Importance of Natural killer (NK) cells in therapy of cancer.

Richard Bachman*

Department of Immunology, University of London, London, United Kingdom

Introduction

Both innate and adaptive immunity actively prevent neoplastic development in the process called "cancer immunosurveillance." In the early 1970s, Dr. Ronald Herberman and colleagues discovered a new class of lymphocytes that they called natural killer (NK) cells. Subsequently, these investigators were among the first to demonstrate that effector lymphocytes from athymic nude mice are highly reactive against several syngeneic and allogeneic tumors in a 51Chromium-release cytotoxicity assay. They recognized that anti-tumor reactivity was not T-cell dependent. Foreign, damaged, malignant and viral transformed cells may lose expression of major histocompatibility antigen (MHC) class I in a process of "loss of self" and, as a result, become "susceptible" to autologous NK-cell killing. NK cells are educated by interaction with MHC class I molecules to gain potent function to kill malignantly transformed cells without prior sensitization by either direct cellular cytotoxicity, antibody-mediated cellular killing, or release of potent cytokines, such as interferon gamma (IFN-γ), that lyse susceptible targets.

The initial application of autologous NK-cell–enriched cellular products to treat cancer was pioneered at the National Cancer Institute in 1980. Basic principles postulated in these trials laid the foundation for the adoptive cell therapy field. The potential role of allogeneic NK cells in cancer elimination has been more difficult to demonstrate. The most direct evidence comes from clinical observations following allogeneic donor stem cell transplantation. NK cells rapidly reconstitute after donor stem cell transplantation. In instances where haploidentical donor and recipients were mismatched in KIR–KIR ligands (class I HLA), donor NK cells mediated strong anti-leukemia cellular responses capable of protecting patients from leukemia relapse [1].

Autologous NK cells in cancer therapy

Human NK cell activity is under the control of signals from the killer immunoglobulin receptors (KIR) complex. KIRs are expressed on the NK cell surface and most commonly interact with the MHC class I molecule HLA-Bw4, HLA-C1, and HLA-C2 groups. In most circumstances, autologous NK cells are under the dominance of inhibitory signals. NK cell cytotoxicity is triggered by the loss of MHC class I on tumor cells [2]. Under normal homeostatic conditions, a balance of activating and inhibitory signals tightly control NK cell function. Activating NK-cell receptors include natural cytotoxicity receptors NKp30, NKp44, and NK46 and, importantly, NKG2D and DNAM-1, which is constitutively expressed on all NK cells. Activating receptors recognize stress-induced molecules, HLA class 1–related MICA and MICB, class I–like cytomegalovirus-homologous ULBP proteins, and ligands CD155 (Poliovirus receptor) and CD112 (Nectin −2), which are expressed on some tumors, making them sensitive to NK-cell–mediated killing. In vitro, NK cells can mediate the direct killing of freshly isolated human tumor cells from acute myeloid leukemia, acute lymphoblastic leukemia, multiple myeloma, neuroblastoma, ovarian carcinoma, and colon, renal cell, and gastric carcinomas. Many lymphoma tumors express high levels of HLA class I receptors and lack ligands that signal through activating NK-cell receptors. Such tumors may be resistant to the NK-cell–mediated lysis. After incubating NK cells with cytokines, particularly IL-2 or IL-15, NK cells acquire the capacity to lyse a broad array of fresh and cultured tumor targets not normally sensitive to NK lysis, including the Raji lymphoma cell lines [3].

Allogeneic NK cells in acute myeloid leukemia therapy

Recent advances in the understanding of basic NK cell biology has shed light on the processes of NK cell education by which NK cells acquire self-tolerance and "alloreactivity." This developmental mechanism is an adaptive process that NK cells undergo in response to the HLA class 1 environment. Several lines of evidence suggest that functional activity of mature NK cells can be reset when the cells are exposed to change MHCs and that NK-cell education is a continuous process. These findings are important to NK-cell immunotherapy; they suggest that donor NK cells unlicensed by HLA alleles absent in the donor may become licensed by host HLA alleles, leading to activity of donor NK cells against host tumor cells lacking HLA expression [4].

Conclusion

The ultimate goal is to enhance the therapeutic benefit of NK-cell–based cancer therapy while minimizing risks and toxicities. Important questions remain to be answered, including determination of minimum NK expansion needed for clinical anti-tumor activity. At present, the success of NK-cell expansion interventions remain unpredictable, particularly for solid tumors in which an immunosuppressive tumor-induced microenvironment dominates and interferes with immune responses. The product characteristics and effective cytokine cocktail proportions vary for different tumor types and patient populations. Future clinical trials will be designed to exploit strategies to overcome the host immune barriers of NK anti-

***Correspondence to:** Richard Bachman, Department of Immunology, University of London, London, United Kingdom, E-mail: richarrba @city.ac.uk

***Received:** 01-Jun-2022, Manuscript No. AAJCIT-22-65545; **Editor assigned:** 03-Jun-2022, PreQC No. AAJCIT-22-65545 (PQ); **Reviewed:** 17-Jun-2022, QC No. AAJCIT-22-65545; **Revised:** 20-Jun-2022, Manuscript No. AAJCIT-22- 65545 (R); **Published:** 27-Jun-2022, DOI: 10.35841/aajcit- 5.3.114*

***Citation:** Bachman R. Importance of Natural killer (NK) cells in therapy of cancer. J Cancer Immunol Ther 2022; 5(3):114*

tumor reactivity. Likewise, strategies to exploit favorable donor immunogenetics and NK-cell expansion ex vivo from blood, lymphoid progenitors, or pluripotent progenitors will be explored. Limitations to implementation of complex NK-cell therapies include requirements for Good Manufacturing Practice facilities and expertise as well as significant financial resources. Enormous progress has been made in the nearly four decades since Dr. Herberman and his colleagues first identified and characterized the NK cell. Ongoing basic and clinical research is progressively translating into promising approaches for more successful outcomes in the treatment of malignant disease.

References

1. Herberman RB, Nunn ME, Holden HT, et al. Natural cytotoxic reactivity of mouse lymphoid cells against syngeneic and allogeneic tumors. II. characterization of effector cells. Int J Cancer. 1975;16(2):230–9.
2. Zinkernagel RM, Doherty PC. MHC-restricted cytotoxic T cells: Studies on the biological role of polymorphic major transplantation antigens determining T-cell restriction-specificity, function, and responsiveness. Adva Immunol. 1979;27:51-177.
3. Lanier LL. Up on the tightrope: Natural killer cell activation and inhibition. Nat Immunol. 2008;9(5):495–502.
4. Dorshkind KE, Pollack SB, Bosma MJ, et al. Natural killer (NK) cells are present in mice with severe combined immunodeficiency (scid). J Immunol. 1985;134(6):3798-801.

Citation: *Bachman R. Importance of Natural killer (NK) cells in therapy of cancer. J Cancer Immunol Ther 2022;5(3):114*