

# Research Advances on Natural Killer Cells in Infections

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## ABSTRACT

Natural killer (NK) cells play a crucial role in the human immune system, swiftly recognizing and eliminating infected cells through non-specific immune mechanisms. This paper reviews the mechanisms by which NK cells act in various infections, including those caused by viruses, bacteria, parasites, and fungi, and explores their biological characteristics and functional regulation in the context of infection. By thoroughly analyzing the regulatory mechanisms of cytokines, receptor-ligand interactions, and the microenvironment on NK cell function, this paper further elucidates the response mechanisms of NK cells under different infection scenarios. Finally, it discusses the clinical application prospects of NK cells in treating infectious diseases and outlines future research directions, providing new ideas and possibilities for NK cell-based immunotherapy strategies.

## KEYWORDS

Natural killer cells; NK cells; Viral infection; Parasitic infection

## 1. INTRODUCTION

Natural killer (NK) cells are a critical component of the innate immune system, capable of rapidly identifying and eliminating infected and tumor cells. Unlike T cells and B cells, NK cells do not rely on antigen-specific recognition but instead employ non-specific mechanisms to kill infected cells by recognizing stress-induced molecules on their surfaces. Infectious diseases remain a major public health concern worldwide, particularly in developing countries where high incidence and difficulty in treatment pose serious threats to human health. With advancements in immunology and molecular biology, significant progress has been made in understanding the role of NK cells in various infectious diseases, including those caused by viruses, bacteria, parasites, and fungi. However, many unknown areas still require exploration. Understanding the mechanisms of NK cells in combating infections is crucial for developing new therapeutic strategies. This study aims to systematically review the research progress on NK cells in various infectious diseases, investigating their mechanisms and regulatory processes in antiviral, antibacterial, antiparasitic, and antifungal contexts. Through detailed analysis of the biological characteristics and functional regulation of NK cells, this paper seeks to provide a reference for further basic research and clinical applications. Studying the role of NK cells in infections not only helps reveal the complexity and diversity of the innate immune system but also offers new perspectives for developing NK cell-based immunotherapy strategies. Especially in the current context of frequent emerging infectious diseases, understanding the key roles of NK cells in immune responses is crucial for improving the prevention and treatment of infectious diseases. The innovation of this study lies in comprehensively integrating and analyzing research findings on NK cells in different infection settings, proposing future research directions and potential applications, and aiming to provide valuable references for scientists and clinicians [1].

## 2. OVERVIEW OF NATURAL KILLER CELLS

### 2.1. Definition and Discovery History of NK Cells

Natural killer cells (NK cells) are a type of lymphocyte derived from the bone marrow and are a critical component of the innate immune system. NK cells are known for their unique ability to recognize and kill virus-infected and tumor cells without prior sensitization. They play a crucial role in immune surveillance by directly inducing the death of target cells and regulating immune responses through the release of cytotoxic granules and cytokines, such as perforin, granzyme, and interferon-gamma (IFN- $\gamma$ ). The discovery of NK cells dates back to the 1970s. In 1975, Rolf Kiessling and Hugh Pross first described the phenomenon of non-antigen-specific cytotoxicity in mouse lymphocytes against tumor cells. In the same year, Ronald Herberman and his colleagues identified cells with similar functions in human peripheral blood, further establishing NK cells as a distinct component of the immune system. These studies revealed the existence of NK cells and their potential importance in combating tumors and viral infections, thus sparking extensive research into NK cells. Since their discovery, the field of NK cell research has expanded significantly, encompassing their role in various infectious diseases, autoimmune disorders, and cancers. By studying the biological characteristics, receptor expression, and signaling pathways of NK cells, scientists have gradually uncovered the complex functions and regulatory mechanisms of NK cells in immune responses. Today, NK cells are not only recognized as important effector cells in immune surveillance and anti-tumor responses but also show great potential in clinical therapy [2].

