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Malaria and Immune Memory

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ABSTRACT

Malaria remains one of the world's most devastating infectious diseases, caused by Plasmodium parasites and transmitted through Anopheles mosquitoes. Despite repeated exposure in endemic regions, the development of long-lasting immunity remains elusive due to complex host–parasite interactions, immune evasion mechanisms, and antigenic variation. This paper examines the multifaceted immunological responses to malaria, emphasizing how Plasmodium falciparum manipulates host immunity through antigenic variation, immune modulation, and persistence mechanisms that prevent sterilizing immunity. The roles of humoral and cellular immune responses, particularly memory B cells, T follicular helper (Tfh) cells, and tissue-resident memory T cells (Trm), are discussed in relation to their contribution to long-term protection. Global initiatives such as the Roll Back Malaria campaign, WHO's Global Technical Strategy for Malaria (2016–2030), and community-based engagement efforts highlight the progress and challenges in malaria control and eradication. Advances in vaccine research, including whole-organism vaccines, recombinant platforms, and bispecific antibody therapies are reshaping prospects for immunological protection. However, ethical considerations concerning human challenge trials, gene-drive technology, and the management of G6PD deficiency remain critical in global malaria research. Understanding the molecular mechanisms underlying immune memory, immune evasion, and vaccine-induced immunity is pivotal to accelerating the development of next-generation vaccines and innovative therapeutics essential for malaria elimination and eventual eradication.

Keywords: Malaria Immunology, Antigenic Variation, Immune Memory, Vaccine Development and Global Eradication Efforts.

INTRODUCTION

Malaria is a mosquito-transmitted infectious disease that affects humans throughout much of the world. Of more than 100 different species of Plasmodium parasites, six regularly infect humans [1]. In 2017 there were an estimated 216 million clinical cases and 450,000 deaths worldwide, predominantly in children <5 years of age living in sub-Saharan Africa [1]. Disease is caused by the asexual blood-stage parasites, which develop within red blood cells and so can reach very high numbers within the host. Strategies to reduce the burden of malaria include chemotherapy, insecticide-treated bed nets, and a RTS,S/AS01 vaccine; but resistance threatens many of these. Most endemic regions are characterized by seasonal variations in transmission that result in seasonal variation in the numbers of circulating parasites within the vertebrate host, a pattern that is rarely seen in other infections [2].

The Immune System Overview

The vertebrate immune system protects against infections through a complex interplay of innate and adaptive responses [9]. The innate immune response recognizes pathogen-associated molecular patterns through germ-line encoded receptors such as Toll-like receptors (TLRs) with the complement cascade acting in parallel to phagocytose and kill pathogens. The adaptive immune response has the ability to recognize a virtually limitless diversity of pathogens, through diverse B- and T-cell receptors generated by somatic rearrangement of their respective genes [5]. While the innate immune response is essentially identical throughout the host's life, the adaptive immune arm contains highly diverse T-lymphocyte and B-lymphocyte repertoires generated in the bone marrow and thymus before immigrating to the periphery, where they become activated through antigen recognition and subsequent proliferation. This generates effector cells capable of killing infected cells, secreting cytokines or producing antibodies [1]. The adaptive immune system can subsequently establish long-lived memory populations that allow rapid recall responses free of the lag phase present during primary responses [3]. The cytokine environment present during T-cell activation or innate defenses engaged during B-cell activation also modulates the type of effector or memory pathways that develop [8].

Malaria Pathophysiology

Malaria remains a global public health burden and is caused by infection with the protozoan parasite Plasmodium spp. Sporozoite forms are transmitted via Plasmodium-infected female Anopheles mosquitoes to the skin and then enter the bloodstream, which then migrates to the liver within one hour [7]. Here, they infect hepatocytes and develop into thousands of merozoites, which subsequently leave the liver and initiate the blood stage that is responsible for disease pathogenesis [1]. The pathogenesis of malarial disease arises from the effects of both host and parasite, including sequestration of blood-stage parasites in the microvasculature and inflammation induced by the parasites and their toxic products [8]. All clinical manifestations of malaria are associated with the blood stage of infection. Natural immunity to malaria requires years of repeated exposure to Plasmodium parasites, yet children living in high transmission regions become immune to severe malaria after only a relatively few symptomatic infections [6]. Protection, known as clinical immunity, is achieved by reducing parasite burdens, but it does not prevent re-infection, and adults often harbour low-density asymptomatic infections [7]. Such naturally acquired immunity targets blood-stage parasites and is dependent on antibodies, as demonstrated by transfer studies. Delineating the cellular mechanisms underlying the slow and imperfect development of immunity to malaria, and identifying ways to improve it, is a crucial goal of ongoing research [12].

Types of Malaria

Malaria, a parasitic disease transmitted by the bite of the female Anopheles mosquito, affected over 228 million individuals worldwide in 2018, with 405,000 deaths attributed to the infection [1]. Of the six Plasmodium species that commonly infect humans, Plasmodium falciparum is the most deadly, while Plasmodium vivax is responsible for a substantial proportion of non-lethal burden [2]. Listed in order of decreasing severity of malaria, the species are P. falciparum, P. knowlesi, P. vivax, P. ovale, and P. malariae. Exposure in areas of consistency leads to the development of a robust immune response. The remaining sections document the nature of the human immune response to Plasmodium infection [8].

Plasmodium falciparum

Plasmodium falciparum is the most virulent human malaria parasite and the leading cause of severe disease and mortality, particularly in vulnerable populations including young children, pregnant women, immuno-compromised individuals, and residents of low-endemic regions[4]. P. falciparum has a complex life cycle that involves sporozoite inoculation via mosquito bite, progression to liver stages multiplying to schizonts, release of merozoites into the bloodstream, and infection of red blood cells[4]. The parasite evades immunity through antigenic variation of the clonally variant protein PfEMP1 on infected erythrocytes, encoded by approximately 60 var genes that are expressed singularly and switched sequentially, enabling cytoadhesion and immune evasion during the asexual blood stage [4].

