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DECIPHERING THE IMMUNE LANDSCAPE: A COMPREHENSIVE REVIEW OF HUMAN IMMUNE RESPONSES TO MALARIA

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Abstract

This comprehensive review examines the complex human immune response to malaria, a significant global health challenge caused by Plasmodium parasites. The innate and adaptive immune systems play pivotal roles in defending against malaria, with mechanisms involving various immune cells like dendritic cells, natural killer cells, eosinophils, basophils, T cells, and B cells. These cells operate in a dynamic interaction, recognizing and responding to the parasite at different stages of its life cycle. Our review methodologically analyzed recent studies and literature on the immune response to malaria, focusing on the roles of different immune cells and the production of cytokines and antibodies. We also explored the epidemiology of malaria, with particular attention to regions like Indonesia, where climate, geography, and socio-economic factors influence transmission dynamics. The findings highlight the innate immune system's crucial role in early pathogen detection and response, particularly through PAMPs recognition by PRRs such as TLRs and scavenger receptors. Additionally, the adaptive immune response's complexity, including anti-sporozoite antibodies and T cell immunity, is emphasized, particularly in recognizing parasite-exported antigens and developing memory responses for long-term immunity. The immune response's intricacy, coupled with the challenges in vaccine and therapy development due to the parasite's complex life cycle and varying epidemiological patterns, underscores the need for continued research and innovation in malaria immunology and public health strategies. This review contributes to a deeper understanding of the immune mechanisms against malaria and the ongoing efforts to control and eradicate this pervasive disease.

Keywords*: Malaria Immunology, Plasmodium Parasites, Innate and Adaptive Immune Responses, Immune Cell Dynamics*

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INTRODUCTION

Parasitic infections pose a significant global health challenge, with malaria being one of the most critical due to its profound impact on human health and socio-economic development, particularly in developing countries. Understanding the immune response to malaria is crucial as it provides insights into the complex interactions between the Plasmodium parasite and its human host. The immune response to malaria involves both innate and adaptive components, each playing a vital role in defense, pathogenesis, and the potential development of protective immunity. The innate immune response includes the roles of key cell types such as dendritic cells, natural killer cells, eosinophils, and basophils, and their interactions with the Plasmodium parasite. The adaptive immune response involves T and B cells and the production of various cytokines and antibodies, which vary based on factors such as infection intensity, age, genetics, and environmental exposure.(Aly et al., 2009; Nureye & Assefa, 2020)

Malaria continues to be a major global health concern. The World Health Organization reported an estimated 241 million cases of malaria worldwide in 2020, predominantly in the WHO African Region. However, Asia also faces a significant burden, with countries like India reporting substantial numbers of cases. In Indonesia, malaria is a major public health issue, particularly in eastern provinces such as Papua and West Papua. The transmission dynamics in Indonesia are influenced by factors such as climate, geography, and socio-economic conditions, and the archipelagic nature of the country presents unique challenges in controlling and eliminating malaria. Indonesian strategies to combat malaria include the distribution of insecticide-treated bed nets, indoor residual spraying, and the provision of antimalarial drugs. These efforts align with the global objective to reduce the incidence and mortality of malaria, as outlined in the Sustainable Development Goals. A comprehensive understanding of malaria's epidemiology and immune response is essential for developing effective control strategies and contributes to the global effort to eradicate this pervasive disease.(Guttery et al., 2012; Torgerson, 2013)

METHOD

This literature review was conducted to enhance current knowledge on the human immune response to parasitic infections, specifically focusing on malaria. Relevant studies were systematically identified through database searches, including PubMed, Scopus, Web of Science, and Google Scholar. The search terms and phrases used in this investigation included "parasitic infection", "immune response to parasites", "malaria", "innate immunity", "adaptive immunity". The search was limited to articles published in English and Indonesian from January 2010 to the present to ensure the inclusion of recent developments in the field. Both research articles and review articles were included in this study. Discussions on the immune mechanisms against malaria, 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 the humoral response. Additional emphasis was placed on understanding variations in the immune response due to factors such as infection intensity, genetic predisposition, and environmental exposure. The collected data were critically reviewed to evaluate the current understanding of immune mechanisms in response to malaria infection.

