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Role of Eosinophils in the Context of Vertical Transmission of HIV during Pregnancy

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Abstract: Vertical transmission of HIV from mother to child during pregnancy remains a significant public health challenge, particularly in resource-limited settings. Despite advancements in antiretroviral therapy (ART), many infants are still born with HIV, underscoring the need for a deeper understanding of the immunological landscape during pregnancy. Eosinophils, traditionally associated with allergic reactions and parasitic infections, are increasingly recognized for their complex roles in immune modulation. This review explores the potential contributions of eosinophils to the vertical transmission of HIV, focusing on their interactions with other immune cells, cytokine production, and the implications for maternal-fetal health. Eosinophils are multifunctional granulocytes involved in both innate and adaptive immunity. They produce a variety of cytokines and chemokines, influencing the activity of other immune cells such as T cells and macrophages. During pregnancy, the maternal immune system undergoes significant changes to tolerate the semi-allogeneic fetus, with eosinophils playing a role in tissue remodeling, angiogenesis, and the regulation of immune responses. Their presence at the maternal-fetal interface suggests they could be crucial in modulating the immune environment, potentially impacting HIV transmission dynamics.

Keywords: Eosinophils, Vertical transmission, HIV, Pregnancy, Maternal-fetal health.

Review Paper

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INTRODUCTION

The vertical transmission of HIV, where the virus is passed from an HIV-positive mother to her child during pregnancy, childbirth, or breastfeeding, remains a critical issue in global health [1]. Despite significant progress in the prevention of mother-to-child transmission (PMTCT) programs, an estimated 150,000 children were newly infected with HIV in 2021, predominantly in sub-Saharan Africa [2]. While the implementation of antiretroviral therapy (ART) has significantly reduced these numbers, challenges persist, particularly in resource-limited settings where access to consistent healthcare is a major barrier. Pregnancy induces profound changes in the maternal immune system to accommodate the developing fetus, which is genetically distinct from the mother [3]. These changes involve a delicate balance between immune tolerance to avoid fetal rejection and maintaining sufficient immunity to protect both the mother and the fetus from infections. This immunological adaptation includes shifts in the numbers and activity of various immune cells, including T cells, natural killer cells, macrophages, and granulocytes such as eosinophils. Eosinophils are a type of white blood cell, part of the granulocyte family, characterized by their bilobed nuclei and granules containing a variety of cytotoxic proteins, including major basic protein (MBP), eosinophil cationic protein (ECP), and eosinophil peroxidase (EPO) [4]. These cells are primarily known for their role in combating parasitic infections and contributing to allergic reactions. However, their functions extend beyond these classical roles, including involvement in tissue remodeling, modulation of immune responses, and interactions with other immune cells. Eosinophils contribute to immune modulation through the release of cytokines, chemokines, and growth factors. They can influence the activity of other immune cells, such as T cells, B cells, dendritic cells, and macrophages, thereby shaping the immune response. This modulatory capability is crucial in maintaining immune homeostasis and responding to various pathogens, including viruses. Their presence and activity at mucosal surfaces, including the gastrointestinal and respiratory tracts, underline their importance in local immune defense.

In the context of HIV infection, eosinophils exhibit both beneficial and detrimental roles. They can produce cytokines that either enhance or suppress HIV replication. Moreover, eosinophils can interact with viral

particles directly, influencing viral load and dissemination. The dual role of eosinophils in HIV pathogenesis makes them a subject of interest, particularly concerning their potential impact on the transmission of the virus from mother to child [5-7]. The risk of vertical transmission of HIV is influenced by several factors, including maternal viral load, the integrity of the placental barrier, and the presence of co-infections. ART during pregnancy significantly reduces the maternal viral load, thereby lowering the risk of transmission. However, incomplete adherence to ART, drug resistance, and late initiation of treatment remains significant challenges [8, 9]. The placenta serves as a critical interface between the mother and the fetus, facilitating nutrient exchange while providing a barrier to infections. Immune cells, including eosinophils, are present within the placental tissues and contribute to its function and integrity. The interactions between maternal immune cells and the placental environment are complex and can influence the risk of vertical transmission of infections, including HIV. Investigating these interactions can provide insights into novel preventive measures [10-12]. Given their immunomodulatory capabilities, eosinophils may play a role in the vertical transmission of HIV. Their ability to produce cytokines and chemokines, interact with other immune cells, and influence tissue remodeling could impact the maternal-fetal transmission of the virus.

