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REVIEW ARTICLE

Functional crosstalk and regulation of natural killer cells in tumor microenvironment: Significance and potential therapeutic strategies

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Abstract Natural killer (NK) cells eliminate a large variety of tumor cells and abnormal cells. However, NK cells in the tumor microenvironment (TME) are often functionally depleted. A few subsets of NK cells even promote tumor growth. This study reviewed the biological properties of NK cells, the dynamic phenotypic changes of NK cells in the TME, and the communication between NK cells and other immune and nonimmune cells.

Introduction

Natural killer (NK) cells are large granular lymphocytes of nonthymus origin and innate immunity. They constitute approximately 10% of lymphocytes in peripheral blood. They develop and differentiate in the bone marrow, and do not express CD3. Traditionally, NK cells are clustered based on CD56 and CD16 expression: $CD56^{dim}CD16^{+}$ and $CD56^{bright}CD16^{low/-}$. $CD56^{dim}CD16^{+}$ NK cells are more

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mature and account for about 90% of circulating NK cells. $CD56^{dim}CD16^{+}$ NK cells express the FcγRIII receptor (CD16) and mediate ADCC or release granzyme and perforin, resulting in lethal effect.[1] $CD56^{bright}CD16^{low/-}$ NK cells are more naive, secrete IFN-γ and TNF-α, and regulate immune function.[2–4] $CD56^{superbright}$ $CD16^{-}$ NK cells, also known as decidual NK cells (dNKs), secrete placental growth factor (PlGF), CXCL8, and VEGF to promote angiogenesis and immunosuppressive effects.[5] However, some T cell subsets also express CD56, and the fractionation of NK cells and their markers needs further exploration.[2–4] CD27 is a marker of NK cell activation, while CD107α (LAMP-1) is a marker of NK cell degranulation.[6] The NK cell—activating receptors include natural cytotoxicity receptors, killer-IgG-like receptors (KIRs), NKG2D, NKp30, NKp44, NKp46, 2B4, NKG2C, DNAM-1, NTBA, and signaling lymphocytic activation molecules (SLAMs). SLAMs are generally present in all immune cells and participate in NK cell activation.[7–9] The inhibitory receptors present on NK cells include KIRs, CTLA-4, TIGIT, PD-1, TIM-3, LAG-3, NKG2A, and CD96.[9] NK cells kill tumor cells without damaging normal cells depending on the balance between NK cell activation and inhibitory receptors. MHC-1-like molecules are present in most normal cells in the body and bind to MHC inhibitory receptors (KIRs and CD94/NKG2A) on NK cells. Consequently, NK cells are not involved in killing MHC-like molecules. Tumor cells downregulate the expression of MHC-1-like molecules and upregulate the expression of corresponding ligands (NKp30, NKp44, NKp46, NKG2D, CD94/NKG2C, DNAM1, and 2B4) of NK cell—activating receptors. Therefore, NK cells are activated to kill tumor cells.[10] NK cells recognize target cells to release granzyme and perforin. Perforin creates holes in target cells. Granzyme enters target cells to activate caspases and induce apoptosis via mitochondrial dysfunction. In addition, NK cells also express tumor necrosis factor (TNF) superfamily of ligands [Fas ligand and TNF-related apoptosis-inducing ligand (TRAIL)] that bind to the death receptors of target cells, resulting in their death.[11–13] The mechanism of NK cell-mediated death of tumor cells is shown in Figure 1.

Dynamic changes in NK cell phenotype in the TME

The chemokine receptors of NK cells include CCR2, CCR5, CCR7, CXCR3, and CX3CR1.[14] Chemokines in the TME bind to these receptors to recruit NK cells. The recruited NK cells recognize and activate tumor cells, resulting in their death. However, tumor cells can alter the expression of chemokines, and thereby alter NK cell recruitment.[15] After entering the TME, NK cells are lethal in the early stage, and then their cytotoxic function declines eventually, resulting in their exhaustion and death.[16] NK cell phenotypic alterations in the TME are mainly attributed to: (1) reduced expression of NK cytotoxic receptors (NKp30, NKp44 and NKp46), (2) decreased levels of NKG2D activation markers, (3) increased NK cell depletion markers (NKG2A, TIGIT, CD96 and PD-1) and impaired degranulation, and (4) inhibition of NK cell function by components and conditions in the TME (TGF-β, prostaglandin-E2, hypoxia, low pH, MDSCs, and Tregs).[17–19]

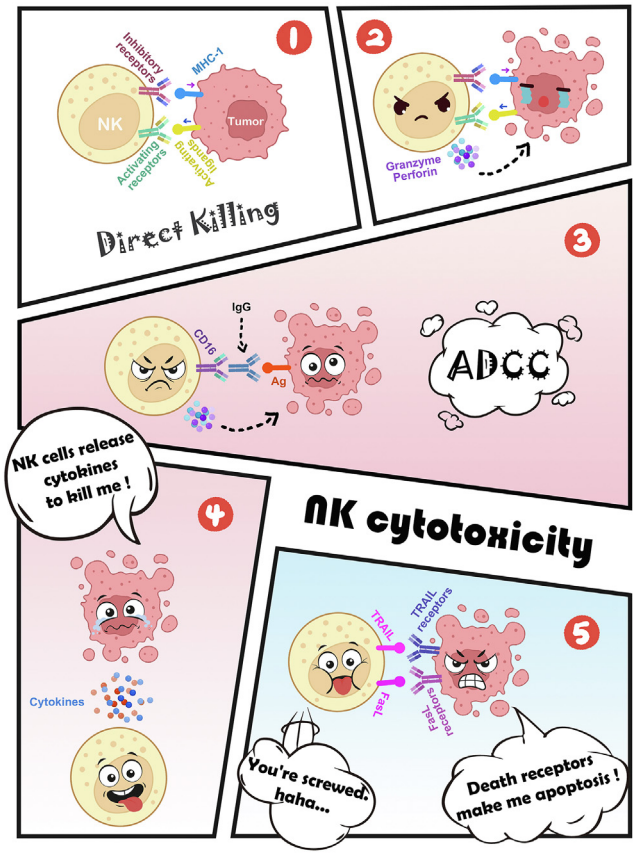

Figure 1 The mechanism of NK cell-mediated tumor cell death.

