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ELUDICATING THE HUMAN IMMUNE RESPONSE TO HOOKWORM INFECIONS: LITERATURE REVIEW

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Abstract

Parasitic infections, particularly those caused by hookworms, pose a significant challenge to global health, affecting millions in developing regions. Understanding the human immune response to such infections is crucial for developing effective interventions. This review provides a comprehensive overview of the innate and adaptive immune responses mobilized against hookworms, emphasizing the roles of various immune cells and the interplay between different immune mechanisms. A systematic literature review was conducted, focusing on studies published from January 2010 to the present. Databases such as PubMed, Scopus, Web of Science, and Google Scholar were searched using terms related to parasitic infections, immune responses, and hookworm pathology. Both experimental and review articles were included to extract detailed information on cellular and molecular immune responses to parasitic infections. The review highlights the dual role of innate and adaptive immunity in combating hookworm infections. Innate immunity acts as the first line of defense through mechanisms like inflammation and the production of antimicrobial peptides. Adaptive immunity provides a more targeted response, involving T and B cells and the production of specific antibodies. The interaction between these immune components and the modulation of immune responses, including the Th1/Th2 balance, are critical for the host's defense and the pathogenesis of hookworm infections. The intricate immune responses to hookworm infections underscore the complexity of host-parasite interactions. Understanding these responses is essential for developing novel therapeutic and preventive strategies against hookworm and other parasitic infections. Future research should focus on unraveling the detailed mechanisms of immunity and exploring the potential for vaccine development and immune-based therapies.

Keywords*: Hookworm Infections, Human Immune Response, Innate Immunity, Adaptive Immunity, Parasitic Diseases*

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INTRODUCTION

Parasitic infections, caused by a diverse array of organisms, present a significant global health challenge, particularly in developing nations. These infections, including helminthiasis by hookworms and filarial nematodes, along with protozoan assaults such as malaria, have profound impacts on human health and socio-economic development. This discourse explores the intricate immune responses elicited by the human body in reaction to various parasitic infections. Understanding the immune mechanisms against parasitic infections is crucial as it sheds light on the complex interactions between parasites and their human hosts. The immune response to parasites encompasses both innate and adaptive components, each playing a critical role in defense, pathogenesis, and the potential development of protective immunity. This includes innate immune responses, focusing on the roles of key cell types such as dendritic cells, natural killer cells, eosinophils, and basophils and their interactions with various parasites. The adaptive immune response involves T and B cells and the production of a range of cytokines and antibodies. These responses vary greatly based on factors such as infection intensity, age, genetics, and environmental exposure.(Han et al., 2020) By examining the body's immune responses, this discussion aims to provide a comprehensive overview of human defense strategies against some of the most common and impactful parasitic infections affecting individual health quality.

METHOD

This literature review was conducted to enhance current understanding of the body's immune responses to parasitic infections, focusing on helminthic infections (such as hookworm and filarial nematodes) and protozoan infections (such as malaria and Toxoplasma gondii). Relevant studies were identified through systematic database searches, including PubMed, Scopus, Web of Science, and Google Scholar. The search terms and phrases used included "parasitic infection," "immune response to parasites," "helminthic infection," "nematodes," "hookworm," "protozoan infection," "malaria," "innate immunity," "adaptive immunity." The search was limited to articles published in English or Indonesian from January 2010 to the present to ensure inclusion of the latest developments in the field. Both research articles and literature review articles were included in this study. Discussions on immune response mechanisms from various parasites, including cellular and molecular aspects, were extracted. Special focus was given to the roles of various immune cells (dendritic cells, NK cells, eosinophils, basophils), cytokine profiles, and the development of humoral responses. Additional emphasis was placed on understanding variations in immune responses due to factors such as infection intensity, genetic predispositions, and environmental exposures. The collected data were critically reviewed to evaluate the current understanding of immune mechanisms in response to parasitic infections.