Eosinophils

Eosinophils are a type of white blood cell belonging to the granulocyte family, characterized by their distinct bilobed nuclei and cytoplasmic granules that stain red-orange with eosin dye. These cells are derived from bone marrow progenitors and are present in peripheral blood at low concentrations, typically constituting 1-3% of the total white blood cell count. Eosinophils are equipped with an array of granules that contain potent cytotoxic proteins, including major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), and eosinophil peroxidase (EPO), which they release upon activation [13]. Eosinophils are traditionally known for their role in combating parasitic infections, particularly helminths. They contribute to the immune defense against these parasites by adhering to their surface and releasing cytotoxic granule contents, which can damage and kill the parasites. Additionally, eosinophils play a significant role in allergic reactions and asthma. Upon exposure to allergens, eosinophils are recruited to the site of inflammation, where they release their granules, leading to tissue damage and the characteristic symptoms of allergic reactions. Beyond their roles in parasitic infections and allergies, eosinophils are recognized for their complex immunomodulatory functions [14]. They produce a variety of cytokines, chemokines, and growth factors, such as interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-13 (IL-13), and transforming growth factor-beta (TGF-β). These molecules enable eosinophils to influence the activity of other immune cells, including T cells, B cells, macrophages, and dendritic cells. Eosinophils can thus modulate both innate and adaptive immune responses, contributing to immune regulation and homeostasis. Under normal conditions, eosinophils are primarily found in the thymus, gastrointestinal tract, spleen, and lymph nodes. Their numbers in peripheral tissues increase significantly during inflammatory responses. Chemokines such as eotaxin (CCL11), eotaxin-2 (CCL24), and eotaxin-3 (CCL26) play crucial roles in the recruitment of eosinophils to sites of inflammation or infection. The interaction between eotaxins and the chemokine receptor CCR3 on eosinophils facilitates their migration from the bloodstream to target tissues.

During pregnancy, the maternal immune system undergoes adaptations to tolerate the semi-allogeneic fetus while maintaining defense against infections. Eosinophils are present in the maternal-fetal interface and contribute to the immune environment of the placenta. They are involved in tissue remodeling, angiogenesis, and regulation of other immune cells within the placenta, potentially influencing pregnancy outcomes. The role of eosinophils in pregnancy extends to their potential impact on maternal-fetal transmission of infections, including HIV. Eosinophils interact with a variety of other immune cells, including T cells, B cells, macrophages, and dendritic cells. These interactions are mediated through direct cell-to-cell contact and the secretion of cytokines and chemokines. For example, eosinophils can present antigens to T cells and modulate their responses, influencing the balance between different T cell subsets. Eosinophils also produce factors that can affect macrophage activation and function, thereby shaping the overall immune response [13]. In HIV-infected individuals, eosinophils are often found in increased numbers in various tissues. Their role in HIV pathogenesis is complex and multifaceted. Eosinophils can produce cytokines that modulate HIV replication and the activation of other immune cells. Additionally, eosinophils have been shown to interact with HIV particles, potentially influencing viral load and dissemination [15-18]. The multifunctional nature of eosinophils has significant clinical implications. In the context of allergic diseases and asthma, eosinophil-targeted therapies, such as monoclonal antibodies against IL-5, have been developed to reduce eosinophil levels and mitigate symptoms. Similarly, understanding eosinophils' roles in other conditions, such as parasitic infections and autoimmune diseases, can inform the development of targeted treatments. In the context of HIV, elucidating the contributions of eosinophils to immune modulation and viral dynamics may reveal new therapeutic targets for preventing vertical transmission [19-21].