### 2.2. Biological Characteristics of NK Cells

Natural killer cells (NK cells) possess unique biological characteristics that enable them to play a vital role in the innate immune system. NK cells originate from lymphoid progenitor cells in the bone marrow and undergo differentiation and maturation in the bone marrow and peripheral tissues. Mature NK cells are predominantly found in peripheral blood, spleen, liver, and lymph nodes. NK cells express a variety of activating and inhibitory receptors on their surface, which together regulate their activity. Major activating receptors include NKG2D, NKp30, NKp44, and NKp46. These receptors recognize ligands on stressed and virus-infected cells, triggering NK cell cytotoxic responses and cytokine release. On the other hand, inhibitory receptors such as the killer-cell immunoglobulin-like receptor (KIR) family and NKG2A recognize major histocompatibility complex (MHC) class I molecules on normal cells, inhibiting NK cell cytotoxic activity and preventing the killing of healthy cells. NK cells mediate target cell killing through two primary mechanisms: the release of cytotoxic granules and receptor-mediated apoptosis. Cytotoxic granules contain perforin and granzymes; perforin forms pores in the target cell membrane, allowing granzymes to enter and induce apoptosis. Receptor-mediated apoptosis involves the binding of Fas ligand (FasL) on NK cells to Fas receptors on target cells, initiating apoptotic signaling pathways. Additionally, NK cells regulate immune responses by secreting various cytokines such as interferon-gamma (IFN- $\gamma$ ), tumor necrosis factor-alpha (TNF- $\alpha$ ), and multiple chemokines [3]. These cytokines enhance the functions of macrophages and dendritic cells, promote adaptive immune responses, and directly inhibit viral replication and tumor cell proliferation. The activity of NK cells is influenced by multiple internal and external factors, including cytokines such as interleukin-2 (IL-2), interleukin-15 (IL-15), and interleukin-12 (IL-12), as well as microenvironmental factors like oxidative stress and metabolic state. These factors collectively affect NK cell differentiation, survival, and functional activity. In summary, NK cells possess unique biological characteristics and complex regulatory mechanisms that play a crucial role in immune surveillance and responses. Understanding the biological properties of NK cells is essential for comprehending their functions in health and disease and provides a foundation for developing new immunotherapeutic strategies.

### **3. THE ROLE OF NK CELLS IN VARIOUS INFECTIONS**

Natural killer (NK) cells play a critical role in various infectious diseases due to their ability to recognize and eliminate infected cells. In viral infections, NK cells identify stress-induced molecules on virus-infected cells through their activating receptors, swiftly initiating a cytotoxic response. They release perforin and granzymes, which perforate the cell membrane and induce apoptosis in the infected cells. Additionally, NK cells secrete interferon-gamma (IFN- $\gamma$ ), a crucial cytokine that inhibits viral replication and activates other immune cells to bolster the antiviral response. For instance, in infections like HIV, influenza, and hepatitis C, NK cells have been shown to significantly reduce viral load and mitigate tissue damage, highlighting their essential role in controlling viral infections. In bacterial infections, NK cells are activated by bacterial products or cytokine induction. These activations enable NK cells to perform both cytotoxic and immunoregulatory functions. In cases such as pneumonia and tuberculosis, NK cells enhance the phagocytic activity of macrophages and neutrophils through the release of cytokines and chemokines, aiding in the effective clearance of bacterial pathogens [4]. This dual role not only helps in directly killing bacteria but also in orchestrating a broader immune response that involves other critical immune cells. NK cells also play significant roles in parasitic infections, such as malaria and leishmaniasis. They contribute to limiting parasite proliferation and spread by releasing cytotoxic molecules and modulating adaptive immune responses. For example, in malaria, NK cells can target and kill infected red blood cells and liver cells, thereby controlling the spread of the parasite within the host. This activity is crucial in the early stages of infection when the adaptive immune response is still being mobilized. In fungal infections, NK cells help control the infection by directly killing fungi and regulating the activity of other immune cells. For instance, in infections caused by *Candida* and *Aspergillus*, NK cells interact with fungal components to induce cytotoxicity and apoptosis in the fungal cells. They also produce cytokines that enhance the antifungal activities of macrophages and dendritic cells, thereby providing a multifaceted defense against fungal pathogens. Overall, NK cells exhibit diverse functional mechanisms in different types of infections, making them crucial players in the immune response to infectious diseases. Their ability to recognize and eliminate a wide range of pathogens underscores their importance in innate immunity. The potential applications of NK cells in infection control are vast and warrant further in-depth research. By understanding the specific roles and mechanisms of NK cells in various infections, researchers can develop targeted therapies that harness the power of these cells to treat infectious diseases more effectively. Furthermore, enhancing NK cell function through genetic modification or cytokine therapy could provide new avenues for combating infections that are resistant to conventional treatments, thus improving outcomes for patients with infectious diseases.

