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Review

The interleukin-10 family: Major regulators of the immune response against *Plasmodium falciparum* infections

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ABSTRACT

Malaria caused by the *Plasmodium falciparum* strain is more severe because of this protozoan's ability to disrupt the physiology of host cells during the blood stages of development by initiating the production of the interleukin-10 (IL-10) family of cytokines. *P. falciparum* feeds on hemoglobin and causes host cells to adhere to the walls of blood vessels by remodeling their composition. IL-10 is produced by CD4+ T cells that inhibits antigen-presenting cells' activity to prevent inflammation. This cytokine and its family members are crucial in promoting malarial infection by inhibiting the host's protective immune response, thus initiating *Plasmodium* parasitemia. IL-10 is also responsible for preventing severe pathology during *Plasmodium* infection and initiates several signaling pathways to alter the physiology of host cells during malarial infection. This review summarizes the critical aspects of *P. falciparum* infection, including its role in signaling pathways for cytokine exudation, its effect on microRNA, the human immune response in malaria, and the role played by the liver hormone hepcidin. Moreover, future aspects of vaccine development and therapeutic strategies to combat *P. falciparum* infections are also discussed in detail.

Contents

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1. Introduction

Malarial infections are caused by *Plasmodium* (a protozoan-class sporozoan parasite) and transmitted by mosquitoes (WHO, 2020). *P. falciparum* is the major malarial species (WHO, 2016), which caused approximately 229 million cases of malaria, with 409,000 fatalities in Africa in 2019 (WHO, 2020). The intricate life cycle of *P. falciparum* (Fig. 1) involves an insect vector and a vertebrate (human) host: female *Anopheles* mosquitoes transmit *Plasmodium* parasites between individuals. *P. falciparum* is a daunting parasite that hinders the advancement of vaccines (Votýpka et al., 2017; Abosalif et al., 2019) as immunity takes several years to develop, making it difficult to combat this infection. Furthermore, naturally acquired immunity is antigen-specific, whereas different strains of *Plasmodium* display antigenic variation (Plebanski and Hill, 2000). In addition, pediatric patients living in malarial-endemic zones are more likely to fall ill, and other factors including genetics, pregnancy, nutrition, and co-infections also affect antimalarial immunity (Plebanski and Hill, 2000). Despite existing for thousands of years, *Plasmodium* still elicits a wide range of immune responses from the host involving specific cytokines, antibodies, and cell types (Mandala et al., 2021).

Anti-inflammatory cytokine (AIC) and pro-inflammatory cytokine (PIC) responses determine the level of containment of malarial infection (Rovira-Vallbona et al., 2012). Multiple exposures to malaria may change the host immune system's responses, pushing it toward an anti-inflammatory profile associated with silent infections (Kimenyi et al., 2019). However, it is still unclear how *Plasmodium* antibodies and cytokine responses (anti-inflammatory mediators) are sustained to prevent symptoms from occurring throughout an infection. It has been proposed that chronic parasitemia in asymptomatic individuals is necessary for antimalarial immunity, and its disruption could increase host vulnerability to severe illness (Fogang et al., 2022).

It is believed that IL-10 is a potent AIC that is capable of protecting the host by counteracting the inflammatory response to a pathogen attack (Freitas do Rosário et al., 2012; Junaid et al., 2021). T helper 2 (Th2) cells were the first to be identified as IL-

