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Immune Evasion by *Plasmodium falciparum* Parasites: Converting a Host Protection Mechanism for the Parasite's Benefit

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Abstract

Immune evasion is a strategy used by pathogenic microbes to evade the host immune system in order to ensure successful propagation. Immune evasion is particularly important for the blood stages of *Plasmodium falciparum*, the causative agent of the deadly disease malaria tropica. Because *Plasmodium* blood stage parasites require human erythrocytes for replication, their ability to evade attack by the human immune system is essential for parasite survival. In order to escape immunity-induced killing, the intraerythrocytic parasites have evolved a variety of evasion mechanisms, including expansion of plasmodial surface proteins, organ-specific sequestration of the infected red blood cells and acquisition of immune-regulatory proteins by the parasite. This review aims to highlight recent advances in the molecular understanding of the immune evasion strategies by *P. falciparum*, including antigenic variation, surface protein polymorphisms and invasion ligand diversification. The review will further discuss new findings on the regulatory mechanisms applied by *P. falciparum* to avoid lysis by the human complement as well as killing by immune factors of the mosquito vector.

Keywords

Malaria, *Plasmodium falciparum*, Immune Evasion, Infected Red Blood Cell, Merozoite, Antibody, Complement, Factor H

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1. Introduction

With an estimated 214 million cases annually among 3.3 billion people at risk, the tropical disease malaria is a leading cause of death worldwide. Particularly affected are children under 5 years of age and pregnant women in sub-Saharan Africa [1]. Global efforts to roll back malaria are undermined by the spread of parasite resistance against commonly used drugs. Acute is the increasing resistance against artemisinin-based medications, which till recently were highly recommended by the WHO to treat malaria infections [2] [3]. To date, there is no preventive vaccine available and besides drugs, malaria control measures are mostly based on insecticide-treated bed nets as well as spraying vector resting and breeding sites.

Malaria is caused by intracellularly living parasites of the genus *Plasmodium* and transmitted through the bite of a female *Anopheles* mosquito. Of the five *Plasmodium* species that are known to infect humans, *P. falciparum* causes the majority of deaths. During a mosquito bite, sporozoites are released from the mosquito salivary glands into the human dermis, enter the bloodstream, and circulate to the liver. In the liver, a single sporozoite will undergo asexual replication within approximately 5 days to release thousands (10,000 - 30,000) of merozoites, which then infect red blood cells (RBCs). During erythrocytic schizogony, which takes approximately 48 hours for *P. falciparum*, a single merozoite grows from the ring to the trophozoite stage, eventually resulting in a schizont containing 16 - 32 daughter merozoites. These are released into circulation upon erythrocyte rupture and can each infect new erythrocytes to begin the cycle again. This erythrocytic replication phase can continue for weeks and, in the case of *P. falciparum*, months and is responsible for the clinical symptoms of malaria. While acute clinical symptoms of malaria include fever, headache or nausea, severe malaria results in anemia, excessive inflammation, and the sequestration of infected RBCs (iRBCs) in small blood vessels of select organs, particularly the brain. Due to stress factors like lack of nutrition or host immune pressure, a small proportion of merozoites eventually develop into sexual precursor cells, the male and female gametocytes. Within minutes after their intake by the Anopheline mosquito, the gametocytes transform to male and female gametes and fertilization occurs in the mosquito midgut. The resulting zygote develops into an infective ookinete within the following 20 hours, which breaks through the gut epithelium and settles down at its basal site to transform into an oocyst. Sheltered by the oocyst wall, a final round of replication occurs, during which the sporozoites are formed, which then migrate to the mosquito salivary gland to wait for the next mosquito bite [4]-[7].

The obligate intracellularly living plasmodia reside within a membrane-bound vacuole for the most part of their life-cycle. Cell invasion by the sporozoites and merozoites occurs by active penetration of the hepatocyte and the erythrocyte, respectively, resulting in the formation of a parasitophorous vacuole (PV). In order to adapt the host cell for its own purpose, *Plasmodium*, however, has to insert its own proteins, like receptors, transporters or adhesins, into the PV membrane or the host cell plasmalemma [8] [9]. The subcellular compartmentalization is a measure of the malaria parasites to avoid the human immune system and theseparasites aim to minimize the time spent outside host cells. However, the infective sporozoite and merozoite stages are exposed to the human immune system during the minutes they need to infect their target cells. Also, the modified iRBCs can be recognized by the immune components.