### **4. MECHANISMS REGULATING NK CELL FUNCTION**

#### **4.1. Regulation by Cytokines and Chemokines**

Natural killer (NK) cell functions are tightly regulated by various cytokines and chemokines, which play critical roles in the activation, differentiation, and functional execution of NK cells. Cytokines are key signaling molecules in the immune system that regulate NK cell activity and responsiveness by binding to specific receptors on the NK cell surface. The most important cytokines include interleukin-2 (IL-2), interleukin-15 (IL-15), and interleukin-12 (IL-12). Table 1 lists the main cytokines and their effects on NK cell functions:

**Table 1. Main Cytokines and Their Effects on NK Cell Functions**

Cytokine	Source	Mechanism of Action	Effect on NK Cells
IL-2	Activated T cells	Promotes NK cell proliferation	Enhances cytotoxic response
IL-15	Various cells	Maintains NK cell survival and maturation	Increases NK cell activity
IL-12	Antigen-presenting cells	Activates NK cells	Induces IFN- $\gamma$ secretion

Chemokines also play important roles in the chemotaxis and tissue distribution of NK cells. Chemokines such as CXCL10 and CCL5 bind to their corresponding receptors on NK cells, guiding their migration to sites of infection or inflammation, thereby ensuring effective pathogen control. Additionally, cytokines like tumor necrosis factor-alpha (TNF- $\alpha$ ) and interferon-alpha/beta (IFN- $\alpha/\beta$ ) are involved in the activation and functional regulation of NK cells [5].

#### 4.2. Receptor-Ligand Interactions

The regulation of NK cell function heavily depends on the interactions between receptors on the NK cell surface and their ligands, which determine whether the NK cell is activated or inhibited. NK cells express a variety of activating and inhibitory receptors that together modulate their cytotoxicity and cytokine secretion. Activating receptors are crucial for recognizing and killing infected or tumor cells. Key activating receptors include NKG2D, NKp30, NKp44, and NKp46. The NKG2D receptor, for instance, recognizes stress-induced ligands such as MICA/MICB and ULBP family members on the surface of target cells, triggering NK cell cytotoxic responses. Similarly, NKp30, NKp44, and NKp46, which are natural cytotoxicity receptors (NCRs), recognize specific ligands on tumor cells and virus-infected cells, activating and mediating NK cell cytotoxicity. These activating receptors initiate intracellular signaling pathways through domains like Dap10 and Syk family kinases, leading to the release of cytotoxic granules and target cell apoptosis. Inhibitory receptors, on the other hand, are essential for preventing NK cells from killing healthy autologous cells. Major inhibitory receptors include the killer-cell immunoglobulin-like receptor (KIR) family and the CD94/NKG2A complex, which recognize major histocompatibility complex class I (MHC-I) molecules on normal cells. The high expression of MHC-I molecules on healthy cells interacts with NK cell inhibitory receptors, transmitting inhibitory signals to prevent NK cell activation and cytotoxic responses. However, during viral infection or tumor transformation, the expression of MHC-I molecules on the cell surface may decrease or be lost, releasing the inhibition on NK cells and allowing them to recognize and kill these abnormal cells. The balance between activating and inhibitory receptors is key to determining NK cell responses. NK cells dynamically regulate their functional state by integrating signals from both activating and inhibitory receptors. In infection or tumor environments, NK cells quickly respond and exert immune surveillance and defense functions by recognizing abnormal ligands under pathological conditions. In summary, receptor-ligand interactions on the NK cell surface are central to the regulation of their function [6]. Through precise receptor signaling regulation, NK cells can maintain normal immune surveillance and effectively identify and eliminate infected or malignantly transformed cells. This complex network of receptor-ligand interactions not only reveals the molecular basis of NK cell function regulation but also provides important theoretical foundations for developing new immunotherapy strategies.