Eosinophils and Immune Modulation in Pregnancy

Pregnancy induces significant immunological changes to support fetal development while protecting both the mother and fetus from infections. The maternal

immune system undergoes adaptations to tolerate the semi-allogeneic fetus, striking a balance between immune tolerance and defense. This delicate equilibrium involves shifts in the activity and distribution of various immune cells, including T cells, natural killer cells, macrophages, and eosinophils. These changes are essential for maintaining a healthy pregnancy and ensuring optimal fetal growth. Eosinophils, although traditionally associated with allergic reactions and parasitic infections, are present at the maternal-fetal interface, where they contribute to the local immune environment. Their presence in the decidua and placental tissues indicates their potential role in supporting pregnancy. Eosinophils in the placenta can influence immune responses through the release of cytokines and chemokines, which help modulate the activities of other immune cells and maintain immune homeostasis [13]. Eosinophils produce a variety of cytokines and growth factors that play crucial roles in immune modulation. During pregnancy, eosinophils release cytokines such as interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13). These cytokines can promote a Th2-skewed immune response, which is generally associated with immune tolerance and anti-inflammatory effects. This Th2 dominance is important in preventing maternal immune rejection of the fetus and ensuring a successful pregnancy outcome. Eosinophils contribute to tissue remodeling and angiogenesis, processes that are vital for the establishment and maintenance of a healthy pregnancy. The remodeling of uterine tissues and the development of new blood vessels are essential for providing adequate blood supply and nutrients to the growing fetus. Eosinophils release matrix metalloproteinases (MMPs) and other enzymes that facilitate the breakdown and remodeling of extracellular matrix components, aiding in tissue restructuring and angiogenesis.

Eosinophils can influence the activity of other immune cells at the maternal-fetal interface. They interact with T cells, macrophages, and dendritic cells through direct cell-to-cell contact and the secretion of immunomodulatory molecules. For instance, eosinophils can present antigens to T cells and modulate their responses, impacting the balance between different T cell subsets. They also produce factors that affect macrophage activation and polarization, contributing to the regulation of immune responses in the placenta [14]. The immunomodulatory functions of eosinophils can have significant implications for maternal-fetal health. Proper regulation of immune responses by eosinophils helps prevent excessive inflammation, which could be detrimental to both the mother and the fetus. By contributing to immune tolerance and maintaining a balanced immune environment, eosinophils play a role in protecting against adverse pregnancy outcomes, such as preterm labor and pregnancy complications associated with immune dysregulation. In the context of HIV-positive pregnancies, the role of eosinophils becomes even more critical. The immune system of HIV-infected mothers is already compromised, and the presence of the virus can further complicate the immune dynamics at the maternal-fetal interface. Eosinophils' ability to modulate immune responses and interact with other immune cells may influence the risk of vertical transmission of HIV. The mechanisms through which eosinophils modulate immune responses during pregnancy are complex and multifaceted. Eosinophils can impact the local immune environment through the release of their granule contents, which include cytotoxic proteins, cytokines, and chemokines. These molecules can influence the behavior of other immune cells, promote tissue remodeling, and support angiogenesis. Additionally, eosinophils' interactions with viral particles and their ability to influence viral replication and dissemination highlight their potential role in modulating HIV transmission dynamics [22-25].

HIV (Human Immunodeficiency Virus) is a retrovirus that targets the immune system, particularly CD4+ T cells, leading to a progressive decline in immune function. This results in increased susceptibility to opportunistic infections and certain cancers. The complexity of HIV infection is compounded by the interplay of various immune cells, including eosinophils, which have emerged as important yet often overlooked players in HIV pathogenesis. In individuals living with HIV, the dynamics of eosinophils can change significantly. Studies have reported alterations in eosinophil counts and activity in HIV-infected patients, often showing increased eosinophilia in the context of co-infections or specific inflammatory responses. Eosinophils are found in elevated numbers in various tissues, including lymph nodes, blood, and the gastrointestinal tract, indicating their potential involvement in the immune response to HIV and related opportunistic infections. Eosinophils can be activated by various stimuli, including cytokines, chemokines, and viral components. In the context of HIV, eosinophil activation may be influenced by the presence of other infections, such as tuberculosis or parasitic infections, which are prevalent in many HIV-endemic regions. The activation of eosinophils can lead to the release of their cytotoxic granules and pro-inflammatory cytokines, potentially impacting viral replication and the immune response [26-30]. Eosinophils produce a range of cytokines and chemokines, such as interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-13 (IL-13), and tumor necrosis factor-alpha (TNF-α), which can modulate immune responses during HIV infection.[31] The Th2 cytokine profile associated with eosinophil activity may promote a particular immune environment that could influence HIV pathogenesis. For example, IL-4 and IL-13 can support B cell activation and antibody production, potentially affecting the overall immune response to HIV.

