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REVIEW

Tumor microenvironment-driven natural killer cell diversity: mechanisms and therapeutic opportunities

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ABSTRACT Natural killer (NK) cells are key effector cells involved in tumor immune surveillance, yet their function within the tumor microenvironment (TME) exhibits considerable complexity and plasticity that cannot be adequately explained by the classical CD56/CD16 dichotomy. This functional diversity arises from the phenotypic adaptability and dynamic differentiation of distinct NK cell subsets shaped by the TME. In this review, we systematically examine the defining characteristics and functional roles of recently identified NK cell subsets in the TME; elucidate the molecular mechanisms governing their regulation; and highlight the functional transitions and cooperative interactions among these subsets. Moreover, building on current evidence, we summarize emerging immunotherapeutic approaches targeting specific NK cell subsets. Together, these perspectives offer new insights and strategic directions for deciphering the multifaceted roles of NK cells in antitumor immunity and advancing the development of subset-targeted therapies.

KEYWORDS Tumor microenvironment; natural killer cell subsets; regulatory mechanism; treatment strategies

Introduction

Natural killer (NK) cells play central roles in antitumor immunity, because of their unique direct cytotoxicity independent of prior antigen sensitization[1]. Through recognition of "missing-self" or "induced-self" signals, they rapidly eliminate target cells while secreting cytokines such as interferon-gamma (IFN-γ) that bridge innate and adaptive immune responses[2]. However, this critical function is substantially shaped by the complex tumor microenvironment (TME)[3].

The conventional classification of NK cells into $CD56^{bright}$ $CD16^{dim}$ (immunoregulatory) and $CD56^{dim}CD16^{bright}$ (cytotoxic) subsets, which is based primarily on peripheral blood studies[4], does not reflect their functional heterogeneity and phenotypic plasticity within the TME. Emerging evidence indicates that TME-specific factors, such as hypoxia, metabolic stress, and upregulated immune checkpoint molecules, not only suppress NK cell function but also drive the formation of specialized subsets with distinct profiles. These subsets include tumor-infiltrating NK (TiNK) cells, tissue-resident NK (TrNK) cells, and adaptive NK cells[5-8], each of which has unique differentiation pathways, surface marker signatures, and antitumor capabilities.

This review systematically examines how the TME shapes NK cell diversity and function. We provide a comprehensive analysis of the characteristics and regulatory mechanisms of specialized NK cell subsets, highlight their functional plasticity and cooperative networks. Furthermore, we explore emerging subset-specific immunotherapeutic strategies, thereby offering new perspectives for developing targeted interventions against cancer.

NK cell biology: from ontogeny and spatial distribution to functional subset classification

NK cells are critical innate effectors whose antitumor functions are rooted in their developmental biology and functional specialization. This section reviews their ontogeny, spatial distribution, and subset classification, to provide a framework for decoding their complex behaviors within the TME.

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Immune localization and lineage signatures

NK cells were first identified in 1975 as a distinct lymphocyte population with innate cytotoxic capabilities[9]. Despite lacking T-cell receptor (TCR) and CD3 expression, and developing outside the classical T-cell lineage, NK cells form a functionally integrated network with T cells and natural killer T (NKT) cells. Phenotypically defined as $CD56^{+}CD16^{+}CD3^{-}$, NK cells act as rapid innate responders that eliminate abnormal cells *via* "missing-self" recognition without prior antigen sensitization[10].

In contrast, T cells, the central mediators of adaptive immunity, are $CD3^{+}TCR^{+}$ and require antigen presentation *via* major histocompatibility complex (MHC) molecules for activation. $CD8^{+}$ cytotoxic T lymphocytes (CTLs) mediate precise target cell killing, whereas $CD4^{+}$ helper T cells orchestrate immune responses and establish immunological memory[11].

Bridging innate and adaptive immunity, NKT cells uniquely co-express T-cell markers (CD3 and TCR) and NK-cell markers such as CD56. Their restricted TCR repertoire recognizes lipid antigens presented by CD1d, thereby enabling rapid cytokine release that supports antitumor, antimicrobial, and immunoregulatory functions[12]. The differences and synergies among these lymphocytes in antigen recognition, activation requirements, and effector functions highlight the complexity of the immune network. The distinct role of NK cells is closely tied to their unique developmental pathway and spatial distribution.

Spatial ontogeny of NK cells

NK cell heterogeneity arises from their complex ontogeny and spatial origins. Conventionally, NK cells develop from bone marrow common lymphoid progenitors (CLPs) and undergo a tightly regulated multistage differentiation process culminating in mature effector cells and characterized by stage-specific marker expression (**Table 1**)[13]. This development depends on key cytokines and transcription factors, including IL-15[14], nuclear factor interleukin-3-regulated protein (NFIL3), and

Table 1 Summary of the expression and functional significance of key markers defining human NK cell development

Key marker	Primary stage*	Functional significance
ID proteins	Early development (CLP)	• HLH transcriptional regulators that antagonize E-proteins at the CLP stage • Inhibits commitment to the B- and T-cell lineages • Directs progenitors toward the innate lymphoid/NK cell pathway
CD122	From NKP through iNK to mature stages	• Critical subunit for IL-2/IL-15 signaling • Supports survival, proliferation, and maturation from the NKP stage onward
CD56	• $CD56^{bright}$: early mature • $CD56^{dim}$: terminally mature	• Definitive surface marker for human NK cells • $CD56^{bright}$ cells are potent cytokine producers • $CD56^{dim}$ cells are mature cytotoxic effectors
NKG2D	From iNK onward; sustained in all mature NK cells	• Potent activating receptor expressed from iNK to mature stages • Recognizes stress ligands (e.g., MICA or ULBP) on abnormal cells • Triggers direct cytotoxicity for anti-tumor/viral responses
KIR	Mature stages	• Central to NK cell "education" and establishment of self-tolerance • Inhibitory KIRs prevent attack on healthy cells • Activating KIRs trigger killing after loss of MHC class I
NKG2A	Mature stages	• Inhibitory receptor that forms a CD94 heterodimer • Recognizes the non-classical MHC-I molecule HLA-E • Dampens excessive immune activation and fine-tunes immune responses
NKG2C	Mature stages	• Activating receptor that forms a CD94 heterodimer • Recognizes HLA-E with peptide requirements distinct from NKG2A • Drives expansion of adaptive NK cells
CD16	Terminally mature	• Low-affinity FcγR expressed on mature $CD56^{dim}$ NK cells • Mediates ADCC • Hallmark of terminal maturation and cytotoxic competence

*See **Figure 1A** for the developmental stages. ADCC, antibody-dependent cellular cytotoxicity; CLP, common lymphoid progenitor; FcγR, Fc gamma receptor; HLH, helix-loop-helix; HLA-E, human leukocyte antigen-E; ID proteins, inhibitor of DNA-binding proteins/inhibitor of differentiation proteins; iNK, immature natural killer cell; KIRs, killer-cell immunoglobulin-like receptors; MHC, major histocompatibility complex; MICA, MHC class I polypeptide-related sequence A; NKG2A/C/D, natural killer group 2, member A/C/D; NKP, natural killer progenitor; ULBP, UL16-binding protein.

Eomesodermin (EOMES)[15,16]. In mouse models, maturation follows a defined sequence from $CD27^{+}CD11b^{-}$, through $CD27^{+}CD11b^{+}$, to terminally differentiated $CD27^{-}CD11b^{+}$ cells representing an effector pool with elevated inhibitory receptors such as killer cell lectin-like receptor G1[17,18]. Human NK cell development parallels this trajectory, progressing from $CD34^{+}$ progenitors that gradually downregulate CD34 and upregulate CD56[19]. Immature cells express early activation receptors such as natural killer group 2, member D (NKG2D), whereas inhibitory/activating receptors such as killer-cell immunoglobulin-like receptors (KIRs) and natural killer group 2, member A/C (NKG2A/C) remain minimal or undetectable[20]. Mature human NK cells ultimately differentiate into major subsets defined by CD56 and CD16 expression, thus forming the basis for their functional specialization (**Figure 1**)[4].

