Engineered CAR-NK Cells for the Treatment of Solid Tumors: Biological Foundations, Recognition Strategies, and Approaches to Enhance Antitumor Efficacy

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ABSTRACT

Cell-based immunotherapy has emerged as one of the most important innovative approaches in cancer research and treatment. Despite the success of chimeric antigen receptor-engineered T cells in certain hematological malignancies, extending this success to solid tumors is hindered by antigen heterogeneity, tumor immune escape, insufficient trafficking of therapeutic cells, hypoxia, metabolic dysfunction, and immunosuppressive factors. This review aimed to examine the biological foundations of the antitumor activity of natural killer cells and analyze the therapeutic potential of CAR-NK cells in solid tumors, with particular emphasis on triple-negative breast cancer and non-small cell lung cancer. In this review, data from scientific articles addressing NK-cell biology, chimeric antigen receptor structure and function, tumor target recognition, and factors limiting CAR-NK activity were qualitatively examined, categorized, and analyzed according to the major thematic areas of the study. The reviewed evidence indicates that the intrinsic capacity of NK cells to recognize stressed and malignant cells, combined with CAR-dependent specific recognition, enables multimodal antitumor responses. However, factors such as TGF-β, hypoxia, mitochondrial dysfunction, and heterogeneous antigen expression may reduce the persistence and cytotoxic activity of these cells. Multi-target strategies, reduced sensitivity to inhibitory pathways, support of cellular survival, and complementary interventions represent major approaches currently being investigated to improve CAR-NK function. Overall, the successful development of CAR-NK cells for solid tumors requires designs that account for tumor biology while preserving cellular function under restrictive conditions.

Keywords: Natural killer cells; CAR-NK; Cell-based immunotherapy; Solid tumors; Cellular engineering

1. INTRODUCTION

Solid tumors remain among the leading causes of cancer-related mortality, and achieving durable therapeutic control in many advanced malignancies continues to present substantial challenges. Triple-negative breast cancer (TNBC) and non-small cell lung cancer (NSCLC) are two important examples of tumors in which molecular and antigenic heterogeneity, adaptation to therapeutic pressure, and multiple mechanisms of immune escape can limit treatment responses. Although the development of targeted therapies and immune checkpoint inhibitors has improved clinical outcomes in selected patients, therapeutic responses remain inconsistent, and primary or acquired resistance continues to represent a major challenge in the management of these malignancies.

The success of T cells engineered to express chimeric antigen receptors has clearly demonstrated the potential of engineering immune cells to recognize tumor-associated targets. CD19-targeted CAR-T cells can induce complete and durable responses in certain B-cell malignancies. In contrast, although BCMA-targeted CAR-T therapies produce substantial initial response rates in multiple myeloma, response durability is more limited in many patients. This difference suggests that the success of cellular therapy does not depend solely on antigen

recognition; factors including tumor biology, baseline disease burden, depth of response, expansion of engineered cells, and cellular persistence also play determining roles.

The translation of CAR technology to solid tumors faces additional and more complex barriers. The absence of completely tumor-specific antigens, heterogeneous expression of surface targets, antigen downregulation or loss under therapeutic pressure, and insufficient migration of transferred cells into tumor tissues are among the principal limitations. Moreover, unfavorable metabolic conditions and inhibitory signals may reduce the cytotoxic capacity of therapeutic cells even after successful recognition of malignant targets.

Natural killer (NK) cells are major components of innate immunity and can recognize and eliminate infected, stressed, and malignant cells without prior sensitization. Unlike T-cell receptor-dependent recognition, the functional decision of an NK cell results from the balance between multiple activating and inhibitory signals. This characteristic allows NK cells to detect alterations such as reduced expression of human leukocyte antigen (HLA) class I molecules or increased expression of stress-associated ligands.

Engineering NK cells to express chimeric antigen receptors has led to the development of CAR-NK cells. In this approach, CAR-dependent specific recognition is integrated with the natural recognition and cytotoxic mechanisms of NK cells. From a biological perspective, this characteristic is particularly important because reduction or loss of the CAR-targeted antigen does not necessarily eliminate the entire antitumor capacity of the NK cell.

