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Malaria and Immune Response Modulation: Insights into Host-Parasite Interactions and Vaccine Development

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ABSTRACT

Malaria remains a global health challenge, with over 200 million cases annually, particularly affecting sub-Saharan Africa. The disease is caused by Plasmodium parasites, primarily P. falciparum, and transmitted via female Anopheles mosquitoes. A central factor in malaria pathogenesis and persistence is the complex interplay between the parasite and the host immune system. Plasmodium has evolved diverse strategies to evade immune detection, including antigenic variation, immune suppression, and manipulation of host cytokine responses. Conversely, the human immune system mounts both innate and adaptive responses, albeit often insufficient to confer lasting immunity after infection. This review explores the mechanisms by which Plasmodium modulates host immunity, focusing on innate recognition pathways, dendritic cell dysfunction, T-cell exhaustion, and B-cell dysregulation. We also examine the role of immunological memory in malaria and its implications for natural immunity. Despite advances, vaccine development faces challenges such as the antigenic diversity of Plasmodium and its ability to manipulate immune memory. However, novel vaccine candidates, including RTS, S/AS01, R21/Matrix-M, and whole sporozoite-based vaccines, demonstrate varying degrees of efficacy, particularly in children. Advancements in systems immunology, adjuvant technologies, and structure-based antigen design offer new hope for a highly efficacious and durable malaria vaccine. Understanding the host-parasite immunological dialogue is crucial not only for vaccine design but also for the development of immune-based therapies to reduce disease burden and transmission.

Keywords: Malaria Immunology, Host-Parasite Interaction, Immune Evasion Mechanisms, Plasmodium falciparum, Malaria Vaccine Development

INTRODUCTION

Malaria continues to be one of the world's most devastating infectious diseases, responsible for hundreds of thousands of deaths annually, particularly in sub-Saharan Africa and parts of Southeast Asia [1]. It is caused by protozoan parasites of the genus Plasmodium, among which Plasmodium falciparum is the most virulent and life-threatening species [2]. The parasite's lifecycle involves both the Anopheles mosquito vector and the human host, with distinct developmental stages in the liver and red blood cells [3]. Each stage poses unique challenges to the human immune system and provides opportunities for the parasite to evade detection and elimination. The human immune response to malaria is a complex and dynamic process involving a delicate balance between pro-inflammatory and regulatory mechanisms [4]. While the immune system attempts to control parasite replication and prevent severe disease, Plasmodium has developed intricate strategies to modulate and escape immune surveillance [5]. These host-parasite interactions play a critical role in the clinical manifestations of malaria, ranging from asymptomatic infections to severe complications such as cerebral malaria and multi-organ failure. Understanding these immunological dynamics is essential not only for improving clinical management but also for informing vaccine design and the development of immunotherapeutic strategies.

2. Immune Response to Plasmodium Infection

2.1 Innate Immunity

Innate immunity serves as the first line of defense against Plasmodium infection. Upon mosquito transmission, sporozoites enter the bloodstream and travel to the liver, where they infect hepatocytes [6]. During this early stage, innate immune cells such as macrophages, dendritic cells (DCs), and natural killer (NK) cells become activated [7]. These cells recognize pathogen-associated molecular patterns (PAMPs) on the parasite through pattern recognition receptors (PRRs), including Toll-like receptors (TLRs). For example, glycosylphosphatidylinositols (GPIs) from Plasmodium trigger TLR2 and TLR4 signaling pathways, leading to the production of inflammatory cytokines like interleukin-12 (IL-12) and interferon-gamma (IFN-γ) [8]. This initial cytokine response is crucial for containing the early stages of infection and priming adaptive immunity. However, an exaggerated or poorly regulated innate response can lead to immunopathology [9]. In cases of severe malaria, excessive inflammation contributes to complications such as cerebral malaria, anemia, and vascular leakage, emphasizing the need for a balanced immune response [10].

2.2 Adaptive Immunity

Adaptive immunity plays a central role in controlling Plasmodium during the blood stage, when merozoites infect red blood cells [11]. CD4+ T helper cells, particularly Th1 subsets, secrete IFN-γ and tumor necrosis factor-alpha (TNF-α) to activate macrophages and promote parasite clearance [12]. CD8+ T cells are more relevant during the liver stage, where they target and eliminate infected hepatocytes [13]. B cells produce antibodies targeting parasite antigens, especially those expressed on the surface of merozoites and infected red blood cells [14]. These antibodies inhibit parasite invasion, promote opsonization, and mediate antibody-dependent cellular cytotoxicity. Despite the generation of specific immune responses, long-lasting protective immunity is difficult to achieve. In endemic regions, individuals may require repeated exposure over several years to develop partial immunity that reduces disease severity but does not prevent reinfection [15].

