WJPMR, 2025, 11(11), 101-108

Review Article

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Impact Factor: 6.842

ISSN (O): 2455-3301

ISSN (P): 3051-2557

Coden USA: WJPMBB

A REVIEW ON NATURAL KILLER CELLS (NK) IN CANCER

Poonam Goswami[1], Povel V. Modi[2], Parthiv Patel[3], Arpit Patel[4], Hiren Makwana[5], Niyati Nayak[6], Ms. Divya Mahyavanshi[7]*

Students[1,2,3,4,5,6], Assistant Professor[7]

Department of Pharmacology, Sharda School of Pharmacy Pethapur, Gandhinagar.

***Corresponding Author: Ms. Divya Mahyavanshi**

Assistant Professor, Department of Pharmacology, Sharda School of Pharmacy Pethapur, Gandhinagar.

DOI: https://doi.org/10.5281/zenodo.17483200

How to cite this Article: Poonam Goswami, Povel V. Modi, Parthiv Patel, Arpit Patel, Hiren Makwana, Niyati Nayak, Ms. Divya Mahyavanshi*. (2025). A Review On Natural Killer Cells (NK) In Cancer. World Journal of Pharmaceutical and Medical Research, 11(11), 101–108.

Article Received on 01/10/2025 **Article Revised on 22/10/2025** **Article Published on 01/11/2025**

ABSTRACT

Natural killer (NK) cells represent a critical component of the innate immune system with potent anti-tumor capabilities. These cytotoxic lymphocytes provide rapid, MHC-unrestricted responses against malignant cells, making them attractive candidates for cancer immunotherapy. This review explores the fundamental biology of NK cells, their role in cancer surveillance and elimination, mechanisms of tumor evasion, and the rapidly evolving landscape of NK cell-based therapeutic strategies. We discuss current clinical applications, emerging technologies including chimeric antigen receptor (CAR)-NK cells, and future directions in harnessing NK cell biology for oncological treatment.

KEYWORDS: Natural killer cells, cancer immunotherapy, adoptive cell transfer, CAR-NK cells, tumor immunosurveillance, ADCC, checkpoint inhibitors, cytokine therapy, immunoediting, tumor microenvironment.

INTRODUCTION

Cancer immunotherapy has revolutionized oncological treatment paradigms, with checkpoint inhibitors and CAR-T cell therapies demonstrating remarkable clinical success. However, Natural Killer (NK) cells, the innate immune system's cytotoxic effectors, have emerged as promising alternative therapeutic agents with unique advantages over adaptive immune approaches.[1,2] Unlike T cells, NK cells do not require prior sensitization or MHC restriction for target recognition, enabling rapid responses against malignant cells while maintaining selectivity through a sophisticated balance of activating and inhibitory signals.[1,2,3]

NK cells comprise approximately 5-15% of peripheral blood lymphocytes and 30-50% of liver lymphocytes, positioning them as frontline defenders against transformed cells.[1] Their ability to recognize and eliminate cancer cells through multiple mechanisms, combined with their favorable safety profile and potential for "off-the-shelf" allogeneic therapy, has catalyzed intensive research into NK cell-based cancer treatments.[3,19,25]

2. NK Cell Biology and Function

2.1 Development and Maturation

NK cells develop from common lymphoid progenitors in the bone marrow through a process orchestrated by transcription factors including ID2, NFIL3, TOX, and EOMES.[1] Mature NK cells are typically identified by expression of CD56 and lack of CD3 (CD56+CD3-).[1,2] In humans, two major NK cell subsets exist: CD56bright and CD56dim cells.[2] CD56bright NK cells, comprising 5-10% of peripheral NK cells, are primarily immunoregulatory, producing abundant cytokines including IFN-γ, TNF-α, and GM-CSF.[2,3] CD56dim NK cells, representing 90% of circulating NK cells, exhibit potent cytotoxic activity and express high levels of perforin, granzymes, and Fc receptors (particularly CD16/FcγRIIIA), enabling antibody-dependent cellular cytotoxicity (ADCC).[2,8]

2.2 Recognition and Activation

NK cell function is governed by a sophisticated balance between activating and inhibitory receptors.[4,5] This "missing-self" recognition system allows NK cells to detect malignant transformation and cellular stress while maintaining tolerance to healthy cells.[5]

Inhibitory Receptors: Killer cell immunoglobulin-like receptors (KIRs) recognize MHC class I molecules (HLA-A, B, C), while the NKG2A/CD94 heterodimer binds HLA-E.[4,5] Leukocyte immunoglobulin-like receptors (LILRBs) provide additional inhibitory signals through immunoreceptor tyrosine-based inhibition motifs (ITIMs).[4,5]

