Pharmacological Research 155 (2020) 104691

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Natural killer cells as a double-edged sword in cancer immunotherapy: A comprehensive review from cytokine therapy to adoptive cell immunotherapy

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ARTICLE INFO

Keywords:
Natural killer cells
Cancer immunotherapy
Chimeric antigen receptor
Antibody dependent cell-mediated cytotoxicity

ABSTRACT

Natural killer (NK) cells are immune cells which are able to kill tumor and virus-infected cells and play an important role in both innate immunity and acquired immunity. Tumor immunotherapy is an emerging model of tumor treatment in the clinic. It is a re-emerging type of anticancer immunotherapy with the purpose of killing tumor cells by modulating the body's immune function and enhancing the antitumor immunity in tumor microenvironment. At present, many immune cells including lymphokine-activated killer cells, NK cells, cytokine-induced killer cells, and dendritic cells are involved in tumor immunotherapy studies. NK cells, which lyse tumor cells without prior stimulation, has become a research hotspot in cancer immunotherapy for clinical application. In this article, we discussed the surface receptors of NK cells and the anticancer function of NK cells. We also reviewed the biological characteristics and the current research status of NK cells, their clinical application in cancer immunotherapy and its future perspectives.

1. Introduction

In 1975, Kiessling et al. and colleagues at Herberman's lab found a group of cells, similar to lymphocytes, which could lyse tumor cells without prior stimulation [1]. Unlike T and B cells, this new group of cells could directly kill allogeneic and xenogeneic tumor cells as well as

Abbreviations: ADCC, antibody dependent cell-mediated cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; BCSCs, breast cancer stem-like cells; CAR, chimeric antigen receptor; CD56^{bright}, high CD56 density; CD56^{dim}, low CD56 density; CRPC, castration-resistant prostate cancer; CTLA4, cytotoxic T lymphocyte-associated antigen-4; DAMP, damage-associated molecular patterns; EpCAM, epithelial cell adhesion molecules; GM-CSF, granulocyte-macrophage colony-stimulating factor; GVHD, graft-versus-hostdisease; HIFs, Hypoxia-inducible factors; Hsp70, heat shock protein 70; IDO, indoleamine 2,3-dioxygenase; IFN-γ, interferon γ; ITAM, immunoreceptor tyrosine-based protein activation motif; ITIM, immunoreceptor tyrosine-based protein inhibitory motif; ITT, immunoreceptor tyrosine tail; KIRs, killer immunoglobulin receptors; LAG3, lymphocyte-activation gene 3; MDSCs, myeloid-derived suppressor cells; MHC, major histocompatibility complex; NK cells, natural killer cells; NK1, neurokinin-1; NK2, neurokinin-2; NK3, neurokinin-3; OS, overall survival; PCNA, proliferating cell nuclear antigen; PFS, progression-free survival; PGDF, platelet-derived growth factor; PGE2, prostaglandin E2; QOL, quality of life; scFv, single chain antibody fragment; RCT, radiochemotherapy; TGF-β, Transforming Growth Factor β; TKD, TKI, tyrosine kinase inhibitor; TNF-α, tumor necrosis factor α; TRAIL, necrosis factor-related apoptosis-inducing ligand; Tregs, regulatory T cells; TriKE, trispecific killer engagers; UCB-NK, umbilical cord blood-NK; ULBP1, UL16 binding protein 1; VEGF, vascular endothelial growth factor; ZAP70, zeta-chain-associated protein kinase 70

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https://doi.org/10.1016/j.phrs.2020.104691
Received 27 November 2019; Received in revised form 6 February 2020; Accepted 10 February 2020
Available online 15 February 2020

virus-infected target cells without pre-sensitization which called as natural killer cells (NK cells) [2,3]. In the late 19th century, NK cells were found to recognize tumor cells through activated and inhibitory receptors on their surface [4].

While NK cells killed the major histocompatibility complex (MHC) class I-expressing tumor cells, NK cells caused no damage to mostly healthy cells which expressing MHC class I molecules. Paradoxically, it was demonstrated that there was no MHC limitation on the killing activity of NK cells on tumor cells [5]. The engagement of MHC class I molecules maintains NK cells in a state of responsiveness to subsequent activation, a property has been previously defined as NK cell licensing or NK cell education. These phenomena also indicate that NK cells have diverse functions including stimulating and amplifying inflammatory responses, producing chemokines and cytokines, and cleaving sensitized target cells [6,7]. NK cells are the key effector cells of the natural immune system which morphologically are similar to large granular lymphocytes. The volume of NK cell is twice more than that of erythrocytes. NK cells are widely scattered in tissues with various phenotypes, which distinctly distributed in peritoneal cavity, placenta and uterine mucosa, and especially in liver [8]. The exact source of NK cells is not well understood and is generally thought to be derived directly from the bone marrow, which is dependent on the microenvironment of the bone marrow. $CD3^{-}CD56^{+}$ cells are generally considered as NK cells, the proportion of which in blood mononuclear cells is about 5 %–20 % [9].

According to their migration behavior and cytotoxic response, NK cells are divided into five groups: NK cells interacting with target cells; NK cells do not kill target cells, NK cells kill all target cells, exhausted NK cells, and NK cells stochastically kill target cells based on the net balance of stimuli perceived from activating and inhibitory receptors [10]. The $CD56^{+}$ NK cell subset is thought to mediate antitumor responses usually with high proportion in human peripheral blood NK cell, whereas the $CD56^{bright}$ subset is involved in immunomodulation [9,11]. In human, $CD3^{-}CD56^{+}$ NK cells are divided into two groups according to the CD16 expression. Up to 90–95 % $CD16^{+}$ NK cells are mainly responsible for the cytotoxic function, while the $CD16^{-}$ cells are responsible for the production of cytokines involved in immune response instead of cytotoxic action [12].

In the recent years, adoptive cell immunotherapy has been strongly developed and T-cell based therapies such as KYMRIAH using chimeric antigen receptor (CAR) T cells was approved by U.S Food and Drug Administration (FDA) [13,14]. As NK cells have the potential to be manufactured against certain types of cancer [15], NK cells along with T cells would be the next generation but promising immunotherapy against cancer with less harmful effects on healthy cells [16]. Thus, there is an urgent need to figure out the impact of NK cells in the future of cancer immunotherapy. In this review we discussed the NK cell receptors profile, the antitumor effect of NK cells, and the clinical strategies of manufactured NK cells for cancer treatment and highlighted the related clinical trials to make the readers more familiar with challenges and potential of NK cells in this regard.

2. NK cell receptors expression profile

There are two classes of receptors on NK cells surface, the activating receptors and the inhibitory receptors. The net balance of activating and inhibitory signals regulates NK cells to attack and eliminate a potential target cell. The cytoplasmic domain of the inhibitory receptor contains the immunoreceptor tyrosine-based protein inhibitory motif (ITIM), which can transmit inhibitory signals by recruiting tyrosine phosphatases SHP-1 and SHP-2 [17]. Activation of NK cells are different, mainly through recruiting adapter protein by the transfer membrane domain residues of the activation receptor. The activation of the adapter protein depends on immunoreceptor tyrosine-based protein activation motif (ITAM), in combination with the ZAP70 and Spleen tyrosine (syk) kinase family proteins led to secretion of cytotoxic granules and cytokines by NK cells [18]. In this part, we summarized the different types of receptors on the membrane of NK cells.

2.1. Inhibitory receptors

The inhibitory receptors of NK cells that recognize MHC-I molecules include inhibitory killer immunoglobulin receptors (KIRs), leucocyte immunoglobulin-like receptors (LIRs) and C-type lectin inhibitory receptors CD94/NKG2A. The KIRs are a family of type I transmembrane glycoproteins on the plasma membrane of NK cells and a minority of T cells encoded by a gene cluster at human chromosome 19q13.4 [19]. NK cells characterized based on CD56 density expressed on cell membrane. Low CD56 density ($CD56^{dim}$) NK cells express KIRs such as CD158a, CD158b, and NKB1; however, both low CD56 density ($CD56^{dim}$) and high CD56 density ($CD56^{bright}$) subsets of NK cells contain c-type lectin like receptors (KLR) CD94/NKG2 and CD161. In addition, $CD56^{dim}$ NK cells produce a higher amounts of perforin and granzyme A whereas $CD56^{bright}$ secrets more interferon γ (IFN-γ) and *tumor necrosis factor* α (TNF-α) [20]. Instead of endogenous signaling from the cytoplasmic domain, the CD94 molecule binds to the two ITIMs of NKG2A to form a complex, which delivers the inhibitory signal [21]. Another new found immune receptor, T-cell immunoglobulin and ITIM domain (TIGIT), was associated with NK cells function and high expression level of TIGIT displayed as a suppressive factor to decrease cytotoxic potential of NK cells [22].

2.2. Activating receptors

The activating receptors for NK cells include a variety of cytokine receptors, integrins, killer receptors (CD16, NKp44, NKp46, NKp30), receptors that recognize some of the induced expression molecules (NKG2D, DNAM-1/CD226) (Ly49 H), and other receptors such as NKp80, SLAMs (SLAM, 2B4, NTB-A and CD84), CD18, CD2 and TLR-3. Among them, NKG2D and DNAM-1 are the major activated receptors [23]. NKG2D played a greater role in the killing of IRE1/XBP1 knockout target cells [24]. CD16 is a low affinity receptor for immunoglobulin IgG and is widely expressed on NK cells, dendritic cells, monocytes and T cells. When IgG recognizes tumor cell surface-specific antigens, NK cells bind IgG through CD16, which in turn releases the particles to induce tumor cell death in a process called antibody dependent cell-mediated cytotoxicity (ADCC). Over-activation of ADAM17 and matrix metalloproteinases on surface of NK cells appears to interfere NK activation and cytokines production by down-regulating CD16 expression [25,26].