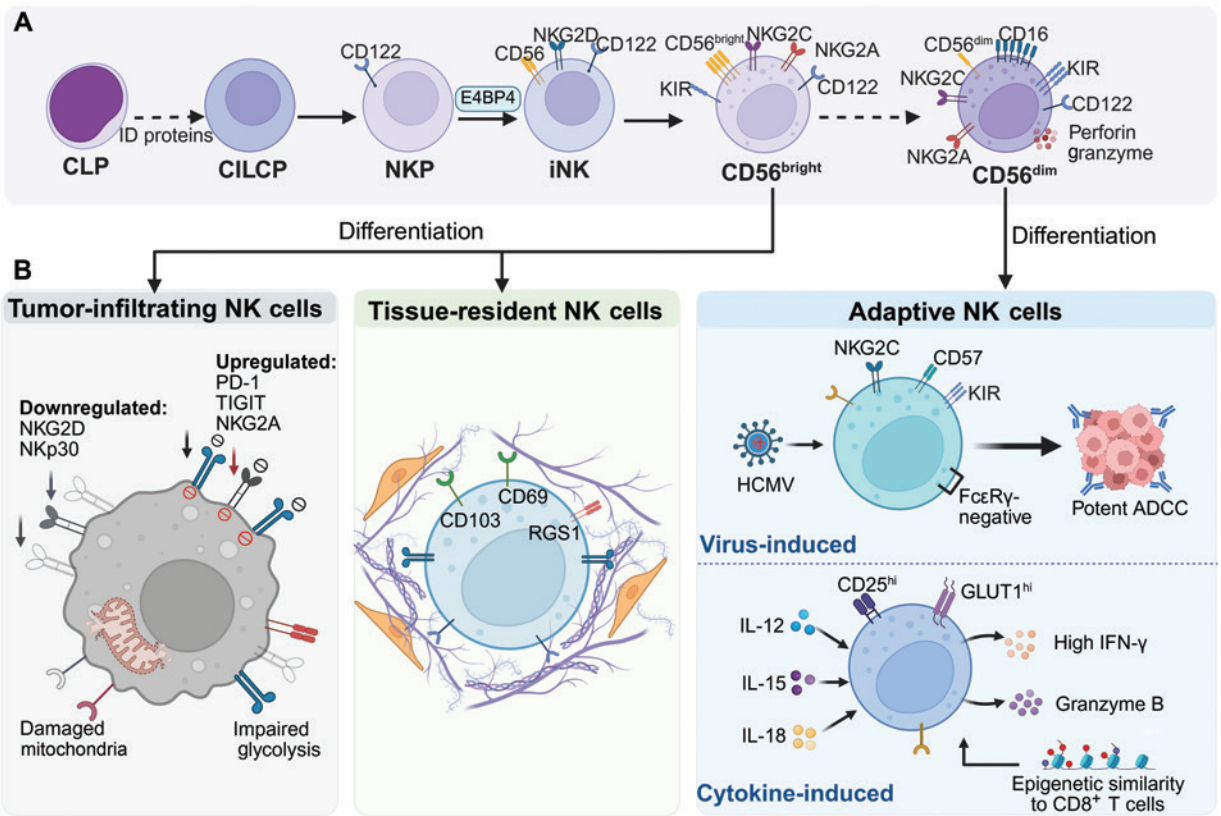


Figure 1 Developmental trajectories and functional subset diversification of NK cells. This schematic illustrates NK cell ontogeny from CLPs to mature subsets, as well as their subsequent tissue-specific diversification. A. NK cell developmental differentiation. Derived from CLP, NK cells progress through a sequential series of differentiation stages and mature into functionally distinct subsets: $CD56^{bright}$ and $CD56^{dim}$ NK cells. Key transcription factors and changes in cell surface markers across differentiation stages are shown. The functional significance of each marker is summarized in **Table 1**. B. Three novel functional subsets of NK cells formed in specific microenvironments, and their primary characteristics. Left: Tumor-infiltrating NK (TiNK) cells originate from $CD56^{bright}$ NK cells and are characterized by upregulation of inhibitory receptors (such as PD-1, TIGIT, and NKG2A), downregulation of activating receptors (such as NKG2D and NKp30), and impaired metabolic functions. Middle: Tissue-resident NK (TrNK) cells also derive from $CD56^{bright}$ NK cells and reside in particular tissues and express CD69/CD103 with tissue-specific and dual functionality. Right: Adaptive NK cells originate from $CD56^{dim}$ NK cells and can be further divided into virus-induced types (triggered by HCMV infection, mediating potent ADCC) and cytokine-induced types (triggered by cytokines such as IL-12/15/18, demonstrating high-effector functions and unique epigenetic features). ADCC, antibody-dependent cellular cytotoxicity; CILCP, common innate-like cell progenitor; CLP, common lymphoid progenitor; E4BP4, E4-binding protein 4; FcεRγ, Fc epsilon receptor I gamma chain; $GLUT1^{hi}$, high expression of glucose transporter 1; HCMV, human cytomegalovirus; ID proteins, inhibitor of DNA-binding proteins/inhibitor of differentiation proteins; IFN-γ, interferon-gamma; IL-12/15/18, interleukin-12/15/18; iNK, immature natural killer cell; KIR, killer-cell immunoglobulin-like receptor; NKG2A/C/D, natural killer group 2, member A/C/D; NKP, natural killer progenitor; NKp30, natural killer p30-related protein; PD-1, programmed cell death protein 1; RGS1, regulator of G-protein signaling 1; TIGIT, T-cell immunoreceptor with Ig and ITIM domains. The scientific illustrations were generated in BioRender (https://BioRender.com).

However, recent studies have expanded this paradigm and revealed alternative developmental pathways in non-lymphoid peripheral tissues. Less differentiated CD56^{bright} NK cells can be recruited into tissues *via* chemotactic signals, locally differentiate into TrNK cells under microenvironmental influences, and acquire specialized functions. Moreover, tissue-committed precursor cells have been suggested to contribute to TrNK populations in various organs[21]. Most human organs bear NK cells expressing the residency markers CD69, CD103, and CD49a, which promote tissue retention and position-specific adaptation[22]. These TrNK cells play crucial roles in local homeostasis and immune surveillance.

In summary, NK cell development involves diverse origins and differentiation pathways. Elucidating the regulatory mechanisms underlying their heterogeneity and spatial organization is essential for understanding their roles in homeostasis and disease.

Trajectories of functional subsets

The established dichotomy classifies mature human NK cells into two functionally distinct populations, according to peripheral blood studies. The CD56^{bright}CD16^{dim} subset (approximately 10%) demonstrates potent immunoregulatory functions and produces substantial cytokines such as IFN-γ while exhibiting relatively weak direct cytotoxicity. In contrast, the CD56^{dim}CD16^{bright} subset constitutes the majority (approximately 90%) and is the primary cytotoxic effector population, characterized by high expression of cytotoxic receptors (KIRs and NKG2A/C) and effector molecules (perforin and granzymes) (**Figure 1**)[23].

Although this classification effectively describes circulating NK cell functions, its main limitation emerges in the context of the TME[24]. The highly heterogeneous and immunosuppressive TME substantially remodels NK cell phenotypes and functions through local signals; therefore, the conventional classification cannot capture the dynamic plasticity and functional diversity of NK cells within tissue contexts.

This limitation has driven a paradigm shift toward context-dependent classification. Beyond recruiting circulating conventional NK (cNK) cells, the TME reprograms TrNK cells and endows adaptive NK cell subsets with memory-like features, and gives rise to distinct populations such as exhausted TiNK cells[5], organ-specialized TrNK cells[6], and adaptive NK cells induced by cytomegalovirus (CMV) infection[7] or cytokine pre-activation[8].

Therefore, understanding NK cells in the TME requires moving beyond the CD56/CD16 dichotomy toward a new paradigm centered on tissue localization, microenvironmental signals, and functional states. This refined perspective is essential for elucidating their roles in tumor immunity and developing effective therapeutic approaches that account for their contextual diversity.

Novel NK cell subsets in the TME: definitions and functional characteristics

In the complex TME, NK cells display functional diversity that extends beyond conventional classifications. This section outlines the defining characteristics of these newly identified NK cell subsets.

TiNK cells

TiNK cells are defined as NK cells recruited from peripheral blood into the tumor parenchyma[25]. Their recruitment is mediated primarily by the C-X-C motif chemokine ligand 9/10/11-C-X-C motif chemokine receptor 3 (CXCL9/10/11-CXCR3) axis, which preferentially recruits the cytokine-productive CD56^{bright} subset[26]. In contrast to those in the peripheral blood, where CD56^{dim} cells dominate, TiNK populations in solid tumors, such as melanoma and breast cancer, are often enriched in CD56^{bright} cells and typically express the early activation marker CD69 (**Figure 1**, **Table 2**)[27].

However, after entry into the TME, TiNK cells frequently become dysfunctional because of immunosuppressive signals. This state is characterized by downregulated activating receptors, such as NKG2D and NK cell activating receptor 30 (NKp30); upregulated inhibitory receptors, including programmed cell death protein 1 (PD-1), T cell immunoreceptor with Ig and ITIM domains (TIGIT), NKG2A; impaired IFN-γ production and diminished cytotoxicity[5]. Metabolically, TiNK cells exhibit impaired glycolysis and dysfunctional mitochondrial respiration, in alignment with their suppressed function (**Figure 1**, **Table 2**)[28].

Notably, TiNK cell abundance has substantial clinical relevance. Increased TiNK cell infiltration generally correlates with prolonged overall survival in patients with cancers such as gastric cancer (GC), colorectal cancer (CRC), and lung cancer (LC) (**Table 2**)[29]. Moreover, the combination of high heat shock protein 70 (Hsp70) expression and low TiNK cell number demonstrates the strongest negative predictive value for poor outcomes in patients with head and neck squamous cell carcinoma (HNSCC) after surgery and chemoradiotherapy[30]. This specific combination is a promising prognostic biomarker, thus underscoring the critical clinical importance of TiNK cells.