Activating Receptors: Natural cytotoxicity receptors (NCRs) including NKp46, NKp44, and NKp30 initiate cytotoxic responses.[4] NKG2D recognizes stress-induced ligands such as MICA/B and ULBP1-6 (13). DNAM-1 (CD226) binds CD112 and CD155, while 2B4 (CD244) interacts with CD48 (4). Activating KIRs and CD16 mediate ADCC.[4,5,8]

The decision to kill or spare a target cell depends on the integrated balance of these signals.[5] Tumor cells frequently downregulate MHC class I to evade T cell recognition, paradoxically making them susceptible to NK cell-mediated lysis through loss of inhibitory signaling.[12,14]

2.3 Cytotoxic Mechanisms

NK cells eliminate target cells through multiple effector mechanisms.[3,6,7] Direct cytotoxicity involves formation of an immunological synapse with target cells, followed by polarized release of cytotoxic granules containing perforin and granzymes.[6,7] Perforin creates pores in target cell membranes, allowing granzymes (particularly granzyme B) to enter and induce apoptosis via caspase activation.[7]

Death receptor-mediated killing occurs through expression of TNF-related apoptosis-inducing ligand (TRAIL) and Fas ligand (FasL), with engagement of death receptors triggering caspase cascades.[3] Antibody-dependent cellular cytotoxicity (ADCC) involves CD16-mediated recognition of antibody-opsonized targets and represents a critical mechanism for therapeutic monoclonal antibodies including rituximab, trastuzumab, and cetuximab.[8,26]

NK cells also perform immunoregulatory functions through rapid production of IFN-γ, TNF-α, and chemokines, regulation of adaptive immune responses, and dendritic cell maturation with subsequent cross-priming of T cells.[3]

3. NK Cells in Cancer Immunosurveillance

3.1 Evidence for NK Cell Tumor Surveillance

Multiple lines of evidence establish NK cells as critical mediators of cancer immunosurveillance.[9,10] Epidemiological studies demonstrate that individuals with low NK cell activity exhibit increased cancer incidence.[9] Mouse models deficient in NK cell function show enhanced susceptibility to spontaneous and chemically-induced tumors.[10] Furthermore, tumor-infiltrating NK cells correlate with improved prognosis across multiple cancer types including colorectal, gastric, lung, and renal cell carcinoma.[10]

The "cancer immunoediting" hypothesis posits three phases: elimination, equilibrium, and escape.[11] NK cells participate prominently in the elimination phase, recognizing and destroying nascent transformed cells before clinical disease manifests.[11,12] However, tumors that survive selective pressure develop mechanisms to evade or suppress NK cell immunity.[12,14]

3.2 Tumor Evasion of NK Cell Immunity

Successful tumors employ diverse strategies to escape NK cell surveillance.[12,14] Receptor-ligand modulation includes downregulation of activating ligands (MICA/B, ULBP, CD155) and shedding of NKG2D ligands through metalloproteases.[13] Tumors maintain inhibitory MHC class I expression and express non-classical HLA molecules including HLA-G and HLA-E.[14]

The immunosuppressive tumor microenvironment recruits regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs).[12,15] Production of immunosuppressive cytokines including TGF-β, IL-10, and IL-6, along with metabolic competition and nutrient depletion (glucose, tryptophan), impairs NK cell function.[12,15] Hypoxia and acidosis further compromise NK cell activity, while expression of immune checkpoint molecules such as PD-L1 and TIGIT ligands suppresses NK cell responses.[12,15]

Direct NK cell inhibition occurs through expression of inhibitory ligands engaging KIRs and NKG2A, production of prostaglandin E2 (PGE2) and indoleamine 2,3-dioxygenase (IDO), accumulation of adenosine through the CD39/CD73 pathway, and chronic activation leading to NK cell exhaustion.[14] Physical barriers including dense extracellular matrix limiting NK cell infiltration and abnormal tumor vasculature impeding immune cell trafficking further compromise NK cell-mediated tumor control.[15]

4. NK Cell-Based Cancer Immunotherapy

4.1 Adoptive NK Cell Transfer

Adoptive transfer of autologous or allogeneic NK cells represents a foundational approach to NK cell therapy.[16,17] The landmark work by Miller and colleagues demonstrated that haploidentical NK cells could mediate antileukemic effects in acute myeloid leukemia (AML) patients, particularly when KIR-ligand mismatched.[16] This "KIR-ligand mismatch" strategy exploits the absence of inhibitory KIR engagement, unleashing NK cell cytotoxicity against malignant cells.[17]

Sources of NK Cells for Therapy

Peripheral blood NK cells are harvested via leukapheresis and enriched through immunomagnetic selection or flow cytometry.[16] Advantages include ease of procurement and autologous options, though

limitations include variable yields and activation states.[16]

Umbilical cord blood NK cells are readily available from cord blood banks, with less stringent HLA matching requirements.[19] Cord blood NK cells exhibit robust proliferative capacity and potent cytotoxicity but require extensive ex vivo expansion.[19,22]