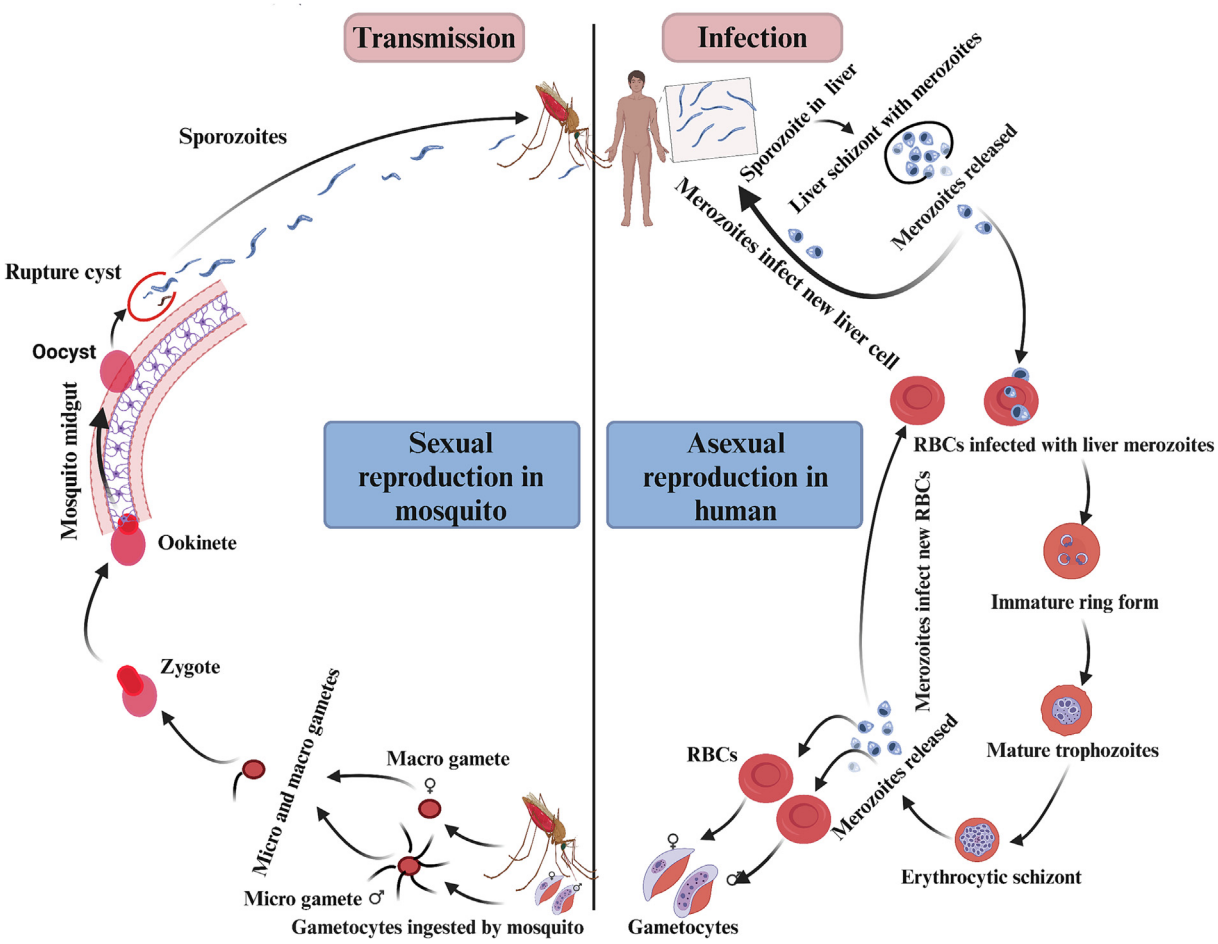

Fig. 1. Life cycle of *P. falciparum*. As an infected mosquito vector bites a human host, sporozoites are released and travel from the liver to the bloodstream, where they grow and multiply. Malarial gametocytes are ingested and mature into male microgametes and female macrogametes in the vector's midgut. Their union produces a zygote, which grows into an ookinete, enters the insect's intestinal wall, and becomes a spherical oocyst. The oocyst's sporoblasts produce sporozoites, which travel to the mosquito's salivary glands and infect another human host.

10 producers; since then, other cell types involved in innate and adaptive immune responses, including Treg cells, Tfh cells, regulatory B cells (Bregs), CD8+ T cells, Th1 cells, and Th17 cells have been identified. In addition to B and T lymphocytes, natural killer (NK) cells, mast cells, macrophages (MCs), dendritic cells (DCs), and neutrophils all release IL-10 (Li et al., 1999). A plethora of evidence indicates that the serum of malaria patients has elevated IL-10 levels; moreover, it plays an important immunoregulatory role in autoimmune disorders (DiLillo et al., 2010).