TrNK cells

Recent studies have identified TrNK cells as a distinct population that resides in specific organs rather than circulating in the blood[31]. Their developmental origins are not fully clarified; they may arise from local precursors or from circulating NK cells that have homed to tissues. TrNK cells are defined

Table 2 Classification and characteristics of NK cell functional subsets

	TiNK cells	TrNK cells	CMV-NK cells	CIML-NK cells
Core definition	NK cells recruited from peripheral blood into the tumor parenchyma	Resident NK subset that settles in specific tissues and does not recirculate	Adaptive-like NK subset induced by specific pathogens (e.g., CMV)	CIML-NK subset generated *via* cytokine pre-activation (e.g., IL-12/15/18)
Key identifiers	• $CD56^{bright}CD69^{+}$ • High PD-1, TIGIT, and NKG2A	• Constitutive CD69 and CD103 • Tissue-specific phenotype	• $NKG2C^{+}NKG2A^{-}KIR^{+}CD57^{+}$ • Frequent FcεRγ or SYK deficiency	• High CD25, CD94, and NKG2A • Upregulated NKG2D and NKp46
Functional status	• Functional exhaustion • Impaired cytotoxicity and IFN-γ production • Metabolic dysregulation	• Anti-tumor or pro-tumor • Key modulator of tissue-immune homeostasis	• Enhanced, sustained functionality • Potent antigen-specific recall response and ADCC	• Hyper-responsive after restimulation with cytokines (e.g., IL-12, IL-15, IL-18) restimulation • Enhanced cytotoxicity and cytokine production • Favorable *in vivo* persistence
Clinical significance	Prognostic biomarker: intratumoral abundance correlates with patient outcomes	Potential therapeutic target	Mediates long-term pathogen-specific surveillance	Ideal "off-the-shelf" candidate for adoptive cell therapy

ADCC, antibody-dependent cellular cytotoxicity; CIML-NK cell, cytokine-induced memory-like natural killer cell; CMV-NK cell, cytomegalovirus-induced natural killer cell; FcεRγ, Fc epsilon receptor I gamma chain; IFN-γ, interferon-gamma; KIR, killer-cell immunoglobulin-like receptor; NKG2A, natural killer group 2, member A; NKG2C, natural killer group 2, member C; NKG2D, natural killer group 2, member D; NKp46, natural killer p46-related protein; PD-1, programmed cell death protein 1; SYK, spleen-associated tyrosine kinase; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; TiNK cell, tumor-infiltrating natural killer cell; TrNK cell, tissue-resident natural killer cell.

by the expression of residency markers, such as CD69 and/or CD103[32], which mediate tissue retention partly through CD69-induced downregulation of the sphingosine-1-phosphate receptor 1 (S1PR1)[33]. Pan-cancer analyses have further identified regulator of G protein signaling 1 (RGS1) as a novel marker that is highly expressed in tumor-associated $CD56^{bright}$ NK cells but absent in their circulating counterparts (**Figure 1**, **Table 2**)[24].

TrNK cells exhibit considerable tissue specificity. Their development and transcriptional programming differ by location. For example, liver TrNK cells depend on NFIL3 but not T-box expressed in T cells, whereas uterine TrNK cells rely on EOMES[32,34]. This specialization enables functional adaptation to local microenvironments. Within the TME, TrNK cells display functional plasticity: they can inhibit tumor progression in LC and ovarian cancer (OC) models by secreting cytotoxic molecules[35,36], yet they may also acquire pro-tumorigenic potential and potentially differentiate into group 1 innate lymphoid cell (ILC1)-like cells (**Table 2**)[37,38]. However, given that these findings were derived largely from mouse studies, their clinical relevance in human TME requires further validation.

Notably, this functional plasticity extends beyond TrNK cells and encompasses other innate lymphocytes, particularly NKT cells, which exhibit dual regulatory ability within the TME. Type I NKT cells recognize CD1d-presented lipid antigens and rapidly secrete IFN-γ, thereby enhancing adaptive antitumor immunity. In contrast, type II NKT cells or exhausted invariant NKT cells may promote pro-tumorigenic outcomes through mechanisms such as IL-13-mediated recruitment of myeloid-derived suppressor cells (MDSCs). The functional outcome is shaped by the dynamic balance among NKT subsets and the local signaling milieu[39].

Among these populations, TrNK cells have emerged as a critical focus, because of their prominent tissue-homing and microenvironment-reprogramming ability. Notably, the TrNK signature score serves as an independent and valuable prognostic classifier. High TrNK scores correlate with enhanced immune infiltration, greater responses to immunotherapy, and more favorable patient outcomes. (**Table 2**)[40]. These findings underscore TrNK cells as critical regulators of the tumor immune microenvironment and a key focus for understanding NK cell mediated antitumor immunity.

Adaptive NK cells

Adaptive NK cells, by exhibiting antigen-specific responses and features of immunological memory akin to those of T cells, challenge the traditional paradigm of NK cells as solely innate immune effectors.

Viral antigen-induced adaptive NK cells

The response to human cytomegalovirus (HCMV) infection is a well-established example. HCMV infection drives

the development of a distinct adaptive NK cell population characterized by an NKG2C$^+$NKG2A$^-$KIR$^+$CD57$^+$ phenotype[41,42]. These cells frequently lack intracellular signaling proteins such as Fc epsilon receptor gamma chain (FcεRγ) and spleen tyrosine kinase (SYK)[43]. The NKG2C receptor recognizes the non-classical MHC class I molecule human leukocyte antigen-E (HLA-E), which presents HCMV-derived UL40 peptides, thereby activating and promoting clonal expansion of these adaptive NK cells[44]. Compared with cNK cells, this subset frequently expresses a limited KIR repertoire, thereby enhancing sensitivity to "missing-self" signals[45]. Moreover, they express relatively low levels of inhibitory ITIM-containing receptors, which confers intrinsic resistance to MDSC-mediated suppression and enhances antibody-dependent cellular cytotoxicity (ADCC) (**Figure 1**, **Table 2**)[46]. Collectively, these properties indicate that adaptive NK cells can maintain effector function within the TME, even in the presence of immunosuppressive cells[47].

Cytokine-induced memory-like NK cells

NK cells can integrate and respond to cytokine signals as well as antigen-specific stimuli such as those elicited during CMV infection, highlighting their ability to dynamically adapt to environmental cues. Pre-activation of NK cells with cytokines such as IL-12, IL-15, and IL-18 drives their differentiation into memory-like NK (MLNK) cells. This process entails a series of phenotypic transitions associated with the memory-like state, including the upregulation of nutrient transporters—[CD71, CD98, glucose transporter 1/3 (GLUT1/3)], alongside activation receptors [NKG2D, NKp30, natural killer cell p44 (NKp44)-related protein], as well as the downregulation of inhibitory receptors, such as KIRs and the transforming growth factor-beta (TGF-β) receptor[48,49].

Epigenetic profiling has further revealed that MLNK cells share DNA methylation patterns with memory CD8$^+$ T cells, thus supporting their classification as an adaptive subset[50]. These cells exhibit elevated expression of CD25, CD94, NKG2A, CD69, and NKp46[51,52]. Functionally, they demonstrate enhanced IFN-γ and tumor necrosis factor (TNF) production, elevated granzyme B (GZMB) and perforin expression, and superior cytotoxicity against tumor targets such as K562 cells. Moreover, they can persist *in vivo* for months and maintain potent antitumor activity even within the TME (**Figure 1**, **Table 2**)[53-55].

Mechanisms of TME-regulated heterogeneity in NK cell function

NK cells' considerable functional heterogeneity within the TME arises from subset-specific responses to local microenvironmental signals. This section systematically delineates the regulatory networks governing TME-mediated NK cell modulation, focusing on four key aspects.

Heterogeneous expression of immune checkpoint molecules

Immune checkpoint molecules critically regulate NK cell function. Within the TME, TiNK cells typically show high expression of inhibitory receptors such as PD-1, TIGIT, and NKG2A. Elevated PD-1 expression correlates with impaired migratory and cytotoxic functions[56]. This phenotype is driven by persistent antigen exposure within the TME and is further stabilized by epigenetic modifications such as DNA methylation. However, because this finding was based on mouse models, and mouse PD-1 function is distinctly weaker than that in humans, its clinical translational value is limited. Furthermore, studies in patients with cervical cancer have revealed that TiNK cells aberrantly upregulate co-stimulatory receptors, including inducible T-cell costimulator (ICOS), tumor necrosis factor receptor superfamily member 9 (4-1BB) and tumor necrosis factor receptor superfamily member 4 (OX-40). Paradoxically, this abnormal signaling triggers dysregulated Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway activation and mitochondrial dysfunction, which ultimately leads to loss of cytotoxic activity (**Figure 2**)[57].

In contrast, TrNK cells display context-dependent checkpoint expression. In the ascites of patients with OC, they express the inhibitory receptor NKG2A while maintaining substantial cytotoxic ability; this plasticity is linked to HLA-E levels and the local IL-15/IL-12 balance, and consequently enables effective tumor cell elimination[36]. However, in hepatocellular carcinoma (HCC), Kupffer cell contact and TGF-β1 secretion drive TrNK cells to specifically upregulate TIGIT and PD-1, thereby promoting tumor progression (**Figure 2**)[58].

The relatively focused and locally reprogrammable regulatory paradigm of TrNK cells sharply diverges from the exhaustion program of T cells in the TME. Although they cooperate in achieving antitumor immunity, TrNK cells and T cells fundamentally differ in function and regulation. Functionally, TrNK cells act as rapid innate responders by executing "missing-self" killing without prior antigen sensitization, whereas T cells require antigen-specific activation to differentiate into tissue-resident memory CTLs (e.g., CD39$^+$CD103$^+$). Even under chronic stimulation, CTLs retain IFN-γ and GZMB secretion, thereby sustaining long-term surveillance and enabling an NK-initiated, CTL-consolidated cooperative response[59]. Mechanistically, the rapid responsiveness of TrNK cells is preserved through a balanced interplay of checkpoint signaling axes, such as the NKG2A-HLA-E inhibitory axis and the CD226/TIGIT activating axis. In contrast, persistently stimulated CD8$^+$ T cells, particularly the CD39$^+$ CTL subset, simultaneously upregulate multiple inhibitory receptors (e.g., PD-1, TIGIT, and NKG2A), downregulate CD28, and face regulatory T cell (Treg)-mediated metabolic competition, thus driving a more complex exhaustion state[59]. This mechanistic divergence underscores the need for selectively targeting context-specific checkpoint axes across distinct lymphocyte populations.

