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NK Cells in Cancer Immunotherapy

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Abstract

Natural killer (NK) cells are crucial components of the innate immune system and play critical roles in host immunity against viral infections and cancer. NK cells' activity is controlled by the interaction of a wide range of receptors expressed on their surfaces with cell surface ligands. Opposite signals delivered by inhibitory and activating receptors tightly regulate NK cells' cytotoxicity. Natural killer cells can discriminate between normal and cancer cells. NK cells are known to directly recognize and kill malignant cells or induce apoptosis. However, tumor cells have the ability to evade those attacks. The main mechanisms involve the lack of expression or downregulation of the expression of major histocompatibility complex (MHC) class I molecules and secretion of soluble NKG2D ligands by tumor cells. Furthermore, tumors harbor a population of cancer stem cells (CSCs), which can drive tumor progression and therapeutical resistance. This chapter highlights the roles of NK cells in tumor immunosurveillance and their applications for cancer immunotherapy. NK cell biology and function as well as the role of their receptor interactions will be described. We will discuss the therapeutic applications of NK cells in cancer and NK cells targeting CSCs as a promising strategy for cancer therapy.

Keywords: NK cells, cancer-immunotherapy, cancer stem cells

1. Introduction

Natural killer (NK) cells constitute a minor subset of lymphocytes that are crucial components of the innate immune system and play critical roles in host immunity against malignant cells and virus-infected cells but also in bacterial, fungal, and parasite immune responses [1]. NK cells represent 10% of the lymphocytes in human peripheral blood, and they comprise the third largest population of lymphocytes following B and T cells.

Natural killer cells have diverse biological functions including killing pathogen-infected cells and cancer cells as well as an immunoregulatory role [2]. Natural killer cells can discriminate between normal cells and cells that do not express adequate amounts of major histocompatibility complex (MHC) class I molecules.

NK cell cytotoxicity is regulated by a balance between activating and inhibitory signals delivered by receptors expressed at the cell surface. These cells are known to directly recognize and kill malignant cells or induce apoptosis. However, tumor cells have the ability to evade immunosurveillance by using multiple mechanisms. Furthermore, tumors harbor a population of cancer stem cells (CSC), which is responsible of tumor progression and therapeutical resistance.

Therapeutic applications of NK cells in cancer and NK cells targeting cancer stem cells (CSCs) represent a promising strategy for cancer immunotherapy.

2. NK cells' biology and function

NK cells originate from common lymphoid progenitor cells and further differentiate into immature/mature NK cells in bone marrow. They are then distributed in peripheral lymphoid and nonlymphoid organs and tissues [3–5], including bone marrow, spleen, peripheral blood, placenta, lung, liver, uterus [6], and peritoneal cavity while limited numbers are localized in lymph nodes [7]. Human NK cell turnover in blood is around 2 weeks [8].

NK cells were originally described as large granular lymphocytes with natural cytotoxicity against tumor cells. NK cells were later recognized as a separate lymphocyte lineage, with both cytotoxicity and immunoregulatory role, as they are involved in the production of cytokines [9]. More recently, data revealed that activated NK cells may also influence the outcome of helminth infections. CD4-NK cells increasing early following nematode infection with *Brugia pahangi* are able to produce IL-4 and then could polarize the immune response toward a Th2 profile [10]. In fact, protection against helminthic infections are usually mediated by Th2 immune response characterized by secretion of IL-4, IL-5, and IL-13, secretion of IgE antibodies, and activation of mast cells [11, 12]. Studies revealed that the clearance of these parasites is more efficient and complete in the presence of NK cells. In the case of Th2 immunity disruption, NK cells may become an important source of IL-13 during murine gastrointestinal nematode infections [13, 14]. Human NK cells can be classified into two major subsets CD56^{dim} and CD56^{bright} depending on their immunophenotype and functions and more recently in terms of their homing properties [15, 16]. CD56^{dim} NK cells are fully mature, make up about 90% of the NK cells in peripheral blood and inflammatory sites, and they express perforin and exhibit a high cytotoxic activity after encountering target cells [17, 18]. These CD56^{dim} NK cells are cytotoxic and produce interferon γ (IFN- γ) upon interaction with tumor cells in vitro [19]. In contrast, CD56^{bright} cells are more immature, make up about 5–15% of total NK cells, and have been considered primarily as cytokine producers, while playing a limited role in cytolytic responses. Approximately, 90% of NK cells in lymph nodes belong