3. Immune Evasion Strategies by Plasmodium

3.1 Antigenic Variation

A hallmark of Plasmodium falciparum is its ability to evade immune detection through antigenic variation. The parasite expresses a diverse family of surface proteins, particularly Plasmodium falciparum erythrocyte membrane protein 1 (PfEMP1), encoded by the var gene family [16]. By switching the expression of different var genes, the parasite alters the antigenic profile of infected red blood cells, thus evading recognition by antibodies generated against previous variants [17]. This process enables the parasite to persist in the host for extended periods and contributes to chronic and severe infections.

3.2 Dendritic Cell and T Cell Dysfunction

Plasmodium infection significantly disrupts the function of antigen-presenting cells, especially dendritic cells [18]. Infected individuals often exhibit reduced dendritic cell maturation and impaired expression of costimulatory molecules, leading to suboptimal activation of naive T cells [19]. This immunosuppressive environment hinders the development of effective adaptive responses. Furthermore, chronic exposure to Plasmodium antigens leads to T cell exhaustion, a state characterized by diminished effector function and sustained expression of inhibitory receptors such as programmed death-1 (PD-1) and lymphocyte activation gene-3 (LAG-3) [20]. These exhausted T cells fail to proliferate or secrete cytokines effectively, compromising the host's ability to control infection.

3.3 Regulatory T Cells and Cytokine Imbalance

Another mechanism by which Plasmodium modulates host immunity is through the induction of regulatory T cells (Tregs), which play a role in dampening excessive immune responses [21]. During malaria, the expansion of Tregs contributes to reduced inflammation but also suppresses protective immune functions [22]. These cells secrete anti-inflammatory cytokines, such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), which inhibit the proliferation of effector T cells and cytokine production [23].

In addition, malaria is often associated with a dysregulated cytokine milieu. Early in the infection, a burst of pro-inflammatory cytokines occurs, followed by a compensatory anti-inflammatory response [24]. This imbalance can either lead to immunopathology or impair parasite clearance, depending on the timing and magnitude of the cytokine response.

4. Vaccine Development and Immune Modulation

Developing a malaria vaccine has remained one of the most significant yet challenging goals in global health [25]. The complexity of the Plasmodium life cycle, its antigenic diversity, and its ability to manipulate the immune system contribute to the difficulty in designing effective and durable vaccines. Unlike many viral and bacterial infections, natural infection with Plasmodium often fails to produce sterilizing immunity, which complicates efforts to mimic protective immune responses through vaccination [26].

4.1 RTS, S/AS01 and R21/Matrix-M

The RTS, S/AS01 (Mosquirix) vaccine is the first malaria vaccine to achieve approval by the World Health Organization (WHO) [27]. It targets the circumsporozoite protein (CSP), which is expressed on the surface of Plasmodium falciparum sporozoites during the pre-erythrocytic stage [27]. By fusing CSP with hepatitis B surface antigen and using the AS01 adjuvant, RTS, S elicits antibody and CD4+ T cell responses that reduce the incidence of clinical malaria, especially in young children [28]. However, its efficacy is moderate, ranging between 30% to 50%, and wanes over time, requiring multiple booster doses.

The R21/Matrix-M vaccine is a next-generation candidate that also targets CSP but uses a higher antigen-to-carrier ratio and the Matrix-M adjuvant to enhance immunogenicity [29]. Phase II trials have reported efficacy above 70%, marking a promising advancement in malaria vaccine development [30]. However, longer-term follow-up and real-world implementation studies are still needed to confirm its sustained protection.

4.2 Whole Sporozoite and Liver Stage Vaccines

An alternative approach involves using whole sporozoites to stimulate broad immune responses. The PfSPZ vaccine by Sanaria uses radiation-attenuated sporozoites delivered intravenously, aiming to elicit robust CD8+ T cell responses targeting liver-stage parasites [31]. These vaccines are immunologically potent but face practical challenges, including cold chain requirements, production costs, and the need for intravenous administration. Liver-stage vaccines focus on eliciting strong cellular immunity, particularly cytotoxic T cells that can detect and destroy infected hepatocytes before parasites reach the blood stage [32]. Success in this domain could prevent clinical disease and reduce transmission, as the liver stage is asymptomatic and a bottleneck in the parasite lifecycle.

