzyme B and perforin are the core proteins required for NK cell mediated tumor killing, although the death-receptor pathways (involving FasL and TRAIL) are sometimes involved [9]. Furthermore, NK cells secrete a large number of cytokines (such as IFN-γ, TNF-α, TNF-β, IL-6, GM-CSF) and chemokines (such as CCL3, CCL4, CCL5), which can shape B cell and T cell activation, and impact the function of macrophages, dendritic cells (DCs), and neutrophils [10]. The wealth

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Abbreviations

ADO	Adenosine
ADCC	Antibody dependent cell-mediated cytotoxicity
ACT	Adoptive cell therapy
CRS	Cytokine release syndrome
CAR	Chimeric antigen receptor
CTLA4	Cytotoxic T-lymphocyte-associated protein 4
CaP	CpG loaded-phosphate calcium
COX2	Cyclooxygenase-2
DCs	Dendritic cells
DCNP	Down-conversion nanoparticles
DDEs	DC-derived exosomes
DNase I	Deoxyribonuclease I
ECM	Extracellular matrix
FasL	Fas ligand
FLI	Fluorescence imaging
GVHD	Graft-versus-host disease
GOX	Glucose oxidase
GNSs	Gold nanoclusters
HCC	Hepatocellular carcinoma
HLA	Human leukocyte antigen
HSP	Heat shock protein
IDO1	Indoleamine 2,3-dioxygenase 1
IFN-γ	Interferon gamma
IL	Interleukin
iPSC	Induced pluripotent stem cells
ITAMs	Immunoreceptor tyrosine-based activation motifs
KIR	Killer cell immunoglobulin-like receptor
LDHA	Lactate dehydrogenase A
MDSC	Myeloid-derived suppressor cells
MHC I	Major histocompatibility complex class I molecules
MICA	MHC I polypeptide-related sequence A
MICB	MHC I polypeptide-related sequence B
MRI	Magnetic resonance imaging
NAD^+	Nicotinamide adenine dinucleotide
NDEs	NK cell-derived exosomes
NETs	Neutrophil extracellular traps
NK	Natural killer
NKCEs	Natural killer cell engagers
NMN	Nicotinamide mononucleotide
PAI	Photoacoustic imaging
PDT	Photodynamic therapy
PD-1	Programmed death-1
PET	Positron emission tomography
PFC	Perfluorohexane
PGE2	Prostaglandin E2
PTT	Photothermal therapy
RBCs	Red blood cells
ROS	Reactive oxygen species
SHP-1	Src homology 2 domain-containing protein tyrosine phosphatase-1
TCRs	T cell receptors
TDEs	Tumor cell-derived exosomes
TIGIT	T-cell Ig and ITIM domain
TIM3	T cell immunoglobulin domain and mucin domain-3
TLR4	Toll-like receptor 4
TME	Tumor microenvironment
TRAIL	Tumor necrosis factor-related apoptosis-inducing ligand
Treg	Regulatory T cells
ULBPs	UL16-binding proteins

properties of NK cells indicate their related complicated biological mechanism network and support the great potential of NK cell-based tumor immunotherapy.

Based on the powerful selective anti-tumor efficacy and immune-surveillance function, NK cell-based immunotherapy has been widely investigated both in hematologic and solid malignant cancers, such as myeloid leukemia [11,12], cervical cancer [13,14], melanoma [15,16], glioblastomas [17], and hepatocellular carcinoma [18,19]. However, NK cell-based immunotherapy is less effective in treatment of solid tumors because of the following challenges [20,21]. The tumor microenvironment (TME) and suppressive immunity of solid tumors lead to the dysfunction and poor infiltration of NK cells into the tumors [22–24]. Furthermore, the expression of ligands on tumor cell surface for activation of NK cells is reduced, which is contrast to the expression of inhibitory ligands [25–27]. Therefore, development of innovative methods to boost NK cell-based tumor immunotherapy is highly desired.

A possible solution for improving the efficacy of NK cell-based tumor immunotherapy is the nanotechnology. Over the past few decades, the application of nanotechnology in immunotherapy has attracted extensive attention [28–32]. The unique physical and chemical properties of nanoscale materials lay a solid foundation for tumor therapy [33–35]. Nanomaterials can be modified to selectively penetrate into tumor tissue to overcome several limitations of tumor immunotherapy [36,37]. They can selectively target immune or tumor cells by modification with targeting molecules, peptides or antibodies, and thus enhance the efficacy of immunotherapy [38–40]. In this article, we will review the recent advances in NK cell-based tumor immunotherapy, including the mechanism of NK cell activation and inhibition in tumor, rational design, fabrication and application of bionanomaterials for enhancing efficacy of NK cell-based tumor immunotherapy, and the new trends and clinical challenges (Fig. 1).

2. Sources, expansion, activation and inhibition of NK cells

2.1. Sources, expansion, and clinical trials of clinical-grade NK cells

NK cells used for infusion can be obtained from either the patients themselves or the donors. The purification/expansion of clinical-grade NK cells can be produced by using the peripheral blood, cord blood, and embryonic stem cells [41–44]. In autologous transplantation, NK cells from the patients are activated and expanded *in vitro* in the presence of cytokines. The research results suggest that the combination of IL-12, IL-15, and IL-18 may produce NK cells with stronger functions and memory properties. Irradiated human lymphoblastocytes K562 are often used as feeder cells in the medium and can be modified to express cytokines (such as IL-15 and IL-21) and/or co-stimulatory molecules. Then, the activated and amplified NK cells are transferred back into the patients, who are typically administrated with cytokine administration (IL-2) to maintain the expansion and function of the injected NK cells [45]. In allogeneic transfer, NK cells can be obtained from HLA-matched or haploidentical donors.

NK cells are expanded through the processes similar to those used for autologous transfer, but T cells should be removed to avoid GVHD [46]. In recent years, various NK cell-mediated tumor therapies were tested in clinical trials and yielded promising results in patients (Table 1). A growing number of clinical studies have shown the safety and efficacy of NK cells derived from induced pluripotent stem cells (iPSC), peripheral blood mononuclear cells, cord blood, and cells lines in the treatment of malignant tumors [47–67]. For example, in a phase I trial, iPSC-NK cells expressing CAR showed encouraging results in treatment of patients with relapsed or refractory B-cell lymphoma [48,68].

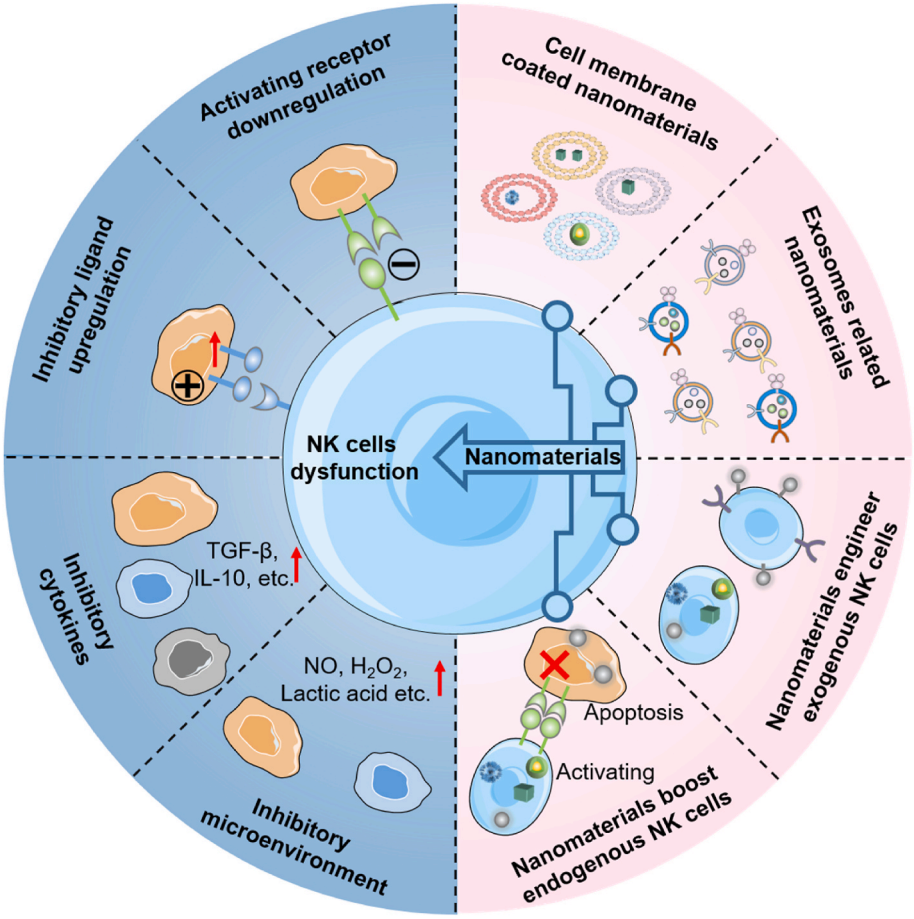

Fig. 1. Illustrative representation of NK cell dysfunction in tumor and nanomaterials mediated NK cell-based tumor immunotherapy. The left half of Fig. 1 shows several major causes of NK cell dysfunction: (1) Downregulation of activating receptors on NK cells; (2) Upregulation of inhibitory ligands on tumor cells; (3) Inhibitory cytokines secreted by tumor cells, myeloid-derived suppressor cells (MDSC), and regulatory T cells (Treg); (4) Immunosuppressive tumor microenvironment. The right half of Fig. 1 shows several nanomaterial-mediated strategies for enhancing NK cell immunotherapy: (1) Encapsulation of core materials with the cell membrane from tumor cells, macrophages, red blood cells, or NK cells; (2) Use of exosomes and exosome-related nanomaterials from different parental cells (NK cells, DCs, or tumor cells); (3) Engineering of exogenous NK cells by nanomaterials to enhance their tumor targeting capability; (4) Regulation of tumor microenvironment, tumor or/and NK cells by nanomaterials to boost endogenous NK cells.

2.2. Receptors, cytokines and small molecule drugs used for NK cell activation

NK cell activation and inhibition is mainly controlled by a series of activating, co-stimulatory and inhibitory receptors. The net balance of activating and inhibiting signals of these receptors determines the state of NK cells. The activating receptors include the Fcγ receptor CD16, the natural cytotoxicity receptors family (NKp30, NKp44 and NKp80, *etc.*), *C*-type lectin receptors (NKG2D, CD94/NKG2C, *etc.*), killer cell immunoglobulin-like receptors (KIRs) (KIR-2DS, KIR-3DS, *etc.*) (Fig. 2).

CD16 is a potent activating receptor of NK cells, which can recognize the Fc portion of IgG antibodies specifically for activating NK cells through a process termed antibody dependent cell-mediated cytotoxicity (ADCC) [69]. It is the only receptor that can activate NK cells independently, without any additional activation through other receptors [70]. Preventing the down-regulation of CD16 in the NK cells might enhance their activity [71]. In addition to CD16, members of natural cytotoxicity receptors family (NKp30, NKp44 and NKp80, *etc.*) can also directly bind to tumor associated ligands to trigger the apoptosis of tumor cells [72]. NKG2D is a widely studied homodimeric *C*-type lectin receptor, and its ligands on tumors include MHC I polypeptide-related sequence A (MICA), MHC I polypeptide-related sequence B (MICB), and UL16-binding proteins (ULBPs) [73]. Inhibition of MICA and MICB shedding on the tumor surface by antibodies may promote NK cell-based tumor immunotherapy [74]. CD94/NKG2C is a heterodimer *C*-type lectin receptor and binds to HLA-E ligand, which is typically associated with inhibition signals *via* the NK cell inhibitory receptor NKG2A [75]. KIRs family of NK receptors can be divided into activating receptors and inhibitory receptors, depending on their transmembrane and intracellular domain. The activating receptors (KIR-2DS, KIR-3DS *etc.*) can produce activating signals through their association with adaptor proteins that contain ITAMs [76]. NK cell activation also depends on co-stimulation molecules such as 4-1BB (also known as CD137) [77], 2B4 (also known as CD244) [78], DNAM1 (also known as CD226) [79], and OX40 (also known as CD134) [80].

Ligation of individual activating receptors (except CD16) is usually not enough to trigger the cytotoxicity or cytokine secretion of naive NK cells. The secretion of cytokines is the key to pre-activation of NK cells [81]. Various cytokines, including IL-2, IL-12, IL-15, IL-18, and IL-21, can be used for enhancing the activation of NK cells (Fig. 2) [82–84]. In autologous NK cell transfer, IL-2 has been usually used for activation and expansion of NK cells [85]. Patients received infusion of NK cells are usually given IL-2 to promote *in vivo* expansion [86]. However, the anti-tumor effect of individual IL-2, IL-12 or IL-18 is rather limited. In contrast, the combination of IL-12, IL-15 and IL-18 may induce considerable biological changes and a population of memory NK cells, including enhanced responses to IL-2, more secretion of IFN-γ and greater cytotoxicity [45,81]. In addition, the combination of IL-21 and tumor targeted monoclonal antibodies can enhance the activity of NK cells and improve their anti-tumor effects [87–89]. However, among these cytokines, IL-15 is the most promising one for activating NK cells. Infusion of IL-15 into the patients with metastatic malignancies in clinical trials showed proliferation and substantial increase of NK cells [90].

In addition to cytokines, small molecule drugs can also effectively enhance the anti-tumor activity of NK cells. SIS-3, a specific Smad3 inhibitor, is used as an immunotherapeutic stimulant for promoting the activity and proliferation of NK cells [91–93]. It has been found that the dysregulated NAD^+ metabolism contributes to the dysfunction of tumor-infiltrating NK cells. Supplementation of the NAD^+ precursor

Table 1
Clinical trials of tumor immunotherapy by using NK cells in recent years.

