parasitologia

MDPI

Review

Dendritic Cells in Blood-Stage Malaria: Orchestrators of Immune Responses and Pathogenesis

Takahiko Tamura

School of Pharmacy, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan; tamura99@p.kanazawa-u.ac.jp; Tel./Fax: +81-76-234-4464

Abstract

Malaria remains a major global health burden, and immune responses during the blood stage are essential for both parasite control and disease pathogenesis. Conventional dendritic cells (cDCs) occupy a central position at the interface between innate and adaptive immunity, yet their diverse roles during blood-stage malaria remain incompletely understood. This review summarizes current knowledge of cDC biology in malaria, with particular emphasis on findings from murine models. Blood-stage *Plasmodium* infection alters splenic cDC populations and activates cDCs through parasite-derived and host-derived signals, including glycosylphosphatidylinositols, nucleic acids, hemozoin, and uric acid. Activated cDCs regulate $CD4^+$ T-cell differentiation, including Th1, Th2, Tfh, and Th17 responses, and cDC1-mediated cross-presentation contributes to pathogenic $CD8^+$ T-cell responses in experimental cerebral malaria. cDCs also interact with macrophages, γδ T cells, NK cells, and other innate lymphoid populations, thereby shaping both protective immunity and immunopathology. Important unresolved questions include the roles of cDCs in immunity to gametocytes, placental malaria, repeated malaria exposure, trained immunity, and vaccine responsiveness. Further characterization of cDC subset-specific functions may improve understanding of malaria immunity and identify new strategies for vaccines and immunomodulatory interventions.

Keywords: malaria; dendritic cells; cerebral malaria; immunopathology; T cells

1. Introduction

Malaria is an infectious disease caused by protozoan parasites of the genus *Plasmodium* [1]. In humans, *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi* are known to cause malaria (for details, see [2]). It remains one of the most serious public health challenges in tropical and subtropical regions, particularly in developing countries, where it continues to threaten millions of lives. According to the World Malaria Report 2025, an estimated 282 million malaria cases and approximately 610,000 malaria-related deaths occurred worldwide in 2024, highlighting the substantial global burden of this disease [3].

The life cycle of *Plasmodium* alternates between the vertebrate host and the *Anopheles* mosquito vector. During a blood meal, infected mosquitoes inoculate sporozoites into the skin of the host. These sporozoites rapidly enter the bloodstream and migrate to the liver, where they invade hepatocytes and undergo extensive replication during the liver stage of infection. Mature liver-stage parasites are subsequently released into the circulation as merozoites, which invade erythrocytes and initiate the blood stage of infection. Within erythrocytes, parasites sequentially develop through the ring, trophozoite, and schizont stages before releasing newly formed merozoites that invade additional red blood

Check for updates

Academic Editor: Mark F. Wiser

Received: 21 August 2026
Revised: 27 September 2026
Accepted: 16 October 2026
Published: 19 October 2026

Copyright: © 2026 by the author. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

cells. A small proportion of blood-stage parasites commit to sexual differentiation and develop into male and female gametocytes rather than continuing asexual replication. Following ingestion by an *Anopheles* mosquito, gametocytes undergo fertilization in the mosquito midgut, develop into ookinetes, and subsequently form oocysts with meiosis. After sporogony, sporozoites migrate to the mosquito salivary glands, where they become ready for transmission to a new vertebrate host. Comprehensive descriptions of the *Plasmodium* life cycle and its developmental stages are provided by reviews elsewhere [4].

The clinical manifestations of malaria arise almost exclusively during the erythrocytic stage of infection. Although liver-stage parasites induce relatively limited immune activation, blood-stage infection elicits vigorous innate and adaptive immune responses. It has been suggested that the inflammatory response induced by malaria is rather modest considering the enormous parasite burden in blood compared with many bacterial infections [5]. Nevertheless, blood-stage malaria triggers robust inflammatory responses that are responsible for both parasite control and disease pathogenesis. In *P. falciparum* infection, excessive inflammatory responses contribute to severe malaria syndromes, including cerebral malaria, which represents one of the major causes of malaria-associated mortality. Furthermore, *P. falciparum* infection during pregnancy frequently results in placental malaria, leading to adverse outcomes such as fetal growth restriction, preterm birth, and fetal loss. Consequently, among the *Plasmodium* species infecting humans, *P. falciparum* is responsible for the vast majority of severe disease and malaria-related deaths, followed by *P. vivax* [4].

The immune response to malaria parasites consists of two major components, innate and adaptive immunity. Upon *Plasmodium* infection, innate immune cells rapidly detect invading parasites and initiate the early immune response during the liver and blood stages in mammalian hosts. This is followed by the activation of adaptive immune cells, which act in concert with innate immune cells to eliminate the parasites. Conventional dendritic cells (cDCs), occupy a central position at the interface between innate and adaptive immunity. By integrating innate immune sensing with antigen presentation and T-cell priming, cDCs are key regulators of the magnitude and quality of the immune responses induced during malaria infection.

As described above, the *Plasmodium* life cycle consists of distinct developmental stages in the mosquito vector, the liver, and erythrocytes, including the sexual gametocyte stage. Experimental mouse models have become indispensable tools for investigating host–parasite interactions and the immune responses elicited during malaria infection (reviewed in [6,7]). In particular, rodent malaria parasites have provided fundamental insights into the immunobiology of malaria that are highly relevant to understanding human disease. Among these models, infection with *P. berghei* ANKA(PbA) induces experimental cerebral malaria (ECM), a syndrome that reproduces several pathological and immunological features of human cerebral malaria caused by *P. falciparum* [7]. However, an important difference is that the PfEMP1-mediated cytoadhesion of infected erythrocytes to endothelial receptors such as EPCR and ICAM-1, which is a characteristic feature of human *P. falciparum* cerebral malaria, is not directly reproduced in the PbA ECM model [8]. Although mouse models cannot fully recapitulate malaria infection in humans and have several limitations [9], they remain valuable for elucidating the mechanisms underlying host immunity and disease pathogenesis.

In this review, we summarize current knowledge regarding the roles of cDCs in immune responses induced during the erythrocytic stage of malaria, with particular emphasis on findings obtained from mouse models. Where available, findings from human studies are also discussed, with particular attention to differences between murine and human systems and to the potential relevance and applicability of findings from mouse models to

human malaria. Understanding how cDCs regulate innate and adaptive immunity during blood-stage infection will provide important insights into malaria immunopathogenesis and may facilitate the development of improved therapeutic and vaccine strategies.

2. Dendritic Cells

Dendritic cells (DCs) are widely distributed throughout both lymphoid and non-lymphoid tissues [10]. As professional antigen-presenting cells, cDCs constitute a crucial link between innate and adaptive immunity. They efficiently capture and process antigens and are the most potent activators of naïve T cells. cDCs express a wide array of pattern recognition receptors (PRRs), including multiple pattern-recognition molecules that recognize pathogen-associated molecular patterns (PAMPs). Recognition of these signals induces cDC maturation, accompanied by the production of numerous cytokines and costimulatory molecules. Consequently, cDCs regulate innate immune responses while simultaneously orchestrating T-cell activation and differentiation. In this regard, cDCs can be regarded as central coordinators of the immune response during malaria infection. Although plasmacytoid dendritic cells (pDCs) are conventionally included within the dendritic cell family, they differ substantially from cDCs in terms of ontogeny, phenotype, and function. Their classification remains under debate, with some investigators proposing that pDCs be considered a distinct innate lymphoid population, whereas others argue that they remain an integral component of the dendritic cell lineage [11,12]. In this review, I focus primarily on cDCs.

cDCs comprise a highly heterogeneous population, and their classification varies depending on the tissue of origin and developmental lineage. During blood-stage malaria, the spleen serves as the principal secondary lymphoid organ responsible for initiating and regulating immune responses against infected erythrocytes. Indeed, the spleen has been described as the "epicenter" of malaria immunity [13]. The spleen is a highly specialized blood-filtering and secondary lymphoid organ composed of white pulp, marginal zones, and red pulp. In the red pulp, the unique open microcirculation exposes circulating erythrocytes to mechanical filtration, allowing poorly deformable infected erythrocytes to be retained and removed. The spleen can also pit intraerythrocytic malaria parasites from infected erythrocytes without destroying the host cell, while splenic phagocytes and antigen-presenting cells contribute to parasite clearance and the initiation of adaptive immune responses [13]. Importantly, however, the structure of the human spleen differs from that of the mouse spleen. For example, whereas the mouse spleen contains a clearly defined marginal zone, the corresponding region in the human spleen is anatomically distinct and is more appropriately described as a perifollicular zone rather than a direct equivalent of the murine marginal zone [14,15]. These anatomical differences indicate that immune responses mediated by the spleen in murine malaria models may not necessarily apply directly to human malaria and should therefore be interpreted with caution. Recent advances have further refined our understanding of splenic cDC biology under both homeostatic and inflammatory conditions [16]. In this review, we focus primarily on cDCs in the murine spleen.

cDCs can be broadly classified into tissue-resident and migratory populations [17,18]. Unlike lymph nodes, the spleen lacks afferent lymphatic vessels and therefore does not receive migratory cDCs from peripheral tissues under steady-state conditions. Consequently, splenic cDCs are considered to consist almost exclusively of tissue-resident cells. In mice, splenic cDCs are generally identified as $Lin^{-}CD11c^{+}$MHC class II^{+} cells. Splenic cDCs have traditionally been divided into two major subsets, cDC1 and cDC2. cDC1 are characterized by the expression of XCR1, and the absence of CD11b ($XCR1^{+}CD11b^{-}$), whereas cDC2 are defined as $CD11b^{+}SIRP\alpha^{+}$ cells. Compared with cDC1, which represent

a relatively homogeneous population, cDC2 have long been recognized as phenotypically and functionally heterogeneous.

Recent advances in single-cell transcriptomic and immunophenotypic analyses have substantially refined the classification of cDC2 subsets [19]. In mice, cDC2 can be broadly subdivided into cDC2A and cDC2B populations. cDC2A development depends on Notch2 signaling and is characterized by the expression of T-bet and ESAM. In contrast, cDC2B differentiation is KLF4 dependent and is associated with the expression of CLEC12A in the absence of T-bet. Phenotypically, cDC2B share several surface markers with monocytes and macrophages, suggesting a closer relationship to mononuclear phagocytes than previously appreciated. Although the functional specialization of these subsets has not yet been fully elucidated, accumulating evidence indicates that they make distinct contributions to immune regulation. In particular, the respective roles of cDC1, cDC2A, and cDC2B in directing $CD4^+$ T-cell activation and helper T-cell differentiation are becoming increasingly clear. Elucidating the functions of these cDC subsets during malaria infection will therefore be essential for understanding how protective immunity and immunopathology are orchestrated during blood-stage malaria.

During blood-stage malaria, the intense inflammatory environment profoundly alters the composition of splenic cDC populations. Several studies have reported the appearance of inflammatory DCs, particularly monocyte-derived dendritic cells (moDCs), in the spleen during infection [20]. These cells are thought to arise from circulating monocytes in response to inflammatory cytokines and growth factors, including Flt3 ligand (Flt3L) and granulocyte-macrophage colony-stimulating factor (GM-CSF). Phenotypically, moDCs have been reported to share several characteristics with cDC2 [21], making their discrimination from conventional cDC2 challenging in some experimental settings. In addition to the emergence of inflammatory DCs, blood-stage malaria infection has been shown to induce a marked reduction in the number of splenic cDCs through an interferon-dependent mechanism [22]. Thus, malaria infection not only alters the development, maintenance, and composition of splenic DC populations but is also likely to influence their functional properties. These dynamic changes are expected to have a profound impact on the initiation and regulation of immune responses during blood-stage malaria infection.

Although human and murine DC systems share several conserved features in terms of developmental origin and function, the classification of DC subsets based on surface marker expression is not fully equivalent between the two species. Detailed comparisons of human and murine DC subsets have been described in previous reviews [19,23]. Therefore, findings obtained from murine DCs, particularly those based on genetic manipulation of specific molecules, should be extrapolated to human DCs with caution when the corresponding molecule does not have a comparable expression pattern or functional role in humans. Thus, although mouse models provide major advantages for dissecting the mechanisms and functions of DCs, species differences in DC development, phenotype, and function remain an important consideration in translating these findings to human disease.