Diminished toxic function of different NK cell subpopulations in TME

CD57, CD56, and NKp46 are often used as markers of tumor-infiltrating NK cell clusters.[17,20] Tumor-infiltrating NK cells are mainly $CD56^{bright}$ cell clusters with impaired cytotoxic function.[21,22] A large number of $CD49a^{+}$ NK cells with high expression of PD-1, CD96, and TIGIT in human hepatocellular carcinoma (HCC) negatively regulate immune response and are often associated with poor prognosis in patients with HCC.[23] $CD11b^{-}$ $CD27^{-}$ NK cells in the HCC microenvironment exhibit inactive and immature phenotype and cellular dysfunction associated with HCC progression.[24] NKp30 is an NK cell—activating receptor. Natural cytotoxicity receptor-3 (NCR3) is transcribed with several spliceosomes. In advanced HPCC, the NCR3 stimulatory spliceosome expression is reduced and inhibitory spliceosome expression is increased in $NKp30^{+}$ NK cells. Ligand B7 homolog 6 (B7—H6) secreted by HCC cells significantly downregulates NKp30, leading to NKp30-mediated NK cell dysfunction, which drives HCC progression.[25] Peripheral blood and tumor-infiltrating NK cells derived from patients with clear cell renal cell carcinoma (ccRCC) exhibit a predominantly immunosuppressive phenotype characterized by the overexpression of CD85j, CD45, CD48, and PD-1. Tumor-infiltrating NK cells were more immunosuppressive than peripheral blood NK cells from patients with ccRCC, with reduced expression of activating receptors (DNAM-1,

NKp30, NKp46, NKp80, and CD16).[26] Progressive tumor malignancy results in null effect, exhaustion, and pro-angiogenic phenotype of the infiltrating NK cells. TGF-β induces $CD56^{bright}CD9^{+}CD49a^{+}$ decidual-like phenotype (dNK cells). The dNK-like cells secrete angiogenin, MMPs, VEGF, PlGF, and CXCL8 to promote angiogenesis.[22,27,28] The dNK-like cells also decrease the expression of NKG2D activation marker, increase the levels of TIM-3 depletion marker, and induce M2 macrophages and TAMs.[28,29] TIMP1 and TIMP2 downregulate TGF-β to inhibit the decidual-like phenotype of NK cells.[28] PVRIG is highly expressed in exhausted NK cells in the TME. The blockade of PVRIG inhibits NK cell and $CD8^{+}$ T cell depletion in a tumor-bearing mouse model.[30] NK cells are exhausted in B- and T-cell acute lymphoblastic leukemia (B/T-ALL), but strongly express CD56 and CD69.[31] After entering the TME, NK cells often differentiate into a variety of subpopulations that perform different functions, but most of the NK cell subpopulations highly express depletion markers and show diminished anti-tumor immunity.

NK cell—activating and NK cell—inhibitory receptors interact with tumor cell ligands

NK cells exert antitumor immunity mainly through activated NKG2D and CD16 Fc receptors.[32] NKG2D ligands include MICA, MICB, ULBP1, and ULBP2. The activated NK cell receptor (NKG2D) binds to NKG2D ligands secreted by tumor cells.[33] Many tumor cells express MICA and MICB, which are eliminated by binding to NKG2D receptors on cytotoxic lymphocytes. As tumors progress, the tumor cells shed MICA and MICB to escape killing.[32] However, in another study, the expression of MICA and MICB ligands was associated with HCC invasion. The expression of MICA, MICB, ULBP1, and ULBP2 was associated with poor prognosis in patients with HCC. The expression of ULBP1/2 negatively correlated with β-catenin target genes. The expression of NKG2D ligand in HCC cells is downregulated by β-catenin signaling, which inhibits HCC invasion.[33] Tumor-derived soluble MIC (sMIC) also reprogrammed NK cell phenotypes by activating CBM-signalosome inflammatory pathways.[34] NKG2A on NK cells and the expression of its ligand HLA-E were increased in HCC, which were probably induced by IL-10. These NK cells exhibit functional collapse often associated with poor prognosis.[35] The blockade of inhibitory NKG2A receptors promoted NK and $CD8^{+}$ T cell cytotoxic functions.[36] Human and murine NK cell receptors (NKp46 and Ncr1) induced IFN-γ secretion by tumor-infiltrating NK cells. Increased IFN-γ upregulated fibronectin 1 (FN1) in the extracellular matrix under the TME to alter primary tumor structure and inhibit tumor metastasis.[37] The activating and inhibitory signals of NK cells are balanced; this balance is disrupted when tumor cells are encountered. The activating receptors of NK cells bind to ligands secreted by tumor cells, resulting in NK cell activation and lethal effects.

Effect of immune checkpoints on NK cells

NK cell dysfunction and its phenotypic alterations in the TME are often associated with immune checkpoint inhibitory molecules. The number of CTLA-4 and KLRC1 inhibitory molecules increased in infiltrating NK cells of non-small cell lung carcinoma (NSCLC).[38] NK cells in the NSCLC microenvironment strongly expressed PD-1, bound to PD-L1 on tumor cells, resulting in Inactivation.[39] NK cells in the ccRCC microenvironment highly expressed PD-L1 and inhibited $CD8^{+}$ T cell proliferation.[40] Glucocorticoids and cytokines (IL-12, IL-15, and IL-18) induce PD-1 expression in tumor-infiltrating NK cells.[41] IL-18 secreted by triple-negative breast cancer cells increased PD-1 expression on NK cells and enhanced immunosuppression.[42] Depleted NK cells in advanced tumors co-expressed TIM-3 and PD-1. The low expression of MHC-1 on tumors induced NK cell exhaustion. IL-21 reversed NK cell exhaustion to promote the death of MHC-1-deficient tumors.[43] The number of NK cells was decreased in the infiltrated areas of endometrial cancer. As tumors progress, $CD103^{+}$ NK cells in the TME express additional co-suppressor molecules such as TIGIT and TIM-3, and altered the expression of CXCL12, IP-10, CCL27, IL-1β, and IL-6 in the TME inhibited NK cell function and recruitment.[44] High expression of TM4SF5 in mouse HCC cells led to NK cell exhaustion-like phenotypes (NK cell number or functional exhaustion) and downregulated the expression of toxic receptors and ligands on NK cells (SLAMF6, SLAMF7, and MICA/B).[45] Prostaglandin E2 (PGE2) secreted by thyroid cancer cells inhibited the cytotoxic effect of NK cells by suppressing the expression of NKp44, NKp30, and TNF-related apoptotic ligands. PGE2 also inhibited NK cell maturation and promoted the immune escape of thyroid cancer cells.[46] The binding of CD226, CD96, and TIGIT to CD155 ligand regulated NK cell function. CD226 expression positively correlated with CD96 levels. CD155 expression was increased in pancreatic cancer. The decreased number of infiltrating $CD226^{+}$ and $CD96^{+}$ NK cells in the TME was associated with pancreatic cancer metastasis.[47] Breast cancer cells overexpressing CD155 were associated with depleted lymphocytes in the TME and patients with extremely poor relapse-free and overall survival.[48] High TIGIT expression in the colon cancer microenvironment was associated with NK cell depletion. Blocking TIGIT promoted NK-dependent T cell-mediated antitumor immunity.[49] However, IL-10 upregulated TIGIT expression in NK cells and transformed NK cells into dysfunctional NK cells, often associated with poor prognosis in patients with AML.[50] Tumor cells can evade killing by NK cells via immune checkpoint molecules. Inhibition of the binding of immune checkpoint-associated receptor ligands thus enhances the aggressiveness of the host immune system against tumor cells.