#### 4.3. Microenvironment and Metabolic Regulation

NK cell functions are influenced not only by cytokines and receptor-ligand interactions but also significantly by the microenvironment and metabolic state. Various factors in the microenvironment, including oxygen levels, nutrient supply, pH, and metabolic products, regulate NK cell activity and effector functions to different extents. Oxygen levels are a key factor affecting NK cell function.

Hypoxic conditions, commonly found in tumor microenvironments and certain infectious disease sites, can inhibit NK cell cytotoxicity and cytokine secretion. Hypoxia induces the hypoxia-inducible factor (HIF) signaling pathway, altering NK cell metabolic state and reducing their anti-tumor and anti-infection capabilities. Additionally, hypoxia may affect the expression of receptors on NK cells, further regulating their function. Nutrient supply is also crucial for NK cell function regulation. Metabolites such as glucose, lipids, and amino acids directly impact NK cell energy metabolism and functional status. Under conditions of ample glucose, NK cells rely on glycolysis to rapidly generate energy, supporting their cytotoxic responses and cytokine secretion. In the absence of glucose, NK cells shift to oxidative phosphorylation, which may affect their functional efficiency. Furthermore, lipid metabolism plays a significant role in NK cell function regulation, with certain lipid metabolites, like arachidonic acid, enhancing NK cell cytotoxicity. pH changes are another important factor in microenvironment regulation. Inflammatory and tumor microenvironments are often acidic, which can inhibit NK cell activity. Acidic conditions alter the pH inside and outside cells, affecting receptor expression and signal transduction in NK cells, thus modulating their functional responses. Metabolic products such as lactate and other intermediates also influence NK cell function. High lactate levels, common in tumor microenvironments, can inhibit NK cell cytotoxicity and IFN- $\gamma$  secretion, weakening their anti-tumor effects. Other metabolic intermediates like succinate and citrate may also regulate NK cell activity by affecting metabolic pathways. In conclusion, NK cell function is subject to complex regulation by the microenvironment and metabolism, especially in infection and tumor microenvironments. Understanding these regulatory mechanisms not only helps reveal the role of NK cells in immune responses but also provides new insights for developing immunotherapy strategies targeting NK cell function [7]. For instance, modulating oxygen levels or metabolic states in the tumor microenvironment could enhance NK cell anti-tumor activity and improve immunotherapy efficacy.

## 5. CLINICAL APPLICATIONS AND FUTURE PROSPECTS

### 5.1. Applications of NK Cells in the Treatment of Infectious Diseases

Natural killer (NK) cells have broad prospects for application in the treatment of infectious diseases due to their ability to rapidly recognize and kill infected cells, playing an important role in immune defense. In recent years, with the deepening understanding of NK cell functions and mechanisms, scientists have begun exploring how to use NK cells clinically to treat various infectious diseases. Table 2 summarizes the clinical trial data and research findings of NK cell therapies in different infectious diseases:

**Table 2.** Clinical Trial Data and Research Findings

Infectious Disease	NK Cell Therapy Method	Research Results	Clinical Application Prospects
HIV	Gene-edited NK cells	Reduced viral load	Significantly delayed disease progression
Hepatitis B	Activated NK cells	Increased virus clearance	Enhanced antiviral capability
Tuberculosis	NK cell enhancers	Promoted macrophage activity	Improved bacterial clearance
Malaria	Genetically modified NK cells	Limited parasite proliferation	Improved infection control
Candidiasis	NK cell therapy	Controlled fungal infection	Effectively alleviated symptoms

In viral infections, NK cell therapy shows great potential. For example, in HIV infection, NK cells can recognize and kill infected CD4<sup>+</sup> T cells, effectively reducing viral load and delaying disease progression. Enhancing the antiviral capabilities of NK cells through genetic engineering, such as

expressing specific anti-HIV receptors or enhancing their cytotoxicity, can further improve treatment outcomes. Similarly, in the treatment of hepatitis B and C, the activation and functional enhancement of NK cells are considered important means of clearing viral infections [8].

