Mini Review
Volume 9:3, 2023

Journal of Pharmacognosy & Natural Products

ISSN: 2472-0992 Open Access

Natural Killer T Cells: Bridging Innate and Adaptive Immunity for Immunotherapy and Disease Regulation

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Abstract

Bridging Innate and Adaptive Immunity for Immunotherapy and Disease Regulation Natural Killer T (NKT) cells are a unique subset of immune cells that bridge the innate and adaptive immune systems. These cells play a crucial role in the immune response, providing rapid and potent immune defence against various pathogens, as well as participating in the regulation of autoimmune diseases, allergies, and cancer. In this comprehensive essay, we will explore the biology, functions, activation, and therapeutic potential of Natural Killer T cells.

Keywords: Natural killer T cells • NKT cells • Innate immunity

Introduction

Natural Killer T (NKT) cells are a distinct population of T lymphocytes that express both NK cell markers and T Cell Receptors (TCRs). They were identified and were initially thought to be a subset of natural killer (NK) cells due to their surface marker expression and cytotoxic capabilities. However, subsequent studies revealed that NKT cells have characteristics of both NK cells and T cells, making them a unique population within the immune system. NKT cells can be classified into two major subsets based on the expression of different TCRs: type I and type II NKT cells. Type I NKT cells, also known as invariant NKT (iNKT) cells, are the most extensively studied subset. They express an invariant TCRα chain (Vα14-Jα18 in mice and Vα24-Jα18 in humans) paired with a limited repertoire of TCRβ chains. Type I NKT cells recognize glycolipid antigens presented by the MHC class I-like molecule CD1d. Upon activation, they rapidly produce large amounts of cytokines, such as interferon-gamma (IFN-γ), tumour necrosis factor-alpha (TNF-α), and interleukin-4 (IL-4), which can modulate immune responses [1].

Type II NKT cells are a more diverse subset and do not express the invariant TCRα chain found in type I NKT cells. They recognize a broader range of lipid and glycolipid antigens presented by CD1d or other CD1 molecules. Type II NKT cells also exhibit regulatory functions and can either enhance or suppress immune responses depending on the context. NKT cells develop in the thymus, similar to conventional T cells. However, their development is distinct and requires specific transcription factors and cytokines. The transcription factor PLZF (Promyelocytic Leukaemia zinc Finger) is critical for NKT cell development, as it regulates the expression of genes involved in NKT cell differentiation and effector functions. NKT cells can be activated by various mechanisms. One of the primary modes of activation is through the recognition of lipid antigens presented by CD1d molecules. These antigens can be derived from self or microbial sources and are recognized by the TCR on NKT cells. Upon activation, NKT cells rapidly release a wide range of cytokines, including both Th1 and Th2 cytokines, which can influence immune responses [2].

Literature Review

In addition to TCR engagement, co-stimulatory molecules play a crucial role in NKT cell activation. Co-stimulatory receptors, such as CD28 and CD40L, interact with their respective ligands on Antigen-Presenting Cells (APCs) to provide the necessary signals for NKT cell activation. NKT cells act as immune regulators by modulating the activity of other immune cells. They can stimulate or suppress the immune response depending on the context. Type I NKT cells are generally associated with pro-inflammatory responses and can enhance the activity of dendritic cells, NK cells, and conventional T cells. On the other hand, type II NKT cells have been shown to have immune regulatory functions and can suppress immune responses, playing a role in preventing autoimmune diseases. NKT cells contribute to the early defence against microbial pathogens. They can recognize microbial lipid antigens and rapidly secrete cytokines that promote the recruitment and activation of other immune cells. By doing so, NKT cells help in the elimination of pathogens and the initiation of an appropriate immune response. NKT cells also play a role in tumour surveillance and immunosurveillance. They can recognize glycolipid antigens expressed by tumour cells and directly kill them or produce cytokines that recruit and activate other immune cells to eliminate the tumour [3].