Cell source	Cancer type	Study phase	Trail Name	Ref
Not disclosed	Relapsed or refractory B cell non-hodgkin lymphoma	Early Phase I	NCT04639739	[47]
iPSC	Relapsed/refractory B-cell lymphoma; Chronic lymphocytic leukemia	Phase I	NCT04245722	[48]
iPSC	Relapsed/refractory acute myelogenous leukemia; Relapsed/ refractory multiple myeloma	Phase I	NCT04614636	[49]
Peripheral blood	Acute myeloid leukemia; Myelodysplastic syndrome	Phase I	NCT04623944	[50]
iPSC	Ovarian cancer	Phase I	NCT04630769	[51]
iPSC	Advanced solid tumors	Phase I	NCT04551885	[52]
Peripheral blood	Relapsed/refractory non-hodgkin lymphoma; chronic lymphocytic leukemia; B cell acute lymphoblastic leukemia	Phase I	NCT05020678	[53]
Peripheral blood from HLA-haplo-identical donor	Refractory/relapsed B-cell NHL	Phase I	NCT04887012	[54]
Cord blood	Relapsed or refractory hematological malignancies	Phase I	NCT04796675	[55]
Not disclosed	Relapsed or refractory hematological malignancies	Phase I	NCT04796688	[56]
Not disclosed	Relapsed/refractory acute myeloid leukemia	Phase I	NCT05008575	[57]
Cord blood	Relapse/refractory hematological malignances	Phase I	NCT05092451	[58]
Not disclosed	Relapsed or refractory multiple myeloma	Early phase I	NCT05008536	[59]
Modified NK-92	Recurrent/metastatic gastric or head and neck cancer	Phase II	NCT04847466	[60]
Not disclosed	Relapsed/refractory B-cell acute lymphoblastic leukemia	Phase I	NCT05379647	[61]
iPSC	Relapsed/refractory CD19-positive B-cell malignancies	Phase I	NCT05336409	[62]
Not disclosed	Acute myeloid leukemia	Early phase I	NCT05215015	[63]
iPSC	Relapsed/refractory multiple myeloma	Phase I	NCT05182073	[64]
Not disclosed	Refractory metastatic colorectal cancer	Phase I	NCT05213195	[65]
Cord blood	Relapsed/refractory acute myeloid leukemia	Not Applicable	NCT05247957	[66]
Not disclosed	Advanced solid tumors	Early phase 1	NCT05194709	[67]

nicotinamide mononucleotide (NMN) significantly enhanced NK cell-based tumor immunotherapy [94]. Natural compounds extracted from plants also possess the capability of activating NK cells [95], mainly including the vitamins and phytochemicals. Vitamins play crucial functions in cell metabolism. Retinoids (Vitamin A) can effectively increase the activity of splenic NK cells and suppress tumor growth [96]. Another study showed that the NK cell activity was increased after oral administration of vitamin C and returned to normal level after 48 h [97]. Apart from several vitamins, various phytochemicals have been identified as activators of NK cells [98]. Astragaloside III, a natural compound from astragalus, can significantly elevate the expressions of NKG2D, Fas, and IFN-γ in NK cells, leading to the increased infiltration of NK cells into tumor to upregulate the anti-tumor response [99]. Although various natural compounds can effectively activate NK cells for immunotherapy, their activation molecular mechanisms are still elusive and need to be comprehensively investigated.

2.3. Receptors, cytokines and immunosuppressive environment for NK cell inhibition

NK cells also express various inhibitory receptors, which provide immune self-tolerance and negative feedback mechanisms, and counteract the activation signals from activating receptors (Fig. 3). There are multiple families of NK cells inhibitory receptors, and the autoreactivity in human NK cells is controlled by KIRs and CD94/NKG2A inhibitory receptors specifically for recognizing human leukocyte antigen class I (HLA I) molecules. Under normal conditions, the interactions between these inhibitory receptors and their specific HLA I ligands inactivate NK cells, thus preventing cytolysis of healthy cells [7]. On the contrary, the overexpression of HLA-E in some tumors is associated with the worse outcome. Reducing the function of inhibitory KIRs by specifically blocking ligand recognition in the treatment of patients with HLA-E overexpression tumors would be particularly effective [100,101]. Other inhibitory immune checkpoints have also been found in NK cells, which are responsible for maintaining the homeostasis of immune cells, include PD-1, T-cell Ig and ITIM domain (TIGIT), CTLA4, TIM-3, CD96, *etc.* Several tumor mouse models showed that PD-1/PD-L1 interactions potently suppress NK cell-mediated immunotherapy [102]. TIGIT and CD96 are members of a group of Ig superfamily receptors. Their corresponding ligands CD112 and CD155, are usually upregulated in tumor cells. The upregulation of TIGIT and PD-1 has been reported in different malignancies, and they are usually related to the immunosuppression of T cells and NK cells in tumor [103]. It has been shown that TIGIT blocked with specific mAbs can induce excellent anti-tumor immune activity when it is combined with other checkpoints [104]. T cell immunoglobulin domain and mucin domain-3 (TIM-3) is a type 1 glycoprotein co-expressed with PD-1 on matured NK cells, and its ligand is Galecin-9 [105]. Previous studies have demonstrated that the upregulation of TIM-3 on NK cells in tumor impaired their effector function. The blockade of TIM-3 could restore T-cell effector function in preclinical models and result in an increased NK cytotoxicity [106,107]. In summary, blocking the interactions of inhibitory receptors or their ligands is still an attractive strategy in NK cell-based tumor immunotherapy.

In addition to inhibitory receptor, intracellular checkpoint molecules (*e.g.* SHP-1 and Cbl-b/c-Cbl) are also engaged and functioned in the downstream of inhibitory and activating receptors of NK cells. Src homology 2 domain-containing protein tyrosine phosphatase-1(SHP-1) has been shown to inhibit NK cell activity by dephosphorylating the guanine nucleotide exchange factor (Vav1) [108], and the acute loss of SHP-1 abundance or activity is needed for enhancing anti-tumor function of NK cells [109,110]. In addition to SHP-1, the E3 ubiquitin ligases Cbl-b and c-Cbl, as the key negative regulators of NK cell activity, can block NK cells recognizing and killing tumor cells [111,112]. For example, a series of small-molecule Cbl-b inhibitors activate NK cell activity by inhibiting ubiquitination of TAM receptors [113,114].

During tumor progression, tumor cells in the TME have several ways to either evade from NK-cell recognition, or induce dysfunction of NK cells. The TME consists of immunosuppressive cytokines (*e.g.* TGF-β, IL-6, IL-8, IL-10, prostaglandin E2 (PGE2), adenosine (ADO)), immunomodulatory enzymes (*e.g.* CD39, CD73, indoleamine 2,3-dioxygenase 1 (IDO1), low nutrients (*e.g.* glucose and amino acid), hypoxia and acidity, which synergistically suppress the maturation, proliferation and activation of NK cells (Fig. 3) [115–118]. In addition, the accumulation of extracellular matrix and increased interstitial fluid pressure can prevent the tissue penetration of immune cells [119].

TGF-β is a major immunosuppressive cytokine that reduces the anti-

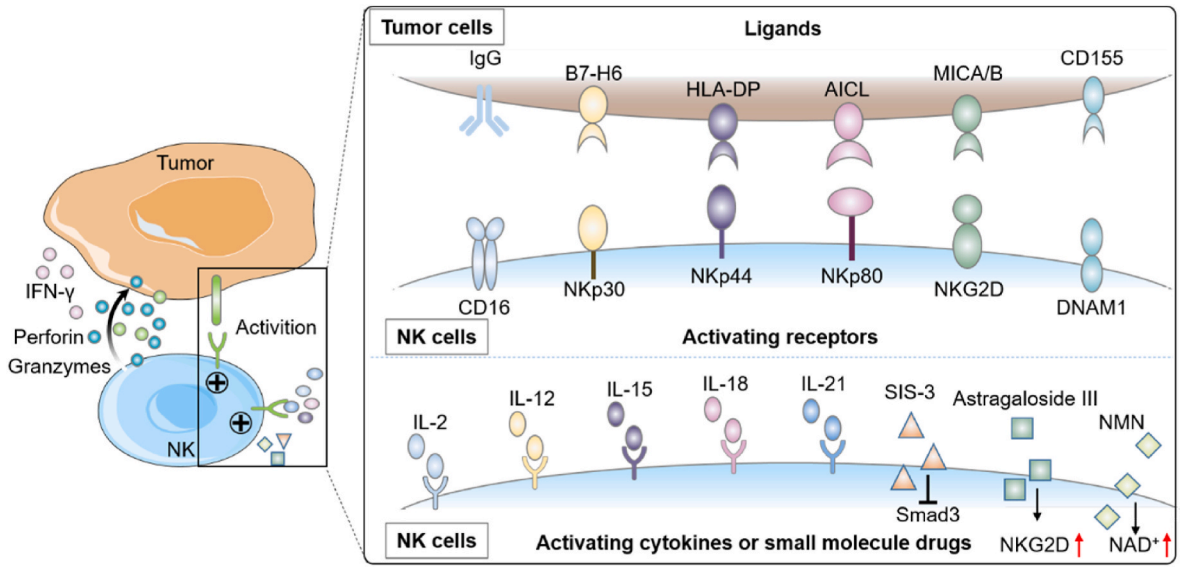

Fig. 2. Schematic illustration of receptors, cytokines and small molecule drugs used for activating NK cells. (1) Activating receptor transduce signals through various pathways. The interactions between activating receptors and their ligands can activate NK cells and trigger the apoptosis of tumor cells. Activated NK cells can release chemokines for attracting multiple subsets of immune cells, and the release of cytolytic granules containing granzyme B and perforin. (2) The anti-tumor activity of NK cells can also be enhanced by cytokines (IL-2, IL-12, IL-15, IL-18, IL-21) or specific small molecules (SIS-3, Astragaloside III, NMN, *etc*.).

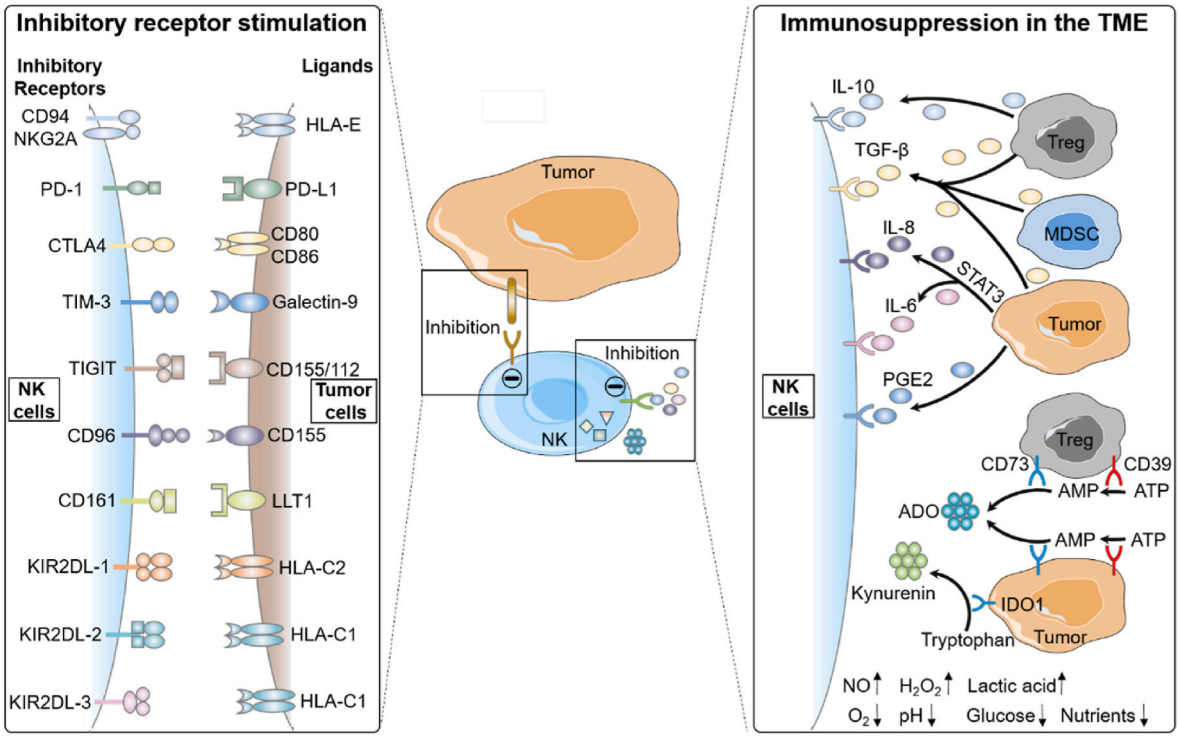

Fig. 3. Schematic illustration of receptors, cytokines and immunosuppressive environment for inhibiting NK cells. The left half of Fig. 3 shows the interactions of NK cell inhibitory receptors with their ligands. The overexpression or overstimulation of inhibitory receptors leads to inhibition of infiltrating NK cell activity in many malignant solid tumors. The right half of Fig. 3 shows that NK cell inhibition is associated with the immunosuppression of cytokines, immunomodulatory enzymes, and TME.

tumor activity of NK cells. In glioblastoma, TGF-β can reduce the expression of the major activating receptors on NK cells [117,120]. Patients with colorectal and lung cancers have higher level of plasma TGF-β than healthy volunteers, which leads to the decreased NKG2D expression on NK cells and the damage to NK cell function [121]. STAT3 signaling plays a key role in the secretion of IL-6 and IL-8, downregulates the activation receptors (NKG2D and NKp30) on NK cells in various primary tumors, decreases NK cell activity, and contributes to tumor progression and poor survival [122]. Apart from immunosuppressive cytokines, various cell types in the TME can downregulate immune response including regulatory T (Treg) cells, myeloid-derived suppressor cells (MDSC), and fibroblasts [123–125]. Treg cells play an immunosuppressive role by inhibiting NK cells and $CD8^+$ T cells *via* secretion of the IL-10 and TGF-β [126,127]. MDSC of tumor patients significantly

inhibits NK cell-mediated ADCC by producing nitric oxides [128]. PGE2 is a small molecule upregulated in various cancers, produced by tumor cells and tumor-associated mesenchymal stem cells, which can reduce NK cytotoxicity [129,130].

In the TME, the immunoregulatory enzymes can produce immunosuppression through their catalytic products, which act as negative regulators of T cells and NK cells to inhibit their metabolism and effector functions. CD39 and CD73 are two immunoregulatory enzymes expressed in the TME, which contribute to the conversion of extracellular ATP into the immunosuppressive metabolite ADO [131]. IDO1 as a metabolic enzyme overexpressed in various tumors can convert the tryptophan into kynurenine to suppress the activation of NK cells [132,133]. The strategies for overcoming immunosuppressive factors mediated NK cell dysfunction include inhibiting immunosuppressive cytokines and immunoregulatory enzymes *via* small molecule inhibitors, or blocking metabolic enzymes with antagonistic antibodies [134–137].

Apart from immunosuppressive cytokines and enzymes, most solid tumors are featured with hypoxia, low nutrients, and acidity due to their heterogeneity. Hypoxia is a common driver of NK cell dysfunction in solid tumors [138,139]. It promotes tumor cells to exhibit an abnormal metabolic behavior and result in a high level of lactic acid, over consumption of vital nutrients, high concentrations of toxic catabolites and the formation of tumor acid microenvironment, which further affects the recognition and response of the immune system to tumor cells [140]. To overcome the detrimental effects of hypoxia and metabolic immunosuppression, the current strategies mainly focus on two aspects: improving hypoxia or changing the metabolic constitutions of tumors to boost NK cells in the immunosuppressive TME. The cytotoxic activity of NK cells can be promoted by reducing the immunosuppressive metabolites [141,142]. For example, the lactate in the TME can be decreased by targeting lactate transporters, leading to improved anti-tumor cytotoxicity of T cells and NK cells *in vivo* [143,144].

It is important to keep physiological balance during the regulation of hypoxia and immune metabolism in TME, because some metabolites are important components of normal metabolism. Although many strategies are still in the stage of basic research or clinical trials, the combined methods involving TME regulation and NK cell immunotherapy could reduce immunosuppression to achieve better anti-tumor therapy.