During the liver phase of *Plasmodium*, naturally acquired immunity is not very effective. It has previously been reported, however, that infected hepatocytes can be destroyed by antibody (Ab)-dependent cellular cytotoxicity, or by the action of CD4+ and CD8+ T-cells and NK-cells, which induce final effectors such as nitric oxide [10]. The subsequent blood-stage infection, on the other hand, is characterized by a pro-inflammatory cytokine response, which enhances phagocytosis and killing of iRBCs by macrophages [11] [12]. Phagocytosis of the iRBCs is augmented by Ab-mediated opsonisation, which bind to plasmodial proteins that had been exported to the iRBC surface. However, these antigens are highly polymorphic and undergo clonal antigenic variation, meaning that effective opsonisation may only develop after many and varied malaria infections [13] [14]. Despite the fact that antigens on the merozoite surface are also polymorphic, Abs against conserved or semi-conserved epitopes can develop and then either inhibit RBC invasion or result in complement-mediated killing of the merozoites [15].

In order to avoid killing by human immune components, the blood stages of *P. falciparum* parasites have evolved multiple immune evasion strategies in parallel. In this review, the immune evasion mechanisms employed by *P. falciparum* to establish persistent infections and thereby increasing its chances of survival and transmission are described. Here we also focus on what is known about the underlying molecular mechanisms underpinning complement evasion in falciparum malaria and highlight the latest findings and prospects of this interesting area of research.

2. Immune Evasion by the Intraerythrocytic Parasites

The success of evasion of the human immune system by the malaria parasite blood stages depends on the large repertoire of anti-genetically diverse parasite proteins displayed on the surfaces of merozoites and iRBCs. Switching in the expression of the polymorphic proteins between blood stage generations offers an efficient mechanism for the blood stages to escape Ab-mediated recognition and to thus establish chronic asymptomatic infections [16]. It also remains a possibility that immune evasion can occur at the level of gametocyte-iRBCs. Generally, the mechanisms of immune evasion by the intraerythrocytic parasites are by antigenic variation and sequestration.

2.1. Antigenic Variation

In the malaria-endemic areas adults and older children develop non-sterile immunity to malaria. The acquisition of this immunity is slow and initially protects endemic individuals from susceptibility to severe malaria symptoms. Subsequently, continuous exposure to malaria infections leads to the development of natural immunity that offers protection from clinical disease [16]-[18]. The development of clinical immunity to malaria only happens after repeated reinfections, because the parasite has evolved mechanisms to efficiently evade the human immune response via antigenic variation. This strategy is the expression of variable and distinct proteins at the different life-cycle stages of the parasites. This changes the proteins exposed to and recognized by the immune system, thereby enabling the parasite to evade immune clearance and to establish chronic infections. Despite the ability to evade immunity, some gene products involved in switching are important candidate vaccine targets because they play a role in the development of non-sterile protective immunity [16] [19] [20]. It is known that antigenic diversity develops from two mechanisms: 1) the presence of multicopy gene families encoding variant surface antigens (VSA), and 2) the presence of polymorphic alleles in the parasite population [16] [21]. While the first measure is prominent in the intraerythrocytic parasites, the second measure is better known for the merozoites.

After merozoite invasion of an RBC, the parasite undergoes a series of drastic morphological and biochemical changes from rings to trophozoites to schizonts [22]-[24]. It is thought that during the 24-hours lasting development of the ring stages, which are found in circulation, the machinery for RBC modifications necessary for the export and surface exposure of parasite proteins involved in immune escape is installed [25]. The resulting modifications reshape the interphase between the iRBC and the host mediating their ability to sequester in microvasculature [16].

The *var* multigene family encodes *Plasmodium falciparum* erythrocyte membrane protein 1 (PfEMP1) proteins [26]-[28] and there are approximately 60 copies of *var* genes per parasite genome [29] [30]. A single *var* gene is expressed at one time during the ring stage while the others are silenced [31], and in the trophozoite and schizont stages, only a single antigenic variant PfEMP1 is expressed on the RBC surface (**Table 1**; **Figure 1**). However, parasites switch the expression of *var* genes, leading to different PfEMP1 molecules within a clonal population. *Var* gene silencing and switching is mediated by a variety of epigenetic mechanisms, like the involvement of histone modifications and the heterochromatin protein (HP1) [32]. The phenomenon of *var* gene switching enables the parasite to avoid immunity acquired to the already expressed PfEMP1 and this helps maintain a chronic infection via the process of clonal antigenic variation [16] [33]. The human immune response to the *P. falciparum* blood stages is determined mainly by recognition of the clonally variant PfEMP1 surface molecules [34] [35].

