

**Plasmodium and Host Immune Responses: Evasion Strategies**

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**Summary**

Malaria is an infectious disease caused by *Plasmodium* species, with a complex pathophysiology, influenced by both the host's immune defences and the parasite's species-specific evasion strategies. This complexity has posed a significant challenge to vaccine development, malaria control and elimination. Therefore, the purpose of this review is to highlight the host immune responses, the parasite's escape mechanisms, and how these two factors interact in the control of *Plasmodium* infection.

**Keywords:** Plasmodium, innate immunity, adaptive immunity, evasion mechanisms

**Introduction**

The immune system plays a critical role in controlling and eliminating *Plasmodium* infection. The various stages of the malaria parasite in the human host elicit both innate and adaptive immune responses, which involve both humoral and cellular arms of the immune response. These responses against the parasite encompass a complex network of defense mechanisms, that result in the release of molecules capable of limiting the growth and further development of the parasite or causing immunopathology, which may lead to life-threatening conditions such as cerebral malaria and severe malaria-associated anaemia (O'Neill *et al.*, 2013). Malaria parasites lead to approximately 212 million infections and 429,000 deaths each year, with *P. falciparum* accounting for about 99% of these fatalities (WHO, 2023). The high virulence of *P. falciparum* is primarily due to its sophisticated

ability to evade the immune system. The parasite employs distinct immune evasion strategies in both the *Anopheles* mosquito vector and the human host. In mosquitoes, immune evasion mainly involves the *Pfs47* gene, which suppresses Janus kinase-mediated immune activation. Additionally, host-derived complement factors protect extracellular gametes in the mosquito midgut from immune attack. In humans, *P. falciparum* avoids immune detection through mechanisms such as antigenic variation, genetic polymorphism, and sequestration. During the pre-erythrocytic stage, the parasite induces apoptosis in Kupffer cells, while in the erythrocytic stage, it disrupts macrophage phagocytic function via hemozoin. Furthermore, the absence of major histocompatibility complex class I (MHC-I) molecules on red blood cells prevents recognition by CD8+ T cells. Some complement proteins may even facilitate parasite entry into red blood cells. The parasite's intracellular lifestyle also contributes to its ability to escape immune responses. Understanding the invasion and immune evasion mechanisms in both mosquito vectors and human hosts is essential for developing effective vaccines (Five *Plasmodium* species are known to infect humans, each varying in geographical distribution, clinical presentation, and disease severity: *P. falciparum*: the most dangerous and deadly species, predominant in sub-Saharan Africa, and responsible for the majority of malaria-related deaths. *P. vivax*: common in Asia and Latin America; can cause recurring infections due to dormant liver stages (hypnozoites). *P. ovale*: relatively rare; similar to

*P. vivax* and also capable of causing relapses. *P. malariae*: associated with chronic infections; less severe but can persist for years. *P. knowlesi*: a zoonotic species that primarily infects macaques but can cause severe infections in humans in Southeast Asia (Singh and Daneshvar, 2018). Among these, *P. falciparum* is particularly notorious for its capacity to evade the host immune system. This evasion allows the parasite to establish long-lasting infections, increasing its transmission potential and complicating treatment efforts (Belachew, 2018)

### Innate immunity

The innate immune system is the body's first line of defence against infections. It provides a rapid, non-specific response to pathogens (bacteria, viruses, fungi, parasites) and harmful substances. Unlike the adaptive immune system, it does not require prior exposure to recognise threats and has no immunological memory. The main components of the innate immune system are:

1. Physical and chemical barriers: skin, mucous membranes, stomach acid, enzymes in saliva, and tears.
2. Cellular defences: phagocytic cells (neutrophils, macrophages), natural killer (NK) cells, dendritic cells, mast cells, basophils, eosinophils.
3. Soluble mediators: complement system and complement proteins, cytokines, chemokines, and acute-phase proteins (. In short, the innate immune system acts as the immediate protective shield of the body, buying time for the adaptive immune system to mount a more specific and long-lasting response (Lemon, 2020). The innate immune response starts when certain cells like macrophages, dendritic cells, Fibroblasts, Pericytes and endothelial cells, recognize an invading pathogen. These cells trigger the response by identifying the pathogen. Through special receptors called pattern-recognition receptors (PRRs), which include Toll-like receptors, NOD-like receptors, and scavenger' receptors. These receptors are found in the cell membrane or cytosol. When they detect pathogens, they activate the sentinel cells, leading to the release of signaling molecules like cytokines and chemokines. The released cytokines and

chemokines activate endothelial cells, which then produce chemokines and adhesion molecules. This helps recruit other immune cells to the site of infection. The activated endothelial cells recruit and bind neutrophils, monocytes, macrophages, and platelets. This leads to the migration of these myeloid cells into tissues, allowing them to reach and target the infection site (Goswami *et al.*, 2023).

### Innate immune response of the host against Plasmodium species

The innate immune response to Plasmodium parasites involves: Innate immune receptors recognizing malaria parasites through various pathogen-associated molecular patterns (PAMPs), including Glycosylphosphatidylinositol (GPI) anchors, Lipophosphoglycan (LPG), Parasite DNA/RNA, Haemoglobin-derived peptides. The key Innate Immune Receptors in Malaria are:

1. Toll-like receptors (TLRs): TLR2, TLR4, and TLR9
2. NOD-like receptors (NLRs): NLRP3, NLRP12
3. RIG-I-like receptors (RLRs): RIG-I, MDA5
4. C-type lectin receptors (CLRs): Dectin-1, DC-SIGN
5. Scavenger receptors (SRs): SR-A, MARCO (O'Neill *et al.*, 2013).