Plasmodium vivax

Plasmodium vivax, accounting for a considerable fraction of global malaria cases, is dominant throughout Asia and the South and Central Americas, reaching latitudes close to the Arctic Circle [3]. Although infection rarely causes death and most symptomatic cases are clinically uncomplicated, it contributes to significant morbidity, including severe anaemia and impaired growth in children; it also places a substantial burden on public health systems. Immunity against symptomatic malaria can be acquired after repeated infections in endemic areas [3]. Longitudinal analyses of two villagers throughout the 1960s documented the development of immunity, providing detailed life histories and shedding light on the parasite's populations [1]. A butchery technique for sporozoite counts was developed in the early 1960s and used to assess injected numbers in wild-caught mosquitoes belonging to the Anopheles punctulatus complex [1,3].

Plasmodium ovale

The parasites Plasmodium ovale curtisi and P. ovale wallikeri are the causative agents of ovale malaria, a form of malaria contracted mainly in Africa but also reported from other parts of the world [1]. Plasmodium ovale does not thrive as well in the Anopheles stephensi mosquito vector as P. falciparum and P. vivax, extending parasite development time and producing fewer sporozoites that do not persist long in the salivary gland [3]. The epidemiology of P. ovale remains ill-defined[1]. Plasma antibody titres and B-cell-memory (Bmem) responses to the human malaria species, especially the recently emerged P. ovale curtisi and P. ovale wallikeri species, offer insights into their environmental prevalence and the development of sustaining immune memory[1,3].

Plasmodium malariae

Plasmodium malariae ranges throughout all malarial areas and is found in co-infections with other Plasmodia. P. malariae is gentler than the others; forms of this malaria may persist for years in the human body without causing symptoms or detectable parasitaemia [1]. At times renewed parasitaemia may appear. P. malariae is widely distributed in the tropics and subtropics worldwide and inaccuracy of diagnosis probably accounts for the fact that it is recorded rather less frequently than it deserves [2]. In many places P. falciparum and sometimes P. vivax have practically eliminated it but often also apparently coexist with the more virulent species, at least in local foci, where their prolonged course and lack of symptoms appear to offer an added risk from a public-health point of view[6].

Immune Response to Malaria

Once a mosquito has introduced Plasmodium sporozoites into the skin, the parasites quickly enter the bloodstream and are carried to the liver [2]. Within the hepatic body, the parasites replicate for 1–2 weeks before emerging once more. During this stage, the host remains asymptomatic; nonetheless, infection can be detected through a sensitive polymerase chain reaction (PCR) [1]. Following release from the hepatic parenchyma, apicomplexan parasites invade the cells of the erythrocyte lineage and initiate cycles of replication and re-invasion that continue throughout the blood stage of the replication cycle [18]. An essential innate immune response to the parasite involves natural killer (NK) cells. In the erythrocyte stage, some merozoites differentiate into male and female gametocytes. When taken up by the mosquito, these gametocytes establish sexual and sporogonic replication, culminating in the formation of an infectious sporozoite[17]. The first line of defence against any pathogen is the innate immune response, which provides the host with an immediate reaction against infection; the adaptive arm follows few days later and provides the host with long-lasting pathogen specific protection [15]. Although attempts have been made to harness immunity against malaria through vaccination, it is often only partially effective and short-lived [12]. Induction of protective immune responses through natural infection has been relatively rare and is understood to be generated slowly [1]. In addition to limiting parasitemia during clinical disease, a range of immune mechanisms protects against subsequent infection or clinical disease following re-exposure to the parasite. Key questions concern the identity of the immune mechanisms responsible for protection and the factors that influence their development [6]. Despite the presence of potent antigens displayed on the surface proteins of infected erythrocytes, there is minimal evidence for immune-mediated eradication of parasites following exposure through natural infection[1].

Role of Antibodies in Malaria

Antibodies are a major component of natural and vaccine-induced immunity to clinical Plasmodium infection [1]. Passive transfer of immune IgG to infected humans reduces parasite burdens and symptoms, and agents with high anti-parasite plasma antibody titres are less susceptible to febrile malaria, indicating that control of blood-stage parasitaemia by antibody-dependent mechanisms is a major contributor to clinical immunity [1]. Antibodies may function by neutralizing free merozoites, targeting blood-stage sporozoites to prevent hepatocyte invasion, directly neutralizing blood-stage parasites, or clearing infected erythrocytes through opsonization, antibody-dependent cellular cytotoxicity, or phagocytosis [5]. The broad diversity of antigens targeted by these various mechanisms has complicated the characterization of protective antibody responses and vaccine target prioritization. Antibodies are essential during the blood and pre-erythrocytic stages of the parasite life cycle, but their targets vary depending on parasite developmental stage [5]. Antibody responses are the correlates of vaccine-induced protection in irradiated sporozoite vaccine cohorts. Heat-killed erythrocytic parasite vaccines demonstrate that parasite-specific antibodies can mediate potent anti-parasite immunity independently of CD8+ T cells [7]. Naturally acquired clinical immunity to malaria largely overlaps with vaccine-induced immunity in target specificity and effector mechanisms, although clinical immunity does not provide sterile protection [8]. Unlike other types of infection, clinical immunity to malaria may therefore be a correlate of immunological memory rather than an endpoint [9]. Evidence from human challenge and epidemiological cohorts showing the durability of post-infection immunity implies that protective immunological memory does develop following Plasmodium infection[10].

Cellular Immunity in Malaria

The contribution of cellular immunity has been evident for several decades in malaria infection. Early work on the role of T cells showed that specific antibody responses that provide sterile immunity require CD4+ T cells [1]. Later, a role for CD4+ T cells in controlling blood-stage infection was demonstrated and models generally favored a T-helper 1 (Th1) response dominated by IFN-γ, IL-12, and TNF. Recent studies in mice have shown that IL-10-producing regulatory CD4+ T cells are paramount in down-regulating this highly inflammatory response, thus protecting the host against fatal disease. CD8+ T cells are instrumental in the liver stage, regulating parasite burden and preventing progression to the symptomatic blood-stage infection [7]. In contrast, natural killer (NK) cell depletion in outbred mice impairs the longitudinal control of blood-stage parasitemia and causes premature death, which can be prevented via the adoptive transfer of IFN-γ-producing NK cells [9].