The central problem addressed in the present study is the limited functional activity of engineered cellular therapies under the complex conditions associated with solid tumors. This review aims to examine the biological foundations of NK-cell antitumor activity, the rationale for using NK cells in CAR-based systems, and the strategies proposed to preserve and enhance CAR-NK function. The main research question is which biological and functional factors limit CAR-NK activity in solid tumors and which approaches have been proposed to mitigate these barriers. Accordingly, the conceptual hypothesis of this study is that specific recognition of a single antigen is insufficient to generate a durable response and that CAR-NK design should simultaneously account for tumor heterogeneity and factors restricting cellular function. The scope of this review focuses on NK and CAR-NK cells in solid tumors, with particular emphasis on TNBC and NSCLC.

2. METHODS

The present study was conducted as an analytical review. The units of analysis consisted of collected scientific articles related to natural killer cell biology, chimeric antigen receptors, CAR-NK cells, solid tumors, triple-negative breast cancer, and non-small cell lung cancer.

In the first stage, studies addressing the biological and molecular foundations of NK cells were examined. Information related to activating and inhibitory receptors, malignant-cell recognition pathways, immune synapse formation, and cytotoxic mechanisms, including perforin/granzyme-mediated killing, FasL/TRAIL signaling, and antibody-dependent cellular cytotoxicity, was extracted and categorized. The principal mechanisms underlying NK-cell recognition and elimination of tumor cells are summarized in Figure 1.