Furthermore, NKp44 is expressed only on activated NK cells, while NKp30 and NKp46 are expressed on both resting and activated NK cells. NKp46 possesses a transmembrane structure that can bind to the adapter molecule CD3ζ. Activation of NKp46 or co-stimulation with other signaling mobilizes calcium currents and affects the expression of effector molecules. Monoclonal antibodies targeting NKp46 significantly inhibit NKp46 receptor-mediated tumor cell killing activity [27]. The expression of NKp44 is induced by the cytokine IL-2, IL-15, and its signal is mainly transmitted by the ITAM of the adapter protein DAP12 [28–30]. However, activating NKp44 was recently found to result in activation or inhibition of NK cell cytotoxicity by recognizing the cancer cell-produced damage-associated molecular patterns (DAMP) that either activate (if containing MLL5 on the surface of tumor cells) or inhibit (if exosomal proliferating cell nuclear antigen (PCNA) and HLA I produced by tumor cells) NK cell function [30,31].

The NK activating signal mainly involves the NKp30 natural cytotoxicity receptor, and not the NKp46 or NKp44 receptor. The adapter molecules of NKp30, CD3ζ and FcRγ I induce tumor cell death by binding to an HLA-B related transcriptional marker BAT3 or B7-H6 [32,33]. Meanwhile, NKp30 also cooperates with NKp44 and NKp46 to exert cytotoxic function through an ERK-dependent mechanism [34]. Dendritic cells also activate resting NK cells and are recognized by the

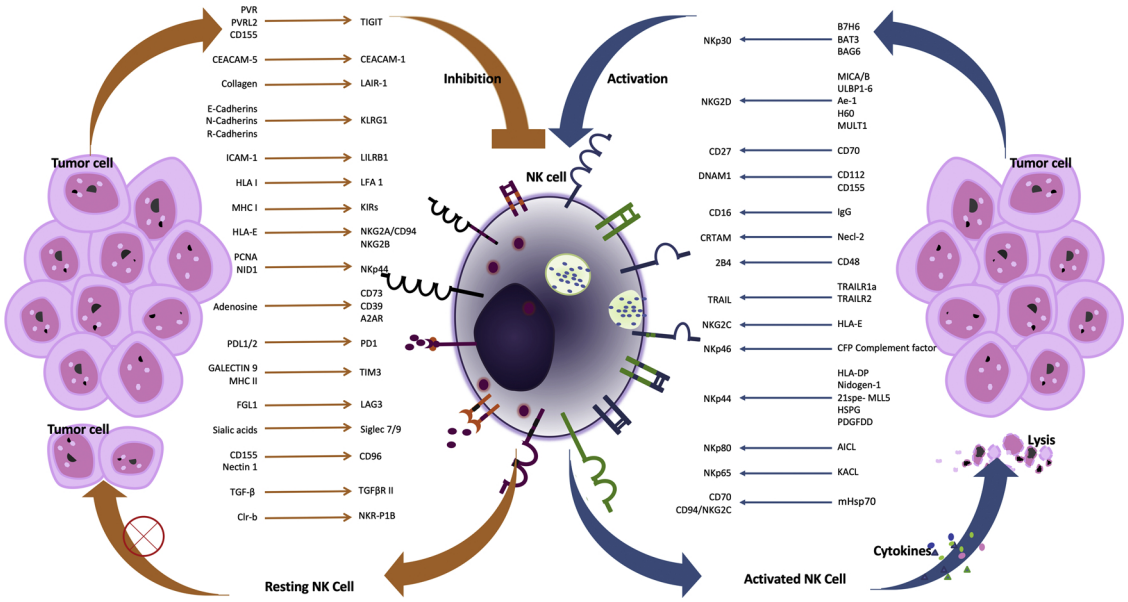

Fig. 1. NK cell opposing functions. On the right side, NK cells activation relies on stimulation of activating receptors on the surface of NK cells such as NKG2D, DNAMQ, CD16, *etc,* which finally trigger the expression of inflammatory cytokine including IFN-γ, TNF-α, IL2 and IL18 and then, mediates the killing ability of NK cells. On the other hand, inhibiting receptors on NK cell surface functioned as negative regulator of NK cell-mediated cytotoxicity (on the left side), which decreases cytokines production of NK cells. Thus, suppression of these kinds of receptors such as PD-1 and KIRs alter NK cells status in tumor microenvironment. The corresponding ligands of NK cell surface receptors was also stated.

NKp30 receptor of activated NK cells. However, it has been suggested a NKp30 independent mechanism is also involved in stimulate resting NK cells [35]. The details of individual classes of receptors on cell surface of NK cells as well as their as well as their corresponding ligands on tumor cells are schematically described in Fig. 1.

3. NK cell activation and effector function

Unlike T cells and B cells, NK cells do not rearrange the genes during antigen recognition. Instead, NK cells directly recognize the target cells through the activated and inhibitory receptors. Under physiological conditions, ligands of activated receptors are poorly expressed in human cells and then, NK cells are maintained in a resting state controlled by inhibitory receptors. Signals in some circumstances such as viral infections or malignant transformation suppress expression of inhibitory receptor in NK cells and stimulate activated receptor, which in turn result in secretion of interferons and cytokines [36]. The activated NK cells leave the blood circulation and enter the peripheral tissues as a result of chemotaxis media. Activated NK cells may also have an ability to antigen presentation and stimulate immune response of T cells [9].

At first, NK cells are targeted to kill tumor cells in several ways, among which perforin/granzyme-mediated cytotoxicity is the most effective way. Cytotoxic granules contain perforin and are able to destroy tumor cell membranes. When perforin is released from NK cells, serine proteases enter tumor cells and cause intracellular substance efflux, leading to target cell lysis [37–39]. Secondly, NK cell-induced tumor cell cytotoxicity is mediated by secretion of multiple cytokines. Activated NK cells secrete a variety of cytokines, such as TNFs and granulocyte-macrophage colony-stimulating factor (GM-CSF) [40], IL-5 [41], IL-10 [42], IL-13 [43] and so forth. Cytokine-dependent mechanisms involved in killing target cells inhibit the proliferation and invasion of tumor cells, regulate and promote dendritic cells, macrophages, and T cells. It was indicated that IL-2 could increase perforin gene transcription and IL-6 could promote the induction of perforin through IL-2 [44,45]. The process of TNF-induced cell death is significantly slower than that of perforin-lysed cells. IFN-γ also stimulate antigen presenting cells to secrete IL-12, which in turn activates T-cell immune responses and eventually kill tumor cells [46,47]. The last approach is death receptor-mediated apoptosis in target cells. NK cells express Fas ligand and kill target cells by binding to the corresponding death receptors on tumor cell surface [48,49]. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) expressed by both NK cells and T cells induces apoptosis of target cells and play a key role in antitumor function of NK cells [50]. The killing mechanisms of NK cells was also summarized in Table 1.

On the other hands, many cytokines also promote cancer progression and are correlated with poor prognosis in patients with malignant diseases. It was shown that the indoleamine 2,3-dioxygenase (IDO) and prostaglandin E2 (PGE2) induced by IFN-γ enhanced the expression of HLA-G on tumor cells, resulting in poor prognosis for cancer patients suggesting the immune-suppressive effect of NK cells [78–80]. Moreover, NK cells produce soluble factors such as VEGF and PDGF supporting tumor angiogenesis, indicating the opposing function of cytokines in cancer treatment [81–83]. NK cells activation was schematically shown in Fig. 2A, while signaling pathways related NK cell-induced tumor cell cytotoxicity was demonstrated in Fig. 2B.

4. NK cells as a double-edged sword in tumor immunity

Immunosuppressive effect and killing capacity of NK cells in tumor both found due to activation of the receptors in NK cells. While the activating receptors are stimulated or the inhibiting receptors are suppressed, NK cells are induced to kill tumors cells, exhibiting the antitumor function. However, tumor cells would get away from the surveillance of NK cells while the activating receptors are restrained or the inhibiting receptors are stimulated, thereby resulting immune escape.

4.1. Natural killer cells involved in immune escape function

Immune evasion is a well-recognized hallmark of cancer. *in vitro* studies have found that the ability of NK cells in tumor tissue to kill cancer cells is significantly lower than that of NK cells from normal tissues, suggesting that the function of NK cells in the tumor microenvironment is inhibited led to tumors immune escape [84]. NK cells gradually exhibited an exhausted status [85] with reduced proliferation and cytotoxicity. Recently studies stated exhausted NK cells are closely

Table 1
The killing mechanisms performed by NK cells.