T Cells

Malaria, a parasitic disease endemic to the tropics, causes nearly a million deaths annually, although at least five different species of Plasmodium contribute to this disease. Several vaccines have attempted to target malaria, but none have yet induced durable immunity; this outcome suggests intrinsic problems with the generation or maintenance of immune memory to the parasite. Immune memory is widely held to be fundamental to disease control, yet in the case of malaria, the development of long-term memory, both T and B cell, is compromised [9]. At the same time, chronic infection improves the ability to mount effective recall responses, even if the memory response itself decays during sterile protection [9]. The immune system a collection of cells, proteins, and organs that both prevent and control the infection of the body by pathogens [7]. Diverse pathogens have evolved strategies that exploit and circumvent immune responses, and the Plasmodium parasite responsible for malaria is no exception. The lifecycle of Plasmodium is complex, involving different forms of the parasite that migrate between host and vector tissues [7]. This movement of the parasite necessitates the deployment of different immune components to control it since the parasite is both intracellular and extracellular, existing in different forms in the tissues of the host [6]. Understanding the mechanisms that can generate protective, long-lived immunity has been the primary goal of research into malaria immunology; as such knowledge is fundamental to vaccine design. T cells specific for Plasmodium antigens often express markers defining them as effector memory cells [6]. These cells can be further divided according to anatomical location, cytokine secretion, and coreceptor expression [7]. All major memory subsets are represented in the antigen-specific population and these subsets show phenotypic, transcriptional, and functional signatures conserved even between disparate infections.

Natural Killer Cells

Natural killer (NK) cells contribute to the immune response to malaria at multiple stages, utilising diverse effector mechanisms [9]. These innate lymphocytes can directly lyse infected hepatocytes liver-stage liver-stage Plasmodium, IFN-γ production by NK cells promotes macrophage-mediated parasite clearance, while antibody-dependent cellular cytotoxicity (ADCC) represents an NK cell-mediated adaptive response that targets blood-stage parasite-infected red blood cells, and is associated with protection from infection. NK cells are the predominant innate lymphocyte subset found in the human liver, with the liver also representing the major site of parasite replication following infection [9]. In mice, liver NK cells exhibit cytotoxic activity and can contribute to control of Plasmodium infection through elimination of infected hepatocytes [8]. Liver-resident NK cells express killer-cell immunoglobulin-like receptors (KIR), which might influence their contribution to the early immune response to liver-stage malaria through interaction with class I human leucocyte antigens (HLA). During blood-stage malaria, circulating CD56dim NK cells inhibit parasite growth and selectively kill IgG3-opsonized infected red blood cells through ADCC [8]. Adaptive NK cells identified on the basis of a promyelocytic leukemia zinc finger protein-negative phenotype are expanded in the peripheral blood of children living in a malaria-endemic region of Mali; these antigen-experienced cells show enhanced ADCC activity in the presence of anti-parasite antibodies, and subjects with higher frequencies of adaptive NK cells exhibit lower parasitaemia[8]. The development of adaptive NK cells is strongly associated with cytomegalovirus (CMV) seropositivity, lending support to the idea that prior CMV infection can influence the subsequent immune response to malaria infection [8]. Throughout a Plasmodium infection, NK cells produce a range of immunomodulatory cytokines including IFN-γ, tumour necrosis factor α (TNF-α), interleukin-10 (IL-10), granulocyte-macrophage colony-stimulating factor and CC-chemokines (CCL3, CCL4 and CCL5). In the Rodent malaria model, IL-10 production by NK cells prevents the progression to cerebral malaria [8]. Although NK cells nonetheless exert important anti-parasitic functions, they can also be detrimental if directed predominantly against uninfected red blood cells; the net impact of an individual's NK cell response may therefore depend on the distribution of NK cell effector functions during infection [9]. Variation in HLA receptors modulates NK cell effector potential during malaria infection [13]. When not bound to ligand, e.g., when an infected or malignant cell downregulates HLA expression, the lack of inhibitory signal triggers NK cell activation and cytotoxicity; conversely, NK cell ligation to self HLA suppresses effector function[9]. Several inhibitory NK cell receptors prime function at rest through interactions with self HLA molecules a process known as NK cell education while the same receptors suppress effector responses when engaged during an immune challenge [13]. As a result, the relationship between receptor genotype and ligand expression can have a major influence on the efficacy of an individual's NK cell response [9].

Memory Immune Responses

Immunological memory, allowing the immune system to mount enhanced secondary responses on re-exposure to pathogens, underpins the principle of vaccination [1]. A primary encounter typically generates memory cells and high-affinity antibodies, inducing a rapid and effective response upon subsequent challenge [4]. Following infection, coinhibitory receptors which down-modulate immune cell function decline, facilitating efficient parasite clearance [1]. Subsequently, Plasmodium-specific memory T and B cells decay gradually, potentially remaining for life in some individuals; this sustained presence is likely necessary to explain the durability of laboratory-observed protection [5].

Factors Influencing Immune Memory

Immune memory enables the host to mount rapid and effective responses upon subsequent encounters with the same pathogen [1]. Understanding of the factors influencing the development and maintenance of immune memory remains incomplete [1]. In the context of malaria, the duration of protective responses is notably shorter than that observed following other infections; the determinants of this abbreviated memory are poorly characterized. Immune memory is a polygenic trait shaped by genetic variation within immune response genes and is influenced by environmental factors [2]. Polymorphisms of the major histocompatibility complex exert an important influence, but considerable phenotypic variation is also associated with human leukocyte antigen heterozygosity, ethnicity and gender [4]. Socio-economic conditions influence an individual's immune response through an impact on nutrition, which in turn affects tumour necrosis factor and interleukin-8 levels. The maintenance of hippocampal volume, which can influence memory, has been shown to benefit from an aerobically active lifestyle [1].