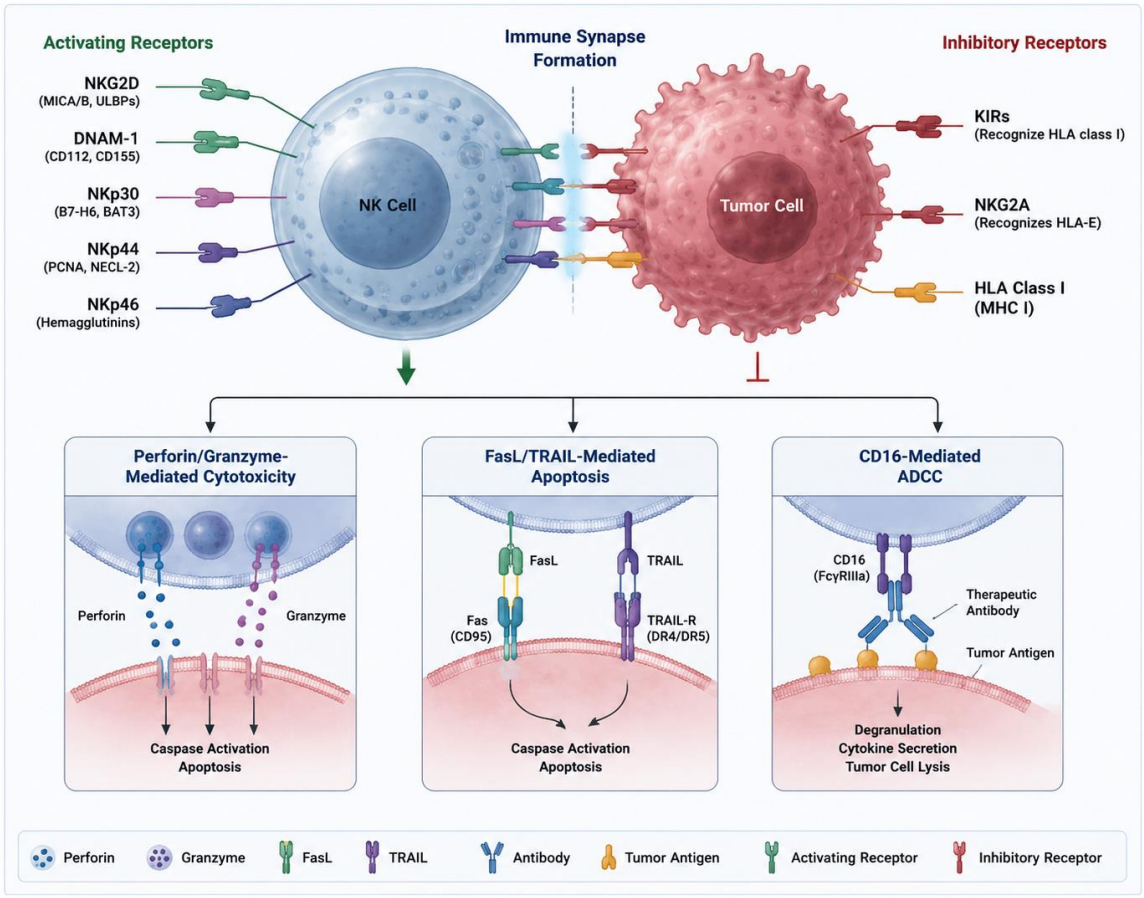

Figure 1. Major mechanisms of tumor-cell recognition and cytotoxicity mediated by natural killer cells. NK-cell activity is regulated by the integrated balance between activating and inhibitory receptor signals. Recognition of stress-associated ligands through activating receptors promotes immune synapse formation and tumor-cell elimination via perforin/granzyme release, FasL/TRAIL-mediated death receptor signaling, and CD16-dependent antibody-dependent cellular cytotoxicity (ADCC). In contrast, recognition of HLA class I molecules by inhibitory receptors, including KIR and NKG2A, suppresses NK-cell activation and limits cytotoxic responses.

In the second stage, chimeric antigen receptor architecture and the rationale for transferring CAR technology to NK cells were examined. Data concerning the antigen-recognition domain, hinge region, transmembrane domain, and intracellular signaling domains were analyzed. The ability of CAR-NK cells to simultaneously employ CAR-dependent recognition, endogenous NK-cell receptors, and the CD16 pathway was also evaluated. This multimodal recognition pattern is illustrated in Figure 2.

