INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Paper

Car-NK Cells In Cancer Therapy: Unleashing the Next Generation of Immunotherapeutics

Subrahmanya Pradeep P.*, Yuktha S. K., Ranjan K, Ramdas Bhat

Srinivas College of Pharmacy, Valachil, Farangipete Post, Mangalore, Karnataka, India. 574143.

ARTICLE INFO

Published: 27 Jan. 2025
Keywords:
CAR-NK cells, immunotherapy, natural killer cells, tumor microenvironment, hematological malignancies.
DOI:
10.5281/zenodo.14745164

ABSTRACT

CAR-NK cells are a novel development within cancer immunotherapy that merges the innate cancer killing features of NK cells with the targeted nature of CAR technologies. Unlike CAR-T cells, CAR-NK compels cells among which there are lower side effects and the ability to target cancer cells regardless of MHC expression. These kinds of NK cells are readily available for application in a variety of solid tumors and as well as against hematologic malignancies hence the biology and bioengineering aspects are explained in this CAR-NK review. The ongoing progress in gene editing tools based on the CRISPR/Cas9 system, as well as increased productivity and cloning of these cells, greatly expands their possible applications. New strategies including cytokine support and combination therapy are instrumental in improving the functionality of CAR-NK cells while dealing with challenges including a short persistence time and immunosuppressive tumor microenvironments. Increasingly adaptive therapeutic models and systems are starting to produce positive results in the treatment of solid and hematological malignancies using CAR-NK cells. This is not so far as to claim that CAR-NK cells will self propel in further advance of phase 4 or beyond as it seems as though it is a new pathway for cancer therapeutics that is patient centered

INTRODUCTION

Cancer comes second to heart attacks as the leading cause of death worldwide. There are various approaches to treating cancer; they include Chemotherapy, surgery, and radiotherapy. A major downside to these three methods is that they come with a range of side effects and there is a good chance that they may cause cancer to recur[1,2]. However, the newest and most efficient approach to cancer treatment is immunotherapy. More recent literature has shown that immunotherapy works for several forms of cancer, including lymphomas and myelomas[3,4]. Natural killer (NK) cells, which include effector cells such as cytotoxic T lymphocytes (CTLs), are among the immune response cells that target the primary

***Corresponding Author:** Subrahmanya Pradeep P.
Address: *Srinivas College of Pharmacy, Valachil, Farangipete Post, Mangalore, Karnataka, India. 574143.*
Email ✉: pradeepasubrahmanya@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

malignant cell and metastatic cells by blocking tumor cell proliferation and movement[5]. Whether or not NK cells are cytotoxic, they can secrete different cytokines, specifically interferon-γ (IFN-γ), to help induce regulatory immune responses and other important processes. Most importantly, NK cells can tell the difference between healthy and malignant cells and therefore have less cross reactivity after anti-tumor cytotoxicity and targeting[6,7]. There are numerous examples from both in vitro and in vivo studies that indicate that immunological escape can be prevented using NK cells modified with the chimeric antigen receptor (CAR)[8,9]. The emerging technology of CAR-modified NK cells seems to give a chance of developing a new generation of anti-cancer immunotherapeutic agents[10]. Cancer target cells are destroyed by CAR-NK cells via both NK cell receptors and CAR which is designed to target tumor-associated antigens (TAAs)[7]. This review aims to highlight the importance of the advancement of CAR-NK cell therapy as an advanced solution for cancer immunotherapy and summarize the latest advances in the field of treating human cancers with this therapy.

METHODOLOGY

The scope of the systematic review extends to the following keywords: CAR-NK cells, immunotherapy, tumor microenvironment, and hematologic malignancies. This review covers the period from 2000 to 2024. Articles from the source were collected, analyzed and discussed. It was not necessary to get ethical clearance. The results will be published in academic journals, presented at conferences and researchers.

Chimeric Antigen Receptor Structure

Chimeric antigen receptors are a category of artificial receptors that merge the ability to recognize an antigen with that of cell-activating T-cells (CAR-T) into one single polypeptide[12,13,14]. A typical CAR is composed of four distinct areas: an extracellular structural domain, the hinge region, a membrane-spanning domain and an intracellular T cell activating domain or an endodomain[11,23,24].