Cytokines or proteins secreted by NK cells	Mechanisms	Function	Ref.
Perforin	Inserted into a target cell's plasma membrane forming a pore	Mediating Granzyme entry into target cell cytoplasm	[51,52]
Granzyme A	Damaged single-stranded DNA	Activating the caspase-independent death pathway	[53,54]
	Cleaved the nuclear lamina, Lamins A, Lamins B, Lamins C	Activating caspase-mediated apoptosis	[55]
	Cleaved synthetic substrates with a P1 arginine or lysine	Induction of cellular apoptosis characteristics	[56]
Granzyme B	Cleaved and activated initiator caspases 8 and 10, and executioner caspases 3 and 7	Activation of the caspase death pathway	[57,58]
	Cleaved BID	Resulting in BAX/BAK oligomerisation and cytochrome c release	[58]
	Generated mitochondrial ROS ang disruption	Mediating cell death	[59]
	Cleaved ICAD	Resulting in DNA fragmentation	[58]
	Bound Hsp70 specially and uptake of Granzyme B	Mediating perforin-independent apoptosis	[60]
Granzyme K	Accompanied by the production of ROS, Delta Psim, and DNA fragmentation	Induction of Perforin-dependent cell death	[61]
Granzyme M	Direct DNA damage	Activating the caspase-independent death pathway	[62]
	Cleaved methionine and leucine residues	Mediating non-specific cell death	[62,63]
NK cytotoxicfactors	Recognized, bound, and lysed specific target cells	Inducing cytotoxicity	https://doi.org/10.1007/978-1-4612-4586-5_9
TNF-α	Recruited of the death domain-containing adaptor protein FADD	Triggering a caspase cascade and subsequent cell death	[61]
Apo2 ligand/TRAIL	Combined with the cell surface death receptors	Activating intracellular caspases, resulting in apoptosis	[64]
	Facilitated IL-2 activated NK cell-mediated cytotoxicity	Regulating cells of the immune system	[65]
	Assisted by IFN-α	Synergistically induces apoptosis	[66]
IFN-γ	Promoted MHC expression via induction of some APM components	Regulating immune cell viability	[67–70]
	Induced caspase 1 expression via STAT1	Induction of cell apoptosis	[71]
	Up-regulated the transcription factor t-bet	Promoting the differentiation of type I helper T cells	[72]
Fas/CD95 ligand	Recruited of the death domain-containing adaptor protein FADD	Activating apoptosis-mediating caspases	[73]
CD16	Activated β2-integrins and induced TNF-α secretion;	Mediating the direct killing	[74]
	Induced TNFR expression on target cells	Triggering TNF-α-mediated cell death	[75]
	Bound to the Fc portion of IgG antibodies to induced gene transcription of surface activation molecules and inflammatory cytokines	Activating ADCC	[76]
	Acted as a lysis receptor	Mediating direct NK cells cytotoxicity	[77]

ICAD, Inhibitor of caspase-activated DNase; APM, antigen-processing machinery; FADD, Fas-associated protein with death domain; ROS, reactive oxygen species; ADCC, antibody-dependent cell-mediated cytotoxicity.

related several factors including dysregulated NK cell receptors signaling, suppressive effects by Treg cells or suppression factors in the microenvironment [86]. Firstly, as the main reason that affects the function of NK cells, the expression of cytotoxic molecules in NK cells is decreased [87]. Secondly, the expression of surface-activated receptors on NK cells is declined, which induces insufficient amounts of activated receptors to recognize the corresponding ligands, resulting in inactivation of NK cells. A study found that the expression levels of NK cell surface-active receptors including NKG2D and natural killer receptor NKp30, NKp44 and NKp46 were significantly decreased in lung and liver cancers [88,89], Thirdly, the expression of immunosuppressive receptors on the surface of NK cells is up-regulated. NK cells express many inhibitory receptors to maintain their own immune homeostasis in order to prevent their own excessive immune responses from causing tissue inflammatory lesions [90]. Upregulation of the immunosuppressive receptors on the surface of NK cells resulted in enhanced transduction of the negative regulatory signals and then, decreased the activity of NK cells in the tumor tissues [91]. A research reported that the inhibitory receptor TIGIT was associated with NK cell exhaustion in different tumor models and patients with colon cancer [92]. In addition, High expression of the inhibitory receptors CD94/NKG2A in $NKp46^{neg-low}/CD56^{dim}/CD16^{neg}$ NK cells also significantly inhibited the generation of $NKp46^{pos}/CD56^{bright}/CD16^{neg-low}$ subset as well as the immune responses in haploidentical hematopoietic stem cell transplantation [93]. This suggests a new way of immunotherapy with blocking NKG2A check-point. Fourthly, the expression of MHC-1 on tumor cells is changed. Through proteolytic shedding of MICA and MICB (major histocompatibility complex class I chain-related protein A/B), tumors can escape the activation of NK cells by blocking NKG2D signal pathway, resulting in escaping the cytotoxicity of NK cells in cancer disease [94]. Fifthly, NK cells function may be absent in the tumor microenvironment due to immune subversion, editing or selection of poorly immunogenic tumor cells. Recent findings suggested that the phenotype and function of NK cells is altered in breast cancer with low expression levels of NKp46, perforin, and granzyme B to create favorable conditions for tumor development [95]. Immune suppressive cells including myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) as well as related cytokines secreted in the tumor microenvironment also affected NK cells function, resulting in NK cells' exhaustion. Treg cells have been described to suppress both autologous and allogeneic NK cells and impair NK cell effector functions, which might be mediated by the negative role of allorecognition or Tregs TCR on NK cell activation [96]. In addition. Tregs also secreted kinds of inhibitory cytokines, such as TGF-β [97,98], IL-35 [99], IL-37 [100]. which could suppress NK cells killing capacity. An *in vitro* study proved that the cytotoxic ability of NK cells was evidently limited by TGF-β in the TGF-β-rich medulloblastoma tumor microenvironment [101], indicating the negative potential of Tregs on NK cells. Several studies

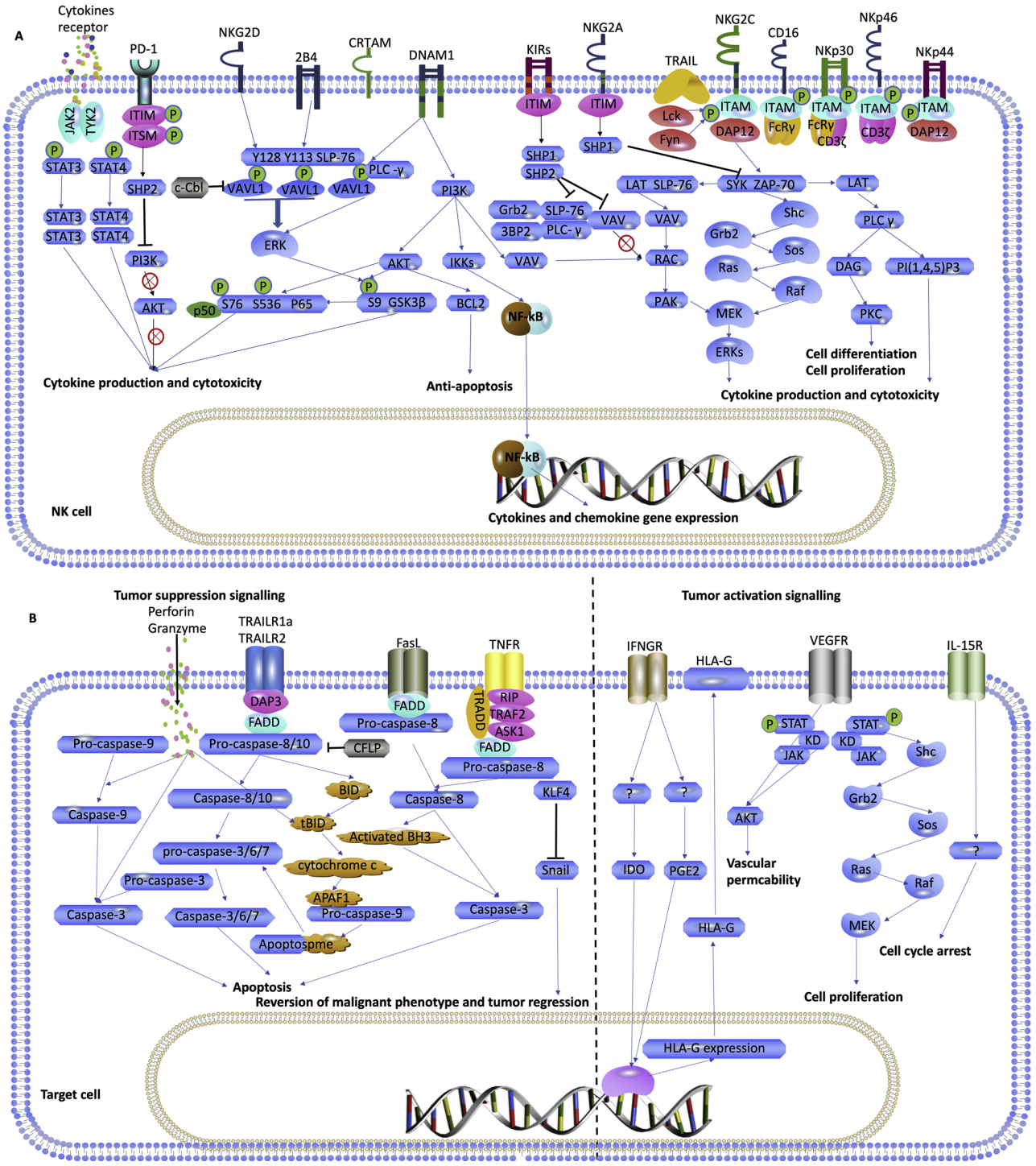

Fig. 2. Antitumor function of NK cells and Immune suppressive effect. (A) NK intracellular functions. Inhibitory receptors (TIGIT, KLRGI, LAIR-1, CEACAM-1, LILRB1, LFA I, KIRs, CD94/NKG2A/B) on the surface of NK cells mediate decreased activity of NK cells in the tumor tissues through transduction of the negative regulatory signal. Besides, downregulation of activating signals would also lead to a decline of the antitumor immune response. NKG2A/B interaction with its ligand HLA-G suppresses activating signaling. KIRs are a big family of highly polymorphic inhibitory receptors that serve as key regulators in regulating human NK cell function. (B) The activating receptors (NKp30, NKp44, NKp46, NKG2D, CD27, DANM1, CD16, CRTAM, 2B4, TRAIL, NKG2C) on the surface of NK cells mainly mediate the cytolytic activity of NK cells. On the left side, apoptotic pathways in cancer cells is displayed which triggered by perforin and granzyme secreted by NK cells. On the right side, stimulation of cancer cell has been shown which is triggered by NK cells secreted IFN-γ, IL-15, VEGF and HLA-G. IFN-γ increases HLA-G expression on tumor cells, resulting in tumor escape. IL-15 leads to NK cell cycle arrest and VEGF directly improve tumor cell proliferation, indicating the diverse function of NK cells on tumor cells.