Hypoxia impairs NK cell function

Hypoxia often occurs during the malignant progression of tumors. Hypoxia inhibited NK cell function and reduced the ability of NK cells to release cytokines, such as IFN-γ, TNF-α, GM-CSF, CCL3, and CCL5.[51,52] Hypoxia decreased the expression of granzyme B and degranulation marker CD107a and facilitated tumor immune escape.[53] Decidual NK (dNK, $CD56^{+}CD16^{dim/-}$) cells in renal cell carcinoma (RCC) promoted angiogenesis. RCC-infiltrated NK cells adapted to the hypoxic environment by upregulating HIF-1α, and the increased HIF-1α expression inhibited NK cell function and antitumor effects.[54,55] Hypoxia downregulated the

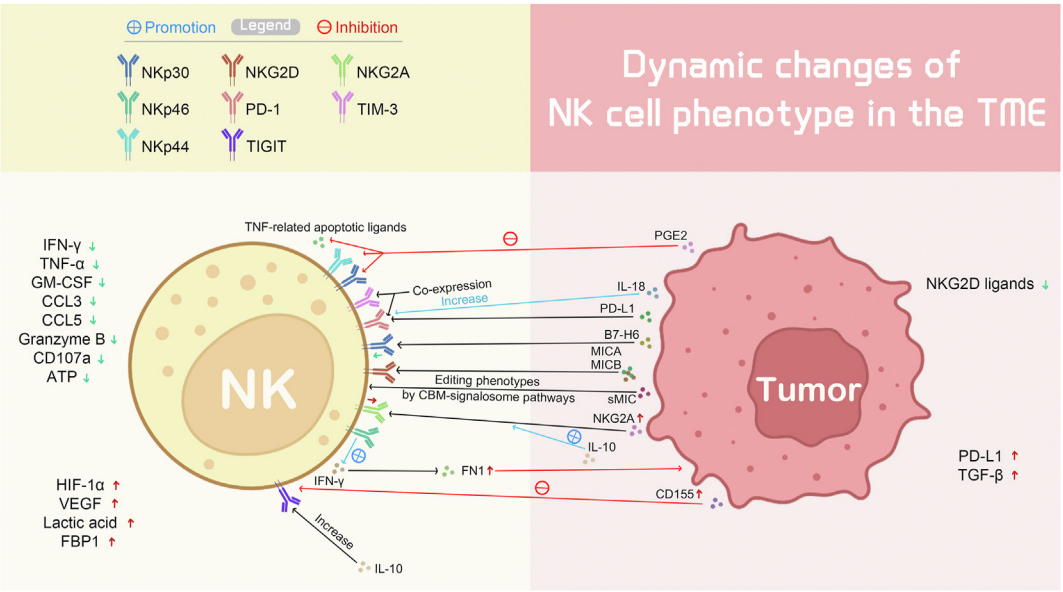

Figure 2 Interactions between NK and tumor cells in TME.

expression of the NKG2D ligand, the NK cell—activating receptor, which was secreted by tumor cells, resulting in immune escape. The circ_0000977/miR-153 axis modified the HIF1A-mediated immune escape of pancreatic cancer cells by regulating the miR-153 downstream targets HIF1A and Disintegrin and Metalloproteinase Domain 10 (ADAM10).[56] Hypoxia-induced PD-L1 expression was increased and NKG2D-associated ligand expression decreased in castration-resistant prostate cancer (CRPC) cells. Inhibiting the JAK1,2/STAT3 signaling pathway reduced PD-L1 expression in CRPC cells and reversed the reduced NKG2D-related ligand expression and NK cell dysfunction.[57] Hypoxia reduced ERK and STAT3 phosphorylation through Src homology region 2 domain—containing phosphatase-1 (SHP-1), thereby reducing tumor-infiltrating NK cytotoxicity.[53] Mitochondria are mostly small and fragmented in the cytoplasm of HCC-infiltrating NK cells, which reduces the toxicity of NK cells and the number of infiltrating cells. Hypoxia also drives sustained activation of rapamycin-GTPase dynamin-related protein 1 in NK cells, leading to further mitochondrial fragmentation and evasion of HCC cells from NK cell-induced lethal effects.[58] Tumor cells exhibit high metabolic rate, induce hypoxic microenvironment, activate the signaling of hypoxia-inducible factors and damage NK cell mitochondria to inhibit anti-tumor immunity in NK cells, thus promoting tumor immune escape.

Low pH induces apoptosis of NK cells

Glycolysis is a marker of NK cell activation, and activated NK cells depend on LDHA for killing function and clonal proliferation. LDHA-dependent glycolysis promotes the antitumor function of NK cells.[59] Tumor cells consume glucose mainly through the glycolytic pathway, which leads to the accumulation of lactic acid in the TME, thus decreasing the pH value. Low pH decreases the secretion of IFN-γ by NK cells, affecting cytotoxicity and promoting the immune escape of tumor cells.[60,61] In colorectal liver metastasis, lactate induces mitochondrial dysfunction and promotes NK cell apoptosis by lowering the pH and ATP levels in infiltrating NK cells.[62] The malignant progression of the tumor leads to an abnormal increase in FBP1 expression in NK cells, and the upregulation of FBP1 is associated with an increased concentration of TGF-β in the TME. The increase in FBP1 diminishes the glycolytic capacity of NK cells, which leads to dysfunctional NK cells.[63] For example, increased FBP1 expression, decreased glycolytic rate, and reduced cytokine secretion and cytotoxicity were observed in mouse lung cancer—infiltrating NK cells.[64] The interactions between NK and tumor cells in TME are summarized in Figure 2. The TME shows acidic pH due to altered metabolism of tumor cells. In this state, the tumor cells preferentially use glycolysis rather than oxidative phosphorylation for energy supply, resulting in lactic acid accumulation in the extracellular environment. Low pH has a broad impact on TME, leading to immunosuppression, immune escape and disease progression. The acidic pH inhibits NK cytotoxicity and mitochondrial function, eventually leading to apoptosis.

Communication between NK and other cells in the TME

There are different types of cells in TME that secrete cytokines, which determine the direction of NK cell differentiation in the TME. Different NK cell subpopulations also influence the proliferation and differentiation of these cell populations. Some subpopulations of NK cells synergize with immune or non-immune cell subpopulations in the TME to promote anti-tumor immunity, but may also promote malignant tumor progression. It is essential to explore the crosstalk between NK cells and other cells in the TME to

identify cell populations with anti-tumor immunity for clinical application.