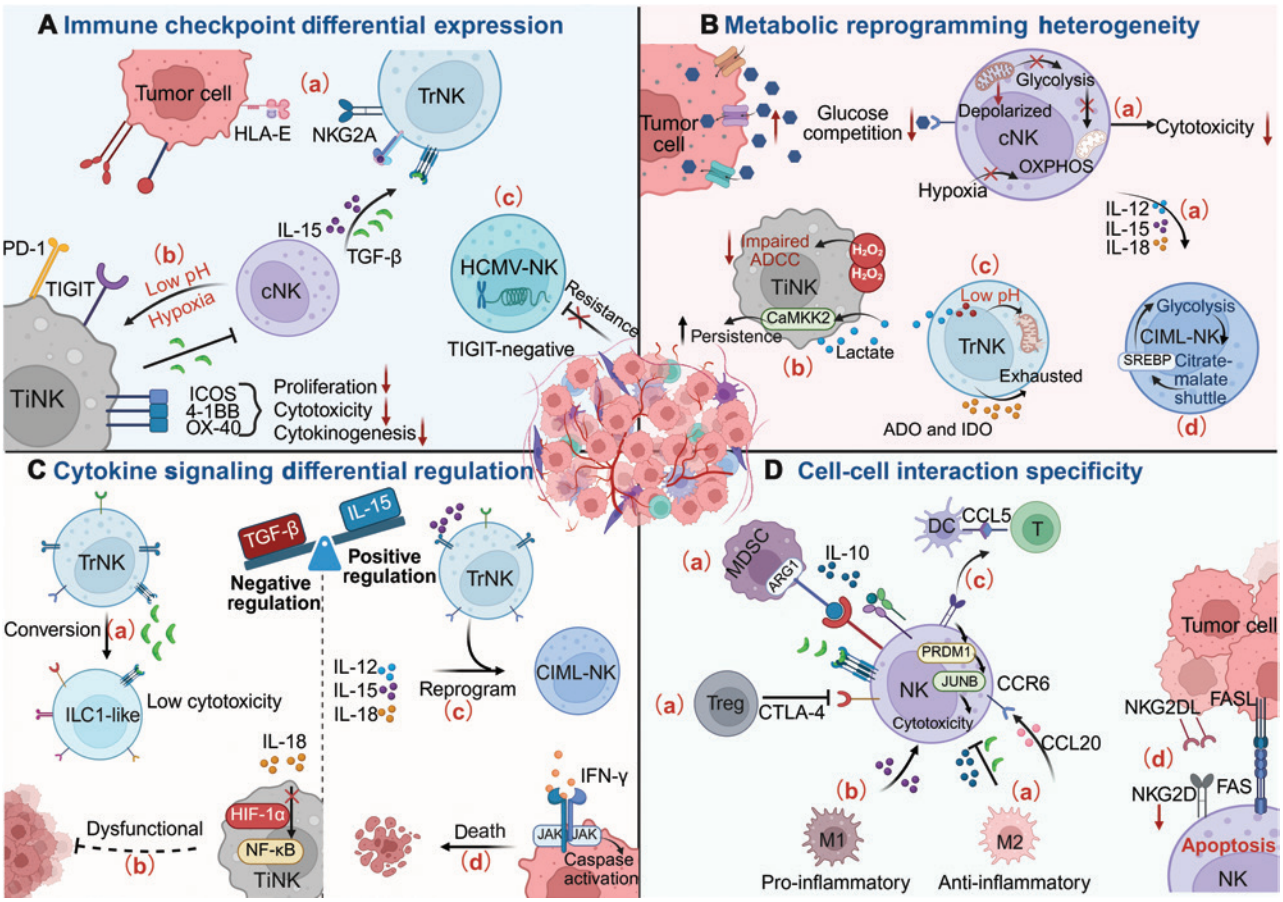


Figure 2 Mechanisms of TME-regulated heterogeneity in NK cell function. This schematic delineates how complex factors within the TME differentially regulate the functional fates of NK cell subsets. A. Differential expression of immune checkpoints. (a) Inhibitory checkpoint in TrNK: TrNK cells highly express NKG2A and interact with HLA-E on tumor cells. (b) Exhaustion receptor upregulation: Under inhibitory signaling, cNK cells differentiate into TiNK cells, which upregulate PD-1, TIGIT, and co-stimulatory receptors (ICOS and 4-1BB). (c) TIGIT-deficient resistance: HCMV-NK cells lack TIGIT and resist suppression. B. Heterogeneity in metabolic reprogramming. (a) Metabolic impairment and rescue: Glucose competition and hypoxia impair cNK cell glycolysis/OXPHOS, whereas IL-12, IL-15, and IL-18 promote their differentiation into adaptive NK cells. (b) Oxidative stress and adaptation: H_2O_2 in the TME impairs NK cell ADCC, whereas adaptive survival is mediated partially through the lactate–CaMKK2 axis. (c) Metabolite-driven dysfunction: metabolic waste, such as lactate and adenosine, drives TrNK cell exhaustion. (d) Shuttle pathway regulation: CIML-NK cells demonstrate metabolic plasticity by regulating the citrate-malate shuttle *via* SREBP. C. Differential cytokine regulation. Negative regulation: (a) TGF-β-induced conversion: TGF-β drives TrNK to ILC1-like conversion, thus impairing tumor surveillance. (b) HIF-1α-mediated inhibition: HIF-1α inhibits IL-18/NF-κB in TiNK cells. Positive regulation: (c) Cytokine-induced memory programming: IL-12/IL-15/IL-18 reprograms TrNK into ML-NK cells. (d) IFN-γ-enhanced apoptosis: IFN-γ enhances caspase-mediated apoptosis *via* JAK/STAT1. D. Specific intercellular interactions. (a) Suppressive myeloid network: MDSCs, Tregs, and M2-TAMs suppress NK cells *via* TGF-β, IL-10, ARG1, and CCL20-CCR6. (b) M1-mediated activation: M1-macrophages enhance NK activity *via* IL-15. (c) DC-T cell crosstalk: DC-T cell crosstalk *via* CCL5 further modulates NK function. (d) Ligand shedding for immune evasion: Tumor cells evade NK recognition by shedding NKG2D ligands. 4-1BB, tumor necrosis factor receptor superfamily member 9; ADCC, antibody-dependent cell-mediated cytotoxicity; ADO, adenosine; ARG1, arginase-1; CaMKK2, calcium/calmodulin-dependent protein kinase kinase 2; CCL5, C–C motif chemokine ligand 5; CCL20, C–C motif chemokine ligand 20; CCR6, C–C motif chemokine receptor 6; cNK, conventional natural killer cell; CIML-NK, cytokine-induced memory-like NK cells; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DC, dendritic cell; FAS, Fas cell surface death receptor; FASL, Fas ligand; HCMV-NK, human cytomegalovirus-induced NK cells; HIF-1α, hypoxia-inducible factor 1-alpha; HLA-E, human leukocyte antigen E; ICOS, inducible T-cell co-stimulator; IDO, indoleamine; IFN-γ, interferon-gamma; IL-15, interleukin-15; ILC1, type 1 innate lymphoid cell; JAK, Janus kinase; JUNB, JunB proto-oncogene, AP-1 transcription factor subunit; M1, classically activated macrophage; M2, alternatively activated macrophage; MDSC, myeloid-derived suppressor cell; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NKG2A,

natural killer group 2, member A; NKG2D, natural killer group 2, member D; NKG2DL, NKG2D ligands; OX-40, tumor necrosis factor receptor superfamily member 4; OXPHOS, oxidative phosphorylation; PD-1, programmed cell death protein 1; PRDM1, PR domain zinc finger protein 1 (Blimp-1); SREBP, sterol regulatory element-binding protein; TGF-β, transforming growth factor-beta; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; TiNK, tumor-infiltrating natural killer cell; Treg, regulatory T cell; TrNK, tissue-resident natural killer cell.

Notably, adaptive NK cells, particularly the HCMV-induced subset, display a unique checkpoint profile. These cells inherently lack expression of TIGIT, which confers intrinsic resistance to immunosuppressive factors within the TME (**Figure 2**)[46]. This functional persistence results from virus-induced epigenetic reprogramming characterized by modified DNA methylation patterns that facilitate chromatin closure at the TIGIT locus, alongside sustained expression of infection-specific transcription factors such as members of the interferon regulatory factor family. Concurrent metabolic remodeling, particularly enhanced oxidative phosphorylation (OXPHOS), provides the bioenergetic foundation for their long-term functional activity. Collectively, these findings highlight that substantial heterogeneity in checkpoint expression across NK cell subsets directly dictates their divergent functional states and responsiveness in the TME.

Heterogeneous responses to metabolic reprogramming

Metabolic stress in the TME differentially influences the functional states of various NK cell subsets. cNK cells face considerable metabolic challenges in maintaining their function. Competition for glucose with highly metabolic tumor cells deprives cNK cells of the fuel required for proliferation, activation, cytokine production, and cytotoxicity[60]. Concurrently, cNK cells show suppressed glycolytic and OXPHOS pathways, and consequently diminished expression of IFN-γ and Fas ligand (FasL), which ultimately impaired cytotoxic function. This mechanism substantially contributes to the progression of HCC, CRC, GC, and lung squamous cell carcinoma[61,62]. Notably, obesity impairs mechanistic target of rapamycin complex 1 signaling and further constrains the anti-tumor response of cNK cells. Compared with those from healthy donors, cNK cells from obese individuals exhibit blunted metabolic response to cytokine stimulation, which might contribute to obesity-associated cancer risk[63]. However, findings from diet-induced obesity mouse models might have limited clinical translatability, given their pathophysiological differences from spontaneous obesity in humans. Furthermore, hypoxic conditions in the TME activate the protein tyrosine phosphatase Src homology region 2 domain-containing phosphatase-1 (SHP-1), thereby suppressing phosphorylation of extracellular signal-regulated kinase (ERK) and STAT3 signaling pathway proteins, and ultimately impairing NK cell activation and cytotoxic ability (**Figure 2**)[64].