NK cell lines, including immortalized lines such as NK-92, KHYG-1, and NKL, provide unlimited, standardized cell sources.[18] NK-92 cells, derived from a non-Hodgkin lymphoma patient, have demonstrated safety in clinical trials but require irradiation before infusion to prevent proliferation.[18,54,55] These cells lack CD16 and KIRs, limiting ADCC but avoiding potential graft-versus-host disease.[18,63]

Induced pluripotent stem cell (iPSC)-derived NK cells represent a renewable, genetically engineerable source enabling standardized "off-the-shelf" products with consistent quality and potency.[20,43]

Clinical Experience

Adoptive NK cell therapy has demonstrated safety with minimal toxicity compared to CAR-T cells, notably avoiding cytokine release syndrome (CRS) and neurotoxicity.[39,52] Clinical efficacy has been most evident in hematological malignancies, particularly AML and B-cell lymphomas.[42,48] Response rates in solid tumors remain modest, reflecting challenges in NK cell trafficking, tumor infiltration, and persistence within immunosuppressive microenvironments.[44,49]

4.2 Chimeric Antigen Receptor (CAR)-NK Cells

CAR technology, which redirects lymphocyte specificity through engineered receptors combining antigen recognition domains with signaling modules, has been adapted for NK cells.[19,24] CAR-NK cells offer several advantages over CAR-T cells, including enhanced safety profile with lower CRS and neurotoxicity risk[22,24], multiple intrinsic killing mechanisms beyond CAR-mediated recognition[24], capacity for allogeneic use without graft-versus-host disease[24,38], shorter lifespan potentially limiting long-term on-target off-tumor toxicity, and retained ability to recognize tumor cells independent of CAR through natural receptors.[37]

CAR Design for NK Cells

First-generation CARs contain an antigen-binding domain (typically single-chain variable fragment, scFv) fused to CD3ζ signaling domain.[37] Second- and third-generation CARs incorporate costimulatory domains including CD28, 4-1BB, 2B4, and DNAM-1 optimized for NK cell biology.[37,41] NK cell-specific modifications include incorporation of NKG2D, NKp44, or NKp46 signaling domains to leverage natural cytotoxicity pathways.[41]

Targeted Antigens

CAR-NK cells have been developed against numerous tumor antigens including CD19, CD20, CD33, HER2, EGFR, mesothelin, GD2, and BCMA.[38,41] CD19-directed CAR-NK cells have advanced furthest clinically, with promising results in relapsed/refractory B-cell malignancies.[22,23]

Clinical Development

A phase I/II trial of cord blood-derived CAR-NK cells targeting CD19 in relapsed/refractory non-Hodgkin lymphoma and chronic lymphocytic leukemia reported a 73% overall response rate with no CRS, neurotoxicity, or graft-versus-host disease.[22] These encouraging results have catalyzed expanded clinical investigation across multiple tumor types.[23,36,40]

4.3 Antibody-Based Strategies

Monoclonal Antibodies and ADCC

Therapeutic antibodies including rituximab (anti-CD20), trastuzumab (anti-HER2), and cetuximab (anti-EGFR) mediate substantial antitumor activity through CD16-dependent ADCC.[8,26] Polymorphisms in FCGR3A (encoding CD16) influence antibody therapy efficacy, with high-affinity variants (158V) associated with improved clinical outcomes.[26]

Fc Engineering: Antibody Fc region modifications enhance CD16 binding and ADCC potency.[8] Afucosylation, glycoengineering, and amino acid substitutions increase antibody affinity for CD16, amplifying NK cell-mediated tumor destruction.[8] Obinutuzumab, a glycoengineered anti-CD20 antibody with enhanced ADCC, demonstrates superior efficacy compared to rituximab in chronic lymphocytic leukemia.[8]

Bispecific and Trispecific Engagers

These molecules simultaneously bind NK cell activating receptors and tumor antigens, creating immunological synapses and triggering cytotoxicity.[27,28] AFM13 (anti-CD30/CD16A) has shown promise in Hodgkin lymphoma.[27] Tri-specific killer engagers (TriKEs) incorporate IL-15 to enhance NK cell activation, proliferation, and persistence.[28] GTB-3550, a CD33/CD16/IL-15 TriKE, has demonstrated encouraging activity in AML and myelodysplastic syndrome.[29]

Checkpoint Inhibition

Blocking inhibitory receptors unleashes NK cell antitumor activity.[30,39] Anti-KIR antibodies including lirilumab and IPH2101 have been evaluated clinically with modest single-agent activity but potential synergy with other immunotherapies.[39] Monalizumab, blocking NKG2A, shows promise in combination with EGFR inhibitors in head and neck cancer.[30] Anti-TIGIT antibodies are under investigation given TIGIT's inhibitory effects on both NK and T cells.[30]