Among the NK cell-based tumor immunotherapy strategies, the recent trend is to develop effective targeted nanomaterials to promote anti-tumor immune response of NK cells. Because of the unique physical and chemical properties, nanomaterials have been widely explored in tumor immunotherapy. They can target specific immune cells to transport immunomodulators, kill tumor cells to enhance antigen release, regulate immunosuppressive microenvironment and enhance the efficacy of immunotherapy. In this review, we will focus on the recent advances in nanomaterials mediated NK cell immunotherapy, along with the perspectives and challenges.

3. Nanomaterials for enhancing NK cell immunotherapy

Benefited from the excellent biocompatibility and biodegradability, various bioactive nanomaterials have shown great potential in enhancing efficacy of NK cell immunotherapy. This section introduces different strategies for enhancing engineering NK cell-based tumor immunotherapy by different types of nanomaterials, including cell membrane coated nanomaterials, exosome related nanomaterials, nanomaterials engineer exogenous NK cells, and nanomaterials boost endogenous NK cells (Fig. 4).

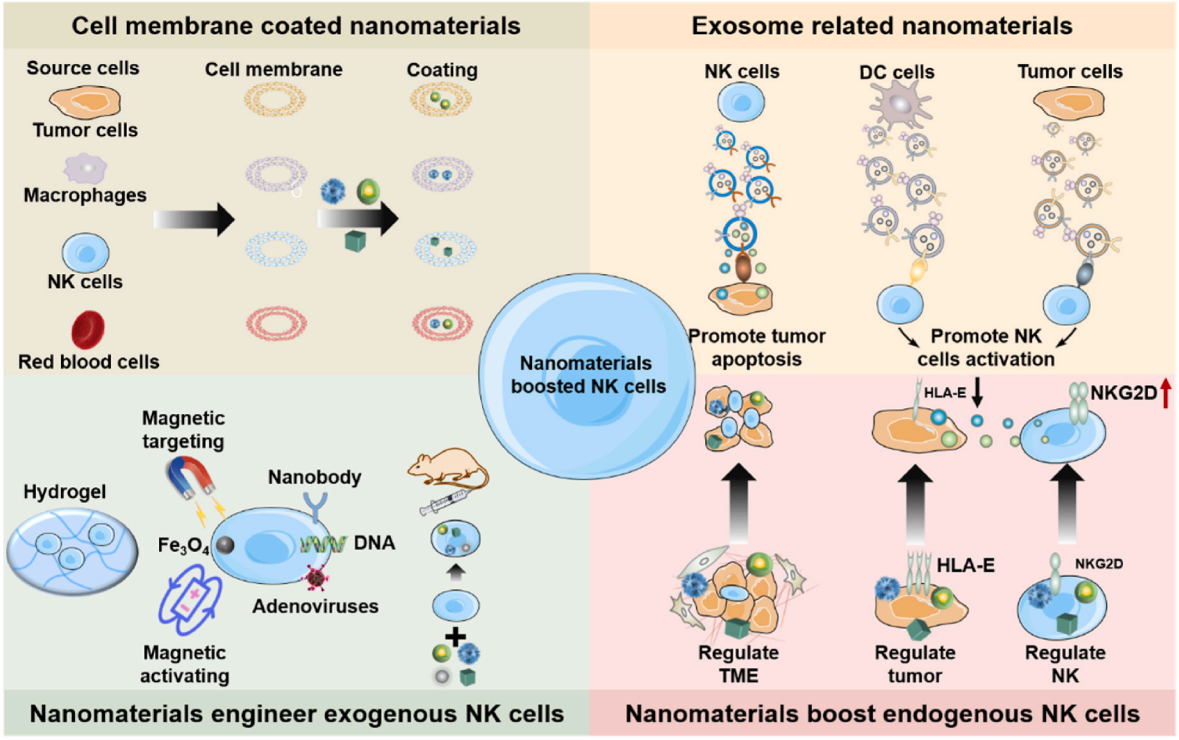

Fig. 4. Schematic illustration of the nanomaterials boosting NK cell-based tumor immunotherapy. Four types of nanomaterials were used for enhancing NK cell immunotherapy: (1) Nanoparticles coated with cell membranes from different sources show the advantages of immune evasion, long blood circulation, tumor targeting, and good biocompatibility; (2) Exosomes and exosome-related nanomaterials from different parental cells (NK cells, DCs, or tumor cells) show the advantages of excellent biocompatibility, low toxicity, and biostability; (3) Nanomaterials promote the infiltration and activation of engineered exogenous NK cells in tumor site; (4) Nanomaterials boost the performance of endogenous NK cells in the following methods: (a) Regulating the tumor microenvironment; (b) Reducing the negative effects by regulating tumor cells or NK cells; (c) Acting as nanoengagers to co-regulate tumor and endogenous NK cells; (d) Promoting the immunogenic cell death of tumor cells for enhancing NK cell-based tumor immunotherapy.

3.1. Cell membrane coated nanomaterials

Coating nanomaterials by the natural cell membrane has attracted great attention to improve tumor therapy [36,145,146]. Tumor cells, macrophages, red blood cells (RBCs), NK cells are different sources for extraction of cell membrane. Tumor cell membrane modified nanomaterials can provide tumor associated antigen to activate immune response. Chen *et al.* synthesized CpG loaded-phosphate calcium nanoparticles coated with artificial membrane-mimicking phospholipid bilayer, which can be incorporated with B16OVA cell membrane and HSP70p in a self-assembled manner (Fig. 5A). The biomimetic nanomaterials can be delivered to the lymph nodes efficiently to activate the immune response of both innate NK cells and adaptive cytotoxic T cells [147]. Macrophages play an important role in the TME and affect the tumor progression and metastasis directly. Macrophage membrane modification can promote the infiltration of nanomaterials into tumor and synergize with *anti*-PD-L1 to restore their tumoricidal function for cancer immunotherapy (Fig. 5B) [148]. RBC membrane modified nanomaterials show long circulation life, they can also evade the immune system due to the presence of self-markers in the membrane [149,150]. Zhang *et al.* constructed the artificial NK cells (aNK) by emulsifying the mixture of RBC membrane, perfluorohexane (PFC), and glucose oxidase (GOX). On the one hand, aNK could directly kill tumor cells by the exhaustion of glucose and the generation of toxic H_2O_2. On the other hand, the produced H_2O_2 could re-educate macrophages and generate inflammation to activate the immune system, similar to the secretion of cytokines and chemokines by NK cells (Fig. 5C) [151]. NK cells can induce the polarization of pro-inflammatory M1 macrophages and target tumors through activating receptors on the NK cell membrane. Cai *et al.* synthesized the NK cell membrane cloaked TCPP-loaded mPEG-PLGA polymeric nanoparticles (NK-NPs) for targeting tumors and enhancing the M1 macrophage polarization to generate anti-tumor immune response (Fig. 5D). Furthermore, the photosensitizer TCPP loaded in the NK-NPs not only induced tumor cell death through photodynamic therapy (PDT), but also promoted the release of tumor-associated antigens for enhancing the NK cell-mediated immunotherapy (Fig. 5D) [152]. Table 2 provides the information of different cell membranes and the encapsulated core materials.

To sum up, the cell membrane coated NPs exhibit the characteristics of immune evasion, long blood circulation, tumor targeting capability, and good biocompatibility, all of which play great roles in NK cell-based tumor immunotherapy. Cell membrane coating can combine the merits of cell membrane and nanomaterials. The sources of cell membrane effects the function of cell membrane coated NPs, and specific cell membrane can be selected according to the desired application. The cell membrane can also be modified using various methods, thus adding additional opportunity and flexibility for the treatment. However, since membrane coated NPs are relatively new for NK cell-based tumor immunotherapy, the investigation of their pharmacokinetics or pharmacodynamics is limited. In addition, it is great of interests to develop the functional modification and hybridization of membranes for enhancing NK cell-based tumor therapy.

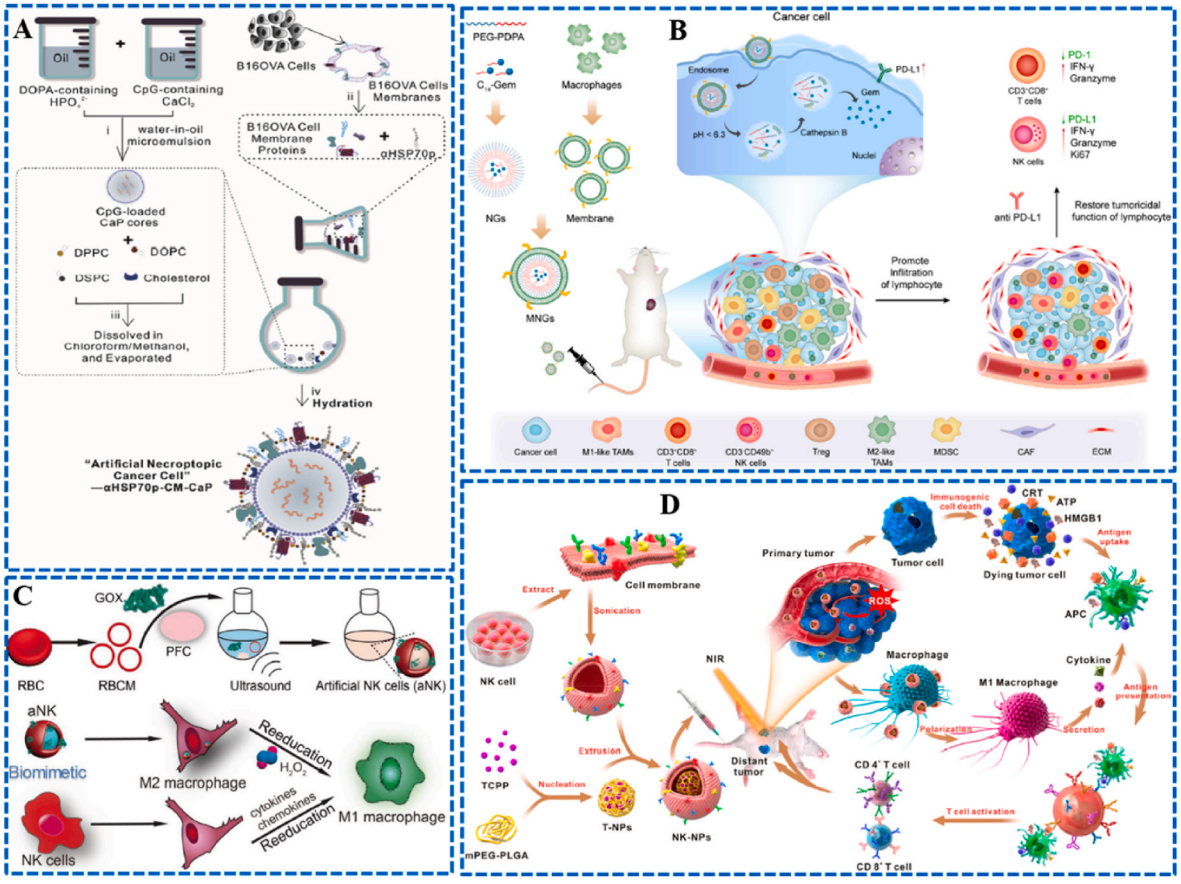

Fig. 5. Cell membrane coating nanomaterials for NK cell-based tumor immunotherapy. (A) B16OVA cell membrane proteins coated adjuvant CpG and an a-helix peptide modified HSP70p for activating the innate NK cells and adaptive cytotoxic T cells [147]. (B) Schematic illustration of the macrophage membrane coated nano-gemcitabine system (MNGs) for promoting intratumor permeation and lymphocyte infiltration to synergistically treat tumor by combining with *anti*-PD-L1 therapy [148]. (C) The red blood cell membrane cloaked perfluorohexane (PFC) and glucose oxidase (GOX) to construct the aNK for killing tumor cells and educating M2 macrophages into M1 macrophages [151]. (D) Schematic illustration of NK cell membrane coated nanoparticles for PDT-enhanced immunotherapy [152]. Adapted with permission [147], Copyright 2018, Elsevier; adapted with permission [148], Copyright 2023, American Chemical Society; adapted with permission [151], Copyright 2019, Wiley-VCH; adapted with permission [152], Copyright 2018, American Chemical Society.

Table 2
Summary of encapsulation of core materials with the cell membrane from different cells.

Source cells	Core materials	Application	Tumor cell type	Size (nm)	Ref.
Tumor cells	CpG, αHSP70p, phosphate calcium	Kill tumor cells and activate the innate NK cells and adaptive cytotoxic T cells immune response for tumor regression	B16OVA	200	[147]
Macrophages	Nano-gemcitabine System	Promote the $CD8^+$ T cells and NK cells infiltration in tumors and synergize *anti*-PD-L1 to restore their tumoricidal function for cancer immunotherapy	4T1, CT-26, PANC02	94	[148]
Red blood cells	Perfluorohexane, glucose oxidase	Exhaust glucose to produce the toxicity of H_2O_2 for killing tumor cells and re-educating M2-type TAMs into M1 type	4T1	190	[151]
NK cells	TCPP, mPEG-PLGA	Cause tumor cell death through photodynamic therapy and enhance the efficacy of anti-tumor immunity	4T1	80 ± 1.5	[152]
NK cells	DOX	Extend the circulation half-life and enhance tumor homing efficiency of nanomaterials for tumor chemotherapy and immunotherapy	MCF-7	70	[153]
NK cells	AIEdots	Cross the BBB for high contrast tumor imaging and photothermal therapy of glioma	U-87 MG	78	[154]
NK cells	Hollow mesoporous silica loaded with AIPH and (TA)/Fe^{3+}	Consume GSH and enhance free radical therapy	HepG2	153.2 ± 16.2	[155]

Table 3
Summary of exosomes from different parental cells and exosome-related nanomaterials.