documented that IL-35 increased in several cancers and influenced NK cells immune responses through downregulation of TIM3, resulting in increased tumor progression and angiogenesis [102]. IL-2 was routinely used in NK-based immunotherapy. However, Low-doses of IL-2 lead to the preferential expansion of Tregs [103], thereby impairing the anti-tumor activity of cytotoxic T-lymphocytes. IL-4 partly prolonged the survival of Tregs through suppression of the apoptosis of Tregs, increased the expression of granular enzymes [104], as well as inhibited

proliferation of NK cells and IFN-g production by T cells [105], which supporting Tregs-mediated immunosuppression. Targeting Tregs therapy might facility NK cells efficacy in cancer immunotherapy. On the other hand, tumor cell-derived exosomes suppressed NK cell function by expressing TGF-β and inhibiting NK cells activation though NKG2D signal pathway [106] suggested that it might be involved in the exhausted of NK cells. In addition, compared with para-tumor tissues, galectin-9 was high expressed in colon tumor tissues, contributing to a poor outcome by inhibiting NK cell chemotaxis partially through the Rho/ROCK1 signaling pathway. These studies represented another mechanism for tumors to escape immune surveillance in tumors [107]. Recently, accumulating evidences indicated that hypoxia, commonly phenomenon in the tumor microenvironment, played an important role in tumor cell immune escape and impaired NK cell-mediated cytotoxicity through variety of hypoxia-inducible factor (HIF)-related signaling pathways [108,109]. It was reported that hypoxia induced immune escape of tumor cells escape from NK cells through HIF-1α-mediated downregulation of both NK cell ligands MICA/B and heat shock protein 70 (Hsp70) [110]. HIF-1α also induced metabolic dysfunction of NK cells through upregulation of CD73 in solid tumor, thereby contributing the impairment of NK cells-mediated cancer cell lysis [111]. Moreover, overexpression of Hypoxia-inducible gene 2 in liver cancer cells was found to decrease NK cells killing activity through IL-10/STAT3 signaling pathway, thereby promoting liver cancer progression and recurrence [109]. In addition, autophagy also plays an important role in hypoxia-induce tumor evasion from the immune surveillance, due to the degradation of gap-junctional Cx43 protein [112]. As a significant and negative regulator in solid tumor, hypoxia-exerted immunosuppressive effect especially in NK cells as well as the related mechanisms could really provide new insights in cancer immunotherapy.

In conclusion, the function of NK cells is affected by the activity of NK cells and the change of tumor MHC and the tumor microenvironment, which may be influenced by a specific factor or synergistic effects. The mechanisms involved in immune escape function of NK cells were systematically described in Fig. 3.

4.2. Antitumor function of natural killer cells

The therapeutic role of NK cells in hematological malignancies has clearly been established [113]. As anticancer activities of NK cells do not depend on any specific neo-antigen recognition, it is suggested that they may function as a novel potential marker or target for tumor diagnosis and immunotherapy respectively. While the role of NK cells in tumor progression and angiogenesis not yet been fully investigated, the underlying mechanisms of NK cells-mediated antitumor activity might be relaying on a variety of signaling pathways, including blocking inhibitory receptor and the activation of activating receptors, and then, facilitating the immune cytolytic activity to inhibit tumor differentiation and metastasis, and increasing sensitivity to chemotherapeutic drugs [114,115]. Some data have suggested that NK cells may serve as a new potential approach for anticancer therapeutic interventions. Extracellular histones from NK cells boosted immune cell anti-tumor activity by recruiting immune-tumor cell clusters through binding to CD138 receptor on the surface of multiple myeloma cells, promoting both NK and T cell function [116]. $NKp46^{+}$ cell population was found necessary in inhibitory effect of NK cells in melanoma metastasis [117,118]. NK cells activated by tumor-expressed PDGF-DD were shown to bind to tumor cells though the interaction between NKp44 and PDGF-DD, which limits tumor growth in transgenic mice [119].

Recent studies demonstrated that low IFN-γ production of NK cells was related to advance gastric cancer progression, indicating that Natural killer cell activity -IFN-γ production could be used as a potentially diagnostic marker for gastric cancer [120]. There were also many reports on the association between infiltrating immune cells and cancer prognosis. Research data showed that low cell surface expression of UL16 binding protein 1 (ULBP1) on the tumor cells and NKG2D receptor on NK cells was correlated with poor prognosis in gastric cancer, and the interaction between ULBP1 and NKG2D was associated with improved overall survival (OS) in patients with gastric cancer [121]. In addition, it was also found that recombinant soluble MICB impaired the cytolytic ability of NK cells via decreasing NKG2D receptor [122]. What's more, it's reported sulforaphane (SFN) has an immunotherapeutic potential by upregulating MICA/MICB expression as

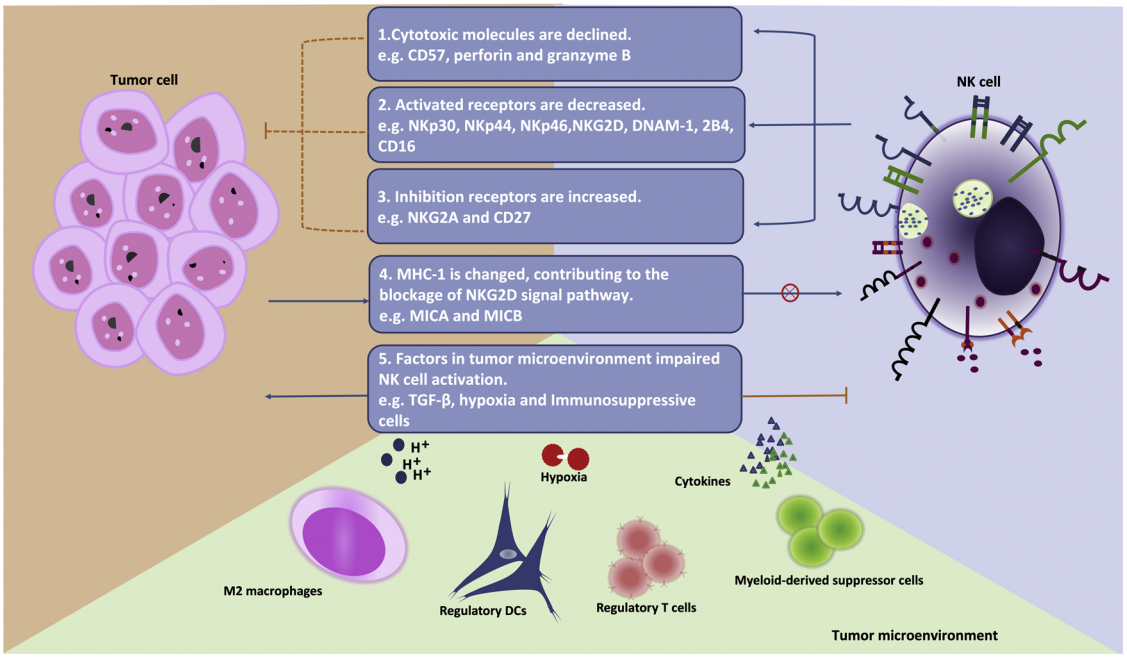

Fig. 3. The mechanisms involved in immune escape function of NK cells. There are several aspects of action involved in NK cells related immune escape, mainly including the suppression of activating receptors on NK cells, the activation of inhibitory receptors on NK cells and some tumor microenvironment factors such as hypoxia-induced NK cells deactivation. On the other hand, alteration of MHC-1 expression on tumor cells also impaired NK cell function through blocking NKG2D signaling. These actions might provide novel perspectives on application of NK cells with more efficacy in cancer treatment.

well as increasing susceptibility to NK cell mediated cytotoxicity [123].

Studies also showed that NK lysis receptors (NKLR) and NKLR-ligands improved cytotoxic activity of NK cells against malignant melanoma. Moreover, combined suppression of JAK1/2/PD-L1 and Stat3/PD-L1 signaling pathways exhibited more effect in enhancing the cytolytic activity of NK cells in hypoxia-induced castration-resistant prostate cancer (CRPC) cells [124], providing novel ideas and targets for NK cells-based cancer immunotherapy.

5. NK cells-based cancer immunotherapy and related clinical trials

More and more clinical studies have shown that boosting autoimmunity benefit a lot for cancer treatment and interesting number of clinical trials support that acute exercise NK increase cell function [125], suggesting that NK cells may have broad application prospects in cancer immunotherapy. NK cells infusion, one of the effective methods for cancer treatment, consists of autologous NK cell therapy and allogeneic NK cells. Autologous NK cell therapy is a commonly used immunotherapy technique for tumor treatment. The immature NK cells were extracted and isolated from patients themselves, and re-injected into the body after induction of amplification and maturation *in vitro*, while the sources of allogeneic NK cells ranged from haploidentical donors, unrelated donors, umbilical cord blood and engineered NK cells including CAR-NK cells. The autologous NK cell therapy is safer and tolerable and can be harnessed to increase the antitumor activity, while the allogeneic NK cells cause more adverse events due to the mismatch between the KIR and HLA. Recently, the efficacy of allogeneic NK cells has also been widely investigated in the treatment of hematologic malignancies and solid tumors. Both autologous and allogeneic NK cells have potential efficacy, including breast cancer [126], lung cancer [127,128], liver cancer [129,130], bladder cancer [131], primary neuroblastoma [132], ovarian cancer [133]. In addition, clinical trials based on adopting NK cell immune response have been carried out for more than ten years. A new study proved that UCB-NK cell therapy and NK cell expansion without Cy/Flu pretreatment was safety in recurrent ovarian carcinoma, which supported UCB-NK cell infusion after regular second-line chemotherapy [134]. Further, a mathematical model was also set up to evaluate the function and activity of NK cells by testing anti-myeloma activity of natural killer cells in microfluidic system, greatly promoting the application of NK cell-based immunotherapy, including immunotherapy screening, biocomputation and detection of patient-specific cell response [135]. As great progress has been made in NK cell related cancer treatment in basic researches, preclinical studies and dynamic monitor system, the clinical application of NK cells for cancer therapy has been also emerging as an effective approach for patients with cancer. We summarized the NK cell associated clinical trials in Table 2. Besides, Fig. 4 also illustrated approaches related to NK cell-based cancer immunotherapy.