3. Activation of cDCs During Blood-Stage Malaria

During blood-stage malaria infection, *Plasmodium* merozoites invade erythrocytes and develop sequentially through the ring, trophozoite, and schizont stages. At the end of each erythrocytic cycle, mature schizonts rupture, releasing newly formed merozoites into the circulation together with a variety of soluble and particulate parasite-derived products, including hemozoin. Components derived from disrupted parasites and infected erythrocytes can subsequently be detected by pattern-recognition receptors (PRRs) expressed by innate immune cells [24]. These receptors include Toll-like receptors (TLRs), as well

as cytosolic nucleic acid sensors and NOD-like receptors that promote the assembly of inflammasomes [25,26].

Infected erythrocytes are also phagocytosed by macrophages and cDCs [27]. In addition, parasite-derived components may reach cDCs through alternative mechanisms, including membrane transfer processes such as trogocytosis and extracellular vesicles. Following their uptake and degradation within intracellular vesicular compartments, parasite-derived molecules, including nucleic acids, become accessible to PRRs located in endosomes or the cytosol. cDCs express a broad range of PRRs and can therefore respond to both pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) generated during blood-stage malaria infection. Recognition of these molecules induces cDCs activation, cytokine production, and changes in antigen-presenting capacity, thereby influencing the subsequent innate and adaptive immune responses.

3.1. Parasite-Derived PAMPs

Several *Plasmodium*-derived molecules have been identified as PAMPs, among which glycosylphosphatidylinositols (GPIs), DNA, and RNA have been studied most extensively [25]. Many *Plasmodium* surface proteins, which could be involved in invasion into erythrocytes, are attached to the parasite plasma membrane through GPI anchors. A considerable amount of GPI is present on the *Plasmodium* surface in non-protein-linked form, which is thought to contribute to its recognition by innate immune cells. GPIs derived from *P. falciparum* can activate macrophages, predominantly through TLR2-dependent signaling [28]. GPIs were also shown to activate mouse bone marrow-derived DCs and promote the production of inflammatory cytokines, including TNF-α and IL-12p40 [29].

Plasmodium-derived nucleic acids can be sensed by multiple innate immune receptors, including endosomal TLR7 and TLR9, as well as cytosolic sensors such as MDA5 and cGAS, leading to the induction of inflammatory cytokines. A detailed description of nucleic acid sensing and its downstream signaling pathways has been reviewed elsewhere [5,25]. The *P. falciparum* genome is characterized by an exceptionally high adenine–thymine content. AT-rich stem-loop DNA motifs derived from the parasite genome have been shown to activate splenic DCs and stimulate IFN-β production through a signaling pathway involving STING, TBK1, and IRF3 [30]. Parasite nucleic acids can also activate inflammasome pathways. Genomic DNA and RNA derived from *P. yoelii* have been reported to induce IL-1β production in LPS-primed DCs and macrophages. Parasite DNA is primarily detected through the AIM2 inflammasome, whereas parasite RNA and particulate parasite products can promote activation of the NLRP3 inflammasome [31]. These observations demonstrate that nucleic acids derived from *Plasmodium* parasites can stimulate distinct cytosolic sensing pathways in addition to endosomal TLR signaling.

3.2. Hemozoin and Danger-Associated Signals

Hemozoin is generated from heme originally contained within host erythrocyte hemoglobin [32]. During intraerythrocytic development, malaria parasites internalize large amounts of host hemoglobin into their acidic digestive vacuole and degrade it to obtain amino acids required for parasite growth and protein synthesis. This process releases free heme, which is highly cytotoxic because of its redox activity and its ability to promote oxidative damage. To avoid heme-mediated toxicity, the parasite converts free heme into the insoluble crystalline pigment hemozoin through a biocrystallization process that remains incompletely understood.

When infected erythrocytes rupture, hemozoin is released into the circulation and can subsequently be internalized by macrophages and DCs. Naturally derived hemozoin is associated with parasite-derived DNA, proteins, and lipids [25]. Consequently, some

of the immunostimulatory activity attributed to hemozoin may arise not only from the physicochemical properties of the crystal itself but also from parasite molecules carried on or within the hemozoin particles. Hemozoin can facilitate the delivery of parasite DNA to intracellular nucleic acid sensors, while its crystalline structure may promote NLRP3 inflammasome activation.

Hemozoin has been reported to affect DC activation through several PRRs. However, its effects on DC function appear to be complex. Some studies have shown that hemozoin induces DC maturation and inflammatory cytokine production, whereas others have reported impaired DC maturation, cytokine production, antigen presentation, or T-cell-stimulatory capacity [33,34]. These apparently conflicting findings may reflect differences in the origin and purity of hemozoin preparations, the amount and duration of exposure, the DC population examined, and the presence of associated parasite-derived molecules [35–37]. Further studies will therefore be required to define precisely how hemozoin modulates cDC functions during malaria infection.

Uric acid represents another danger-associated molecule implicated in malaria-induced inflammation [25,38,39]. Crystalline monosodium urate is recognized through the NLRP3 inflammasome and is a major cause of the inflammatory response observed in gout. Uric acid precipitates have also been observed within *P. falciparum*-infected erythrocytes and accumulate during intraerythrocytic parasite development. These precipitates can be released into the extracellular environment when mature infected erythrocytes rupture.

P. falciparum-derived uric acid precipitates have been shown to promote the maturation of human DCs, including increased expression of the costimulatory molecules CD80 and CD86 [40]. These findings suggest that uric acid precipitates released from infected erythrocytes function as endogenous danger signals that enhance cDC activation during blood-stage malaria.

Much of the mechanistic evidence regarding DC responses to PAMPs and DAMPs during malaria infection has been obtained using murine DCs. However, the expression and distribution of TLRs and other pattern-recognition receptors differ between mice and humans [41,42]. Therefore, it is important to consider that, in human malaria, cell populations other than cDCs may contribute to the recognition of parasite-derived PAMPs and host-derived DAMPs.

4. Interactions Between cDCs and T Cells

Interactions between cDCs and T cells are particularly important during blood-stage malaria. cDCs can process and present blood-stage malaria antigens to both $CD4^+$ and $CD8^+$ T cells, thereby inducing antigen-specific T-cell activation. In our previous study using mice infected with green fluorescent protein (GFP)-expressing PbA, GFP fluorescence was detected in splenic cDCs, indicating that infected erythrocytes or parasite-derived material had been taken up by these cells in vivo [43]. Moreover, cDCs isolated from PbA-infected mice exhibited increased expression of the costimulatory molecules CD80, CD86, and CD40, consistent with phenotypic maturation and retained T-cell-stimulatory capacity, as similarly shown in *P. yoelii* infection [22,44,45]. These observations support a role for cDCs in priming malaria-specific effector T-cell responses during blood-stage infection. However, the functional state of cDCs may vary depending on the stage and context of infection, and cDCs may exhibit impaired activation and T-cell-stimulatory capacity under certain conditions [46]. Even so, regulation of T-cell activation and differentiation is one of the most important functions of cDCs in malaria, because T-cell responses are central to both parasite control and malaria-associated immunopathology. cDCs play particularly important roles in directing the differentiation of $CD4^+$ T cells into distinct helper T-cell subsets [18,21]. The cDC subsets and signals required for individual T-helper-cell programs

are being increasingly defined. Blood-stage malaria induces several $CD4^+$ T-cell subsets, among which T helper 1 (Th1) and T follicular helper (Tfh) cells have been most clearly linked to parasite control, humoral immunity, and disease pathogenesis [47,48].

Some cDC-dependent T-cell responses contribute to protection against blood-stage parasites [48,49]. cDC-mediated activation of $CD4^+$ T cells and their differentiation into Th1 cells promotes the production of interferon-γ (IFN-γ), which activates macrophages and can enhance the phagocytic clearance of infected erythrocytes. cDCs may also facilitate Tfh-cell differentiation and thereby promote the production of parasite-specific antibodies by B cells. Such antibodies can inhibit merozoite invasion of erythrocytes and promote parasite clearance through opsonic phagocytosis, complement activation, and other Fc-dependent effector mechanisms. These processes are directly relevant to the development of effective malaria vaccines. Conversely, cDC-driven T-cell responses can also contribute to host-damaging immunopathology, of which cerebral malaria is a prominent example. Although pDCs are known to become activated during malaria infection, pDC depletion has been reported to have little effect on T-cell activation, ECM, or parasitemia in *P. berghei* and *P. chabaudi* infections [50,51]. Therefore, the role of pDCs is not discussed here.

4.1. Induction of Th1 Responses

Blood-stage malaria generally induces a strong Th1-polarized response [48]. IFN-γ produced by Th1 cells contributes to parasite control by activating macrophages and other innate effector cells, and the importance of Th1 immunity in controlling blood-stage parasite replication is well established. However, an excessive or prolonged Th1 response is also associated with severe inflammatory manifestations of malaria. In addition, high levels of IFN-γ and Th1-biased inflammation may compromise humoral immunity by promoting dysfunctional or atypical B-cell phenotypes [52,53] and by constraining Tfh-cell and germinal-center responses [54].

Studies using experimental models mainly in mice have demonstrated an important role for cDC1 in Th1-cell differentiation [18,21]. Following activation, cDC1 constitute an important source of IL-12, which promotes T-bet expression and Th1 polarization in responding $CD4^+$ T cells. Functional impairment of cDC1 markedly reduces malaria-induced Th1 responses in *P. berghei* infection [55,56]. In *P. chabaudi* infection, cDC1, not cDC2, expressed IL-12 [57] as shown in other parasitic infections [58]. Thus, cDC1-dependent IL-12 production would represent an important pathway through which innate recognition of blood-stage parasites is translated into Th1 type adaptive immunity. IFN-γ produced by $CD4^+$ T cells promotes the development of ECM by enhancing the accumulation and effector differentiation of $CD8^+$ T cells in the brain in PbA infection model [59]. A more comprehensive understanding of the mechanisms by which cDC1s become activated and subsequently induce Th1 responses during blood stage malaria infection may help to reduce the detrimental aspects of Th1 responses observed in malaria.

4.2. Induction of Th2 Responses

The importance of cDC2 in promoting Th2 differentiation has been demonstrated in a variety of experimental systems [18,21,60]. In particular, KLF4-dependent cDC2B populations have been implicated in the induction of Th2-type immunity in an allergic and helminth infection model. IL-4-producing $CD4^+$ T cells are also generated during blood-stage malaria [61]. In *P. chabaudi* infection, the immune response evolves from an early Th1-dominated phase, characterized by IFN-γ production and control of acute parasitemia, to a later Th2-type and antibody-associated response that contributes to more complete parasite clearance [62]. However, in *P. chabaudi* infection models, IL-4 deficiency has little effect on the course of blood-stage infection, although this does not necessarily exclude a

role of Tfh cells or other cell populations for infection control [48]. The *P. chabaudi* model has been particularly informative in demonstrating this temporal transition; however, the classical Th1/Th2 framework does not fully account for the contribution of Tfh cells and other $CD4^+$ T-cell populations to humoral immunity [61].

Th2 responses initially attracted considerable attention because of their association with antibody production. More recent studies, however, have established Tfh cells as the principal $CD4^+$ T-cell subset supporting germinal-center reactions and high-affinity antibody responses [61]. Consequently, the specific contribution of conventional Th2 cells to protective antibody production during blood-stage malaria remains incompletely defined. Although cDCs are generally required for efficient Th2 priming, they are not usually regarded as a major source of IL-4 [60]. Nevertheless, certain *Plasmodium*-derived components have been reported to induce IL-4 production by DCs under particular experimental conditions [63]. The physiological relevance of DC-derived IL-4 during malaria infection therefore requires further investigation. Overall, conventional Th2 responses appear to make a context-dependent contribution to parasite control during blood-stage malaria, whereas Tfh cells have a more clearly established role in germinal-center formation and protective antibody responses. The extent to which cDC-mediated Th2 priming contributes to parasite control, humoral immunity, or other functional outcomes during blood-stage malaria remains poorly defined.

4.3. Induction of Tfh Responses

Tfh cells are essential for humoral immunity [21]. Within secondary lymphoid organs, they support germinal-center formation, affinity maturation, immunoglobulin class switching, and the differentiation of B cells into memory B cells and long-lived plasma cells. Tfh-cell development is a multistep process. During the initial phase, antigen-presenting cells such as cDCs prime naïve $CD4^+$ T cells and initiate the expression of molecules associated with the Tfh program, including BCL6, CXCR5, ICOS, and PD-1. The developing Tfh cells subsequently migrate toward B-cell follicles, where sustained interactions with cognate B cells stabilize and further refine their differentiation. In several non-malarial models of splenic immune responses, Notch2-dependent $ESAM^{high}$ cDC2, broadly corresponding to a cDC2A-like population, are required for efficient Tfh-cell and germinal-center responses [18,21,60]. Loss of this cDC2 population results in impaired splenic Tfh-cell differentiation and antibody production. Whether the same cDC2 subset has an equivalent role during blood-stage malaria has not yet been established.