Genetic Factors

Immunological memory represents the capacity of the immune system to mount a rapid and potent response after a second encounter with previously encountered antigens [1]. There is an ongoing debate about its existence and persistence following a Plasmodium infection, with conflicting data in the literature. Memory formation represents a major goal in vaccine development, underscoring the importance of elucidating its potential after malaria infection [3]. Protective immunity that develops in response to a malaria infection usually takes several infections over many years to be established and notably is only partially protective [2]. Genetic differences have been linked not only to human susceptibility to malaria but also to the rate of acquisition of protection and the host's susceptibility to severe malaria [5]. Several genetic variants have been identified through association studies as being involved in susceptibility to severe disease or death, including genes coding for cytokines and their receptors, such as tumor necrosis factor (TNF), interleukin 10 (IL10), and IL13, as well as human leucocyte antigen (HLA) genes[7]. Severe malaria is often the result of an excessive inflammatory reaction, and these genetic studies have shown that polymorphisms that increase pro-inflammatory cytokines are associated with the disease. Protection against severe malaria has also been linked to an increased Th2/counter-inflammatory response [6]. For instance, IL4-589, an IL4 promoter polymorphism resulting in increased IL4 production, is associated with protection against severe malaria, while the IL4 receptor I50V variant, which correlates with a decreased response to IL4, is associated with increased disease severity [1]. In addition, polymorphisms in genes associated with the regulation of the B cell compartment have been linked to severe malaria, such as those coding for BAFF and BLyS receptors [1].

Environmental Factors

Despite some success in elimination programs, malaria continues to impose a substantial public health burden, particularly in Africa and parts of Asia and Latin America [1]. Starting with skin inoculation by an infectious mosquito, few sporozoites leave their injection site in the skin, entering blood vessels and traversing the liver before invading hepatocytes [2]. A single parasite can give rise to thousands of merozoites that burst from the hepatocyte before invading erythrocytes. After repeated cycles of invasion and rupture of erythrocytes, the infection transforms into the sexual stages, gametocytes, which when ingested by a mosquito, continue the cycle [3]. Although immune memory forms following nearly all infections, often resulting in lifelong protection, in malaria, a protective memory response fails to develop [5]. So, humans infecting mosquitoes for many months post parasite clearance from the blood as well as repeatedly suffering illness are common[8]. Even intravenous inoculation of millions of sporozoites of irradiated parasites fails to induce protection in this important infection. Evidence indicates that memory responses against malaria are not only insufficient but also short-lived and unprotective, consistent with the epidemiologic patterns [9]. Immune responses that fail to lead to protective memory constitute a missed opportunity, highlighting an unexploited mechanism of immune subversion and a research opportunity with relevance to malaria and other diseases [10].

Immunological Memory in Malaria

Immunological memory is an essential feature of the adaptive immune response and develops with age following malaria, a disease caused by billions of Plasmodium parasites and resulting in hundreds of millions of infections and millions of deaths annually [1]. Despite a high pathogen load and the theoretical potential for long-lived adaptive immunity to develop, immunity to malaria is slow to arise and often requires years of repeated parasite exposure [3]. In endemic areas, immunity to severe or life-threatening malaria develops before protection against mild or asymptomatic infection, and clinical protection is commonly short-lived without continual exposure that boosts immunity [4]. The multifaceted nature of the immune response to malaria infection, together with the numerous life-cycle stages of Plasmodium parasites, allows antibody-secreting plasma cells and memory B cells to develop and confer protection [3]. However, longstanding questions persist concerning why immunity is acquired so slowly, is difficult to maintain, and generally requires repeated exposure to malaria parasites [3]. Some studies report the generation of memory B cells and plasma cells in humans and mouse models, while others suggest that immunological memory to malaria fails to develop or is actively sabotaged by continuous exposure to Plasmodium parasites [4, 1, 3].

Vaccination Strategies against Malaria

Immunization mimicking natural exposure is considered the most promising approach for preventing malaria infection and disease [10]. Developing an effective vaccine against malaria is challenging. Strain specificity against polymorphic antigens further complicates vaccine evaluation and application. P. falciparum clinical malaria is largely an inflammatory immune response to blood stage infection [10]. Vaccine-induced immune memory might reduce the pathogenic consequences of repeated infection, even if it is not protective against infection itself. For most people, passive transfer of sera from immune donors can reduce parasitemia and improve symptoms. Antibody-mediated immunity plays an important role in parasite clearance and memory response [15]. A better understanding of the role of humoral immune memory involved in parasite infection is necessary to develop further immunotherapy against malaria. The first scenario of protective immunity was revealed by experimentally malaria-infected volunteers in 1960[11]. Immunity was induced after repeated exposure to P. falciparum sporozoite infection under chloroquine chemoprophylaxis. Another landmark vaccine trial is the RTS,S vaccine. There have been many recent advances in vaccination using genetically attenuated parasites and radiation-attenuated sporozoites[10]. These vaccines extend the basic concept of using the whole organism to immune protection. RTS,S/AS01 consists of a recombinant protein expressing the repeat region and carboxyl terminus of the CSP of P. falciparum fused to hepatitis B surface antigen co-expressed with the unfused HBsAg in the AS01 adjuvant system. A phase III trial showed it to be moderately protective against clinical malaria [11]. Many next-generation vaccines are in a preclinical or early clinical development stage[11]. Novel targets are being identified in both the pre-erythrocytic stage and the transmission-blocking stages of the life cycle [10].

Current Vaccines

Despite decades of effort, malaria remains the most devastating parasitic killer of humankind. Malaria causes up to 247 million cases and 619,000 deaths annually worldwide. This enormous toll has inspired much effort by basic and translational immunologists [10, 11]. Malaria interacts with and modulates the immune response in complex ways, helping to establish a large and geographically widespread reservoir of chronic subclinical infections [10]. A highly effective malaria vaccine has long been a critical missing element in the control and eradication of the disease. Recent development of effective vaccines has both encouraged optimism and emphasized how little is understood about the malaria-specific immune response [11].