TiNK cells exhibit unique adaptive features in their metabolic profiles. In HCC, upregulated metabolic pathway genes in TiNK cells are closely associated with functional impairment, including diminished degranulation, autophagy, and glucose consumption[28]. In GC and esophageal cancer models, TME-derived hydrogen peroxide (H_2O_2) impairs ADCC and decreases the infiltration of $CD56^{dim}$ NK cells[65]. However, TiNK cells can also adapt metabolically: lactate promotes their survival and proliferation by modulating Ca^{2+}/calmodulin-dependent protein kinase kinase 2 (CaMKK2) expression, thereby partially mitigating the suppressive effects of a lactate-rich TME (**Figure 2**)[66]. However, these findings were based on mouse models with artificially elevated lactate loads and homogeneous genetic backgrounds, which do not fully reflect human TME complexity. Therefore, the therapeutic potential of targeting CaMKK2 requires careful evaluation for safety and efficacy in clinical translation.

TrNK cells show heightened sensitivity to the local metabolic environment. Tumor-derived lysophosphatidylserine (LysoPS) inhibits the antitumor activity of ILC1s through the G protein-coupled receptor 34 (GPR34)[67], a pathway validated in both mouse models and human samples. In colorectal cancer liver metastases, lactate accumulation lowers intracellular pH in TrNK cells, and consequently causes mitochondrial dysfunction and apoptosis[68]. Moreover, TME-associated mediators such as adenosine and indoleamine contribute to the functional exhaustion of TrNK cells and decrease secretion of type-1 cytokines (**Figure 2**)[69]. This metabolic vulnerability renders TrNK cells particularly susceptible to functional suppression in metabolically stressed TME. Although mouse models have provided valuable mechanistic insights, species-specific differences in immunology and metabolism limit the direct clinical translation of these findings.

In contrast, cytokine-induced memory-like NK (CIML-NK) cells demonstrate superior metabolic fitness. This subset exhibits enhanced glycolytic ability and remodeled fatty acid metabolism under hypoxia[55]. The enhancement of citrate-malate shuttle, which is regulated by the transcription factor sterol regulatory element-binding proteins (SREBPs), is essential for sustaining the antitumor activity of CIML-NK cells after adoptive transfer (**Figure 2**)[70]. This metabolic plasticity allows CIML-NK cells to maintain durable function within the nutrient-deprived, immunosuppressive TME. Although this mechanism has been confirmed in human NK cells and has translational promise, it awaits validation in clinical trials.

Overall, NK cell subsets exhibit substantial heterogeneity in their response to TME metabolic stress, and their metabolic adaptability directly dictates their functional state and fate.

Differential regulation of cytokine signaling networks

The functional state of NK cells within the TME is finely tuned by a complex cytokine network, which exerts precise positive and negative regulation across distinct subsets.

Immunosuppressive cytokines play a central role in negative regulation. TGF-β is a well-characterized, potent inhibitor that directly suppresses NK cell proliferation and cytotoxicity[71]. Notably, this inhibition exhibits subset specificity; for example, TGF-β can induce conversion of TrNK cells into pro-tumor ILC1-like populations with impaired tumor surveillance ability[72]. Although mouse models have elucidated key TGF-β-mediated pathways, the species-specific functional dynamics requires further validation in human primary cells or clinical specimens. Notably, extensive crosstalk occurs between physicochemical factors and the cytokine signaling network within the TME. Single-cell RNA sequencing studies have shown that, in TiNK cells, hypoxia-inducible factor-1α (HIF-1α) suppresses IL-18-driven nuclear factor-κB (NF-κB) signaling and consequently impairs their anti-tumor activity (**Figure 2**)[73]. This finding has revealed a mechanism through which the hypoxic microenvironment regulates NK cell function through interference with cytokine signaling.

In contrast, the IL-15 signaling axis plays a critical positive role in regulating NK cell function. In clear cell renal cell carcinoma, the presence of TrNK cells correlates with IL-15 levels and is associated with better patient prognosis[74]. Meanwhile, IFN-γ is a key NK cell effector whose production reflects activation status. For example, MLNK cells exhibit a substantial increase in IFN-γ and TNF-α production after antigen re-stimulation[75]. Mechanistically, IFN-γ activates the JAK/STAT1 signaling pathway, which in turn promotes caspase activity and directly induces tumor cell apoptosis (**Figure 2**)[76]. However, the potency of IFN-γ-mediated responses observed in mouse models might differ from that in humans, because of divergence in immunoregulatory networks. Clinical translation therefore will require careful evaluation across tumor types and microenvironmental contexts.

Preclinical studies have shown that optimized cytokine combinations (e.g., IL-12, IL-15, and IL-18) together with tailored stimulation protocols epigenetically reprogram NK cells, thus enhancing their expansion and antitumor function even in immunosuppressive settings. However, their therapeutic efficacy awaits validation in clinical trials (**Figure 2**)[54]. In summary, NK cell activity within the TME is finely regulated by a multilayered and subset-specific cytokine network that dynamically integrates with the physicochemical microenvironment.

Specific patterns of cell-cell interaction

The functional state of NK cells within the TME is precisely regulated by diverse stromal components through dynamic intercellular crosstalk.

In cNK cells, the transcriptional regulator PR domain zinc finger protein 1 (Prdm1) is a key functional modulator that governs cytotoxicity and metabolic homeostasis by influencing the *JunB* proto-oncogene, AP-1 transcription factor subunit (*JUNB*) signaling pathway, which in turn mediates crosstalk between cNK cells and macrophages[77]. Furthermore, the functional potency of cNK cells correlates with their local density and is shaped by C–C motif chemokine ligand 5 (CCL5)-dependent interactions between dendritic cells and T cells (**Figure 2**)[78]. However, given the differences in immune interaction mechanisms between mouse and human TMEs, these findings should be validated in human systems.

Among immunosuppressive cell populations, MDSCs and Tregs inhibit NK cell function through both direct cell contact and soluble mediators. Emerging evidence indicates that MDSCs impair NK cell antitumor activity by secreting immunosuppressive cytokines such as IL-10 and TGF-β, as well as through the arginase 1 (ARG1)/L-arginine metabolic axis[79]. Additionally, MDSCs disrupt the cytotoxic ability of NK cells through close-contact interactions[80]. Similarly, Tregs suppress NK cell activation through cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)-mediated signaling, TGF-β secretion, and contact-dependent pathways (**Figure 2**)[81]. Notably, TiNK cell function is particularly sensitive to proximity-dependent modulation by MDSCs and Tregs, showing a strong inverse correlation with the abundance of these immunosuppressive cells[82].

Tumor-associated macrophages (TAMs) play a context-dependent role in regulating NK cell function. M1-polarized TAMs enhance NK cell survival and cytotoxicity *via* cytokines such as IL-15[83]. In contrast, M2-polarized TAMs suppress NK cell activity *via* the secretion of inhibitory factors, including TGF-β[84]. Notably, the heterogeneity and dynamics of macrophage polarization within the human TME create a complex regulatory network that poses challenges in clinical translation. In HCC, peritumoral M2 TAMs have been found to recruit liver-resident NK cells *via* the CCL20-C-C motif chemokine receptor 6 (CCR6) axis and subsequently impair their cytotoxicity through IL-10/TGF-β signaling (**Figure 2**)[85]. This mechanism illustrates how TAMs spatially coordinate both recruitment and pathway-specific suppression, thereby establishing a localized immunosuppressive niche.

In addition, direct interactions between tumor cells and NK cells critically regulate NK cell function. To evade immune surveillance, certain tumors downregulate the activating receptor NKG2D on NK cells by releasing its soluble ligands or packaging them into exosomes[86]. Additionally, tumor cells of CRC and HCC can induce NK cell apoptosis by expressing

FasL, which in turn engages the death receptor Fas (CD95) on NK cells and triggers intrinsic apoptosis (**Figure 2**)[87].

Dynamics of NK cell subsets: functional interconversion and cooperative regulation

Prior sections systematically characterized distinct NK cell subsets and their regulatory mechanisms within the TME. But these subsets function as a dynamic and interconnected network rather than in isolation. This section focuses on their functional interconversion and cooperative regulation.

Phenotypic plasticity of NK cell subsets

NK cells display considerable phenotypic plasticity within the TME, and undergo interconversion driven by specific microenvironmental cues. cNK cells, primarily the $CD56^{dim}$ subset, are a key precursor pool. Under signals such as TGF-β and IL-15, cNK cells upregulate tissue-resident markers such as CD69 and CD103, gradually adopt a TrNK–like phenotype, adapt their transcriptional profiles to tissue-specific demands, and shift from migratory to resident state (**Figure 2**)[34]. In contrast, under conditions of persistent antigen exposure, checkpoint upregulation, and inhibitory metabolites, cNK cells acquire an exhausted TiNK phenotype with diminished antitumor function (**Figure 2**)[88]. Notably, stimulation with exogenous cytokines such as IL-12, IL-15, and IL-18 reverses this suppression, by reprogramming exhausted TiNK or TrNK cells into adaptive NK cells with memory-like properties and restoring effector activity (**Figure 2**)[89]. This plasticity indicates that although the TME can drive NK cells toward exhaustion, it also offers a therapeutic window: targeted interventions might therefore reprogram these constrained subsets into potent, sustained antitumor effectors, thereby reshaping antitumor immunity.

