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Review Article

Advancing Cancer Immunotherapy: The Promise and Challenges of CAR-NK Cell Therapy

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Abstract

Cancer immunotherapy has revolutionized the therapy landscape, particularly with the advent of Chimeric Antigen Receptor (CAR) therapies, which enhance the immune system to target and kill cancer cells. While CAR-T cell therapy has shown remarkable responses in treating certain hematological cancers, astronomical costs, laborious manufacturing processes, and toxicities restricted its use.

Key Words: cancer; chimeric antigen receptor; immunotherapy; nk cells

Introduction

Cancer immunotherapy has revolutionized the therapy landscape, particularly with the advent of Chimeric Antigen Receptor (CAR) therapies, which enhance the immune system to target and kill cancer cells. While CAR-T cell therapy has shown remarkable responses in treating certain hematological cancers, astronomical costs, laborious manufacturing processes, and toxicities restricted its use. This immunotherapy opened the door to exploring CAR-NK (Naturel Killer) cells as a promising alternative. These CAR-NK cells combine the intrinsic tumor-killing capabilities of NK cells with the CAR specificity and make cancer therapies safer, less expensive, and more accessible. In this editorial, we describe the present status of CAR-NK cell therapy, including the possible benefits, limitations, and perspectives of this developing area.

CARs promote immune responses and cellular activation by enabling effector cells to target specific antigens. Precision in such a scenario is critical in cancer therapy, with a chance to destroy malignant cells and spare surrounding healthy tissue. Natural Killer (NK) cells contribute to function in the immune system for fighting off tumors by employing a combination of inhibitory and activation receptors, enabling them to detect and destroy malignant or virus-infected cells. Several new strategies in immunotherapy employing NK cells have been developed, with each having its respective strengths and weaknesses (Figure 1) [1].

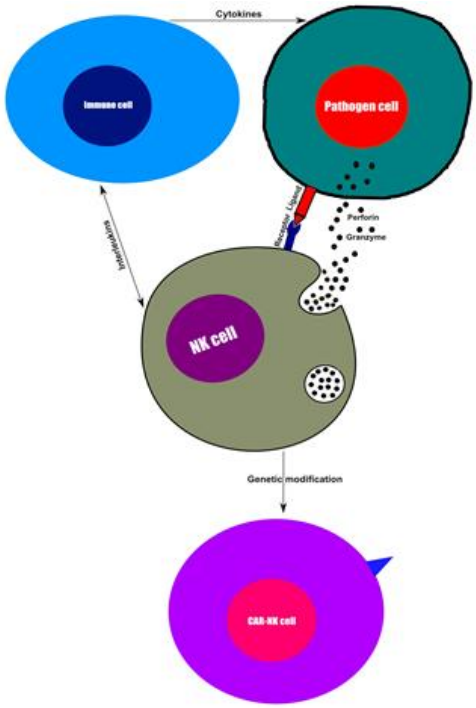

Figure 1: Activities of Natural killer cells.

One approach is the administration of cytokines, such as IL-2 or IL-15, which indirectly activates NK cells. While IL-2 does enhance NK cell activity, it has associated toxicities that limit its application to combination treatments, whereas IL-15 demonstrates a similar activating capacity with fewer side effects. Another approach is adoptive immunotherapy, which implies the isolation of NK cells, their expansion ex vivo, genetically engineered, and reinfusion into the patient for targeting tumor cells. CAR-NK cells bear chimeric antigen receptors that attack tumor cells, reducing the risk of graft-versus-host disease and offering "off-the-shelf" availability. However, the tumor microenvironment limited their effectiveness [2].

Haploidentical stem cell transplantation is another strategy involving the transplantation of hematopoietic stem cells along with NK and γδT cells from a partially matched donor, which has successfully lowered relapse rates and infections in leukemia patients. Finally, checkpoint inhibitors, which utilize monoclonal antibodies to block immune checkpoints like PD-1 and CTLA-4, can enhance NK cell function, especially against tumors that lack HLA class I molecules, and evade immune detection. Despite these advances, the inhibitory tumor microenvironment remains an obstacle to suppressing NK cell activity. To address this challenge, researchers are investigating combination therapies to disrupt the tumor microenvironment and improve NK cell efficacy to make these treatments more effective and widely accessible (Figure 2) [3].