to the CD56^{bright} subset and lack perforin [20]. These cells exert immunoregulatory function by producing abundant cytokines such as IFN- γ in response to stimulation with interleukins (IL)-12, IL-15, and IL-18 [21]. In response to nematode infection, CD56^{bright} NK cells can bind with a secreted protein ES from the human hookworm *Necator americanus* and induce IFN-gamma production [22]. Natural killer cells have diverse biological functions, which include recognizing and killing pathogen-infected and cancer cells. Circulating NK cells are mostly in their resting phase, but after activation by cytokines and chemokines, they are capable of extravasation and recruitment into distinct inflamed or malignant tissues [9, 23]. NK cells also have an immunoregulatory role as their ligand interaction with cell-surface receptors lead to the production of several cytokines.

NK cells mediate two predominant pathways of cell death. The first pathway, a granule exocytosis pathway [24], involves the release of cytotoxic granule, perforin (a membrane-disrupting protein), and granzymes (a family of structurally related serine proteases) responsible for NK cell-mediated killing by inducing apoptosis of the target cell [25–27]. In the second pathway, a caspase-dependent apoptosis involves the association of death receptors such as first apoptosis signal (Fas) cell surface death receptor and tumor-necrosis-factor-related apoptosis inducing ligand receptor (TRAILR) on target cells with their corresponding ligands, members of the tumor necrosis factor (TNF) family of cytokines, expressed by NK cells, and regulated by IFN- γ , such as FASL, and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), resulting in caspase-dependent target cell apoptosis [28–32]. Antibody-dependent cellular cytotoxicity (ADCC) can also be a mechanism of killing of tumor cells by NK cells by triggering the NK CD16 receptor (Fc γ RIII), which binds to the IgG and antibody-coated targets [33].

Natural killer cells can discriminate between normal cells and those that do not express adequate amounts of MHC class I molecules. They were originally defined by their ability to spontaneously eliminate cells lacking expression of MHC class I molecules. NK cells express receptors that bind to MHC class I molecules including the killer cell immunoglobulin-like receptors (KIRs) that play major roles in regulating the activation thresholds of NK cells in humans [34].

3. NK cell cytotoxicity

NK cell cytotoxicity is tightly regulated by a balance between activating and inhibitory signals [35] delivered by a multitude of receptors expressed at the cell surface [36] (**Figure 1**). The inhibitory NK cell receptors interact with MHC class I molecules expressed on almost all nucleated cells, preventing NK cell activation against healthy cells (**Figure 2a**). NK cell activation is blocked through engagement of their KIR receptors [37]. This explains self-tolerance and prevention of host cell killing. NK cells can discriminate between normal host cells and infected or abnormal cells by recognition of MHC class I molecules. It was earlier discovered that NK cells are activated when they encounter cells that lack self-MHC class I molecule. For example, under stress conditions, such as cellular transformation, cells down-regulate MHC-I expression causing NK cells to lose inhibitory signaling and be activated in