4.4 Cytokine Therapy and NK Cell Activation

Interleukin-15

IL-15 is essential for NK cell development, survival, and function.[31] IL-15 monotherapy and IL-15 superagonist (ALT-803) administration enhance NK cell numbers and cytotoxic activity in cancer patients.[32] IL-15 is frequently incorporated into NK cell expansion protocols and combination immunotherapy regimens.[33] Novel IL-15 formulations including long-acting IL-15 (N-803) and IL-15/IL-15Rα complexes demonstrate improved pharmacokinetics and potency.[32]

Interleukin-12 and Interleukin-18: These cytokines synergistically activate NK cells, inducing IFN-γ production and cytotoxicity.[34] IL-12/IL-18 combination therapy has shown antitumor activity in preclinical models, though clinical translation has been limited by toxicity concerns.[34]

Interleukin-21

IL-21 enhances NK cell maturation, activation, and antibody-dependent cellular cytotoxicity.[31] Clinical trials combining IL-21 with therapeutic antibodies or adoptive cell therapy are ongoing.[31]

4.5 Combination Strategies

Rational combination approaches aim to overcome tumor immunosuppression and enhance NK cell efficacy.[12,39] Strategies include combining NK cells with checkpoint inhibitors to counteract T cell and NK cell exhaustion, therapeutic antibodies to enhance ADCC[8], immunomodulatory drugs such as lenalidomide and pomalidomide that enhance NK cell activation and ADCC, chemotherapy that induces immunogenic cell death and upregulates activating ligands, targeted therapy that can modulate tumor immunogenicity and NK cell function, and oncolytic viruses that enhance tumor NK cell infiltration and activation while inducing immunogenic tumor cell death.[12,39]

5. Enhancing NK Cell Therapy: Emerging Technologies

5.1 Genetic Engineering Strategies

Enhancing activation through overexpression of activating receptors (NKG2D, DNAM-1), expression of chimeric cytokine receptors converting inhibitory signals to activating signals, and introduction of activating KIRs represents one approach.[57,58,64] Improving persistence via IL-15 or IL-15/IL-15Rα co-expression for autocrine stimulation, introduction of anti-apoptotic molecules, and deletion of inhibitory receptors offers another strategy.[57,64]

Overcoming immunosuppression involves dominant-negative TGF-β receptor II to resist TGF-β inhibition, PD-1 deletion or switch receptors converting PD-1 signals to activating signals, and expression of IL-12 or IL-18 for paracrine immune activation.[58] Improving tumor trafficking utilizes expression of chemokine receptors matching tumor chemokine profiles (CCR2, CCR4, CXCR1/2) and heparanase expression to degrade extracellular matrix.[58]

5.2 Memory-Like NK Cells

Brief cytokine preactivation with IL-12, IL-15, and IL-18 generates "memory-like" or "cytokine-induced memory-like" (CIML) NK cells exhibiting enhanced functionality lasting weeks to months.[21,34] These cells demonstrate increased IFN-γ production, cytotoxicity, and ADCC.[34] Clinical trials of CIML NK cells in AML have shown promising response rates with acceptable safety profiles.[33,51] The mechanisms underlying NK cell memory challenge traditional innate versus adaptive immunity distinctions and offer new therapeutic opportunities.[34]

5.3 Targeting the Tumor Microenvironment

Engineering NK cells to secrete checkpoint inhibitors (anti-PD-L1, anti-TIGIT antibodies) creates localized immunomodulation within the tumor microenvironment while limiting systemic toxicity.[58] Enhancing NK cell metabolic fitness through overexpression of nutrient transporters, metabolic enzymes, or mitochondrial protective factors may improve function in nutrient-poor, hostile tumor microenvironments.[58] Engineering NK cells to secrete immune-stimulatory cytokines (IL-15, IL-12) or express switch receptors that convert inhibitory signals into activating signals creates "armored" NK cells resistant to tumor immunosuppression.[58,59]

5.4 Manufacturing and Expansion Technologies

Irradiated feeder cells expressing membrane-bound IL-15 or IL-21 support robust NK cell expansion.[53,65] K562 cells engineered to express 4-1BBL and membrane-bound IL-15 or IL-21 are commonly employed, achieving 1000-fold or greater expansion within 2-3 weeks.[53,65]

Development of GMP-compliant, automated bioreactor systems enables standardized, scalable NK cell production reducing cost and variability while enhancing product quality and accessibility.[52] Induced pluripotent stem cells offer unlimited expansion potential and precise genetic engineering capabilities.[20] iPSC-derived NK cells can be generated with defined genetic modifications, providing uniform, renewable "off-the-shelf" therapeutic products.[43] FT516 and FT596 (iPSC-derived CAR-NK cells) are under clinical investigation.[35]