5.1. Cytokines activated NK Cells infusion therapy

Clinical trials stated that high-does NK cells infusion is safe and feasible way to maintain the host immune response in patients with malignant lymphoma or advanced solid tumors [136–138]. It has been shown that lymphocytes, when exposed to IL-2, are able to lyse fresh, non-cultured cancer cells, both primary and metastatic [139]. Thus, the most common used cytokine in NK cell culture is IL-2. Intravenous injection administered with high-dose of IL-2 for renal cell carcinoma patients with bone and liver metastasis has produced favorable outcome with improved overall survival in patients [140], which might rely on the activation of NK cells. A recombinant IL-2 immunocytokine comprising a tumor-targeting antibody (Ab) and a super mutant IL-2 (sumIL-2) shows good in preclinical studies, have broad application prospects [143].

However, IL-2 has cytotoxicity and does not conduct the antitumor response of NK cells when IL-2 dose is too high. IL-2 induces the proliferation and differentiation of regulatory T cells [141,142] IL-12, emerged as one of the most potent cytokines in mediating antitumor activity in a variety of preclinical models, while the mechanisms underlying the immunoregulation and antitumor activities of IL-12, as well as its combination in tumor immunotherapy is under investigation [144–146]. Other receptors found in cytokines such as IL-7, IL-15 [147–150], IL-12 [148] and IL-21 [145] exhibited similar capability in activation of NK cells. Recombinant IL7/IL15 has a higher antitumor activity than the combination of the individual factors in melanoma and colon cancer cells, which associated with a decrease in Tregs and an increase in tumor infiltration of T cells, DCs, and NK cells [151]. It was reported IL-15 increased expansion of the NK cells in prostate cancer, which might rely on the upregulation of NKG2D expression [152]. These differential effects on diverse immune components result in enhanced tumor immunity.

IL-18 not only increases activity of NK cells, but it also alters the phenotype of NK cells. The present studies demonstrated that the biologically active IL-18R complex plays important role in IL-18-induced IFN-gamma in NK cells [153]. IL-2/IL-18-induced NK cells expansion might benefit for cancer immunotherapy [154]. It is worth mentioning that NK cell-enriched lymphocytes (NKL) expanded by cytokines (IL-2, IL-12 and IL-18) plus agonistic antibodies (CD16, CD56 and NKp46) showed apparent antitumor effective on liver cancer both *in vitro* and *in vivo* [155], indicating the promising potential for application of autologous NK cells in clinical trials. IL-27 has also been shown to enhance IL-15/IL-18 mediated NK cell activation [156]. These cytokines activate NK cells in cancer immunotherapy in preclinical studies, providing effective strategy for preparation of clinical studies [149]. A new study revealed amplification a special activated NK cells subset, NKG2C + NK cells, by kinds of cytokines and other immune cells may be a promising therapeutic strategy to be exploited in NK cell-based intervention strategies against cancer [157]. In addition, Cytokines as monotherapy have not fulfilled their early goals because they are not meet sufficient concentrations in the tumor and are associated with severe toxicity to bodies [150]. At the same time, using cytokines to activate and expand human NK cells are limited by low-fold expansion and expansion-related senescence [150]. Therefore, other methods are generated to induced NK-cell expansion and activation to meet the needs of clinical utilization, including the use of genetically engineered cell lines to “feed” cells, such as K562 and K562-OX40L [158,159]. Those feeder cells triggered a significant increase of NK cell numbers, which has been proved to be applicable with assured activity and safety in clinical application [160,161].

5.2. Chemotherapy combined with NK cell infusion therapy

Chemotherapy combined with NK cell activation might achieve better outcomes in clinical application. Data showed that co-injection of IL-2 and trastuzumab significantly increased antibody-induced antitumor immune responses [162]. It was also reported that cisplatin could enhance the cytotoxicity of NK cells on hepatocellular carcinoma [163]. High-dose fludarabine and cyclophosphamide plus daily injection of IL-2 combined with short-term chemotherapy can amplify NK cells derived from the same haploid donor [164]. A phase IIa study stated that it was tolerable to combined autologous ex vivo-expanded NK cell with docetaxel as second- or third-line treatment in patients with advanced non-small cell lung cancer and they will further confirm whether the PFS and RS will be improved [165].

In addition, transplant combined with donor NK cell therapy, mycophenolate mofetil, and tacrolimus in treating patients with hematologic cancer showed disease relapsed in part of patients with dose limiting toxicities in phase 1 and phase 2 (ClinicalTrials.gov Identifier: NCT00789776). Cord blood-derived NK cells infusion for multiple

Table 2
The clinical trials related to NK cell-based cancer immunotherapy.

Condition or disease	Phase	Intervention/treatment	Result	Conclusion	Ref.
Recurrent ovarian carcinoma [n = 12)	phase I	T: UCB-NK cells infusion C: Cy/Flu + UCB-NK cell infusion	UCB-NK cells were highly activated. Profound toxicity	UCB-NK cell therapy and NK cell expansion without Cy/Flu pretreatment were tolerate in recurrent ovarian carcinoma	[134]
Malignant lymphoma or advanced, recurrent solid tumors [n = 17)	Phase I	Infusion NK cells [MG4101)3 × 10^7 cells/kg	8 patients (47.1 %) showed stable disease 9 (52.9 %) showed progressive disease NKG2D expression on CD8(+) T cells upregulated No significant adverse events	High-does MG4101 cells infusion is Safe and feasible Maintain the host immune response	[136]
Advanced digestive cancer	Phase I	Autologous NK cells stimulated by PBMCs with OK432, IL-2, and modified FN-CH296 induced T cells	No severe adverse events Expanded about 4720-fold The NKG2D and CD16 expression increased Cytotoxicity of peripheral blood increased	ex vivo expanded NK cells were safe and suitable for the next round of clinical trials	[137]
Advanced, treatment-resistant malignancies (n = 17)		NK-92 cells	No severe adverse events 10^{10} cells/m^2 was the maximum expandable cell dose Anti-tumor response: 75 % NK-92 cells (male origin) were in the circulation	Infusions ofallogeneic NK-92 cells were well tolerated with favorable responses	[138]
Metastatic renal cell carcinoma (n = 192)	phase III	T: high-dose IL-2and IFN-α-2b C: IL-2and IFN-α-2b	T vs C: Higher response rate:23.2 % (22 of 95) vs 9.9 % (9 of 91), (P = 0.018) Progression-free at 3 years:10 vs 3 (P = 0.082). The median response durations:24 vs 15months (P = 0 .18) Median survivals:17.5vs 13 months (P = 0 .24). Survival rate: metastases (P = 0.001) Primary tumor (P = 0 .040)	High-dose IL-2 remains the preferred therapy for selected patients with metastatic renal cell carcinoma	[140]
Leukemia	Phase I	T: NK-cell doses (1 × 10/kg to 1 × 10/kg per dose) n = 13 C: not receiving NK cells	Improved NK-cell quantitatively, phenotypically, and functionally (T vs C) No infusion reactions No dose-limiting toxicities 54 % grade 1–2 aGVHD No grade 3–4 aGVHD	High doses of NK cells(mbIL21-expressing) can be safe. Infusion of NK cells improve NK-cell function, low relapse and incidence of viral infections	[144]
Stage IV malignant melanoma	phase IIa	rIL-21	Stage I(n = 14):1 patient confirmed CR stage II(n = 24):1 patient confirmed CR., 1 patient confirmed partial response Acceptable adverse events CD25 in CD25 (+) NK and CD8 (+) T cells increased IFN-γ, perforin, and granzyme B in CD8(+) T and NK cells increased	RIL-21 administered at 30 mg/kg/d in 5-day cycles every second week is biologically active and well tolerated in patients with metastatic melanoma	[145]
Advanced renal cell cancer (n = 60)		T: cryoablation + allogenic NK cells (n = 30) C: cryoablation (n = 30)	No severe adverse events QOL improved The tumor volume was decreased RR: increased (T vs C, 80 % vs 53.33 %; P < 0.05) CR increased (T vs C, 7 vs 4; P < 0.05)	Cryoablation + allogenic NK cells had synergistic effect, but still required further research	[160]
Non-small cell lung cancer (n = 60)		T: cryoablation + allogenic NK cells (n = 30) C: cryoablation (n = 30)	The number and function of lymphocytes enhanced QOL improved RR and DCR increased	Cryoablation + allogenic NK cells could be a potential novel therapeutic strategy for its favorable outcome in advanced NSCLC patients	[161]
Advanced non-small cell lung cancer (n = 19)	phase IIa	T: chemotherapy or two regimens docetaxel + NK cell-enriched lymphocytes C: weekly docetaxel regimen	No serious adverse effects PFS (T vs C, 3 vs 2.9 months)	Further study was needed to evaluate the anticancer effect as well as the clinical response such as PFS of the combination of NKL and chemotherapy	[165]
Metastatic colorectal cancer (n = 11) and non-small cell lung cancer (n = 1)	phase I	T: TKD + IL-2 activated NK cells (0.1–1.5 × 109) after platinum-based RCTx C: platinum-based RCTx	The expression of CD94 on NK cells enhanced 10 of 12 patients showed enhanced the cytolytic activity of NK cells 1 patient felt restless 2 patients felt itching No negative side effects 1 patient showed stable disease 1 patient showed mixed response	Reinfusion of Hsp70 peptide TKD plus IL-2 -activated autologous NK cells is safety and tolerability	[184]
Breast cancer (n = 35)		T: patients developed a contralateral recurrence or metastases within the first 2 years after RT C: disease-free patients	Higher serum Hsp70 and lower NK cells counts (T vs C) Hsp70 levels were not impacted clinicopathological parameters No significant changes of the proportion of T and B cells	The levels of Hsp70 in serum up to 6 weeks and NK cell counts may be predictive the prognosis in breast cancer patients	[185]