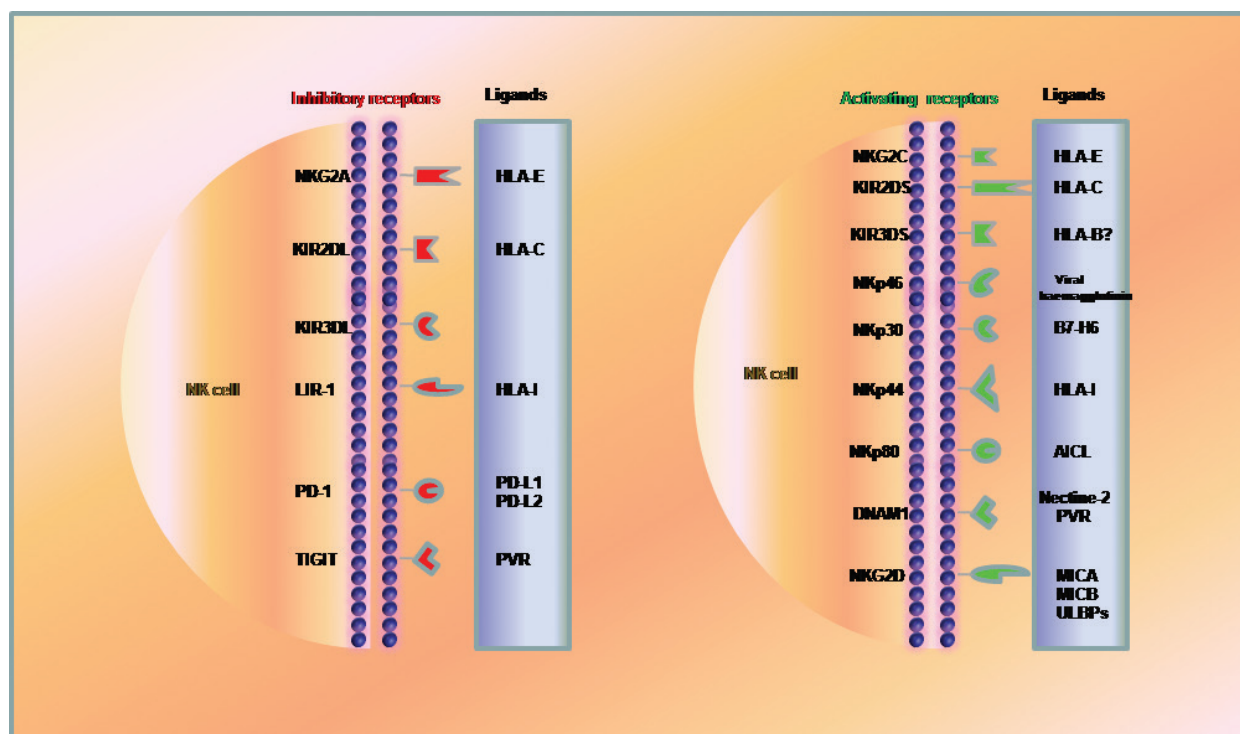


Figure 1. Examples of activating and inhibitory NK cell receptors and their respective ligands. AICL: activation-induced C-type lectin; B7-H6: Member of the B7 family of immunoreceptors; DNAM-1: DNAX accessory molecule 1; HLA: human leucocyte antigen; KIR2DL: killer-cell immunoglobulin-like receptor 2DL; KIR3DL: Killer-cell immunoglobulin-like receptor 3DL; LIR-1: leukocyte inhibitory receptor 1; MICA: MHC class I polypeptide-related sequence A; MICB: MHC class I polypeptide-related sequence B; NKG2A: natural killer group protein 2 family member A; NKG2C: natural killer group protein 2 family member C; NKp30: natural killer Cell P30-related Protein; NKp46: natural killer Cell P46-related Protein; NKp80: Natural killer Cell P80-related Protein; PD1: programmed cell death 1; PD-L1: programmed death-ligand 1; PD-L2: programmed death-ligand 2; PVR: polio virus receptor; TIGIT: T cell immunoreceptor with Ig and ITIM domains.

a process called “missing-self recognition” [38]. This model is based on the fact that NK cell activity is normally controlled by self-MHC molecules that interact with a large repertoire of inhibitory NK receptors. In this condition, activation receptors are no longer suppressed and they induce potent stimulatory signals, resulting in NK cell activation including cytokine production and granule release leading to cytotoxicity [39, 40]. Abnormal cells can also upregulate the expression of ligands to activate receptors on the NK cells that can overcome the inhibitory signals.

3.1. Activating NK cell receptors

NK cells require external signals to begin the process of cell activation, which usually occurs via triggering receptors. A number of receptors have been identified that allow NK cells to become activated. The major activating receptors expressed on human NK cells include the natural cytotoxicity receptors (NCRs: NKp30, NKp44, NKp46), the immunoglobulin gamma Fc-region receptor III (Fc γ RIII/CD16), activating forms of killer cell Ig-like receptors (KIR:

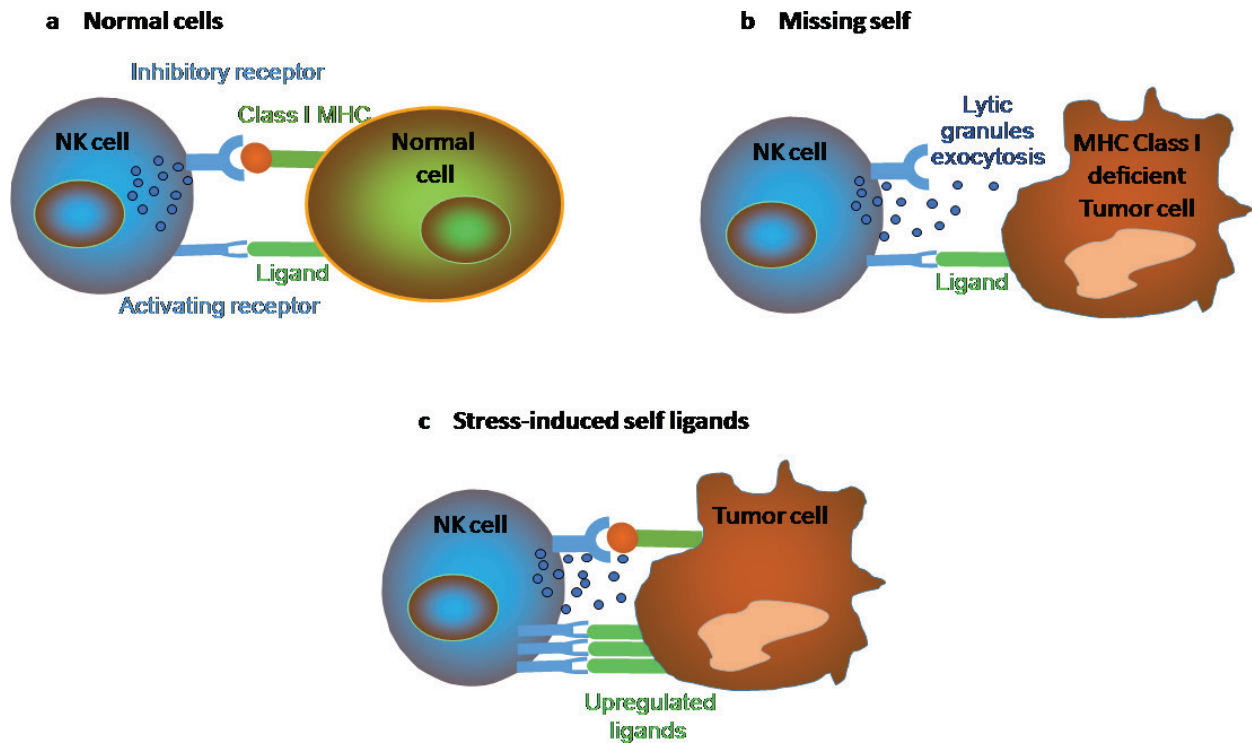


Figure 2. NK cell functions. (a) Inhibitory NK cell receptors interact with MHC class I molecules expressed on nucleated cells, preventing NK cell activation and lysis against normal cells. (b) NK cells can eliminate tumor cells that downregulate major histocompatibility complex (MHC) class I molecules causing NK cells to lose inhibitory signaling and be activated in a process called “missing-self recognition.” (c) NK cells can kill tumor cells that retain full expression of MHC class I but overexpress induced stress ligands recognized by activating NK cell receptors, which override the inhibitory signals and elicit target cell lysis.

KIR2DS and KIR3DS), NKG2D, C-type lectin receptors (CD94/NKG2C, NKG2E/H, and NKG2F), NKp80, and 2B4 [41]. NKG2D and NCRs are particularly important receptors for triggering NK cell responses toward tumor cells [42].

A new family of receptors that recognize nectin and nectin-like molecules has recently emerged as a critical regulator of NK cell functions – DNAX accessory molecule 1 (DNAM-1, CD226) is an adhesion molecule that controls NK cell cytotoxicity and interferon- γ production against a wide range of cancer and infected cells [43].

The B7 family member B7-H6 is a tumor cell ligand for the activating natural killer cell receptor NKp30 in humans [44]. Activating KIR receptor recognizes classical MHC-I molecules [45], whereas NKG2D recognizes the nonclassical MHC-I molecules, MICA/MICB, retinoic acid early transcript 1E protein (RAET1E), RAET1G, RAET1H, RAET1I, RAET1L, and RAET1N (also known as ULBP1–ULBP6) [46, 47]. These ligands are not present on the cell surface of most normal cells, but are upregulated at the cell surface after cellular stress, on rapidly proliferating cells, infected cells, transformed cells, and tumor cells [48], further increasing the NK cell activity [49]. CD16 binds the Fc portion of IgG antibodies to initiate antibody-dependent cellular cytotoxicity (ADCC) and provides NK cells with the ability to recognize

and kill target cells coated with antibodies [50]. DNAM-1 ligands CD112 and CD155 have been described in different pathological conditions, and recent evidence indicates that their expression is regulated by cellular stress.