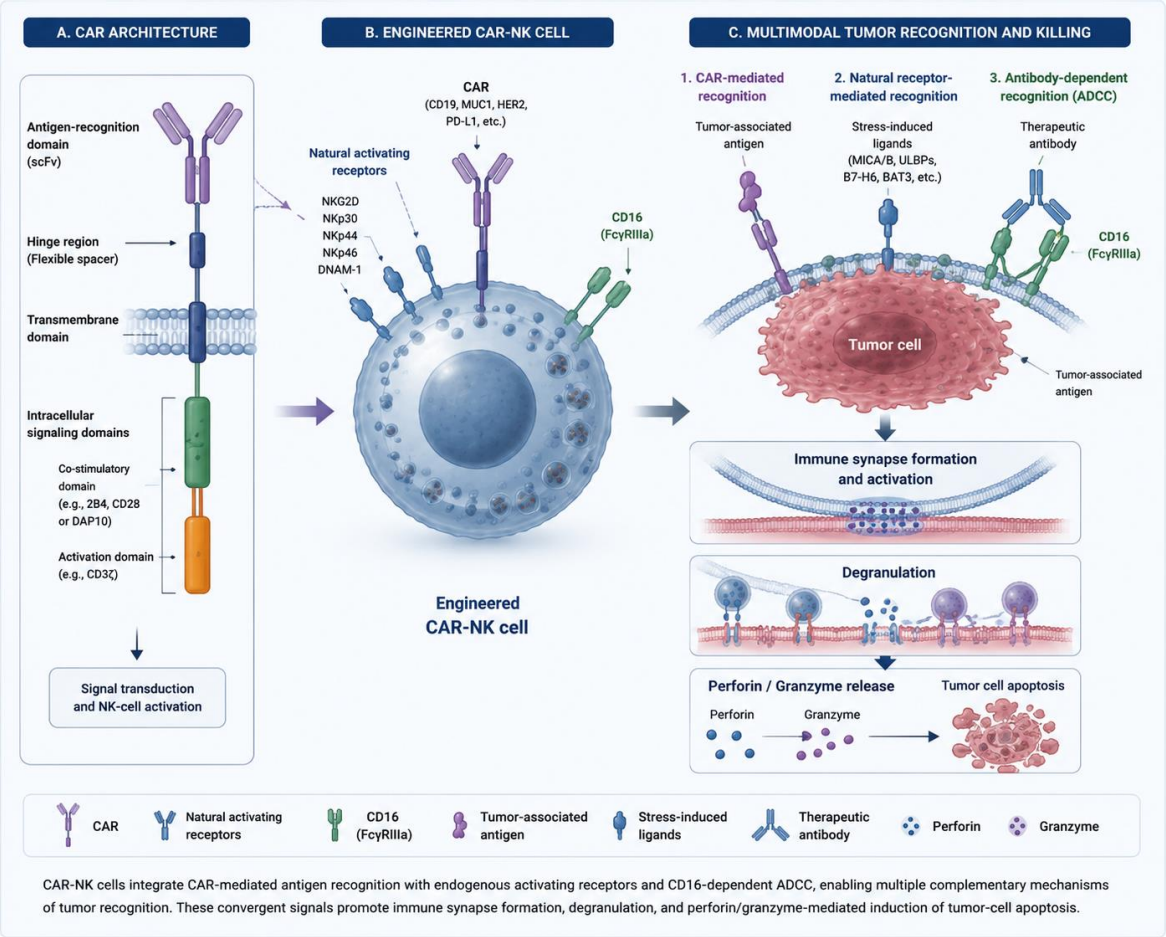

Figure 2. CAR architecture and multimodal tumor recognition by engineered CAR-NK cells. Chimeric antigen receptors consist of an extracellular antigen-recognition domain, a hinge region, a transmembrane domain, and intracellular signaling domains. CAR-NK cells combine CAR-mediated recognition of tumor-associated antigens with endogenous NK-cell recognition of stress-associated ligands and CD16-mediated antibody-dependent cellular cytotoxicity. These complementary pathways promote immune synapse formation, degranulation, and perforin/granzyme-mediated tumor-cell apoptosis.

In the third stage, data related to surface target selection in solid tumors and the challenge of antigen heterogeneity were examined. Targets including MUC1, PD-L1, HER2, EGFR, mesothelin, B7-H3, and MICA/B were considered in terms of biological significance and limitations associated with heterogeneous expression or expression in normal tissues.

Subsequently, factors associated with reduced CAR-NK activity, including TGF-β, hypoxia, mitochondrial dysfunction, increased reactive oxygen species, nutrient restriction, and inhibitory signals, were examined. Strategies proposed to address these barriers were qualitatively compared according to their targeted biological mechanisms. The principal barriers and improvement strategies considered in this review are summarized in Table 1.

Table 1. Major biological and functional barriers limiting CAR-NK cell efficacy in solid tumors and potential strategies for functional improvement

Major barrier	Biological effect on CAR-NK cells	Key molecular or functional mechanism	Potential improvement strategy
TGF-β-mediated suppression	Reduced cytotoxicity, degranulation, and activating receptor activity	SMAD2/3-dependent inhibitory signaling	TGFBR2 disruption or dominant-negative TGF-β receptor strategies
Hypoxia	Reduced survival and antitumor activity	Mitochondrial dysfunction, decreased membrane potential, and increased ROS	Modulation of mitochondrial dynamics and preservation of metabolic fitness
Antigen heterogeneity	Incomplete tumor recognition and survival of antigen-negative clones	Variable target expression and antigen escape	Dual or tandem CAR designs and multi-target recognition
Limited cellular persistence	Reduced duration of therapeutic activity	Insufficient survival and proliferative support	IL-15- or IL-21-associated support strategies
Immunosuppressive signaling	Functional inhibition of engineered cells	Inhibitory pathways and immune checkpoints	Immune checkpoint inhibition
Restrictive metabolic conditions	Reduced proliferation, degranulation, and cytokine production	Nutrient deprivation, inhibitory metabolites, and oxidative stress	Metabolic adaptation and preservation of mitochondrial function
Dependence on a single recognition pathway	Reduced efficacy following antigen downregulation or loss	Loss of the CAR-targeted antigen	Integration of CAR-mediated recognition with endogenous NK receptors and CD16-mediated ADCC

