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Natural Killer Cells: Future Role for Cancer Immunotherapy

Joseph Murphy

Immune LLC Quincy MA 02169. Founder and President

ABSTRACT

Abstract: Natural killer (NK) cells are cytotoxic lymphocytes of the innate immune system that are capable of killing virally infected and physiologically stressed cells, like tumor cells. In addition to their ability to directly kill cancer cells, NK cells are capable of enhancing both antibody and T-cell responses. Moreover, ex vivo activation, expansion, and genetic modification of NK cells can greatly enhance their anti-tumor activity and equip them to overcome resistance. As a result of these observations, NK cells are currently the focus of intense investigation with the potential to become a key therapeutic modality in the next wave of cancer treatments.

Keywords: Natural killer cells, immunotherapy, chimeric antigen receptor, tumor.

ARTICLE DETAILS

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NATURAL KILLER CELLS

NK cells are lymphocytes from the same family as B- and T-cells. Since they are cells of the innate immune system, they are classified as innate lymphocytes (ILCs) and represent 5-20% of all circulating lymphocytes in humans. Their name derives from the fact that they can target cells without the need for prior activation. NK cells are essential for the management of immunological responses and for innate immunity. Although they are primarily responsible for killing virally infected cells, they are also useful for detecting and arresting early signs of cancer. Tumor-infiltrating NK cells function within a hypoxic environment, such as the tumor microenvironment (TME). They are unique in that they have the ability to recognize and kill stressed cells without the need for the major histocompatibility complex (MHC) or antibodies (Murphy, 2022).

The surface of NK cells consists of different activating and inhibitory receptors that recognize different membrane proteins. The presence of NK cells within several different cancers, including squamous cell lung, gastric, and colorectal cancers have been reported to be a positive prognostic factor for these patients (Gillgrass et al 2015). There is a correlation between the presence of NK cells in a tumor and a positive clinical benefit for cancer patients and the potential to kill parts of the tumors resistant to other therapies. NK cells can swiftly kill multiple adjacent cells that express surface markers associated with oncogenic transformation, a unique trait among immune cells. Moreover, their capacity to enhance antibody and T-cell Responses support the role of NK cells as anticancer agents (Shimasaki et al 2020).

CELLULAR IMMUNOTHERAPY

Cellular Immunotherapy, also known as adoptive cell therapy, is an innovative treatment approach that harnesses the body's immune system to eliminate cancer and has long been considered an attractive therapeutic approach (Murphy, 2020). NK cells secrete cytokines like interferon-□ (IFN-□), tumor necrosis factor-□ (TNF-□), chemokines, and other factors that modulate the functions of other immune cells. A major challenge for NK cells is that tumors develop several different strategies to avoid NK cell attack. For example, mature NK cells express the PD-1 receptor, and engagement with the programmed death-ligand 1 (PD-L1) ligand results in impaired antitumor NK cell activity (Del Zotto et al 2017).

Tumors may develop several mechanisms to resist attacks from endogenous NK cells. However, ex vivo activation, expansion, and genetic modification of NK cells can greatly increase their anti-tumor activity and ability to overcome resistance. Some of the ex vivo expansion and activation methods used have translated into clinical-grade platforms, and clinical trials of NK cell infusions in patients have yielded promising results so far (Daher et al, 2021). Several companies are currently focusing on NK cells to develop technologies and methods that increase their expansion and activation. Using cells from both the patient and donor-

derived sources renders autologous or allogeneic NK cell therapy an attractive therapeutic option.

ADVANTAGES OF NK CELLS OVER T-CELLS

Both NK cells and $CD8^+$ cytotoxic T-cells can kill target cells through similar cytotoxic mechanisms. Over the last few years, chimeric antigen receptor (CAR) T-cell therapy has shown spectacular success in treating hematological malignancies. Currently, there is a growing interest in developing CAR-engineered NK (CAR-NK) cells for cancer therapy as they potentially confer a number of advantages over the CAR-T therapies (Xie et al, 2020). Some of these advantages include safety, multiple mechanisms, and reduced alloreactivity, as outlined here.

Safety: Due to the limited lifespan of CAR-NK cells there is less risk of on-target/off-tumor toxicity. Allogeneic CAR-NK therapy has reduced the risk of graft versus host disease (GVHD) due to the amount of cytokine release. Whereas activated CAR-NK cells normally release IFN-g and granule-macrophage colony-stimulating factor (GMCSF), CAR-T cells can produce multiple cytokines that include interleukin (IL)-1a, IL-1Ra, IL-2, IL-2Ra, IL-6, IL-8, IL-10, IL-15, and TNF-α, which are associated with severe neurotoxicity.

MULTIPLE MECHANISMS

CAR-NK cells, not alone kill tumor cells in a CAR-dependent manner, but can also eliminate cancer cells in a CAR-independent manner. In addition to eliminating tumor cells through CD16 mediated antibody-dependent cell-mediated toxicity (ADCC), CAR-NK cells also possess their natural cytotoxic activity that can be activated through CAR-independent mechanisms.

REDUCED ALLOREACTIVITY

The reduced risk for alloreactivity potentially allows CAR-NK cells to be generated from multiple sources, including NK92 cell lines, peripheral blood mononuclear cells (PBMCs), umbilical cord blood (UCB), and induced pluripotent stem cells (iPSCs). Therefore, CAR-NK cells potentially offer an “off-the-shelf” allogeneic product, eliminating the need for a personalized and patient-specific product associated with current CAR-T cell therapies.

SUMMARY

The field of NK cell-based cancer therapy currently constitutes a major area of immunotherapy research. Two of the major focal points include optimizing the source of cells and enhancing the cell toxicity/persistence in vivo. They are emerging as both safe and efficacious treatments for some cancers with the potential to become an off-the-shelf allogeneic therapy. Some of the current challenges are enhancing both activating signals and proliferation, in addition to suppressing inhibitory signals and honing cells to tumor sites. Taken together, these observations suggest that NK cells will continue to evolve and lead to major improvements in the treatment and survival of cancer patients.

REFERENCES

I. Murphy, JF (2022). Angiogenesis and the Tumor Microenvironment. Handbook of Cancer Immunology. In Press. Ed: Nima Rezaei. Springer.
II. Gillgrass AE et al (2015). Recent advances in the use of NK cells against cancer. Cancer Immunology: Bench to Bedside Immunotherapy of Cancers. Springer. Ed: Nima Rezaei. Springer.
III. Shimasaki, N et al (2020). NK cells for cancer immunotherapy. Nat Rev Drug Discov 19, 200–218. https://doi.org/10.1038/s41573-019-0052-1.
IV. Murphy, JF (2020) Frontiers in Cancer Immunotherapy (2nd edition). Cancer Immunology: Bench to Bedside Immunotherapy of Cancers. Ed. Nima Rezaei. Springer. https://www.springer.com/gp/book/9783030502867
V. Del Zotto, G et al (2017) Markers and function of human NK cells in normal and pathological conditions. Cytometry B Clin Cytom 92(2):100-114. Doi: 10.1002/cyto.b.21508.
VI. Daher, M et al (2021). CAR-NK cells: the next wave of cellular therapy for cancer. Clin Trans Immunology. 10(4). doi: 10.1002/cti2.1274.
VII. Xie, G et al (2020). CAR-NK cells: a promising cellular immunotherapy for cancer. eBiomedicine. 59: 102975. https://doi.org/10.1016/j.ebiom.2020.102975.