All of these activating receptors promote cytotoxicity and cytokine production responses through stimulating intracellular protein tyrosine kinase cascades.

3.2. Inhibitory NK cell receptors

Inhibitory receptors are able to prevent the activation of NK cells and have been thought of as fail-safe mechanisms to prevent attack on normal cells and tissues. In general, these receptors express one or more immunoreceptor tyrosine-based inhibition motifs (ITIM), and they recruit SH2-containing phosphatase-1 (SHP1), SH2-containing phosphatase-2 (SHP2), and/or SH2-containing inositol phosphatase (SHIP) proteins upon binding to their ligands [51]. These phosphatases prevent the activation of cellular signaling cascades by inhibiting phosphorylation of proteins.

The inhibitory receptors encompass two distinct classes: the monomeric type I glycoprotein of the immunoglobulin superfamilies KIR2DL and KIR3DL [51], leukocyte immunoglobulin-like receptors (ILT2), and the hetero-dimeric C-type lectin-like receptor (CTLR) called CD94/NKG2A (natural killer group protein 2 family member A) [52, 53].

4. NK cells in tumor immunosurveillance and cancer

NK cells are innate cellular components that regulate adaptive immune responses in the immune surveillance of cancer. Primary immunodeficiencies affecting NK cells were associated with higher rates of malignancy and a higher risk of developing various types of cancer [54, 55]. NK cells have been shown to control the growth and metastasis of transplantable tumors in numerous mouse models by antibody depletion of NK cells [56].

NK cells can eliminate tumors that downregulate expression of MHC class I (**Figure 2b**), possibly in response to selective pressure exerted by CD8⁺ T cells. Furthermore, NK cells can kill tumor cells that retain full expression of MHC class I if they have upregulated ligands that engage activating NK cell receptors, thus overriding the inhibitory signals (**Figure 2c**).

For example, NKG2D ligand expression on tumor cells induces NK cell activation and is sufficient to overcome inhibitory signals delivered by MHC class I receptors, thereby enabling NK cells to eliminate tumors expressing normal levels of MHC class I [48, 57]. Mice deficient of NKG2D (*Klrk1*^{-/-}) are more susceptible to tumorigenesis [58] confirming the crucial role of NKG2D in tumor immunosurveillance.

However, tumor cells are able to evade immunosurveillance by using multiple mechanisms. Tumor cells can secrete inhibitory cytokines such as transforming growth factor- β (TGF β) that suppresses the activity of NK cells. Furthermore, tumor cells can express inhibitory receptor-specific ligands such as glucocorticoid-induced TNFR-related protein (GITR) that

can downmodulate activating receptors NKG2D on NK cells. To escape to NK cell immunosurveillance, tumor cells can also secrete immunomodulatory molecules such as prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase (IDO), adenosine, TGF β , and interleukin-10 (IL-10). Tumor cells can proteolytically shed NKG2D ligands (NKG2DLs) leading to a decreased amount of NKG2DL and to the production of soluble ligands that downmodulate NKG2D receptor on NK cells [59, 60]. Finally, secretion of immunosuppressive molecules or expression of NKG2DLs by cells of the tumor microenvironment can downmodulate NKG2D receptor on NK cells.

Soluble NKG2DLs have been detected at high levels in the serum of cancer patients [61] and might be used as a diagnostic marker [62]. Tumor cells can escape immunosurveillance by the secretion of soluble factors such as lactate dehydrogenase, leading to NKG2DLs expression on healthy host myeloid cells [63]. NKG2D Downregulation could be the result of its chronic exposure to NKG2D ligand on tumor cells [64]. Recent work in a mouse model suggests that a shed NKG2D ligand, MULT1, stabilizes expression of NKG2D on NK cells and increase their antitumor activity [65]. Controlling NKG2DL expression level on tumors provides an attractive therapeutic strategy for immunotherapy.

In patients and animal models, impaired NK cells or NK cell deficiency have been associated not only with recurring viral infections, but also with an increased incidence of various types of cancer [55]. Tumor cells often acquire the ability to escape NK cell-mediated immune surveillance. In fact, during tumor development and progression, many malignant cells acquire the ability either to evade from NK cell recognition or to impair NK cell function.