Research has shown that eosinophils can influence viral replication dynamics in HIV-infected individuals. Some studies suggest that eosinophil-

derived factors may enhance or inhibit viral replication, depending on the specific context and stage of infection. Eosinophils have been observed to interact with HIV particles, which could impact viral load and dissemination. HIV-infected individuals often experience co-infections that can complicate disease progression. Eosinophils play a critical role in the immune response to many co-infections, particularly parasitic infections. The presence of co-infections can alter eosinophil dynamics and function, potentially impacting HIV progression and immune reconstitution in patients undergoing ART. Studying the interactions between eosinophils, HIV, and co-infections can provide insights into the complex immune landscape in HIV-infected individuals. Eosinophil-targeted therapies, such as monoclonal antibodies against IL-5, may offer new approaches to modulate the immune response in HIV-infected patients, particularly in those with high eosinophil counts. Additionally, assessing eosinophil levels and function could provide valuable information for monitoring disease progression and treatment response in HIV-infected individuals [32-36]. The role of eosinophils in the vertical transmission of HIV is an area of emerging interest. Eosinophils are present at the maternal-fetal interface and may influence the immune environment in pregnant women living with HIV. Their interactions with HIV and other immune cells could impact the risk of mother-to-child transmission. Further research is needed to understand the specific mechanisms through which eosinophils contribute to vertical transmission dynamics and maternal-fetal health [37-41].

Potential Mechanisms of Eosinophil Involvement in Vertical Transmission of HIV

The placenta acts as a crucial barrier and facilitator of nutrient and waste exchange between mother and fetus. Eosinophils are present in the placental tissue and contribute to its immune environment through cytokine and chemokine secretion. Their role in modulating immune responses at the maternal-fetal interface may influence the risk of vertical transmission of HIV [42]. By affecting local immune cell dynamics and maintaining a balanced immune environment, eosinophils can potentially impact the integrity of the placental barrier and the maternal viral load. Eosinophils secrete a variety of cytokines and chemokines, such as interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13), which can modulate the immune response. These cytokines promote a Th2-skewed immune response, generally associated with anti-inflammatory effects and immune tolerance. In the context of HIV, this Th2 dominance could potentially reduce the activation and replication of the virus, thereby lowering the risk of vertical transmission. However, an excessive Th2 response might also impair the body's ability to control the virus, highlighting the complexity of eosinophil involvement [43-46]. Eosinophils can interact directly with HIV particles. Studies suggest that eosinophils can capture and internalize viral particles, which may impact viral replication and dissemination [47]. By sequestering HIV particles, eosinophils might reduce the viral load in the maternal bloodstream, thereby lowering the risk of the virus crossing the placental barrier. Conversely, if eosinophils serve as reservoirs for the virus, they could facilitate its transmission to the fetus. Eosinophils release enzymes such as matrix metalloproteinases (MMPs) that contribute to tissue remodeling and repair. In the placenta, this activity can influence the structural integrity and function of the tissue [13]. Proper remodeling is essential for maintaining a healthy placental environment, which can protect against infections and other complications. However, excessive or dysregulated eosinophil activity could damage placental tissues, potentially increasing the permeability of the barrier and facilitating vertical transmission of HIV.