The major Functions of Innate Immune Receptors in Malaria is or are: 1. Activation of immune cells: dendritic cells, macrophages, neutrophils, leading to Phagocytosis and parasite clearance. 2. Production of pro-inflammatory cytokines: Like TNF- $\alpha$ , IL-12 and IL-6. 3. Induction of type I interferons (IFN- $\alpha/\beta$ ). 4. Activation of the complement system.

### Recognition of the Plasmodium parasite by pattern recognition receptors (PRRs)

The innate immune system has developed pattern-recognition receptors (PRRs) to detect and respond to Plasmodium parasites. These receptors include Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), and NOD-like receptors (NLRs), which provide rapid defense against various infections. These receptors trigger specific genetic programs, leading to the production of cytokines and chemokines that help eliminate

Plasmodium pathogens and activate the adaptive immune response (Abraha, 2020). PRRs recognize conserved Pathogen-associated molecular patterns (PAMPs), which distinguish foreign organisms from self. PRRs reside in different cellular compartments (Li *et al.*, 2021). While TLRs detect PAMPs on the cell membrane of endosomes or the cell surface, RLRs and NLRs are cytosolic. Innate immune responses begin in the early pre-symptomatic stages of plasmodial infection, when parasitaemia is still very low. At this stage, innate immunity genes such as TLRs, PRRs and many proinflammatory cytokines are already upregulated. A small number of TLRs are responsible for the recognition of a broad range of PAMPs. TLRs recognize pathogens, triggering a rapid innate immune response by producing pro-inflammatory cytokines and increasing co-stimulatory molecules. Toll was originally discovered in *Drosophila melanogaster*, which has eight additional related receptors (Toll 2–9). TLRs can detect parasite components, including those from Plasmodium species and other related pathogens (Kumar and Barrett, 2022).

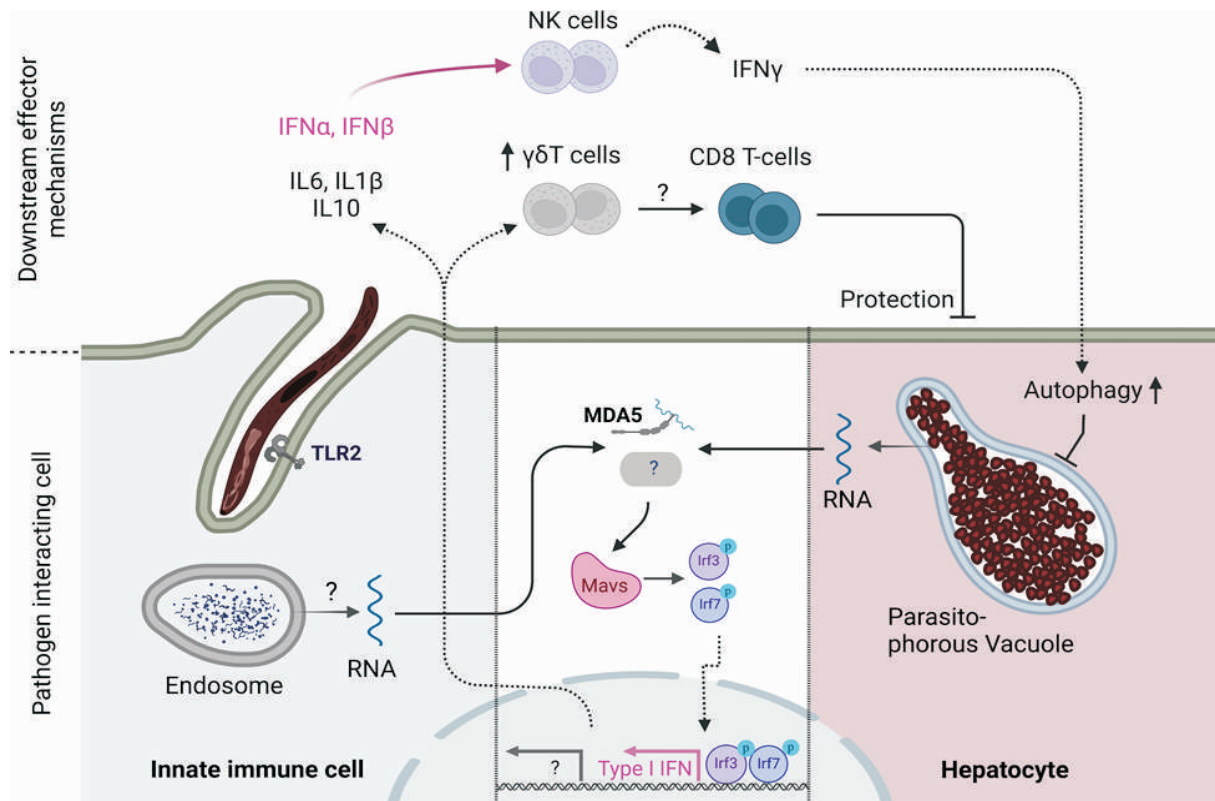
#### **Innate immunity to pre-erythrocytic stages**