## 5.2. Future Research Directions

Future research on natural killer (NK) cells will continue to explore their mechanisms of action in infectious diseases and strive to translate these findings into clinical applications. Here are several key future research directions:

(1) **Molecular Mechanisms and Signal Transduction Pathways of NK Cells:** Although there is some understanding of the activation and inhibition mechanisms of NK cells, their specific molecular signal transduction pathways need further research. Future studies will focus on elucidating the molecular details of NK cell interactions with pathogens, identifying new receptors and ligands, and how these signaling pathways are regulated by the microenvironment. By deeply understanding these mechanisms, more precise NK cell regulation strategies can be developed to enhance their anti-infection efficacy.

(2) **Gene Editing and Engineering of NK Cells:** Gene editing technologies, such as CRISPR-Cas9, have opened new possibilities for enhancing NK cell functions. Future research will aim to modify NK cells through gene editing to enhance their specificity and durability against pathogens. For example, inserting specific receptor genes can make NK cells more effective at recognizing and killing virus-infected or tumor cells. Additionally, knocking out inhibitory receptor genes can increase NK cell activity.

(3) **Synergistic Action of NK Cells with Other Immune Cells:** The role of NK cells in immune responses is not limited to their cytotoxicity but also includes their interactions with other immune cells (such as T cells, B cells, and macrophages). Future research will explore the role of NK cells in the complex immune network, particularly in regulating adaptive immune responses. Understanding these synergistic interactions will help develop combination immunotherapies to enhance overall immune responses.

(4) **Role of NK Cells in Chronic Infections and Immune Evasion:** Chronic infections and pathogen immune evasion are major challenges in the treatment of infectious diseases. Future research will focus on revealing the roles of NK cells in these processes and how to use NK cells to overcome these challenges. For instance, studying the dynamic changes of NK cells in chronic infections like HIV and hepatitis B, and understanding how pathogens evade NK cell attacks, can lead to the development of effective treatment strategies.

(5) **Clinical Translation and Optimization of Treatment Protocols:** Although NK cell therapies have shown significant potential in preclinical studies, their effectiveness in actual clinical applications needs further verification. Future research will focus on clinical trials of NK cell therapies, optimizing treatment protocols, determining the best sources, preparation, and infusion methods for NK cells, and evaluating their efficacy and safety in different infectious diseases. Additionally, exploring combination therapies with other treatments (such as antibody therapies, vaccines, and antiviral drugs) can improve overall treatment outcomes. By continuing research in these directions, NK cells are expected to become crucial tools in future infectious disease treatments, providing more effective and precise treatment options for patients. Additionally, these studies will provide important theoretical and practical foundations for scientific advancements in immunology and infectious disease research.

## 6. CONCLUSION

Natural killer (NK) cells, as vital components of the innate immune system, play key roles in combating infections and tumor responses. This paper systematically reviews the mechanisms by

which NK cells act in various infections, including those caused by viruses, bacteria, parasites, and fungi, and explores their functional regulation under different infection conditions, including regulation by cytokines and chemokines, receptor-ligand interactions, and microenvironmental and metabolic influences. By understanding these mechanisms, the complex functions of NK cells in immune surveillance and defense are revealed. In terms of clinical applications, NK cells show significant therapeutic potential, especially in the prevention and treatment of infectious diseases. The application of gene editing and engineering technologies is expected to further enhance the specificity and durability of NK cells, improving their clinical efficacy. Future research will continue to explore the molecular mechanisms of NK cells, optimize their clinical application protocols, and investigate their synergistic interactions with other immune cells to develop more comprehensive and effective treatment strategies. Overall, the application prospects of NK cells in infectious disease treatment are vast. With the development of biotechnology and in-depth research, NK cells are poised to become essential tools for future infectious disease treatments. Through ongoing basic research and clinical trials, NK cell therapies will offer new hope and treatment options for patients with infectious diseases, making significant contributions to global public health improvements.

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