DISCUSSION

Human Body Immune System

The human body employs external physical barriers, such as the skin, sweat secretions containing salt, lysozyme, and sebum, and mucous membranes coated with a mucous layer, to prevent pathogen invasion. When these protective barriers are breached, the body activates immune responses, mobilizing immune cells to eliminate the intruders. The immune response is orchestrated by various immune cells derived from progenitor stem cells located in the bone marrow. While most cells mature in the bone marrow, T cells undergo further development in the thymus. The regulation of immune cell numbers, known as homeostasis, is intricately controlled through precise mechanisms that govern hematopoiesis in the bone marrow. This microenvironment is rich in growth factors, such as colony-stimulating factors and cytokines, facilitating the growth and differentiation of immune cells. The bone marrow and thymus are considered primary lymphoid organs due to their central roles in the development and maturation of the body's immune cells.(Institute for Quality and Efficiency in Health Care (IQWiG), 2020; Nguyen & Soulika, 2019)

Once immune cells reach maturity, they leave the bone marrow (or thymus for T cells) and settle in organized structures known as secondary lymphoid organs. Although initial immune responses begin at the point where the body's external barriers have been penetrated, the formation of a comprehensive immune response, particularly the adaptive component, occurs within secondary lymphoid organs connected to the infection site. The immune system has developed various mechanisms to combat pathogenic organisms. The immune response can be categorized as innate or adaptive, with the innate immune system identifying pathogens in a

nonspecific manner and rapidly using general mechanisms to eliminate them. In contrast, the adaptive immune system displays specificity towards particular pathogens but requires several days to develop a targeted response.(Institute for Quality and Efficiency in Health Care (IQWiG), 2020)

Innate Immunity Mechanisms

The innate immune system can immediately initiate an immune response upon encountering foreign pathogens or elements deemed 'dangerous' to the human body, as proposed in Matzinger's 'Danger Hypothesis.' The innate immune response is nonspecific and triggered when recognizing pathogen-associated molecular patterns (PAMPs) commonly found on or produced by pathogenic organisms. These PAMPs are identified by pattern recognition receptors (PRRs), primarily found on and within phagocytic antigen-presenting cells (APCs), including macrophages, dendritic cells (DCs), and certain granulocyte types. PRRs can also detect host molecules containing damage-associated molecular patterns (DAMPs). DAMPs are molecules often released from necrotic cells damaged by invading pathogens.(Anaya et al., 2013; Mogensen, 2009)

Upon recognizing PAMPs or DAMPs, innate immune cells initiate a series of innate immune processes contributing to pathogen elimination. The term 'inflammation' is commonly used to describe the expansion of blood vessels and increased permeability in response to leukotrienes and prostaglandins released by phagocytes upon detecting pathogens. Inflammation enhances blood flow and the leakage of fluid and serum components from capillaries into surrounding tissues. Additionally, it facilitates the migration of white blood cells to the infection site. (Brahmana & Firmansyah, 2024; Lie & Firmansyah, 2024) On the surface, inflammation is responsible for visible symptoms such as swelling, pain, and redness in the infected tissue. The acute phase response begins when macrophages are activated by binding pattern recognition receptors (PRRs) to pathogen-related molecules. This term refers to the production of various proteins that enhance the containment and elimination of invading pathogens.(Anaya et al., 2013; Mogensen, 2009)

The production of acute phase cytokines, including interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF), collectively known as endogenous pyrogens, triggers the production of prostaglandin E2. Prostaglandin E2 acts in the hypothalamus, causing fever. Fever is an effective mechanism that inhibits the growth of certain pathogens and can enhance the performance of phagocytes. However, if uncontrolled, fever can be harmful to the body. IL-6 stimulates the liver to produce acute phase proteins such as C-reactive protein, serum amyloid protein, and mannose-binding lectin (MBL). These acute phase proteins coat invading pathogens, promoting their uptake by phagocytes and activating the complement pathway to facilitate pathogen lysis. Specifically, mannose-binding lectin (MBL) plays a crucial role in activating the lectin pathway of the complement system.(Anaya et al., 2013; Sahib El-Radhi, 2019)
Antimicrobial peptides vary in length, typically ranging from 12 to 50 amino acids, and possess ionic charges, being either anionic or cationic molecules. In mammals, two prominent families of antimicrobial peptides are defensins and cathelicidins. These peptides can opsonize pathogens, binding and inserting themselves into the pathogen membrane. This interaction alters membrane fluidity and results in pore formation, ultimately leading to lysis and destruction of the pathogen. Furthermore, it has been proposed that specific antimicrobial peptides exert antimicrobial effects by crossing the pathogen membrane and inhibiting essential enzymes required for nucleic acid and protein synthesis. This inhibition effectively starves the pathogen, leading to its death. Antimicrobial peptides are effective not only against bacteria but also against several protozoan pathogens.(Huan et al., 2020; Mogensen, 2009)