Future Perspectives

In human malaria, the maintenance of circulating memory B cell (MBC) and serum antibody responses is markedly short-lived [1, 9]. MBCs decline sharply in the absence of infection but are rapidly reactivated and can expand even when present at very low numbers [9]. Emerging evidence from human and murine studies addresses how humoral immune responses become compromised during acute malaria and the subsequent effect on long-term B cell memory [1, 10]. Exposure to Plasmodium parasites is linked to altered proportions of circulating MBCs, including an expansion of atypical MBCs [1, 9]. Further research is required to determine the origin, function and protective capacity of the different B cell subpopulations observed [1, 8]. Similarities between human and mouse MBC subsets are poorly defined, particularly with respect to surface markers, limiting the utility of murine malaria models [1, 5]. Gene expression analysis offers a potential means to establish direct correlations between human and mouse populations[1]. Gaining an in-depth understanding of the factors delaying the development of humoral memory will be essential for the design of novel therapies that enhance the immune response and promote protection. Characterizing the generation of B cell memory in malaria and identification of the protective effector subpopulation will also support the ongoing development of refined vaccines that target the induction of long-lived immunity and efficient parasite clearance [1].

Challenges in Malaria Immunology

One of the most enduring challenges in malaria immunology concerns the mechanisms responsible for the very slow acquisition of immunological memory following infection. In contrast to most immunogenic infections, where memory is generated rapidly and confers long-term protection [3], Plasmodium species display the pronounced ability to circumvent immunological memory strategies [4]. The process by which an individual acquires a degree of immune protection against malaria after repeated infections represents a unique model to examine the complex balance between parasite and host [5]. A central objective in contemporary malaria immunology is to elucidate how the parasite mediates evasion of the adaptive immune response and clearance, and to uncover the molecular basis of this property. This has direct implications for vaccine development, which ultimately seeks to circumvent immune evasion mechanisms and establish durable protective immunological memory similar to that induced by other acute infections [1]. Both classical antigenic polymorphism and antigenic variation classically defined as alterations in expressed variant surface antigens observed on the infected erythrocyte surface following every new cycle of intra-erythrocytic replication continue to compromise the longevity of exposure-induced immunological memory [1, 5].

Antigenic Variation

Plasmodium falciparum malaria parasites feature an antigenic variation mechanism enabling evasion of the host's immune system and establishment of chronic infections [12, 13]. Antigenic variation thus constitutes an important obstacle to the acquisition of protective immunity [12]. Parasite surfaces are the primary targets for protective antibody responses [12]. Antigenic variation of P. falciparum is linked to the presence of a limited number of clone-specific antigens on the surfaces of infected erythrocytes. The infected erythrocyte membrane antigen PfEMP1 is principally responsible for cytoadherence and antigenic variation of P. falciparum and is one of the most promising candidates for a malaria vaccine [13].

Immune Evasion

One cardinal feature underpinning the generation of long-lived immunity is the survival of a pool of rare and quiescent memory lymphocytes [3]. However, for malaria, this hallmark of naturally acquired immunity has been difficult to clearly establish. Indeed, although a large body of evidence shows that immunity can develop and is long-lived, results from numerous endemic regions demonstrate distinct situations where immunity needs to be repeatedly re-activated to be effectively maintained [3]. Key to sustaining such immune responses are the molecular processes that govern memory longevity. In addition, a further central property of memory immune responses is the ability to differentiate into secondary effector lymphocytes upon re-infection and provide protection [1, 3]. In this regard, it is important to note that sterility is rarely achieved during clinical immunity in malaria-endemic individuals, despite often very high circulating antibody titres [1]. Such immunity therefore requires a highly effective memory response that supports multiple rounds of differentiation and continued protection following each reinfection [10]. Together, these observations suggest that the generation of memory B- and T-cell responses following repeated infection requires fine balancing to generate sufficient protective immunity to prevent uncontrolled parasite growth, but, simultaneously, avoid a response so robust as to induce sterilising immunity that would otherwise abrogate subsequent antigenic re-exposure and put memory longevity in jeopardy [14]. The ability of Plasmodium to employ multiple mechanisms of immune evasion in order to establish a successful infection is well documented [12]. As described throughout this book, the parasite at various stages of its life cycle confronts and responds to potent pressure from the host immune system [12]. Yet, paradoxically, despite the immune response it elicits, the parasite succeeds in generating prolonged infections that frequently last for several months in humans and mouse models of malaria [14]. This outcome is further compounded by the requirement for prolonged parasite persistence to establish robust transmission between vertebrate host and mosquito vector, itself dependent on sufficient movement of mature stage gametocytes through peripheral blood [14]. Various immunomodulatory processes that play central roles in enabling this parasite persistence, largely acting to diminish parasite-specific responses, are described later in this chapter. Prior to this, the following section now considers the different mechanisms utilised by Plasmodium to evade humoral-mediated immunity, which contributes importantly to naturally acquired protection [14].

Implications of Immune Memory

For the millions infected annually, malaria remains a substantial global burden [1]. Although recent increases in reported cases call for urgent action, the interaction between malaria infection and immunity continues to offer novel insights into the molecular basis of the disease and avenues for therapeutic intervention and vaccine development [1, 14]. Collectively, the clinical implications of immune memory highlight its potential to address key challenges in malaria control and patient care [1, 13]. Despite the global impact of the disease, relatively little is known about the development of long-term memory and the generation of protective immunity following natural malaria infection [13]. A precise understanding of the factors required to confer long-lived protection remains an important gap in knowledge that directly impedes the rational development of vaccines capable of reducing the growing burden of malaria worldwide [11]. Numerous issues from the dangerous side effects of infection to the costly production of vaccines complicate progress towards an effective and persistent protective agent [18]. Further advances therefore require a detailed understanding of the mechanisms underlying long-term immunological memory in response to malaria infection [1, 8]. Long-lasting protective immunity typically involves long-lived plasma cells or memory B-cell production, as both of these cell types are capable of mounting an enhanced secondary response to previously encountered pathogens [7]. The establishment and maintenance of a long-lived humoral immune response relies on assistance from T follicular helper (Tfh) cells, a specialized subset of CD4+ T cells, within lymph node and splenic germinal centres[5]. A robust CD4+ T-cell response is consequently required for the generation of both sterile and nonsterile immunity to malaria, providing a stringent requirement for memory-immune induction [4]. Despite this, reports on the persistence of specific-parasite immune responses are not widely consistent, with data demonstrating variable longevity of malaria-specific antibodies in different individuals or populations [1]. In contrast, durable cellular immunity has been demonstrated in malaria-naïve individuals, with measurable T-cell responses persisting for up to 14 months post-infection 15. Although pre-existing immune responses may quench antigens on subsequent exposure, thereby influencing the induction of immune memory, prolonged cellular immunity also relies upon the cell-intrinsic capacity to generate effective responses following repeat infection [1]. The fact that parasite antigen-specific cellular immune responses can be maintained for more than a year following a single episode suggests that antigen-dependent mechanisms are not a prerequisite [3].