During *Plasmodium* infection, Bregs have an immunomodulatory function that appears to be influenced by the virulence of particular parasite species (Han et al., 2018). Furthermore, neither murine nor human malarial parasites have revealed cell surface markers specific to Bregs and their role in fatal and non-fatal malaria (Kalkal et al., 2022). Therefore, it is necessary to study this unclassified subset of B cells throughout the disease to determine how infection susceptibility and resistance are affected.

Iron, which is required by erythroblasts, is also responsible for *P. falciparum* infections. Iron is stored in the bone marrow by MCs and plays a vital role in producing red blood cells, as the absence of iron would result in anemia. Hepcidin, a liver hormone that regulates iron homeostasis, blocks iron absorption, resulting in lower ferroprotein levels in MCs and enterocytes (Nemeth et al., 2004b). Increased hepcidin production can be attributed to inflammation or a depletion of iron stores (Armitage et al., 2011), whereas iron deficiency with low oxygen levels suppresses it (Piperno et al., 2011). Hepcidin inhibits *Plasmodium* liver-stage growth and is secreted during parasitemia (Huang et al., 2014). Thus, infected RBCs may induce hepcidin formation by peripheral blood mononuclear cells (PBMCs). This review focuses on the role of IL-10 cytokines in regulating *P. falciparum* infection and the development of overall immunity in host cells. Furthermore, immune signaling pathways, host microRNA (miRNA) expression, the role of hepcidin in malarial anemia, and aspects of vaccine development are discussed. For this purpose, 140 articles were retrieved from PubMed and Google Scholar. The keywords searched were "IL-10 and malaria, interleukin 10, immune regulation and *Plasmodium* infection, cytokines in malarial infection, immune response, and malaria" for all the available years. We selected 59 studies for this review, while the remaining articles were rejected due to their duplicity or lack of relevance.

2. Functions of the IL-10 family of cytokines

The IL-20 subfamily, a subset of the larger IL-10 family, includes IL-19, IL-20, IL-22, IL-24, and IL-26. The IL-20 receptor (IL-20R) subunits IL-20RA, IL-20RB, IL-10RB, and IL-22RA1 work together to form heterodimeric receptors that transmit signals for IL-10 formation (Rutz et al., 2014). The cytokines IL-19, IL-20, and IL-24 are collectively known as the IL-20 receptor cytokines due to their shared use of the IL-20RA/IL-20RB receptor complex for signal transmission. The IL-20RB/IL-22RA1 receptor complex is also involved in signal transduction following IL-20 and IL-24 binding. IL-22 and IL-26 signaling are regulated by the IL-22RA1/IL-10RB receptor complex and the IL-20RA/IL-10RB complex (Rutz et al., 2014). Taken together, the IL-10 family regulates signaling pathways to produce a particular immune response against malarial infections and affect a patient's overall condition during the course of malarial disease.

2.1. IL-20R cytokines

By binding to the IL-20RA/IL-20RB or IL-22RA1/IL-22RA3 receptor complexes, IL-19, IL-20, and IL-24 trigger intracellular signaling (Wirtz and Keller, 2016). IL-20RB, a subunit of IL-20R, also inhibits T-cell responses. Therefore, T cells respond to in vitro stimulation by producing more IL-2 and IFN-γ and less IL-10 when the quantities of IL-20RB, CD4+, and CD8+ are not adequate (Wahl et al., 2009).

2.2. IL-19

Many immune cells, such as T cells and myeloid cells, are regulated by IL-19. In addition to being produced by Th2 cells, IL-19 promotes the development and production of other Th2 cytokines (Liao et al., 2004). IL-19 was found to suppress the ability of human PBMCs to generate IL-17A in response to *Staphylococcus aureus* infection (Reiss-Mandel et al., 2018). Accordingly, inhibiting IL-19 causes CD4+ and CD8+ T cells in whole-blood cultures from filaria-infected human beings to produce more Th1 and Tc1, respectively (Anuradha et al., 2016).

2.3. IL-20

Only a few studies have examined IL-20's role in acquired T-cell responses (Myles et al., 2013). Unlike other cytokines, IL-20 can specifically boost DC maturation, and the increase in CD86 expression on human monocyte-derived DCs due to IL-20 implies that IL-20 may mediate the indirect regulation of T-cell activation during antigen presentation.