Synergistic and antagonistic interplay among subsets

Within the TME, NK cell subsets collectively shape antitumor immunity through synergistic and antagonistic interactions. Functionally, they have complementary roles: tissue-resident TrNK cells act as first-line sentinels providing rapid local surveillance. After breach of this frontline or adequate antigen presentation, adaptive NK cells are recruited to mount a more potent and sustained attack[90]. This hierarchical response, transitioning from "standing forces" to "specialized effectors", illustrates the spatiotemporal cooperation between distinct subsets. In contrast, functional antagonism can arise. In an immunosuppressive TME, exhausted TiNK cells may secrete factors such as TGF-β that suppress neighboring TrNK or newly recruited cNK cells (**Figure 2**). Moreover, metabolic competition further modulates subset dynamics: metabolically fit adaptive NK cells outcompete constrained TiNK cells under nutrient scarcity and consequently exacerbate the latter's functional decline. In summary, NK cells form a plastic and dynamic network in the TME, wherein cooperative and competitive interactions collectively determine the overall strength of the antitumor response.

Targeting NK cell subsets: from immunotherapy strategies to clinical translation

Building on an enhanced understanding of TME-mediated regulation of NK cell function, along with systematic integration and dynamic analyses, researchers have developed targeted immunotherapies for distinct NK cell subsets. This section systematically reviews these strategies and evaluates their clinical translational potential.

Adoptive cell therapy strategies

cNK cell infusion

The infusion of cNK cells has demonstrated therapeutic potential in various hematological malignancies and solid tumors (**Figure 3**). Allogeneic NK cell therapy, which carries a low risk of graft-*vs.*-host disease, is a major focus of current research. Several clinical trials have been approved by the U.S. Food and Drug Administration, including a phase II trial investigating autologous cNK cells combined with gemcitabine and carboplatin for non-small-cell lung cancer (NSCLC)[91], and a phase II trial of umbilical cord blood-derived NK cells combined with chemotherapy for relapsed solid tumors[92]. In the treatment of hematological malignancies, infusion of haploidentical cNK cells has shown favorable safety and efficacy in patients with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)[93,94]. Notably, umbilical cord blood-derived NK cells are particularly promising, because of their strong proliferative ability and enhanced antitumor activity. A phase II clinical trial in relapsed/refractory multiple myeloma has achieved an objective response rate exceeding 50%, with no severe graft-*vs.*-host disease reported (**Table 3**)[95]. However, the clinical efficacy remains limited by poor *in vivo* persistence, rapid exhaustion in the hypoxic/adenosine-rich TME, and challenges in achieving effective dosing, which collectively restrict durable responses and broad applicability.

Engineered NK cells

Chimeric antigen receptor (CAR)-NK cell technology significantly enhances tumor-specific recognition and cytotoxicity by introducing engineered receptors that target tumor-associated

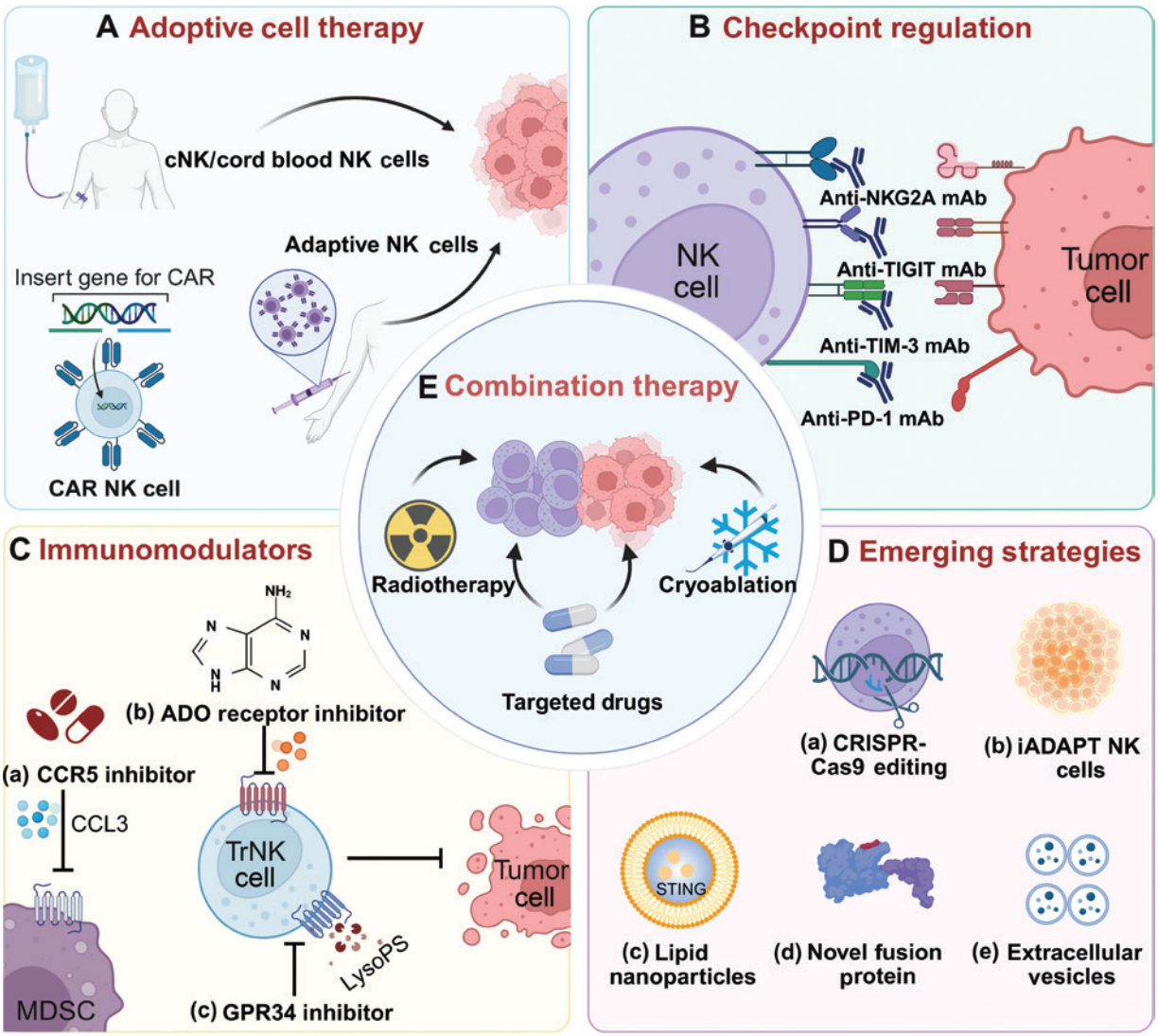


Figure 3 Five core approaches to NK cell-mediated tumor immunotherapy. A. Adoptive cell therapy: Infusion of conventional NK cells or cord blood-derived NK cells; Engineering NK cells into CAR-NK cells *via* genetic modification; expanding and reinfusing adaptive NK cells. B. Immune checkpoint regulation: monoclonal antibodies block inhibitory receptors on NK cells. C. Immunomodulators: (a) CCR5 inhibitors suppress the CCL3 and consequently decrease MDSC infiltration. (b) Adenosine receptor inhibitors reverse functional exhaustion in TrNK cells. (c) GPR34 inhibitors antagonize LysoPS and specifically activate TrNK cells. D. Emerging strategies: (a) CRISPR-Cas9 knockout of inhibitory genes. (b) Novel engineered cells including iADAPT NK cells. (c) Innovative delivery systems such as lipid nanoparticles loaded with STING agonists. (d) Engineered cytokines exemplified by IL-15 superagonist fusion proteins. (e) Cell-derived therapies, such as extracellular vesicles from cytotoxic MLNK cells. E. Combination therapy strategies: combination treatment with targeted drugs (such as ramucirumab or sorafenib) and local treatments (such as cryoablation and radiotherapy). ADO, adenosine; CAR, chimeric antigen receptor; CCR5, C–C chemokine receptor type 5; CCL3, C–C motif chemokine ligand 3; cNK, conventional natural killer cell; CRISPR-Cas9, clustered regularly interspaced short palindromic repeats-associated protein 9; GPR34, G protein-coupled receptor 34; iADAPT, induced pluripotent stem cell-derived armored dual-adjusted and precision-engineered; LysoPS, lysophosphatidylserine; mAb, monoclonal antibody; MDSC, myeloid-derived suppressor cell; NKG2A, natural killer group 2, member A; PD-1, programmed cell death protein 1; STING, stimulator of interferon genes; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; TrNK, tissue-resident natural killer cell.

antigens (**Figure 3**). Compared with CAR-T cells, CAR-NK cells exhibit a more favorable safety profile and lower toxicity. Moreover, compared with CAR-NKT cells, CAR-NK cells possess relative advantages in source accessibility and manufacturing feasibility, and therefore become a promising candidate for tumor immunotherapy.