Cells undergoing malignant transformation often downregulate their expression of MHC class I molecules, and the absence of inhibitory signaling on NK cells permits their function. A defective immunity has been well established in different types of cancer. The imbalance of immune status is inclined to immunosuppression in cancer patients, which results in tumor immune evasion. Such immunosuppression is characterized by a decrease in NK cell numbers in peripheral blood and a decreased tumor infiltrate as compared to normal tissues. Moreover, in many types of cancer, a defective expression of activating receptors and overexpression of inhibitory receptors is observed [66].

The role of NK cells against parasites that may promote or impede carcinogens is poorly understood. Chronic inflammation is a key feature in carcinogenesis associated with helminth infections. For example, *Strongyloides stercoralis* infection was associated with an increased occurrence of lymphoid cancers [67]. An association of colorectal cancer with chronic *S. stercoralis* infection has also been reported in a Columbian patient [68]. This nematode is not only a cofactor for the development of lymphoid cancers induced by HTLV-1 [69] but is also associated with the development of colon adenocarcinoma by activating the host immune response. A study reports a case of *Strongyloides* infection in a 72-year-old man presenting a large population of cells (NK-LGL) with a natural killer phenotype abnormally activated and diagnosed with NK-LGL leukemia [70]. The role of NK cells in the immune response to *Strongyloides* is not defined, but it is possible that an abnormal or clonal expansion of NK cells could suppress antihelminth immunity. Activated NK cells, perhaps producing interferon, suppressed the T-helper 2 response that previously controlled the *Strongyloides* infection.

5. NK cell in cancer immunotherapy

Cancer immunotherapy is the targeted therapy designed to induce antitumor response against malignancies by harnessing the power of the immune system [71]. The ability to recognize and lyse transformed cells without prior immunization, the ease of isolation and expansion *ex vivo*, and the shorter life span make NK cells a good alternate to immunotherapy. Furthermore, NK cell can kill cancer cells without damaging healthy tissues or risking the T cell–driven inflammatory cytokine storm that can accompany other immunotherapies. The NK cells derived from peripheral or umbilical cord cells, embryonic or induced pluripotent stem cells, and NK cell lines were being tested for treating various malignancies. Several promising clinical therapies have been used to exploit NK cell functions in treating cancer patients.

5.1. Adoptive NK cell transfer therapy

Adoptive NK cell transfer therapy is a strategy aimed at enhancing the biological function of the immune system by means of autologous or allogeneic NK cells. NK cells for adoptive NK cell transfer therapy (autologous or allogeneic) are usually obtained from the peripheral blood of the patient or from a donor. They can also be derived from the bone marrow, umbilical-cord blood, human embryonic stem cells, or induced pluripotent stem cells and are now considered as alternative sources of therapeutic NK cells [72].

Various approaches exist for the therapy with the adoptive transfer of NK cells. In autologous transfer, NK cells from the patient are activated and expanded *in vitro* in the presence of cytokines. IL-2 has been used for this purpose, but recently, the combination of IL-12, IL-15, and IL-18 might generate NK cells that are more functional and have memory properties. The expanded and activated NK cells are then transferred back into the patient. To sustain the expansion and function of the infused NK cells, patient receives IL2 cytokine administration. Although autologous NK cells might recognize activating signals such as stress molecules on cancer cells, their anti-tumor activity is limited by the inhibitory signal transmitted by self-HLA molecules.

In allogeneic transfer, NK cells can be obtained from HLA-matched or haploidentical (partially matched) donors. The best responses are obtained when haploidentical donors do not express KIRs that recognize the patient's HLA molecules, because donor NK cells do not receive an inhibitory signal from the patient's cancer cells. NK cells are expanded through processes similar to those used for autologous transfer except that T cells should be removed.

5.1.1. CAR-engineered NK cells

NK cells can be transduced with activating chimeric antigen receptors (CARs) that specifically bind to antigens overexpressed by tumor cells. CARs are designed by the fusion of an antigen binding with a hinge region, a transmembrane domain and one or more stimulatory molecules.

