

Chimeric Antigen Receptor (CAR)-NK Cells: Emerging Immunotherapy for the Treatment of Cancer

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Received date: September 13, 2019, **Accepted date:** September 18, 2019

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Keywords: CAR-NK cells, Immunotherapy, NK cells, Chimeric antigen receptor, Novel therapies

Natural killer cells (also known as NK cells) are a type of cytotoxic lymphocytes that serves as the first line of defense against foreign agents including bacteria, and virally-infected cells.

Although NK cells are recognized as effector lymphocytes of the innate immune system, they also regulate the adaptive immune response by releasing inflammatory cytokines and developing immunological memory. Unlike other lymphocytes such as T or B cells, NK cells do not express rearrangeable, antigen-specific receptors. After interaction with target cells or their ligands, NK cells receptor such as killer-cell immunoglobulin-like receptors (KIRs) induces either activating or inhibitory signals which regulate the NK cell effector functions [1]. Normal cells are protected from NK cells lysis activity by the recognition of “self” HLA molecules on their surface. Cancer cells often repress or lose their HLA as an escape mechanism from T cells; however, downregulation of HLA makes them susceptible to NK cell lysis [2, 3]. Potent cytolytic activities and the immense potential of NK cells in destroying foreign entity and abnormal cells of the body offers an excellent opportunity to harness the feasibility of the use of these cells in cancer immunotherapy. Immune checkpoint PD-1/PD-L1 and CTLA4 blockade therapy, and chimeric antigen receptor (CAR)-T cells has led to a breakthrough in the treatment of multiple types of advanced malignancies and added a new dimension in the fight against cancer with remarkable success in the clinic. Modification of NK cells with chimeric antigen receptor (CAR-NK cells) protein that enables NK cells to target a specific protein expressed on tumor cells has generated additional hopes

to manage cancer in a better way and improve clinical outcomes. CD4-CD3 ζ (CD4 ζ) fusion receptor was the first CAR-NK cells used successfully to target either HIV-infected CD4⁺ T cells or tumor cells expressing gp120 [4]. NK-92 cell lines expressing a CAR specific for the tumor-associated ErbB2 (HER2/neu) antigen demonstrated efficient cytolytic activity against ErbB2-expressing tumor cells *in vivo* [5]. CAR-NK cells designed utilizing CD19, a surface antigen, widely expressed by malignant B cells showed promising result against autologous leukemia cells [6]. Moreover, for the treatment of hematological cancers and solid malignancies, several CAR-NK cells are under clinical evaluation.

CAR-T cell therapy has several practical limitations. Generation of autologous CAR-T cells is a complex process and takes a few weeks, which makes it impossible for the patients with aggressively advanced malignancies. Besides, production of the viable and clinically relevant amount of CAR-T cells is impractical from the patients with disease or condition like lymphopenia. On the other hand, CAR-NK cells are easy to isolate and their relatively shorter lifespan reduces the potential risk of overexpansion of transfected CAR-NK cells in the cancer patient. Also, limited life-span of NK cells reduces the long-term adverse effects including the off-target toxicity. Engineered NK cells usually retain their native receptors which help them in the identification of tumor cells and establish them as better candidate compared to CAR-T cells. CAR-NK cells can induce tumor cells lyses in both CAR-dependent and CAR-independent manner, unlike T cells which require secondary co-stimulatory signal for their biological activity [7]. Activated CAR-T cells

produced cytokines TNF- α and IL-6 may result in life-threatening cytokine release syndrome, however, NK cells primarily release IFN- γ and GM-CSF which are relatively safer than the cytokines released by CAR-T cells [8]. The allogeneic “off-the-shelf” T cells bear a potential risk of graft-versus-host disease (GVHD) mediated through their native receptor. In contrast, NK cells are known for their inability to induce GVHD, which offer an advantage to generate “off-the-shelf allogeneic” NK cells. The source of CAR-NK cells can be hematopoietic stem cell progenitors, NK cell lines as well as primary human NK cells isolated from peripheral blood. Primary human NK cells derived from hematopoietic stem cell progenitors, peripheral blood or NK cell lines have been effectively altered to express CARs against multiple targets [9]. CAR-NK therapy appears to be less laborious, less time-consuming and cost-effective than the CAR-T cells [8].

For the successful execution of CAR-NK therapy, several issues need to be addressed, including detailed information of the optimal structure of CARs on NK cells that trigger the effective immune response has been yet to be studied. Also, the distance of CAR-NK cell surface and CAR-binding epitope that influence the interaction with antigen and subsequently trigger immune system need further investigation for the ideal effects. Moreover, the requirement of differential costimulatory signals between primary NK cells, NK-92 cell line, and hematopoietic stem cell progenitors-derived NK cells also needs careful planning. The efficacy of CARs is largely attributed to the ability of cells to recognize the antigen differentially expressed on cancer cells. However, non-specific binding of CARs to the antigen expressed on normal tissue could result in toxicity. CAR-T cells generated against CD19 for the treatment of B cell malignancies have demonstrated strong off-target toxicity [10]. However, to date, no clinical data is available on the off-target toxicity of CAR-NK cells.

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