Cell types	Exosome-containing materials	Therapeutic effect	Target	Tumor cell type	Ref.
NK	Perforin, Granzyme A/B, granulysin, FasL	Mediate cytotoxicity against cancer cells	Tumor cells	SupB15, CHLA255	[160]
	CD16, CD69, NKp44, NKG2D, IFN-γ, LFA-1, DNAM1, PD-1	Promote tumor cell apoptosis through DNAM1 pathway	Tumor cells	NALM-18	[161]
	CD56, Perforin, FasL	Enhance cytotoxic activity against tumor cells	Tumor cells	Jurkat, K562, DAUDI, SKBR3	[162]
	Perforin, Granulysin, Granzymes A/B	Activate multiple caspase pathways in tumor cells	Tumor cells	NALM-6, SupB15, CHLA-255, CHLA-136, MCF-7	[163]
	FasL, Perforin	Promote anti-tumor effect	Tumor cells	B16F10	[164]
	Perforin, Granzyme B, FasL, TRAIL	Enhance the anti-tumor effects in HCC	Tumor cells	Hep3B, HepG2; Huh7	[165]
	CD56, NKG2D, FasL, NKp30, NKp44, NKp46	Enhance cytotoxicity against neuroblastoma tumor *in vivo*	Tumor cells	Neuroblastoma	[166]
	miR-186	Inhibit neuroblastoma growth	Tumor cells	CHLA-136	[167]
	Dendrimer, miRNA	Promote the synergistic apoptosis of tumor cells	Tumor cells	MDA-MB-231	[168]
	BCL-2 siRNAs	Promote tumor apoptosis	Tumor cells	HEK293T, K562, MCF-7, MEC-1, SKBR3, MCF-10 A, MDA-MB-231	[169]
	siRNA, Ce6	Enhance tumor photodynamic and immunotherapy	Tumor cells	HepG2	[170]
DCs					
	HLA-B-Associated Transcript-3	Promote NK cells activation	NK cells	Not mentioned	[173]
	TNF, FasL, TRAIL	Promote NK cells activation and tumor apoptosis	NK cells	B16 melanoma cells	[174]
	IL-15 Rα, ULBP	Promote the IL-15 Rα and NKG2D-dependent NK cells proliferation and activation	NK cells	B16F10	[175]
	TLR4 and TLR1/2 ligand	Promote NK and Dendritic cells activation	NK cells	Not mentioned	[176]
	Lysates of RAE-1γ-expressing CML cells	Simultaneously activate NK cells and T lymphocytes	NK and T cells	BP210, BP210-T315I	[177]
	IFN-γ, MHC I/II restricted cancer antigens	Nkp30-related NK cells response	NK cells	NSCLC	[178]
Tumor					
J588HSP cells line	HSP70	Simultaneously activate NK cells and $CD8^+$ T cells	NK and T cells	J558	[186]
Human pancreas (Colo357), colon (CX2) carcinoma cells	HSP70, Bag-4	Stimulate the migratory capacity and cytolytic activity of NK cells	NK cells	Colo357; CX2	[187]
The human melanoma cell line Ge (Ge-HSP70, Ge-con sublines)	HSP70	Promote mouse NK cells activation	NK cells	YAC-1, Ge-con	[188]
Human hepatocellular carcinoma (HepG2)	HSP60, HSP70, HSP90	Promote NK cells activation	NK cells	HepG2	[189]
Human multiple myeloma cell lines (SKO-007 (J3), ARK)	HSP70	Promote the secretion of IFN-γ by CD56high NK cell	NK cells	SKO-007 (J3), ARK,	[190]
Human multiple myeloma cell lines (SKO-007 (J3), ARK, and RPMI8226)	IL-15 R A, IL-15	Promote NK cells activation and proliferation	NK cells	Not mentioned	[191]
K562 cells	IL15, IL-18, 4-1BBL	Promote NK cells proliferation in a short time (4 h)	NK cells	HepG2, HeLa, MCF-7, K562, Jurkat	[192]

3.2. Exosome related nanomaterials

Exosomes are a group of nano-sized membrane vesicles (30–200 nm), which can transfer proteins, cytokines, and nucleic acids to nearby cells, and play an important role in the intercellular communication within the extracellular environment [156–158]. The exosome functions are determined by the specific carried cargos. Therefore, incorporation of therapeutic molecules into exosomes or exosome-mimetics have been widely explored. In this section, we will review recent advances in exosomes from different parental cells and exosome-related nanomaterials for enhancing NK cell-based tumor immunotherapy (Table 3).

3.2.1. Immune cell-derived exosomes

Immune cell derived-exosomes as a potential therapeutic agents have been extensively investigated to verify their anti-tumor effect [159]. For NK cell-based tumor immunotherapy, they are mainly from NK cells and DCs.

NK cell-derived exosomes (NDEs): As mentioned above, NK cells can kill tumor cells and stimulate adaptive immune response by secreting pro-inflammatory cytokines and chemokines. Similar to parental cells, NDEs express NK cell markers (*e.g.* CD56) and receptors (*e.g.* NKG2D), which can specifically bind to ligands expressed by malignant tumor cells. In addition, NDEs contain cytolytic molecules such as FasL, perforin, granzymes, and TRAIL (Fig. 6) [160,161]. In the early research of NDEs, Lugini *et al.* reported that NDEs contained not only NK cell marker CD56, but also FasL and perforin, and showed anti-tumor and immune homeostatic activities in hematological malignancies [162]. The exosomes isolated from the activated NK cells showed their cytotoxic activity against several cancer types *via* activating multiple caspase pathways [163]. In addition, NDEs can also induce apoptosis of various tumor cells and inhibit the growth of their xenograft tumors, such as melanoma [164], HCC [165], and neuroblastoma [166,167]. Ahn *et al.* found that NDEs effectively inhibited the growth of xenografted melanoma [164]. Choi *et al.* observed that NDEs regulated the active targeting and cell death of HCC through two different mechanisms, *i.e.* membrane fusion (perforin and granzyme B) and ligand receptor interaction (FasL and TRAIL) [165]. In addition, NDEs carried the tumor suppressor microRNA (miR)-186 exhibited cytotoxicity against neuroblastoma *in vitro* and *in vivo* [167]. These results support the therapeutic potential of NDEs against various tumors.

In addition to exosomes themselves, their loaded nanomaterials, nucleic acid (mi RNA, siRNA), and other therapeutic drugs can further enhance their efficacy in tumor therapy. Xu *et al.* developed a "cocktail therapy" for neuroblastoma, based on the self-assembly of NDEs and dendrimers loaded with therapeutic miRNA [168]. NDEs loaded with BCL-2 siRNAs enhanced the intrinsic apoptosis of breast cancer cells, without affecting normal cells [169]. Combined with external light stimulation, NDEs loaded with siRNA and hydrophobic photosensitizer Ce6 can effectively induce tumor cell death *via* NK cell-like cytotoxicity [170]. Meanwhile, ROS generated upon laser irradiation not only achieved an effective PDT, but also facilitated polarization of tumor-associated macrophages from M2 type into M1 type, and maturation of DCs in the TME. In addition, the released siRNA triggered robust gene silencing of PD-L1 for activating $CD4^+$ T cells and $CD8^+$ T cells in the TME [170].

DC-derived exosomes (DDEs): Dendritic cells are the main sentinel, antigen presenting and regulating cells of the immune system, and play the role in communication between innate and adaptive immunity [171]. Therefore, DDEs can serve as tumor vaccines. DDEs haven been proved to eradicate tumors in a T cell-dependent and MHC-restrictive manner (Fig. 6) [172]. DDEs contain a variety of ligands on their surface, such as BAT3, TNF, FasL, TRAIL, NKG2D ligands *etc.*, leading to the direct binding and activation of NK cells [173–175]. In a phase I clinical trial, DDEs based vaccines displayed the capability of restoring the number and NKG2D-dependent function of NK cells in 7/14 patients [175]. Furthermore, the capability of DDEs boosting NK cells can be enhanced by modification [176–178]. Chaput *et al.* synthesized the IFN-γ-DDEs loaded with class I- and class II restricted cancer antigens to boost the NK cells for anti-tumor immunotherapy in a phase II clinical trial. The results confirmed that IFN-γ-DDEs enhanced the anti-tumor immunity of NK cells in patients with advanced NSCLC [178].

In conclusion, immune cell-derived exosomes have been extensively used for cell-free immunotherapy due to their higher stability under the same storage conditions, lower risks of CRS, higher resistance to the immunosuppressive TME, and potential therapeutic effects on various solid tumors [179–181].

3.2.2. Tumor cell-derived exosomes

Tumor cell-derived exosomes (TDEs): Compared with immune cell-derived exosomes, tumor cell-derived exosomes (TDEs) are mostly described by their immunosuppressive roles in tumor [182,183]. Nevertheless, some studies show that TDEs may also take part in the

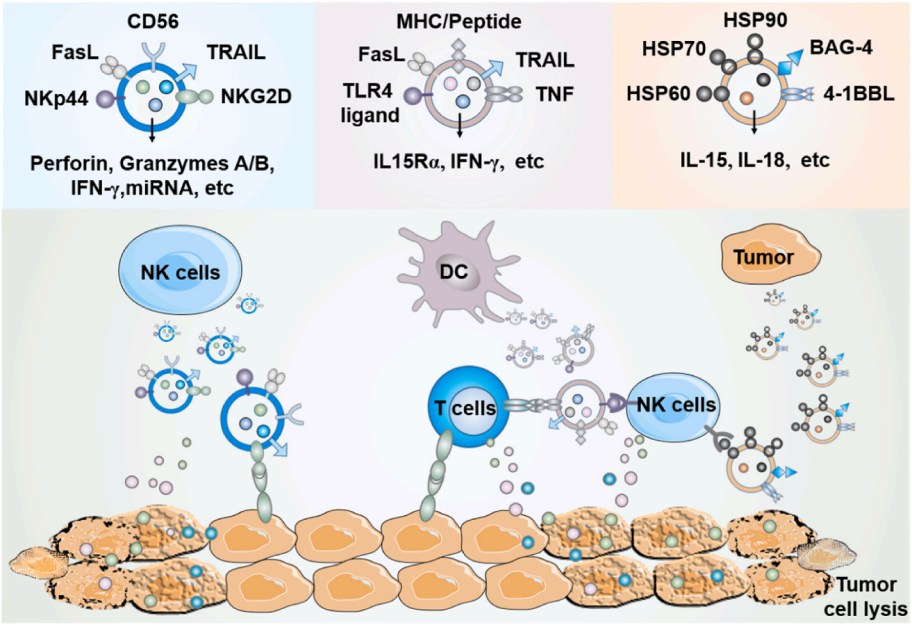

Fig. 6. Schematic illustration of exosomes and exosome-related nanomaterials from different parental cells for enhancing NK cell-based tumor immunotherapy. NK cell-derived exosomes, which express NKp44, FasL, CD56, TRAIL or NKG2D and contain cytotoxic molecules such as perforin, granztmes A/B, IFN-γ, and miRNA, induce tumor cell death and inhibit tumor growth. DC-derived exosomes induce the activation of T cells and NK cells through the expression of some ligands such as TLR4 ligands, FasL, MHC/Peptide, TRAIL, TNF and co-stimulatory molecules. Tumor cell-derived exosomes induce the activation of NK cells through presenting HSP60, HSP70, HSP90, BAG-4, or 4-1BBL and cytokines such as IL-15, IL-18, *etc*.

activation of cytotoxic immune cells, mainly by presenting antigens to DCs, and then triggering the activation of $CD8^+$ T cells, or directly activating NK cells [184–187]. In this section, we will focus on their roles in activating NK cells (Fig. 6). TDEs are capable of stimulating the NK cells in the TLR4 (or TLR2)/HSP70-dependent manner. Multhoff *et al.* showed that exosomes presenting HSP70/Bag-4 on their surface stimulated migration and lytic activity in NK cells against HSP70 membrane-positive tumors [187]. Similar results were observed, in which the cytotoxic of NK cells induced by HSP70-positive TDEs was dependent on the expression of NKG2D ligands on the surface of target tumor cells. Compared with HSP70-negative TDEs, HSP70-positive TDEs can activate mouse NK cells *in vitro*, thus killing YAC-1 cells with expression of NKG2D ligands [188]. Interestingly, TDEs isolated from HepG2 cells pretreated with anti-tumor drugs can efficiently stimulate the cytotoxicity and granzyme B of NK cells, and confer superior immunogenicity of HSP-specific NK cell response [189]. Nevertheless, melphalan-treated multiple myeloma cells released more exosomes, which can stimulate the production of IFN-g by NK cells through the activation of the NF-kB pathway in a TLR-2/HSP70-dependent manner, but not affect the cytotoxic activity of NK cells [190].

Apart from HSP proteins, IL-15, IL-15RA, IL-18, and 4-1BBL are also expressed on the TDE isolated from multiple myeloma cells, promoting the proliferation of human NK cells [191,192]. However, with the extension of treatment time (48 h), the TDEs could inhibit the cytotoxicity of NK cells by inhibiting the expression of activated receptors on NK cells after a long-term treatment (48 h) [192]. This suggests that TDEs-mediated immune activation may trigger immune cell exhaustion due to the long exposure to stimuli.

To sum up, exosomes as therapeutic agents for enhancing NK cell-based tumor immunotherapy have distinguished advantages, including excellent biocompatibility, low toxicity, and biostability. Several clinical studies have been carried out to verify the anti-tumor effect of exosomes [175,178,193]. However, one of the bottlenecks in the exosome-based clinical practice is how to produce large-scale clinical grade exosomes [194]. In addition, in the absence of specific modification and natural targeting ability, most exosomes are captured by liver after intravenous administration, resulting in a significant decrease in the delivery efficiency. Therefore, studies on the generation of clinical-grade exosomes in a large scale, decoration of targeting motifs and the mechanism of exosomes from different parental cells will be an important topic of exosomes for enhancing NK cell-based tumor immunotherapy.

3.3. Nanomaterials engineer exogenous NK cells

During the process of NK cell-based tumor immunotherapy, the tumor vascular structure, chemokine expressions, and stromal tissue barriers in the TME prevent NK cells from homing, infiltration, proliferation, and activation. Highly localized abundant NK cells in tumor are

Table 4
Summary of nanomaterials in combination with engineered exogenous NK cells.