While sporozoites are evolutionarily optimized for their journey to the liver, only a few manage to infect hepatocytes, with the remaining sporozoites being cleared by cells of the innate immune system (Ezema *et al.*, 2023). These unsuccessful sporozoites are likely to contribute to innate immune activation and are a source of antigen for T and B cells. In vivo tracking of fluorescent sporozoites after intradermal injection revealed that similar numbers of viable *P. berghei* sporozoites reached the liver or remained in the skin (Patel *et al.*, 2025). Importantly, sporozoites were found in subcapsular zones of skin draining lymph nodes (DLNS) before being taken up into DLN resident CD8<sup>+</sup> Dendritic cells (DCs), which efficiently prime CD8<sup>+</sup> T-cells (Pohl and Cockburn, 2022). Otun and Achilonu (2025) reported, the *P. yoelii* model suggests priming in DLNS after subcutaneous sporozoite injection is sufficient to induce protective immunity (Otun and Achilonu, 2025). The innate immune responses provide a powerful front-line defence against invasive malaria by inhibiting parasite growth and initiating the development of adaptive immunity

(Ezema *et al.*, 2023). During the liver stage of malaria infection, recent studies have demonstrated that sporozoites can be phagocytized by neutrophils, which are usually the first circulating cells to respond to an invading Plasmodium sporozoite through a mosquito bite (Ezema *et al.*, 2023). During the blood stage of infection, neutrophils eliminate merozoites through phagocytosis, generating reactive oxygen species (ROS) and other antimicrobial substances or by creating neutrophil extracellular traps (NETs) (Omar and Abdelal, 2023). Monocytes and macrophages play a key role in eliminating Plasmodium parasites, protecting the host from disease (Sellau *et al.*, 2021). Human plasmodium infection studies, including clinical trials of whole sporozoite vaccines, have shed light on protective immune responses (Moita *et al.*, 2023). In the liver, the rodent malaria parasite *P. berghei* triggers the production of type I interferons (IFNs). The response relies on parasite replication, as irradiated parasites (which can't replicate properly) trigger much weaker interferon expression (Perera, 2023). The response was eliminated in mice lacking MAVS (mitochondrial antiviral-signalling protein). MAVS is the adaptor protein for the cytosolic RNA sensors Melanoma differentiation-associated protein 5 (MDA5) and Reticularic acid inducible gene I (RIG-I). When activated, MAVS triggers Type I IFN expression, helping cells defend against pathogens internally and externally. Cytokine production was not fully blocked in MDA5-deficient mice and was normal in RIG-I-deficient mice, hinting at another cytosolic sensor detecting parasite molecules. The cell type that senses Plasmodium RNA was not identified and could be either innate immune cells or the hepatocyte itself (Jha *et al.*, 2023). Another study suggested type I IFN might recruit NK cells that produce IFN-gamma to the liver, helping reduce the parasite load (Ding *et al.*, 2022). IFN-gamma might reduce liver-stage parasites by triggering autophagy, a process that kills the parasites within liver cells. TLR2 has been identified as an innate sensor of sporozoite infection in vitro, in addition to cytosolic RNA sensors found in vivo (Munoz-Caro *et al.*, 2021). TLR2 is part of the Toll-like receptor family that detects pathogen molecules

(PAMPs) in the extracellular space or within endosomes. Most TLRs signal through MyD88, triggering NF-κB activation, which leads to pro-inflammatory gene expression and cytokine release, including IL-6 and TNF-α. TLR2-deficient mice had higher parasite loads in the liver and did not produce inflammatory cytokines, indicating TLR2's role in fighting infection. It's unclear if TLR2 works with MDA5 and MAVS to trigger a Type I IFN response in the

liver (Colasanti, 2024). A recent study found that when human immune cells (macrophages and DCs) were exposed to *Plasmodium* sporozoites, they engulfed the parasites and produced cytokines like IL-6, IL-1β, and IL-10. Spores trigger strong pro-inflammatory responses that boost adaptive immunity, but the specific cells and molecular interactions involved are not well understood (Lionakis *et al.*, 2023).



**Figure I: Innate immune response in the pre-erythrocytic stage of Plasmodium infection**

**Innate immunity to blood stage Plasmodium infection**

Although sporozoites strongly trigger immune responses, the pre-erythrocytic stage of *Plasmodium* infection is often asymptomatic due to the small number of parasites involved (Moita *et al.*, 2022). In contrast, the blood stage of *Plasmodium* infection causes symptoms, often marked by excessive inflammation similar to sepsis, especially in people without prior exposure. Kupffer cells play a key role in limiting malaria severity by controlling the release of parasites into the bloodstream (Vijayan *et al.*, 2021). During malaria's blood stage, monocytes help control the infection by:

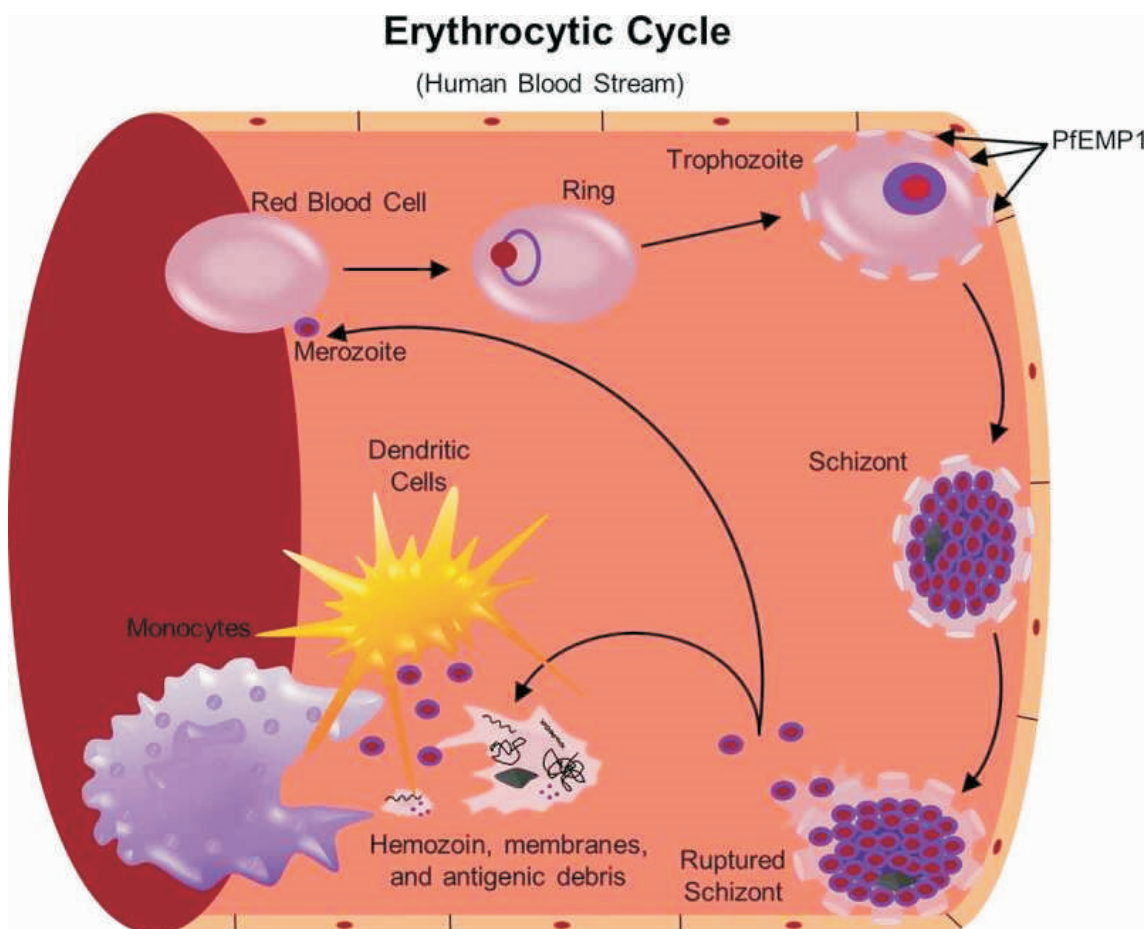
Engulfing parasites and infected red blood cells, producing inflammatory cytokines (IFN-α, IFN-γ, and IL-6), and Releasing chemokines (CCL2, CCL3, CCL4 and CXCL10). This immune response helps limit parasite growth. Splenic macrophages help control malaria by engulfing infected red blood cells and producing reactive oxygen species to fight the parasites (Ezema *et al.*, 2023). During the blood stage of malaria, type I IFNs are among the first cytokines produced by plasmacytoid dendritic cells (PDCs) through the TLR7-MyD88-IRF7 pathway (Du *et al.*, 2022). Monocytes can exacerbate severe disease by releasing inflammatory cytokines that cause widespread

inflammation and damage to blood vessels. Dendritic cells (DCs) are strategically located at sites relevant to malaria infection, where they play a crucial role in connecting the innate and adaptive immune responses. When dendritic cells (DCs) encounter malaria parasites or foreign antigens, they mature and effectively present these antigens to T cells via MHC molecules, triggering a specific immune response. Dendritic cells release cytokines and chemokines to orchestrate an immune response, recruiting other cells and regulating T and B cells to help clear malaria parasites (Obeagu and Surgery, 2024).

Malaria's virulence factors include variant surface antigens encoded by:

- Var genes (~60) for PfEMP1,
- Rif genes (~200) for RIFIN,
- Stevor genes (~30) for STEVOR (Vasileva, 2025).

These polymorphic genes enable immune evasion. PfEMP1 allows infected red blood cells to adhere to blood vessel walls, hiding them from the spleen's filtering mechanism and avoiding removal. The adhesion of infected red blood cells to blood vessel walls can lead to severe malaria, particularly cerebral malaria, by obstructing blood flow in the brain. Three human receptors have been found to bind to *P. falciparum* RIFINs, LAIR1, LILRB1 and LILRB. These receptors (LAIR1 and LILRB1) are part of the Ig superfamily, featuring ITIM motifs, and are widely expressed on immune cells, including myeloid cells and lymphocytes. ITIM motifs suppress cell activation by counteracting activation signals in various immune processes, including NK cell activation, T and B cell activation and Myeloid cell activation (Buckle and Guillerey, 2021). This helps regulate and prevent excessive immune responses.



**Figure 2: Innate immune response to the erythrocytic stage of Plasmodium infection**

### **Mechanism of Adaptive Immune Response of the Host Against Plasmodium**

Adaptive immunity is the branch of immunity that provides a specific, long-lasting defence against pathogens. Unlike the innate immune system, it develops slowly, but becomes stronger and more precise with repeated exposure, due to specificity, memory and diversity. The adaptive immune response to the malaria parasite involves a complex interplay between T cells and B cells, orchestrated by cytokines. This collaboration is crucial for activating T cells, producing antibodies, and coordinating cytokine signalling to eliminate malarial parasites (Obeagu and Surgery, 2024). During Plasmodium infection, adaptive immunity is triggered when parasite antigens are presented by antigen-presenting cells (APCs) such as dendritic cells to naïve T lymphocytes. This leads to the activation and differentiation of CD4<sup>+</sup> helper T cells, CD8<sup>+</sup> cytotoxic T cells, and B cells. The type and strength of adaptive immune responses depend on the stage of the parasite's life cycle, pre-erythrocytic (liver) stage or erythrocytic (blood) stage (Obeagu and Surgery, 2024).