Tfh cells are clearly important for the development of protective humoral immunity against malaria [64]. However, the requirement for cDCs in malaria-induced Tfh differentiation remains controversial. One study demonstrated that B cells, not cDCs, were both necessary and sufficient to prime the dominant Tfh response during the early phase of *P. yoelii* infection [65]. Nevertheless, cDCs could still influence the magnitude and quality of Tfh- and B-cell responses through early antigen presentation, cytokine production, or indirect regulation of the splenic microenvironment. B-cell-activating factor (BAFF), which can be produced by DCs as well as other myeloid and stromal cells, may also modulate B-cell survival and differentiation and could indirectly affect Tfh responses during malaria [66,67]. In addition, DCs have been proposed to contribute directly to B-cell activation by capturing intact antigen and facilitating its presentation or transfer to antigen-specific B cells [68,69]. Thus, although the importance of Tfh cells during blood-stage malaria is increasingly well established, the precise and potentially stage-dependent contribution of individual cDC subsets to their induction remains unresolved. Defining these subset-specific pathways may provide opportunities to modulate cDC–Tfh interactions to enhance durable protective humoral immunity and improve malaria vaccine efficacy.

4.4. Induction of Th17 Responses

Th17 cells are particularly important for host defense against extracellular bacteria and fungi at barrier sites, including the intestinal and respiratory mucosa, and they also contribute to the pathogenesis of several autoimmune and inflammatory diseases. Notch2-dependent cDC2A populations have been shown to promote Th17 differentiation in mucosal tissues such as the intestine and lung [18,21,60].

The importance of Th17 responses during blood-stage malaria has not been firmly established. Th17 cells and IL-17 production have been detected during *P. berghei* and *P. yoelii* infection, although their magnitude is generally modest compared with that of Th1 responses [70]. IL-17 deficiency had no significant effect on the development of ECM or parasitemia following PbA infection [71]. Studies of human *P. vivax* infection have also associated Th17-related responses with particular clinical or protective immune phenotypes [72], but their causal contribution to parasite control remains uncertain. Collectively, there is still limited evidence of the anti-parasitic or pathogenic roles of Th17 cells. As the functions of Th17 cells in blood-stage malaria become better defined, it should also become possible to determine which cDC subsets and signals are responsible for their induction.

4.5. Induction of Regulatory CD4$^+$ T Cells Responses

Regulatory CD4$^+$ T-cell populations may contribute to the regulation of immune responses during malaria infection. Foxp3$^+$ regulatory T cells (Tregs) comprise thymus-derived Tregs (tTregs) and peripherally induced Tregs (pTregs) [49,73]. These populations are difficult to distinguish definitively based on surface markers or transcription factor expression alone to date. Although pTregs may be relevant to this review, their specific contribution to the regulation of immune responses during malaria remains poorly defined. Several studies have used anti-CD25 antibodies to deplete Tregs in *P. yoelii* and *P. berghei* models [74,75]; however, these approaches generally do not distinguish the functional contributions of tTregs and pTregs to immune responses during malaria infection. Recent genetic approaches have enabled selective impairment of tTreg or pTreg development, providing new opportunities to investigate their distinct functions [76]. Applying such approaches to malaria models may help clarify how cDCs in the spleen and other secondary lymphoid tissues regulate the induction and function of pTregs during malaria infection, and how these cells influence parasite control and immunopathology.

In addition to Foxp3$^+$ Tregs, Foxp3$^-$ IL-10-producing regulatory CD4$^+$ T cells, commonly referred to as type 1 regulatory T (Tr1) cells, have also been described (reviewed in [47–49]). These cells are thought to arise, at least in part, from Th1 cells under inflammatory conditions. DC-derived IL-10 has been shown to promote the induction of IL-10-producing CD4$^+$ Tr1 cells in *P. yoelii*-infected mice [77]. The contribution of specific cDCs subsets to the induction and regulation of pTregs and Tr1 cells during malaria remains poorly defined. Both pTregs and Tr1 cells have been reported in human malaria [78,79]. Elucidating their precise functional roles and their regulation in both mouse and human malaria may provide a basis for developing strategies to improve parasite control while limiting malaria-associated immunopathology.

4.6. Activation of CD8$^+$ T Cells

CD8$^+$ T cells play a central role in immunity to intracellular pathogens and are particularly important for eliminating *Plasmodium*-infected hepatocytes during the liver stage [80]. Their role in blood-stage malaria is more complex. Mature erythrocytes do not express MHC class I molecules and therefore cannot ordinarily present parasite-derived peptides directly to cytotoxic CD8$^+$ T cells. Consequently, direct killing of infected mature erythrocytes is not generally considered a major mechanism of blood-stage parasite clearance.

There are, however, important exceptions to this conventional view. Reticulocytes, not mature erythrocytes, retain MHC class I expression. *P. vivax*-infected human reticulocytes have been shown to express HLA class I, present parasite-derived antigens, and undergo antigen-specific killing by cytotoxic $CD8^+$ T cells [81].

$CD8^+$ T cells have a prominent role in cerebral malaria pathogenesis [82]. ECM is considered a valuable animal model for human cerebral malaria, and the mechanisms underlying ECM pathogenesis have been extensively investigated. Disruption of the blood–brain barrier is a central event in ECM, and cytotoxic $CD8^+$ T cells are critical mediators of cerebral vascular injury. cDC1 are essential for the development of this response. As previously described, cDC1 prompt Th1 response, in which IFN-γ is critical to pathogenesis of ECM. In addition, cDC1 efficiently acquire malaria antigens and cross-present them on MHC class I molecules in the spleen, thereby priming and expanding parasite-specific cytotoxic $CD8^+$ T cells. Consistent with this role, BATF3 deficient mice lacking cDC1 are strongly protected from ECM and exhibit impaired cytotoxic T-cell responses [56,83].

Activated parasite-specific $CD8^+$ T cells subsequently migrate to the brain. This recruitment is mediated in part by CXCR3 and its ligands, particularly CXCL9 and CXCL10, whose expression is enhanced by IFN-γ-driven inflammation. During PbA infection, infected erythrocytes and parasite-derived material accumulate within the cerebral microvasculature. In ECM, brain microvascular endothelial cells, rather than brain-resident cDCs or micoglia, are well-established local cross-presenting cells that provide cognate antigenic stimulation to parasite-specific $CD8^+$ T cells [84]. IFN-γ-activated brain endothelial cells can acquire and cross-present malaria antigens through MHC class I, making them susceptible to recognition by parasite-specific $CD8^+$ T cells. Cytotoxic attack on the cerebral endothelium, involving perforin- and granzyme-dependent mechanisms, promotes vascular dysfunction and breakdown of the blood–brain barrier, culminating in ECM. This cDC1–$CD8^+$ T-cell–brain endothelial-cell axis is therefore a central mechanism of immunopathology in the murine ECM model, although the extent to which the same pathway contributes to human cerebral malaria remains under investigation. A major challenge for future research is to determine how the mechanisms identified in murine ECM translate to human cerebral malaria and whether these pathways can be therapeutically targeted.

5. Interactions Between cDCs and Other Innate Immune Cells

In addition to their well-established interactions with adaptive immune cells, particularly T cells, cDCs communicate extensively with cells of the innate immune system. Through cytokine production, antigen presentation, and cell–cell interactions, cDCs can regulate the activation and effector functions of macrophages, natural killer (NK) cells, and other innate lymphoid populations. Importantly, these interactions are often bidirectional, because signals derived from innate immune cells can, in turn, modulate the maturation and functional properties of cDCs. Thus, cDCs participate in a complex cellular network that coordinates both innate and adaptive immune responses during blood-stage malaria.

5.1. Interactions Between cDCs and Myeloid Cells

Monocytes and macrophages possess potent phagocytic activity and play important roles in the clearance of blood-stage malaria parasites. During malaria infection, hemozoin frequently accumulates in circulating monocytes and tissue macrophages, reflecting their uptake of parasite-derived material, including hemozoin released from ruptured infected erythrocytes as well as material acquired through phagocytosis of infected erythrocytes [85–87]. Macrophages can remove both merozoites and infected erythrocytes through opsonic and non-opsonic mechanisms [14,88]. In non-opsonic phagocytosis, sev-

eral scavenger and pattern-recognition receptors are involved. CD36, in particular, has been implicated in the recognition and phagocytosis of *P. falciparum*-infected erythrocytes [89]. In opsonic phagocytosis, parasite-specific antibodies bind to merozoites or antigens exposed on infected erythrocytes, allowing their recognition through Fc receptors expressed by macrophages and thereby enhancing their phagocytic clearance.

cDCs may promote these macrophage-mediated effector mechanisms through several pathways. First, cDCs activated during the early phase of infection produce inflammatory cytokines, including IL-12 and TNF, which contribute to the activation of macrophages [90]. Second, as described in Section 4.1, cDC-derived IL-12 promotes the activation and differentiation of malaria-specific Th1 cells. IFN-γ produced by these cells further enhances macrophage antimicrobial and phagocytic functions. Third, cDCs contribute indirectly to antibody-mediated parasite clearance by promoting T-cell-dependent humoral immune responses. Parasite-specific antibodies generated through these responses opsonize merozoites and infected erythrocytes and facilitate their uptake by Fc receptor-expressing macrophages. A recent study suggests that depletion of cDCs alters the abundance of splenic macrophage subpopulations and their cytokine production profiles during *P. yoelii* infection [91]. Thus, interactions among cDCs, T cells, B cells, and macrophages form an integrated cellular network contributing to parasite control during blood-stage malaria. Determining how cDC-dependent regulation of macrophage populations and functions contributes to parasite clearance and disease outcome, and whether similar interactions occur in human malaria, may provide important insights into the regulation of protective immunity during blood-stage infection.

5.2. Interactions Between cDCs and Innate Lymphocyte Populations

cDCs also interact with several lymphocyte populations other than conventional B and T cells. For the purposes of this review, these populations can broadly be considered in two groups. The first comprises innate-like T cells, including γδ T cells, invariant natural killer T (iNKT) cells, and mucosal-associated invariant T (MAIT) cells. These cells express T-cell receptors generated by somatic gene rearrangement but have restricted or strongly biased antigen receptor repertoires and often recognize non-classical antigens. They can therefore respond rapidly to infection and exhibit several functional characteristics more typically associated with innate immune cells. The second group comprises innate lymphoid cells (ILCs), including NK cells and the helper-like ILC1, ILC2, and ILC3 populations. Like B and T cells, ILCs arise from lymphoid progenitors, but they do not express somatically rearranged antigen receptors such as TCRs or BCRs. Increasing evidence has demonstrated important roles for ILCs in immunity to a wide range of infectious agents, and reciprocal interactions between ILCs and DCs have emerged as an important mechanism regulating tissue immune responses. However, with the notable exception of NK cells, the functions of ILCs during blood-stage malaria and their interactions with cDCs remain poorly understood.

5.2.1. Innate-like T Cells

Innate-like T cells express rearranged TCRs but differ from conventional αβ T cells in their antigen recognition and response characteristics. Their TCR repertoires are generally restricted or biased, and many innate-like T-cell populations recognize conserved microbial metabolites or non-peptide antigens presented by non-classical antigen-presenting molecules. These properties with the memory-like features often observed in these cells allow them to respond rapidly during infection [92].