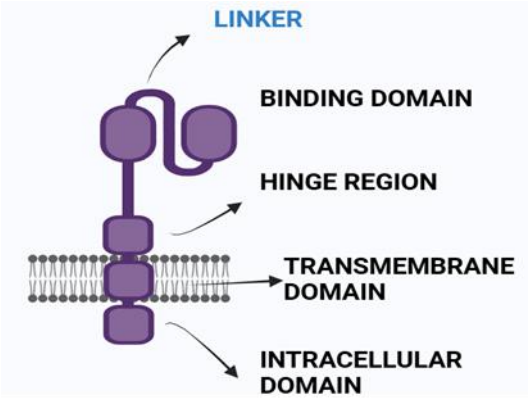

Fig 1 Structure of CAR

- ***Antigen Recognition Domain*** this domain recognizes antigens present in the receptor's epiderm[15]. This domain is linked together as a single chain of variable fragments[16,17].
- ***Hinge Region*** The hinge region is a small area between the antigen recognition domain and the outer membrane of the T cell[18]. Provides extra flexibility to CARs[19] .
- ***Transmembrane Domain of CAR*** Present in between Hinge domain and intracellular signaling domain[20]. Derived from CD3-ζ, CD4, CD8, and sometimes CD28 molecules.It plays a critical role in the influence of CAR-T-cell effector function[21].
- ***Intracellular T-cell Signaling Domain*** In the Endodomain, the intracellular T cell signaling

domain is present[22]. When a protein (antigen) binds to the antigen recognition region, CARS receptors cluster together, resulting in the transmission of an signal of activationfor the intracellular T cell signaling domain. Co-stimulatory domains like CD-27, CD-28, CD-134, and CD-137 are successfully used as signaling domains[11].

Evolution Of Cars.

Initial T-cell receptor (TCR) provided by first-generation CARs, but immunotherapy was ineffective due to insufficient T-cell persistence. Second and third-generation CARs incorporate co-stimulatory domains, such as CD28, CD137 (4-1BB), OX40 or ICO improving CAR efficacy. Fourth-generation CARs have additional signals for potency. CAR T-cells bind antibody-like manner, targeting is independent of HLA haplotype or tumor-associated HLA downregulation, and non-protein antigens can be engaged[25,26].

Enumerated Achievements In Car-NK Therapy

The development of CAR T cell therapy began in 1989 with the introduction of effector T cells. It has since been used against prostate cancer, leukemia, and refractory leukemia. CD19 CAR T cell therapy has been successful in treating pediatric Acute Lymphoblastic leukemia. The concept of CAR-NK cell was introduced in 2015. The FDA approved CAR T cell therapy in 2017 and 2018 for Acute Lymphoblastic Leukemia[11].

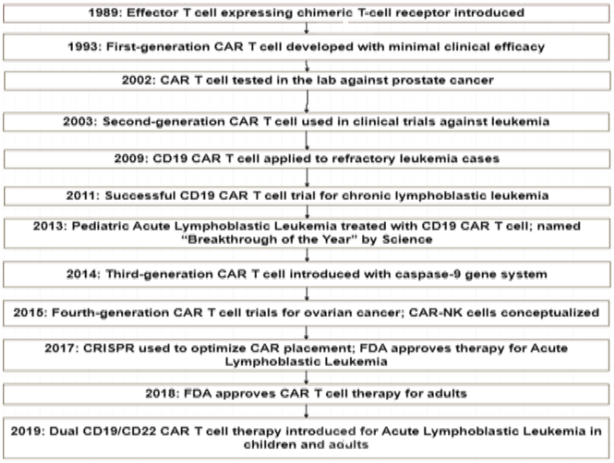

Fig 2. Development of CAR NK therapy

Role Of Nk Cells In Cancer Progression

NK cells are involved in cancer biology, more so in hematological malignancies[27]. According to the preceding literature, they possess synthetic receptors that bind to tumor-associated antigens enabling them to efficiently target cancer cells[28,29,30]. They have a remarkable capacity to detect and destroy abnormal cells with no prior sensitization such that they become ideal tools for therapeutic applications[31]. When activated, they secrete perforin and granzymes, trigger apoptosis and death receptor pathways[32,33,34]. They secrete cytokines such as IFN-γ and TNF-α which are also able to activate the immune system[35]. However, there are various challenges hampering their use, including the inability to effectively infiltrate solid tumors and the complex tumor microenvironments (TME)[36]. To eliminate these TME barriers, NK cells have to penetrate through the immunosuppressive factors along with the suppressive immune cells residing in the tumor microenvironment[37]. In spite of these issues, the TME infiltration of NK cells correlates with positive outcomes in several cancers so far studied, including breast cancer, cervical cancer, liver cancer, and melanoma[38,39]. They can kill tumor cells by different ways including the secretion of perforin, granzymes, apoptosis, lymphokines and

neoantigens[40]. Further advancing comprehension of activating NK cells, the convoluted TME and new relative tools such as iPSC derived NK cells can help introduce new therapeutic concepts[41,42,43,44].