Finally, the extracted information was descriptively and qualitatively analyzed according to the relationships among NK-cell biological characteristics, target recognition, functional limitations in solid tumors, and proposed strategies for cellular improvement. The purpose of this analysis was to conceptually compare the available evidence and identify the major factors influencing CAR-NK development for solid tumors.

3. DISCUSSION AND CONCLUSION

The reviewed evidence indicates that the biological characteristics of NK cells provide an important foundation for the development of engineered cellular therapies. NK-cell activity is determined by a dynamic balance between activating and inhibitory receptors. Receptors such as NKG2D, DNAM-1, and the natural cytotoxicity receptors NKp30, NKp44, and NKp46 participate in recognizing stress signals and malignant alterations. In contrast, KIR family receptors and NKG2A generate inhibitory signals through recognition of HLA class I molecules.

Reduced HLA class I expression in some cancer cells may increase their susceptibility to NK-cell activity. Decreased HLA-dependent inhibitory signaling, together with increased expression of stress-associated ligands, shifts the signaling balance toward NK-cell activation. Following receptor activation, pathways including JAK/STAT, PI3K/AKT/mTOR, MAPK, and NF-κB participate in regulating survival, proliferation, metabolism, and cytokine production.

As illustrated in Figure 1, NK cells employ multiple independent mechanisms to eliminate target cells. The perforin/granzyme pathway represents one of the principal cytotoxic mechanisms. In addition, FasL and TRAIL can induce apoptosis through death receptors. CD16 recognizes the Fc region of antibodies bound to

target cells and activates antibody-dependent cellular cytotoxicity. The presence of these multiple pathways is one of the major biological reasons for considering NK cells as a platform for cellular therapy.

Engineering NK cells to express chimeric antigen receptors enables the integration of specific recognition with natural cytotoxic capacity. As summarized in Figure 2, a CAR-NK cell can recognize a target antigen through its engineered receptor while simultaneously using endogenous NK receptors to respond to stress-associated ligands. The CD16 pathway also preserves the capacity for antibody-dependent responses. Theoretically, this feature may reduce complete therapeutic dependence on a single recognition pathway.

Several cellular sources, including peripheral blood NK cells, umbilical cord blood NK cells, the NK-92 cell line, and NK cells derived from induced pluripotent stem cells, have been investigated for CAR-NK production. Primary cells are phenotypically closer to natural NK populations; however, extensive expansion and gene transfer can be challenging. NK-92 cells exhibit favorable expansion and engineering properties, although their cellular origin and requirement for irradiation before administration impose limitations on clinical application. Stem cell-derived sources may enable the production of more uniform and expandable populations, although standardization of differentiation and confirmation of phenotypic stability remain important considerations.

Antigen selection represents one of the major challenges in developing CAR-NK cells for solid tumors. Unlike certain hematological malignancies, most solid tumors lack a completely tumor-specific and uniformly expressed surface antigen. In TNBC and NSCLC, targets including MUC1, PD-L1, HER2, EGFR, mesothelin, B7-H3, and MICA/B have been investigated.

MUC1 has attracted attention because of its increased expression and altered glycosylation patterns in many malignant cells. However, the presence of its normal form in epithelial tissues indicates that increased expression alone is insufficient to establish target safety. PD-L1 has also been investigated because of its role in suppressing immune responses; however, its expression is dynamic and influenced by inflammatory signals and therapeutic pressure.

Antigen heterogeneity and antigen escape provide a major rationale for the development of multi-target strategies. Selective elimination of antigen-positive cells may generate selective pressure and facilitate the survival of clones with low or absent antigen expression. Dual and tandem CAR designs have been proposed to expand the range of tumor recognition. Nevertheless, increasing the number of targets may also increase the probability of recognizing normal tissues. Therefore, target combinations should be selected based on careful evaluation of expression patterns in malignant and normal tissues.