Among these populations, γδ T cells have been investigated in malaria [93]. During blood-stage infection, γδ T cells become activated and can expand substantially and pro-

duce multiple cytokines, including IFN-γ. In humans, the Vγ9Vδ2 T-cell subset responds strongly to phosphoantigens generated by blood-stage *P. falciparum* [94], providing a mechanism for rapid recognition of malaria infection. Vδ1 T cells were shown to expand in the peripheral blood of individuals from endemic regions [95]. In mice, there is no direct counterpart of the human Vγ9Vδ2 T-cell subset [93]. Nevertheless, γδ T cells are also activated and expand during blood-stage infection with rodent malaria parasites, including *P. chabaudi*, *P. berghei*, and *P. yoelii*, and can contribute to early IFN-γ production and control of parasitemia [94]. Importantly, γδ T cells can interact functionally with cDCs during blood-stage malaria. Recent evidence indicates that γδ T cells promote the activation and maturation of cDC1 and thereby enhance cDC1-dependent Th1 responses during *P. chabaudi* infection. Thus, rather than functioning independently, γδ T cells and cDC1 can participate in a reciprocal network that promotes Th1 immunity [57]. Cooperative interactions between γδ T cells and cDCs have also attracted attention in pre-erythrocytic malaria, where they may contribute to the generation of effective $CD8^+$ T-cell responses against liver-stage *P. berghei* parasites [96,97]. In humans, activated Vγ9Vδ2 T cells can promote the maturation and IL-12 production of monocyte-derived DCs in vitro [98,99]. However, whether a similar γδ T-cell–DC interaction occurs in humans during malaria infection remains unclear. Although Vγ9Vδ2 T cells are strongly activated by *P. falciparum* infection, direct evidence that these cells modulate DC function during the course of malaria infection is currently limited.

5.2.2. Innate Lymphoid Cells

Innate lymphoid cells are lymphoid-lineage cells that lack rearranged antigen-specific receptors. Helper-like ILCs are conventionally classified into ILC1, ILC2, and ILC3 according to their transcriptional programs and cytokine profiles. NK cells and ILC1 are both classified as group 1 ILCs because they share several functional and phenotypic properties, including expression of T-bet and production of IFN-γ. However, NK cells and helper-like ILC1 are now recognized as developmentally and functionally distinct populations.

Interest in the roles of ILCs during infectious diseases, including protozoan infections, has increased [100–102]. Nevertheless, relatively little is known about helper-like ILCs during blood-stage malaria. The spleen is a central organ in immunity to blood-stage parasites, whereas ILC2 and ILC3 are particularly enriched at barrier sites such as the intestine, lung, and skin. Although these cells can also be detected in lymphoid organs, including the spleen, their abundance is relatively low under steady-state conditions. This anatomical distribution may partly explain why their contributions to blood-stage malaria have received less attention. Despite their relatively small numbers, several observations suggest that helper-like ILCs may influence malaria immunity. At present, however, their quantitative contribution to parasite control or malaria-associated immunopathology has not been firmly established, and interactions between helper-like ILC populations and cDCs during blood-stage infection remain largely unexplored.

Group 1 ILCs and NK Cells

ILC1 respond predominantly to intracellular pathogens and are characterized by their capacity to produce IFN-γ. NK cells share this type 1 cytokine program but, unlike helper-like ILC1, possess potent cytotoxic activity and generally represent a distinct developmental lineage.

The roles of NK cells in malaria have been extensively reviewed elsewhere [103]. NK cells become activated during blood-stage malaria and can contribute to immunity through cytokine production and cytotoxic effector mechanisms. NK cells can recognize *Plasmodium*-infected erythrocytes under certain experimental conditions and produce IFN-γ and cytotoxic granules following interaction with infected cells [104]. More recently, parasite-

specific antibodies have been shown to promote NK-cell responses against *P. falciparum* merozoites through Fc receptor-dependent mechanisms [105]. Antibody-opsonized merozoites induce NK-cell degranulation and IFN-γ production, and this antibody-dependent NK-cell activity can inhibit subsequent erythrocyte invasion.

Reciprocal interactions between NK cells and DCs have also been demonstrated during blood-stage *P. chabaudi* and *P. berghei* infection [106,107]. Cytokines produced by activated DCs, particularly IL-12, contribute to NK-cell activation and IFN-γ production. In turn, NK-cell-derived IFN-γ can promote DC activation and support the development of type 1 adaptive immune responses. Thus, DC–NK-cell cross-talk provides an important mechanism linking early innate recognition of blood-stage parasites to subsequent cellular immunity.

The possible contribution of helper-like ILC1 to blood-stage malaria is much less clear. Because malaria induces a pronounced type 1 inflammatory response, an involvement of IFN-γ-producing ILC1 is biologically plausible. However, NK cells and ILC1 share several surface markers and transcription factors, which historically made these populations difficult to distinguish [108,109]. For example, in C57BL/6 mice, NK1.1 is expressed by both conventional NK cells and subsets of ILC1. Consequently, some cells classified as "NK cells" in earlier malaria studies, particularly studies relying on a limited number of surface markers, may represent heterogeneous group 1 ILC populations. Re-evaluation of these responses using contemporary markers that distinguish NK cells from tissue-resident ILC1 may therefore provide new insights into type 1 innate lymphocyte responses during blood-stage malaria.

ILC2

ILC2 are best known for their roles in type 2 immunity against helminths, allergic inflammation, and tissue repair. They respond strongly to epithelial-derived cytokines such as IL-33, IL-25, and thymic stromal lymphopoietin and characteristically produce IL-5 and IL-13.

A potential contribution of ILC2 to malaria immunopathology has been demonstrated in the PbA model of ECM [110,111]. Administration of IL-33 protects mice from ECM and is associated with expansion and activation of ILC2, together with polarization of macrophages toward an alternatively activated phenotype and expansion of regulatory T cells [111]. These observations suggest that enhancement of the ILC2-associated type 2 immune environment can counterbalance the pathogenic type 1 inflammatory response that drives ECM. However, whether endogenous ILC2 make a major contribution to the immune response during natural blood-stage infection in the absence of exogenous IL-33 remains unclear.

ILC3

ILC3 are particularly abundant at mucosal surfaces and contribute to immunity against extracellular bacteria and fungi, principally through the production of IL-17 and IL-22. Although IL-17 production has been reported during blood-stage malaria infection, whether and to what extent ILC3s are involved remains unclear [101]. Similarly, while IL-22 has been reported to contribute to protection from tissue damage during blood-stage *P. chabaudi* infection [112], the involvement of ILC3 in this context also remains unclear.

An additional reason to consider ILC3 in the context of splenic malaria immunity is their ability to regulate DC homeostasis. Under steady-state conditions, splenic ILC3 have been shown to control the differentiation and maintenance of cDC populations through lymphotoxin-dependent mechanisms [113]. Thus, ILC3 could potentially influence malaria immunity indirectly by altering the composition or functional state of splenic cDC populations. Whether this homeostatic ILC3–cDC axis is maintained, enhanced, or disrupted during blood-stage *Plasmodium* infection has not yet been determined.

Taken together, current evidence suggests that ILC2 and ILC3 have the potential to modulate immune responses during blood-stage malaria, either directly through cytokine production or indirectly through their effects on other immune populations. However, in contrast to the relatively well-characterized DC–NK-cell interaction, the functional relationships between cDCs and helper-like ILC1, ILC2, and ILC3 during blood-stage malaria remain poorly elucidated. Defining these interactions, particularly within the spleen, represents an important area for future investigation and may reveal previously unrecognized mechanisms regulating the balance between protective immunity and immunopathology during malaria.

6. Future Perspectives

6.1. cDCs and Immunity Against Sexual-Stage Parasites

Although the roles of cDCs in immune responses against asexual blood-stage parasites have been extensively investigated, their contribution to host immunity against the sexual stages of *Plasmodium* remains poorly understood. Gametocytes represent the sexual-stage parasites that develop within the vertebrate host and are ultimately responsible for transmission to the mosquito. Gametocyte-infected erythrocytes can themselves become targets of host immune responses [114,115]. In particular, macrophages have been shown to phagocytose erythrocytes containing immature gametocytes [116], suggesting that phagocytic clearance may contribute to the elimination of sexual-stage parasites before they reach full maturity. It is therefore conceivable that modulation of cDC activity could indirectly enhance macrophage-mediated clearance of immature gametocyte-infected erythrocytes through cytokine-mediated activation of phagocytes or through the induction of adaptive immune responses. Antibodies recognizing antigens associated with gametocytes or gametocyte-infected erythrocytes are also generated during natural malaria infection [117]. However, the extent to which cDCs contribute to the induction and maintenance of these antibody responses remains largely unknown. Similarly, although cDCs phagocytose infected erythrocytes and parasite-derived material during asexual blood-stage infection, whether they directly capture gametocyte-infected erythrocytes and subsequently present gametocyte-derived antigens has not been well characterized.

Immature *P. falciparum* gametocytes preferentially accumulate in extravascular niches of the bone marrow, where they undergo maturation before mature stage V gametocytes re-enter the peripheral circulation [118]. The molecular mechanisms responsible for this sequestration and tissue localization remain incompletely understood. If gametocyte or host-cell molecules involved in bone marrow localization could be identified, these molecules might represent potential targets for transmission-blocking immunity. For example, efficient delivery of such antigens to cDCs might enhance the production of antibodies capable of interfering with the localization or retention of immature gametocytes in the bone marrow. In principle, disruption of this process could expose immature gametocyte-infected erythrocytes to circulating or splenic phagocytes, thereby promoting their premature clearance and reducing the number of mature gametocytes available for transmission to mosquitoes. This possibility remains highly speculative but represents an interesting direction for future studies examining the contribution of cDCs to transmission-blocking immunity.

6.2. cDCs in Placental Malaria

Placental malaria is one of the most serious complications of *P. falciparum* infection, particularly because of its adverse consequences for both the mother and fetus [1,119–121]. Infected erythrocytes expressing var2CSA accumulate within the placental intervillous space, where they induce local inflammatory responses. Increasing evidence indicates that

innate immune responses make important contributions to the pathogenesis of placental malaria [122,123]. Murine models using *P. berghei* and *P. chabaudi* have been used to investigate placental pathology and adverse pregnancy outcomes during malaria infection [121,124,125]. However, rodent malaria parasites lack orthologs of the *P. falciparum* var gene family, including var2CSA, which plays a central role in parasite sequestration in the human placenta. Although these murine models recapitulate certain aspects of placental malaria, no currently available murine models fully reproduce the characteristic features of human placental malaria. Therefore, findings obtained from these murine models should be interpreted with caution when extrapolating them to human placental malaria.

In addition to the prominent accumulation of monocytes and macrophages, alterations in placental DC populations have also been reported during *P. berghei* infection [126]. The expression of Mgl2 (CD301b), a marker associated with cDCs, was increased in the placenta following *P. berghei* infection. However, it remains unclear whether this increase reflects an increased abundance of Mgl2-expressing cDCs or upregulation of Mgl2 expression on individual cells. More fundamentally, the specific functions of cDCs within the infected placenta remain poorly defined. cDCs could potentially influence placental pathology through several mechanisms, including cytokine production, antigen presentation to T cells, modulation of macrophage activity, and regulation of local inflammatory responses. Conversely, changes in the placental inflammatory environment may alter the phenotype and function of resident or recruited DC populations. A better understanding of the roles of individual cDC subsets in placental malaria may therefore reveal previously unrecognized mechanisms underlying placental inflammation and tissue damage. Such information could ultimately contribute to the development of approaches aimed at preventing placental immunopathology or reducing the severity of placental malaria.

6.3. cDCs, Repeated Malaria Exposure, and Clinical Immunity

The contribution of cDCs to the development of clinical immunity following repeated malaria exposure also remains incompletely understood. A single malaria infection generally fails to induce complete and durable protective immunity. However, individuals living in malaria-endemic areas gradually acquire partial immunity after repeated exposure [127]. This state, commonly referred to as clinical immunity, does not necessarily prevent infection but enables individuals to control parasite densities more effectively and markedly reduces the risk of severe manifestations of malaria.

Traditionally, the gradual acquisition of clinical immunity has been discussed mainly in the context of adaptive immunity, particularly the development and maintenance of parasite-specific antibody and T-cell responses [52,128,129]. More recently, however, it has become clear that innate immune cells can also undergo long-lasting functional reprogramming following infection or other inflammatory stimuli [130]. This phenomenon, generally referred to as trained immunity, can alter the magnitude or quality of innate immune responses upon subsequent exposure to the same or unrelated pathogens.