2.4. IL-24

Disorders associated with the immunoregulatory cytokine IL-24 include autoimmune, infectious, and malignant diseases. Its possi-

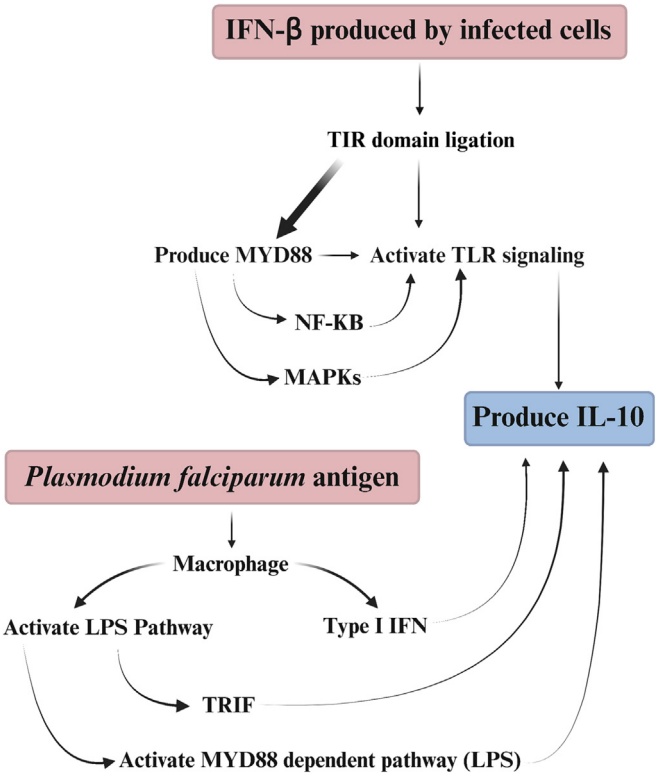

Fig. 2. Pathways for the production of IL-10. The first involves a TIR domain that stimulates IFN-β, activating the TLR, as a result of which pro-inflammatory cytokines including IL-10 are produced. Additionally, due to TLR signaling via MYD88, NF-κB produces IL-10 and its family members. The second pathway is implemented when macrophages respond to lipopolysaccharide in the presence of type 1 IFN signaling.

ble involvement in tumor growth inhibition has received particular attention (Poindexter et al., 2005). IL-24 stimulates human PBMCs to produce more cytokines, that is, IL-6, IFN-γ, and TNF-α (Chen et al., 2018).

3. Production of IL-10 by immune cells

The immune system produces IL-10 when pattern recognition receptors (PRRs) that identify pathogen-derived components activate DCs and MCs, inducing the release of cytokines and other substances. Following the stimulation of specific PRRs, DCs and MCs can generate IL-10 in vitro (Geijtenbeek et al., 2003). IL-10 is expressed in vivo in neutrophils, DCs, and MCs. Toll-like receptor 2 (TLR2) ligands are thought to preferentially stimulate antigen-presenting cells to produce IL-10. TLR2 significantly influences IL-10 production by MCs in response to pneumococcal cell wall stimulation. However, in this regard, nucleotide-binding oligomerization domain 2 (NOD2) signaling has been shown to have a TLR2-independent role (Moreira et al., 2008). MCs and myeloid DCs generate large quantities of IL-10 following activation by TLR4 and TLR9 ligands, whereas MCs to TLR3 stimulation. TLR4 activation can cause mast cells to produce IL-10, contributing to skin allergies and adverse parasitic reactions (Saraiva and O'Garra, 2010).

4. Signaling pathways of IL-10

Numerous pathways are involved in IL-10 production, with TIR-domain-containing adaptor protein-inducing IFN-β (TRIF, also known as TICAM1) activating signaling cascades in response to TLR ligation, producing PICs and IL-10. Nuclear factor kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs) are activated in response to TLR signaling via myeloid differentiation primary response 88 (MYD88) protein, resulting in the production of IL-10 and its related proteins. (Akira and Takeda, 2004). The activation of the TRIF and MYD88 is also necessary to maximize IL-10 formation by MCs in response to lipopolysaccharides (LPSs). To maximize IL-10 synthesis, type I IFN synthesis requires additional signals. The productivity of type I IFN as an anti-inflammatory agent is significantly impacted by the subsequent activation of IL-10, as shown in Fig. 2 (Saraiva and O'Garra, 2010).