As shown in Table 1, antigen recognition represents only one stage of the CAR-NK antitumor response. Following entry into tumor tissue, engineered cells must maintain their migratory capacity, survival, and metabolic function in the presence of multiple inhibitory signals.

TGF-β is one of the major soluble factors associated with NK-cell dysfunction in solid tumors. Activation of SMAD2/3-dependent signaling may reduce the expression of certain activating receptors, degranulation, and cytokine production. Strategies such as TGFBR2 deletion and expression of a dominant-negative TGF-β receptor II have been investigated to reduce the sensitivity of engineered cells to this pathway. However, because TGF-β has broad biological functions, the consequences of sustained intervention in this signaling pathway require careful evaluation.

Hypoxia is another common feature of solid tumors and is associated with mitochondrial dysfunction, reduced mitochondrial membrane potential, and increased production of reactive oxygen species. These alterations may limit energy production, proliferation, degranulation, and cytokine production. Modulation of mitochondrial dynamics has been proposed as a potential strategy to preserve cellular function under low-oxygen conditions. However, approaches such as DRP1 manipulation should still be regarded as investigational, and further studies are required to determine their direct relevance to CAR-NK function across different solid tumor models.

Supportive cytokines also play important roles in NK-cell survival and activity. IL-15 is a major regulator of NK-cell homeostasis, survival, and proliferation, whereas IL-21 can influence the expansion and functional characteristics of these cells. However, the consequences of cytokine stimulation depend on signal intensity, duration, and cellular differentiation status, and increased stimulation does not necessarily result in durable functional improvement.

In addition to direct cellular modification, complementary interventions may create more favorable conditions for CAR-NK activity. Immune checkpoint inhibition, radiotherapy, monoclonal antibodies, and other interventions that modulate antitumor responses are among the investigated approaches. Monoclonal antibodies are particularly relevant because of their capacity to activate CD16-mediated antibody-dependent cellular cytotoxicity, providing a strong biological rationale for combination with NK-cell-based therapies.

Despite current advances, the broad translation of CAR-NK cells to solid tumor treatment remains challenged by biological, engineering, manufacturing, and clinical barriers. Antigen heterogeneity, limited cellular persistence, and factors including TGF-β, hypoxia, adenosine, IDO, nutrient deprivation, and oxidative stress may reduce the metabolic capacity and cytotoxic function of NK cells.

Gene editing enables the deletion of inhibitory receptors or signaling components; however, each additional genetic modification may produce unexpected effects on cellular proliferation, differentiation, and metabolism. Therefore, future CAR-NK designs should be based on a clearly defined biological rationale, and the effects of each engineering modification should be evaluated in a stepwise manner.

In conclusion, CAR-NK cells represent an emerging and promising approach in cancer cell-based immunotherapy. The integration of CAR-dependent specific recognition with the natural recognition and cytotoxic mechanisms of NK cells enables a multimodal response against malignant cells. Nevertheless, experience with cellular therapies indicates that antigen recognition alone is insufficient to generate durable therapeutic responses.

In solid tumors, antigen escape, TGF-β, hypoxia, mitochondrial dysfunction, and metabolic restrictions can reduce therapeutic cell activity. Multi-target strategies, reduced sensitivity to inhibitory pathways, and support of cellular survival and metabolic capacity represent major research directions in the development of next-generation CAR-NK cells. However, a substantial proportion of the available evidence remains preclinical, and translation into human applications requires carefully designed and controlled clinical studies.

Accordingly, the future of CAR-NK therapy in TNBC and NSCLC will likely depend on the development of systems that address multiple determinants of therapeutic response rather than focusing on a single barrier. Rational target selection, preservation of cellular function under restrictive conditions, and stepwise evaluation of engineering modifications may facilitate the development of safer and more effective CAR-NK therapies.

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