Table 3 Clinical application prospects of NK cell subsets in cancer treatment

Cell subtype	Source	Tumor type	Clinical trial	Regimen	References
cNK cells	Autologous	NSCLC	NCT04872634 (phase I/IIa)	cNK cells combined with gemcitabine and carboplatin	91
	Umbilical cord blood	Relapsed or drug-resistant solid tumors	NCT03420963 (phase I)	cNK cells combined with chemotherapeutic agents	92
	Haploidentical	AML and ALL	NCT00799799 (phase I)	Myeloablative conditioning and haploidentical stem cell infusion	93,94
	Umbilical cord blood	MM	NCT01729091 (phase II)	Cord blood-derived NK cell infusion combined with chemotherapy and autologous stem cell transplantation	95
	Umbilical cord blood	Relapsed/refractory B-cell malignancies	NCT03056339 (phase I/II)	Infusion of CD19-targeted CAR-NK cells	96
	Healthy donors	MM	Preclinical	CRISPR-Cas9-based gene editing of the NKG2A gene in *ex vivo*-expanded NK cells	97
TiNK cells	Patients with cancer	NSCLC, UC	NCT04995523 (phase I/II), NCT05327530 (phase II)	Anti-TIGIT/anti-PD-1 bispecific antibody rilvegostomig	98
	Patients with cancer	HNSCC, NSCLC	NCT02643550 (phase II)	Monalizumab and cetuximab combination therapy	99,100
	Patients with cancer	HNSCC	NCT02325401 (phase I), NCT02083692 (early phase I)	Preoperative metformin treatment	101
TrNK cells	Healthy donors and patients with cancer	CRC and HCC	Preclinical	GPR34 inhibitors combined with anti-TIGIT antibodies	67
	Patients with cancer	PDAC	Preclinical	Radiotherapy combined with CCR5i/PD-1 inhibitors	102
Adaptive NK cells	CMV-seropositive healthy donors	AML	Preclinical	Infusion of *ex vivo*-expanded, terminally differentiated adaptive NK cells	103
	Healthy donors	Drug-resistant leukemia/lymphoma	Preclinical	MLNK cell differentiation combined with CAR engineering	104
	Healthy donors	Leukemia	Preclinical	Novel fusion protein scaffold 18/12/TxM	105
	Healthy donors	HCC	Preclinical	iRGD promotes deep tumor delivery of CIML-NK cells	106
	Healthy donors	OC	Preclinical	Armed CIML-NK cells with CARs targeting the mesothelin	107
	iPSC-derived	MM and AML	NCT04614636 (phase I)	IADAPT NK cells combined with daratumumab	108
	CMV-seropositive healthy donors	AML	NCT03081780 (phase I)	$NKG2C^+$ adaptive NK cell infusion combined with lymphodepleting chemotherapy and subcutaneous IL-2	109
	Allogenic	HCC	NCT02849015 (phase I/II)	Cryoablation combined with allogenic NK cells	110
	Haploidentical	AML	NCT01898793 (phase I)	Systemic IL-15 after chemotherapy and NK cell infusion	111

Table 3 Continued

Cell subtype	Source	Tumor type	Clinical trial	Regimen	References
	Haploidentical	HNC	NCT04290546 (phase I)	IL-15 super-agonist combined with CTLA-4 blockade	112
	Healthy donors	HCC	Preclinical	Sorafenib combined with MLNK cell immunochemotherapy	113
	NK-92MI cell line	HCC	Preclinical	Intravenous administration of NK-92MI cell-derived exosomes	114

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CAR, chimeric antigen receptor; CCR5i, C–C chemokine receptor type 5 inhibitor; CRC, colorectal cancer; CRISPR-Cas9, clustered regularly interspaced short palindromic repeats-associated protein 9; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; GPR34, G protein-coupled receptor 34; HCC, hepatocellular carcinoma; HNC, head and neck cancer; HNSCC, head and neck squamous cell carcinoma; IADAPT, iPSC-derived armored dual-adjusted and precision-engineered; IPSC, induced pluripotent stem cell; IRGD, internalizing RGD; MM, multiple myeloma; NKG2A, natural killer group 2, member A; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PD-1, programmed cell death protein 1; PDAC, pancreatic ductal adenocarcinoma; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; UC, urothelial carcinoma.

To date, CAR-NK cells targeting CD19 or CD20 have shown promising efficacy in B-cell malignancies. In a phase I/II trial, allogeneic CD19-targeted CAR-NK therapy has achieved a 73% overall response rate in relapsed/refractory patients, with no severe cytokine release syndrome or neurotoxicity observed[96]. Additionally, CAR-NK cells engineered from MLNK cells, designated CAR-ML-NK cells, exhibit enhanced persistence and antitumor activity. A preclinical study has demonstrated that CAR-ML-NK cells effectively expand *in vivo* and suppress drug-resistant leukemia and lymphoma progression, thus offering a novel therapeutic strategy for hematologic malignancies[104].

In solid tumors, mesothelin-targeted CARs engineered into CIML NK cells have been shown to significantly enhance cytotoxicity against OC cell lines and exhibit superior antitumor and antimetastatic activity in preclinical xenograft models (**Table 3**)[107]. However, most CAR-NK studies have relied on humanized mouse models. Although these models offer greater clinical relevance than conventional mouse systems, they often use artificial tumor cell lines that diverge from patient-derived tumors, and immunodeficient recipient mice cannot fully replicate human immunity or adoptive cell dynamics. Therefore, the safety and long-term efficacy of CAR-NK therapy remain to be validated clinically.

Nevertheless, conventional CAR-NK therapy remains limited by antigen escape. For example, leukemia stem cells can evade immune recognition by downregulating CD33 while upregulating ligands for NKG2D and CD226, such as major histocompatibility complex class I polypeptide-related sequence A and B (MICA/B). To address this evasion, a triple-targeting strategy integrating CD33-CAR, TCR-CD1d, and NKG2D/CD226 co-stimulation has been developed. This design enables elimination of CD33-negative leukemia stem cells *via* natural cytotoxicity receptor pathways when CAR/TCR signals are absent. Hypomethylating agents can further enhance this axis by upregulating NKR ligands and CD1d on cancer stem cells[115], combining CAR specificity with NKR–cancer stem cell interactions to provide dual-mechanism protection against antigen escape.

In recent years, substantial progress has been achieved in CAR-engineered induced NK (CAR-iNK) cell technology derived from pluripotent stem cells, including human induced pluripotent stem cells and human embryonic stem cells. These cells demonstrate high homogeneity and scalability for "off-the-shelf" therapy[116]. Standardized protocols enable the directed differentiation of CAR-iNK cells from cord blood-derived $CD34^+$ hematopoietic stem and progenitor cells. Through a three-step process involving expansion, organoid-based induction, and maturation amplification, tens of millions of CAR-iNK cells can be generated from a single $CD34^+$ hematopoietic stem and progenitor cells (HSPCs), while decreasing viral vector usage to one-tenth to one-hundred-thousandth of conventional levels, thereby substantially lowering production costs[117].

In summary, CAR-NK technology, particularly when MLNK cells are used as a platform, is a promising therapeutic approach for hematological and solid tumors. Ongoing innovations in stem cell-derived platforms are expected to accelerate clinical translation, yet long-term immune safety monitoring, particularly regarding potential effects on autoimmune homeostasis, remains essential during clinical application.

Expansion and infusion of adaptive NK cells

Adoptive immunotherapy using adaptive NK cells is a major research direction in cancer biotherapy. Current efforts focus predominantly on two subsets: HCMV-induced adaptive NK cells and CIML-NK cells (**Figure 3**).

Research on HCMV-induced adaptive NK cells has substantially advanced. Investigators have successfully isolated and expanded highly active NKG2C$^+$ NK cells from cytapheresis products obtained from CMV-seropositive donors. The establishment of a GMP-compliant manufacturing process has provided a solid foundation for clinical translation[103]. Clinical studies have shown that infusing NKG2C$^+$ adaptive NK cells has substantial therapeutic potential[109]. Notably, in patients experiencing CMV reactivation after hematopoietic stem cell transplantation, the expansion of adaptive NK cells significantly correlates with lower leukemia relapse rate, thus underscoring their importance in post-transplant immune protection[118].

Research on CIML-NK cells has also achieved important breakthroughs. In a phase I trial involving patients with AML, CIML-NK cell infusion induced remission in 44% of patients, with persistence exceeding 3 months, thereby indicating favorable durability and antitumor activity (**Table 3**)[111]. Despite this promise, the clinical translation of adaptive NK cell therapy faces substantial challenges. The NKG2C$^+$ subset is scarce and requires 2–3 weeks of high-dose IL-15 stimulation for expansion yet remains prone to premature senescence. Additional risks include CMV reactivation and inflammatory cytokine storms. Moreover, manufacturing is complex and exhibits batch-to-batch variability. In summary, adaptive NK cell-based immunotherapy is an emerging strategy with considerable translational potential for both virally induced and cytokine-preconditioned subsets. However, systematic resolution of these challenges remains essential for successful clinical application.

Strategies for modulating immune checkpoints

Targeting immune checkpoints expressed on NK cells has become a major research focus (**Figure 3**). TiNK cells exhibit high TIGIT expression, which correlates closely with tumor progression. Anti-TIGIT monotherapy has exhibited notable antitumor efficacy in CRC, breast cancer, and melanoma models in preclinical studies[119,120]. Moreover, TIGIT/PD-1 bispecific antibodies have been developed and are under evaluation in phase I/II trials for NSCLC and urothelial carcinoma, with preliminary results indicated considerable clinical promise[98].

Concurrently, NKG2A has emerged as a key therapeutic target. In clinical studies, the combination of the anti-NKG2A antibody monalizumab with the PD-1 inhibitor durvalumab and the epidermal growth factor receptor (EGFR) inhibitor cetuximab has shown synergistic activity[99]. Currently, NKG2A inhibitors, as monotherapy or in combination, are being evaluated in registered clinical trials across multiple cancers, to assess their safety and efficacy (**Table 3**)[100,121].

Furthermore, T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) is gaining attention in NK cell-based immunotherapy research. Anti-TIM-3 has been shown to restore cNK and liver-resident NK cell function and suppress primary HCC progression in preclinical studies[122]. Collectively, these findings expand the potential target repertoire for NK cell immunotherapy. Immune checkpoint blockade enhances NK cell activity but increases the risk of immune-related adverse events[123]. Future research should prioritize balancing potent antitumor responses with systemic immune homeostasis.