CARs can be engineered in autologous or allogeneic NK cells or in NK cell lines such as NK-92. Each CAR has the CD3 ζ chain (or sometimes the FcR γ chain) as its main signaling domain. To increase persistence and superior functionality, co-stimulatory domains, usually from CD28 or CD137, can be added to the CAR construct. CARs from the first generation have no stimulatory domain, whereas CARs from the second generation and third generation have one co-stimulatory domain or two co-stimulatory domains, respectively. CAR engineering endows NK cells with antigen specificity. The binding of a CAR to the tumor antigen delivers a potent activating signal that triggers NK cell cytotoxicity, which results in the elimination of cancer cells. Several recent studies have documented a success using NK cells engineered to express activating chimeric antigen receptors (CARs) specific to tumor antigens [73]. Many B-cell acute and chronic leukemia can escape killing by natural killer cells. The introduction of chimeric antigen receptors (CAR) into T cells or NK cells could potentially overcome this resistance [74]. NK-92 leukemia cell lines were transduced to express CARs specific for CD19 [75] and CD20 [76] expressed on B cell malignancies and also for disialoganglioside GD2, a glycolipid expressed on neuroblastoma and various other cancer types [77].

In glioblastoma, the most aggressive primary brain malignancy, intracranial administration of NK-92-EGFR-CAR cells represents a promising therapy [78]. In human multiple myeloma (MM), CS1-specific (a surface protein highly expressed on MM cells) chimeric antigen receptor (CAR)-engineered natural killer cells [79] enhance responses to tumor cells in vitro and suppressed tumor growth when tested in vivo in xenograft models [65, 78, 80]. Autologous or allogeneic transplantation of CS1-specific CAR NK cells may be a promising strategy to treat multiple myeloma.

5.2. Cytokine-induced NK cell activation

To promote NK cell expansion, the use of IL-2 has demonstrated the effectiveness on NK cell activation and anti-tumor responses [81]. It was reported that NK cells from lung cancer patients could regain the cytotoxicity against targets after activation by IL-2 [82]. However, NK cells activation using high-dose IL-2 has some side effects because of severe capillary leaky syndrome. To improve the therapeutic efficacy and safety, a different strategy combining IL-2 with other NK cell activators was used. Hellstrand et al. [83] administered IL-2 together with histamine to 22 acute myeloid leukemia (AML) patients and showed a good clinical outcome. IL-2 diphtheria toxin (IL2DT), a recombinant cytotoxic fusion protein has been used in order to increase the depletion of regulatory T cells (Treg) and therefore improving in vivo donor NK cell expansion and remission induction [84].

5.3. NK cells targeting cancer stem cells

Tumor harbors a population of cancer cells with “stem-cell” like properties including self-renewal and the ability to produce differentiated progeny [85]. These cells termed cancer stem cells (CSCs) can drive tumor progression and therapeutic resistance to standard cancer therapy. In fact, cancer stem cells have been proposed as an important mechanism of tumor initiation and/or repopulation after tumor debulking by chemotherapy and/or by radiotherapy.

In addition, CSCs have been associated with tumor relapse and metastasis, even in cases of apparent complete response to systemic therapy [86]. Then, targeting CSCs is a promising strategy for cancer therapy. Natural killer cells have the ability to reject allogeneic hematopoietic stem cells, and there are increasing data demonstrating that NK cells can selectively identify and lyse CSCs. Tallerico et al. [87], for example, demonstrated that metastatic colorectal cancer, which contains a high proportion of CSCs, showed increased susceptibility to NK cytotoxicity. Similarly, Castriconi et al. [88] reported that glioblastoma-derived CSCs were susceptible to NK cell cytotoxicity. Human cancer cells with stem cell-like phenotype exhibit enhanced sensitivity to the cytotoxicity of IL-2 and IL-15 activated natural killer cells [89]. IL-2- and IL-15-activated NK cells were found to be cytotoxic against human breast cancer stem cells and CD 133+ melanoma CSCs [90]. Recently, Ames et al. [91] showed that NK cells kill CSCs from different kinds of tumors, through the interaction of the NKG2D activating receptor with its ligand (MICA/B).

6. Conclusions

NK cells have a crucial role in immunosurveillance against tumor development. However, when both the innate and adaptive immune systems fail and tumors develop, NK cells and their receptors can still be targeted in many therapeutic approaches. NK cells are more effective in treating hematologic malignancies than in treating solid tumors. This might result from inefficient homing of NK cells to the site of tumor. Therefore, NK cell-based immunotherapy can be successfully exploited in the hematopoietic stem cell transplantation for the treatment of hematological malignancies, but efforts have to be made to improve the homing and in vivo persistence of NK cells. Targeting CSCs with NK cell-based immunotherapy represents an attractive strategy for cancer therapy.

NK cells clearly have a role in future immunotherapies of the treatment of cancer and should continue to be evaluated in clinical trials.

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