Interaction between NK cells and T cells

NK cells may inhibit T-cell function via NKG2D, NKp46, and cytokines, and mediate T cell death through perforin.[65] NK cells also increase the expression of CXCL9 and CXCL10 to promote T cell recruitment.[66] Tregs cells release TGF-β to reduce the expression of NKG2D and NKp30 in NK cells to inhibit NK cell proliferation and function.[67,68] TGF-β and Tregs may reduce the expression of granzyme B and perforin via Smad signaling in NK cells.[69] Tregs secrete IL-10 to inhibit NK cell function.[70] Activated Tregs may inhibit the secretion of IFN-γ by NK cells mediated via IL-12.[71] In the esophageal squamous cell carcinoma (ESCC) microenvironment, the interaction between NK cells and Tregs may be mediated by HLA-E, B2M, and KLRC1.[72] Tregs upregulate the expression of CCR4, which binds to chemokines to recruit Tregs into the lung cancer microenvironment ($NK1.1^{+}CD11b^{dim}CD49b^{+}CD122^{+}CD27^{+}CD19^{+}$ $CD3^{-}$) NK cells secrete CCL22 to bind to CCR4 on Tregs and attract additional Tregs into the TME.[73–75] $CD4^{+}$ T cells secrete IL-2 to stimulate NK cell cytotoxicity.[76] Tregs may inhibit the function of $CD4^{+}$ T cell–derived IL-2 and suppress NK cell activation.[77] Regulatory NK cells ($CD73^{+}$) overexpress VISTA, LAG3, PD-1, and PD-L1. They produce IL-10 and inhibit the proliferation of autologous $CD4^{+}$ T cells.[70] The expression of KLRC1 and CTLA4 by a few tumor-infiltrating NK cell subsets may inhibit the function of $CD8^{+}$ T cells.[70] NK cells secrete IFN-γ to promote Th1-cell polarization.[78] NK cells promote T-cell recruitment and suppress T-cell function, and Tregs generally suppress the anti-tumor immunity of NK cells. Some NK cell subpopulations recruit Tregs in the TME (Fig. 3).

Interaction between NK cells and DCs

Chemokines CCL5 and XCL1/2 mediate the recruitment of cDC cells in the TME.[79] DCs act as antigen-presenting cells that present extracellular antigens to $CD8^{+}$ T cells and induce adaptive immune responses. In the TME, NK cells increase cDC1 cell recruitment, differentiation, and maturation, and cDC1 cells promote NK cell activation.[80] CCL3 expression in the TME recruits NK cells. Tumor-infiltrating NK cells secrete IFN-γ to promote $CD103^{+}$ DC enrichment.[66] However, IL-12 secreted by $CD103^{+}$ DCs is essential for NK cell–mediated inhibition of tumor metastasis.[81] DC cells secrete IFN-α/β to promote NKG2D expression, cytotoxicity, and proliferation of NK cells.[82] The interaction between $CD14^{+}CD16^{-}$ monocytes and NK cells drives the differentiation of $CD14^{+}CD16^{-}$ monocytes into DCs. NK cell–induced DCs drive the production of type 17 $CD8^{+}$ T cells (Tc17). Tc17 secretes IFN-γ and IL-17A. GATA2 mutations impair the interactions between NK cells, DCs, and Tc17. However, whether this regulatory relationship exists in the TME needs to be further explored.[83] Mature DCs upregulate the expression of CD155 and CD112, while TIGIT expressed by infiltrating NK cells often competes with DNAM-1 for binding to CD155 and CD112.[84–89] NK cells promote DC activation and induce DC-mediated antitumor immunity via IL-18. When exposed to inflammatory factors (IL-2, IL-15, IL-12, and IFN-α) and tumor cells, IL-18-induced helper NK cells attract immature DCs mediated via CCR5, increasing the number of DCs expressing CXCR3 and CCR5 ligands (CCL5, CXCL9, and CXCL10) and subsequently

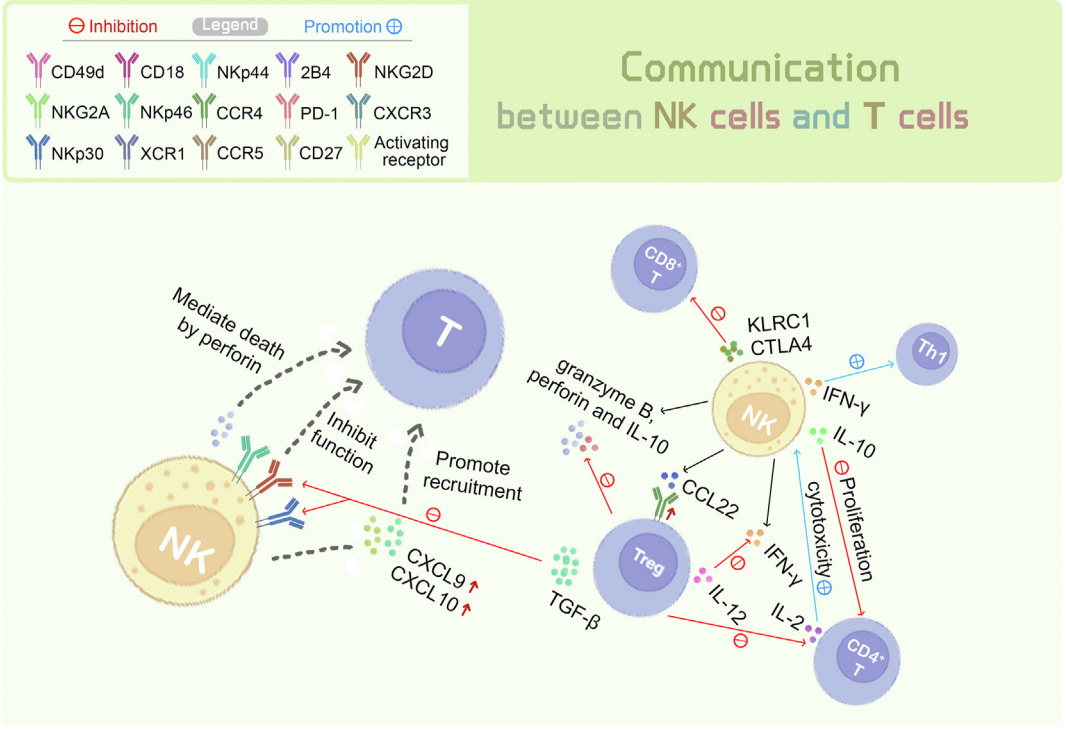

Figure 3 Communication between NK and T cells in the TME.

promoting type-1 effector $CD8^+$ T cell recruitment in the TME.[90] Activated NK cells secrete cytokines to regulate the immune response to influence tumor progression. Activated NK cells secrete CCL4, CCL5, CXCL1, and XCL1, which in turn recruit DCs expressing CCR5 and XCR1 in the TME.[85,91,92] DCs secrete CXCL9 and CXCL10, which in turn recruit NK cells and $CD8^+$ T cells. TNF-α and IFN-γ secreted by NK cells induce DC maturation. Immunosuppressive molecules (TGF-β, soluble MIC A + B, and PGE2) secreted by tumor cells reduce NK cell—activating receptor expression to diminish NK-DC intercellular communication.[93] HMGB1 secreted by NK cells promotes DC maturation, while the Flt3L ensures survival and abundance of cDCs in the TME.[79] GM-CSF secretion by NK cells activates DCs.[82] DCs produce IL-21 to promote NK cell toxicity, proliferation, and expression of activating receptors.[82] DCs secrete IL-32α to inhibit the release of granzyme and perforin B from NK cells.[82] DCs also produce IL-1α to inhibit NK cell maturation.[82] DCs as antigen-presenting cells activate NK cells and promote NK cell proliferation and function, while NK cells recruit DCs and promote the differentiation and maturation of DCs under a positive feedback mechanism. However, some DC subpopulations secrete cytokines to inhibit NK cell function (Fig. 4).