### **Cell-mediated immunity**

At the pre-erythrocytic stage, Plasmodium sporozoites infect hepatocytes, where CD8<sup>+</sup> cytotoxic T cells play a dominant protective role. These T cells recognise parasite peptides presented by MHC class I molecules on infected hepatocytes and kill these cells through perforin- and granzyme-mediated cytotoxicity, thereby halting parasite development before blood-stage infection begins. Additionally, CD4<sup>+</sup> T cells produce cytokines such as interferon-gamma (IFN- $\gamma$ ) and tumour necrosis factor (TNF), which activate macrophages and enhance their ability to destroy infected cells (Hassert and Mordmuller, 2023). Memory CD8<sup>+</sup> T cells, especially tissue-resident memory T cells (Trm) in the liver, are essential for long-term protection against reinfection. These cells rapidly respond upon re-exposure to the parasite, producing cytokines and cytotoxic molecules that eliminate infected hepatocytes. However, in humans, the maintenance of long-lasting liver-stage memory T cell responses remains difficult to achieve, which limits the duration of immunity (Lefebvre *et al.*, 2019).

### **Humoral immunity**

The humoral arm of the adaptive immune response is vital during the blood stage of malaria. When merozoites infect red blood cells, B cells recognise parasite surface antigens and differentiate into plasma cells that secrete antibodies. These antibodies neutralise merozoites, block invasion of erythrocytes, and promote opsonisation, thereby facilitating phagocytosis by macrophages and activation of the complement cascade (Long and Miller, 2017). Specific antibodies against merozoite surface proteins, such as merozoite surface protein 1 (MSP1) and apical membrane antigen 1 (AMA1), have been associated with reduced parasite density and clinical protection. However, the parasite's high antigenic diversity, particularly in the var gene family encoding PfEMP1, allows immune evasion through antigenic variation (Claessens *et al.*, 2014). This variation leads to a delay in the acquisition of broad and long-term antibody-mediated immunity. T follicular helper (Tfh) cells, a subset of Cd4<sup>+</sup> T cells, are crucial for effective B cell activation and the formation of germinal centres in secondary lymphoid organs, within germinal centres, affinity maturation and class switching occur, leading to the production of high-affinity antibodies and memory B cells. However, plasmodium infection often disrupts germinal centre formation and Tfh function, resulting in short-lived and less effective antibody responses (Chan *et al.*, 2020).

### **Memory responses and immunity development**

Repeated malaria infections in endemic areas lead to a gradual buildup of acquired immunity, which reduces the severity of infection rather than providing sterile protection. This partial immunity reflects the slow development of high-quality memory B cells and long-lived plasma cells. Over time, individuals develop the capacity to control parasitemia and avoid severe disease, although reinfection remains common (Chan *et al.*, 2020).

Despite repeated exposure, long-lasting immunity is rare because of parasite immune evasion and dysregulated immune memory. Chronic infections can cause immune exhaustion and disrupt the maintenance of long-

lived plasma cells in the bone marrow. This may explain why adults in endemic areas experience milder disease but can still harbour low-level parasitemia (Deroost *et al.*, 2016).

### **Immune evasion mechanisms**

Immune evasion mechanisms are strategies that pathogens (bacteria, viruses, parasites, fungi, and even tumour cells) use to avoid detection or destruction by the host immune system. These mechanisms allow them to persist, replicate, and sometimes cause chronic or recurrent infections. Some of the mechanism of immune evasion are Inhibition of phagocytosis, survival inside phagocytes, resistance to complement lysis, killing or suppressing immune cells, antigenic variation, inhibition of antigen presentation, production of decoy molecules, downregulation of MHC molecules to avoid cytotoxic T cells response, expression of immune checkpoint ligands (e.g. PD-L1) to inactivate T cells and secretion of immunosuppressive cytokines (e.g. TGF- $\beta$ ).

### **Immune evasion mechanism of the Plasmodium species**

Malaria parasites developed various immune escape strategies to survive within their host. Malaria parasites thrive in red blood cells because they lack a nucleus and immune genes, evading immune detection. *P. falciparum* and *P. vivax* infections trigger various symptoms as the parasite infects red blood cells, while key events also unfold during the pre-erythrocytic stages (Muhwezi, 2023). *P. falciparum* has developed multiple evasion strategies, allowing it to successfully infect even individuals with strong immune systems despite their robust immunological defences. Deciphering malaria parasites' immune evasion tactics can guide the development of innovative treatments and potent vaccine candidates (Su *et al.*, 2025).

### **Immune evasion mechanisms of the malaria parasite in the mosquito vector**

Mosquitoes rely on their innate immune system to combat microbial invaders. Notably, female *Anopheles gambiae* mosquitoes have been shown to initiate immune responses against *Plasmodium* parasites. A key defense mechanism involves midgut epithelial cells

initiating nitration reactions during *Plasmodium* infection, which reduce parasite viability by promoting lysis through the action of thioester-containing protein 1 (TEP1) (Blandin *et al.*, 2019). TEP1 is a crucial element of the mosquito's complement-like immune system. Recent research has revealed that certain *Plasmodium* parasite strains, particularly those from regions where *A. gambiae* is also endemic and can evade this immune response. Co-infection experiments further demonstrated that parasite survival varies depending on the genetic makeup of different *Plasmodium* strains. Subsequent genetic mapping, linkage group selection, and functional genomics analyses identified the female gamete-specific six-cysteine protein Pfs47 as essential for *P. falciparum* to circumvent the TEP1-mediated immune response in *A. gambiae*. It is believed that Pfs47 facilitates immune evasion by inhibiting midgut epithelial nitration, thereby preventing TEP1-triggered parasite lysis (Muhwezi, 2023).