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Table 2 (*continued*)

Condition or disease	Phase	Intervention/treatment	Result	Conclusion	Ref.
Head and neck cancer (n = 74)	phase II	PD-L1 antibody	Patients with higher PD-1 + NK cells achieved better clinical outcome. PD-L1 ligation inhibited the function of PD-1 + NK cells. Cetuximab increased PD-1 + NK cells in PD-L1low/– tumors PD-1 blockade enhanced cetuximab-mediated NK cell activation and cytotoxicity against PD-L1 high tumor cells.	Blocking the PD-1/PD-L1 might be a useful strategy to reverse immune evasion of HNC tumors with high PD-L1 expression during cetuximab therapy through reviving NK cell function	[198]
Leukemic cancer		haplo-SCT	CD107α expression and IFN-γ upregulated: expressed HLA-I (n = 8) vs lacked HLA-I (n = 21) Recipient expression of HLA-I for donor inhibitory KIRs predicted relapse occurrence— the lowest 7-year relapse (n = 188, $p < 0.05$)	Haplo-SCT reconstitutes NK cells decrease relapse rates	(205)
Pancreatic cancer (n = 40)		T: IRE-NK(n = 20) C: IRE(n = 20)	T vs C:CA19-9 and CA242 reduced Good short-term outcome QOL improved. No difference in adverse events (P = 0.6848)	Proves the safety and efficacy of the treatment	[228]
Pancreatic cancer (stage III/IV) n = 67 (stage III (n = 35): T/C,19/16, stage IV (n = 32): T/C,18/14,)		T: IRE-NK C: IRE	CA19-9 descend: T vs C (P < 0.05) Stage III: Median PFS improved(T vs C, 9.1 vs 7.9 months, P = 0.0432) Median OS improved(13.6 vs 12.2 months; P = 0.0327) RR improved(T vs C,63.2 % vs 50.0 %; P < 0.05) Sage IV: Median OS improved(T vs C,10.2 months vs 9.1 months; P = 0.0367) DCR improved(T vs C,66.7 % vs 42.9 %; P < 0.05) Adverse events: grades A and B	IRE-NK significantly increased median PFS and median OS in stage III pancreatic cancer and extended the median OS of stage IV pancreatic cancer	[229]
Breast Cancer (n = 48, T/C,16/32)	Phase II	T: Cryoablation-NK cells therapy -Herceptin C: Cryoablation or cryoablation-NK cells therapy	QOL and PFS improved CEA, CA15-3, and CTC reduced Immune function enhanced Acceptable adverse events	Cryoablation-NK cells therapy-Herceptin have a good efficacy	[231]
Acute myeloid leukemia	Phase I	Two cell-dose levels (1×10^9 cells/m^2 vs 3×10^9cells/m^2)	No changes in lymphocyte counts, subsets frequency, phenotype or activity (P > 0.05) Cell dose-dependent effects No dose-limiting toxicities No grade 3–4 toxicities Transient activity in 3 patients	The foundation for future combination immunotherapy trials and the optimization of aNK cell	[232]
Multiple myeloma	Phase I	T: high dose chemotherapy + auto-HCT + CB-NK (n = 12) C: high dose chemotherapy + auto-HCT	10 patients achieved good partial response 8 patients complete response No infusion toxicities No graft-versus-host disease	CB-NK may be a novel cellular therapy	[233]
Acute myeloid leukemia (n = 7)	Phase I	high toxicity of TpNK cell infusions + chemotherapy and peripheral blood apheresis	3 patients remained in CR, 1 achieved CR1, 2 had relapsed and 1 had died (6 mouths follow-up) 1 patient remained in CR. 4 patients remained in CR (1 year post-treatment) Median overall survival: 400 days (at 2 years follow-up) No infusion toxicity. Profound myelosuppression	The HLA-mismatched NK cells survived and expanded in vivo without on-going host Immunosuppression and appeared to exert an anti-leukemia effect in 4/7 patients treated	[234]
Metastatic melanoma (n = 16)	Phase I	bortezomib and IFN-α-2b	Maximum tolerated dose for bortezomib was 1.3 mg/m 1 patient had a partial response 7 patients showed stable disease Progression-free survival: 2.5 months Overall survival was 10.3 months	Combine bortezomib and IFN-α can be safely administered to melanoma patients	[235]
Malignant melanoma	Phase I Phase II	Phase I: 6 cycles of 3/w with 4 different dose levels vs 3 cycles of 5 + 9 with 6 different dose levels (n = 29) Phase II: three cycles of 5 + 9 (n = 24)	No changes in lymphocyte counts, subsets frequency, phenotype or activity ($p > 0.05$) Cell dose-dependent effects No dose-limiting toxicities No grade 3-4 toxicities Activity was transient in 3 patients	New data analytical approach to visualize novel correlations between laboratory parameters	[236]
Advanced HER2-overexpressing breast cancer (n = 78)		T: HER2-positive + NC C: HER2-negative + NC	T vs C: NK cells and regulatory T cells increased. Higher percentages of T helper cells after pCR. Activated NK cells increased in HER2-positive patients achieving pCR Partial response reduced	Maintenance of functional T cell response and improvement of NK cell proficiency during NC are probably critical requirements for the pCR induction of HER2-overexpressing breast cancer patients	[237]

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Table 2 (*continued*)

Condition or disease	Phase	Intervention/treatment	Result	Conclusion	Ref.
Older acute myeloid leukemia (n = 10)		CB CD34 + HSPC-NK	Well tolerated No graft-versus-host disease No toxicity CD16 and KIR expressed rapidly Activating receptors was sustained expression MRD changed into negative (n = 2–4)	CB CD34 + HSPC-NK cells a promising novel therapeutic strategy	[238]
Myeloma	phase II	Monoclonal Antibody IPH2101	IPH2101exhibited cytotoxicity in KIR2Ddull patient NK cells The NK cell responsiveness and KIR2D expression reduced rapidly The overall response was diminished	Monoclonal Antibody IPH2101 was lack of clinical efficacy	[239]

UCB-NK, umbilical cord blood-NK; aGVHD, acute graft-versus-host disease; rIL-21, recombinant human IL-21; CR, Complete Remission; QOL, quality of life; RR, response rate; DCR, disease control rate; PFS, progression free survival; RCTx, radiochemotherapy; RT, adjuvant radiotherapy; Haplo-SCT, haploidentical stem cell transplantation; IRE-NK, IRE plus allogeneic NK cell therapy; IRE, irreversible electroporation; CA19-9, carbohydrate antigen 19-9; CA242, carbohydrate antigen 242; OS, overall survival; CEA, carcino-embryonic antigen; CA15-3, cancer antigen 15-3; CTC, circulating tumor cells; aNK, Activated NK cells; CB-NK, blood-derived (CB) NK cells; auto – HCT, autologous haematopoietic stem cell transplantation; TpNK, tumor-primed NK cells; NC, neoadjuvant chemotherapy, Paclitaxel and Trastuzumab, or Docetaxel and Epirubicin, respectively; pCR, pathological complete responses; MRD, minimal residual disease; T, treatment; C, control.

myeloma patients combined with high dose chemotherapy and autologous haematopoietic stem cell transplantation also showed a very good response with well tolerance and feasibility.

5.3. Traditional antibody therapy

The clinical efficacy of the antitumor drugs such as rituximab (anti-CD20 antibody) [166], trastuzumab (anti-Her2/neu antibody) [167], and cetuximab (anti-epidermal growth factor receptor antibody) [168,169] was at least partially achieved through ADCC activation. Dasatinib, a tyrosine kinase inhibitor (TKI), activated NK cells through JAK/STAT signaling, which will be useful for clinical evaluation [170]. It was stated that bortezomib sensitized cancer cells to NK-mediated cytotoxicity in multiple types of cancer including hepatocellular carcinoma, breast cancer and prostate cancer *in vitro* [171–173]. Elotuzumab, the therapeutic SLAMF7 antibody, could also trigger NK cell cytotoxicity through interacting with CD16 in preclinical studies. The underlying mechanism of elotuzumab in activating NK cells might rely on CD16-mediated ADCC and interaction with SLAMF7, thereby enhancing the antibody-dependent cellular phagocytosis (ADCP) of macrophages in multiple myeloma [174]. In phase I clinical trial, enriched NK cells with high expression of NKG2D and CD16, in combination with trastuzumab or cetuximab were well tolerated with no severe adverse effects on the treatment of advanced gastric and colorectal cancers [175].

However, the cytokine secretion of NK cells was reduced due to TKI sensitization, while tumor cells pretreated with anti-EGFR TKIs showed increased sensitivity towards NK cell-mediated ADCC in certain ovarian cancer cells [176]. It's remarkably important to consider the interactions between anti-EGFR TKIs and NK cells, when designing combination therapies in solid tumors.