Application of immunomodulatory agents

Chemokine receptor inhibitors and metabolic modulators are promising immunomodulatory strategies for regulating NK cell function, particularly in targeting TrNK cells (**Figure 3**). In chemokine receptor-targeted therapy, C-C chemokine receptor type 5 (CCR5) inhibitors decrease immunosuppressive MDSC and Treg infiltration in the TME by blocking the CCL3-CCR5 axis, and have been shown to enhance NK cell antitumor activity in pancreatic ductal adenocarcinoma (PDAC) models[102]. Because this finding was based on mouse studies, its translational relevance to human pancreatic cancer requires validation in human tissue or humanized models. Regarding metabolic modulation, GPR34 inhibitors enhance TrNK cell function by antagonizing LysoPS-mediated immunosuppression. In HCC and CRC models, combining GPR34 inhibitors with anti-TIGIT antibodies has shown synergistic efficacy[67]. Additionally, adenosine receptor inhibitors reverse TrNK cell exhaustion and restore cytotoxicity in melanoma models by blocking the adenosine signaling pathway (**Table 3**)[124].

Although these preclinical findings are promising, most studies have been exploratory, and clinical translation pathways remain undefined. Future efforts should prioritize advancing clinical trial design to accelerate bench-to-bedside translation.

Combination therapy strategies

Combination strategies are critical for increasing NK cell-based antitumor efficacy (**Figure 3**). Among these approaches,

the monoclonal antibody-NK cell cooperative strategy based on ADCC is systematically optimized through two primary pathways: antibody engineering and effector cell engineering[125]. In antibody engineering, the Fragment crystallizable (Fc) region is modified to enhance affinity for CD16A on NK cells, thereby amplifying ADCC. These strategies include site-specific mutations (e.g., GASDALIE, Variant 18)[126,127] and glycoengineering such as afucosylation[128]. These optimizations have been clinically validated in agents such as margetuximab (anti-human EGFR 2)[129] and obinutuzumab (anti-CD20)[130]. At the effector cell level, genetic modification of NK cells to express engineered Fc receptors fundamentally increases their responsiveness to antibody signals. For example, the expression of a non-cleavable CD16A prolongs cellular activation[131], whereas the introduction of high-affinity chimeric receptor systems such as CD64/16A provides a platform for universal effector cell development[132]. Ultimately, these approaches converge on an integrated strategy that combines Fc-optimized antibodies with "off-the-shelf" NK cells engineered to express enhanced Fc receptors. When further combined with immune checkpoint inhibitors and other modalities, this multi-layered cooperative system provides a novel paradigm to overcome tumor heterogeneity and therapy resistance[133].

Beyond the aforementioned ADCC-based synergistic strategies, additional combination modalities have shown considerable therapeutic potential. In NK-cell/targeted-drug combinations, preclinical and clinical studies have revealed synergistic effects. In HCC studies, the combination of sorafenib with MLNK cells reprogrammed the immunosuppressive TME to enhance NK cell activation, ultimately suppressing tumor progression[113]. Notably, in a trial involving patients with HNSCC, preoperative metformin treatment significantly increased intratumoral NKp46$^+$ cell infiltration. Subsequent co-culture experiments further revealed that TiNK cells from metformin-pretreated patients exhibited stronger cytotoxicity; these findings support the synergistic potential of combining targeted therapy with NK cell-based immunotherapy (**Table 3**)[101].

Substantial progress has also been achieved in combining NK cells with local therapies. A phase II trial in advanced HCC has demonstrated that combining allogeneic NK cell therapy with cryoablation significantly prolongs median progression-free survival[110]. Additionally, in PDAC models, radiotherapy combined with a CCR5 inhibitor and a PD-1 inhibitor has been found to activate TrNK cells. This approach, which enhances the antitumor immune response by modulating the TrNK–conventional type 1 dendritic cell (cDC1)–CD8$^+$ T-cell axis, provides a novel rationale for combination strategies (**Table 3**)[102]. In summary, NK cell-based combination strategies, through coordinated multi-mechanistic actions, offer promising directions for improving antitumor immunotherapy.

Emerging technologies and future directions

Beyond the aforementioned approaches, emerging technologies are driving innovative breakthroughs in NK cell therapy, spanning genetic engineering, delivery systems, and cellular derivatives, which have demonstrated considerable translational potential (**Figure 3**).

Genetic and cellular engineering has opened new avenues. For example, Woan et al. have used triple-gene editing to generate induced pluripotent stem cells (iPSCs) that are subsequently differentiated into iPSC-derived armored dual-adjusted and precision-engineered (iADAPT) NK cells. These cells exhibit prolonged persistence without exogenous cytokines and potent cytotoxicity against multiple myeloma (MM) and AML cells[108]. Notably, CRISPR/Cas9 also enables precise functional engineering. For example, knockout of the killer cell lectin-like receptor subfamily C, member 1 (*KLRC1*) gene (encoding the inhibitory receptor NKG2A) significantly enhances NK cell cytotoxicity against MM cells (**Table 3**)[97].

Advancements in delivery systems are addressing key technical challenges. Dong et al. have engineered CIML-NK cells with the tumor-penetrating peptide iRGD, thus improving their infiltration and cytotoxicity in deep tumor tissues, as demonstrated in 3D spheroid and HCC xenograft models[106]. Furthermore, Khalifa et al. have developed lipid nanoparticles co-loaded with a stimulator of interferon genes (STING) agonist and cytosine-phosphate-guanine oligodeoxynucleotides, which have been found to induce long-term persistence of MLNK cells and durable antitumor immune memory, and achieve prophylactic efficacy in a melanoma lung metastasis model (**Table 3**)[134].

Innovative cytokine engineering and agent design continue to emerge. Cubitt et al. have developed a fusion protein (18/12/TxM) combining the IL-15 superagonist N-803 with IL-18/IL-12 components, which has effectively activated and enhanced MLNK cell antitumor function in preclinical studies, thereby offering a new approach for adoptive cell expansion[105]. Importantly, a phase I trial has confirmed that allogeneic CIML-NK cells combined with N-803 and ipilimumab achieve sustained expansion and tumor regression in advanced head and neck cancer, thus underscoring the clinical feasibility and safety of this combinatorial strategy (**Table 3**)[112].

In the application of cellular derivatives, extracellular vesicles (EVs) derived from MLNK cells present distinctive advantages. These EVs have cytotoxic and antitumor activities, including enhanced tumor cell uptake in acidic microenvironments[135]. Notably, in HCC models, NK cell-derived EVs selectively target and kill tumor cells while sparing normal hepatocytes, and therefore have potential as a safe and effective therapeutic strategy (**Table 3**)[114]. Together, these emerging approaches reflect the rapid advancement of NK cell therapy toward more precise, efficacious, and safer treatments, and the expansion of the therapeutic options for cancer immunotherapy.

Disease heterogeneity in NK cell function and therapeutic challenges

Although current therapeutic strategies are aimed at enhancing the anti-tumor activity of NK cells, their inherent functional plasticity offers both benefits and drawbacks. Under physiological conditions, NK cells maintain immune homeostasis through anti-tumor defense, anti-infection responses, and senescent cell clearance. However, in pathology, TME-derived suppressive signals drive NK cell exhaustion. In autoimmune diseases such as multiple sclerosis and rheumatoid arthritis, they might contribute to immune dysregulation through functional impairment or numerical reduction, or, in contrast, exacerbate tissue damage *via* excessive activation[136,137]. However, in chronic inflammatory settings, such as inflammatory bowel disease, persistent aberrant signaling can cause NK cells to release pro-inflammatory mediators while attempting to suppress inflammation, and ultimately exacerbate disease progression[138]. This context-dependent shift from physiological protection to pathological damage highlights that NK cell fate is governed by the dynamic balance of signals within the microenvironment.

This functional heterogeneity complicates clinical translation. Although checkpoint inhibitors and CAR-NK therapies can reverse TME immunosuppression, their limited systemic specificity poses risks of off-target effects, such as cytokine release syndrome or autoimmune reactions[139]. Therefore, future efforts should focus on developing TME-selective activation strategies, including conditionally activated antibodies and localized drug delivery systems; identifying predictive biomarkers for response and toxicity to guide patient stratification; and systematically evaluating autoimmune risks as key safety endpoints in trials. These approaches would maximize anticancer efficacy while mitigating immune-related adverse events, thereby advancing NK cell-based therapies toward safer clinical application.

Conclusions

This review comprehensively examined the characteristics, functions, regulatory mechanisms, and therapeutic potential of novel NK cell subsets within the TME, emphasizing the dynamic and interconnected networks governing their behavior. As crucial innate immune effectors, NK cells are essential for tumor immune surveillance. However, the traditional NK cell dichotomy, which was derived primarily from peripheral blood studies, does not capture the functional diversity and phenotypic plasticity of NK cells within the TME. Through multifaceted regulation, the TME shapes functionally distinct subsets, such as TiNK, TrNK, and adaptive NK cells, each with unique differentiation pathways, phenotypes, and effector profiles. The dynamic interconversion among these subsets critically shapes immune surveillance outcomes.

The complexity of the TME impedes the broad application of therapies targeting emerging NK cell subsets. Therefore, future research should prioritize elucidating how the TME shapes the *in vivo* functionality of these subsets, which is a critical step for effectively harnessing NK cells to enhance anti-tumor immunity. Although therapies based on novel NK cell subsets are advancing, their clinical implementation remains constrained by several key limitations: the lack of consistent subset biomarkers, incomplete understanding of their regulatory networks, and the immaturity of therapies designed for precise subset targeting.

Future efforts should focus on identifying reliable subset-specific markers, deciphering their spatiotemporal regulatory networks, designing novel combination therapies, and establishing robust translational platforms. In summary, a pressing need exists to clarify the molecular mechanisms through which the TME drives functional transitions among NK cell subsets and, in parallel, to develop corresponding precision-targeting strategies. Such efforts would advance subset-based NK cell immunotherapy from bench to bedside, and ultimately provide more effective therapeutic options for patients with cancer.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

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