5. MicroRNA expression upon *p. Falciparum* infection

Like other kinetoplastid parasites, *Plasmodium* species lack miRNA pathways (Xue et al., 2008). However, these parasites use human miRNA with RNA-induced silencing complex (RISC) to regulate their gene expression (Chakrabarty et al., 2017). Some host cell miRNAs contribute to the progression of malarial infection, whereas others mediate resistance and a protective immune response (Martin-Alonso et al., 2018). Thus, human malarial infection results in the altered expression of 50 miRNAs (seven upregulated and 43 downregulated). In cerebral malaria, miRNAs contribute substantially to the persistence of neuropathogenesis (Martin-Alonso et al., 2018). The pathogenesis of cerebral arteries can also be influenced by immune system dysregulation, apoptosis, and hypoxia (Hearn et al., 2000). Similarly, infections caused by diverse *Plasmodium* species result in the dysregulation of 12 unique host miRNAs. MiRNAs frequently target the genes forkhead box O (FoxO), TGF-β, adherens junctions, endocytosis, and IFN-β. Notably, many of the signaling pathways inhibited by these miRNAs are linked to *Plasmodium*'s defense mechanisms (Nguetse et al., 2015). The TGF-β levels are remarkably increased at the beginning of malarial disease and decline during the active multiplication of the malarial parasite (Wu et al., 2023). By assisting in maintaining the body's "immune balance" while battling the infection, TGF-β, for instance, affects the immunological response to *Plasmodium* infection. By inducing signaling for growth factors, oxidative stress, and inflammation, FoxO supports redox balance. FoxO also regulates glucose metabolism, apoptosis, and cell proliferation (Nguetse et al., 2015; Abdalla et al., 2020).

MiRNAs mediate a protective immune response against the parasite in non-cerebral malaria. *P. falciparum* hijacks many host cell miRNAs and uses them to suppress parasite gene expression (Dandewad et al., 2019). Most miRNAs prevent parasite growth by inhibiting ribosomal function (Ojha et al., 2016). Moreover, miRNAs are a potential therapeutic target for various disorders, including infections. As a result, tracking variations in miRNA expression can help diagnose diseases, especially since they are tissue-specific. In addition, there are numerous strategies to alter the synthesis or mode of action of miRNAs (Rojas-Pirela et al., 2022).

6. The effect of IL-10 levels on *p. Falciparum*

In individuals with symptomatic *P. falciparum* malaria, IL-10 levels correlate favorably with parasite density (Luty et al., 2000). However, the role of IL-10 in parasite mortality is still unclear, although baseline-level IL-10 secretion in response to parasite density might be the deciding factor in parasite clearance (Sukhbaatar et al., 2020). Parasiticidal efficacy in *P. falciparum* infection is thus indicated by the levels of IL-10 released during the disease, signifying the severity of parasitemia (Villegas-Mendez et al., 2016). Moreover, it is difficult to estimate the level of cytokines in the malarial patient's body because cytokine measurement following the in vitro stimulation of cultured cells may not accurately reflect the in vivo environment. Re-stimulating previously activated cells in vivo may cause cell death or anergy in vitro, thereby causing the underestimation of in vivo cytokine output. Despite mixed results, serum cytokine production should be compared to ex vivo cytokine synthesis during viral infections (Mordmüller et al., 1997). Another challenge is the detection of immune responses in immune organs and tissues other than peripheral blood. Though, during the blood phases of malaria, peripheral blood should be considered an essential immunological parameter for studying regulatory cytokines like IL-10. Studies have found that serum IL-10 levels correspond substantially to clinical symptoms (Othoro et al., 1999).

