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HIV and Natural Killer (NK) Cell Responses in Neonates: A Review

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Abstract

Natural killer (NK) cells are innate immune effectors critical for early host defense against viral infections, including HIV. In neonates, NK cells undergo developmental maturation and play a pivotal role in immune surveillance and cytotoxicity. However, vertical transmission of HIV from infected mothers to neonates profoundly impacts NK cell function. HIV can directly infect NK cells, alter their phenotype, and impair their cytotoxic capabilities, thereby compromising innate immune responses essential for viral clearance and immune surveillance. This review examines the current understanding of NK cell responses in neonates exposed to HIV, highlighting mechanisms of immune evasion, alterations in NK cell maturation, and the implications for therapeutic interventions, particularly antiretroviral therapy (ART). Vertical transmission of HIV introduces viral antigens to neonatal NK cells during a critical period of immune development, influencing their functional competence and interactions with other immune cells. HIV-mediated immune dysregulation often leads to chronic immune activation and exhaustion of NK cells, exacerbating immunodeficiency and increasing susceptibility to opportunistic infections in neonates. Antiretroviral therapy (ART) represents the standard of care for managing HIV infection by suppressing viral replication and preserving immune function. In neonates exposed to HIV, early initiation of ART is essential for preventing viral dissemination, reducing immune activation, and potentially preserving NK cell cytotoxicity. However, optimizing ART regimens for neonates, including ensuring drug penetration into tissues and minimizing long-term toxicity, remains a challenge.

Keywords: *HIV, neonates, natural killer cells, immune responses, vertical transmission*

Introduction

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Natural killer (NK) cells are integral components of the innate immune system, recognized for their ability to rapidly respond to virally infected or transformed cells through cytotoxicity and cytokine secretion. In neonates, NK cells play a crucial role in early immune defense, serving as frontline effectors against pathogens encountered shortly after birth. Their developmental trajectory in early life involves maturation processes that shape their functional capacity and responsiveness. However, in the context of HIV infection, particularly in neonates born to HIV-positive mothers, NK cell responses undergo significant alterations that can impact both innate immune defense and adaptive immune maturation.[1-5] Neonatal immune development is characterized by a period of gradual maturation, during which the immune system transitions from a state of relative immaturity at birth to one capable of robust responses against pathogens. NK cells, along with other innate immune cells, contribute to this process by providing immediate defense mechanisms in the absence of antigen-specific memory. In the presence of HIV, which targets CD4+ T cells primarily but also affect various immune cell types including NK cells, the dynamics of neonatal immune development are disrupted. Vertical transmission of HIV from mother to child introduces viral antigens early in life, potentially altering NK cell maturation pathways and functional responses crucial for immune surveillance and viral control.[6-10] The impact of HIV on neonatal NK cells extends beyond direct infection to encompass broader immune dysregulation. HIV can directly infect NK cells, altering their phenotype and impairing their cytotoxic capabilities. This direct interaction compromises NK cell-mediated cytotoxicity against infected cells and reduces their ability to contribute to viral clearance. Moreover, HIV-induced immune activation and chronic inflammation can lead to functional exhaustion of NK cells, further diminishing their effectiveness in immune surveillance and contributing to overall immunodeficiency in HIV-exposed neonates.[11-13]

These interventions aim to enhance NK cell responses, mitigate immune dysfunction, and improve clinical outcomes in HIV-exposed neonates. Furthermore, elucidating the interactions between HIV and NK cells can provide insights into viral evasion strategies and immune escape mechanisms employed by the virus, which are crucial for advancing our understanding of HIV pathogenesis and informing the development of novel treatment approaches.[14-17] Antiretroviral therapy (ART) plays a pivotal role in the management of HIV infection by suppressing viral replication and preserving immune function. In neonates exposed to HIV, early initiation of ART is critical for preventing viral dissemination and minimizing the impact of HIV on immune development, including preserving NK cell cytotoxicity. However, optimizing ART regimens for neonates poses challenges, such as ensuring adequate drug penetration into tissues, minimizing drug toxicity, and addressing the potential for viral resistance.[18-20] The immune responses of NK cells in neonates exposed to HIV are also influenced by factors such as maternal health, gestational age, and the timing of viral exposure. Maternal factors, including maternal HIV viral load and the presence of co-infections, can impact the extent of vertical transmission and the severity of neonatal immune dysfunction. Gestational age at the time of viral exposure may influence immune development trajectories, affecting the timing and effectiveness of immune responses against HIV and other infections early in life.[21-23] Moreover, the functional plasticity of NK cells allows for adaptation to different environmental and pathophysiological conditions. In the context of HIV infection, NK cells may exhibit phenotypic changes and altered expression of activating and

inhibitory receptors that influence their responsiveness to viral antigens and infected cells. Understanding these phenotypic changes and their implications for NK cell function in neonatal HIV infection is crucial for tailoring therapeutic strategies aimed at enhancing NK cell-mediated immune responses and improving clinical outcomes.[24-26] NK cells not only contribute directly to early antiviral defenses but also interact with dendritic cells, macrophages, and other immune cells to coordinate immune responses against HIV. Dysregulation of these immune interactions, as seen in HIV infection, can disrupt immune homeostasis and impair the ability of neonates to mount effective immune responses against HIV and other pathogens.[27-29]