Interaction between NK cells and macrophages

The intercellular communication in the TME is mediated via secreted factors, such as pro-inflammatory factors (IFN-α, IFN-γ, IL-2, IL-12, IL-15, and IL-18) and immunosuppressive factors (IL-10, PGE2, IDO1/2, and TGF-β).[18,76] Pro-inflammatory and immunosuppressive factors released by macrophages may influence the maturation and function of NK cells. Macrophages secrete IL-12, IL-15, and IL-18 to activate NK cells, which in turn secrete TNF-α, IFN-γ, and GM-CSF to promote IL-12 and IL-18 secretion by macrophages under a positive feedback.[94–97] IL-12 promotes M1 macrophage polarization and increases CXCL9, CXCL10, and CXCL11. These chemokines bind to CXCR3 receptors on NK cells to promote the NK cell recruitment and induce the expression of B7—H1 on NK cells.[98] IL-23 and IL-1β secreted by M1 macrophages synergistically upregulate NKG2D, thereby increasing NK cell-induced death of tumors.[99] IFN-β activates CXCL10 and CXCL11 expression in TAMs, thereby promoting NK cell recruitment in the TME.[100,101] TNF-α is involved in the recruitment and activation of monocytes and macrophages, and NK cells and monocytes/macrophages induce tumor cell apoptosis via TNF-TNFR.[102,103] Macrophages secrete TNF to promote NK cell cytokine secretion.[82] IFNγ may induce IDO1, which induces NK cell death in the TME via inhibition of IL-12 synthesis by IL-10 and TGF-β and depletion of tryptophan, thereby converting macrophages into an immunosuppressive phenotype.[104] Both M2 macrophages and TAMs inhibit CD27 expression in NK cells, which affects their degranulation. Both M2 macrophages and TAMs also release TGF-β to inhibit NK cell activity.[105] The binding of HLA-E of TAMs and NKG2A/CD94 of NK cells not only protects TAM degraded by NK cells but also promotes the synthesis of immunosuppressive factors (TGF-β and IL-10) by NK cells.[106] The CD48 expression in

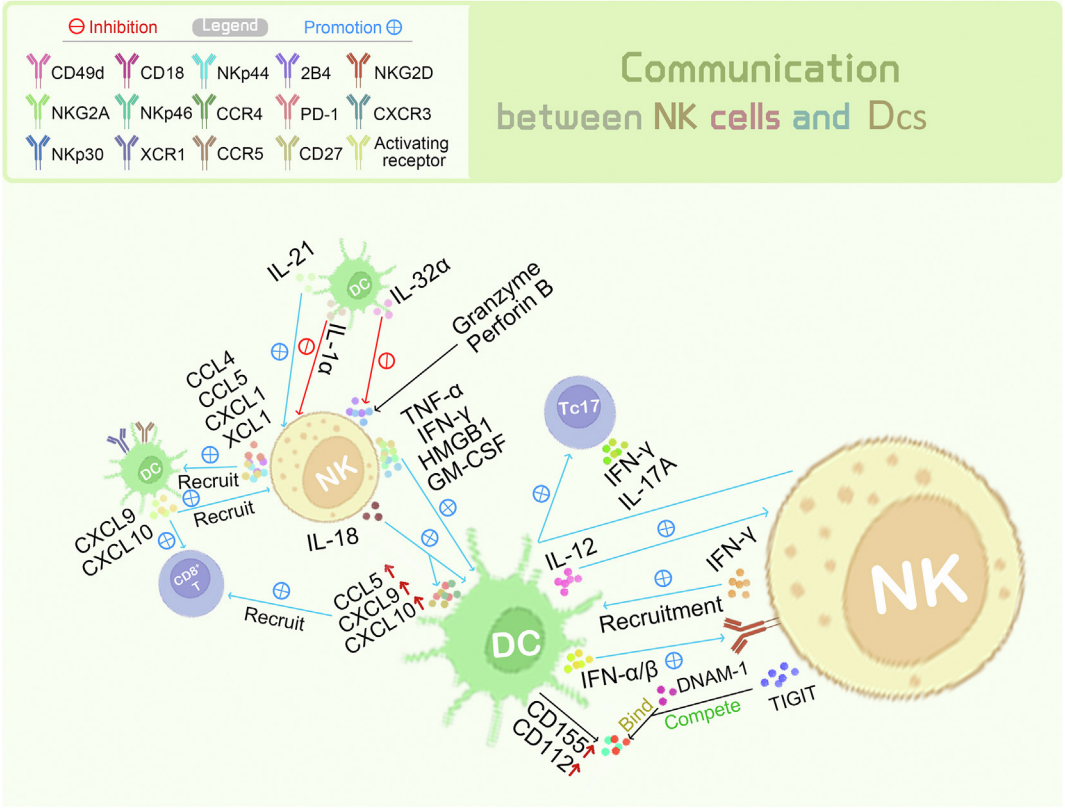

Figure 4 Communication between NK cells and DCs in the TME.

$CD68^+$ monocytes/macrophages and 2B4 expression on NK cells increases in advanced HCC microenvironment, which further enhances CD48/2B4 binding. The interaction between macrophages and NK cells leads to NK cell activation, exhaustion, and eventually, apoptosis.[107] The secretion of TNF-α and GM-CSF by NK cells polarizes TAMs into pro-inflammatory macrophages.[82] Also, macrophages generate IL-1α to inhibit NK cell maturation.[82] Macrophages secrete cytokines to recruit and activate NK cells. Similarly, macrophage subpopulations inhibit the lethal effect of NK cells. For example, M1 macrophages promote NK cytotoxic effects, whereas M2 macrophages and TAMs inhibit NK cell activity. NK cells also determine the direction of macrophage polarization (Fig. 5).