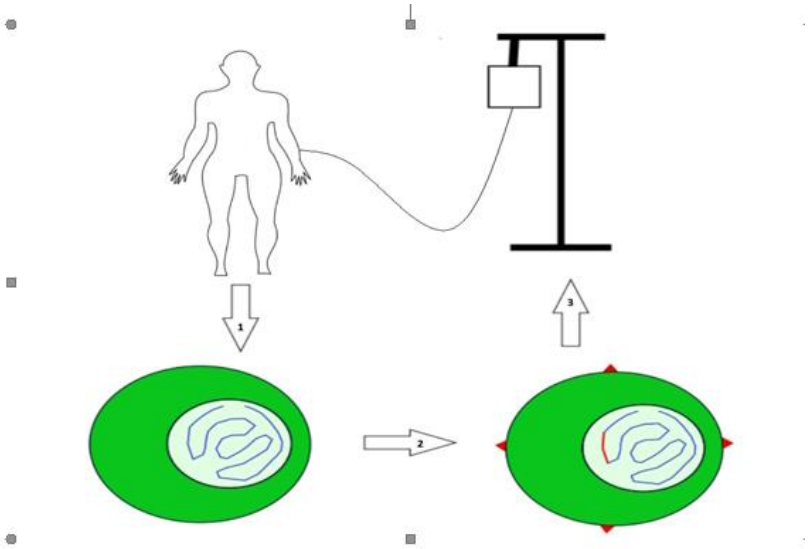

Figure 2: CAR-NK cell therapy involves a multi-step process : (1) NK cells are extracted from the patient, (2) A gene encoding a chimeric antigen receptor is introduced into these NK cells, granting them the ability to target a specific antigen, (3) The genetically modified NK cells are infused into the patient's body.

CAR T cell therapy has made strides in treating cancer, particularly blood cancers, using a patient's genetically engineered immune cells. However, its application has high costs, the need for a personalized treatment approach, and serious risks such as cytokine release syndrome and neurotoxicity. In response, scientists pay attention to CAR NK cells obtained from donors. This alternative offers a safer, more affordable, and widely accessible "off-the-shelf" treatment option. However, challenges remain in CAR-NK cell therapy. Further research tries constantly to overcome these challenges to maximize the benefits of cancer treatment [4, 5].

Compared with CAR T cells, several advantages of CAR NK cells represent a novelty of cancer immunotherapy and are beginning to come into view: preparation is possible from universal donor sources for immediate "off-the-shelf" availability without personalized cell preparation. Serious side effects like GvHD, cytokine release syndrome, or neurotoxicity are limited, and CAR NK cells are safer for clinical use on an extensive basis. More importantly, CAR NK cells possess an inherent affinity to tumors and persistence efficacy. Nonetheless, tumor microenvironment penetration and persistence of therapeutic effect still have their challenges. Active efforts allow us to overcome these obstacles and improve CAR NK cells for cancer therapy [6, 7].

It also becomes clear that CAR-NK cell therapy could be a very active alternative to CAR-T cell therapy in hematological malignancy treatment, with possible advantages in safety and costs. Unlike CAR-T cells, CAR-NK cells utilize the natural killer cells' inherent antitumor capabilities, reducing the risk of immune-related toxicities and graft-versus-host disease. More importantly, CAR-NK cells can be made as "off-the-shelf" products and would be more accessible tos patients. Despite these advantages and disadvantages, the persistence and proliferation of NK cells in the body remain essential. During ongoing development, CAR-NK therapy holds much promise as an alternative option that is more effective and accessible for cancer treatment [8-10].

From such a concept, CAR-NK cell therapies now represent the next leap in cancer immunotherapy and a much safer, more accessible alternative to CAR-T cell therapies. By harnessing the innate tumor-targeting capabilities of NK cells and overcoming some of the limitations associated with T cell-based therapies, CAR-NK cells change hematological malignancy treatments. While progress in fully realizing the promise of CAR-NK therapy, challenges in improving NK cell persistence and function within the tumor microenvironment still need to be overcome. More research can make it a mainstay in cancer treatment over such hurdles [11-33].

Abbreviations

CAR: Chimeric antigen receptor

CAR-NK cells: Natural Killer cells

CTLA-4: Cytotoxic T-lymphocyte associated protein 4

GvHD: Graft-versus-host disease

HLA: Human leukocyte antigen

IL: Interleukine

PD-1: Programmed cell death protein 1

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