5.4. Hsp70 targeted therapy

Hsp70, a membrane-bound, stress-inducible protein, is over-expressed on almost all tumor cells; while it is absent or minimally present on normal, healthy cells. Previous studies reported that Hsp70 was critical for NK cell function and membrane Hsp70 (mHsp70) could be identified as a tumor-specific target for CD94/NKG2C NK cells [177–179]. Either membrane-bound or extracellular HSPs can stimulate T cells and NK cells mediated anti-tumor immune responses [180]. What's more, autologous Hsp70 peptide activated NK cells have been tested preclinically and clinically. The membrane Hsp70+ tumors actively release Hsp70 surface-positive lipid vesicles, which increased cytotoxicity of NK cells through granzyme B release [181]. A peptide containing 14 amino acid, TKDNNLLGRFELSG (TKD, aa 450-463, N-terminal of HSP 70 protein), was identified by peptide screening assay and was able to boost killing and proliferative activity of NK cells [182]. Furthermore, mouse monoclonal antibody targeting TKD, cmHsp70.1 mAb, was derived and could induced cytotoxicity of membrane Hsp70+ tumor cells *in vitro* [183]. TKD of Hsp70 was identified as a tumor-selective recognition structure for NK cells. It has been confirmed that reinfusion of TKD-activated autologous NK cells is safe in clinical phase I trial [184]. Using TKD/IL-2 activated autologous NK cells to treat patients with non-small cell lung cancer after radiochemotherapy (RCT) is under testing in clinical phase II trial (NCT02118415). Studies on breast cancer patients who suffered a breast-conserving surgery and adjuvant radiotherapy indicated that high Hsp70 serum level and decreased NK cell number might associate with poor prognosis of breast cancer patients [185]. These studies provided evidences for targeting Hsp70 as an effective therapy in NK cells-based cancer immunotherapy and Hsp70 could also be considered as the predict factor for NK cell function in cancer patients.

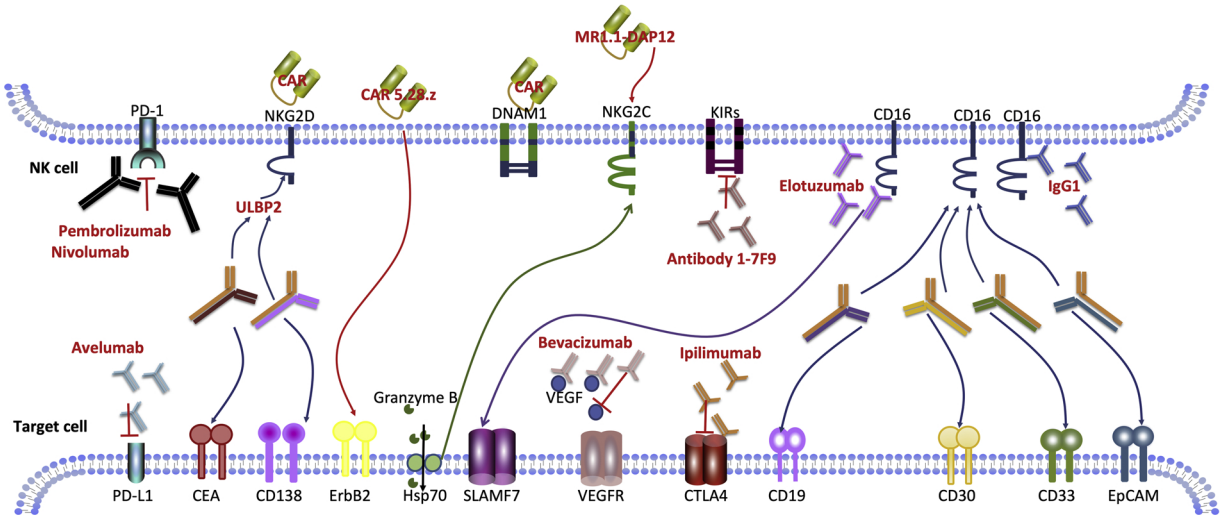

Fig. 4. NK cell-based therapeutic approach. This picture shows a detailed view of the effects of monoclonal antibodies used to suppress corresponding proteins on the surface of both cells. PD-1, KIRs, NKG2D, and CD16 are targeted by monoclonal antibodies on the surface of NK cells. On the other hand, PD-L1, VEGFR (through suppressing VEGF), CTLA4, CD19, CD30, and CD33 are inhibited by monoclonal antibodies on the cancer cells. Specific antibodies targeting PD-1/PD-L1 or CTLA4 immune checkpoint block the immunosuppressive effect, thereby increasing the cytotoxicity of NK cells. Similarly, antibodies targeting NK cell inhibitory receptors such as KIRs also increase killing ability of NK cells. Antibody dependent cell-mediated cytotoxicity (ADCC) also plays an important role in NK cell-based cancer treatment. For example, SLAMF7 antibody activates NK cells through interacting with CD16, resulting lysis of target cells (Purple arrow). On the other hand, bispecific antibodies contain two domains, which directly or indirectly bind to the activating receptors on NK cells and the target sites on tumor cells, thereby enhance NK cells specificity and mediate the cytotoxicity of NK cells (Blue arrow). Besides, Hsp70 not only bind to the activating receptors on NK cells, but also serving as an entry port for granzyme B into target cells (Green arrow). Moreover, CAR-NKs kill tumor cells with enhanced stimulation and targeting ability to tumor antigens or endogenous antigen (Red arrow). These strategies provide potential effective methods for extension of NK cells associated immunotherapy to cancer patients and would provoke great progress in treatment of different kinds of human malignancies.

5.5. Chimeric antigen receptor therapy

Although the current genetic engineering of immune cells focuses on T cells, NK cells also have great prospects in tumor immunotherapy at genetic level [186]. Compared with the immunotherapy, cost and severe toxicity of CAR-modified T cells, CAR-modified NK cells may be better than CAR-modified T cells, serving as a safe, effective, and alternative immunotherapeutic strategy in the clinic [187,188]. CAR-modified NK cells expressing specific receptors target $Her2^{+}$ cancer cells both *in vivo* and *in vitro* [189]. Studies also found that CAR-modified NK cell therapy obtained good outcome and significantly prolonged overall survival in tumor-bearing mice, suggesting a promising clinical strategy to treat glioblastoma [190,191]. The mechanism might rely on the stronger affinity of CARs to the ligand and the modified cytoplasmic regions of CARs, which would generate enhanced intracellular signals to exert increasing cytotoxicity of NK cells.

Moreover, even if the target antigen on the tumor is rapidly lost, CAR-modified NK cells are still stimulated by their endogenous receptors such as NKG2D and NDAM1. It was reported that NK-92 cells expressed a modified CAR on which intracellular domain of the NKG2D receptor was fused to the extracellular and transmembrane domain of TGF-βR II (TN receptor). Accordingly, TGF-β-induced signaling is transferred to NKG2D-induced NK cells to activate killing ability of NK cells [192]. In addition, NK cells were modified with a specific receptor containing the cytotoxic ζ-chain of the T-cell receptor and NKG2D receptor (NKG2D ζ receptor). The antitumor effect of NKG2D ζ-modified NK cells on MDSCs was enhanced in a xenograft TME model, indicating potential of NKG2D ζ-NK cells in application in immunosuppression microenvironment [193]. Now, research data in clinical trials is required to evaluate the safety and efficacy of CAR-modified NK cells based on codified standards and rules, which help to further understand the difference between NK cells and T cells expressing CARs in application for cancer immunotherapy in clinic [194]. The inability for CAR-NK cells to reproduce in vivo would lead to the need for an increased frequency and quantity of the product to be transferred, leading to a drain on resources and patient morale

5.6. Immune checkpoint blocking therapy

In recent years, studies have reported that activated NK cells in some cases express immune suppressing factors such as programmed death 1 (PD-1) and cytotoxic T lymphocyte-associated antigen-4 (CTLA4) [195]. Inhibitors of PD-1 and CTLA4 have been developed rapidly for treatment of cancer patients. Related drugs approved by the FDA are aimed to block the immune suppressive factors and therefore, enhance T cell activity. The tumor-killing activity of NK cells is also retrieved after being treated with anti-PD-L1 monoclonal antibodies. PD-1 was also expressed on NK cells in patients with myeloma and blocking PD-1/PD-L1 by anti-PD-1 monoclonal antibody CT-011 restored NK cell-mediated antitumor activity [196]. A novel anti-PD-L1 antibody, avelumab (MSB0010718C), was designed to augment NK cell-mediated ADCC on breast cancer cells, which also stimulates NK cells by the activation of FcγRIII (CD16). Moreover, IL-2 induces antitumor effect of avelumab through NK cells-mediated ADCC to lyse the tumor cell [197]. What's more, a new clinical study proved that blocking the PD-1: PD-L1 axis may be a useful strategy to reverse immune evasion of head and neck cancer patients with high PD-L1 expression during cetuximab therapy through repairing NK cell dysfunction [198].

Although the role of CTLA4 in NK cells remains unclear, studies have shown that CTLA4 is also expressed on cell membrane of some tumor cells. Ipilimumab, a monoclonal antibody against CTLA4, triggers CD16 mediated ADCC and induces TNF-α production in metastatic melanoma [199]. It was also found that oncolytic viral infection enhances tumor cell secretion of ligands for the activating receptors NKp44 and NKp46, thereby potentiates antitumor effect of NK cells [200]. In addition, suppression of the CTLA4 pathway combined with re-infecting oncolytic viruses cause strong antitumor effects, which was

partly dependent on NK cell activation [201]. Anti-CTLA-4 therapy significantly triggered intratumoral NK cells activation and decreased tumor growth when combined with IL15/IL15R [202]. Since some monoclonal antibodies targeting the PD-1 and CTLA4 pathways have passed or entered clinical trials, it is particularly important to further study their effects on NK cell activity.