RESULT AND DISCUSSION

Immune System

The human body have external physical barriers, namely the skin, sweat secretions containing salt, lysozyme, and sebum, and mucous membranes covered by a mucus layer, as primary defenses against pathogen invasion. Upon breach of these protective barriers, the body initiates an immune response, mobilizing immune cells to eliminate the intruders. The regulation of the immune response is facilitated by a variety of immune cells, which originate 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 the quantity of immune cells in the body, known as homeostasis, is intricately controlled through precise mechanisms that govern hematopoiesis in the bone marrow. This microenvironment is enriched with growth factors, such as colony-stimulating factors and cytokines, which aid in the growth and differentiation of immune cells. The

bone marrow and thymus are referred to as primary lymphoid organs due to their central role in the development and maturation of the body's immune cells.(Apriyanti & Dhilon, 2022; Han et al., 2020)

Once immune cells reach maturity, they exit the bone marrow (or the thymus in the case of T cells) and settle in organized structures known as secondary lymphoid organs. While the initial immune response commences 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 these secondary lymphoid organs connected to the site of infection. The immune system has developed a variety of mechanisms to combat pathogenic organisms. The immune response can be categorized as either innate or adaptive. The innate immune system identifies pathogens in a non-specific manner and swiftly employs general mechanisms to eliminate these pathogens. Conversely, the adaptive immune system exhibits specificity towards particular pathogens but requires several days to develop a targeted response.(Institute for Quality and Efficiency in Health Care (IQWiG), 2020; Nguyen & Soulika, 2019)

Immune System Mechanism Against Malaria

Malaria, a disease caused by protozoan parasites from the genus Plasmodium, poses a risk to over half of the global population. Historically misattributed to poor sanitary conditions or 'mal-air' (bad air), the breakthrough in the early 20th century by Sir Ronald Ross established that the disease is transmitted via bites from infected Anopheles mosquitoes. Among the five Plasmodium species that infect humans, Plasmodium falciparum and Plasmodium vivax are the most prevalent, accounting for the majority of malaria morbidity and mortality. Plasmodium ovale and Plasmodium malariae, though less common, also contribute to the disease burden. Additionally, Plasmodium knowlesi, once regarded as a primate-specific malaria, has emerged as a significant human pathogen in Southeast Asia. Malaria, caused by the protozoan parasites of the genus Plasmodium, remains a significant threat to global health. In 2022, there were an estimated 249 million cases of malaria and approximately 608,000 malaria-related deaths reported in 85 countries. The majority of these cases and deaths were concentrated in the WHO African Region, which accounted for 94% of malaria cases (233 million) and 95% (580,000) of the deaths. Children under five years old were particularly affected, accounting for about 80% of all malaria deaths in the region.(Samrot et al., 2021; Utami et al., 2014)

The recent increase in malaria cases and deaths post the COVID-19 pandemic is concerning. Between 2021 and 2022, an additional 5 million cases were observed, mainly concentrated in Ethiopia, Nigeria, and Uganda. The pandemic period saw a rise in cases and deaths globally, reversing the declining trend observed since 2000. 11 countries have been identified as ‘High Burden to High Impact’ (HBHI) by WHO and the RBM Partnership to End Malaria, including Burkina Faso, Cameroon, the Democratic Republic of the Congo, Ghana, India, Mali, Mozambique, Niger, Nigeria, Uganda, and the United Republic of Tanzania, with Sudan joining in 2022. These countries collectively accounted for an estimated 167 million cases (67% of the global total) and 426,000 deaths (73% of the global total) in 2022.(Fikadu & Ashenafi, 2023; Zekar & Sharman, 2024)

The relationship between climate change and malaria is also a significant concern. A changing climate affects malaria transmission due to the sensitivity of the malaria parasite and mosquito to temperature, rainfall, and humidity. Additionally, indirect effects of climate change, such as disruptions to healthcare services, population displacement, and food insecurity, can exacerbate the impact of malaria. Core interventions for malaria control and elimination include insecticide-treated mosquito nets (ITNs), indoor residual spraying (IRS), antimalarial medicines, rapid diagnostic tests (RDTs), and vaccines (RTS, S/AS01 and R21/Matrix-M). These strategies play a crucial role in reducing transmission and mortality rates and contribute to broader public health gains and economic stability in affected regions. The findings from the 2023 World Malaria Report underscore the heavy burden of malaria in Africa and highlight the opportunities to accelerate progress toward malaria elimination.(Escalante & Pacheco, 2019; Singh & Daneshvar, 2013)