Parasites may also enhance anti- and pro-inflammatory immune responses to protect themselves, thereby enhancing IL-10 formation. According to in vitro research, *P. falciparum* infection modulates DC maturation by increasing IL-10 production and reducing IL-12 release (Urban et al., 1999). This DC response is comparable to the exposure of apoptotic cells or the ligation of CD36, and DC in recurrent infections likely override such mechanisms because neither elevated IL-10 nor specific PIC responses have been observed in asymptomatic pediatric patients in endemic zones (Casals-Pascual et al., 2012).

7. IL-10 regulates hepcidin

Researchers have discovered a correlation between hepcidin and IL-10 in pediatric cases of acute *P. falciparum* infection (Casals-Pascual et al., 2012). Hepcidin mRNA levels increased in response to high IL-10 concentrations (1–30 ng/mL), showing a dose–response relationship. Researchers have successfully suppressed IL-10′s effect on hepcidin by pre-incubating cells with anti-IL-10 antibodies. Moreover, signal transducers and activator of transcription 3 (STAT3) phosphorylation is prevented by a particular STAT3 inhibitor (Stattic, 10 mg/mL) (Armitage et al., 2011). Hepcidin production via IL-10 in primary MCs but not

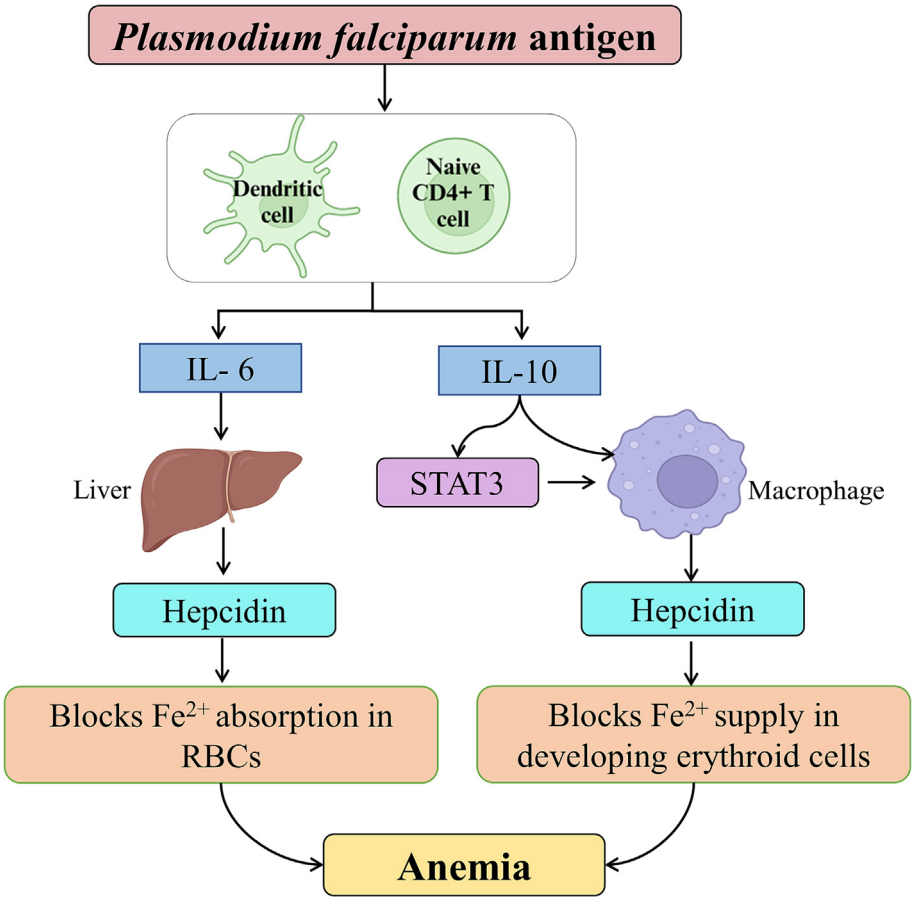

Fig. 3. Stimulation of DCs and native CD4+ T cells by *Plasmodium* antigens. This stimulation generates IL-6 and IL-10, which act on the liver to cause hepcidin release, which then prevents Fe^{2+} absorption in RBCs. The end effect is anemia in malarial infection, which worsens the condition. In a second pathway, *Plasmodium* antigens activate native CD4+ T cells and DCs to generate IL-10, which acts on macrophages in the presence of STAT3 to release hepcidin, thereby blocking the Fe^{2+} supply in growing erythroid cells of the bone marrow. Thus, malarial infection causes anemia, leading to further complications.