NK Cell Biology and Function

Natural Killer (NK) cells are critical components of the innate immune system, recognized for their ability to detect and eliminate infected or transformed cells without prior sensitization. They play a pivotal role in immune surveillance, particularly in identifying cells that have downregulated major histocompatibility complex class I (MHC-I) molecules, a hallmark of virally infected or cancerous cells. NK cells execute their cytotoxic functions through the release of cytolytic granules containing perforin and granzymes, which induce apoptosis in target cells. Additionally, NK cells produce cytokines such as interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α), which exert broad immunomodulatory effects by enhancing antigen presentation, activating other immune cells, and influencing adaptive immune responses.[30-35] The function of NK cells is tightly regulated by a balance between activating and inhibitory signals received through their surface receptors. Activating receptors include natural cytotoxicity receptors (NCRs) such as NKp46, NKp30, and NKp44, as well as NKG2D and DNAM-1 (CD226), which recognize stress-induced ligands on target cells. In contrast, inhibitory receptors, predominantly killer cell immunoglobulin-like receptors (KIRs) and CD94/NKG2A, interact with MHC-I molecules on healthy cells to prevent NK cell activation and maintain tolerance. This dual receptor system enables NK cells to distinguish between healthy cells and those that have been altered by infection or malignancy, ensuring effective immune surveillance and minimizing autoimmune responses.[36-40] NK cell development occurs primarily in the bone marrow, where hematopoietic stem cells give rise to NK cell progenitors that differentiate and mature under the influence of cytokines such as IL-15 and IL-12. This process leads to the generation of functionally mature NK cells that traffic to peripheral tissues, including lymphoid organs, blood, and mucosal surfaces. Importantly, NK cell maturation involves sequential acquisition of surface markers and functional competence, which enables them to respond swiftly to pathogens encountered in various tissues.[41-43]

In addition to their cytotoxic and cytokine-producing functions, NK cells exhibit functional plasticity and can adapt their responses based on the microenvironmental cues they encounter. For instance, NK cells can differentiate into memory-like cells after encountering certain pathogens or cytokine signals, which enhances their ability to mount rapid and robust responses upon re-exposure to the same pathogen. Moreover, NK cells play a role in regulating adaptive immune responses by interacting with dendritic cells and influencing the initiation and polarization of T cell responses.[44-46] In the context of HIV infection, NK cells play a dual role: they contribute to

early antiviral defenses through direct recognition and elimination of HIV-infected cells, and they modulate immune responses that influence disease progression. However, HIV has evolved mechanisms to evade NK cell recognition and attack, including downregulation of ligands for activating NK cell receptors and inducing dysfunction or exhaustion of NK cells through chronic immune activation. Understanding these interactions between HIV and NK cells is crucial for developing strategies to harness NK cell function in the context of HIV therapy and vaccine development.[47-50]

Impact of HIV Infection on Neonatal NK Cells

HIV infection profoundly impacts neonatal NK cells, altering their development, function, and overall contribution to immune responses in early life. Vertical transmission of HIV from mother to child introduces the virus to neonates during a critical period of immune system maturation, significantly influencing NK cell biology and immune responses from the outset. One of the primary impacts of HIV on neonatal NK cells is direct infection. HIV can infect NK cells themselves, leading to viral replication within these immune effectors. This direct infection not only impairs NK cell function but also alters their phenotype, potentially skewing their responses towards exhaustion or dysfunction. Infected NK cells may exhibit reduced cytotoxicity and cytokine production, compromising their ability to effectively recognize and eliminate virally infected cells. This phenomenon contributes to immune evasion strategies employed by HIV, allowing the virus to evade NK cell-mediated immune surveillance and persist within the host.[51-53] Moreover, HIV-induced immune dysregulation and chronic inflammation can further impair NK cell function in neonates. HIV infection triggers a state of persistent immune activation characterized by elevated levels of pro-inflammatory cytokines and immune activation markers. This chronic immune activation can lead to NK cell exhaustion, where prolonged exposure to inflammatory signals renders NK cells less responsive to subsequent stimuli and less effective in carrying out their cytotoxic functions. As a consequence, neonates born with HIV exposure may experience impaired NK cell-mediated immune surveillance, increasing their susceptibility to infections and potentially impacting their overall health outcomes.[54-55]