The *rif* and *stevor* gene families form part of known multigene families possibly involved in antigenic variation and immune evasion during the erythrocytic stages of *P. falciparum*. They encode the repetitive interspersed family (RIFIN) and sub-telomeric variable open reading frame (STEVOR) proteins, respectively, contributing to the iRBC surface repertoire [36] [37] (**Table 1**; **Figure 1**). Both, STEVORS and RIFINs, are expressed in a clonal fashion and undergo switches in gene expression, therefore supporting a role in antigenic variation and immune escape [38] [39] The expression of STEVOR influences the mechanical properties of the RBC membrane in asexual- and sexual-stage parasites, making them more rigid, which possibly enhances sequestration of immature gametocytes and iRBCs [40]-[42]. The role of RIFINs and STEVORs in sequestration as a mechanism of immune evasion was further supported by a case report of a patient who after splenectomy experienced a malaria relapse with an expansion of parasites that had lost transcription of PfEMP1, STEVOR and A-type RIFINs [43]. In volunteer infections, Abs to RIFINs were rapidly acquired, supporting the idea that their

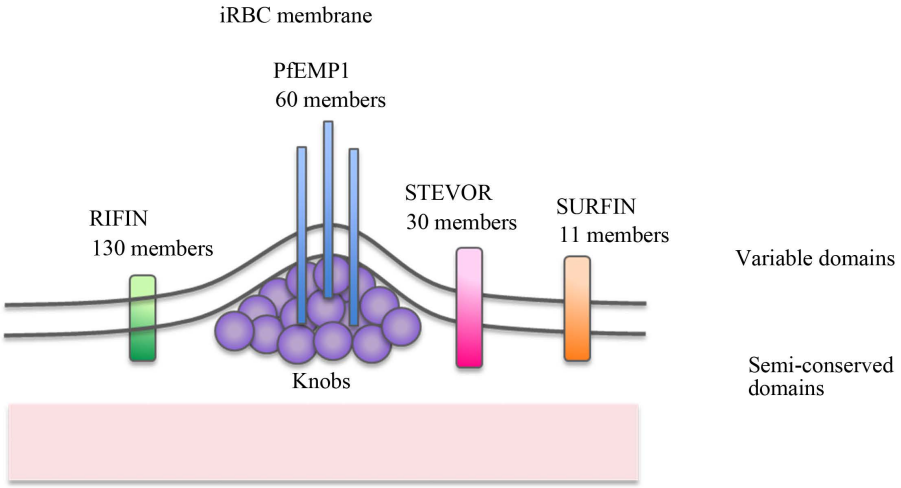

Figure 1. VSAs on the iRBC surface. Schematic representation of gene families coding for VSAs associated with the surface of *P. falciparum*-iRBCs. The immunodominant PfEMP1/*var* molecule is responsible for the adhesion of iRBC to microvasculature in deep tissues contributing to immune escape of parasites. PfEMP1/*var* is the driving force for antigenic variation in *P. falciparum*. Members of the other gene families, *rif*, *stevor* and *surfin* encoding RIFINS, STEVOR and SURFIN proteins respectively, undergo clonal variation, therefore playing a role in evasion of the host immune response. Abbreviations: PfEMP1/*var*, *Plasmodium falciparum* erythrocyte membrane protein 1; RIFINS/*rif*, repetitive interspersed family; STEVOR/*stevor*, subtelomeric variable open reading frame; SURFIN/*surf*, surface associated interspersed genes.

Table 1. Variant gene families of the *Plasmodium falciparum* blood stages.

Gene	Protein	Function	Related references
var	PfEMP1s	Antigenic variation, cytoadherence, immune evasion	[26] [28] [34] [35]
stevor	STEVORs	Sequestration of immature gametocytes, immune escape	[36] [40]-[42]
rif	RIFINs	unknown	[36]-[38]
surf	SURFINs	unknown	[67]

variability serves a function in immune evasion [44]. However, it appears that PfEMP1 is the major immune target of the iRBC and that RIFINs and STEVORs comprise minor epitopes [45].

