Editorial

Ann Lab Med 2022;42:619-620
https://doi.org/10.3343/alm.2022.42.6.619
ISSN 2234-3806 • eISSN 2234-3814

ANNALS OF LABORATORY MEDICINE

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Ex Vivo Expansion of Highly Cytotoxic Natural Killer Cells Using Optimal Culture Medium

Cancer immunotherapy helps a patient's immune system fight cancer by using immune components. The success of cancer immunotherapy as an alternative to conventional chemotherapy has shifted the paradigm of oncology care. In particular, the promising clinical outcomes of chimeric antigen receptor (CAR)-T cell therapeutics for blood cancer compensate the low response rates to immune checkpoint inhibitors [1]. Natural killer (NK) cells of the innate immune system readily recognize and kill infected cells and tumor cells without immune priming [2]. A recent clinical study demonstrated that the infusion of CAR-NK cells into patients with CD19-positive cancers (non-Hodgkin's lymphoma or chronic lymphocytic leukemia) is a powerful therapeutic approach, with low toxicity [3]. Thus, the development of NK cell therapies may mark a turning point in cancer immunotherapy.

For successful NK or CAR-NK cell therapy, generating a sufficient number of cells for infusion is a prerequisite. At present, NK cells are mostly cultured in Roswell Park Memorial Institute (RPMI)-1640 medium (Gibco, Thermo Fisher Scientific, MA, USA), X-VIVO 10 medium (Thermo Fisher Scientific), stem cell growth medium (Thermo Fisher Scientific), and CTS AIM V serum-free medium (SFM) (Thermo Fisher Scientific) supplemented with serum. Human serum, platelet lysate, and plasma have been suggested to support optimal cell proliferation. However, there are concerns about lot-to-lot variability and risk of infection. While T cell expansion using good manufacturing practice-grade SFM has been validated, in clinical trials, NK cells are still produced using media containing serum-based supplements [4]. SFM for the large-scale production of NK cells has not been developed. Therefore, an SFM solution should be validated for the expansion of primary NK cells.

In this issue, the study by Koh, *et al.* [5] authors show culturing NK cells in three types of basal media, i.e., RPMI-1640 medium and Dulbecco's modified Eagle's medium (DMEM) (Thermo Fisher Scientific) supplemented with serum, and CTS AIM V SFM with immune cell serum replacement, using genetically engineered K562 cells expressing OX40 ligand and membrane-bound interleukin (IL)-18 and IL-21 as feeder cells. Adding serum increased the expansion rate of NK cells but reduced their cytotoxicity due to a delay in target cell recognition. These results supported the need for optimized SFM culture conditions for NK cells, and therefore, the authors established new culture conditions for NK cells to increase the expansion rate. The cells were initially cultured in DMEM supplemented with serum and changed to CTS AIM V SFM on day 14. Their findings suggest that the newly developed culture medium is a competitive alternative to serum-containing media for expanding primary NK cells for adoptive immunotherapy.

Cancer immunotherapy is a promising new frontier therapeutic strategy for cancer treatment. Although cytotoxic T lymphocytes are a major focus of immunotherapy, an increasing number of reports of successful NK cell therapy suggest that other

effector populations are also important for a positive therapeutic response and deserve the same level of attention in clinical treatment strategies.

AUTHOR CONTRIBUTIONS

Kim SH drafted the manuscript. The author read and approved the final manuscript.

CONFLICTS OF INTEREST

The author declares no potential conflicts of interest.

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Key Words: Natural killer cell, Culture media, Immunotherapy, Cancer