As KIRs interact with its own MHC I molecules to inhibit NK cell-mediated cytotoxicity, KIRs may serve as a target for NK cell immune checkpoint blockade. Preclinical study demonstrated that monoclonal antibody 1-7F9 interacts with the three inhibitory receptors KIR2DL1, KIR2DL2, and KIR2DL3 to block their inhibitory signaling pathways, and then, the antitumor activity of NK cells is increased without any effect on normal cells [203]. A recent study shows that genetic variability influences the expression of KIR2DL1 and KIR2DS1 in NK cells leading to NK cell activation, and has a potential to be selected as donors for adoptive NK therapies [204]. Clinical trial stated that uneducated NK cells provide better outcomes in haploidentical stem cell transplantation (haplo-SCT) and haplo-SCT recipients presenting class I ligands for donor inhibitory KIR enhances NK cell function to control leukemic recurrence incidence [205]. Thus, the method of blocking KIRs provides an attractive approach for tumor immunotherapy.

NKG2A is another inhibitory receptor expressed on NK cells that recognizes the HLA-E of MHC I ligand and restrains the activity of NK cells. Recently, studies have found two negative immune regulators, mucin-domain-containing molecular-3 (TIM3) [206] and lymphocyte-activation gene 3 (LAG3) [207], expressed on NK cells. It was indicated that targeting TIM3 or LAG in combination with anti-PD-1 antibodies significantly improved survival rate of tumor-bearing mice compared with PD-1 blockers alone [208]. This suggested that this new combination therapy might be an effective way to increase the killing activities of NK cells [209]. Moreover, it seems that the expression of KIRs in NK cells was correlated with poor prognosis of non-small cell lung cancer (NSCLC) and might be positively correlated with PD-1/PD-L1 expression in NSCLC. Therefore, combination treatment of anti-KIRs antibodies with PD-1/PD-L1 blockers would be more effective in treatment of NSCLC [210]. On the other hand, stimulated CD357 and CD27 expressed on NK cells also enhance NK cells ability to lyse tumor cells [211]. To sum up, treatment of stimulating agonists of activating receptors as a combination with inhibitors of inhibitory receptors expressed on T cells or NK cells may lead to a trend for the development of tumor immunotherapy.

5.7. Bispecific antibody therapy

Compared with the traditional antibodies that trigger ADCC's tumor-specific antigens, the idea of bispecific antibodies caught great attention of researchers in recent years. A bispecific antibody is that one end of the antibody recognizes the tumor antigen and the other end interacts with the receptor to activate NK cells. This cross-linking promotes the interaction between NK cells and tumor cells and stimulates the NK cells to lyse the target cells with specificity. Considering the potency of ADCC, most bispecific antibodies are designed so that the Fc segment are more potent against CD16 than the Fc segment of a normal antibody, such as using a high-affinity CD16 target [212] or adding CD16 binding sites [213]. By linking these anti-CD16 fragments of variable region (Fv) domains with other molecules, different types of tumor cells can be targeted. For example, linking the Fv domain of CD16 to anti-CD19 antibody and anti-HLA II antibodies targets CD19 and B-cell neoplasia with highly expressed HLA II [214,215]. When Fv domain of CD16 is linked to anti-CD30 antibody, it targets CD30 high expression in Hodgkin's lymphoma, and linked to human epidermal growth factor receptor-2 (HER2) antibody targets $Her2^+$ breast cancer [216,217]. Accordingly, linking to CD33 antibodies targets acute myeloid leukemia (AML) [218,219], while linking epithelial cell adhesion molecules (EpCAM) targets malignant tumors developed from epithelial tissues. The efficacy of these proteins in promoting specific antitumor activity *in vivo* and *in vitro* needs further clinical studies.

In addition, a novel modified human IL15 crosslinker, IL15 trispecific killer engagers (TriKE), not only makes NK cells specific to $CD33^+$ myeloid cells, but it also induces NK cells survival and expansion [220]. The fusion of recombinant protein of human unique long 16 binding protein 2 (ULBP2) and anti-CD138 antibody is emerging. The anti-CD138 antibody targets CD138-highly expressed multiple myeloma, while ULBP2 binds specifically to NKG2D receptors on NK cells, thereby increases the interaction of NK cells with myeloma cells [221]. The similar kind of bispecific antibody had a fusion protein that was co-interacted with ULBP2 and carcinoembryonic antigen (CEA), which could promote NK cells to target CEA-expressing colon cancer cells *in vivo* and *in vitro*, exhibiting a therapeutic effect on colon cancer [222]. Recombinant monoclonal antibodies conjugated with MICA, bound to tumor surface antigens such as CEA, HER2 and CD20, led to increased NK cells cytotoxicity to lyse tumor cells mainly in NKG2D-dependent manner [223]. It was also found that a bispecific rG7S-MICA containing protein which has a single chain antibody fragment (scFv) and MICA significantly increases NK cell number in tumor microenvironment and targets $CD24^+$ liver cancer cells. Therefore, it enhances NKG2D-mediated cytotoxicity to kill the tumor cells [224]. Another NK cell receptor that the bispecific antibody also targets NKG2D has a NKG2D ligand at one end and a tumor specific Fv domain at the other end. Because T cells also express NKG2D, all bispecific antibodies that target this receptor simultaneously modulate NK and T cells [225]. Studies have used fusion proteins containing RAET1H and CD33-specific Fv domains to direct NK cells and T cells to lyse AML cells, indicating the promising application of NKG2D-based dual-specific therapy [226].

5.8. Other NK cells therapy

Recently, emerging evidences showed that a new treatment called electric pulse therapy has achieved remarkable results in clinical trials [227]. Irreversible electroporation was combined with allogeneic NK cells to treat metastatic pancreatic cancer in clinical trial with tolerate safety and efficacy [228]. Electroporation combined with allogeneic NK cells significantly increased median PFS and median OS in stage III pancreatic cancer and extended the median OS of stage IV pancreatic cancer [229]. It might become one of the effective methods to cancer treatment and provided more possibilities for the extension of NK cell associated immunotherapy to cancer patients. In addition, NK cell function may be enhanced by an adjuvant chemotherapeutic agent that inhibits the secretion of soluble ligands of NK cell-activated receptors by tumor cells or induces a high expression pathway of activated receptors in tumor cells by radiotherapy. A first-in-dog clinical trial indicated boosted circulating NK cells was found and cytotoxicity of NK cells are activated after radiotherapy in sarcoma patients-derived PDX models [230], which suggested the therapeutic potential for applying radiotherapy to increase NK cell activity in cancer treatment.

What's more, in a clinical trial, the combination of cryoablation and allogenic NK cells therapy showed synergistic effect including improved the QOL and decreased the tumor volume in advanced renal cell cancer, indicating multiple aspects of NK cell immunotherapy [160]. Another trial also confirmed that combination therapy of tumor cryoablation with NK cells and Herceptin treatment achieved a good efficacy in breast cancer patients with HER2 overexpression [231]. The benefit of this strategy requires further research and are still needed to evaluate the efficacy of this combination strategy.

Table 2 listed the clinical trials related to NK cell-based cancer immunotherapy and summarized NK cell-based immunotherapies and therapeutic implications in malignant diseases in clinical trials. The aims of the clinical studies are to determine safety and efficacy of the interventional therapies as well as their efficacy in treatment of malignant diseases. Fig. 4 indicates the approaches for NK cell-based cancer immunotherapy including CAR-NK cell therapy, immune checkpoint therapy, and bispecific antibody therapy.

6. Conclusions/perspectives

From 1973 to the present, the immunological characteristics of NK cells, including the classification of cells, the identification of receptors, and functions have been extensively studied. Based on its powerful antitumor immune response capabilities, NK cell immunotherapy has gradually been applied in clinical practice for treatment of cancer patients. However, implementing cellular therapy in the clinic is a complicated process for which many items should be taking into account to get the final approval from the regulatory bodies. Cell numbers, adaptation to reagents and equipment that are qualified for human use as well as the qualification of reagents and equipment should be established so they would be safety for clinical studies. Although many early investigators used autologous NK cells, including lymphokine-activated killer cells, the clinical efficacies were not satisfactory [114]. There are still some problems and challenges. For example, CAR-NK was restrained in vivo, which leads to the need for an increase in frequency and quantity of the product-transferred, resulting in the consumption of resources and combating patient morale. The laws and regulations applied to cellular therapy in different countries, for example, are varied. Furthermore, the specific role of NK cell subpopulations and dynamic amplification of NK cells *in vitro* and *in vivo* required further study, which are also the crucial challenges of current development and should be solved in the most urgent. Therefore, more in-depth studies of the biological characteristics of NK cells and their regulatory mechanisms in different kinds of tumors are needed to improve our understanding of the precise mechanisms of NK cell immune responses against cancer cells.

Moreover, more antitumor preclinical studies and clinical programs would be developed and optimized to test the efficacy and the safety of NK cells-based therapy. Using new strains of mice engineered IL-15 cytokine has been generated in severe immunodeficient NOD/Shi-scid-IL-2Rγ^{null} (NOG) mouse and human peripheral blood has been transferred to mice helping us to enhance and increase the number of NK cells for establishing NK cell-specific preclinical studies [240]. As already mentioned, NK cells target tumor cells sensitized by monoclonal antibodies. Combining targeted therapy with drugs such as trastuzumab (anti-Her2 breast cancer), cetuximab (anti-EGFR in colorectal, metastatic non-small cell lung cancer and head and neck cancers), bevacizumab (anti-VEGF, anti-angiogenesis) and so forth is a promising therapeutic strategy when NK cells are specifically activated. To activate NK cells, adoptive NK cell therapy is a crucial option. As chemotherapy causes resistance in many kinds of cancer such as breast cancer and melanoma, applying chemotherapy in combination with NK cell immunotherapy and sensitizing cancer cells to chemotherapy, is of greatest interests for the future of anticancer therapeutics.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (NOs.: 81803237, 81672444, 81770562) and grants from the Science and Technology Planning Project of Luzhou, Sichuan Province, China (NO. 2016LZXNYD-Z04, NO. 2017LZXNYD-J02).

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