Generation Process Of CAR-NK Cells

The ability to edit already formed NK cells or even make new NK cells from different cells (Cord blood, Peripheral blood, hiPS, hES, HSC etc[45,46,47,48,49]) with the use of lentivirus or retrovirus vectors is possible, and then culturing them in NK cell culture medium. Heavily enriched CAR-NK cells are also given intravenously so that tumour cells can be selectively eliminated[7,50].

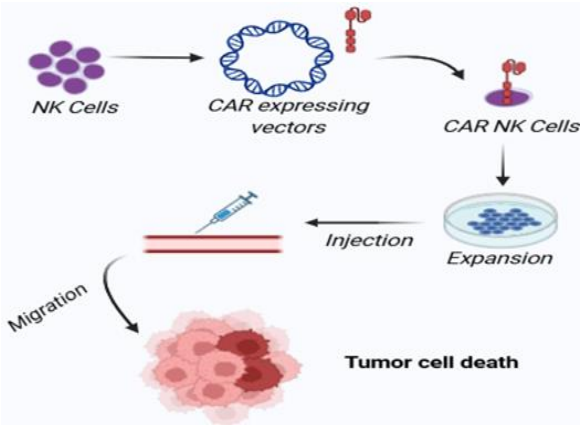

Fig 3. Generation of CAR NK cells

Car-NK Cell-Target Therapy For Human Cancers

CAR-NK therapies target a wide range of tumor antigens across diverse cancers such as leukemia, breast, ovarian, and lung cancers[51,52,53,54,55].

Table 1. CAR-NK cell-target for human cancer therapy

Target	Tumor
CD19, CD7, CD5, FLT3	Acute lymphocytic leukemia (ALL)
CD33, CD123, CD4	Acute myelocytic leukemia (AML)
HER2, EpCAM, TF, EGFR, NKG2D	Breast cancer
CD19	Chronic lymphocytic leukemia (CLL)
EpCAM, CEA, NKG2D	Colorectal cancer
GD2	Ewing sarcoma
HER2	Gastric cancer
EGFRvIII, EGFR, CD73, HER2	Glioblastoma
ROBO1	Glioma and Neuroblastoma
GPC3, NKG2D	Hepatocellular cancer (HCC)
c-MET	liver cancer
NKG2D, B7-H3	Lung cancer
CD19, CD4	Lymphoma
GPA7	Melanoma
CD138, CS1, BCMA	Multiple Myeloma
GD2, CD276	Neuroblastoma

aFR, HER2, Mesothelin, GPC3, NKG2D	Ovarian cancer
Mesothelin, ROBO1	Pancreatic cancer
PSMA	Prostate
HER2, EGFR	Renal cell carcinoma (RCC)
PSCA	Ladder carcinoma
HLA-G	Renal clear cell and renal papillary cell carcinoma, Pancreatic ductal adenocarcinoma, Thyroid cancer
CD20	Lymphoma, Leukemia cells
NKG2D	Osteosarcoma

Ongoing Clinical Trials Targeting Tumors Using Car-NK

Various types of malignancies, such as ovarian, lung, pancreatic, breast, colorectal, and renal cell carcinoma, are the subject of ongoing CAR-NK cell treatment studies. The purpose of these studies, which are mostly in Phase 1 or Phase 1/2 phases, is to evaluate the therapeutic potential, safety, and effectiveness of novel cancer immunotherapy strategies[56,57,58].