Evidence is emerging that malaria infection can induce persistent alterations (e.g., in TLR2 responsiveness in human adherent PBMCs exposed to *P. falciparum*-infected erythrocytes) in innate immune cells that resemble features of trained immunity or, under some conditions, innate immune tolerance [131,132]. Moreover, experimental models of repeated malaria infection have demonstrated long-lasting alterations in the composition and functional properties of cDC populations [133,134]. In splenic cDCs from mice with repeated PbA infection–cure cycles, reduced cytokine production after TLR stimulation, a reduction in the proportion of cDC1, and enhanced phagocytic capacity of the cDC2 subset were demonstrated. These observations raise the possibility that repeated exposure to *Plasmodium* not only reshapes adaptive immunity but also modifies the developmental

and functional state of cDCs and other innate immune cells. Detailed characterization of changes in cDC subset composition, cytokine production, pattern-recognition receptor responsiveness, antigen uptake, and T-cell-stimulatory capacity following repeated malaria infection in murine models may provide a mechanistic framework for generating hypotheses about the effects of repeated *Plasmodium* exposure on cDC function. Whether comparable changes occur in repeatedly exposed humans, and how such changes relate to parasite control, malaria-associated inflammation, and the development of naturally acquired clinical immunity, remain to be clarified for future investigation. An important question is whether these changes represent beneficial adaptation that limits excessive inflammation while maintaining parasite control, or whether they contribute to immune dysfunction and impaired responses to unrelated antigens. These possibilities are not mutually exclusive and may depend on the number and timing of previous infections, parasite burden, host age, and other environmental factors.

6.4. Implications for Vaccination in Malaria-Endemic Areas

Understanding malaria-induced modulation of cDC function may also have important implications beyond immunity to malaria itself. Reduced immunogenicity or efficacy of several vaccines has been reported in some malaria-endemic populations [135–138], although this phenomenon is likely to be multifactorial and cannot be attributed solely to malaria infection. In this context, chronic or repeated exposure to malaria parasites may influence subsequent vaccine responses by modifying the function of innate and adaptive immune cells. Many vaccine adjuvants exert their effects, at least in part, by activating innate immune pathways in cDCs and thereby enhancing antigen presentation, cytokine production, and the subsequent differentiation of antigen-specific T and B cells [139,140]. Consequently, persistent alterations in cDC development or responsiveness induced by repeated malaria infection could potentially modify the efficacy of vaccination by affecting adjuvant properties.

Hemozoin may be particularly relevant in this context. This malaria pigment can persist in phagocytic cells and tissues after the resolution of acute parasitemia, and previous exposure to hemozoin has been reported to interfere with subsequent immune responses, including responses to vaccination in experimental settings [141]. Because hemozoin can affect cDC maturation, cytokine production, and antigen-presenting functions, persistent hemozoin exposure could also influence the generation, differentiation, or functional state of cDC populations in the bone marrow and spleen. Thus, understanding how previous and repeated malaria infections reshape cDC biology may have practical implications for the design of vaccines intended for use in malaria-endemic regions. Future studies should determine whether particular cDC subsets become persistently activated, tolerized, or otherwise functionally reprogrammed following repeated malaria exposure, and whether these alterations influence responses to malaria vaccines as well as vaccines against unrelated pathogens. Such studies may ultimately contribute to the development of vaccination strategies and adjuvants that remain effective in populations repeatedly exposed to malaria.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The author declares no conflicts of interest.

References

1. Li, Q.; Liu, T.; Lv, K.; Liao, F.; Wang, J.; Tu, Y.; Chen, Q. Malaria: Past, Present, and Future. *Signal Transduct. Target. Ther.* **2025**, *10*, 188. [CrossRef] [PubMed]
2. Sato, S. Plasmodium—A Brief Introduction to the Parasites Causing Human Malaria and Their Basic Biology. *J. Physiol. Anthropol.* **2021**, *40*, 1. Correction in *J. Physiol. Anthropol*. **2021**, *40*, 3. [CrossRef] [PubMed]
3. Platon, L.; Lu, F.; Ménard, D. World Malaria Report 2025: Growing Biological Threats, Shrinking Resources. *Decod. Infect. Transm.* **2026**, *4*, 100076. [CrossRef]
4. Cowman, A.F.; Healer, J.; Marapana, D.; Marsh, K. Malaria: Biology and Disease. *Cell* **2016**, *167*, 610–624. [CrossRef] [PubMed]
5. Pohl, K.; Cockburn, I.A. Innate Immunity to Malaria: The Good, the Bad and the Unknown. *Front. Immunol.* **2022**, *13*, 914598. [CrossRef] [PubMed]
6. Olatunde, A.C.; Cornwall, D.H.; Roedel, M.; Lamb, T.J. Mouse Models for Unravelling Immunology of Blood Stage Malaria. *Vaccines* **2022**, *10*, 1525. [CrossRef] [PubMed]
7. De Niz, M.; Heussler, V.T. Rodent Malaria Models: Insights into Human Disease and Parasite Biology. *Curr. Opin. Microbiol.* **2018**, *46*, 93–101. [CrossRef] [PubMed]
8. Ghazanfari, N.; Mueller, S.N.; Heath, W.R. Cerebral Malaria in Mouse and Man. *Front. Immunol.* **2018**, *9*, 2016. [CrossRef] [PubMed]
9. Dormoi, J.; Amalvict, R.; Pradines, B. Beyond the Mouse: Organoids, Spheroids, and Organs-on-Chips as the (Inevitable) Future of Malaria Research? *Malar. J.* **2026**, *25*, 295. [CrossRef] [PubMed]
10. Cabeza-Cabrerizo, M.; Cardoso, A.; Minutti, C.M.; Pereira da Costa, M.; Reis Sousa, C. Dendritic Cells Revisited. *Annu. Rev. Immunol.* **2021**, *39*, 131–166. [CrossRef] [PubMed]
11. Ziegler-Heitbrock, L.; Ohteki, T.; Ginhoux, F.; Shortman, K.; Spits, H. Reclassifying Plasmacytoid Dendritic Cells as Innate Lymphocytes. *Nat. Rev. Immunol.* **2023**, *23*, 1–2. [CrossRef] [PubMed]
12. Reizis, B.; Idoyaga, J.; Dalod, M.; Barrat, F.; Naik, S.; Trinchieri, G.; Tussiwand, R.; Cella, M.; Colonna, M. Reclassification of Plasmacytoid Dendritic Cells as Innate Lymphocytes Is Premature. *Nat. Rev. Immunol.* **2023**, *23*, 336–337. [CrossRef] [PubMed]
13. Ghosh, D.; Stumhofer, J.S. The Spleen: "Epicenter" in Malaria Infection and Immunity. *J. Leukoc. Biol.* **2021**, *110*, 753–769. [CrossRef] [PubMed]
14. Gupta, A.; Kalkal, M.; Das, J. Emerging Role of Splenic Macrophage in Malaria Pathogenesis and Immunity. *Immun. Inflamm. Dis.* **2025**, *13*, e70258. [CrossRef] [PubMed]
15. Steiniger, B.S. Human Spleen Microanatomy: Why Mice Do Not Suffice. *Immunology* **2015**, *145*, 334–346. [CrossRef] [PubMed]
16. Liu, D.; Huo, J. Dendritic Cell Homeostasis in the Splenic Microenvironment. *Curr. Opin. Immunol.* **2026**, *101*, 102788. [CrossRef] [PubMed]
17. Bosteels, V.; Janssens, S. Striking a Balance: New Perspectives on Homeostatic Dendritic Cell Maturation. *Nat. Rev. Immunol.* **2025**, *25*, 125–140. [CrossRef] [PubMed]
18. Hilligan, K.L.; Ronchese, F. Antigen Presentation by Dendritic Cells and Their Instruction of CD4+ T Helper Cell Responses. *Cell. Mol. Immunol.* **2020**, *17*, 587–599. [CrossRef] [PubMed]
19. Ginhoux, F.; Guilliams, M.; Merad, M. Expanding Dendritic Cell Nomenclature in the Single-Cell Era. *Nat. Rev. Immunol.* **2022**, *22*, 67–68. [CrossRef] [PubMed]
20. Hirako, I.C.; Assis, P.A.; Galvão-Filho, B.; Luster, A.D.; Antonelli, L.R.; Gazzinelli, R.T. Monocyte-Derived Dendritic Cells in Malaria. *Curr. Opin. Microbiol.* **2019**, *52*, 139–150. [CrossRef] [PubMed]
21. Yin, X.; Chen, S.; Eisenbarth, S.C. Dendritic Cell Regulation of T Helper Cells. *Annu. Rev. Immunol.* **2021**, *39*, 759–790. [CrossRef] [PubMed]
22. Tamura, T.; Kimura, K.; Yui, K.; Yoshida, S. Reduction of Conventional Dendritic Cells during Plasmodium Infection Is Dependent on Activation Induced Cell Death by Type I and II Interferons. *Exp. Parasitol.* **2015**, *159*, 127–135. [CrossRef] [PubMed]
23. Schlitzer, A.; Ginhoux, F. Organization of the Mouse and Human DC Network. *Curr. Opin. Immunol.* **2014**, *26*, 90–99. [CrossRef] [PubMed]
24. Gazzinelli, R.T.; Kalantari, P.; Fitzgerald, K.A.; Golenbock, D.T. Innate Sensing of Malaria Parasites. *Nat. Rev. Immunol.* **2014**, *14*, 744–757. [CrossRef] [PubMed]
25. Gowda, D.C.; Wu, X. Parasite Recognition and Signaling Mechanisms in Innate Immune Responses to Malaria. *Front Immunol.* **2018**, *9*, 3006. [CrossRef] [PubMed]
26. Wang, Z.X.; Jiao, W.J.; Yang, Y.; Liu, H.L.; Wang, H.L. Role of Inflammasomes in Toxoplasma and Plasmodium Infections. *Parasites Vectors* **2024**, *17*, 466. [CrossRef] [PubMed]
27. Bettiol, E.; Van De Hoef, D.L.; Carapau, D.; Rodriguez, A. Efficient Phagosomal Maturation and Degradation of Plasmodium-Infected Erythrocytes by Dendritic Cells and Macrophages. *Parasite Immunol.* **2010**, *32*, 389–398. [CrossRef] [PubMed]