### **Immune evasion mechanism of malaria parasites in the human host**

When an infected mosquito bites a human, it introduces approximately 100–200 sporozoites into the skin, despite the innate immune system eliminating most of these parasites, a small number still succeed in establishing infection. The skin acts as the initial barrier that sporozoites face upon entering the vertebrate host (Cirimotich *et al.*, 2010). To navigate this challenge, sporozoites have developed mechanical strategies such as motility and cell traversal. These strategies are enabled by specific mechanical proteins that assist sporozoites in penetrating tissues. Research shows that sporozoites lacking SPECT-1 (sporozoite microneme protein essential for cell traversal) and SPECT-2 (also known as perforin-like protein 1 or PLP1) become trapped within the dermis, where they are engulfed by phagocytes, preventing further migration. These proteins are essential for efficient cell traversal and subsequent migration to the liver (Tavares *et al.*, 2013). This traversal process can suppress the activation of immune responses and prevent the sporozoites from being cleared through immune mechanisms such as exocytosis before

they cross the dermal barrier (Sinnis and Zavala 2012). Another critical protein involved in sporozoite movement is TRAP (Thrombospondin-Related Anonymus Protein), which is located on both the micronemes and the parasite's surface. TRAP allows sporozoites to bind to host surface molecules, enabling the gliding motility necessary to exit the dermis. Additionally, TRAP can bind to sulfated glycoconjugate motifs, aiding in the recognition and invasion of hepatocytes. Despite these adaptations, some sporozoites still find their way into the lymphatic system, where they can be identified and destroyed by immune cells such as dendritic cells (Wilson *et al.*, 2016).

### **Immune Evasion Strategies in Liver Cells for Hepatocytic Infection Establishment**

Once sporozoites enter the bloodstream from the skin, they rapidly travel through the vascular system until they anchor themselves within the liver sinusoidal spaces. Despite this regulatory setting, the liver does deploy a range of immune defenses against parasite invasion; however, sporozoites have developed multiple mechanisms to circumvent these responses. One such host defense involves the activation of the interferon (IFN) signalling pathway. Additional defence roles are performed by immune cells such as natural killer (NK) cells, natural killer T (NKT) cells,  $\gamma\delta$ T cells, and the iron-regulating hormone hepcidin, all of which contribute to suppressing parasite development in the liver. Nevertheless, Plasmodium overcomes these defenses primarily by modulating Kupffer cells and hepatocytes during liver entry and infection, ensuring its survival and proliferation within hepatocytic environments (Gomes *et al.*, 2016).

### **Suppression of innate immunity**

Following the bite by an infected female Anopheles mosquito, sporozoites are deposited into the skin and subsequently enter the bloodstream, where they face the challenge of bypassing Kupffer cells (KC) and endothelial cells (EC) to successfully infect hepatocytes (Zheng *et al.*, 2014). To facilitate this process, sporozoites manipulate the immune microenvironment by altering cytokine responses specifically, by enhancing anti-

inflammatory Th2 cytokine levels and suppressing pro-inflammatory Th1 cytokines. Moreover, circumsporozoite protein (CSP), produced by sporozoites, binds to KC surface molecules such as LRP-1 (low-density lipoprotein receptor-related protein) and proteoglycan, leading to the inhibition of reactive oxygen species (ROS) production through the induction of intracellular cAMP/EPAC signalling pathways. In addition, sporozoites can trigger apoptosis in KCs and suppress the expression of MHC-1 molecules via CSP, thereby impairing the antigen-presenting function of KCs. Through these combined strategies, sporozoites effectively weaken KC-mediated immune defenses, enabling their entry into liver hepatocytes (Ikarashi *et al.*, 2013).

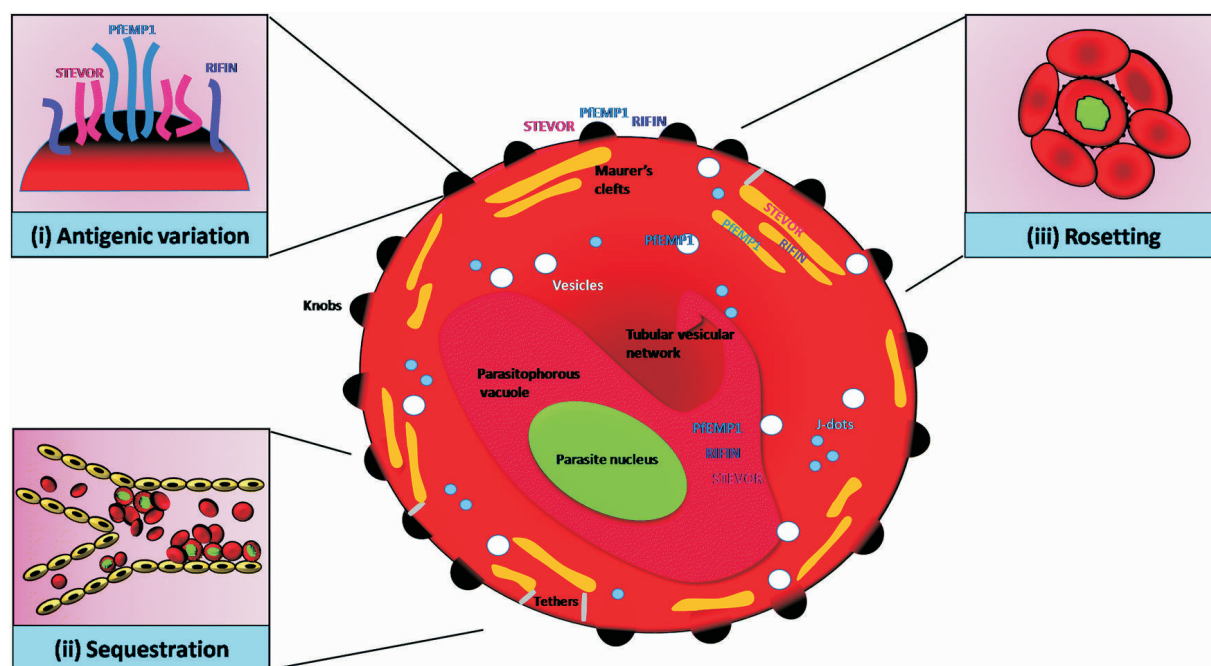
### **Hepatocyte entry and immune stealth**