Interaction between NK and neutrophils

ROS secretion by neutrophils downregulates NKp46 expression by $CD56^{dim}$ $CD16^+$ NK cells but upregulates NKp46 expression by $CD56^{brigth}CD16^-$ NK cells.[108] Neutrophils secrete IL-17 to promote NK cell toxicity and inhibit NK cell maturation.[82] VEGF increases the secretion of ICAM-1 and VCAM-1 by endothelial cells, which bind to CD18 and CD49d on the surface of neutrophils and NK cells.[109–111] Neutrophils secrete IL-12, which in turn induces the synthesis of IFN-γ and perforin by NK cells via STAT4.[82,112,113] IFN-γ secreted by NK cells negatively regulates neutrophil-mediated pro-angiogenesis.[114] Arg1 secreted by TANs is involved in NK cell pro-angiogenesis and inhibits IFN-γ secretion by NK cells.[115] Neutrophils inhibit NK cell infiltration by downregulating CCR1 in NK cells in a mouse model of colorectal cancer. The binding of PD-L1 derived from neutrophils and PD-1 obtained from NK cells decreases IFN-γ secretion from NK cells to reduce antitumor capacity.[116] Neutrophils also secrete cathepsin G, which reduces the expression of NKp46 on NK cells, complicating the activation of NK cells.[117] Neutrophils both promote and inhibit NK cytotoxicity. NK cells inhibit the pro-angiogenic effect of neutrophils, while TANs promote the pro-angiogenic effect of NK cells and inhibit the lethal effects of NK cells (Fig. 6).

Interaction between NK cells and fibroblasts

Activated cancer-associated fibroblasts (CAFs) include myCAF (αSMA^{high} and TGF-β^{high}), iCAF (IL-6^{high}, IL-11^{high}, αSMA^{low}, and TGF-β^{low}), and apCAF (MHC^{high}), which secrete a variety of cytokines, chemokines, and MMPs to inhibit NK cell activity.[118] CAF subpopulations in pancreatic ductal adenocarcinoma (PDAC) are known as pancreatic stellate cells (PSCs). NKG2D on NK cells activates PSCs by interacting with MICA/B secreted by PSCs, resulting in their lysis.[119–121] Activated CAFs reduce the expression of NK cell–activating receptor, IFN-γ, TNF-α, perforin, and granzyme B to reduce NK cell toxicity.[118,122] Poliovirus receptor (PVR/CD155) is a ligand of NK cell–activating receptor. PVR/CD155 secretion by CAF is diminished, thereby inhibiting the lethal activity of NK cells.[123] The increased secretion of MMPs by CAF in the melanoma microenvironment reduces NK cell NKG2D ligand (MICA/B) expression, which further inhibits the killing of tumor cells by NK cells.[122] CAF secretes IDO or PGE2 to reduce the expression of NKG2D in NK cells and secretes TGF-β to reduce the expression of NKG2D, NKp30, and NKp44 to inhibit the cytotoxic effect of NK cells.[124,125] CAFs generally inhibit the antitumor immunity mediated by NK cells. However,

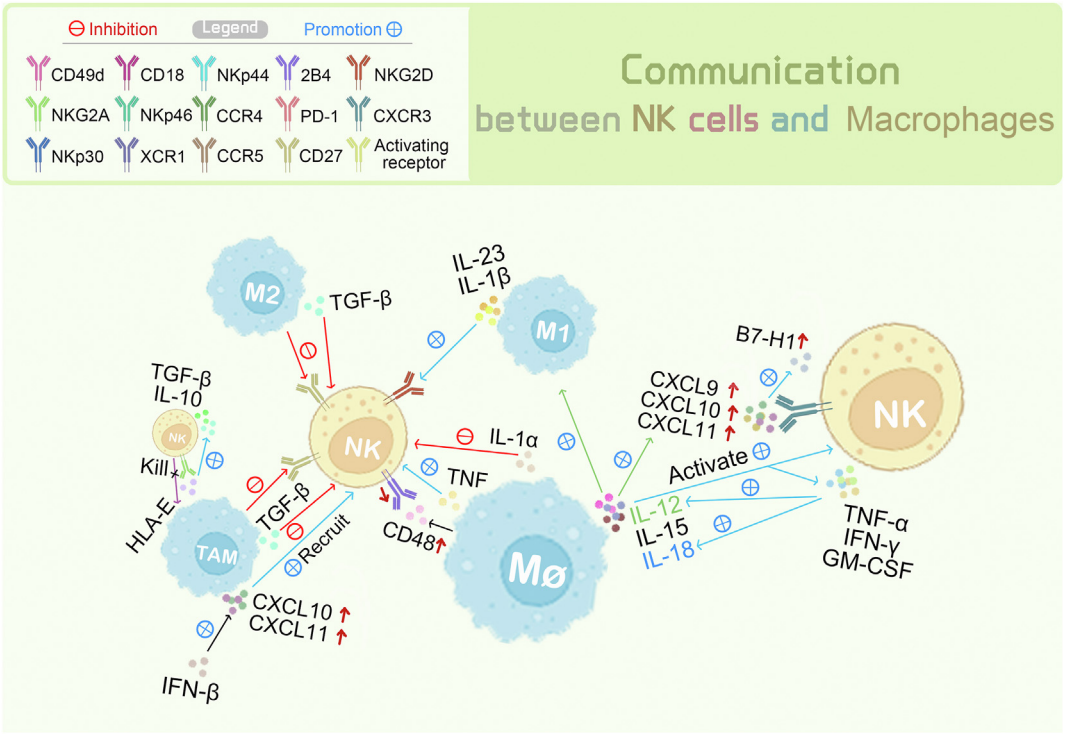

Figure 5 Communication between NK cells and macrophages in the TME.

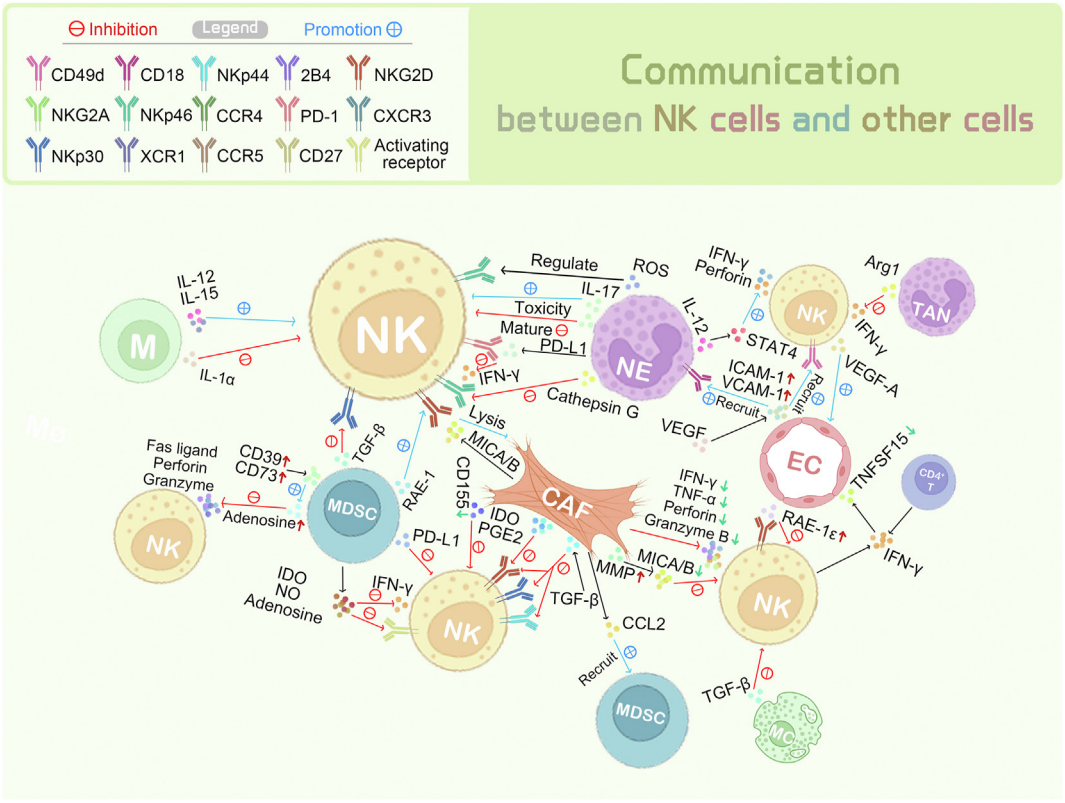

Figure 6 Communication between NK cells and other cells in the TME.

whether subpopulations of CAFs promote antitumor immunity of NK cells requires further exploration (Fig. 6).