6. Clinical Trials and Outcomes

6.1 Hematological Malignancies

NK cell therapies have shown greatest clinical success in blood cancers.[16,17,22,23] Haploidentical NK cell infusions in AML patients following lymphodepleting chemotherapy achieved complete remissions in approximately 30% of patients, with KIR-ligand mismatched donors showing superior outcomes.[16,17] CAR-NK cells targeting CD19 have demonstrated impressive response rates in relapsed/refractory

lymphomas and CLL with favorable safety profiles.[22,23] CIML NK cells have shown promise in AML with 50-60% response rates in some studies (33,51). Ongoing trials are evaluating NK cell therapies across multiple myeloma, T-cell lymphomas, and acute lymphoblastic leukemia.[48,60]

6.2 Solid Tumors

Clinical efficacy in solid tumors remains more challenging.[44,52] Barriers include limited tumor infiltration, immunosuppressive microenvironments, and inadequate in vivo persistence.[44,52] Some encouraging signals have emerged in renal cell carcinoma, hepatocellular carcinoma, and ovarian cancer.[49,54] CAR-NK cells targeting solid tumor antigens including HER2, mesothelin, and PSMA are in early clinical testing.[44] Combination approaches with chemotherapy, targeted therapy, or immune checkpoint inhibitors show promise in enhancing NK cell solid tumor efficacy.[39,44]

6.3 Safety Profile

NK cell therapies have demonstrated remarkable safety across numerous clinical trials.[22,39,52] Unlike CAR-T cells, NK cell therapies rarely cause severe cytokine release syndrome or immune effector cell-associated neurotoxicity syndrome (ICANS).[22,39] Allogeneic NK cells do not cause graft-versus-host disease due to absence of alloreactive T cell contamination and NK cell lack of long-term engraftment. The most common adverse events include transient cytokine-mediated symptoms including fever and fatigue, mild cytopenia, and infusion reactions.[52] This favorable safety profile enables outpatient administration and broader patient eligibility including elderly and frail populations.[52]

7. Challenges and Future Directions

7.1 Current Limitations

NK cells, particularly allogeneic cells, demonstrate poor in vivo persistence compared to T cells, typically lasting days to weeks.[39,52] Strategies to enhance persistence including cytokine support (IL-15), genetic modifications, and memory-like differentiation are under investigation.[21]

Solid tumors present physical and biochemical barriers limiting NK cell penetration.[44] Enhancing chemokine receptor expression, combining with radiotherapy or oncolytic viruses to disrupt tumor architecture, and targeting the extracellular matrix may improve infiltration.[58]

The immunosuppressive tumor milieu impairs NK cell function through multiple mechanisms.[12,15] Combination strategies targeting regulatory cells (Tregs, MDSCs), blocking inhibitory cytokines, checkpoint inhibition, and metabolic interventions are necessary.[39,58]

Producing sufficient clinical-grade NK cells remains technically challenging and expensive.[52] Advances in automated manufacturing, expanded use of NK cell lines, and iPSC-derived products may address scalability and cost concerns.[63,65]

Predictive biomarkers identifying patients most likely to benefit from NK cell therapy are lacking.[40] Understanding the role of KIR genotyping, tumor immunogenicity signatures, and baseline NK cell function may enable precision medicine approaches.[40]

7.2 Emerging Directions

Universal CAR-NK cells expressing multiple CARs targeting different antigens may prevent antigen escape and broaden applicability.[41,59] Approaches stimulating endogenous NK cells through cytokine fusion proteins, agonistic antibodies, or vaccine strategies could provide cost-effective alternatives to ex vivo manufacturing.[61]

Incorporating genetic circuits, inducible kill switches, and logic gates may enable sophisticated control over NK cell function, safety, and persistence.[58] Machine learning approaches to predict optimal CAR designs, identify novel tumor targets, and personalize NK cell products based on patient-specific tumor characteristics represent exciting frontiers.[59]

Understanding and harnessing tissue-resident NK cell populations with unique phenotypes and functions may provide novel therapeutic avenues, particularly in solid tumors and metastatic disease.[60] Given their role in immunosurveillance, strategies to enhance NK cell function in high-risk populations may prevent malignant transformation or detect and eliminate minimal residual disease.[9,10]

8. CONCLUSION

Natural killer cells have evolved from recognition as innate immune effectors to sophisticated therapeutic agents with tremendous potential in oncology. Their unique biology including rapid cytotoxicity without MHC restriction, multiple killing mechanisms, favorable safety profile, and capacity for allogeneic use positions NK cells as compelling alternatives or complements to T cell-based immunotherapies. While clinical success has been most evident in hematological malignancies, ongoing technological advances in genetic engineering, manufacturing, and rational combination strategies are expanding NK cell therapeutic applications to solid tumors.