4.3 Novel Strategies and Immune Engineering

Emerging technologies are revolutionizing malaria vaccine development. mRNA vaccine platforms, as demonstrated during the COVID-19 pandemic, offer the flexibility to encode multiple parasite antigens and rapidly adjust to antigenic variation [33]. Nanoparticle-based vaccines can present antigens in highly immunogenic conformations and enhance uptake by dendritic cells [34].

Adjuvants play a critical role in directing immune responses. For malaria, adjuvants that promote T follicular helper cell activity are essential for generating high-affinity antibodies and long-lived plasma cells [35]. Additionally, structure-guided design of antigens can identify conserved epitopes across parasite strains, potentially overcoming the challenge of antigenic diversity [36]. Systems biology and high-throughput immunoprofiling are also aiding the identification of correlates of protection, allowing researchers to predict vaccine efficacy and optimize dosing schedules [37]. These tools provide critical insights into how host immunity responds to vaccination and can help in tailoring strategies for different age groups and transmission settings.

5. Challenges and Future Perspectives

Despite promising developments, several obstacles hinder the realization of a universally effective malaria vaccine. The high genetic variability of Plasmodium antigens means that immune responses elicited by vaccination may not cross-protect against all circulating strains [38]. The short duration of natural and vaccine-induced immunity remains another critical limitation. Moreover, the immune evasion tactics employed by Plasmodium, including antigenic variation and suppression of dendritic cell function, may diminish the efficacy of vaccines, particularly those relying on T cell activation [39]. Achieving a balance between immune activation and control of immunopathology is also crucial, as overactive responses may contribute to severe disease.

Vaccine deployment faces logistical barriers, especially in remote or resource-limited settings where malaria burden is highest. Effective implementation will require integration with other control measures, such as vector management, chemoprophylaxis, and diagnostics. To overcome these challenges, future research must focus on identifying conserved antigens, optimizing adjuvant formulations, and improving delivery mechanisms. Combining vaccine strategies that target multiple life stages of the parasite may offer synergistic benefits, reducing both morbidity and transmission.

CONCLUSION

Malaria remains a formidable global health threat due to the parasite's complex lifecycle and ability to evade host immunity. The host immune response, although capable of controlling parasite growth, often fails to achieve lasting protection. Plasmodium exploits multiple mechanisms to modulate immune function, including antigenic variation, dendritic cell suppression, T cell exhaustion, and cytokine imbalance. Despite these challenges, advances in immunology, molecular biology, and vaccine technology have led to significant progress in vaccine development. Vaccines such as RTS, S and R21 provide important proof-of-concept, and emerging platforms like whole sporozoite vaccines and mRNA-based approaches hold great promise. A deeper understanding of host-parasite interactions will be instrumental in guiding the design of next-generation vaccines and immunotherapies, ultimately contributing to global malaria control and eradication efforts.

REFERENCES

1. Oladipo HJ, Tajudeen YA, Oladunjoye IO, Yusuff SI, Yusuf RO, Oluwaseyi EM, et al. Increasing challenges of malaria control in sub-Saharan Africa: priorities for public health research and policymakers. Annals of Medicine and Surgery. 2022;81. doi:10.1016/J.AMSU.2022.104366
2. Egwu, C. O., Aloke, C., Chukwu, J., Agwu, A., Alum, E., Tsamesidis, I, et al. A world free of malaria: It is time for Africa to actively champion and take leadership of elimination and eradication strategies. Afr Health Sci. 2022 Dec;22(4):627-640. doi: 10.4314/ahs.v22i4.68.
3. Cowman AF, Tonkin CJ, Tham WH, Duraisingh MT. The molecular basis of erythrocyte invasion by malaria parasites. Cell Host & Microbe. 2017;22(2):232–45. doi:10.1016/J.CHOM.2017.07.003