Immunity Mechanisms Against Hookworm Infections

Hookworms have a long-standing historical relationship with humans, traceable to ancient times in both the Old and New Worlds. Currently, an estimated 740 million people worldwide suffer from infections caused by Necator americanus or Ancylostoma duodenale, with the majority concentrated in sub-Saharan Africa. Despite its widespread prevalence, the manifestation of the disease varies among infected individuals, complicating the assessment of the actual disease burden. Low mortality rates characterize hookworm infections but are a significant source of morbidity, especially in areas with high infection levels. Morbidity rates often correlate directly with infection intensity. Recent insights have elucidated the role of parasitic worms, including hookworms, in modulating inflammation

associated with autoimmune diseases. This aligns with the Hygiene Hypothesis, which argues that reduced exposure to infectious agents, symbiotic microorganisms, and parasites during childhood increases susceptibility to allergic diseases by inhibiting the natural development of the immune system. Therefore, research on hookworms addresses an important global health issue, enhances broader immunological understanding, and opens new potential strategies for treating autoimmune diseases..(Smallwood et al., 2017)

The hookworm life cycle begins with the release of eggs through feces, leading to the first larval stage (L1). Subsequently, the larvae progress to the L2 stage and then the infectious L3 stage, which can actively penetrate the dermis of various mammalian hosts. Once they breach the skin, these larvae navigate the bloodstream, passing through the heart to reach the lungs. In the lungs, they penetrate the alveoli, ascend the trachea, and are eventually swallowed, settling in the small intestine as immature adult worms. In the intestinal environment, the developing adult worms engage in hematophagy, disrupting mucosal capillaries and destroying erythrocytes with pore-forming proteins in their digestive system, releasing proteins, notably hemoglobin. This protein is further degraded by the hookworm's aspartic protease enzyme (APR) -1 through a proteolytic process. The hookworm's digestive tract encounters host antibodies during feeding, which is a primary focus in vaccine research. Antibodies that inhibit the function of the enzyme APR-1 can impede nutrient absorption in the adult worm's intestine, potentially causing the worm's death. Adult hookworms reproduce within the small intestine of their host, laying eggs that are expelled through feces, thus completing their life cycle. These eggs hatch only under favorable environmental conditions, and the infectious larvae can survive for several weeks, although they are vulnerable to desiccation, particularly under direct sunlight.

Innate Immunity Mechanisms Against Hookworm Infeciton

The innate immune response to hookworm infection is a multifaceted process involving several key cell types, each playing a distinct role in combating the infection. For instance, dendritic cells (DCs) exhibit a decreased activation capacity following hookworm infection. Infected individuals show reduced expression of CD11c, CD14, CD86, MHC-I, and MHC-II on DCs, indicating an impairment in their ability to present antigens to T cells. Compounds secreted by hookworms, such as Ac-TMP-1, can influence DC maturation, leading to T cell differentiation into regulatory phenotypes, which can impact the overall immune response. Natural Killer (NK) cells also play a critical role in the innate response to hookworms. An increase in circulating NK cells is observed during infection, with these cells being spontaneously activated and producing interferon-gamma (IFN-γ). Intriguingly, NK cells derived from individuals infected with hookworms show a decreased production of IFN-γ upon stimulation compared to NK cells from uninfected individuals. This phenomenon could be attributed to the influence of specific molecules released by hookworms, which may recruit and expand NK cells, potentially as part of an immune evasion strategy.(Loukas & Prociv, 2001; McSORLEY & LOUKAS, 2010; Nair & Herbert, 2016)

Eosinophils represent another vital component in the response to hookworm infection, characterized in infected individuals. These eosinophils exhibit upregulated activation markers and can act as antigen-presenting cells. Eosinophils may play a crucial role in linking innate and adaptive immunity during hookworm infection by presenting processed antigens through MHC class II molecules and stimulating T cells. Basophils play a significant role in initiating the Th2 immune response, particularly in the context of hookworm infection. Experimental studies indicate that basophils become activated around eight weeks post-hookworm infection, maintaining this active state for an extended period. Basophil activation can occur due to cross-linking between surface-bound IgE or surface-bound IgG specific to hookworms. Although the impact of IgG binding on basophils is not fully understood, these cells are known to produce IL-4 and IL-13 in response to protease-containing products from Necator americanus (NaES), which may be protease-dependent. This basophil response, especially its role as an antigen-presenting cell and its ability to release IL-4 and thymic stromal lymphopoietin (TSLP) upon activation by proteases, indicates significant involvement in initiating and sustaining the Th2 immune response during hookworm infection. This aspect highlights the potential of hookworm protease-driven basophil activation as a critical factor in developing a Th2-type immune response.(Bouchery et al., 2014; McSORLEY & LOUKAS, 2010)