Upon successfully breaching the liver's sinusoidal immune defenses, sporozoites utilize a distinctive cholesterol uptake pathway to enter hepatocytes, an approach that sets them apart from other parasitic invaders. Inside the hepatocyte, the sporozoites secrete circumsporozoite protein (CSP). Research indicates that CSP modulates the host's inflammatory response by suppressing the NF- $\kappa$ B signalling pathway and enhancing the expression of heme oxygenase-1 (HO-1) (Ikarashi *et al.*, 2013). Additionally, CSP influences the mechanistic target of rapamycin (mTOR) pathway, which governs crucial cellular processes such as survival, proliferation, growth, autophagy, and anabolism. Once infection is established, the parasite becomes encased in a parasitophorous vacuole membrane (PVM), which acts as a protective barrier, shielding it from endocytic and lysosomal degradation within the hepatocyte cytoplasm (Rashidi *et al.*, 2021). PVM further safeguards the infected cell by inhibiting both apoptosis and selective autophagy, thus promoting parasite survival. Eventually, the liver-stage sporozoite differentiates into merozoites, which are released from the liver wrapped in membrane-bound structures called merozoites. These merozoites help the parasite evade phagocytic clearance and other immune mechanisms, thereby enabling a successful transition into the bloodstream for the next phase of erythrocyte infection (Rashidi *et al.*, 2021).

### Immune evasion strategies during the erythrocytic stage

Upon release into the bloodstream, Plasmodium merozoites invade host red blood cells (RBCs) and commence their maturation process within membrane-bound parasitophorous vacuoles inside the RBCs. The parasite progresses into the

trophozoite stage, which subsequently undergoes schizogony to form a multinucleated schizont containing multiple daughter merozoites. Once mature, the infected RBCs (iRBCs) rupture, releasing these merozoites into circulation, thereby perpetuating the asexual replication cycle within new host (Yam and Preiser 2019).



**Figure 3: Immune evasion mechanisms in the Erythrocytic stage .**

#### Antigenic Variation

*P. falciparum*-infected erythrocytes (IEs) display a group of surface antigens known as variant surface antigens (VSAs), which are recognized and targeted by the host's immune system, particularly through antibody responses. One of the primary targets is the *P. falciparum* erythrocyte membrane protein 1 (PfEMP-1), against which antibodies can effectively mediate the clearance of IEs. To circumvent this immune recognition, *P. falciparum* employs a strategy where it synthesise members of multigene families such as PfEMP-1 and STEVOR but restricts their expression to a limited subset. Specifically, only a single var gene is actively transcribed and translated to produce PfEMP-1, while just a few *stevor* genes are expressed at a time. The remaining genes are transcriptionally silenced. This process, known as antigenic variation, enables the parasite to evade immune detection by periodically altering the antigenic

profile of the IEs. The underlying mechanism of this variation, particularly in the var gene family encoding PfEMP-1, is largely governed by epigenetic regulation (Guizetti and Scherf 2013).

#### Cytoadherence and sequestration as evasion mechanisms

As the spleen filters out abnormal RBCs and eliminates circulating pathogens, iRBCs risk immune clearance. To counter this, the parasite induces cytoadherence where iRBCs bind to endothelial cells and sequester within the microvasculature, effectively evading splenic clearance (Yam and Preiser 2019). This process is predominantly mediated by PfEMP1, encoded by var genes. PfEMP1 exhibits domain structures such as Duffy binding-like (DBL) and cysteine-rich interdomain regions (CIDRs), which contribute to antigenic diversity and binding specificity. The acidic terminal segment (ATS) of PfEMP1 aids in its anchoring to the

RBC surface. PfEMP1 interacts with multiple host receptors, including ICAM-1, CD36, chondroitin sulfate A (CSA), endothelial protein C receptor, heparan sulfate, IgM,  $\alpha$ 2-macroglobulin, thrombospondin, and complement receptor 1 (CR1), facilitating sequestration and immune evasion (Turner *et al.*, 2013).