4. Obeagu EI. Role of cytokines in immunomodulation during malaria clearance. Annals of Medicine and Surgery. 2024. doi:10.1097/MS9.0000000000002019
5. Kungu, E., Inyangat, R., Ugwu, O.P.C. and **Alum, E. U.** (2023). Exploration of Medicinal Plants Used in the Management of Malaria in Uganda. NEWPORT INTERNATIONAL JOURNAL OF RESEARCH IN MEDICAL SCIENCES 4(1):101-108.https://nijournals.org/wp-content/uploads/2023/10/NIJRMS-41101-108-2023.docx.pdf
6. Obeagu, E. I., **Alum, E. U.** and Ugwu, O. P. C. Hepcidin's Antimalarial Arsenal: Safeguarding the Host. NEWPORT INTERNATIONAL JOURNAL OF PUBLIC HEALTH AND PHARMACY. 2023; 4(2):1-8. https://doi.org/10.59298/NIJPP/2023/10.1.1100
7. Ayalew H, Xu C, Adane A, Sanchez ALB, Li S, Wang J, et al. Ontogeny and function of the intestinal epithelial and innate immune cells during early development of chicks: to explore in ovo immunomodulatory nutrition. Poultry Science. 2024;104(1):104607. doi:10.1016/J.PSJ.2024.104607
8. Emmanuel Ikechukwu Nnamonu., Ogonna Christiana Ani., Felix Joel Ugwu., Simeon Ikechukwu Egba., Ifeanyi Oscar Aguzie., Obiageli Panthe Okeke., Christian Enyi Dialoke., Lilian Obinna Asogwa and Solomon Ikechukwu Odo. Malaria Prevalence in Rice Farm Settlements South East Nigeria. *IJTDH*, 2020; 41(9): 64-74
9. Aja O. A., Egba S. I., Omoboyowa D. A., Odo C. E., Vining-Ogu I. C., Oko F. O (2020) Anti-anaemic and immunomodulatory potentials of aqueous, chloroform and methanol leaf extracts of *whitfieldia lateritia* on 2, 4-dinitrophenylhydrazine induced anaemia in rats. World Journal of Pharmacy Research 2020; 9(10): 44-58
10. Obeagu EI. Role of cytokines in immunomodulation during malaria clearance. Annals of Medicine and Surgery. 2024. doi:10.1097/MS9.0000000000002019
11. Belachew EB. Immune response and evasion mechanisms of Plasmodium falciparum parasites. Journal of Immunology Research. 2018;2018:1–6. doi:10.1155/2018/6529681
12. Egba, S. I., Ikechukwu, G. C and Njoku, O U. Aqueous extracts of *Telfairia occidentalis* leaf reverses pyrogallol induced leucopenia and stimulates the immune system in wistar albino rats. *Journal of Chemical and Pharmaceutical. Research*, 2013; 5(4): 149-153
13. Hassert M, Arumugam S, Harty JT. Memory CD8+ T cell-mediated protection against liver-stage malaria. Immunological Reviews. 2023;316(1):84–103. doi:10.1111/IMR.13202
14. Chan JA, Fowkes FJI, Beeson JG. Surface antigens of Plasmodium falciparum-infected erythrocytes as immune targets and malaria vaccine candidates. Cellular and Molecular Life Sciences. 2014;71(19):3633–57. doi:10.1007/S00018-014-1614-3
15. Emmanuel Ifeanyi Obeagu, Getrude Uzoma Obeagu, Simeon Ikechukwu Egba and Obioma Raluchukwu Emeka Obi. Combatting Anaemia in Paediatric Malaria: Effective management strategies Int. J. Curr. Res. Med. Sci. 2023. 9(11): 1-7
16. Kirkman LA, Deitsch KW. Antigenic variation and the generation of diversity in malaria parasites. Current Opinion in Microbiology. 2012;15(4):456–62. doi:10.1016/J.MIB.2012.03.003
17. Alum EU, Ugwu OPC, Egba SI, Uti DE, Alum BN. Climate Variability and Malaria Transmission: Unraveling the Complex Relationship. INOSR Scientific Research, 2022; 11(2):16-22. https://doi.org/10.59298/INOSRSR/2024/1.1.21622
18. Turner TC, Arama C, Ongoiba A, Doumbo S, Doumtabé D, Kayentao K, et al. Dendritic cell responses to Plasmodium falciparum in a malaria-endemic setting. Malaria Journal. 2021;20(1). doi:10.1186/S12936-020-03533-W
19. Miller E, Bhardwaj N. Dendritic cell dysregulation during HIV-1 infection. Immunological Reviews. 2013;254(1):170–89. doi:10.1111/IMR.12082
20. Illingworth J, Butler NS, Roetynck S, Mwacharo J, Pierce SK, Bejon P, et al. Chronic exposure to Plasmodium falciparum is associated with phenotypic evidence of B and T cell exhaustion. The Journal of Immunology. 2012;190(3):1038–47. doi:10.4049/JIMMUNOL.1202438
21. Frosch AEP, John CC. Immunomodulation in Plasmodium falciparum malaria: experiments in nature and their conflicting implications for potential therapeutic agents. Expert Review of Anti-infective Therapy. 2012;10(11):1343–56. doi:10.1586/ERI.12.118
22. Hansen DS, Schofield L. Natural regulatory T cells in malaria: host or parasite allies? PLoS Pathogens. 2010;6(4):e1000771. doi:10.1371/JOURNAL.PPAT.1000771
23. Taylor A, Verhagen J, Blaser K, Akdis M, Akdis CA. Mechanisms of immune suppression by interleukin-10 and transforming growth factor-β: the role of T regulatory cells. Immunology. 2006;117(4):433–42. doi:10.1111/J.1365-2567.2006.02321.X