In summary, the innate immune response to hookworm involves complex interactions

among various cell types, each uniquely contributing to the body's defense mechanisms. This includes alterations in dendritic cell function, increased activation and modulation of NK cells, an enhanced role of eosinophils as antigen-presenting cells, and the crucial involvement of basophils in initiating the Th2 immune response. Collectively, these responses play a significant role in hookworm infection and pave the way for understanding hookworm disease pathology and exploring potential therapeutic strategies.(Loukas & Prociv, 2001)

Adaptive Immunity Mechanisms Against Hookworm Infection

The adaptive immune response to hookworm infection exhibits a complex and sophisticated interaction between T and B cell mechanisms, which is critical in the development of effective treatments and vaccines against this infection. In hookworm-endemic areas, there is a decrease in the number of circulating CD4+ T cells and CD19+ B cells among infected individuals. Despite the decrease, these T cells showed increased activation, as evidenced by increases in activation markers such as CD69 and HLA-DR. This indicates not only its activation but also the potential for migration to the site of infection or lymph nodes. Simultaneously, the immune system response to hookworm infection triggers the production of diverse antibody isotypes, including IgG1, IgG4, IgM, IgD, IgA, and IgE. Specifically, in human infections under experimental conditions, IgM antibodies targeting the parasite can be detected approximately six weeks after infection, followed by IgG antibodies at approximately eight weeks. The IgE response, which is important in fighting hookworm infections, tends to develop gradually and is often not very visible in primary infections. Research shows the protective role of IgE, the levels of which are inversely proportional to the intensity of infection. In contrast, IgG4 levels showed a direct correlation with the severity of infection. This pattern suggests that parasite-specific IgG4 may indicate a modified Th2 response in hookworm infections, a phenomenon also observed in other helminth infections.(Andiarsa et al., 2012; Loukas & Prociv, 2001; Nair & Herbert, 2016)

Another important aspect of the immune response is the role of IgD, which increases in levels after antihelminthic treatment, meaning its suppression during active hookworm infection. The involvement of IgD in basophils and induction of IL-4 production further underscores its importance in regulating Th2 responses. Overall, the adaptive immune response to hookworm involves a mixture of Th1 and Th2 responses, accompanied by the production of different antibody isotypes. Understanding these immune dynamics is critical for advancing therapeutic and preventive strategies against hookworm disease. Comprehensive studies, especially those that explore mucosal immunity, are needed to fully understand the host immune response during the initial phase of infection and subsequent reinfection. Insights such as these are critical to advances in the field of parasitology and improving public health outcomes in areas affected by hookworm disease.(Andiarsa et al., 2012; Loukas & Prociv, 2001)

CONCLUSION

The exploration of the human immune system's response to parasitic infections, particularly those caused by hookworms and other helminths, underscores the complexity and sophistication of our innate and adaptive immune mechanisms. These infections, which are prevalent in many developing regions, have significant implications for public health and socio-economic development. Through an in-depth analysis of the immune responses elicited by the human body, this discourse has highlighted the critical roles played by various immune cells, including dendritic cells, natural killer cells, eosinophils, and basophils, in orchestrating a defense against these parasites. The innate immune response, with its rapid and nonspecific mechanisms, serves as the first line of defense, identifying and combating pathogens through a variety of cells and processes. This includes the production of acute phase cytokines and antimicrobial peptides, which play pivotal roles in controlling infections. The adaptive immune response, characterized by its specificity and memory, involves a complex interplay between T and B cells, producing a range of antibodies that target specific antigens presented by invading parasites. Research into hookworm infections has provided valuable insights into the immune system's capacity to adapt and respond to persistent parasitic threats. The modulation of immune responses, particularly the balance between Th1 and Th2 responses, highlights the immune system's versatility in addressing different types of pathogens. The understanding of these mechanisms not only contributes to our knowledge of immunology and parasitology but also opens avenues for the development of effective

treatments and vaccines against parasitic diseases. This comprehensive review underscores the importance of continued research in the field of parasitic infections and their impact on the immune system. By advancing our understanding of the immune response to parasites, we can develop more effective strategies for prevention, treatment, and ultimately, the eradication of these diseases that disproportionately affect the world's most vulnerable populations.

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