NK interacts with MDSC, monocytes, mast cells, and endothelial cells

Mesenchymal stem cells (MSCs) in squamous cell lung carcinoma exhibit a strong inhibitory effect on NK cells, which can be converted into the $CD56^{dim}$ phenotype. MSCs mainly inhibit IFN-γ expression by $CD56^{bright}$ NK cells, affect degranulation, and activate receptors in $CD56^{dim}$ NK cells.[126] IDO, nitric oxide (NO), and adenosine are involved in MDSC-mediated decreased expression of NK cell—activating receptor (NKGD or NKR) and inhibited IFN-γ secretion from NK cells.[78] NO released by MDSCs in patients with cancer significantly inhibited FcR-mediated functions and signaling pathways in NK cells.[127] The secretion of adenosine was significantly increased due to the high expression of CD39 and CD73 in MDSCs in the TME. Adenosine inhibits Fas ligand- and perforin-mediated cytotoxic activity and blocks the cytosolic effect of granzyme to suppress the antitumor activity of NK cells.[78] CCL2 secreted by FAP^+ CAFs recruits MDSCs.[128,129] Membrane-bound TGF-β on MDSCs may interact with NKp30 on NK cells to inhibit NK cytotoxicity and cytokine secretion.[67,130] MDSCs express RAE-1 to activate NK cells via the NKG2D receptor.[77] Monocytes secrete IL-12 to promote the cytotoxic effects of NK cells.[82] Tumor cells upregulate the PD-L1 expression of MDSCs, while PD-L1 inhibits NK cell activity.[131] Monocytes secrete IL-15 to promote NK cell toxicity, activating receptors and proliferation.[82] Monocytes also secrete IL-1α to inhibit NK cell maturation.[82] MDSCs and mast cells secrete TGF-β to inhibit the expression of NK cell—activating receptors and cytokines and suppress NK cell proliferation.[82] NK cells secrete VEGF-A to promote endothelial cell proliferation and metastasis.[82] RAE-1ε is highly expressed on tumor-associated endothelial cells. RAE-1ε binds to the NKG2D receptor on NK cells, leading to the internalization of NKG2D that impairs antitumor response of NK cells.[132] IFN-γ production by NK cells and $CD4^+$ T cells in the TME downregulates TNFSF15 expression in vascular endothelial cells.[133] MDSCs generally inhibit both activating receptors and cytokine secretion by NK cells but can also activate NK cells. NK cells promote proliferation and metastasis of endothelial cells, while endothelial cells inhibit NK cytotoxic effects. Additional subpopulations of cells in TME and their interactions with NK cells may reshape our current understanding of these cells. The communication between NK cells and other cells in the TME is summarized in Figure 6.

NK cell—targeted tumor therapy

Abundant infiltration of NK cells in tumors increases patients' overall survival and improves their prognosis.[134,135] In a phase I clinical trial, infusion of autologous *ex vivo* expanded NK cells into children with recurrent medulloblastoma yielded good therapeutic results.[136] In a phase I clinical trial, a combination of autologous NK cell infusion and trastuzmab promoted antitumor immunity in patients with HER2-positive solid tumors.[137] Low expression of ASK1

Table 1 NK cell-targeted tumor therapy.

Treatment	Effects	Phase
Autologous NK cell infusion	Promoting antitumor immunity	Phase I clinical trial[136,137]
ASK1 (Selonsertib)	Inhibiting tumor metastasis and liver fibrosis	Phase II clinical trial[138,139]
IL-15 superagonist/IL-15Rα fusion complex (ALT-803)	Inhibiting depleted NK cells; increasing NK cytotoxic effects and infiltration	Phase Ib clinical trial[140–142]
DRD2 (ONC201)	Promoting recruitment and toxicity of NK cells, inhibiting tumor proliferation and metastasis	First-in-human clinical trial[143,144]
SIRT2	Inhibiting the number and function of NK cells in murine melanoma	*In-vivo* experiments (mice)[145]
PD-L1 antibody + targeted sMIC antibody	Increasing IL-2Rα (CD25) expression on NK cells, improving the treatment outcome of patients with MIC/sMIC + metastatic melanoma	*In-vivo* (mice) and *in-vitro* experiments[147]
PD-1/PD-L1 inhibitor + cetuximab	Reversing NK cell dysfunction, inhibiting the immune escape of HNSCC	Phase III/IVA clinical trial[148,149]
IL-6 and IL-8	Activating the STAT3 signaling pathway on NK cells and downregulating NK cell-activating receptors (NKp30 and NKG2D) to impair NK cell activity in ESCC	*In-vivo* (mice) and *in-vitro* experiments[150]
Chemotherapy (Cisplatin, 5-fluorouracil, docetaxel and gemcitabine) + PD-1 antibodies	Making NPC cells more susceptible to killing by NK cells	Phase III clinical trial[151,152]
Taxane and anthracycline	The expression of surface receptor genes from NK cells significantly reduced in drug-resistant breast cancer	Phase II/III clinical trial[153–155]
BMS-986156	Promoted the proliferation of NK cells	Phase I/IIa clinical trial[156]