28. Krishnegowda, G.; Hajjar, A.M.; Zhu, J.; Douglass, E.J.; Uematsu, S.; Akira, S.; Woods, A.S.; Gowda, D.C. Induction of Proinflammatory Responses in Macrophages by the Glycosylphosphatidylinositols of Plasmodium Falciparum: Cell Signaling Receptors, Glycosylphosphatidylinositol (GPI) Structural Requirement, and Regulation of GPI Activity. *J. Biol. Chem.* **2005**, *280*, 8606–8616. [CrossRef] [PubMed]
29. Kumar, S.; Gowda, N.M.; Wu, X.; Gowda, R.N.; Gowda, D.C. CD36 Modulates Proinflammatory Cytokine Responses to Plasmodium Falciparum Glycosylphosphatidylinositols and Merozoites by Dendritic Cells. *Parasite Immunol.* **2012**, *34*, 372–382. [CrossRef] [PubMed]
30. Sharma, S.; DeOliveira, R.B.; Kalantari, P.; Parroche, P.; Goutagny, N.; Jiang, Z.; Chan, J.; Bartholomeu, D.C.; Lauw, F.; Hall, J.P.; et al. Innate Immune Recognition of an AT-Rich Stem-Loop DNA Motif in the Plasmodium Falciparum Genome. *Immunity* **2011**, *35*, 194–207. [CrossRef] [PubMed]
31. Yu, X.; Du, Y.; Cai, C.; Cai, B.; Zhu, M.; Xing, C.; Tan, P.; Lin, M.; Wu, J.; Li, J.; et al. Inflammasome Activation Negatively Regulates MyD88-IRF7 Type I IFN Signaling and Anti-Malaria Immunity. *Nat. Commun.* **2018**, *9*, 4964. [CrossRef] [PubMed]
32. Dalapati, T.; Moore, J.M. Hemozoin: A Complex Molecule with Complex Activities. *Curr. Clin. Microbiol. Rep.* **2021**, *8*, 87–102. [CrossRef] [PubMed]
33. Parroche, P.; Lauw, F.N.; Goutagny, N.; Latz, E.; Monks, B.G.; Visintin, A.; Halmen, K.A.; Lamphier, M.; Olivier, M.; Bartholomeu, D.C.; et al. Malaria Hemozoin Is Immunologically Inert but Radically Enhances Innate Responses by Presenting Malaria DNA to Toll-like Receptor 9. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 1919–1924. [CrossRef] [PubMed]
34. Pack, A.D.; Schwartzhoff, P.V.; Zacharias, Z.R.; Fernandez-Ruiz, D.; Heath, W.R.; Gurung, P.; Legge, K.L.; Janse, C.J.; Butler, N.S. Hemozoin-Mediated Inflammasome Activation Limits Long-Lived Anti-Malarial Immunity. *Cell Rep.* **2021**, *36*, 109586. [CrossRef] [PubMed]
35. Yap, X.Z.; Lundie, R.J.; Beeson, J.G.; O'Keeffe, M. Dendritic Cell Responses and Function in Malaria. *Front. Immunol.* **2019**, *10*, 357. [CrossRef] [PubMed]
36. Osii, R.S.; Otto, T.D.; Garside, P.; Ndungu, F.M.; Brewer, J.M. The Impact of Malaria Parasites on Dendritic Cell–T Cell Interaction. *Front. Immunol.* **2020**, *11*, 1597. [CrossRef] [PubMed]
37. Boura, M.; Frita, R.; Góis, A.; Carvalho, T.; Hänscheid, T. The Hemozoin Conundrum: Is Malaria Pigment Immune-Activating, Inhibiting, or Simply a Bystander? *Trends Parasitol.* **2013**, *29*, 469–476. [CrossRef] [PubMed]
38. Orengo, J.M.; Evans, J.E.; Bettiol, E.; Leliwa-Sytek, A.; Day, K.; Rodriguez, A. Plasmodium-Induced Inflammation by Uric Acid. *PLoS Pathog.* **2008**, *4*, e1000013. [CrossRef] [PubMed]
39. Orengo, J.M.; Leliwa-Sytek, A.; Evans, J.E.; Evans, B.; van de Hoef, D.; Nyako, M.; Day, K.; Rodriguez, A. Uric Acid Is a Mediator of the Plasmodium Falciparum-Induced Inflammatory Response. *PLoS ONE* **2009**, *4*, e5194. [CrossRef] [PubMed]
40. van de Hoef, D.L.; Coppens, I.; Holowka, T.; Ben Mamoun, C.; Branch, O.L.; Rodriguez, A. Plasmodium Falciparum-Derived Uric Acid Precipitates Induce Maturation of Dendritic Cells. *PLoS ONE* **2013**, *8*, e55584. [CrossRef] [PubMed]
41. Iwasaki, A.; Medzhitov, R. Toll-like Receptor Control of the Adaptive Immune Responses. *Nat. Immunol.* **2004**, *5*, 987–995. [CrossRef] [PubMed]
42. Ariffin, J.K.; Sweet, M.J. Differences in the Repertoire, Regulation and Function of Toll-like Receptors and Inflammasome-Forming Nod-like Receptors between Human and Mouse. *Curr. Opin. Microbiol.* **2013**, *16*, 303–310. [CrossRef] [PubMed]
43. Tamura, T.; Kimura, K.; Yuda, M.; Yui, K. Prevention of Experimental Cerebral Malaria by Flt3 Ligand during Infection with Plasmodium Berghei ANKA. *Infect. Immun.* **2011**, *79*, 3947–3956. [CrossRef] [PubMed]
44. Lundie, R.J.; de Koning-Ward, T.F.; Davey, G.M.; Nie, C.Q.; Hansen, D.S.; Lau, L.S.; Mintern, J.D.; Belz, G.T.; Schofield, L.; Carbone, F.R.; et al. Blood-Stage Plasmodium Infection Induces CD8+ T Lymphocytes to Parasite-Expressed Antigens, Largely Regulated by CD8alpha+ Dendritic Cells. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 14509–14514. [CrossRef]
45. Perry, J.A.; Rush, A.; Wilson, R.J.; Olver, C.S.; Avery, A.C. Dendritic Cells from Malaria-Infected Mice Are Fully Functional APC. *J. Immunol.* **2004**, *172*, 475–482. [CrossRef] [PubMed]
46. Perry, J.A.; Olver, C.S.; Burnett, R.C.; Avery, A.C. Cutting Edge: The Acquisition of TLR Tolerance during Malaria Infection Impacts T Cell Activation. *J. Immunol.* **2005**, *174*, 5921–5925. [CrossRef] [PubMed]
47. Soon, M.S.F.; Haque, A. Recent Insights into CD4+ Th Cell Differentiation in Malaria. *J. Immunol.* **2018**, *200*, 1965–1975. [CrossRef] [PubMed]
48. Kumar, R.; Loughland, J.R.; Ng, S.S.; Boyle, M.J.; Engwerda, C.R. The Regulation of CD4+ T Cells during Malaria. *Immunol. Rev.* **2020**, *293*, 70–87. [CrossRef] [PubMed]
49. Kurup, S.P.; Butler, N.S.; Harty, J.T. T Cell-Mediated Immunity to Malaria. *Nat. Rev. Immunol.* **2019**, *19*, 457–471. [CrossRef]
50. Voisine, C.; Mastelic, B.; Sponaas, A.M.; Langhorne, J. Classical CD11c+ Dendritic Cells, Not Plasmacytoid Dendritic Cells, Induce T Cell Responses to Plasmodium Chabaudi Malaria. *Int. J. Parasitol.* **2010**, *40*, 711–719. [CrossRef] [PubMed]
51. DeWalick, S.; Amante, F.H.; McSweeney, K.A.; Randall, L.M.; Stanley, A.C.; Haque, A.; Kuns, R.D.; MacDonald, K.P.A.; Hill, G.R.; Engwerda, C.R. Cutting Edge: Conventional Dendritic Cells Are the Critical APC Required for the Induction of Experimental Cerebral Malaria. *J. Immunol.* **2007**, *178*, 6033–6037. [CrossRef] [PubMed]

52. Ly, A.; Hansen, D.S. Development of B Cell Memory in Malaria. *Front. Immunol.* **2019**, *10*, 559. [CrossRef] [PubMed]
53. Obeng-Adjei, N.; Portugal, S.; Holla, P.; Li, S.; Sohn, H.; Ambegaonkar, A.; Skinner, J.; Bowyer, G.; Doumbo, O.K.; Traore, B.; et al. Malaria-Induced Interferon-γ Drives the Expansion of Tbethiatypical Memory B Cells. *PLoS Pathog.* **2017**, *13*, e1006576. [CrossRef] [PubMed]
54. Ryg-Cornejo, V.; Ioannidis, L.J.; Ly, A.; Chiu, C.Y.; Tellier, J.; Hill, D.L.; Preston, S.P.; Pellegrini, M.; Yu, D.; Nutt, S.L.; et al. Severe Malaria Infections Impair Germinal Center Responses by Inhibiting T Follicular Helper Cell Differentiation. *Cell Rep.* **2016**, *14*, 68–81. [CrossRef]
55. Draheim, M.; Wlodarczyk, M.F.; Crozat, K.; Saliou, J.M.; Alayi, T.D.; Tomavo, S.; Hassan, A.; Salvioni, A.; Demarta-Gatsi, C.; Sidney, J.; et al. Profiling MHC II Immunopeptidome of Blood-Stage Malaria Reveals That CDC1 Control the Functionality of Parasite-Specific CD4 T Cells. *EMBO Mol. Med.* **2017**, *9*, 1605–1621. [CrossRef]
56. Fernandez-Ruiz, D.; Lau, L.S.; Ghazanfari, N.; Jones, C.M.; Ng, W.Y.; Davey, G.M.; Berthold, D.; Holz, L.; Kato, Y.; Enders, M.H.; et al. Development of a Novel CD4+ TCR Transgenic Line That Reveals a Dominant Role for CD8+ Dendritic Cells and CD40 Signaling in the Generation of Helper and CTL Responses to Blood-Stage Malaria. *J. Immunol.* **2017**, *199*, 4165–4179. [CrossRef]
57. Ibraheem, Y.; Bayarsaikhan, G.; Macalinao, M.L.; Kimura, K.; Yui, K.; Aoshi, T.; Inoue, S.I. γδ T Cell-Mediated Activation of CDC1 Orchestrates CD4+ Th1 Cell Priming in Malaria. *Front. Immunol.* **2024**, *15*, 1426316. [CrossRef] [PubMed]
58. Mashayekhi, M.; Sandau, M.M.; Dunay, I.R.; Frickel, E.M.; Khan, A.; Goldszmid, R.S.; Sher, A.; Ploegh, H.L.; Murphy, T.L.; Sibley, L.D.; et al. CD8α+ Dendritic Cells Are the Critical Source of Interleukin-12 That Controls Acute Infection by Toxoplasma Gondii Tachyzoites. *Immunity* **2011**, *35*, 249–259. [CrossRef] [PubMed]
59. Villegas-Mendez, A.; Greig, R.; Shaw, T.N.; de Souza, J.B.; Gwyer Findlay, E.; Stumhofer, J.S.; Hafalla, J.C.R.; Blount, D.G.; Hunter, C.A.; Riley, E.M.; et al. IFN-γ–Producing CD4+ T Cells Promote Experimental Cerebral Malaria by Modulating CD8+ T Cell Accumulation within the Brain. *J. Immunol.* **2012**, *189*, 968–979. [CrossRef] [PubMed]
60. Tatsumi, N.; Tjitropranoto, A.; Davila-Pagan, A.; Kumamoto, Y. Functional Specialization and Collaboration of CDC2 Subsets in CD4+ T Cell Priming and Differentiation. *Immunol. Rev.* **2025**, *336*, e70069. [CrossRef] [PubMed]
61. Perez-Mazliah, D.; Langhorne, J. CD4 T-Cell Subsets in Malaria: Th1/Th2 Revisited. *Front. Immunol.* **2014**, *5*, 671. [CrossRef] [PubMed]
62. Langhorne, J.; Gillard, S.; Simon, B.; Slade, S.; Eichmann, K. Frequencies of $CD4^+$ T Cells Reactive with *Plasmodium Chabaudi Chabaudi*: Distinct Response Kinetics for Cells with T_{h1} and T_{h2} Characteristics during Infection. *Int. Immunol.* **1989**, *1*, 416–424. [CrossRef] [PubMed]
63. Wu, X.; Gowda, N.M.; Kawasawa, Y.I.; Gowda, D.C. A Malaria Protein Factor Induces IL-4 Production by Dendritic Cells via PI3K–Akt–NF-B Signaling Independent of MyD88/TRIF and Promotes Th2 Response. *J. Biol. Chem.* **2018**, *293*, 10425–10434. [CrossRef] [PubMed]
64. Pérez-Mazliah, D.; Nguyen, M.P.; Hosking, C.; McLaughlin, S.; Lewis, M.D.; Tumwine, I.; Levy, P.; Langhorne, J. Follicular Helper T Cells Are Essential for the Elimination of Plasmodium Infection. *eBioMedicine* **2017**, *24*, 216–230. [CrossRef] [PubMed]
65. Arroyo, E.N.; Pepper, M. B Cells Are Sufficient to Prime the Dominant CD4+ Tfh Response to Plasmodium Infection. *J. Exp. Med.* **2020**, *217*, e20190849. [CrossRef] [PubMed]
66. Liu, X.Q.; Stacey, K.J.; Horne-Debets, J.M.; Cridland, J.A.; Fischer, K.; Narum, D.; Mackay, F.; Pierce, S.K.; Wykes, M.N. Malaria Infection Alters the Expression of B-Cell Activating Factor Resulting in Diminished Memory Antibody Responses and Survival. *Eur. J. Immunol.* **2012**, *42*, 3291–3301. [CrossRef] [PubMed]
67. Chen, Y.; Chen, M.; Liu, Y.; Li, Q.; Xue, Y.; Liu, L.; Liang, R.; Xiong, Y.; Zhao, J.; Chen, J.; et al. BAFF Promotes Follicular Helper T Cell Development and Germinal Center Formation through BR3 Signal. *JCI Insight* **2024**, *9*, e183400. [CrossRef] [PubMed]
68. Qi, H.; Egen, J.G.; Huang, A.Y.C.; Germain, R.N. Extrafollicular Activation of Lymph Node B Cells by Antigen-Bearing Dendritic Cells. *Science* **2006**, *312*, 1672–1676. [CrossRef] [PubMed]
69. Le Roux, D.; Le Bon, A.; Dumas, A.; Taleb, K.; Sachse, M.; Sikora, R.; Julithe, M.; Benmerah, A.; Bismuth, G.; Niedergang, F. Antigen Stored in Dendritic Cells after Macropinocytosis Is Released Unprocessed from Late Endosomes to Target B Cells. *Blood* **2012**, *119*, 95–105. [CrossRef]
70. Keswani, T.; Bhattacharyya, A. Differential Role of T Regulatory and Th17 in Swiss Mice Infected with Plasmodium Berghei ANKA and Plasmodium Yoelii. *Exp. Parasitol.* **2014**, *141*, 82–92. [CrossRef] [PubMed]
71. Ishida, H.; Matsuzaki-Moriya, C.; Imai, T.; Yanagisawa, K.; Nojima, Y.; Suzue, K.; Hirai, M.; Iwakura, Y.; Yoshimura, A.; Hamano, S.; et al. Development of Experimental Cerebral Malaria Is Independent of IL-23 and IL-17. *Biochem. Biophys. Res. Commun.* **2010**, *402*, 790–795. [CrossRef]
72. Ioannidis, L.J.; Pietrzak, H.M.; Ly, A.; Utami, R.A.S.; Eriksson, E.M.; Studniberg, S.I.; Abeysekera, W.; Li-Wai-Suen, C.S.N.; Sheerin, D.; Healer, J.; et al. High-Dimensional Mass Cytometry Identifies T Cell and B Cell Signatures Predicting Reduced Risk of Plasmodium Vivax Malaria. *JCI Insight* **2021**, *6*, e148086. [CrossRef]