Source of NK cells	Nanomaterials and modifications of NK cells	Application methods of NK cells	Functions of nanomaterials	Tumor cell type	Ref.
NK-92 cell lines	Hyaluronic acid based niche loaded unmodified NK cells	Postsurgical implantation	Promote the NK cells proliferation, release cytokines, and enhance tumor-lytic ability	MDA-MB-231	[195]
Primary human NK cells	DNase I@MBGNs and unmodified NK cells	Intravenous injection	DNase I@MBGNs can neutralize tumor acidity and destruct NETs, assist NK cell infusion	Hepa1-6	[196]
Primary human NK cells	AuNSP@ αCD16 and unmodified NK cells	Intravenous injection	Mark CD16 antibody on tumor cells for intravenously injected NK cell recognition	Hela	[197]
NK-92 cell lines	SSB NMs and unmodified NK cells	Intravenous injection	Upregulate the expression of activation receptor-NKG2D on NK92 cells and its ligand-NKG2DL on tumor cells	MDA-MB-231	[198]
NK-92 cell lines	Ru complex and unmodified NK cells	Intravenous injection	Activate multiple receptors (TNF-R1,DR5, Fas) on tumor cells and upregulating NKG2D and its ligand	MDA-MB-231	[199]
NK-92 cell lines	Selenium-bearing ruthenium complex and unmodified NK cells	Intravenous injection	Upregulate DR5 and Fas expression, activate NK cells *via* TRAIL/TRAIL-R and Fas/FasL pathway	PC3	[200]
NK-92 cell lines	NK cells reinforced acid-responsive micelles loaded with DOX	Intraperitoneal injection	NK cells against solid tumors is reinforced with the site-specific diffusion of DOX	MDA-MB-231	[201]
Primary human NK cells	NK cells loaded with GNS@$CaCO_3$/Ce6	Intravenous injection	Bimodal imaging directed PTT, PDT, IT	A549	[202]
Primary human NK cells	NK cells loaded with DCNP@786s	Intravenous injection	NIR-II FLI for assessing intracellular ROS generation and track NK cell viability	MHCC97H	[203]
NK-92 cell lines	NK cells loaded with liposomal ICG NPs	Experiment *in vitro*	NK cell-based tumor immunotherapy and PTT	A549, Hela, MCF-7	[204]
NK-92 cell lines/ Murine NK cells	NK cells incubated with magnetic NPs	Experiment *in vitro*	Not mentioned	Not mentioned	[205]
Primary human NK cells	NK cells coated with iron oxide NPs	Experiment *in vitro*	Increase the homing of NK cells at tumor site	SHSY5Y	[206]
Primary human NK cells	NK cells loaded with Fe_3O_4@PDA NPs	Intravenous injection	Reduce the expression of Ki-67 and increase the apoptosis of A549 cancer cells by magnetic targeting therapy	A549	[207]
NK-92 cell lines	NK cells loaded with Magnetic Cationic NPs	Intratumors injection	Upregulate the expression of CCR4 and CXCR4 of NK cells	MDA-MB-231	[208]
NK-92 cell lines	NK cells loaded with Fe_3O_4/SiO_2 NPs	Intravenous injection	Promote NK cells infiltrating into tumor site by magnetic targeting therapy	RPMI8226	[209]
NK-92 cell lines	NK cells loaded with Zn/Fe magnetic NPs	Intravenous injection	MRI, FLI, and increase the expression of EGFR targeting chimeric antigen receptor	MDA-MB-231	[210]
Rat primary NK cells	NK cells loaded with HAPF complex	Intra-arterial injection	MRI guided magneto-activated NK cells therapy to suppress solid tumor growth	N1S1	[211]
Primary human NK cells	PTAs nanosheets combined with TLS11a aptamer modified NK cells	Intravenous injection	Combine the artificial NK cell adaptive therapy with PTT treatment	HepG2	[212]
NK-92 cell lines	Nanobody 7D12 modified NK cells	Intravenous injection	Specifically recognize and kill the EGFR-positive tumor cells	LoVo	[213]
NK-92 cell lines	NK cells modified with Azide (N_3) and IL-21 NPs	Intravenous injection	Promote proliferation, activation, and persistence of NK cells	Raji	[214]
Mouse NK cells	NK cells modified with adenoviruses	Intravenous injection	Activate NK cells by upregulating the type I interferon signaling in a STAT4-granzyme B-dependent manner	4T1	[215]
Primary human NK cells	NK cells modified with Protein-DNA	Experiment *in vitro*	Eliminate the immunodepression from inhibitor sialic acid ligands at the NK-tumor cell synapse	Not mentioned	[216]

essential for NK cell-based tumor immunotherapy. Therefore, engineering NK cells *via* nanotechnology for improving the enrichment of activated NK cells in tumor has become an important strategy for tumor therapy. Recently, several nanomaterials (such as hydrogel, Fe_3O_4, DCNP, *etc*.) have been successfully constructed to engineer exogenous NK cells for promoting the infiltration and activation of NK cells in tumor (Table 4). In this section, we will review recent advances in nanomaterials used for engineering exogenous NK cells for tumor therapy.

3.3.1. *Nanohybrids enhance the tumor homing ability of exogenous NK cells*

NK cells are highly cytotoxic immune effectors, which can generate and release cytotoxic cytokines to directly kill tumor cells without antigen-restriction. As the innate immune cells, NK cells have a well-established homing ability to accumulate in tumor. Thus, a promising strategy combining the homing capability of NK cells with nanotechnology for tumor therapy has been developed. In a recent work, a biocompatible 3D-engineered hyaluronic acid based niche was constructed to culture NK cells after post-resection implantation (Fig. 7A) [195]. In addition to carrying NK cells, the hydrogel can be loaded with nanomaterials for tumor therapy. A dual pH-responsive hydrogel containing tumor acidity neutralizer and neutrophil extracellular traps (NETs) lyase (Deoxyribonuclease I, DNase I) was developed, and used in combination with NK cell infusion for preventing the recurrence of post-resected HCC. The hydrogel injected at tumor resection margin can neutralize tumor acidity to reduce tumor infiltration. The DNase I released by a pH-responsive manner can degrade NETs for enhancing NK cell infusion to combat the recurrence of post-resected HCC [196]. In line with the regulation of TME, a nano-immunomodulator AuNSP@αCD16 was explored to remodel the TME by modifying tumor cell surface with CD16 antibody for enhancing the recruitment and infiltration of intravenously injected NK cells in tumor (Fig. 7B) [197]. Combined with the regulation of TME, upregulating the expression of activated receptors and ligands also can induce significant anti-tumor effects [198–200]. Chen *et al.* developed a nanoemulsion system (SSB NMs) to co-deliver TGF-β inhibitor and selenocysteine to improve anti-tumor efficacy. SSB NMs can effectively inhibit TGF-β/TGF-β RI/Smad2/3 signaling, which thus enhanced NKG2DL expression on tumor cells and stimulated NKG2D surface expression on NK92 cells.

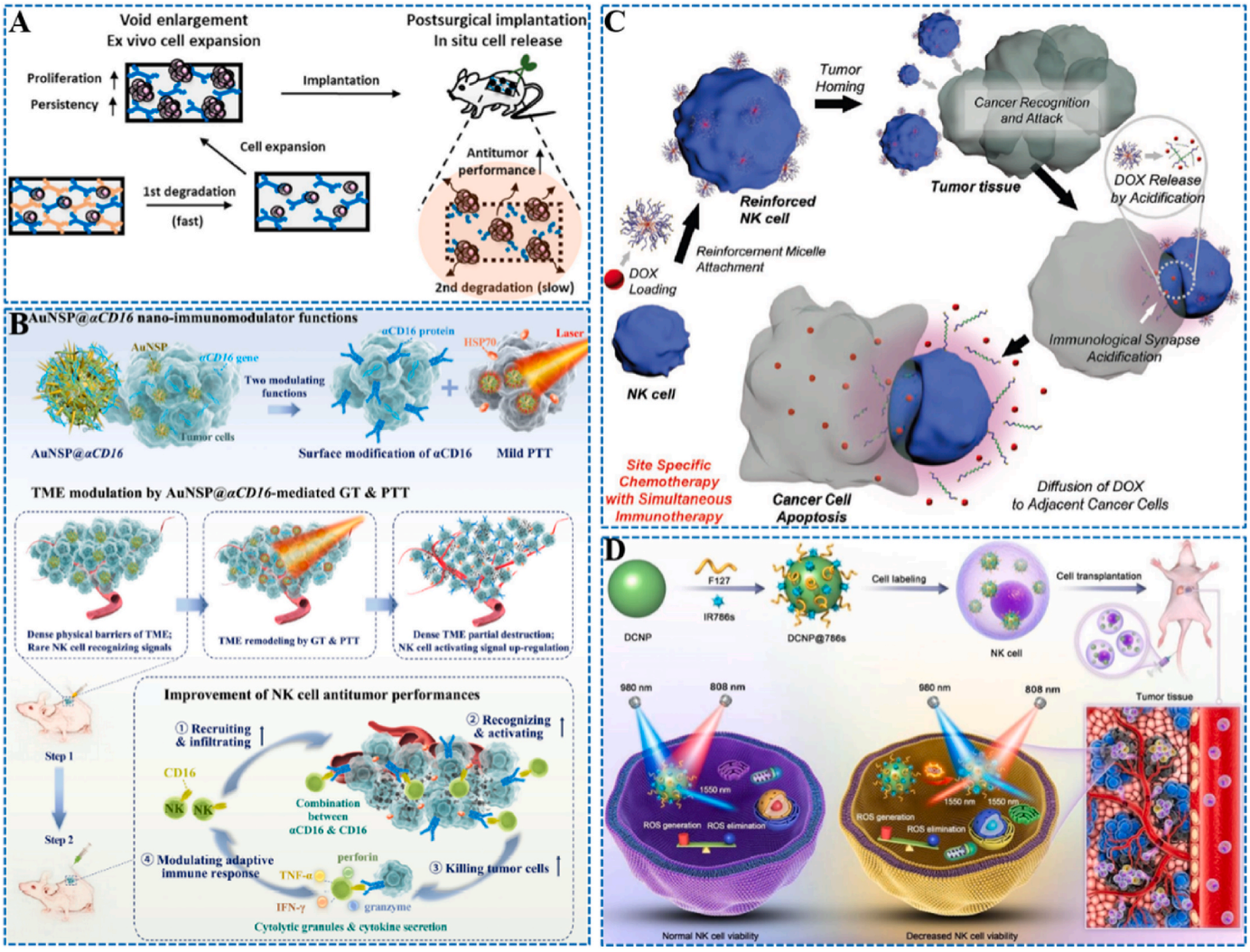

Fig. 7. Tumor homing capability of NK cells combined with nanomaterials for NK cell-based tumor immunotherapy. (A) Schematic illustration of NK cell expansion in 3D-ENHANCE, followed by postsurgical implantation [195]. (B) Schematic illustration of AuNSP@αCD16 mediated TME modulation for enhancing the recruitment and infiltration of intravenously injected NK cells in tumor [197]. (C) Schematic illustration of NK cells reinforced with DOX-loaded acid-responsive micelles (ReNK) and their anti-tumor effect [201]. (D) Schematic illustration of DCNP@786s with ratiometric NIR-II fluorescence for tracking NK cell viability *in vivo* [203]. Adapted with permission [195], Copyright 2020, Elsevier; adapted with permission [197], Copyright 2022, Elsevier; adapted with permission [201], Copyright 2020, Wiley-VCH; adapted with permission [203], Copyright 2021, Wiley-VCH.

The synergistic use of SSB NMs and intravenously injected NK cells can induce significant anti-tumor effect *in vivo* [198].

In addition to combination with exogenous NK cells without any modification, nanomaterials can also be directly modified or loaded onto NK cells to enhance the therapeutic effect. In this strategy, NK cells act as carriers of nanomaterials [201–204]. For example, the DOX-loaded acid-responsive micelles were loaded onto the NK cells to prepare reinforced NK cells (ReNK) (Fig. 7C). The ReNK showed highly tumor-specific release of DOX to enhance therapeutic effect in solid tumors, inhibit tumor growth and reduce systemic toxicity [201]. Cui *et al.* designed a nanoplatform by using the characteristics of human NK cells in conjunction with $CaCO_3$-coated gold nanoclusters (GNSs) carried with hydrophobic photosensitizer Ce6 (GNS@$CaCO_3$/Ce6-NK) for enhancing the photothermal therapy (PTT)/photodynamic therapy (PDT) and immunotherapy of tumor [202]. In addition to enhancing the therapeutic efficacy of NK cells, it is also important to monitor NK cell viability during treatment. Song *et al.* developed a NIR-II fluorescence imaging strategy to quantitively track and visualize the adoptive NK cell viability *in vivo* in real-time [203]. The lanthanide-based down--conversion nanoparticles (DCNP) modified with IR786s (a broad-spectrum ROS-sensitive probe) were loaded onto the NK cells. Upon cell death, excessive ROS was produced in NK cells, along with IR786s degradation, resulting in the increase of NIR-II fluorescence at 1550 nm under 808 nm excitation; while the NIR-II fluorescence at 1550 nm under 980 nm excitation was stable (Fig. 7D). Therefore, the intracellular ROS-induced ratiometric NIR-II fluorescence was explored to track NK cells viability *in vivo* for NK cell-based tumor immunotherapy.

3.3.2. Magnetic nanomaterials enhance the tumor homing ability of exogenous NK cells

To further enhance the accumulation of exogenous NK cells in tumor, the NK cells can also be engineered with magnetic nanomaterials and guided to tumor site for targeted therapy under an external magnetic field. The magnetic NPs loaded onto NK cells did not seriously affect the function of NK cells [205–208]. Cheng *et al.* synthesized the Cy5.5-conjugated and silica coated magnetic iron oxide (Fe_3O_4/SiO_2) NPs to engineer NK cells, and then controlled the NK cells by the magnetic field [209]. Under the guidance of external magnetic field, the relative ratio of NK cells infiltrated into tumor was increased by 17 folds compared with the unmodified NK cells (Fig. 8A). In another work, magnetic Zn/Fe NPs modified with EGFR-CAR plasmids (MF-NPs) were prepared to engineer NK cells [210]. The MF-NPs could deliver plasmid DNA to NK cells and induce the expression of EGFR targeting chimeric antigen receptors on the NK cell surface. Furthermore, they were used to track NK cells *in vivo* through MRI and fluorescence imaging (FLI). Finally, the engineered NK cells enhanced cytotoxicity against xenografted tumor of MDA-MB-231 cells *in vivo* (Fig. 8B).