However, tumour cells can evade NKT cell recognition and suppress their functions, leading to tumour progression. NKT cells have been implicated in the pathogenesis of autoimmune diseases and allergies. Dysregulation of NKT cell activity can contribute to the development of autoimmune disorders such as multiple sclerosis, rheumatoid arthritis, and type 1 diabetes. Additionally, NKT cells can influence the development of allergic responses by promoting Th2 cell differentiation and the production of allergy-related cytokines. The unique properties of NKT cells have attracted significant attention in the field of immunotherapy. Several strategies have been explored to harness the therapeutic potential of NKT cells. Various synthetic or microbial-derived glycolipid antigens have been developed as NKT cell agonists. These agonists can be used to activate and expand NKT cells in vivo and enhance their antitumor or antimicrobial functions. Clinical trials using NKT cell agonists have shown promise in cancer immunotherapy and infectious diseases. Adoptive transfer of NKT cells has been investigated as a potential therapeutic approach. NKT cells can be isolated from the patient, expanded ex vivo, and infused back into the patient to enhance immune responses [4].

Discussion

Modulating the activity of NKT cells through the use of antibodies or small molecules is another therapeutic strategy. By targeting co-stimulatory molecules or inhibitory receptors on NKT cells, it is possible to enhance or suppress their activity, depending on the desired outcome. This approach holds promise for the treatment of autoimmune diseases and allergies. While significant progress has been made in understanding the biology and functions of NKT cells, several challenges and unanswered questions remain. The heterogeneity within the NKT cell population poses a challenge in accurately classifying and characterizing distinct subsets. Further research is needed to elucidate the functional differences and specific roles of different subsets of NKT cells, especially type II NKT cells,

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Received: 01 June 2023, Manuscript No. jpnp-23-104070; **Editor Assigned**: 03 June 2023, PreQC No. 104070; **Reviewed**: 15 June 2023, QC No. Q-104070; **Revised**: 20 June 2023, Manuscript No. R-104070; **Published**: 27 June 2023, DOI: 10.37421/2472-0992.2023.10.245

which are less well-studied compared to type I NKT cells. Although the antigen recognition process by NKT cells has been extensively studied, there is still much to learn about the molecular mechanisms underlying the interaction between NKT cell receptors and lipid antigens presented by CD1d [5].

Understanding these mechanisms in detail can aid in the development of more effective NKT cell-based therapies. While NKT cells have shown promise in tumour surveillance and immunotherapy, tumour cells have evolved various mechanisms to evade NKT cell recognition and suppress their functions. Further research is needed to understand these evasion mechanisms and develop strategies to overcome them, thereby enhancing the efficacy of NKT cell-based cancer therapies. Despite the promising preclinical data, the clinical translation of NKT cell-based therapies faces challenges. Optimizing protocols for the isolation, expansion, and activation of NKT cells, as well as identifying appropriate patient populations and combination therapies are crucial steps in advancing the field. The role of NKT cells in chronic infections and inflammatory diseases, such as HIV, hepatitis B and C, and inflammatory bowel disease, is still not fully understood. Further investigations are necessary to unravel the contribution of NKT cells to these conditions and explore their therapeutic potential [6].

Conclusion

Natural Killer T (NKT) cells represent a fascinating subset of immune cells that exhibit characteristics of both NK cells and T cells. Their unique ability to bridge innate and adaptive immunity makes them important players in immune regulation, antimicrobial defence, and tumour surveillance. Harnessing the therapeutic potential of NKT cells holds great promise for the treatment of various diseases, including cancer, autoimmune disorders, and allergies. However, further research is needed to fully understand the biology, functions, and mechanisms of action of NKT cells, as well as to overcome the challenges associated with their clinical translation. With ongoing advancements in the field of immunology, NKT cells continue to be an exciting area of research with immense therapeutic potential.

Acknowledgement

None.

Conflict of Interest

None.

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How to cite this article: Thiago, Amanda. "Natural Killer T Cells: Bridging Innate and Adaptive Immunity for Immunotherapy and Disease Regulation." *J Pharmacogn Nat Prod* 9 (2023): 245.