Natural killer cell: An immuno-oncology novel target for cancer therapy?

Our body is protected by immune system from pathogens such as bacteria and viruses with layered defenses of increased specificity. The immune system is a host defense system classified as innate and adaptive immunity. Both innate and adaptive immune cells actively prevent neoplastic development in a process called "cancer immunosurveillance." Innate immune cells include monocytes, macrophages, dendritic cells and natural killer (NK) cells which mediate immediate, short-lived responses by releasing cytokines that directly lyse tumor cells or capture debris from dead tumor cells. Adaptive immune cells include T- and B-cells which mediate long-lived, antigen-specific responses and effective memory.[1]

NK cells belong to the group of large granular lymphocytes of innate immune system, phenotypically defined as CD56 +ve and CD3 −ve in humans. They are developed in bone marrow by the lymphoid progenitor cells destined to produce cytokines. They can recognize certain tumor cells and viral-infected cells and kill them by injecting cell degrading protein into malignant cells. They were named "natural killers" because they do not require any activation to kill cells that are missing MHC class I markers which cannot be detected and destroyed by other immune cells such as T lymphocytes. NK cells were discovered in 1975, but still it took almost 30 years to understand its cell biology and function lending novel insights into their role in immunosurveillance. The treatment approaches based on immunotherapy have attracted during the past decade due to its numerous advantages over chemotherapy and radiotherapy. Numerous studies done on mice and humans on NKs have known to play a role in tumor immunosurveillance by directly inducing the death of tumor cells, even in the absence of surface adhesion molecules and antigenic peptides. This role of NK cells is critical to immune success particularly because T cells are unable to recognize pathogens in the absence of surface antigens.[2]

NK cells could directly kill target tumor cells through several mechanisms [Figure 1]:

i. By releasing cytoplasmic granules containing perforin and granzymes that lead to tumor-cell apoptosis by caspase-dependent and caspase-independent pathways
ii. By death receptor-mediated apoptosis by interacting with their receptors, Fas and TRAIL on tumor cells
iii. By secreting various effector molecules such as interferon-c that exert antitumor functions such as tumor angiogenesis and stimulating adaptive immunity
iv. Through antibody-dependent cellular cytotoxicity by expressing CD16 to destroy tumor cells.[3]

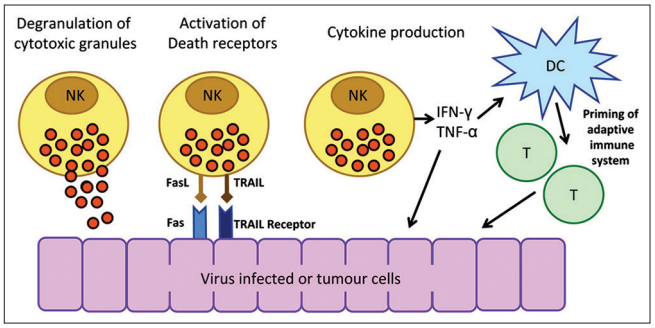

Figure 1: The natural killer cell response to virus-infected or tumor cells

Tumor cells during its progression develop certain mechanisms to escape from NK cell recognition. These include losing their expression of adhesion molecules, ligands for activating receptors, upregulating MHC class I, FasL or NO expression, secreting immunosuppressive factors such as IL-10, transforming growth factor-β and resisting Fas- or perforin-mediated apoptosis. NK cells play critical roles in the first-line of defense against malignancies by direct and indirect mechanisms.

Since NK cells represent only a minor fraction (10%) of the human lymphocyte population, their phenotype and impaired functionality during cancer progression necessitate the development of different clinical protocols to activate and expand to sufficient numbers *ex vivo* to be able to infuse functional NK cells to the cancer patients. The therapeutic use of NK cells in human cancer immunotherapy has been studied using autologous NK cells, allogeneic NK cells, NK cell lines, NK cells via antibody-dependent cell-mediated cytotoxicity and genetically modified NK cells.[4]

Initial clinical trials on NK cells suggested that NK cell infusion was safe and feasible with almost no

NK cell-related toxicity, but in case of patients with hematological malignances, disease-free survival and complete remission were shown in small number of cases. Although NK cells have known to be potential targets on tumor cells, limited antitumor effects have been demonstrated following NK cell infusion in patients with solid tumors. Genetic modification of NK cells may be effective on cancer immunotherapies by improving NK cell responses and making them less susceptible to the tumor microenvironment.[5]

NK cell involvement is not only limited to treatment of cancer but also have been recognized in various disease conditions. Antitumor activity was seen when autologous NK cells were given to patients with lymphoma who underwent bone marrow transplantation, but the outcomes were poor with severe side effects. Recently, *ex vivo*-expanded, allogeneic NK cells from unrelated, random donors were successfully administered to patients with malignant lymphoma or advanced solid tumors. *In vitro* studies with NK cells could mediate the senescence of freshly isolated human.[6]

NK cells are the first line of defense against cancer progression. Recent headway in regenerative medicine has helped us to focus on strengthening our body's own natural capacity with immunotherapy work to boost the body's immune system, enhancing its ability to fight against cancer cells. The therapies are also often associated with fewer side effects compared with other treatments, such as chemotherapy and radiation therapy. More focus should be placed in the field of learning NK cell biology and establishing techniques for the isolation and expansion of these cells in their required numbers which might benefit treatment of cancer patients.

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Conflicts of interest

There are no conflicts of interest.

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