In addition to magnetic targeting and MRI, the magnetic NPs loaded onto NK cells can also be used to activate NK cells. Magnetic

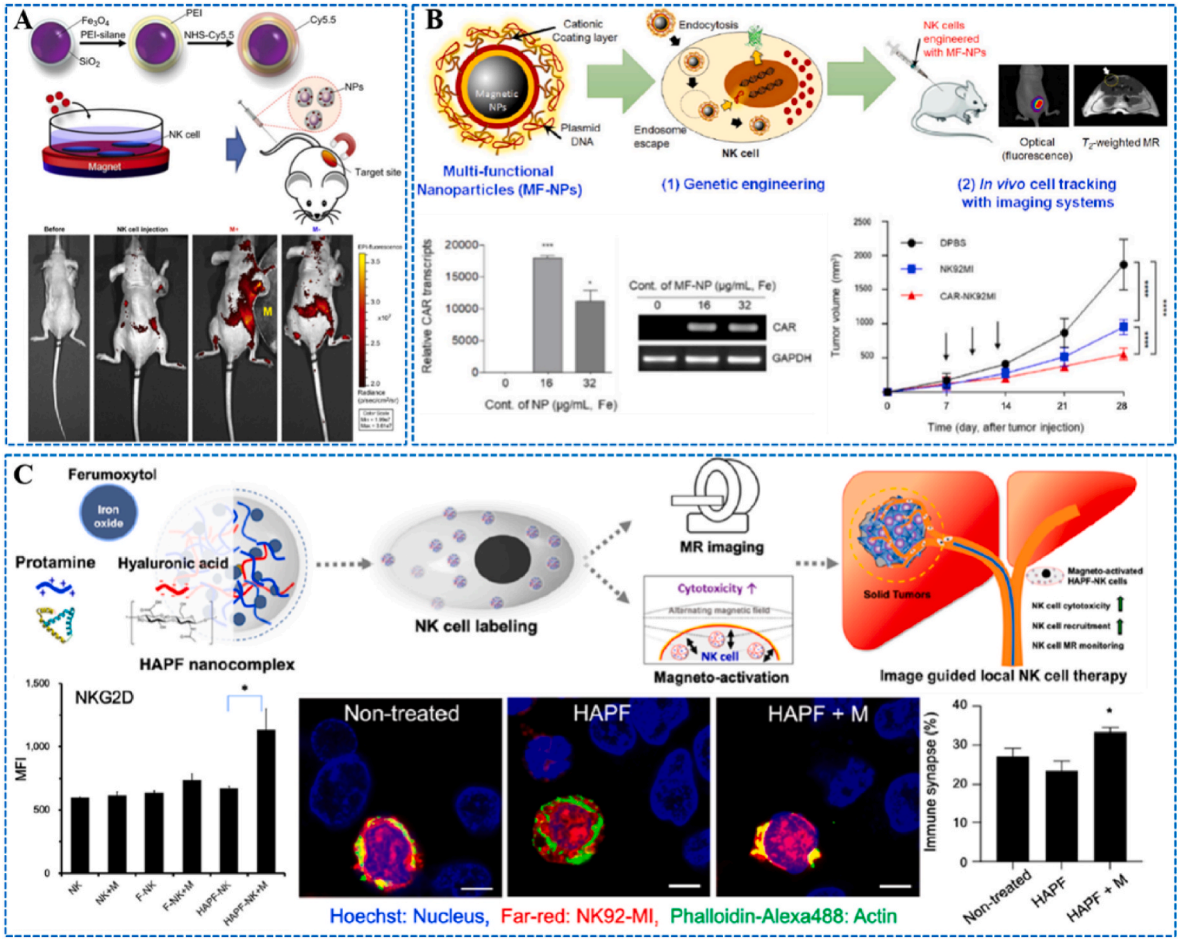

Fig. 8. Magnetic nanomaterials enhance the tumor homing ability of NK cells. (A) Schematic illustration of NK cells loaded with the Cy5.5-conjugated and silica coated magnetic iron oxide (Fe_3O_4/SiO_2) NPs for magnetic targeting and *in vivo* fluorescence imaging [209]. (B) Schematic illustration of the NK cells loaded with EGFR-CAR plasmids modified with magnetic Zn/Fe NPs for inducing the expression of EGFR and tracking NK cells *in vivo* through MRI and fluorescence imaging [210]. (C) Magneto-activated HAPF-labeled NK cells for MRI guided local NK cell therapy to treat hepatocellular carcinoma [211]. Adapted with permission [209], Copyright 2012, Elsevier; adapted with permission [210], Copyright 2019, Elsevier; adapted with permission [211], Copyright 2021, American Chemical Society.

nanocomplexes (HAPF) combining hyaluronic acid (HA), protamine (P), and ferumoxytol (F) were prepared for labeling NK cells [211]. Application of an external magnetic field could effectively activate NK cells, promote the secretion of perforin and granzyme B, as well as upregulate the expression of actin polymerization and mechanosensitive NKG2D for kill tumor cells effectively (Fig. 8C). In general, the NK cells engineered by magnetic nanomaterials can achieve the targeted delivery to enhance the NK cell-based tumor immunotherapy through the guidance of noninvasive imaging.

3.3.3. *Nanomaterials engineer NK cell surface*

Besides the above strategies for engineered NK cells, modification of NK cell surface with aptamers, nanobodies, bio-orthogonal groups, adenoviruses, DNA *etc.* Has also been used to enhance NK cell-based tumor immunotherapy [212–216]. Engineering of NK cells with the hepatocellular carcinoma specific targeting TLS11a-aptamer was carried out to eliminate residual tumor cells after nano-enhanced PTT, systematically improve anti-tumor efficacy and prevent tumor relapse (Fig. 9A) [212]. Nanobodies are novel antibody-like biomolecules with high antigen affinity, low immunogenicity, deep tumor tissue permeability. In a recent study, the nanobody (7D12) was conjugated with NK cells (7D12-NK92MI) *via* bio-orthogonal click chemistry [213]. The 7D12 was used to specifically recognize the human EGFR overexpressed by many solid tumors. The 7D12-NK92MI cells showed high specificity and affinity to EGFR-overexpressing tumor cells and efficiently lysed them (Fig. 9B). Additionally, the bio-orthogonal groups can also be used to enhance the infiltration and migration of NK cells in solid tumors. Cai *et al.* constructed a bio-orthogonal targeted living cell nanocarrier (N_3-NK-NPs) by coupling azide (N_3) on the surface of NK cells with hitchhiked IL-21 delivery system [214]. The N_3-NK-NPs could efficiently recognize and infiltrate into the bicyclo [6.1.0] nonyne (BCN) modified Raji cells through bio-orthogonal reaction. The bio-orthogonal chemical groups (N_3 and BCN) could act as artificial targeting receptors/ligands to achieve efficient recognition between the NK cells and tumors, and further promote the infiltration of NK cells into tumor. Meanwhile, the IL-21 loaded into nanoparticles was released into the surrounding of NK cells, promoting the sustainable and effective activation of NK cells in tumor site (Fig. 9C).

Oncolytic adenoviruses have received extensively attention in tumor therapy because they can directly cause oncolytic infection and

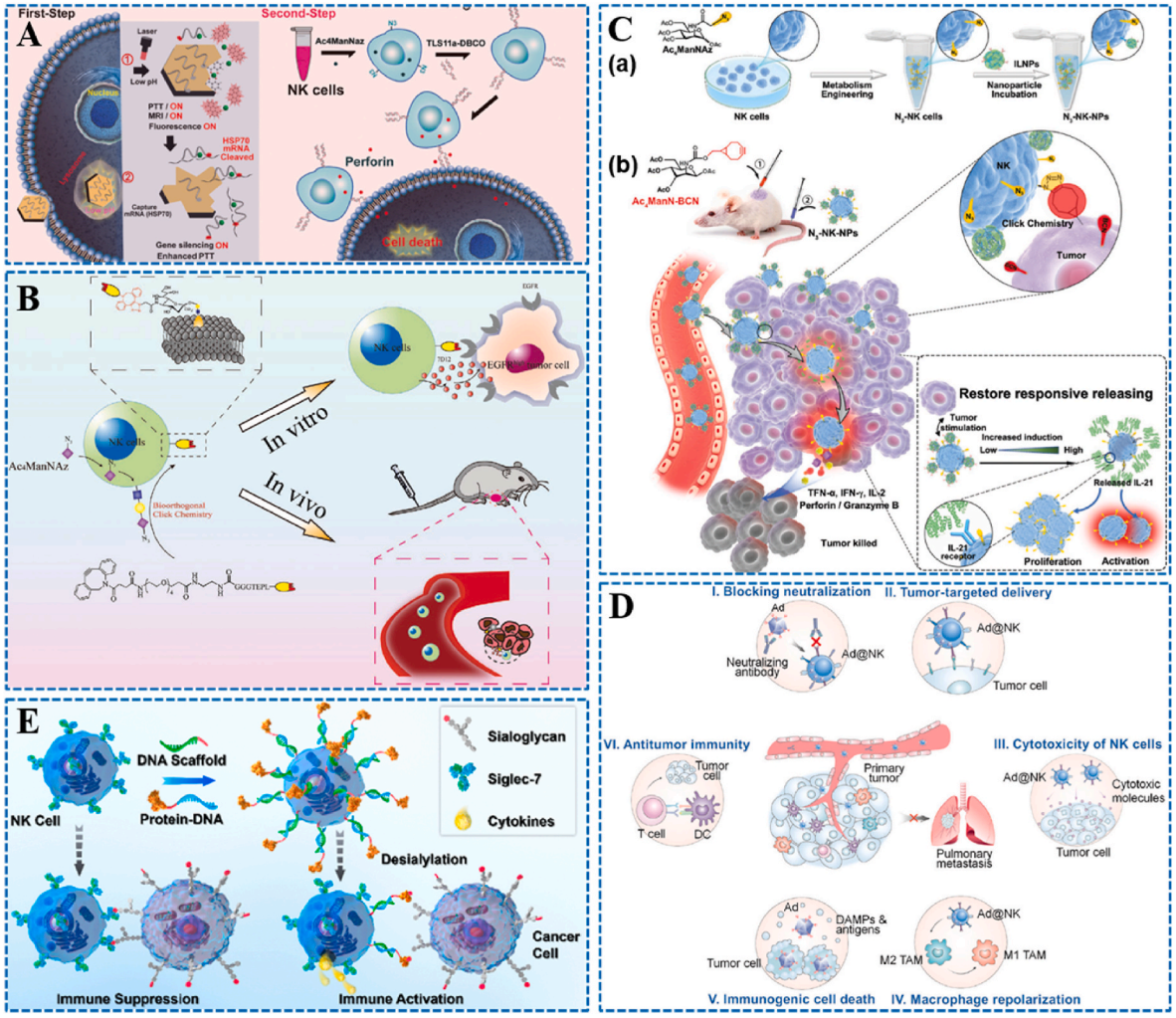

Fig. 9. Modification strategies for engineering NK cell surface. (A) Schematic illustration of antiheat endurance strategy combined with artificial engineered NK cells for improving the therapeutic efficacy of nano-enhanced PTT [212]. (B) Schematic illustration of NK cells modified with the *anti*-EGFR nanobody 7D12 [213]. (C) Schematic illustration of live-cell nano-carrier N_3-NK-NPs based on bio-orthogonal metabolic glycol-engineering and hitchhiking delivery system for improving NK cell-based tumor immunotherapy [214]. (D) Schematic illustration of adenoviruses infected NK cells for conducting a potent tumor targeted virotherapy in combination with immunotherapy [215]. (E) Schematic illustration of DNA-mediated protein anchoring (DMPA) on NK cell surface for enhancing immune response [216]. Adapted with permission [212], Copyright 2019, Wiley-VCH; adapted with permission [213], Copyright 2021, Wiley-VCH; adapted with permission [214], Copyright 2022, Wiley-VCH; adapted with permission [215], Copyright 2022, Wiley-VCH; adapted with permission [216], Copyright 2023, American Chemical Society.

indirectly induce anti-tumor immunity [217]. Adenoviruses infected NK cells (Ad@NK) were used for loading, protection, replication, amplification, and release of adenoviruses at tumor site. As a return, adenoviruses infection provided an enhanced anti-tumor immunity to NK cells by activating type I interferon signal in a STAT4-granzyme B-dependent manner (Fig. 9D) [215]. The complementary interaction between adenoviruses and NK cells in combined immunotherapy and viral therapy is a promising therapeutic strategy in oncology.

Membrane protein engineering shows great potential in functionalization of NK cells. Zhang *et al.* designed a strategy of anchoring exogenous proteins on NK cell membrane through DNA-template [216]. The engineered NK cells displayed the capability of eliminating the immune checkpoints, thus significantly enhanced the activation efficiency of NK cells in the process of immunotherapy (Fig. 9E).

In sum up, the engineered exogenous NK cells have been widely used in tumor treatment, but their efficacy is poor because of the short survival *in vivo*. In the future, combined application of exogenous NK cells with nanomaterials will attract considerable attention for tumor therapy to enhance NK cell priming and expansion, improve their persistence and homing efficiency, and enhance their activation.

3.4. Nanomaterials boost endogenous NK cells

Since the exogenous NK cells could be depleted, apoptotic or unable

Table 5
Summary of nanomaterials activating endogenous NK cells.

Applications	Nanomaterials	Size	Functions of nanomaterials	Tumor cell type	Ref.
Regulate the TME	Vesicular CLAN with siLdha	90 – 100 nm	Knockdown LDHA, reprogram pyruvate metabolism, reduce the production of lactate, neutralize the tumor pH	4T1	[229]
	Nano-carriers encapsulate siRNAs	130 ± 9 nm	Genetically silence the key intrinsic inhibitory NK cell molecules, SHP-1, Cbl-b, and *c*-Cbl	221-Cw4	[230]
	PCM@APAP@RNGs	128.4 ± 0.8 nm	Release acetaminophen to inhibit PGE2 secretion for promoting the activity of NK cells	Panc02	[231]
	Fraxinellone loaded nanoemulsion	145 nm	Remold the TME by anti-fibrotic, combine with BRAF peptide vaccine to enhance anti-tumor efficacy	BPD6	[232]
	Neobavaisoflavone nanoemulsion	100 nm	Reduce ROS production, decrease ECM deposition *via* suppressing TGF-β/SMADs pathway	A549	[233]
	Nanowires coupled with IL-2 antibody	18 ± 4.3 μm (long) and 6 ± 2.1 μm (short)	Capture and potentiate endogenous IL-2 for stimulating NK and T cells	Not mentioned	[234]
	Na–IVAl-DMSN	240 nm	Activate DCs to release cytokines IL-18 and IL-1β for recruit NK cells and T cells.	CT26	[235]
	DAL4-LNP-IL-12 + IL-27 mRNA	130 nm	Intratumorally deliver IL-12 and IL-27 mRNAs induced robust infiltration of immune effector cells	B16F10	[236]
	CLPP/mIL-15	221.3 ± 2.5 nm	Promote the express of IL-15	C26	[237]
	HA/pIL-12/DOX-PMet	122.1 ± 1.1 nm	Promote the express of IL-12 and enhance the M1 macrophage polarization	4T1	[238]
Regulate the tumor cells	Pem/Se	47 ± 2 nm	Suppress the HLA-E expression and release of pemetrexed	MDA-MB-231	[243]
	Pem/Se	150 – 200 nm	Suppress the HLA-E expression, release of pemetrexed, and increase of ROS generation	A549	[244]
	SeP/DOX	240 ± 1.3 nm	Suppress the HLA-E expression and release of DOX at the tumor site	MDA-MB-231	[245]
	PSeR/DOX	87 nm	Suppress the HLA-E expression and release of DOX at the tumor site	MDA-MB-231	[246]
	PSeLYAb NPs	199.7 nm	Suppress the HLA-E expression and release of Cetuximab at the tumor site	HCT-116	[247]
Regulate the NK cells	CrvpPS-nano-Se	1 μm	Increase the thymus index, T cell subpopulations and NK cells	Not mentioned	[248]
	SeNPs@LNT	160 nm	Restore the immunocompetence of dysfunctional immune cells ($CD4^+$ T cells, NK cells, T cells, and B cells)	Lung adenocarcinoma	[249]
	NGO-α-hCD16	150 nm	Stimulate NK cells *via* the CD16 receptor	Not mentioned	[250]
	Cowpea mosaic virus, anti-4-1 B B	36.8 nm	Stimulate tumor-resident and CPMV-recruited NK cells within TME	CT26, B16F10	[251]
	Chiral nanoparticles	140 nm	L-type NPs enhance the activation of $CD8^+$ T and NK cells by stimulating DCs	EG7.OVA	[252]
Co-regulate tumor and NK cells	Trifunctional NK-cell engagers	Not mentioned	Bring tumor cells and NK cells together	Raji	[253]
	IMNs	46 ± 10 nm	Modify the tumor cell surface with NK cell-activating signals to activate tumor-infiltrating NK cells	B16F10	[254]
	α-EGFR/α-CD16/α-4-1 B B EPI NPs	112 ± 7 nm	Target EGFR overexpressing tumors and promote the recruitment and activation of NK cells to eradicate tumor	B16F10	[255]
	Pro-αCD25-NDs	190.1 – 220.2 nm	Increase CD25 expression in target cell to enhance αCD25 binding and NK cell-mediated killing	J-Lat 10.6	[256]
	SeNPs	102 ± 9.6 nm	Upregulate the expression of activation receptor-NKG2D and its ligand-NKG2DL	HepG2	[257]
	(As + Ce6)@MSNs-PEG	121 nm	Activate adaptive immunity and release As to enhance the function of innate immunity in the tumor	CT26	[258]
	Lip-CTN-DNase I–SIS3	37.2 ± 13 nm	Photothermal agents, killing cancer cells to induce ICD, promote activation of NK cells	4T1	[259]
Other methods to activate NK cells	AuNC@MnO2	91 nm	FLI/PAI/MIR guided oxygen-boosted PDT & anti-tumor immunity	4T1	[260]
	AuNPs on fluidic liposomes	Not mentioned	NIR(II) PTT to trigger ICD to potentiate tumor immunotherapy	4T1	[261]
	CD@MSNs	50 – 60 nm	Photothermal imaging guided PTT cooperated with anti-tumor immunity	4T1	[262]
	Nanoscale immunoconjugates	28.0 – 28.5 nm	Increase $CD8^+$ T cells, NK cells and macrophages with a decrease of Tregs in the brain tumor area	GL261	[263]
	ChA CQDs	2 – 5 nm	Enhance ferroptosis to activate anti-tumor immunity	H22	[264]

to survive after infusion, diverse nanomaterials have been developed to promote the targeted delivery of functional small molecules to activate endogenous NK cells or enhance the proliferation of NK cells *in vivo*. In this section, we will summarize the methods of stimulating endogenous NK cell activity by nanomaterials for NK cell-based tumor immunotherapy (Table 5).