Malaria Control and Eradication Efforts

Increased awareness of malaria's public health importance led to major initiatives for control and elimination [17]. Led by the World Health Organization (WHO), the Roll Back Malaria initiative launched in 1998, the Millennium Development Goals, created in 2000, and the establishment of the Global Fund to Fight AIDS, Tuberculosis and Malaria two years later, all marked significant efforts [17]. These initiatives drove a halving of malaria death rates by 2015 and a reduction in incidence of approximately 40% during the same period [11]. Despite this progress, however, the rate of decline stalled and even before the COVID-19 pandemic plausible projections suggested a return to 2000 levels by the year 2035[16]. Assessment of these troubling results led to the launch in 2015 of the WHO's Global Technical Strategy for Malaria. This optimistic new phase outlines a goal of reducing malaria incidence and mortality rates by 90% by 2030[2]. It relies heavily on the development of vaccines and on learning how to make immunity specifically memory immune responses more effective [1].

Global Initiatives

Many countries throughout the world, especially African countries, want to control and eradicate malaria because the disease causes 0.5 million deaths annually, and 80% of Plasmodium falciparum infection results in the death of children under the age of 5 years[15]. Many countries with the highest number of deaths caused by malaria do not have enough resources to control the disease, which contributes to the continuation of the epidemic. Since World War II, various control efforts have been implemented to eradicate malaria. The Indoor Residual Spray (IRS) method, in which pesticides such as DDT are sprayed on internal walls, has been used since the 1930s. Many countries also adopted the use of insecticide-treated mosquito nets (ITNs) to prevent the spread of malaria. Insecticides are useful for controlling the number of mosquitoes carrying malignant parasite species and reducing transmission rates [15]. Malaria vector populations can be locally eliminated in highly modified environments such as urbanized areas, but elimination in rural areas is more difficult [14]. Identifying vulnerable life stages or populations to target to maximize control efforts and reduce costs would benefit vector control in rural areas, as would knowledge of malaria-induced modulation of mosquito life history traits [15]. However, vector control and other interventions in rural Africa are hampered by a lack of qualified personnel and materials and the fact that existing control methods, while effective, have fundamental limitations [14]. Malaria programs are often overseen by individuals with limited public health knowledge and training, and pesticide resistance by mosquitoes is becoming more widespread, emphasizing the need for new insecticide molecules and control strategies [1]. Identifying and adapting control efforts to target mosquito populations at key times and locations would make it possible to increase the efficiency of existing interventions, thereby reducing transmission and alleviating operational costs [12]. Additionally, current control efforts are insufficient to interrupt transmission of the parasite, and the use of vaccines to reduce the incidence of disease and eliminate the use of drugs is necessary [13].

Community Engagement

Policymakers and researchers involved in malaria prevention and control in the Greater Mekong Sub-region (GMS) regarded community engagement as essential for enhancing participation in research and programmatic efforts [16]. Malaria transmission persists in some isolated areas across the GMS, and sustained investment in community engagement is therefore necessary during the 'last mile' to elimination. Community-based malaria workers play a crucial role in extending the reach of elimination initiatives to hard-to-reach populations in remote parts of the sub-region [16].

Future Research Directions

The discovery and characterization of new parasites, hosts and vectors have greatly facilitated malaria research and led to the development of potent and efficient therapeutic agents [16]. Clinical medicine raises the possibilities of combinations with other novel therapeutics, vaccination strategies and intervention targeting the parasite host binding interactions, either to block parasite entry and/or egress or to disrupt intracellular signalling pathways contributing to parasite sequestering or clearance [18]. Fifteen years since the first characterizations of the mode of protective immunity to clinical malaria induced by whole parasite vaccine formulations, the knowledge framed within this Chapter continues to provide a range of avenues for further investigations [17]. Even now, the mechanisms that underpin fundamental biological processes of parasite development, sequestering and clearance are not fully understood, highlighting the central role that host innate, adaptive and memory mechanisms have to play in this dynamic yet still enigmatic relationship between parasite and immune system [12].

Novel Therapeutics

A vast spectrum of methodologies has been utilized for generating therapeutics against malaria [11, 17]. Whole-cell and subunit vaccines, or recombinant proteins, peptides, and attenuated organisms have been employed for different proposed mechanisms of protection against malaria. Most vaccines have attempted to induce protective humoral immunity [18]. Human monoclonal antibodies have shown promise as novel therapeutics [18]. However, protection in malaria is modulated by both humoral and cellular immunity, which can be exploited for immunotherapy. Bispecific antibodies targeting B and T cells have been designed for treating cancers due to the ability of T cells to effectively kill cells recognized by the B cells. Designed bispecific antibodies can target the infected red cells and T cells, thereby facilitating the killing of the infected cells, thus utilizing the cytotoxic properties of the T cells. Under natural conditions, antibody levels appear to be short-lived and rapidly decline in the absence of infection [17]. Immunological memory induced during vaccination or in an experimental murine model of malaria appears to be more long-lasting. Identifying factors associated with the induction and loss of immunological memory is thus crucial in the design of potent vaccines against malaria [17]. MALARIA is one of the most important infectious diseases worldwide. Developing immunity against the parasites takes years and repeated infections, and this immunity seems to be short-lived, allowing re-infections to occur frequently [14]. The exact reasons behind the slow acquisition and the loss of immunity remain unclear. At least in part, the responses induced during malaria cause defects in the immunological memory [15]. The possibility that these defects are caused by the direct activation of T cells by the parasite during infection is intriguing. This mechanism would not be caused exclusively by Plasmodium but could represent a more universal mechanism induced by other pathogens, which could have a different long-term impact [11].