73. Sakaguchi, S.; Yamaguchi, T.; Nomura, T.; Ono, M. Regulatory T Cells and Immune Tolerance. *Cell* **2008**, *133*, 775–787. [CrossRef] [PubMed]
74. Hisaeda, H.; Maekawa, Y.; Iwakawa, D.; Okada, H.; Himeno, K.; Kishihara, K.; Tsukumo, S.I.; Yasutomo, K. Escape of Malaria Parasites from Host Immunity Requires CD4 +CD25+ Regulatory T Cells. *Nat. Med.* **2004**, *10*, 29–30. [CrossRef] [PubMed]
75. Amante, F.H.; Stanley, A.C.; Randall, L.M.; Zhou, Y.; Haque, A.; McSweeney, K.; Waters, A.P.; Janse, C.J.; Good, M.F.; Hill, G.R.; et al. A Role for Natural Regulatory T Cells in the Pathogenesis of Experimental Cerebral Malaria. *Am. J. Pathol.* **2007**, *171*, 548–559. [CrossRef]
76. Yilmazer, A.; Zevla, D.M.; Malmkvist, R.; Rodríguez, C.A.B.; Undurraga, P.; Kirgin, E.; Boernert, M.; Voehringer, D.; Kershaw, O.; Schlenner, S.; et al. Selective Ablation of Thymic and Peripheral Foxp3+ Regulatory T Cell Development. *Front. Immunol.* **2023**, *14*, 1298938. [CrossRef]
77. Loevenich, K.; Ueffing, K.; Abel, S.; Hose, M.; Matuschewski, K.; Westendorf, A.M.; Buer, J.; Hansen, W. DC-Derived IL-10 Modulates pro-Inflammatory Cytokine Production and Promotes Induction of CD4+IL-10+ Regulatory T Cells during Plasmodium Yoelii Infection. *Front. Immunol.* **2017**, *8*, 152. [CrossRef] [PubMed]
78. Boyle, M.J.; Jagannathan, P.; Bowen, K.; McIntyre, T.I.; Vance, H.M.; Farrington, L.A.; Schwartz, A.; Nankya, F.; Naluwu, K.; Wamala, S.; et al. The Development of Plasmodium Falciparum-Specific IL10 CD4 T Cells and Protection from Malaria in Children in an Area of High Malaria Transmission. *Front. Immunol.* **2017**, *8*, 1329. [CrossRef]
79. Walther, M.; Jeffries, D.; Finney, O.C.; Njie, M.; Ebonyi, A.; Deininger, S.; Lawrence, E.; Ngwa-Amambua, A.; Jayasooriya, S.; Cheeseman, I.H.; et al. Distinct Roles for FOXP3+ and FOXP3- CD4+ T Cells in Regulating Cellular Immunity to Uncomplicated and Severe Plasmodium Falciparum Malaria. *PLoS Pathog.* **2009**, *5*, e1000364. [CrossRef] [PubMed]
80. Hassert, M.; Arumugam, S.; Harty, J.T. Memory CD8+ T Cell-Mediated Protection against Liver-Stage Malaria. *Immunol. Rev.* **2023**, *316*, 84–103. [CrossRef] [PubMed]
81. Junqueira, C.; Barbosa, C.R.R.; Costa, P.A.C.; Teixeira-Carvalho, A.; Castro, G.; Sen Santara, S.; Barbosa, R.P.; Dotiwala, F.; Pereira, D.B.; Antonelli, L.R.; et al. Cytotoxic CD8+ T Cells Recognize and Kill Plasmodium Vivax–Infected Reticulocytes. *Nat. Med.* **2018**, *24*, 1330–1336. [CrossRef] [PubMed]
82. Sharma, I.; Kataria, P.; Das, J. Cerebral Malaria Pathogenesis: Dissecting the Role of CD4+ and CD8+ T-Cells as Major Effectors in Disease Pathology. *Int. Rev. Immunol.* **2024**, *43*, 309–325. [CrossRef] [PubMed]
83. Zhao, H.; Aoshi, T.; Kawai, S.; Mori, Y.; Konishi, A.; Ozkan, M.; Fujita, Y.; Haseda, Y.; Shimizu, M.; Kohyama, M.; et al. Olfactory Plays a Key Role in Spatiotemporal Pathogenesis of Cerebral Malaria. *Cell Host Microbe* **2014**, *15*, 551–563. [CrossRef] [PubMed]
84. Howland, S.W.; Poh, C.M.; Rénia, L. Activated Brain Endothelial Cells Cross-Present Malaria Antigen. *PLoS Pathog.* **2015**, *11*, e1004963. [CrossRef] [PubMed]
85. Tamura, T.; Akbari, M.; Kimura, K.; Kimura, D.; Yui, K. Flt3 Ligand Treatment Modulates Parasitemia during Infection with Rodent Malaria Parasites via MyD88- and IFN-Gamma-Dependent Mechanisms. *Parasite Immunol.* **2014**, *36*, 87–99. [CrossRef] [PubMed]
86. Hänscheid, T.; Egan, T.J.; Grobusch, M.P. Haemozoin: From Melatonin Pigment to Drug Target, Diagnostic Tool, and Immune Modulator. *Lancet Infect. Dis.* **2007**, *7*, 675–685. [CrossRef] [PubMed]
87. Pisciotta, J.M.; Scholl, P.F.; Shuman, J.L.; Shualev, V.; Sullivan, D.J. Quantitative Characterization of Hemozoin in Plasmodium Berghei and Vivax. *Int. J. Parasitol. Drugs Drug Resist.* **2017**, *7*, 110–119. [CrossRef] [PubMed]
88. Chua, C.L.L.; Ng, I.M.J.; Yap, B.J.M.; Teo, A. Factors Influencing Phagocytosis of Malaria Parasites: The Story so Far. *Malar. J.* **2021**, *20*, 319. [CrossRef] [PubMed]
89. McGilvray, I.D.; Serghides, L.; Kapus, A.; Rotstein, O.D.; Kain, K.C. Nonopsonic Monocyte/Macrophage Phagocytosis of Plasmodium Falciparum–Parasitized Erythrocytes: A Role for CD36 in Malarial Clearance. *Blood* **2000**, *96*, 3231–3240. [CrossRef]
90. Wu, X.; Gowda, N.M.; Gowda, D.C. Phagosomal Acidification Prevents Macrophage Inflammatory Cytokine Production to Malaria, and Dendritic Cells Are the Major Source at the Early Stages of Infection: Implication for Malaria Protective Immunity Development. *J. Biol. Chem.* **2015**, *290*, 23135–23147. [CrossRef] [PubMed]
91. Falkenstein, J.; Ninnemann, A.; Hose, M.; Elwy, A.; Lang, K.S.; Matuschewski, K.; Buer, J.; Westendorf, A.M.; Hansen, W. Red Pulp Macrophages Clear Parasites, While Marginal Metallophilic and Marginal Zone Macrophages Support CD4+ T Cell Activation during Plasmodium Yoelii Infection. *Front. Immunol.* **2025**, *16*, 1607201. [CrossRef] [PubMed]
92. Ng, S.S.; Engwerda, C.R. Innate Lymphocytes and Malaria—Players or Spectators? *Trends Parasitol.* **2019**, *35*, 154–162. [CrossRef] [PubMed]
93. Dantzler, K.W.; Jagannathan, P. γδ T Cells in Antimalarial Immunity: New Insights Into Their Diverse Functions in Protection and Tolerance. *Front. Immunol.* **2018**, *9*, 2445. [CrossRef] [PubMed]
94. Deroost, K.; Langhorne, J. Gamma/Delta T Cells and Their Role in Protection Against Malaria. *Front. Immunol.* **2018**, *9*, 2973. [CrossRef] [PubMed]