The field stands at an inflection point. Fundamental insights into NK cell biology, enhanced understanding of tumor immune evasion mechanisms, and sophisticated engineering capabilities are converging to overcome historical limitations. CAR-NK cells, iPSC-derived products, memory-like NK cells, and bispecific engagers exemplify innovation translating from bench to bedside. As the complexity of tumor immunity becomes better understood, NK cells with their multifaceted antitumor

capabilities will likely play increasingly prominent roles in cancer treatment paradigms.

The vision of universally applicable, "off-the-shelf" NK cell therapies effective across cancer types while maintaining safety and tolerability is within reach.[43,63] Realizing this vision requires continued investment in basic NK cell biology, clinical translation, manufacturing infrastructure, and rational combination strategies. The renaissance in NK cell cancer immunotherapy promises to deliver new hope to patients across the oncological spectrum.

REFERENCES

1. Caligiuri MA. Human natural killer cells. Blood, 2008; 112(3): 461-469.
2. Cooper MA, Fehniger TA, Caligiuri MA. The biology of human natural killer-cell subsets. Trends Immunol., 2001; 22(11): 633-640.
3. Vivier E, Tomasello E, Baratin M, Walzer T, Ugolini S. Functions of natural killer cells. Nat Immunol., 2008; 9(5): 503-510.
4. Long EO, Kim HS, Liu D, Peterson ME, Rajagopalan S. Controlling natural killer cell responses: integration of signals for activation and inhibition. Annu Rev Immunol., 2013; 31: 227-258.
5. Lanier LL. Up on the tightrope: natural killer cell activation and inhibition. Nat Immunol., 2008; 9(5): 495-502.
6. Orange JS. Formation and function of the lytic NK-cell immunological synapse. Nat Rev Immunol., 2008; 8(9): 713-725.
7. Voskoboinik I, Whisstock JC, Trapani JA. Perforin and granzymes: function, dysfunction and human pathology. Nat Rev Immunol., 2015; 15(6): 388-400.
8. Wang W, Erbe AK, Hank JA, Morris ZS, Sondel PM. NK cell-mediated antibody-dependent cellular cytotoxicity in cancer immunotherapy. Front Immunol., 2015; 6: 368.
9. Imai K, Matsuyama S, Miyake S, Suga K, Nakachi K. Natural cytotoxic activity of peripheral-blood lymphocytes and cancer incidence: an 11-year follow-up study of a general population. Lancet., 2000; 356(9244): 1795-1799.
10. Malmberg KJ, Carlsten M, Björklund A, Sohlberg E, Bryceson YT, Ljunggren HG. Natural killer cell-mediated immunosurveillance of human cancer. Semin Immunol., 2017; 31: 20-29.
11. Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. Annu Rev Immunol., 2004; 22: 329-360.
12. Guillerey C, Huntington ND, Smyth MJ. Targeting natural killer cells in cancer immunotherapy. Nat Immunol., 2016; 17(9): 1025-1036.
13. Raulet DH, Gasser S, Gowen BG, Deng W, Jung H. Regulation of ligands for the NKG2D activating receptor. Annu Rev Immunol., 2013; 31: 413-441.
14. Groth A, Klöss S, von Strandmann EP, Koehl U, Koch J. Mechanisms of tumor and viral immune escape from natural killer cell-mediated surveillance. J Innate Immun., 2011; 3(4): 344-354.
15. Balsamo M, Scordamaglia F, Pietra G, et al. Melanoma-associated fibroblasts modulate NK cell phenotype and antitumor cytotoxicity. Proc Natl Acad Sci U S A., 2009; 106(49): 20847-20852.
16. Miller JS, Soignier Y, Panoskaltsis-Mortari A, et al. Successful adoptive transfer and in vivo expansion of human haploidentical NK cells in patients with cancer. Blood., 2005; 105(8): 3051-3057.
17. Ruggeri L, Capanni M, Urbani E, et al. Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants. Science., 2002; 295(5562): 2097-2100.
18. Klingemann H, Boissel L, Toneguzzo F. Natural killer cells for immunotherapy - advantages of the NK-92 cell line over blood NK cells. Front Immunol., 2016; 7: 91.
19. Rezvani K, Rouce R, Liu E, Shpall E. Engineering natural killer cells for cancer immunotherapy. Mol Ther., 2017; 25(8): 1769-1781.
20. Li Y, Hermanson DL, Moriarity BS, Kaufman DS. Human iPSC-derived natural killer cells engineered with chimeric antigen receptors enhance anti-tumor activity. Cell Stem Cell., 2018; 23(2): 181-192.
21. Romee R, Rosario M, Berrien-Elliott MM, et al. Cytokine-induced memory-like natural killer cells exhibit enhanced responses against myeloid leukemia. Sci Transl Med., 2016; 8(357): 357ra123.
22. Liu E, Marin D, Banerjee P, et al. Use of CAR-transduced natural killer cells in CD19-positive lymphoid tumors. N Engl J Med., 2020; 382(6): 545-553.
23. Tang X, Yang L, Li Z, et al. Safety, efficacy and determinants of response of allogeneic CD19-specific CAR-NK cells in CD19+ B cell tumors: a phase 1/2 trial. Nat Med., 2024; 30(1): 145-153.
24. Klingemann H. Are natural killer cells superior CAR drivers? Oncoimmunology., 2014; 3(4): e28147.
25. Liu S, Galat V, Galat Y, Lee YKA, Wainwright D, Wu J. NK cell-based cancer immunotherapy: from basic biology to clinical development. J Hematol Oncol., 2021; 14(1): 7.
26. Cartron G, Dacheux L, Salles G, et al. Therapeutic activity of humanized anti-CD20 monoclonal antibody and polymorphism in IgG Fc receptor FcgammaRIIIa gene. Blood., 2002; 99(3): 754-758.
27. Rothe A, Sasse S, Topp MS, et al. A phase 1 study of the bispecific anti-CD30/CD16A antibody construct AFM13 in patients with relapsed or refractory Hodgkin lymphoma. Blood., 2015; 125(26): 4024-4031.
28. Felices M, Lenvik TR, Davis ZB, Miller JS, Vallera DA. Generation of BiKEs and TriKEs to improve NK cell-mediated targeting of tumor cells. Methods Mol Biol., 2016; 1441: 333-346.
29. Sarhan D, Brandt L, Felices M, et al. 161533 TriKE stimulates NK-cell function to overcome myeloid-derived suppressor cells in MDS. Blood Adv., 2018; 2(12): 1459-1469.