2.2. Sequestration and Cytoadherence

A second immune evasion strategy of the blood stages is their ability to cytoadhere to human endothelial tissues and to therefore sequester into microvasculature of various organs. Trophozoites and schizonts of *P. falciparum* as well as developing stage I-IV gametocytes are not seen in the peripheral circulation of malaria-infected individuals. Whereas asexual parasites sequester in microvasculature of various tissues [46], maturing gametocytes are thought to sequester in the bone marrow and spleen [47]-[49]. This allows the parasite to leave circulation thereby avoiding immune clearance during passage through the spleen. The parasite VSAs largely mediating sequestration in the asexual blood stages have been identified to be the *var* gene family encoding PfEMP1. However, other gene families such as the *rif*- and *stevor*-encoding RIFINs and STEVOR proteins, respectively, could also play a role in sequestration at these stages. In the gametocyte-iRBCs minimal amounts of PfEMP1 were observed on the surface, which support minimal adhesive interactions with host endothelial receptors [40] [42]. However, STEVOR proteins were implicated in the increased deformability from developing to mature gametocytes. This mechanical property coincided with the deposition of STEVOR proteins on the surface of the gametocyte-iRBCs during their development and the disappearance of STEVORs when mature [40] [42]. In addition, the formation of rosettes by parasites with uninfected RBCs, auto-agglutination with other iRBCs bridged by platelets, contributes to the avoidance of splenic clearance and thereby

immune escape [50]-[53].

3. Immune Evasion by Merozoites

Merozoites are one of the few plasmodial stages that are extracellular and therefore directly exposed to the human immunological response [54]. In order to survive, the merozoite limits the time of exposure to possible neutralization by complement-mediated lysis or opsonization by host Abs. Another strategy is to deploy a range of molecular mechanisms to evade the immune systems so as to complete the invasion process. Blocking merozoite invasion is an attractive vaccine target since invasion is an obligate aspect of the parasite life cycle. However, any successful vaccine strategy targeting these stages would have to overcome the various types of immune evasion during merozoite invasion of RBCs. The mechanisms used by the merozoite to evade immunity include extensive diversity as well as complexity in the number of proteins that have been shown or hypothesized to be involved in the invasion process.

3.1. Polymorphism of Merozoite Surface Proteins

Though the precise function of some of these proteins are not known, surface proteins of *P. falciparum* merozoites have been classed into the merozoite surface proteins (MSPs) which form a permanent structurally complex coat, as well as *P. falciparum* apical membrane antigen 1 (PfAMA1), the group of *P. falciparum* erythrocyte-binding antigens (PfEBA), and the *P. falciparum* reticulocyte-binding proteins (PfRHs), all of which are stored in specialized apical organelles, the micronemes and the rhoptries, respectively [54]-[56].

In order to avoid immune attack, many MSPs are highly polymorphic. Further, *msp* genes frequently bear signatures of being under balancing selection pressure [57] [58]. These mechanisms result in immunologically distinct merozoites within a single infected individual. This distinction is made complex if a malaria patient is infected with multiple genetically distinct strains. As a result a primed immune system is less likely to effectively block the invasion of all merozoites [54]. Though anti-merozoite immune responses are often very strong in adults who have previously been infected with *P. falciparum* multiple times, this immunity is always partially effective at preventing parasite invasion [59]. The levels of MSP polymorphisms and the resulting contribution to immune evasion make them unattractive vaccine candidates. However, it is worth noting that some subdomains of MSPs are quite conserved and might contribute effectively towards a multivalent vaccine approach. The C-terminal domain of MSP1 is a good example of this phenomenon as it can have potent invasive inhibitory effects [15] [54].

3.2. Expansion of Invasion Ligands

Besides the use of polymorphic proteins in the immune evasion process, malaria parasites have evolved functional redundancy in invasion ligands to evade host humoral immune response. Members of the EBA and RH families of invasion proteins are already known to be targets of host Abs [54]. Therefore if the parasite relied on a single ligand to complete the later stages of invasion, the human host could develop sterile protective immunity against this ligand. Thus the parasite responds by expanding these two proteins to create paralogues, which then presents to the host a difficult task of having to block several invasion ligands. This strategy is also known as the “alternative invasion pathway” and phenotypes have been demonstrated in field isolates that have recently been adapted into culture including those in the first round of invasion [60] [61]. Another type of invasion proteins is AMA1, a micronemaltype I transmembrane protein that translocates to the merozoite surface [62]. AMA1 exhibits strain variability meaning that only strains encoding an AMA1 variant immunologically similar or identical to the AMA1 protein sequence variant used in a vaccine are inhibited. In addition, studies using double-knockout parasite lines provided evidence that variation in erythrocyte binding-like protein (EBL) family member expression plays a role in phenotypic variation and immune evasion [63].

Another level of antigenic variation and immune evasion in merozoites could be determined by the expression of RIFINs and STEVORs in these stages. STEVOR variants are exposed on the merozoite membrane [64]-[66] and have been reported to interact with glycophorin C as its host receptor in invasion [66]. It was also shown that Abs targeting STEVORs blocked invasion, but as STEVORs are clonally variant, the use of this avenue to evade immunity was not investigated. The surface associated interspersed gene (*surf*) coding for SURFINs is another gene family implicated in antigenic variation in *P. falciparum* merozoites [67] (**Table 1**). However the importance of these findings in the light of immune evasion remains to be elucidated.