95. Goodier, M.; Krause-Jauer, M.; Sanni, A.; Massougbodji, A.; Sadeler, B.-C.; Mitchell, G.H.; Modolell, M.; Eichmann, K.; Langhorne, J. γδ T Cells in the Peripheral Blood of Individuals from an Area of Holoendemic Plasmodium Falciparum Transmission. *Trans. R. Soc. Trop. Med. Hyg.* **1993**, *87*, 692–696. [CrossRef]
96. Zaidi, I.; Diallo, H.; Conteh, S.; Robbins, Y.; Kolasny, J.; Orr-Gonzalez, S.; Carter, D.; Butler, B.; Lambert, L.; Brickley, E.; et al. γδ T Cells Are Required for the Induction of Sterile Immunity during Irradiated Sporozoite Vaccinations. *J. Immunol.* **2017**, *199*, 3781–3788. [CrossRef] [PubMed]
97. Le, S.; Dooley, N.; Murphy, D.; Liu, S.; Gandolfo, L.C.; Ge, Z.; May, R.; Cozijnsen, A.; Burn, T.N.; Jennison, C.; et al. γδ T Cell-Derived IL-4 Initiates CD8+ T Cell Immunity. *Nat. Immunol.* **2026**, *27*, 295–307. [CrossRef]
98. Ismaili, J.; Olislagers, V.; Poupot, R.; Fournié, J.-J.; Goldman, M. Human γδ T Cells Induce Dendritic Cell Maturation. *Clin. Immunol.* **2002**, *103*, 296–302. [CrossRef] [PubMed]
99. Dunne, M.R.; Madrigal-Estebas, L.; Tobin, L.M.; Doherty, D.G. (E)-4-Hydroxy-3-Methyl-but-2 Enyl Pyrophosphate-Stimulated Vγ9Vδ2 T Cells Possess T Helper Type 1-Promoting Adjuvant Activity for Human Monocyte-Derived Dendritic Cells. *Cancer Immunol. Immunother.* **2010**, *59*, 1109–1120. [CrossRef] [PubMed]
100. Mehrani, Y.; Morovati, S.; Keivan, F.; Tajik, T.; Forouzanpour, D.; Shojaei, S.; Bridle, B.W.; Karimi, K. Dendritic Cells and Their Crucial Role in Modulating Innate Lymphoid Cells for Treating and Preventing Infectious Diseases. *Pathogens* **2025**, *14*, 794. [CrossRef] [PubMed]
101. Ivanova, D.L.; Denton, S.L.; Fettel, K.D.; Sondgeroth, K.S.; Gutierrez, J.M.; Bangoura, B.; Dunay, I.R.; Gigley, J.P. Innate Lymphoid Cells in Protection, Pathology, and Adaptive Immunity during Apicomplexan Infection. *Front. Immunol.* **2019**, *10*, 196. [CrossRef] [PubMed]
102. Neill, D.R.; Fallon, P.G. Innate Lymphoid Cells and Parasites: Ancient Foes with Shared History. *Parasite Immunol.* **2018**, *40*, e12513. [CrossRef] [PubMed]
103. Burrack, K.S.; Hart, G.T.; Hamilton, S.E. Contributions of Natural Killer Cells to the Immune Response against Plasmodium. *Malar. J.* **2019**, *18*, 321. [CrossRef] [PubMed]
104. Artavanis-Tsakonas, K.; Eleme, K.; McQueen, K.L.; Cheng, N.W.; Parham, P.; Davis, D.M.; Riley, E.M. Activation of a Subset of Human NK Cells upon Contact with *Plasmodium Falciparum* -Infected Erythrocytes. *J. Immunol.* **2003**, *171*, 5396–5405. [CrossRef] [PubMed]
105. Odera, D.O.; Tuju, J.; Mwai, K.; Nkumama, I.N.; Fürle, K.; Chege, T.; Kimathi, R.; Diehl, S.; Musasia, F.K.; Rosenkranz, M.; et al. Anti-Merozoite Antibodies Induce Natural Killer Cell Effector Function and Are Associated with Immunity against Malaria. *Sci. Transl. Med.* **2023**, *15*, eabn5993. [CrossRef] [PubMed]
106. Ing, R.; Stevenson, M.M. Dendritic Cell and NK Cell Reciprocal Cross Talk Promotes Gamma Interferon-Dependent Immunity to Blood-Stage Plasmodium Chabaudi AS Infection in Mice. *Infect. Immun.* **2009**, *77*, 770–782. [CrossRef] [PubMed]
107. Ryg-Cornejo, V.; Nie, C.Q.; Bernard, N.J.; Lundie, R.J.; Evans, K.J.; Crabb, B.S.; Schofield, L.; Hansen, D.S. NK Cells and Conventional Dendritic Cells Engage in Reciprocal Activation for the Induction of Inflammatory Responses during Plasmodium Berghei ANKA Infection. *Immunobiology* **2013**, *218*, 263–271. [CrossRef] [PubMed]
108. O'Sullivan, T.E. Dazed and Confused: NK Cells. *Front. Immunol.* **2019**, *10*, 2235. [CrossRef] [PubMed]
109. Vivier, E.; Artis, D.; Colonna, M.; Diefenbach, A.; Di Santo, J.P.; Eberl, G.; Koyasu, S.; Locksley, R.M.; McKenzie, A.N.J.; Mebius, R.E.; et al. Innate Lymphoid Cells: 10 Years On. *Cell* **2018**, *174*, 1054–1066. [CrossRef] [PubMed]
110. Palomo, J.; Quesniaux, V.F.J.; Togbe, D.; Reverchon, F.; Ryffel, B. Unravelling the Roles of Innate Lymphoid Cells in Cerebral Malaria Pathogenesis. *Parasite Immunol.* **2018**, *40*, e12502. [CrossRef] [PubMed]
111. Besnard, A.G.; Guabiraba, R.; Niedbala, W.; Palomo, J.; Reverchon, F.; Shaw, T.N.; Couper, K.N.; Ryffel, B.; Liew, F.Y. IL-33-Mediated Protection against Experimental Cerebral Malaria Is Linked to Induction of Type 2 Innate Lymphoid Cells, M2 Macrophages and Regulatory T Cells. *PLoS Pathog.* **2015**, *11*, e1004607. [CrossRef] [PubMed]
112. Mastelic, B.; do Rosario, A.P.F.; Veldhoen, M.; Renauld, J.C.; Jarra, W.; Sponaas, A.M.; Roetynck, S.; Stockinger, B.; Langhorne, J. Il-22 Protects against Liver Pathology and Lethality of an Experimental Blood-Stage Malaria Infection. *Front. Immunol.* **2012**, *3*, 85. [CrossRef] [PubMed]
113. Vanderkerken, M.; Baptista, A.P.; De Giovanni, M.; Fukuyama, S.; Browaeys, R.; Scott, C.L.; Norris, P.S.; Eberl, G.; Di Santo, J.P.; Vivier, E.; et al. ILC3s Control Splenic CDC Homeostasis via Lymphotoxin Signaling. *J. Exp. Med.* **2021**, *218*, e20190835. [CrossRef]
114. de Jong, R.M.; Tebeje, S.K.; Meerstein-Kessel, L.; Tadesse, F.G.; Jore, M.M.; Stone, W.; Bousema, T. Immunity against Sexual Stage Plasmodium Falciparum and Plasmodium Vivax Parasites. *Immunol. Rev.* **2020**, *293*, 190–215. [CrossRef] [PubMed]
115. Kengne-Ouafo, J.A.; Sutherland, C.J.; Binka, F.N.; Awandare, G.A.; Urban, B.C.; Dinko, B. Immune Responses to the Sexual Stages of Plasmodium Falciparum Parasites. *Front. Immunol.* **2019**, *10*, 136. [CrossRef] [PubMed]
116. Corbett, Y.; Parapini, S.; Perego, F.; Messina, V.; Delbue, S.; Misiano, P.; Falchi, M.; Silvestrini, F.; Taramelli, D.; Basilico, N.; et al. Phagocytosis and Activation of Bone Marrow-derived Macrophages by Plasmodium Falciparum Gametocytes. *Malar. J.* **2021**, *20*, 81. [CrossRef]

117. Bansal, G.P.; Kumar, N. Immune Mechanisms Targeting Malaria Transmission: Opportunities for Vaccine Development. *Expert Rev. Vaccines* **2024**, *23*, 645–654. [CrossRef] [PubMed]
118. Venugopal, K.; Hentzschel, F.; Valkiūnas, G.; Marti, M. Plasmodium Asexual Growth and Sexual Development in the Haematopoietic Niche of the Host. *Nat. Rev. Microbiol.* **2020**, *18*, 177–189. [CrossRef] [PubMed]
119. Gamain, B.; Chêne, A.; Viebig, N.K.; Tuikue Ndam, N.; Nielsen, M.A. Progress and Insights Toward an Effective Placental Malaria Vaccine. *Front. Immunol.* **2021**, *12*, 634508. [CrossRef] [PubMed]
120. Gamain, B.; Smith, J.D.; Viebig, N.K.; Gysin, J.; Scherf, A. Pregnancy-Associated Malaria: Parasite Binding, Natural Immunity and Vaccine Development. *Int. J. Parasitol.* **2007**, *37*, 273–283. [CrossRef] [PubMed]
121. Chua, C.L.L.; Khoo, S.K.M.; Ong, J.L.E.; Ramireddi, G.K.; Yeo, T.W.; Teo, A. Malaria in Pregnancy: From Placental Infection to Its Abnormal Development and Damage. *Front. Microbiol.* **2021**, *12*, 777343. [CrossRef] [PubMed]
122. Kobia, F.M.; Maiti, K.; Obimbo, M.M.; Smith, R.; Gitaka, J. Potential Pharmacologic Interventions Targeting TLR Signaling in Placental Malaria. *Trends Parasitol.* **2022**, *38*, 513–524. [CrossRef] [PubMed]
123. Reis, A.S.; Barboza, R.; Murillo, O.; Barateiro, A.; Peixoto, E.P.M.; Lima, F.A.; Gomes, V.M.; Dombrowski, J.G.; Leal, V.N.C.; Araujo, F.; et al. Inflammasome Activation and IL-1 Signaling during Placental Malaria Induce Poor Pregnancy Outcomes. *Sci. Adv.* **2020**, *6*, eaax6346. [CrossRef]
124. Barateiro, A.; Pereira, M.L.M.; Epiphanio, O.; Marinho, C.R.F. Contribution of Murine Models to the Study of Malaria during Pregnancy. *Front. Microbiol.* **2019**, *10*, 1369. [CrossRef] [PubMed]
125. Hviid, L.; Marinho, C.R.F.; Staalsoe, T.; Penha-Gonçalves, C. Of Mice and Women: Rodent Models of Placental Malaria. *Trends Parasitol.* **2010**, *26*, 412–419. [CrossRef] [PubMed]
126. Barboza, R.; Lima, F.A.; Reis, A.S.; Murillo, O.J.; Peixoto, E.P.M.; Bandeira, C.L.; Fotoran, W.L.; Sardinha, L.R.; Wunderlich, G.; Bevilacqua, E.; et al. TLR4-Mediated Placental Pathology and Pregnancy Outcome in Experimental Malaria. *Sci. Rep.* **2017**, *7*, 8623. Correction in *Sci. Rep.* **2018**, *8*, 4275. [CrossRef]
127. Ryg-Cornejo, V.; Ly, A.; Hansen, D.S. Immunological Processes Underlying the Slow Acquisition of Humoral Immunity to Malaria. *Parasitology* **2016**, *143*, 199–207. [CrossRef] [PubMed]
128. Bediako, Y.; Adams, R.; Reid, A.J.; Valletta, J.J.; Ndungu, F.M.; Sodenkamp, J.; Mwacharo, J.; Ngoi, J.M.; Kimani, D.; Kai, O.; et al. Repeated Clinical Malaria Episodes Are Associated with Modification of the Immune System in Children. *BMC Med.* **2019**, *17*, 60. [CrossRef]
129. Frimpong, A.; Amponsah, J.; Adjokatseh, A.S.; Agyemang, D.; Bentum-Ennin, L.; Ofori, E.A.; Kyei-Baafour, E.; Akyea-Mensah, K.; Adu, B.; Mensah, G.I.; et al. Asymptomatic Malaria Infection Is Maintained by a Balanced Pro- and Anti-Inflammatory Response. *Front. Microbiol.* **2020**, *11*, 559255. Corrigendum in *Front. Microbiol.* **2021**, *12*, 686435. [CrossRef]
130. Netea, M.G.; Joosten, L.A.B.; Latz, E.; Mills, K.H.G.; Natoli, G.; Stunnenberg, H.G.; O'Neill, L.A.J.; Xavier, R.J. Trained Immunity: A Program of Innate Immune Memory in Health and Disease. *Science* **2016**, *352*, aaf1098. [CrossRef] [PubMed]
131. Schrum, J.E.; Crabtree, J.N.; Dobbs, K.R.; Kiritsy, M.C.; Reed, G.W.; Gazzinelli, R.T.; Netea, M.G.; Kazura, J.W.; Dent, A.E.; Fitzgerald, K.A.; et al. Cutting Edge: Plasmodium Falciparum Induces Trained Innate Immunity. *J. Immunol.* **2018**, *200*, 1243–1248. [CrossRef]
132. Boyle, M.J.; Engwerda, C.R.; Jagannathan, P. The Impact of Plasmodium-Driven Immunoregulatory Networks on Immunity to Malaria. *Nat. Rev. Immunol.* **2024**, *24*, 637–653. [CrossRef] [PubMed]
133. Adachi, R.; Tamura, T. Plasmodium Infection Cure Cycles Induce Modulation of Conventional Dendritic Cells. *Microbiol. Immunol.* **2020**, *64*, 377–386. [CrossRef] [PubMed]
134. Adachi, R.; Tamura, T. Plasmodium Infection–Cure Cycles Increase the Capacity of Phagocytosis in Conventional Dendritic Cells. *Pathogens* **2023**, *12*, 1262. [CrossRef] [PubMed]
135. Abuga, K.M.; Jones-Warner, W.; Hafalla, J.C.R. Immune Responses to Malaria Pre-Erythrocytic Stages: Implications for Vaccine Development. *Parasite Immunol.* **2021**, *43*, e12795. [CrossRef] [PubMed]
136. Coulibaly, D.; Kone, A.K.; Traore, K.; Niangaly, A.; Kouriba, B.; Arama, C.; Zeguime, A.; Dolo, A.; Lyke, K.E.; Plowe, C.V.; et al. PfSPZ-CVac Malaria Vaccine Demonstrates Safety among Malaria-Experienced Adults: A Randomized, Controlled Phase 1 Trial. *eClinicalMedicine* **2022**, *52*, 101579. [CrossRef] [PubMed]
137. Dobbs, K.R.; Atieli, H.E.; Valim, C.; Beeson, J.G. Previous Malaria Exposures and Immune Dysregulation: Developing Strategies To Improve Malaria Vaccine Efficacy in Young Children. *Am. J. Trop. Med. Hyg.* **2024**, *110*, 627–630. [CrossRef] [PubMed]
138. Zirimenya, L.; Natukunda, A.; Nassuuna, J.; Kabagenyi, J.; Nkurunungi, G.; Elliott, A.M.; Webb, E.L. The Effect of Malaria on Responses to Unrelated Vaccines in Animals and Humans: A Systematic Review and Meta-Analysis. *Parasite Immunol.* **2024**, *46*, e13067. [CrossRef] [PubMed]
139. Coffman, R.L.; Sher, A.; Seder, R.A. Vaccine Adjuvants: Putting Innate Immunity to Work. *Immunity* **2010**, *33*, 492–503. [CrossRef] [PubMed]

140. Zhao, T.; Cai, Y.; Jiang, Y.; He, X.; Wei, Y.; Yu, Y.; Tian, X. Vaccine Adjuvants: Mechanisms and Platforms. *Signal Transduct. Target. Ther.* **2023**, *8*, 283. [CrossRef] [PubMed]
141. Hassert, M.; Drewry, L.L.; Pewe, L.L.; Hancox, L.S.; He, R.; Arumugam, S.; Mix, M.R.; Salem, A.K.; Harty, J.T. MRNA Vaccination Overcomes Haemozoin-Mediated Impairment of Whole-Parasite Malaria Vaccines in Mice. *Nat. Microbiol.* **2026**, *11*, 718–730. [CrossRef] [PubMed]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.