Table 2. Ongoing clinical trials targeting tumors using CAR-NK

NCT Number	Tumor Type	Phase Stage
NCT05776355	Ovarian Cancer	N/A
NCT05213195	Refractory Metastatic Colorectal Cancer	Phase 1
NCT05410717	Stage IV Ovarian Cancer, Refractory Testis Cancer, Endometrial Cancer Recurrent	Phase 1
NCT06066424	Non-small Cell Lung Cancer, Breast Cancer	Phase 1
NCT05507593	Small Cell Lung Cancer	Phase 1
NCT04847466	Gastric or Head and Neck Cancer	Phase 2
NCT05922930	Ovarian Cancer, Adenocarcinoma, Pancreatic Cancer	Phase 1/2
NCT05703854	Advanced Renal Cell Carcinoma, Mesothelioma Osteosarcoma	Phase 1/2
NCT03383978	Glioblastoma	Phase 1
NCT03940833	Multiple Myeloma	Phase 1/2
NCT02944162	Myeloid Leukemia Acute	Phase 1/2
NCT03415100	Solid Tumors	Phase 1
NCT04623944	AML, AML Relapsed/Refractory, Adult MDS	Phase 1
NCT05020678	Lymphoma, Non-Hodgkin, B-cell Acute Lymphoblastic leukemia, Large B-cell Lymphoma	Phase 1
NCT05110742	Hematological malignancy	Phase 1/2
NCT03692637	Epithelial Ovarian Cancer	Phase 1
NCT03692663	Metastatic Castration-resistant Prostate Cancer	Phase 1
NCT03941457	Pancreatic Cancer	Phase 1/2
NCT03940820	Solid Tumor	Phase 1/2
NCT03931720	Malignant Tumor	Phase 1/2

FDA Approved Car-T Cell Therapies

The FDA has authorised six CAR-T cell treatments for the treatment of haematological malignancies since 2017[59,60,61,62]. They are

- Kymriah (tisagenlecleucel, CD19 CAR-T cells)
- Yescarta (axicabtagene ciloleucel, CD19 CAR-T cells)
- Tecartus (brexucabtagene autoleucel, CD19 CAR-T cells)
- Breyanzi (lisocabtagene maraleucel, CD19 CAR-T cells)
- Abecma (idecabtagene vicleucel B-cell maturation antigen (BCMA) CAR-T cells) and
- Carvykti (ciltacabtagene autoleucel, BCMA CAR-T cells).

Among these, four (Kym-riah, Yescarta, Tecartus, and Breyanzi) are anti-CD19 CAR-T cells and two (Abecma andCarvykti) target BCMA[63,64].

DISCUSSION

A new potential avenue for advancing cancer immunotherapy is CAR-NK cell therapy which has a more of advantages over CAR T therapies that include higher precision, lesser off-targets, and fewer chances of suffering from cytokine release syndrome (CRS)[65,66,67]. Nowadays, more and more practitioners have global access to technology that enhances viral transduction, electroporation, chimeric antigen receptors (CAR), CRISPR/Cas9 gene editing, and effective cell proliferation strategies, all of which might help facilitate the production and characterization of genetically modified NK cells. Those promising inventions assist scientists and clinicians in creating a stronger NK cell for therapeutic applications. In this regard, it must be emphasized that the utilization of a CAR for NK cell rerouting holds great potential for cancer immunotherapy. CAR-NK cells have undergone a range of preclinical and recently clinical trials with targets like high target cell killing with no side effects such as nurotoxicity and cytokine release syndrome that are common with CAR T therapies[68].

Future Prospectives

Strategies to enhance the CAR-NK therapy include the use of cytokines like IL-15 to improve in vivo persistence, improvement in gene editing approaches such as CRISPR/Cas9, and the introduction of viral vectors that are both cheap and easy to administer. Such engineering can also help in combatting TGF-β which is crucial to engage a hostile tumor microenvironment. Like CAR T cells, larger-scale production of CAR NK cells should rely on iPSCs that would make CAR-NK cells widely available and affordable due to their universal “off the shelf” properties. Furthermore, CAR-NK cells can be used along with checkpoint inhibitors and other modalities, and this approach has great promise in achieving a combined effect.

CONCLUSION

Because of their properties CAR-NK cells will surely improve cancer treatments by addressing the limitations that other modified approaches face. There is assurance for continuous development in treating solid tumors and blood cancer even in the early stages of clinical development. For CAR-NK cells to become mainstream therapies, there is a need to work on enhancing their performance, durability, and affordability for maximum acceptance in surgeries.

ACKNOWLEDGMENT:

We would like to take this opportunity to express my heartfelt thanks to everyone who directly and indirectly, helped throughout the my work.

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HOW TO CITE: Subrahmanya Pradeep P.*, Yuktha S. K., Ranjan K, Ramdas Bhat, Car-NK Cells In Cancer Therapy: Unleashing the Next Generation of Immunotherapeutics, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 1, 2225-2234. https://doi.org/10.5281/zenodo.14745164