3.4.1. *Nanomaterials regulate the tumor microenvironment*

The TME is heterogeneously composed of vasculature, various cell subtypes (such as immune cells, fibroblasts and lymphocytes, endothelial and inflammatory cells), extracellular matrix (ECM), interstitial fluid and other tumor-associated components (such as chemokines, secreted proteins, metabolites, *etc.*) [218,219]. The TME plays a key role in the progression of tumor and the development of drug resistance [220]. Recently, reprogramming TME has been used to enhance the efficacy of existing cancer treatment (such as chemotherapy, radiotherapy, immunotherapy [221–225]). Nanomaterials have notable advantages over the traditional platforms, and can target and reprogram the TME by changing its acidity, hypoxia, ROS, and immune modulators [226–228]. For example, vesicular cationic lipid-assisted nanoparticles (CLAN) mediated gene silence efficiently downregulated LDHA expression, decreased lactate secretion, normalized the tumor acidity, increased infiltration of immune cells, and restored the anti-tumor responses of T cells and NK cells (Fig. 10A) [229]. The strategies of regulating immune modulators also have the potential to restore NK cell activity [230,231]. The TME responsive nanogels can release acetaminophen to suppress the secretion of COX2-derived PGE2 in tumor cells and induce the activation of endogenous NK cells (Fig. 10B) [231]. The natural medicines delivered by nanomaterials can inhibit tumor-related fibroblasts activation, reduce extracellular matrix deposition, improve TME, and enhance endogenous NK cells activation [232,233].

In addition to improving the immunosuppressive TME, increasing the cytokines can also effectively activate endogenous NK cells [234–238]. For example, nanowires coupled with *anti*-IL-2 antibody was used for enhancing endogenous IL-2 and activating targeted specific endogenous NK and T cell subsets (Fig. 10C) [234]. In addition to capturing endogenous activating cytokines, increasing their secretion in tumor through immunogenetic therapy is also very effective. Nanomaterials encapsulated with mRNAs encoding cytokines were developed to provide efficient concentration and delivery capability for transportation of mRNA into tumor [236–238]. Dong *et al.* generated lipid NPs loaded with IL-12 and IL-27 mRNA (DAL-LNP). The intratumor administration of DAL-LNP showed a synergistic effect on production of INF-γ and TNF-α, promoting the infiltration of T cells and NK cells in tumor [236].

Different from killing tumor cells directly, regulating TME is a less toxic alternative way for tumor treatment, which can effectively promote the treatment efficacy [239–242]. However, the TME characteristics of different types and different size of tumors may be different. Therefore, there is a huge opportunity to explore innovative nanomaterials to effectively and accurately regulate TME for optimizing NK cell-based tumor immunotherapy.

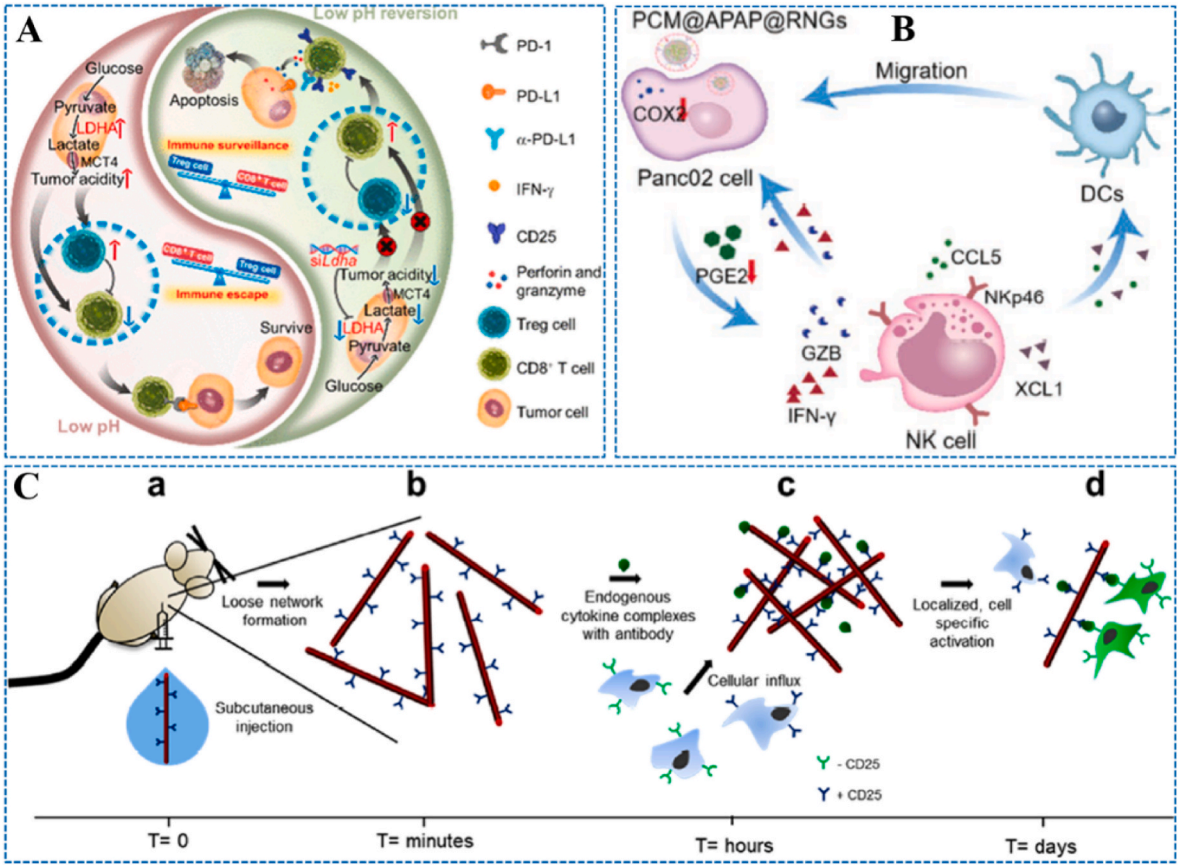

Fig. 10. Nanomaterials regulate the tumor microenvironment for enhancing the endogenous NK cell-based tumor immunotherapy. (A) Schematic illustration of micellar CLAN with siLdha for reversing the tumor immunosuppressive microenvironment and restoring the anti-tumor responses of T cells and NK cells [229]. (B) Schematic illustration of NK activation and DCs recruitment by restraining the secretion of COX2-derived PGE2 in tumor cells [231]. (C) Schematic illustration of nanowires immobilized *anti*-IL-2 antibody as an effective tissue-specific immune regulation platform through passive accumulation of endogenous IL-2 for activating targeted specific natural killer and T cell subsets [234]. Adapted with permission [229], Copyright 2019, American Chemical Society; adapted with permission [231], Copyright 2022, Wiley-VCH; adapted with permission [234], Copyright 2017, American Chemical Society.

3.4.2. Nanomaterials regulate the tumor and endogenous NK cells

The activation and proliferation of NK cells is usually achieved through cytokine-based stimulation, inhibition of inhibitory ligands in tumor cells, and increase of activating receptors in NK cells. However, the direct *in vivo* administration of cytokines, antibodies, and genes can cause serious side effects and degradation during blood circulation. Therefore, nanomaterials are designed to reduce the negative effects by regulating tumor cells and NK cells for enhancing NK cell-based tumor immunotherapy.

Regulate the tumor cells: NK cells can kill tumor cells without presensitization or affinity maturation, which offers great potential for clinical trials of NK cell-based tumor immunotherapy. However, the overexpression of ligands in tumor cells for inhibitory NK cell receptors, such as human leukocyte antigen E (HLA-E), a ligand for the inhibitory receptor NKG2A, can lead to NK cell dysfunction and exhaustion. Therefore, reducing the expression of inhibitory ligands on tumor cells is expected to improve the effectiveness of NK cell-based tumor immunotherapy. Xu *et al.* prepared diselenide-pemetrexed (Pem/Se) self-assemblies combining cancer immunotherapy with radiotherapy and chemotherapy. Under the irradiation of γ-rays, diselenides in Pem/Se were converted into seleninic acid for suppressing the expression of HLA-E, pemetrexed was released from the assemblies to achieve the combined radio-chemotherapy (Fig. 11A) [243]. In line with this strategy, some selenium-containing organic nanomaterials were used to enhance NK cell-based tumor immunotherapy [244–247].

Regulate the endogenous NK cells: In addition to the down-regulation of the recognition ligands on the tumor surface, the low activity of NK cells in the TME will also limit the efficacy of NK cell-based tumor immunotherapy. Recently, nanoparticles have been used to directly activate NK cells by regulating NK-cell functions [248–252]. The earliest research showed that intragastric administration of selenium-containing NPs could increase the thymus index, T cell subpopulations and NK cells [248]. In line with this strategy, Chen *et al.* synthesized selenium containing NPs for potentiating the proliferation and activation of NK cells by increasing expression of NKG2D and NKp30 (Fig. 11B) [249]. Nanomaterials can be also used to deliver antibodies for *in situ* activation of NK cells. For example, Dunlop *et al.* prepared nanoscale graphene oxide templated nanoclustering of α-hCD16 (NGO-α-hCD16), which could stimulate NK cells *via* CD16 receptor [250]. In another work, plant virus Cowpea mosaic virus (CPMV) and anti-4-1BB monoclonal antibody were combined to improve NK cell function and *in situ* cancer vaccination efficacy (Fig. 11C) [251]. Furthermore, the chirality of nanomaterials can influence their interactions with immune cells. Kuang *et al.* synthesized the chiral *L*-type Au NPs with a *g*-factor of 0.44 to enhance the activation of $CD8^+$ T and NK cells by stimulating DCs. The interactions between *L*-type NPs and immune cells were higher than that of *D*-type NPs, which further promoted the activation of NK cells and $CD8^+$ T cells and their infiltration into tumor (Fig. 11D) [252].

Co-regulate tumor and endogenous NK cells: The modifiable

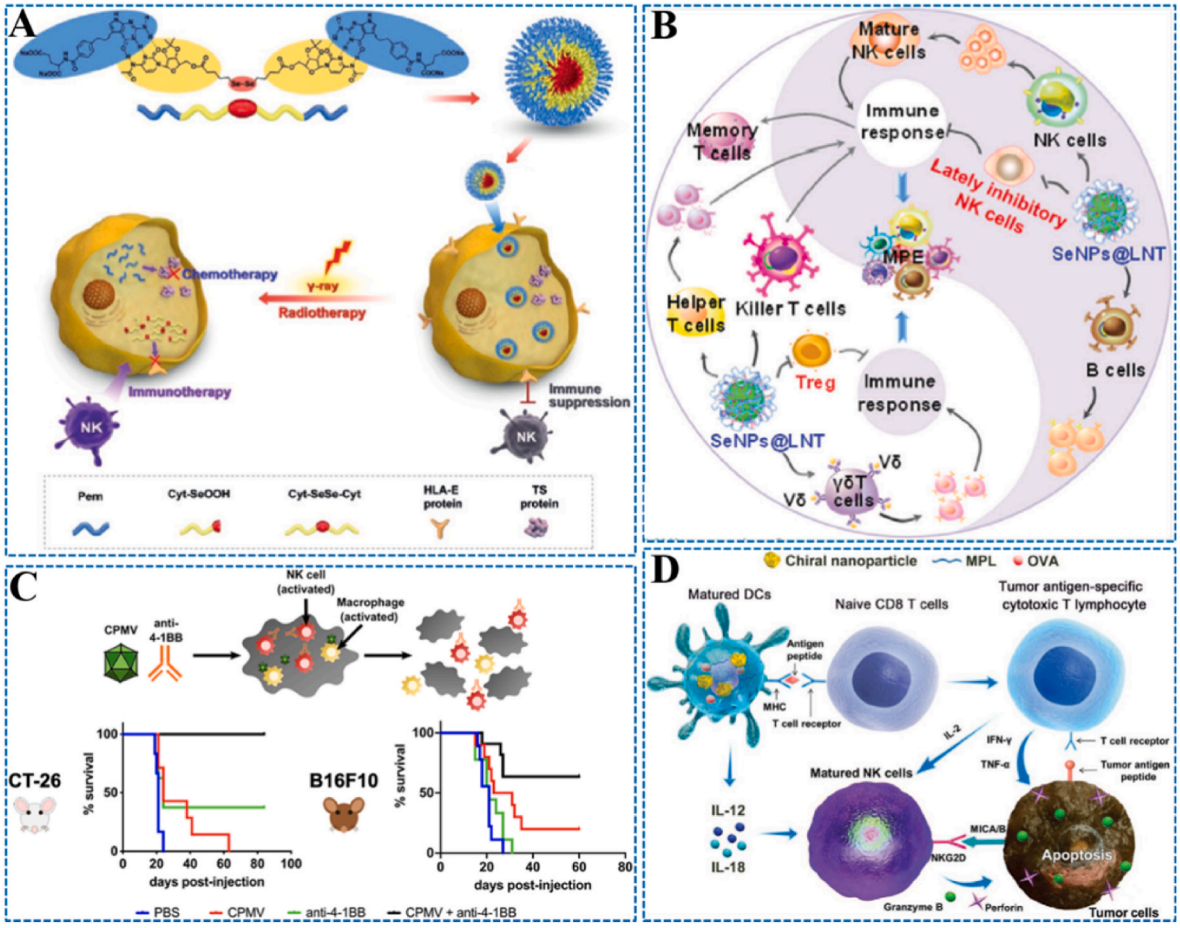

Fig. 11. Nanomaterials regulate the tumor and endogenous NK cells. (A) Schematic illustration of diselenide-pemetrexed assemblies for combined NK cell-based tumor immunotherapy with radiotherapy and chemotherapy [243]. (B) Schematic illustration of SeNPs@LNT regulating various MPE immune cells to enhance immune response [249]. (C) Schematic illustration of recruitment and activation of NK cells in the TME through combined treatment of CPMV and anti-4-1 B B antibody [251]. (D) Schematic illustration of *L*-type NPs exerted mechanical forces on dendritic cells and stimulated cytokine expression to induce cytotoxic activity of NK cells [252]. Adapted with permission [243], Copyright 2020, Wiley-VCH; adapted with permission [249], Copyright 2021, Wiley-VCH; adapted with permission [251], Copyright 2022, American Chemical Society; adapted with permission [252], Copyright 2022, Wiley-VCH.