Additionally, the presence of HIV in neonates can disrupt the normal developmental trajectory of NK cells. Neonatal NK cells undergo maturation processes that are crucial for establishing functional competence and immune surveillance capabilities. However, HIV-mediated immune perturbations, including altered cytokine profiles and dysregulated immune cell interactions, may hinder this maturation process. This disruption can result in aberrant NK cell phenotypes and functional defects that persist into infancy and childhood, potentially affecting long-term immune responses and susceptibility to infections beyond the neonatal period.[56] Furthermore, the impact of HIV on neonatal NK cells extends beyond direct infection and immune dysregulation to include interactions with other immune cells and systemic immune responses. HIV-induced alterations in immune cell populations, such as CD4+ T cells and dendritic cells, can indirectly influence NK cell function through disrupted immune homeostasis and impaired immune cell crosstalk. These interactions contribute to the complex immune landscape observed in HIV-exposed neonates,

where multiple immune deficits may synergistically impair overall immune function and increase vulnerability to infections.[57]

Therapeutic Interventions and Future Directions

Therapeutic interventions aimed at mitigating the impact of HIV infection on neonatal NK cells are crucial for improving immune responses and clinical outcomes in affected infants. While antiretroviral therapy (ART) remains the cornerstone of HIV management, additional strategies targeting NK cell function and immune reconstitution are increasingly recognized as essential components of comprehensive treatment approaches. Here, we discuss current therapeutic interventions and future directions for enhancing NK cell responses in neonates exposed to HIV.

Antiretroviral Therapy (ART): Antiretroviral therapy is fundamental in suppressing HIV replication, preventing disease progression, and preserving immune function in neonates. Early initiation of ART after birth or as soon as HIV infection is diagnosed is critical for reducing viral reservoirs and minimizing immune system damage, including preserving NK cell function. ART regimens typically include combinations of antiretroviral drugs, such as nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), and integrase strand transfer inhibitors (INSTIs), tailored to inhibit different stages of the HIV lifecycle. Optimizing ART in neonates involves considerations such as drug dosing based on weight, pharmacokinetics, and potential long-term effects on immune development.[58]

Immunomodulatory Therapies: Beyond ART, immunomodulatory therapies aim to enhance NK cell function and immune responses in HIV-exposed neonates. Strategies under investigation include cytokine therapy with agents like interleukin-15 (IL-15), which promotes NK cell proliferation and activation, potentially enhancing their cytotoxic capabilities against HIV-infected cells. Additionally, therapies targeting NK cell receptors or signaling pathways involved in immune activation and cytotoxicity may offer novel approaches to augment NK cell-mediated antiviral responses. These approaches aim to restore immune homeostasis, reduce chronic inflammation, and improve immune surveillance in HIV-exposed neonates.[59]

Vaccination Strategies: Vaccination represents a critical component of preventive healthcare in HIV-exposed neonates, aiming to stimulate adaptive immune responses and augment NK cell function indirectly. Early vaccination with age-appropriate vaccines, including those against hepatitis B, pneumococcus, and influenza, is recommended to protect against opportunistic infections. Strategies to optimize vaccine responses in HIV-exposed infants may involve adjusting vaccine schedules, using adjuvanted vaccines, or exploring novel vaccine platforms that enhance immune memory and protective immunity. NK cells play a role in vaccine-induced immune responses, highlighting the potential synergy between vaccination strategies and NK cell function in promoting overall immune health.[51]

Stem Cell and Gene Therapies: Emerging approaches in stem cell and gene therapies hold promise for restoring immune function in HIV-exposed neonates, including enhancing NK cell

development and function. These therapies aim to correct genetic defects or deficiencies that impact immune cell function, potentially offering curative options for HIV-infected infants. Gene editing technologies, such as CRISPR-Cas9, may enable targeted modifications to enhance NK cell cytotoxicity or resistance to HIV infection, although safety and ethical considerations remain paramount in their clinical application.[53]

Integrated Care Models: Comprehensive, integrated care models are essential for optimizing therapeutic interventions and improving long-term outcomes in HIV-exposed neonates. These models encompass multidisciplinary approaches involving pediatricians, infectious disease specialists, immunologists, and social support services to address the diverse medical, developmental, and psychosocial needs of affected infants and their families. Monitoring NK cell function and immune responses through longitudinal assessments can guide personalized treatment strategies and support early intervention to mitigate immune dysfunction and infectious complications.[59]

Conclusion

HIV infection in neonates poses unique challenges to immune development, particularly impacting the critical role of natural killer (NK) cells in early immune surveillance and defense. Vertical transmission of HIV introduces the virus during a period of immune maturation, altering NK cell biology and function from the onset of life. This disruption not only compromises NK cell-mediated antiviral responses but also contributes to broader immune dysfunction and increased susceptibility to infections in HIV-exposed neonates. Therapeutic interventions, centered on early initiation of antiretroviral therapy (ART), play a pivotal role in managing HIV infection by suppressing viral replication and preserving immune function, including NK cell activity. However, optimizing ART regimens and exploring adjunctive therapies aimed at enhancing NK cell responses are crucial for improving outcomes in HIV-exposed neonates. Strategies such as immunomodulatory therapies, vaccination optimization, and emerging technologies in stem cell and gene therapies offer promising avenues to restore immune competence and mitigate the long-term consequences of HIV-induced immune dysfunction.

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