HepG2 hepatocytes depends on STAT3 phosphorylation. It is evident that increased hepcidin is crucial for controlling superinfections of *P. falciparum*. The precise underlying mechanism is unknown, despite evidence that hepcidin mRNA is produced in mononuclear cells during *P. falciparum* blood stages (Armitage et al., 2011). Moreover, IL-6 levels are unquestionably enhanced after acute infection, an observation that has been connected to hepcidin overexpression (Nemeth et al., 2004a). IL-6-dependent hepcidin production occurs in hepatocytes but not MCs, and this production can be reduced in hypoxic conditions. Elevated IL-6 levels do not seem to entirely account for the strong correlation between hepcidin concentration and parasitemia but rather a more systemic acute-phase response. According to several experimental findings, IL-10 promotes hepcidin via the dose-dependent phosphorylation of STAT3 (Huang et al., 2014) (Fig. 3).

8. Role of IL-10 against *p. Falciparum* infection

During malarial infection caused by *P. falciparum*, CD4+ T cells show substantial cross-reactivity to heterologous polyclonal B cell activator (PbA) and produce IFN-γ, a cytokine necessary for the response to malaria (Perez-Mazliah and Langhorne, 2014). IFN-γ stimulates phagocytic activities by stimulating MCs. In addition, it affects the isotype switching of B cells, resulting in the production of cytophilic antibodies that prevent the invasion of RBCs by free parasites. These mechanisms are significant in parasitic growth control during infection (King and Lamb, 2015). IL-10, a potent immunoregulatory mediator, is a crucial regulatory molecule that protects tissue damage by limiting inflammation. On antigen-presenting cells, the expression of MHC-II and co-stimulatory molecules is reduced, whereas the expression of immunological checkpoint molecules is raised (Kumar et al., 2019), both of which contribute to the lowering of inflammation (Fig. 4). DCs and MCs produce less PICs and engage in less antigen presentation and T cell activation when exposed to IL-10, regulating the inflammatory response to infection (Moore et al., 2001).

Furthermore, when cells were infected with PbA and treated with an IL-10R blocker, BALB/c mice, which ordinarily do not grow an extracellular matrix (ECM), did so. The fraction of activated CD4 + T cells rose remarkably but activated CD8+ T cells remained virtually unchanged. Although T and B cell percentages increased, the quantity of anti-*Plasmodium* antibodies in the blood remained the same. Thus, decreasing inflammatory pathophysiology during malaria requires IL-10 (Freitas do Rosario and Langhorne, 2012), which reduces immune defenses, and cross-reactive immunity is thought to weaken in heterologous infections (Nakamae et al., 2019). Due to the coexistence of heterologous species in areas of malarial endemicity, IL-10 can either be protective or lead to pathogenesis contingent on the immune response and parasite presence. These characteristics emphasize IL-10′s role in preserving balance and imply that IL-10′s activity level may change based on the specific *Plasmodium* strains involved in malarial infection.