surface property, adjustable size, and biodegradable property of nanomaterials show great potential in enhancing the binding affinity between tumor cells and endogenous NK cells. Nanoengagers have been designed for binding tumor cells with NK cells [253–256]. The trifunctional natural killer cell engagers (NKCEs) were developed to target an antigen on cancer cells and two activating receptors of NK cells (NKp46 and CD16). They can trigger tumor-cell destruction in solid and transformed tumor models (Fig. 12A) [253]. In line with this strategy, Zhang *et al.* prepared the immunomodulating NPs (IMN) as an engager, which could modify the tumor cell surface with IgG (activating ligand of CD16) to spatially regulate the interaction between NK cells and tumor cells for more effective activation of NK immunity against the tumor growth (Fig. 12B) [254]. Similar to this strategy, selenium nanoparticles (Se NPs) were explored to upregulate the expressions of activation receptor-NKG2D on NK cells and its ligand-NKG2DL on tumor cells (Fig. 12C) [257]. Nanomaterials can be also used as therapeutic agents to kill tumors and release stimulants to activate NK cells for combined immunotherapy of tumor [258,259].

3.4.3. Other methods to activate endogenous NK cells

Besides the above strategies of activating endogenous NK cells with nanomaterials, other joint strategies based on nanomaterials can also activate NK cells [260–266]. For example, nanomaterials under laser irradiation can effectively elicit immunogenic death, promote DCs maturation, and induce activation of $CD8^+$ T cells and NK cells [260–262]. Additionally, nanomaterials combined with checkpoint inhibitors can increase the infiltration of $CD8^+$ T cells and NK cells into tumor [263].

To sum up, precisely targeting tumor cells with nanomaterials can effectively activate endogenous NK cells for tumor therapy. However, there are abundant abnormal blood vessels, immunosuppressive cells and immunosuppressive cytokines in the solid tumors, which drastically inhibit the infiltration, proliferation and activation of immune cells in the solid tumors. Therefore, it is promising to design novel nanomaterials to promote the infiltration of endogenous NK cells in tumor and maintain the activation and function for a long time. When the novel inorganic nanomaterials were used for NK cell-based immunotherapy, the potential impacts of their chemical composition, shape, size, and surface property on the activation and function of NK cells should be comprehensively considered. In addition, most nanomaterials are enriched in the reticuloendothelial system (RES), which can lead to long-term side effects or toxicity. Therefore, the following aspects should be considered during the fabrication and application of inorganic nanomaterials for NK cell-based immunotherapy: (1) The inorganic nanomaterials should be made from the major or trace elements for maintaining good health. More importantly, these elements are conducive to the activation of NK cells and their functions; (2) They should have the ideal physicochemical properties. For example, in term of biodegradability, they should have a suitable degradation rate to not induce any side effects; (3) For the non-degradable nanoparticles, they should be excreted by renal clearance or hepatointestinal metabolism in a short time, after they deliver NK cells to the tumor.

4. Conclusion and perspectives

NK cells are a versatile cell population with “natural killing” character discovered more than 40 years ago. Their capability of killing tumor cells can be enhanced by *in vitro* expansion and gene modification [267]. Engineered NK cells with excellent activation or inhibition performance can enhance their anti-tumor activity. However, the engineered NK cells have been not successfully and fully applied in clinical practice, the challenges mainly include the following aspects. Firstly, it

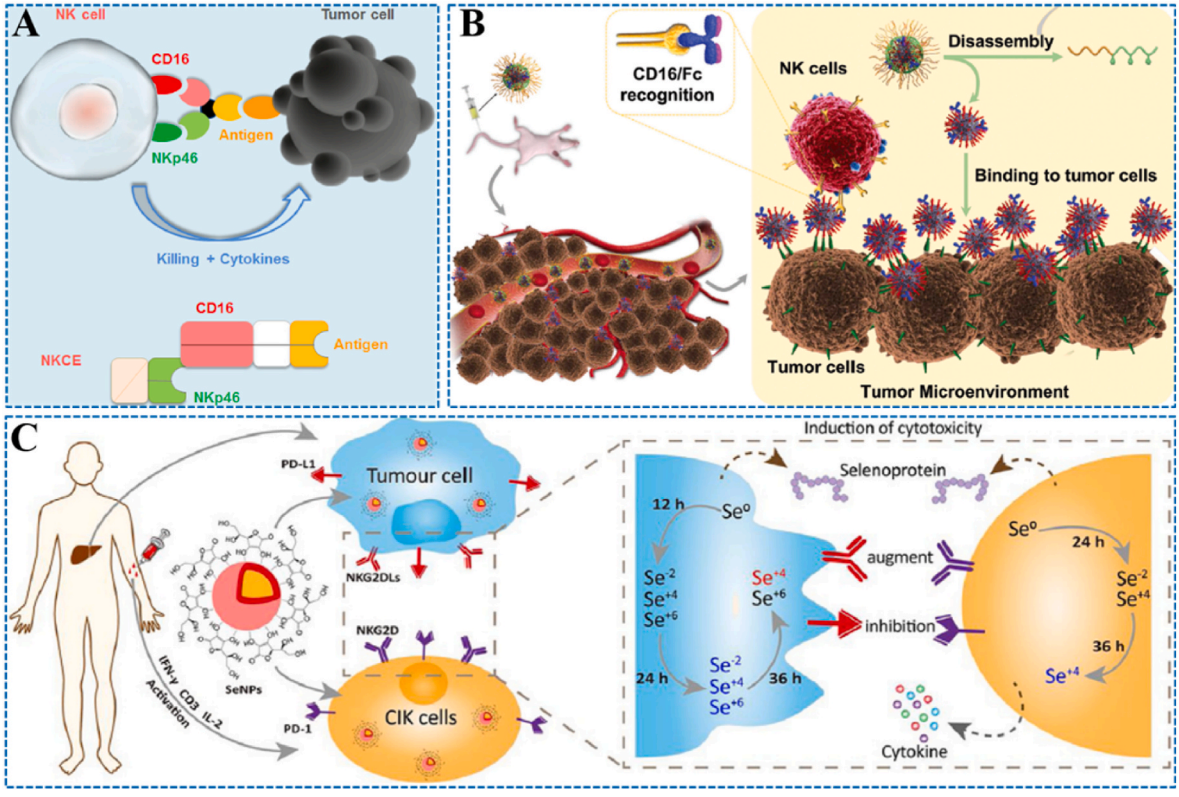

Fig. 12. Nanomaterials regulate the tumor and endogenous NK cells. (A) Schematic illustration of multifunctional engagers (NKCEs) for bringing tumor cells and NK cells together and triggering tumor-cell destruction [253]. (B) Schematic illustration of *in situ* modification of tumor cell surface with immune activation to trigger NK cells for lysis *via* the nano-engager [254]. (C) Schematic illustration of SeNPs enhancing the therapeutic effect of cytokine-induced killer (CIK) cells against liver cancer and the possible mechanism [257]. Adapted with permission [253], Copyright 2019, Elsevier; adapted with permission [254], Copyright 2019, Wiley-VCH; adapted with permission [257], Copyright 2020, Elsevier.

lacks appropriate models to investigate the complexity of human NK cell biology. Secondly, NK cells are poorly delivered to target tumor. Moreover, exogenous NK cells may be depleted, apoptotic, or survived for a short time after infusion. Finally, the expansion and cryopreservation of NK cells are expensive with a high risk of contamination.

To address the above challenges, various nanomaterials have been designed and fabricated to promote NK cell-based tumor immunotherapy. The excellent properties of nanomaterials include simplicity of synthesis, high specific surface area, surface modifiability, and versatility for drug delivery [31]. Different nanomaterials can activate exogenous and/or endogenous NK cells in different ways, and promote their applications for tumor immunotherapy. Unfortunately, the nanomaterials-mediated NK cell immunotherapy has rarely achieved the clinical translation. Extensive studies should be done in the following aspects (Fig. 13).

(I) Design and fabrication of nanomaterials for the precise delivery of NK cells

The adoptive cell therapy (ACT) has been proved to be very effective in treatment of blood cancer, but the traditional ACT is poorly effective in treating solid tumors. The current research of adoptively transferred NK cells mainly focuses on their isolation, activation, propagation and infusion. However, the exogenous NK cells may be depleted and died after infusion, which prevents the homing and infiltration of NK cells into tumor. Hydrogel is an attractive carrier for releasing NK cells at tumor site after postsurgical implantation [195]. Additionally, bio-orthogonal targeted live-cell nanocarriers are also attractive for promoting the specific recognition and migration of NK cells in tumor [214]. Many synthetic methods have been developed to synthesize nanomaterials, but few of them focus on preparation of nanomaterials for promoting the efficient enrichment of exogenous NK cells in tumor. Therefore, the design and fabrication of nanomaterials for precise delivery of NK cells into tumor has shown promise in treatment of solid tumors when compared with the standard intravenous injection method.

(II) **Retention of the activation and function of NK cells**

The challenges of NK cell-based tumor immunotherapy are not only their insufficient homing and infiltration capability, but also the rapid decline of survival and function in the presence of tumor immunosuppressive microenvironment. In section 3.4.1, we review the nanomaterials used for regulating the TME to enhance the NK cell-based tumor immunotherapy. However, nanomaterials cannot activate and maintain NK cell activity for a long time due to their short retention time at tumor site. Most strategies of maintaining the therapeutic efficacy are to increase the frequency or dosage of nanomaterials, which may increase the risks of side effects. Several methods have been developed to prolong the retention of nanomaterials in tumor. In addition to the traditional PEG modification, the use of size-changeable and nanobiomembrane composites has become a mainstream and potential strategy [145,268]. Therefore, tuning the composition, size, morphology, and surface of nanomaterials for maintaining the activation and function of NK cells in the TME has been an important aspect.

(III) Imaging-guided NK cell adoptive therapy by nanomaterials

Although ACT has been explored by promoting the efficient enrichment of exogenous NK cells, and activation of NK cells in tumor site, there are also some challenges for the real-time imaging of patient response during ACT to avoid the cytokine storms. To achieve the real-time monitoring the response of NK cells *in vivo*, immunohistochemistry biopsy is always used in the clinical and current research, which makes the ACT unmanageable. The NIR-IIb molecular imaging of CD8 and PD-L1 in tumor was used to reveal the cytotoxic T lymphocytes in immunotherapy response. The NK cell response and activity in the ACT can be predicted by contrast agents mediated molecular imaging such as immuno-positron emission tomography (PET), immuno-magnetic resonance imaging (MRI), immune-photoacoustic imaging (PAI), and so on [269]. Therefore, design of multimodal imaging nanoagents for *in vivo* real-time monitoring the response of NK cells is of great significance for

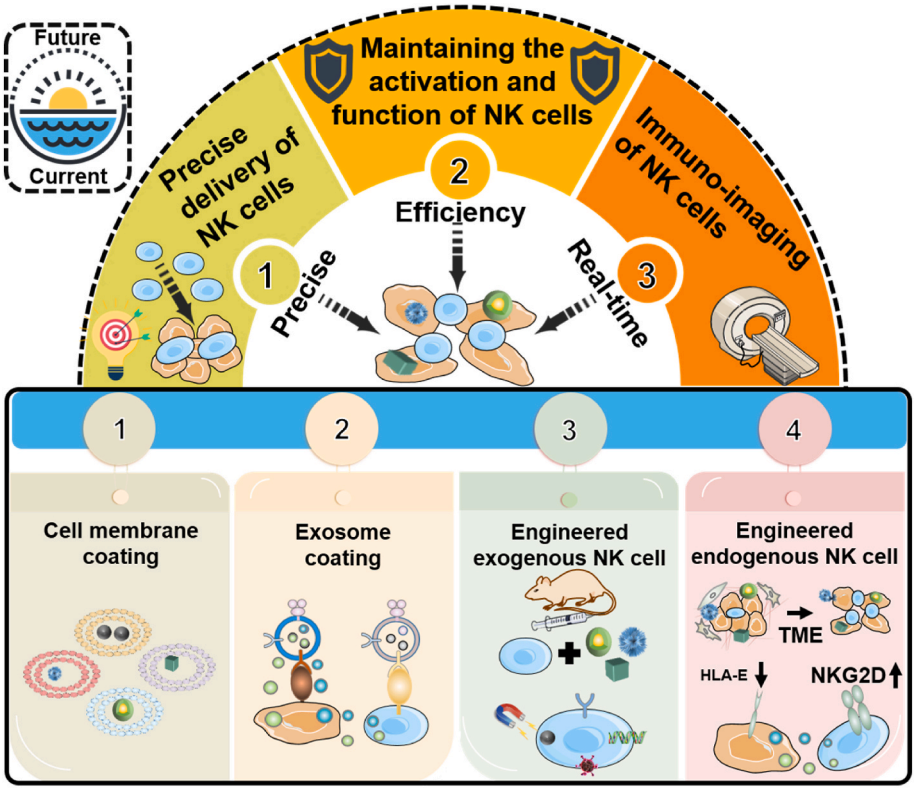

Fig. 13. The state-of-art and prospects of nanomaterials mediated NK cell-based tumor immunotherapy. Research on the application of nanomaterials for enhancing NK cell-based tumor immunotherapy has been extensively investigated, but few of them was used for clinical practice. Extensive studies should be done in the following aspects: (1) Design and fabrication of the precise delivery system for NK cells; (2) Sustainably retaining the activation and function of NK cells; (3) Imaging-guided NK cell adoptive therapy by nanomaterials.

the manageable ACT in future.

Ethics approval and consent to participate

The manuscript is a review article. The authors declare no experimentation on human or animals were designed.

Declaration of competing interest

The authors declare no conflict of interest.

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