24. Obeagu EI. Role of cytokines in immunomodulation during malaria clearance. Annals of Medicine and Surgery. 2024. doi:10.1097/MS9.0000000000002019
25. El-Moamly AA, El-Sweify MA. Malaria vaccines: the 60-year journey of hope and final success—lessons learned and future prospects. Tropical Medicine and Health. 2023;51(1). doi:10.1186/S41182-023-00516-W
26. Kurup SP, Butler NS, Harty JT. T cell-mediated immunity to malaria. Nature Reviews Immunology. 2019;19(7):457–71. doi:10.1038/S41577-019-0158-Z
27. Laurens MB. RTS,S/AS01 vaccine (Mosquirix™): an overview. Human Vaccines & Immunotherapeutics. 2019;16(3):480–9. doi:10.1080/21645515.2019.1669415
28. Genito CJ, Brooks K, Smith A, Ryan E, Soto K, Li Y, et al. Protective antibody threshold of RTS,S/AS01 malaria vaccine correlates antigen and adjuvant dose in mouse model. NPJ Vaccines. 2023;8(1). doi:10.1038/S41541-023-00714-X
29. Genton B. R21/Matrix-M™ malaria vaccine: a new tool to achieve WHO's goal to eliminate malaria in 30 countries by 2030? Journal of Travel Medicine. 2023;30(8). doi:10.1093/JTM/TAAD140
30. Aderinto N, Olatunji G, Kokori E, Sikirullahi S, Aboje JE, Ojabo RE. A perspective on Oxford's R21/Matrix-M™ malaria vaccine and the future of global eradication efforts. Malaria Journal. 2024;23(1). doi:10.1186/S12936-024-04846-W
31. Richie TL, Billingsley PF, Sim BKL, James ER, Chakravarty S, Epstein JE, et al. Progress with Plasmodium falciparum sporozoite (PfSPZ)-based malaria vaccines. Vaccine. 2015;33(52):7452–61. doi:10.1016/J.VACCINE.2015.09.096
32. Mo AX, McGugan G. Understanding the liver-stage biology of malaria parasites: insights to enable and accelerate the development of a highly efficacious vaccine. American Journal of Tropical Medicine and Hygiene. 2018;99(4):827–32. doi:10.4269/AJTMH.17-0895
33. Leong KY, Tham SK, Poh CL. Revolutionizing immunization: a comprehensive review of mRNA vaccine technology and applications. Virology Journal. 2025;22(1). doi:10.1186/S12985-025-02645-6
34. Saleh M, El-Moghazy A, Elgohary AH, Saber WIA, Helmy YA. Revolutionizing nanovaccines: a new era of immunization. Vaccines. 2025;13(2):126. doi:10.3390/VACCINES13020126
35. Chan JA, Loughland JR, De Labastida Rivera F, SheelaNair A, Andrew DW, Dooley NL, et al. Th2-like T follicular helper cells promote functional antibody production during Plasmodium falciparum infection. Cell Reports Medicine. 2020;1(9):100157. doi:10.1016/J.XCRM.2020.100157
36. Chan JA, Loughland JR, De Labastida Rivera F, SheelaNair A, Andrew DW, Dooley NL, et al. Th2-like T follicular helper cells promote functional antibody production during Plasmodium falciparum infection. Cell Reports Medicine. 2020;1(9):100157. doi:10.1016/J.XCRM.2020.100157
37. Van Tilbeurgh M, Lemdani K, Beignon AS, Chapon C, Tchitchek N, Cheraitia L, et al. Predictive markers of immunogenicity and efficacy for human vaccines. Vaccines. 2021;9(6):579. doi:10.3390/VACCINES9060579
38. Ouattara A, Barry AE, Dutta S, Remarque EJ, Beeson JG, Plowe CV. Designing malaria vaccines to circumvent antigen variability. Vaccine. 2015;33(52):7506–12. doi:10.1016/J.VACCINE.2015.09.110
39. Su XZ, Xu F, Stadler RV, Teklemichael AA, Wu J. Malaria: factors affecting disease severity, immune evasion mechanisms, and reversal of immune inhibition to enhance vaccine efficacy. PLoS Pathogens. 2025;21(1):e1012853. doi:10.1371/JOURNAL.PPAT.1012853

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