Vaccine Development

Whole-organism vaccines currently represent the most successful approach for protective immunization against malaria [17]. Effective immunization employing radiation-attenuated sporozoites was first demonstrated in rodent models, leading to successful vaccines in humans [11]. Though initially constrained by complex manufacturing and logistical challenges, whole-organism vaccines have progressed to clinical testing and remain the front-runners in vaccine development [11]. A heterologous prime-boost regimen based on the recombinant simian adenovirus ChAd63 and the orthopoxvirus MVA, both encoding the pre-erythrocytic antigen thrombospondin-related adhesion protein fused to a multiple epitope string (ME-TRAP), is undergoing extensive clinical evaluation, including in malaria-endemic regions [17]. This combination consistently induces high frequencies of antigen-specific CD8+ and CD4+ T cells and strong antibody responses a pivotal advantage since T cell-mediated immunity is essential for protection at the liver stage. Complementing viral-vector strategies, cytomegalovirus (CMV)-based vaccines expressing Plasmodium knowlesi antigens have generated robust immune responses, successfully delaying parasitemia upon sporozoite challenge. Despite these advances, critical challenges remain in the quest for an effective gravity malaria vaccine [17, 11].

Ethical Considerations in Malaria Research

Research into malaria immunology raises a number of ethical concerns [18]. Malaria is a major public health concern in many countries and the challenge to develop an effective vaccine focuses attention on the conduct of research involving Plasmodium-infected subjects and the use of biological samples as well as malaria challenge experiments [11]. An additional critical point concerns progress in gene-drive technology, a powerful advance that promises to radically reduce malaria by suppressing or modifying the mosquito population. Although work is ongoing to assess risks, concerns remain regarding the potential ecological effects of spreading gene-drive organisms and their transfer to related species in areas where these vectors are not endemic[10]. These various ethical issues continue to be the subject of debate throughout the malaria community [9]. A number of concerns regarding the ethics of treatment and research on all aspects of malaria control also arise [9]. Artemisinin resistance is thought to be emerging in Myanmar, which may facilitate the spread of resistant parasites to neighbouring India and possibly other malaria-endemic areas [7]. Accordingly, the well-established principle that research should be responsive to local health needs applies strongly to this area, and community engagement is a core requirement of ethical global health research [7]. Continuing ethical concerns regarding single-dose primaquine as a gametocyte-clearance strategy are also present, as is the related issue of mass drug administration where human reservoirs of infection are targeted with antimalarials irrespective of infection status [6]. In this context, the inflammatory side effects of primaquine together with the presence of G6PD deficiency in humans, which varies in clinical manifestations, prevalence and severity by subtype, complicate the use of any 8-aminoquinoline treatment [18]. G6PD deficiency remains a neglected area of research with an urgent need to estimate the worldwide prevalence and severity of major subtypes [7]. The detection and management of G6PD deficiency therefore continue to be important ethical and practical issues for the safe deployment of 8-aminoquinolines within a range of different P. vivax control, elimination and eradication strategies. Blood transfusion practices in malaria-endemic areas also present complex ethical challenges [2]. Despite all possible precautions, transfusion in these settings is never without risk owing to the difficultly of detecting subclinical infections and low-level parasitaemia, together with unresolved questions about sample-screening strategies and cycles of transmission [1]. Voluntary, non-remunerated blood donation remains the subject of debate in many countries for reasons unrelated to malaria but of particular ethical salience in malaria-endemic regions [12]. Experiments in which human volunteers are infected with malaria to provide a platform for challenge/re-challenge during drug, vaccine, vector and parasite studies or to generate parasite material for the validation of diagnostic tests and new drug discovery tools give rise to more fundamental ethical concerns [15]. These concerns have long been debated in medical ethics, but a clear set of principles governing the conduct of experimental infection studies remained elusive until recently [17]. Earlier challenge studies conducted in higher-transmission settings before the introduction of pre-erythrocytic vaccines, particularly in the 1940s and 1950s, gave rise to no documented complaints but highlight the fundamentally important role of retrospective ethical assessment [18].

Case Studies in Malaria Immunology

The most recent report on tissue-resident memory T cell (Trm) formation emphasizes the need for further investigation in all tissues and across pathogens, highlighting a notable knowledge gap in malaria research where Trm-mediated protection could be pertinent [7]. Contemporary studies in malaria immunology continue to prioritize the examination of immune memory as a primary paradigm for understanding protective immunity against the disease [3]. Numerous definitions of immunological memory exist, each with varying implications for malaria. When present, memory is characterized by two fundamental features: persistence over extended periods and the capacity for enhanced responsiveness upon re-exposure to antigen [1]. Historically, these aspects of memory have served as the conceptual framework guiding investigations among diverse memory subsets, including $CD4^+$ and $CD8^+$ T cells, B cells, and innate populations such as natural killer (NK) cells and macrophages [3]. The present section examines the phenotypic identification of memory lymphocytes in human and murine malaria, critiques the sufficiency of these criteria, and contextualizes recent discoveries within the broader understanding of protective memory in malaria [18].

CONCLUSION

Malaria immunology continues to represent one of the most intricate and critical areas of infectious disease research. The parasite's ability to evade the host immune system through antigenic variation, immune modulation, and persistence strategies fundamentally impedes the development of long-lasting immunity. Despite repeated infections, individuals in endemic regions often fail to develop sterilizing immunity, reflecting the parasite's evolutionary success in manipulating immune responses. Memory B and T cells play vital roles in providing partial and non-sterile protection, yet their short-lived nature and inconsistent activation underscore the need for more robust vaccine-induced immune memory. Recent advancements in immunological research have illuminated how Plasmodium falciparum disrupts the formation of durable memory responses. Understanding the interplay between T follicular helper cells, long-lived plasma cells, and tissue-resident memory T cells offers valuable insights into designing effective vaccines. Whole-organism and subunit vaccines, as well as bispecific antibodies, show promise, but their efficacy remains limited by antigenic diversity and logistical constraints. Integrating these innovations with molecular and genetic research may enable the creation of vaccines capable of overcoming antigenic variability and inducing sustained protection. Globally, initiatives such as WHO's Global Technical Strategy for Malaria and the Roll Back Malaria campaign have made substantial progress in reducing mortality and morbidity. However, challenges persist, particularly in regions with limited resources, widespread insecticide resistance, and inadequate health infrastructure. Community engagement and ethical governance are indispensable to ensuring the success of malaria research and interventions. Ethical issues surrounding gene-drive technologies, human challenge trials, and drug safety, especially in populations with G6PD deficiency must be carefully managed to balance scientific advancement with human welfare. Ultimately, the fight against malaria depends on an integrated approach combining immunological insight, technological innovation, community participation, and ethical responsibility. Strengthening global cooperation, expanding funding for research, and deepening understanding of malaria's immune mechanisms are essential to transforming current control measures into sustainable eradication strategies. Only by bridging these scientific and ethical gaps can the world move closer to a malaria-free future.