Malaria remains endemic in 109 countries across four continents. Annually, there are an estimated 500 million reported cases, with approximately one million resulting in death. Children under five years of age and pregnant

women are particularly vulnerable to the lethal effects of this disease. The exposure to malaria and the consequent risk levels varies significantly based on geographic and environmental factors. In areas where malaria is holoendemic, a majority of the population is infected, often asymptomatically, due to the development of non-sterile immunity over time. This type of immunity allows for asymptomatic infections, particularly in older individuals. However, in other regions, malaria transmission can be seasonal and unstable, largely influenced by rainfall patterns affecting mosquito breeding and population dynamics. The life cycle of the Plasmodium parasite is highly complex, involving various developmental stages both in the human host and the Anopheles mosquito vector. The parasite's life cycle is governed by a genome comprising over 5,000 genes. While Plasmodium primarily replicates in a haploid state within the human host, the only diploid stage occurs within the mosquito, specifically during the ookinete and oocyst stages. This intricate life cycle, coupled with the genetic complexity of the parasite, poses significant challenges to malaria control and eradication efforts. Understanding these dynamics is crucial for developing effective strategies to combat malaria, a disease that continues to have a substantial impact on global public health.(Samrot et al., 2021)

Innate Immunity Mechanisms Against Malaria

Recent research into pathogen-associated molecular patterns (PAMPs) on malaria antigens and various parasitic products has substantially advanced our understanding of how the innate immune system recognizes these pathogens. Recognition of these conserved features across malaria species and strains is facilitated by pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and scavenger receptors. Despite these advancements, a comprehensive understanding of all malaria-derived molecules and the respective PRRs involved in innate immune recognition remains incomplete and occasionally controversial. Studies, particularly using mouse models, have extensively investigated the immune response to the pre-erythrocytic, especially liver, stages of malaria. These studies emphasize the role of interferon-gamma (IFN-γ) secretion by natural killer (NK) cells, NKT cells, and γδ T cells. IFN-γ plays a crucial role in driving the production of interleukin-12 (IL-12) and interleukin-18 (IL-18) by local phagocytes, thereby enhancing NK cell activation. The production of these cytokines and cell activation is vital for mounting an effective immune response against the liver stage of malaria parasites.(Buck & Finnigan, 2024; “Severe Malaria,” 2014)

During the asexual erythrocytic cycle of malaria, various immune cells play a critical role. For instance, macrophages and monocytes increase in number and activation level during infection. They are pivotal in clearing malaria-infected red blood cells (erythrocytes) and produce various cytokines, including pro-inflammatory cytokines like IL-12 and IL-18, as well as acute phase cytokines like tumor necrosis factor (TNF), IL-1, and IL-6. TNF, in particular, is associated with the characteristic cyclic fever of malaria. Phagocytosis of infected erythrocytes by these cells occurs through both antibody-dependent and -independent mechanisms involving receptors like CD36 and Fc receptors. Granulocytes, particularly neutrophils, also show activation during malaria infection. The presence of molecules like myeloperoxidase in the serum indicates neutrophil activation, capable of respiratory burst response to opsonized Plasmodium falciparum merozoites. This suggests their active participation in the body's defense against malaria. NK cells are another critical component of the immune response to malaria. In non-immune humans, NK cells are among the first to respond following P. falciparum infection. Early indicators of this activation include the presence of granzyme A and IFN-γ before the onset of clinical symptoms or detectable parasitemia. During infection, NK cells increase in circulation and exhibit enhanced lytic capacity, underscoring the importance of NK cells in the immune response to malaria. Additionally, γδ T cells emerge in response to infection by P. falciparum and P. vivax. Once activated, these cells produce IFN-γ and can perform cytotoxic actions on infected erythrocytes, contributing to the clearance of malaria parasites from the bloodstream. (Gowda & Wu, 2018; Pohl & Cockburn, 2022)

Dendritic cells (DCs), particularly myeloid DCs, are believed to play a crucial role in shaping T cells during malaria infection. They can uptake infected erythrocytes through both opsonic and non-opsonic pathways. Mouse model studies have shown diverse DC responses to infected erythrocytes, with their activation depending on recognition of parasitic products released during schizogony. This highlights the complex interactions between different immune cells and

malaria parasites, contributing to the overall immune response to the disease. In conclusion, the immune response to malaria involves a sophisticated network of innate and adaptive immune cells, each playing specific roles in recognizing the parasite at various stages of its life cycle. This intricate immune response is critical for controlling infection and forms the basis of ongoing research in malaria immunology and vaccine development. (Gowda & Wu, 2018; Pohl & Cockburn, 2022)