30. André P, Denis C, Soulas C, et al. Anti-NKG2A mAb is a checkpoint inhibitor that promotes anti-tumor immunity by unleashing both T and NK cells. Cell., 2018; 175(7): 1731-1743.
31. Waldmann TA. The biology of interleukin-2 and interleukin-15: implications for cancer therapy and vaccine design. Nat Rev Immunol., 2006; 6(8): 595-601.
32. Rhode PR, Egan JO, Xu W, et al. Comparison of the superagonist complex, ALT-803, to IL15 as cancer immunotherapeutics in animal models. Cancer Immunol Res., 2016; 4(1): 49-60.
33. Cooley S, He F, Bachanova V, et al. First-in-human trial of rhIL-15 and haploidentical natural killer cell therapy for advanced acute myeloid leukemia. Blood Adv., 2019; 3(13): 1970-1980.
34. Romee R, Schneider SE, Leong JW, et al. Cytokine activation induces human memory-like NK cells. Blood., 2012; 120(24): 4751-4760.
35. Bachanova V, Maakaron J, Hirayama AV, et al. Results of a multicenter phase 1 trial of FT516, an off-the-shelf natural killer (NK) cell therapy derived from a clonal master induced pluripotent stem cell (iPSC) line expressing high-affinity, non-cleavable CD16 (hnCD16). Blood., 2020; 136(Suppl 1): 3-4.
36. Daher M, Rezvani K. Outlook for new CAR-based therapies with a focus on CAR NK cells: what lies beyond CAR-engineered T cells in the race against cancer. Cancer Discov., 2021; 11(1): 45-58.
37. Hu Y, Tian ZG, Zhang C. Chimeric antigen receptor (CAR)-transduced natural killer cells in tumor immunotherapy. Acta Pharmacol Sin., 2018; 39(2): 167-176.
38. Xie G, Dong H, Liang Y, Ham JD, Rizwan R, Chen J. CAR-NK cells: a promising cellular immunotherapy for cancer. EBioMedicine., 2020; 59: 102975.
39. Myers JA, Miller JS. Exploring the NK cell platform for cancer immunotherapy. Nat Rev Clin Oncol., 2021; 18(2): 85-100.
40. Laskowski TJ, Biederstädt A, Rezvani K. Natural killer cells in antitumour adoptive cell immunotherapy. Nat Rev Cancer., 2022; 22(10): 557-575.
41. Gong Y, Klein Wolterink RGJ, Wang J, Bos GMJ, Germeraad WTV. Chimeric antigen receptor natural killer (CAR-NK) cell design and engineering for cancer therapy. J Hematol Oncol., 2021; 14(1): 73.
42. Curti A, Ruggeri L, D'Addio A, et al. Successful transfer of alloreactive haploidentical KIR ligand-mismatched natural killer cells after infusion in elderly high risk acute myeloid leukemia patients. Blood, 2011; 118(12): 3273-3279.
43. Siegler EL, Zhu Y, Wang P, Yang L. Off-the-shelf CAR-NK cells for cancer immunotherapy. Cell Stem Cell., 2018; 23(2): 160-161.
44. Wrona E, Borowiec M, Potemski P. CAR-NK cells in the treatment of solid tumors. Int J Mol Sci., 2021; 22(11): 5899.
45. Chen Y, Lu D, Churov A, Fu R. Research progress on NK cell-based cancer immunotherapy. Immunology, 2022; 166(3): 303-315.
46. Zhang C, Oberoi P, Oelsner S, et al. Chimeric antigen receptor-engineered NK-92 cells: an off-the-shelf cellular therapeutic for targeted elimination of cancer cells and induction of protective antitumor immunity. Front Immunol., 2017; 8: 533.
47. Wang W, Jiang J, Wu C. CAR-NK for tumor immunotherapy: clinical transformation and future prospects. Cancer Lett., 2020; 472: 175-180.
48. Nguyen R, Wu H, Pounds S, Cao X, Hayashi RJ, Ribeiro RC, Rooney CM, Dahl GV, Shpall EJ, Bollard CM, Razzouk BI, Rytting ME. A phase II clinical trial of adoptive transfer of haploidentical natural killer cells for consolidation therapy of pediatric acute myeloid leukemia. J Immunother Cancer., 2019; 7(1): 81.
49. Geller MA, Cooley S, Judson PL, et al. A phase II study of allogeneic natural killer cell therapy to treat patients with recurrent ovarian and breast cancer. Cytotherapy., 2011; 13(1): 98-107.
50. Shah NN, Baird K, Delbrook CP, et al. Acute GVHD in patients receiving IL-15/4-1BBL activated NK cells following T-cell-depleted stem cell transplantation. Blood., 2015; 125(5): 784-792.
51. Berrien-Elliott MM, Cashen AF, Cubitt CC, et al. Multidimensional analyses of donor memory-like NK cells reveal new associations with response after adoptive immunotherapy for leukemia. Cancer Discov., 2020; 10(12): 1854-1871.
52. Shimasaki N, Jain A, Campana D. NK cells for cancer immunotherapy. Nat Rev Drug Discov., 2020; 19(3): 200-218.
53. Liu Y, Zhou Y, Huang KH, et al. CRISPR-Cas9 mediated modification of K562 cells generates universal antigen presenting cells for off-the-shelf cellular immunotherapy. J Immunother Cancer., 2021; 9(7): e002844.
54. Arai S, Meagher R, Swearingen M, et al. Infusion of the allogeneic cell line NK-92 in patients with advanced renal cell cancer or melanoma: a phase I trial. Cytotherapy., 2008; 10(6): 625-632.
55. Tonn T, Schwabe D, Klingemann HG, et al. Treatment of patients with advanced cancer with the natural killer cell line NK-92. Cytotherapy., 2013; 15(12): 1563-1570.
56. Clémenceau B, Vivien R, Berthomé M, et al. The human natural killer cytotoxic cell line NK-92, once armed with a murine CD16 receptor, represents a convenient cellular tool for the screening of mouse mAbs according to their ADCC potential. MAbs., 2013; 5(4): 587-594.
57. Pomeroy EJ, Hunzeker JT, Kluesner MG, et al. A genetically engineered primary human natural killer cell platform for cancer immunotherapy. Mol Ther., 2020; 28(1): 52-63.
58. Wang C, Wang J, Zhang X, et al. Natural killer cells in cancer immunotherapy: from basics to clinical