### **Rosetting as a strategy for immune escape**

Rosetting involves the adhesion of iRBCs to uninfected RBCs, forming a cluster of cells called a rosette. This formation protects iRBCs from host immune response and shields newly released merozoites from invasion-inhibitory antibodies. Additionally, it creates a favourable microenvironment for merozoite invasion into fresh RBCs. Recent findings demonstrate that PfEMP1, RIFIN, and STEVOR proteins contribute to rosette formation by binding to RBC receptors such as glycophorin C, complement receptor 1 and blood group A antigens. Distinct variants of PfEMP1 can bind to CR1, heparan sulfate, and  $\alpha$ 2-macroglobulin, mediating rosette formation. Moreover, PfEMP1's interaction with IgM enhances binding avidity, further stabilizing rosettes (Wahlgren *et al.*, 2017). Intriguingly, a single PfEMP1 molecule from a rosetting strain can mediate both cytoadhesion and rosetting concurrently. An A-type RIFIN was shown to form large rosettes by binding to blood group A antigens, while also forming smaller clusters with glycophorin A on type O RBCs. These RIFIN-mediated rosettes appear to conceal PfEMP1 from antibody recognition, suggesting a dual role in immune evasion and survival (Goel *et al.*, 2015). Furthermore, STEVOR proteins have been found to independently mediate rosetting through glycophorin C binding, even in the absence of PfEMP1. Research by Niang *et al.* confirmed that STEVOR-driven rosetting protects merozoites from neutralizing antibodies (Niang *et al.*, 2020). These findings underscore the critical role of rosetting in the survival, transmission, and immune evasion of Plasmodium species.

### **Dendritic cell dysfunction as an immune evasion mechanism**

Dendritic cells (DCs) are pivotal in initiating and regulating adaptive immune responses by

capturing, processing, and presenting antigens to T cells. However, during Plasmodium infection, particularly in the blood stage, the functional capacity of DCs is significantly compromised, aiding the parasite's immune evasion strategy. The maturation of infected red blood cells (iRBCs) into the schizont stage leads to their rupture, releasing merozoites into the bloodstream along with contents from the parasitophorous vacuole (PV), including the parasite's digestive vacuole, which contains hemozoin and metabolic waste products. Free merozoites have a narrow time frame to invade new red blood cells; those that fail to do so remain in circulation and are subsequently phagocytosed by immune cells or removed by the spleen. Parasite waste materials, including hemozoin, interact with dendritic cells (DCs), but their influence on DC function is inconsistent. Some studies have shown that it inhibits DC maturation and function (Millington *et al.*, 2018).

### **Impaired T cell activation and proliferation**

During the blood stage of malaria infection, Plasmodium falciparum manipulates host immune responses, including the suppression of T cell activation and proliferation—an essential component of adaptive immunity. Normally, activated dendritic cells (DCs) present antigens to naïve T cells, initiating their activation and clonal expansion. However, in malaria, several factors compromise this process. Hemozoin, a byproduct of hemoglobin digestion by the parasite, accumulates in DCs and disrupts their function, leading to reduced expression of MHC class II and co-stimulatory molecules necessary for T cell activation (Langhorne 2006). Consequently, impaired DC function results in suboptimal T cell priming. Moreover, malaria infection is associated with elevated levels of immunosuppressive cytokines such as IL-10 and TGF- $\beta$ , which dampen T cell responses (Walther *et al.*, 2009). This immunoregulatory environment leads to a decrease in effector T cell proliferation and survival, limiting the ability of the host to generate a strong and sustained cellular immune response. Additionally, studies have shown that repeated or chronic exposure to malaria can induce T cell exhaustion, characterized by high expression of inhibitory receptors such as PD-1 and CTLA-4 on T cells,

further diminishing their function (Butler *et al.*, 2012). These mechanisms collectively impair effective T cell-mediated immunity, allowing the parasite to persist and evade immune clearance during the blood stage of infection.

### Challenges and future direction

Developing a malaria vaccine that works against *P. falciparum*, the deadliest malaria parasite, is a major goal for global health (Rajneesh *et al.*, 2023). A malaria vaccine would be a powerful addition to existing tools like bed nets, spraying, and proper treatment, helping to tackle the recent slowdown in reducing malaria cases and deaths worldwide (Al-Worafi, 2024). A vaccine will likely be necessary to achieve malaria elimination. After decades of research, RTS, S/AS01 (Mosquirix) is still the only malaria vaccine to have received regulatory approval, granted by the European Medicines Agency (EMA) in 2015 (Syed and Perspectives, 2022). The World Health Organisation (WHO) asked for further testing of RTS, S in ongoing phase 4 trials, set to last until 2024, to investigate rare safety concerns before recommending its widespread use (Asante *et al.*, 2024). The current RTS, S vaccine doesn't meet the World Health Organisation's goal of 75% efficacy, at least in its present form and dosing schedule (Okanda *et al.*, 2024). The goal of vaccination strategies is to prime the immune system by generating protective memory responses prior to exposure, thereby offering defense upon future encounters with the pathogen. Developing an effective malaria vaccine remains a significant scientific challenge due to the parasite's complex life cycle. As *Plasmodium* transitions from sporozoite to liver-stage forms and then to the blood-stage, it undergoes substantial morphological shifts and antigenic variation. These changes enable the parasite to evade host immune responses, hindering the development of long-lasting sterile immunity a hallmark of recovery in many other infectious diseases. Nevertheless, compelling evidence supporting the potential for malaria vaccination has emerged from experimental models in rodents, non-human primates, and humans, where immunization with attenuated sporozoites has led to sterile protection.

### Conclusion

Malaria, particularly caused by *P. falciparum*, remains a significant global health threat due to its complex life cycle and highly evolved immune evasion strategies. Gaining a deep understanding of the immune system's response to malaria is essential for advancing effective prevention and treatment methods for the disease. The complex interaction between the parasite's strategies to evade the immune system and the host's innate and adaptive defences underscores the importance of a comprehensive approach to tackling malaria. By uncovering the critical components and pathways involved in the immune response, scientists can pinpoint promising targets for vaccine development, immunotherapies, and diagnostic advancements for achieving meaningful protection against malaria, which solely depend on sustained interdisciplinary research, collaboration, and innovation.

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