Eosinophils interact with various other immune cells, including T cells, macrophages, and dendritic cells, influencing their functions through direct contact and the secretion of immunomodulatory molecules. In the context of HIV, eosinophils can modulate the activation and responses of these cells, potentially affecting viral replication and the overall immune environment [48]. For example, eosinophils can influence the activation state of macrophages, which play a key role in HIV infection and transmission. By promoting an anti-inflammatory environment, eosinophils might reduce the activation of HIV in macrophages and other cells. The maternal viral load is a critical determinant of the risk of vertical transmission of HIV. Eosinophils, through their immunomodulatory functions, can influence maternal viral load. By producing cytokines that suppress HIV replication and modulating the activity of other immune cells, eosinophils can help reduce the amount of virus in the maternal bloodstream. This reduction in viral load is crucial for minimizing the risk of the virus crossing the placental barrier and infecting the fetus [49-52]. The interactions between eosinophils and HIV also have implications for antiretroviral therapy (ART). ART aims to reduce the viral load in HIV-positive individuals, including pregnant women, to prevent vertical transmission. For example, therapies that enhance the beneficial functions of eosinophils while minimizing their potential to act as viral reservoirs could improve outcomes for both mothers and their infants. Given their multifaceted roles in immune modulation and interaction with HIV, eosinophils represent potential targets for therapeutic interventions aimed at preventing vertical transmission. Strategies that enhance the protective functions of eosinophils, such as their ability to sequester HIV particles and promote a balanced immune response, could be beneficial. Conversely, approaches that mitigate any detrimental effects, such as excessive tissue remodeling or promotion of viral reservoirs, could further reduce the risk of transmission.

Implications for Maternal-Fetal Health

Pregnancy is characterized by a series of complex immune adaptations that enable the mother to tolerate the genetically distinct fetus while simultaneously protecting against infections [12]. The immune system undergoes significant changes, promoting a Th2-skewed response that is associated with increased levels of cytokines like interleukin-4 (IL-4) and interleukin-10 (IL-10). Eosinophils play a critical role in shaping this immune environment, and their function is essential for maintaining maternal-fetal health. Eosinophils contribute to the establishment of immune tolerance at the maternal-fetal interface. Their ability to produce immunomodulatory cytokines and interact with other immune cells helps create a favorable environment for fetal development. This immune tolerance is crucial for preventing maternal immune rejection of the fetus and ensuring a successful pregnancy outcome. Any dysregulation in eosinophil function could lead to increased inflammation and immune responses that may adversely affect maternal-fetal health. The presence and activity of eosinophils during pregnancy have been associated with various pregnancy outcomes. Optimal eosinophil function can help mitigate risks associated with pregnancy complications, such as preterm labor, gestational hypertension, and preeclampsia. Conversely, altered eosinophil dynamics, such as eosinophilia or eosinopenia, may be indicative of underlying immune dysregulation, which could lead to adverse outcomes for both the mother and the fetus. Eosinophils are potent mediators of inflammation, and their dysregulation can contribute to pathological conditions during pregnancy. Excessive eosinophil activation can lead to tissue damage and chronic inflammation, potentially increasing the risk of complications such as pregnancy-induced hypertension or placental abruption. Monitoring eosinophil levels and function in pregnant women may provide insights into potential risks and guide clinical management to optimize maternal-fetal health.

Pregnant women with HIV may also be at higher risk for co-infections, which can further complicate maternal-fetal health [53]. Eosinophils play a vital role in the immune response to various pathogens, including those commonly encountered in co-infected populations. The interactions between eosinophils, HIV, and co-infections can impact the overall immune response and influence the risk of vertical transmission of HIV. Eosinophils are present at the maternal-fetal interface, and their role in vertical transmission of HIV is an area of increasing interest [54]. Eosinophils may influence the immune environment in a way that affects the risk of mother-to-child transmission (MTCT) of the virus. By modulating immune responses and interacting with both maternal and fetal immune cells, eosinophils may help mitigate or exacerbate the risk of MTCT. This emphasizes the need for further research into eosinophil functions in HIV-positive pregnancies. Targeting eosinophil function or modulating their activity through immunotherapies could enhance immune tolerance and improve pregnancy outcomes in women living with HIV [55]. Additionally, interventions aimed at managing eosinophil levels and activity could reduce the risk of complications and promote better health for both mothers and their children.

CONCLUSION

Eosinophils are multifunctional immune cells that play significant roles in modulating immune responses during pregnancy, contributing to the delicate balance between maternal tolerance and fetal protection. Their presence at the maternal-fetal interface and ability to produce a range of cytokines and chemokines underscore their importance in shaping the local immune environment. Proper eosinophil function is essential for maintaining immune tolerance and preventing adverse pregnancy outcomes, such as preterm labor and gestational complications. In the context of HIV, eosinophils emerge as critical players with the potential to influence both maternal and fetal health. Their interactions with HIV and other immune cells can affect viral dynamics and impact the risk of mother-to-child transmission.

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