application. Signal Transduct Target Ther., 2024; 9(1): 157.
59. Wu H, Zhang Q, Liu Z, et al. CAR-NK cells for cancer immunotherapy: recent advances and future directions. Front Immunol., 2024; 15: 1361194.
60. Hu W, Wang G, Huang D, Sui M, Xu Y. Natural killer cell-based cancer immunotherapy: from basics to clinical trials. Exp Hematol Oncol., 2024; 13: 101.
61. Yang L, Liu Y, Yang Y, Wang S. Natural killer cell engagers for cancer immunotherapy. Front Oncol., 2024; 14: 1483884.
62. Mehta RS, Rezvani K. Chimeric antigen receptor expressing natural killer cells for the immunotherapy of cancer. Front Immunol., 2018; 9: 283.
63. Suck G, Odendahl M, Nowakowska P, et al. NK-92: an 'off-the-shelf therapeutic' for adoptive natural killer cell-based cancer immunotherapy. Cancer Immunol Immunother., 2016; 65(4): 485-492.
64. Naeimi Kararoudi M, Dolatshad H, Trikha P, et al. Generation of knock-out primary and pluripotent stem cell-derived natural killer cells for immunotherapy. Methods Mol Biol., 2019; 2048: 191-201.
65. Granzin M, Wagner J, Köhl U, Cerwenka A, Huppert V, Ullrich E. Shaping of natural killer cell antitumor activity by ex vivo cultivation. Front Immunol., 2017; 8: 458.