Adaptive Immunity Mechanisms Against Malaria

The adaptive immune response to malaria involves intricate and specific immunological mechanisms designed to combat the pre-erythrocytic and asexual erythrocytic stages of malaria parasites. This complexity highlights the nuances of the immune system's involvement in confronting this widespread and challenging disease. At the pre-erythrocytic stage, anti-sporozoite antibodies play a crucial role. These antibodies, present in high titers, can immobilize cellular sporozoites, preventing them from invading hepatocytes. Key targets for these antibodies include antigens like circumsporozoite protein (CSP). Immobilized sporozoites become vulnerable to various immune attacks, including complement-mediated lysis, Fc receptor-mediated lysis by NK or NKT cells, and macrophage phagocytosis. T cell immunity, especially involving CD4+ and CD8+ T cells, is also vital at this stage. IFN-γ-dependent CD4+ T cell responses provide protective immunity, while CD8+ T cells are crucial for an effective response to intra-hepatic stages, with their anti-parasitic effects depending on IFN-γ. These T cells can eliminate infected hepatocytes through mechanisms involving cytotoxic molecules or Fas-FasL signaling, with dendritic cells playing a significant role in T cell formation. (Doolan et al., 2009; Rochford & Kazura, 2020; Wang et al., 2021)

The adaptive response to the asexual erythrocytic cycle is equally complex. CD4+ T cells, recognizing parasite-exported antigens on infected erythrocytes, release a range of cytokines. Initially, Th1 phenotype CD4+ T cells predominate, inducing cell-mediated parasiticidal mechanisms. As the infection progresses, Th2 phenotype CD4+ T cells emerge, aiding in antibody production to limit parasite density. B cells and antibodies form another crucial component of immune defense during this stage. Antibodies can control parasite density by opsonizing infected erythrocytes or free merozoites, facilitating their removal and preventing merozoite reinvasion. A critical aspect of defense against malaria is the development of memory responses, essential for building long-term immunity, particularly in endemic areas. Memory B cells and CD8+ T cells are generated in response to malaria, demonstrating persistence and efficacy in combating infection. The recall response of CD4+ T cells to erythrocytic stage malaria peptides further underscores their role in generating protective antibodies. The adaptive immune response to malaria is marked by a coordinated effort among various cell types, each uniquely contributing to the overall immune response. Whether through cytokine secretion, phagocytosis, or direct cytotoxic actions, the roles of these cells in recognizing malaria parasites underscore the importance of both innate and adaptive immunity in controlling and shaping the immune response to this widespread disease. The complexity of this response highlights the challenges in developing effective malaria vaccines and therapies, as they must consider various stages and mechanisms of parasite interaction with the immune system. (Doolan et al., 2009; Rochford & Kazura, 2020)

CONCLUSION

The in-depth exploration of the human immune response to malaria, as elucidated in the preceding sections, underscores the intricacy and sophistication of the body's defense mechanisms against this pervasive disease. The innate and adaptive immune systems collaborate in a complex and dynamic manner to combat malaria, caused by Plasmodium parasites, a significant global health threat. The human immune system's initial line of defense includes physical barriers such as skin and mucous membranes. Upon their breach, a multifaceted immune response is initiated, involving various immune cells originated from the bone marrow and further matured in the thymus for T cells. This highlights the critical roles of primary lymphoid organs – the bone marrow and thymus – in immune cell development and maturation.

In the context of malaria, the innate immune system plays a crucial role in early detection and response to infection. Research has revealed the

importance of pathogen-associated molecular patterns (PAMPs) on malaria antigens and the corresponding recognition by pattern recognition receptors (PRRs) like Toll-like receptors (TLRs) and scavenger receptors. However, challenges remain in fully understanding the spectrum of malaria-derived molecules and their interaction with various PRRs. The response to the pre-erythrocytic liver stages of malaria, particularly involving IFN-γ secretion by NK, NKT, and γδ T cells, exemplifies the innate system's role in controlling infection. The adaptive immune response to malaria is equally intricate, targeting both pre-erythrocytic and asexual erythrocytic stages. Anti-sporozoite antibodies, T cell immunity, and the role of CD4+ and CD8+ T cells are pivotal in this response. The adaptive system's complexity is evident in its ability to recognize parasite-exported antigens, induce cytokine release, and develop memory responses crucial for long-term immunity, especially in endemic areas. The interplay between various immune cells – NK cells, γδ T cells, dendritic cells, macrophages, monocytes, and B cells – demonstrates a coordinated defense strategy. This strategy encompasses cytokine secretion, phagocytosis, cytotoxic actions, and the development of memory responses. However, the complexity of these interactions and the life cycle of the malaria parasite present significant challenges in developing effective vaccines and therapies. These challenges are compounded by the diverse epidemiological patterns and environmental influences on malaria transmission, as observed in the varying impacts of the disease across different regions and populations.

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