in mice promotes tumor cell clearance by NK cells from blood vessels and inhibits tumor lung metastasis.[138] Selonsertib is an inhibitor of ASK1. In a phase II clinical trial, selonsertib reduced liver fibrosis in patients with nonalcoholic steatohepatitis and stage 2–3 fibrosis.[139] The IL-15 superagonist/IL-15Rα fusion complex inhibits the TGF-β1 signaling pathway, thereby suppressing depleted NK cells in the TME and providing a new therapeutic approach for NK cell dysfunction.[140] ALT-803 is a superagonist of IL-15. In phase Ib clinical trials, the combination of ALT-803 with PD-1 antibody significantly increased NK cytotoxic effects and NK cell infiltration in metastatic NSCLC.[141,142] ONC201 is an oral antitumor agent that upregulates the cytotoxic TRAIL signaling pathway to increase NK cytotoxicity. ONC201 exhibits time- and dose-dependent activity against tumor progression and invasive metastasis. It promotes the recruitment of NK cells in tumors. However, NK cell exhaustion affects the therapeutic outcome of ONC201.[143] ONC201 is a selective antagonist of the G protein-coupled receptor DRD2. In the First-in-Human Clinical Trial, 625 mg of ONC201 administered orally every 3 weeks, was biologically active and well-tolerated in patients with advanced cancer.[144] SIRT2 suppresses the NK cell number and function to promote the progression of murine melanoma.[145] Blood NK cells from allogeneic healthy individuals or patients with advanced melanoma can be induced to form memory-like (ML) NK cells by cytokines. ML NK cells may enhance the toxic effects on advanced melanoma, which represents a new immunotherapeutic approach in early clinical trials.[146] Patients with melanoma following PD-1/PD-L1 blockade therapy, expressing a soluble NKG2D ligand (sMIC) in peripheral blood, often show reduced overall survival. The sMIC negatively re-edits the cellular homeostasis and proliferation of NK cells. The sMIC/MIC is also abundantly expressed in metastatic melanoma. Combined treatment of PD-L1 antibody and targeted sMIC antibody increases IL-2Rα (CD25) expression on NK cells and improves the treatment outcome in patients with MIC/sMIC $^{+}$ metastatic melanoma.[147] In a phase III/IVA clinical trial, activated NK cells expressing PD-1 inhibited HNSCC when combined with PD-L1. PD-1^{+} NK cells are associated with a good prognosis in HNSCC patients. Cetuximab increases PD-1 expression in NK cells to mediate NK cell activity. PD-1 blockade elevates cetuximab-mediated NK cytotoxic effects when PD-L1 is highly expressed in HNSCC.

Therefore, the combination of PD-1/PD-L1 inhibitor and cetuximab inhibits the immune escape of HNSCC and reverses NK cell dysfunction to improve the treatment outcome.[148] Cetuximab-activated NK cells promote DC maturation, activate $CD8^+$ T cells, and promote tumor antigen-specific T cell immunity. However, the clinical outcome of cetuximab monotherapy in patients with HNSCC cannot be predicted due to the FcγRIIIa polymorphism.[149] A decrease in activating receptors and granzyme B on the surface of NK cells is associated with increased inhibitory receptors in ESCC. The secretion of IL-6 and IL-8 by ESCC cells activates the STAT3 signaling pathway on NK cells and downregulates NK cell-activating receptors (NKp30 and NKG2D) to impair NK cell activity. IL-6 and IL-8 in the TME are positively associated with poor prognosis and tumor progression.[150] Cisplatin, 5-fluorouracil, and gemcitabine increase the susceptibility of nasopharyngeal carcinoma (NPC) cells to NK cell-induced death. Chemotherapeutic drugs enhance PD-1 expression in NK cells and the PD-L1 expression in NPC cells via NF-κB. The inhibition of PD-1/PD-L1 enhances NK cell toxicity. Chemotherapy combined with PD-1 antibodies may improve the efficacy in patients with NPC. Reducing the dose of radiation therapy can decrease the side effects.[151] In a phase III clinical trial, patients with locally advanced nasopharyngeal carcinoma (NPC) treated with chemotherapy (cisplatin, fluorouracil, and docetaxel) and radiotherapy showed significantly lower survival rates in $PD\text{-}1^-$ patients and expressed high levels of EBV antibodies in $PD\text{-}1^+$ patients.[152] In taxane-anthracycline-treated breast cancer, the expression of NK cell—associated cell surface receptor genes was significantly reduced in drug-resistant tumor samples. NK cell reduction in breast cancer may be a sign of chemotherapy failure.[153–155] In phase I and IIa clinical trials, BMS-986156 promoted the proliferation of NK cells with a good safety profile.[156]

NK cells exhibit strong lethal effect and represent potential therapeutic targets (Table 1). The current focus is on the mobilization of endogenous NK cells, infusion of exogenous NK cells and the application of immune checkpoint blockers. The combination of these strategies is probably the most promising therapeutic modality at this stage.

Conclusions and perspectives

NK cells combine natural immunity with adaptive immunity and exhibit strong lethal effects without prior sensitization, providing the first line of defense against cancer. However, tumor cells can alter the expression of chemokines and thus change the recruitment of NK cells in the TME. NK cell infiltration is rare in solid tumors and often associated with poor prognosis in patients with tumors. The complexity of the TME results in dynamic phenotypic changes in infiltrating NK cells, with a gradual transition from lethal NK cells to depleted or immunosuppressive cells. These NK cell subsets, such as $CD49a^+$ NK cells, $CD11b^-$ $CD27^-$ NK cells, $NKp30^{low}$ NK cells, $CD56^{bright}CD9^+CD49a^+$ $decidual^-$ like NK cells, and $PVRIG^{high}$ NK cells, often appear nonfunctional or promote malignant tumor development. In the TME, one group of NK cells promotes antitumor immunity, while another group induces tumor proliferation and metastasis. However, the subsets, markers, and biological functions of the two types of NK cells are unknown. The mechanisms underlying the transformation of toxic NK cells into functionally depleted and immunosuppressive NK cells in the microenvironment, the subtypes of NK cells transformed, and the appropriate therapeutic approaches are challenges that need to be addressed in the future. In the TME, the NK cell function is affected by hypoxia, low pH, metabolites, cytokines, and intercellular interactions. Further studies are needed to identify the key molecules and pathways mediating the activity of different NK cell subsets and the effects of these metabolites on other cells. The interactions of different NK cell subsets with immune and nonimmune cells, especially B cells, are still unclear. Various components of TME (cells, factors, and stroma) direct the differentiation of NK cells. The crosstalk between cells promotes or inhibits the cytotoxic effects of NK cells, which exert anti-tumor immunity synergistically with some subpopulations of T cells, DCs, macrophages, neutrophils, and stromal cells. However, specific subpopulations of these cells can co-promote tumor malignancy. It is of great interest to identify these subpopulations and markers for clinical diagnosis, treatment and prognosis. The combination of immune checkpoint blockers (e.g. PD-1/PD-L1), endogenous and infused NK cells is currently the most promising targeted therapeutic modality. The effects of immune checkpoint-related targeted therapies vary widely among patients with tumors due to the high degree of tumor heterogeneity. Also, the heterogeneity of infiltrating NK cells among patients with tumors and the use of NK cells in clinical therapy require comprehensive studies to investigate the recruitment of NK cells to the designated sites in different TMEs, the subtypes of transformed NK cells entering the microenvironment, and the mechanisms of resistance to environmental stress, long-term survival, and cytotoxic function.

Author contributions

Liping Wang: writing, original draft preparation. Zhe Chen: validation, and data curation. Guohong Liu: validation, data curation, writing, reviewing, editing, and funding acquisition. Yunbao Pan: conceptualization, supervision, writing, reviewing, editing, and funding acquisition.

Conflict of interests

The authors have no conflict of interests to declare.

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