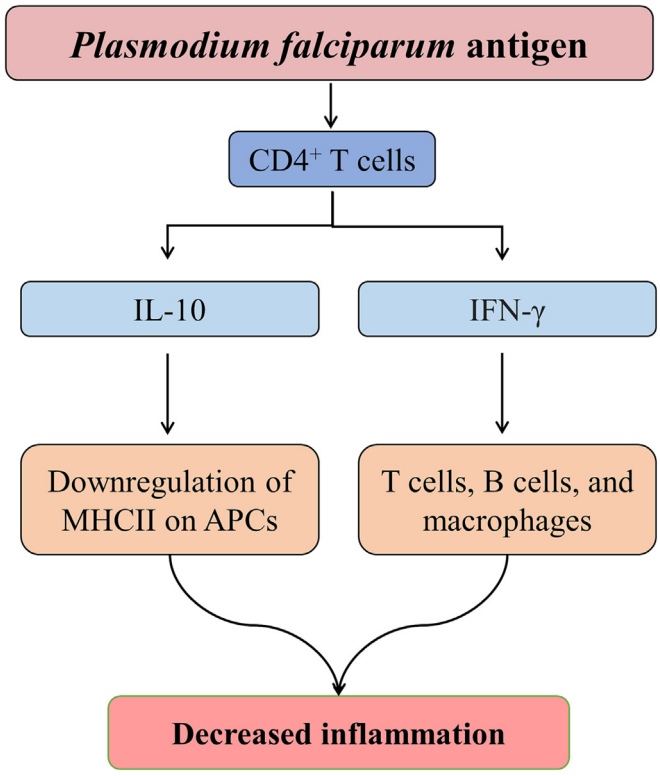

Fig. 4. IL-10-based regulation in *P. falciparum* infection. Infection with *P. falciparum* (antigen) causes CD4+ T cells to release IL-10, downregulating the MHCII on antigen-presenting cells (APCs). IFN stimulates T cells, B cells, and macrophages and manages the parasite's growth. Both reduce the inflammatory pathophysiology of infection and protect host tissue.

9. Thoughts on vaccine development for malaria

In 1973, the first antimalarial vaccine based on irradiated *P. falciparum* sporozoites was tested on humans, with promising results (Clyde et al., 1973). Since then, numerous innovative vaccinations have been evaluated with little success, indicating the need for more work. To tackle the disease, researchers are focusing on isolating and delivering antigen-specific immunizations at different times in the parasite life cycle rather than utilizing live attenuated vaccines. In exploratory clinical studies just completed in Burkina Faso, a novel antimalarial circumsporozoite protein-based vaccine, R21 with a Matrix-M™ (MM) adjuvant, demonstrated up to 77% efficacy. In contrast, the RTS,S vaccine, the only candidate approved thus far, demonstrated a median effectiveness of 55.8% in African youngsters. If additional trials show equal or higher levels of efficacy, the R21/MM vaccine might be a game changer in combating malarial infection (Mandala et al., 2021). The vaccine development is complex and costly because of a lack of sufficient information on malaria immunity. Most experts agree that a multifaceted strategy is the best way forward, but immunizations for certain stages must demonstrate significant and acceptable efficacy first. Furthermore, although malaria can be controlled by developing effective vaccine strategies, vaccine development against the *P. falciparum* strain is challenging due to its complexity and diverse genome (Rappuoli and Aderem, 2011). The infectious cycle of the parasite also hinders vaccine discovery as it invades the host's immune system.

10. Future directions

There is a dire need to conduct more research on IL-10 in the context of *P. falciparum* infections. The processes by which NK cells induce IL-10 production may offer clues for the development of therapeutics, particularly in situations where the host cannot control or clear infections that may result in immunopathology or mortality. Small-molecule drugs, microRNA sponges, and oligonucleotide treatments are a few ways to interfere with biogenesis (miRNA replacement and antisense oligonucleotides) in *P. falciparum* infections. There are few to no detrimental consequences when miRNAs are administered intravenously to living organisms (Rojas-Pirela et al., 2022). Many clinical trials are currently being conducted on the function of miRNAs in *P. falciparum* infections to develop novel therapeutic approaches. However, several important gaps remain in our understanding of IL-10-mediated suppression and its treatment (Wilson and Brooks, 2011). The current scenario marks the beginning of a new age in rational vaccine design since IL-10 acts differently at different stages of immunity.

11. Conclusion

The entry of *P. falciparum* into the blood induces the production of anti-inflammatory mediators by CD4+ T cells, which inhibit antigen-presenting cells' activity. Cytokines such as IL-12, IL-15, IL-18, and IL-10, as well as DCs, monocytes, NK cells, and perhaps other cell types, modulate NK cells for IL-10 production. Furthermore, IL-10 is regulated by transcription factors such as STAT3 and STAT4. However, these variables have a different effect on IL-10 production based on infectious disease status. Critically, the presence of IL-10 plays a distinctive impact on malaria parasite clearance. The regulation of IL-10 during *P. falciparum* infection remains poorly understood, but novel therapeutic approaches based on miRNAs and vaccines are under development.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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