REFERENCES

1. Ly A, Hansen DS. Development of B cell memory in malaria. Frontiers in immunology. 2019 Apr 2;10:559.
2. Wipasa J, Suphavilai C, Okell LC, Cook J, Corran PH, Thaikla K, Liewsaree W, Riley EM, Hafalla JC. Long-lived antibody and B Cell memory responses to the human malaria parasites, Plasmodium falciparum and Plasmodium vivax. PLoS pathogens. 2010 Feb 19;6(2):e1000770.
3. Wipasa J, Suphavilai C, Okell LC, Cook J, Corran PH, Thaikla K, Liewsaree W, Riley EM, Hafalla JC. Long-lived antibody and B Cell memory responses to the human malaria parasites, Plasmodium falciparum and Plasmodium vivax. PLoS pathogens. 2010 Feb 19;6(2):e1000770.
4. Weiss GE, Traore B, Kayentao K, Ongoiba A, Doumbo S, Doumtabe D, Kone Y, Dia S, Guindo A, Traore A, Huang CY. The Plasmodium falciparum-specific human memory B cell compartment expands gradually with repeated malaria infections. PLoS pathogens. 2010 May 20;6(5):e1000912.
5. Pérez-Mazliah D, Ndungu FM, Aye R, Langhorne J. B-cell memory in malaria: Myths and realities. Immunological reviews. 2020 Jan;293(1):57-69.
6. Carpio VH, Opata MM, Montañez ME, Banerjee PP, Dent AL, Stephens R. IFN-γ and IL-21 double producing T cells are Bcl6-independent and survive into the memory phase in Plasmodium chabaudi infection. PloS one. 2015 Dec 8;10(12):e0144654.
7. Jones S. A deadly partnership. Nature Reviews Microbiology. 2007 Aug;5(8):568-.
8. Tukwasibwe S, Nakimuli A, Traherne J, Chazara O, Jayaraman J, Trowsdale J, Moffett A, Jagannathan P, Rosenthal PJ, Cose S, Colucci F. Variations in killer-cell immunoglobulin-like receptor and human leukocyte antigen genes and immunity to malaria. Cellular & Molecular Immunology. 2020 Aug;17(8):799-806.
9. Burrack KS, Hart GT, Hamilton SE. Contributions of natural killer cells to the immune response against Plasmodium. Malaria journal. 2019 Sep 18;18(1):321.
10. Rathay V, Fürle K, Kiehl V, Ulmer A, Lanzer M, Thomson-Luque R. IgG Subclass Switch in Volunteers Repeatedly Immunized with the Full-Length Plasmodium falciparum Merozoite Surface Protein 1 (MSP1). Vaccines. 2024 Feb 17;12(2):208.
11. Hansen SG, Womack J, Scholz I, Renner A, Edgel KA, Xu G, Ford JC, Grey M, St. Laurent B, Turner JM, Planer S. Cytomegalovirus vectors expressing Plasmodium knowlesi antigens induce immune responses that delay parasitemia upon sporozoite challenge. PLoS One. 2019 Jan 23;14(1):e0210252.
12. Hommel MA, David PH, Oligino LD. Surface alterations of erythrocytes in Plasmodium falciparum malaria. Antigenic variation, antigenic diversity, and the role of the spleen. The Journal of experimental medicine. 1983 Apr 1;157(4):1137-48.
13. Tuju J, Mackinnon MJ, Abdi AI, Karanja H, Musyoki JN, Warimwe GM, Gitau EN, Marsh K, Bull PC, Urban BC. Antigenic cartography of immune responses to Plasmodium falciparum erythrocyte membrane protein 1 (PfEMP1). PLoS pathogens. 2019 Jul 1;15(7):e1007870.
14. Chandley P, Ranjan R, Kumar S, Rohatgi S. Host-parasite interactions during Plasmodium infection: Implications for immunotherapies. Frontiers in Immunology. 2023 Jan 4;13:1091961.
15. Teirlinck AC, McCall MB, Roestenberg M, Scholzen A, Woestenenk R, de Mast Q, van der Ven AJ, Hermsen CC, Luty AJ, Sauerwein RW. Longevity and composition of cellular immune responses

following experimental Plasmodium falciparum malaria infection in humans. PLoS pathogens. 2011 Dec 1;7(12):e1002389.
16. Kaehler N, Adhikari B, Cheah PY, von Seidlein L, Day NP, Dondorp AM, Pell C. Community engagement for malaria elimination in the Greater Mekong Sub-region: a qualitative study among malaria researchers and policymakers. Malaria Journal. 2022 Feb 14;21(1):46.
17. Kimani D, Jagne YJ, Cox M, Kimani E, Bliss CM, Gitau E, Ogwang C, Afolabi MO, Bowyer G, Collins KA, Edwards N. Translating the immunogenicity of prime-boost immunization with ChAd63 and MVA ME-TRAP from malaria naive to malaria-endemic populations. Molecular Therapy. 2014 Nov 1;22(11):1992-2003.
18. Jamrozik E, de la Fuente-Nunez V, Reis A, Ringwald P, Selgelid MJ. Ethical aspects of malaria control and research. Malaria journal. 2015 Dec 22;14(1):518.

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