4. Complement Evasion by the Blood and Sexual Stages

The complement system destroys invading microbes by C3b-mediated opsonization, immune cell recruitment mediated by C3a and C5a, and the formation of a terminal complement complex (TCC) to induce targeted lysis of invading microbes. Three major pathways are known, termed the alternative, classical and lectin pathways. While the classical and lectin pathways are initiated in response to bacterial molecular patterns or antigen-immune-complexes, the alternative complement pathway (ACP) is active continuously at a low rate by spontaneous hydrolysis of complement factor C3.

Human complement is abundantly present in the blood and thus it is the first immune defense mechanism the malaria parasite comes into contact with, once it enters the human body. Malaria infections can induce the classical pathway via the formation of antigen-Ab immune complexes or the ACP, among others via the parasite digestive vacuoles, which during schizont rupture are released together with the merozoites into the blood stream [68]-[73]. It is meanwhile postulated that acquired merozoite invasion-inhibitory Abs act through activation of the classical complement pathway rather than through functionally inhibiting the invading merozoites [74].

It is known that a high number of microbial pathogens are able to prevent complement recognition, among others via the recruitment of host regulators to the pathogens' surfaces [75] [76], and increasing insights are currently gained on complement evasion by *P. falciparum*. While complement evasion by the sporozoites has not yet been investigated, several new studies were able to unveil the molecular mechanisms used by the blood and mosquito midgut stages of *Plasmodium* to avoid destruction by the ACP [77]-[79].

4.1. Complement Evasion by the Asexual Blood Stages

In order to prevent any damage by complement, human cells use a variety of complement regulators, which either exhibit decay-acceleration and/or co-factor activity, thus they either help disassembling the C3 and C5 convertase complexes or support cleavage of C3b by factor I. Such inhibitors include membrane-bound regulators like complement receptor 1 (CR-1), cluster of differentiation 55 (CD55) or 59 (CD59), and central fluid-phase regulators like C4-binding protein (C4BP) and factor H (FH) [80]. As the main regulator of the ACP, FH has an important role in discriminating between self and non-self surfaces. The protein comprises 20 complement control protein (CCP) modules, beta-sandwich domains containing about 60 amino acid residues. Besides FH, the FH family consists of FH-like protein (FHL1), an alternative splicing product of FH comprising CCP modules 1-7, as well as the FH-related proteins FHR1-5 (**Figure 2(a)**) [81]-[83].

Two new studies demonstrated that free merozoites as well as intraerythrocytic schizonts acquire FH and FHL1 to inactivate C3b attached to the iRBC surface, in consequence protecting themselves from TCC assembly and subsequent lysis [78] [79]. The schizont-iRBCs further bind FHR1. FH-binding to merozoites was mapped to module CCP5, while schizonts acquire FH via two contact sites, CCP5 and CCP20. Both modules are known binding-sites of bacterial microbes, CCP20 further comprises the binding motif for self-surfaces [76] [84] [85] (**Figure 2(a)**).

The transmembrane protein Pf92 was identified as the FH-binding receptor of merozoites [78] (**Figure 2(b)**). Pf92 is a member of the six-cysteine protein family, which together with other surface molecules like the ones of the MSP1 family forms multi-protein complexes on the merozoite surface. Parasites lacking Pf92 are unable to recruit FH and in consequence inefficient in C3b inactivation. Considering that Ab-mediated inactivation of FH results in significantly impaired blood stage replication [79], plasmodial receptors involved in complement evasion might represent highly attractive targets for malaria vaccines.

Noteworthy in this context, RBC invasion by merozoites involves CR1 (**Figure 2(b)**), which is recognized by Rh4 [86] [87]. The binding site of Rh4 was mapped to CCP1 of CR1, and this region is known to be involved in binding C3b and C4b to accelerate decay of the C3 and C5 convertases [88]. In consequence, Rh4 binding specifically inhibits the convertase decay-acceleration activity of CR1 [89]. However, because merozoite invasion of RBCs is a rapid process, CR1 inhibition should be rather inefficient. It has thus been discussed that the high conservation of CCP1 and not its decay-acceleration activity is the reason for merozoite binding to this module [80].

4.2. Complement Evasion by the Mosquito Midgut Stages

Another point of attack for the complement system to kill the malaria parasite is represented by the extracellular

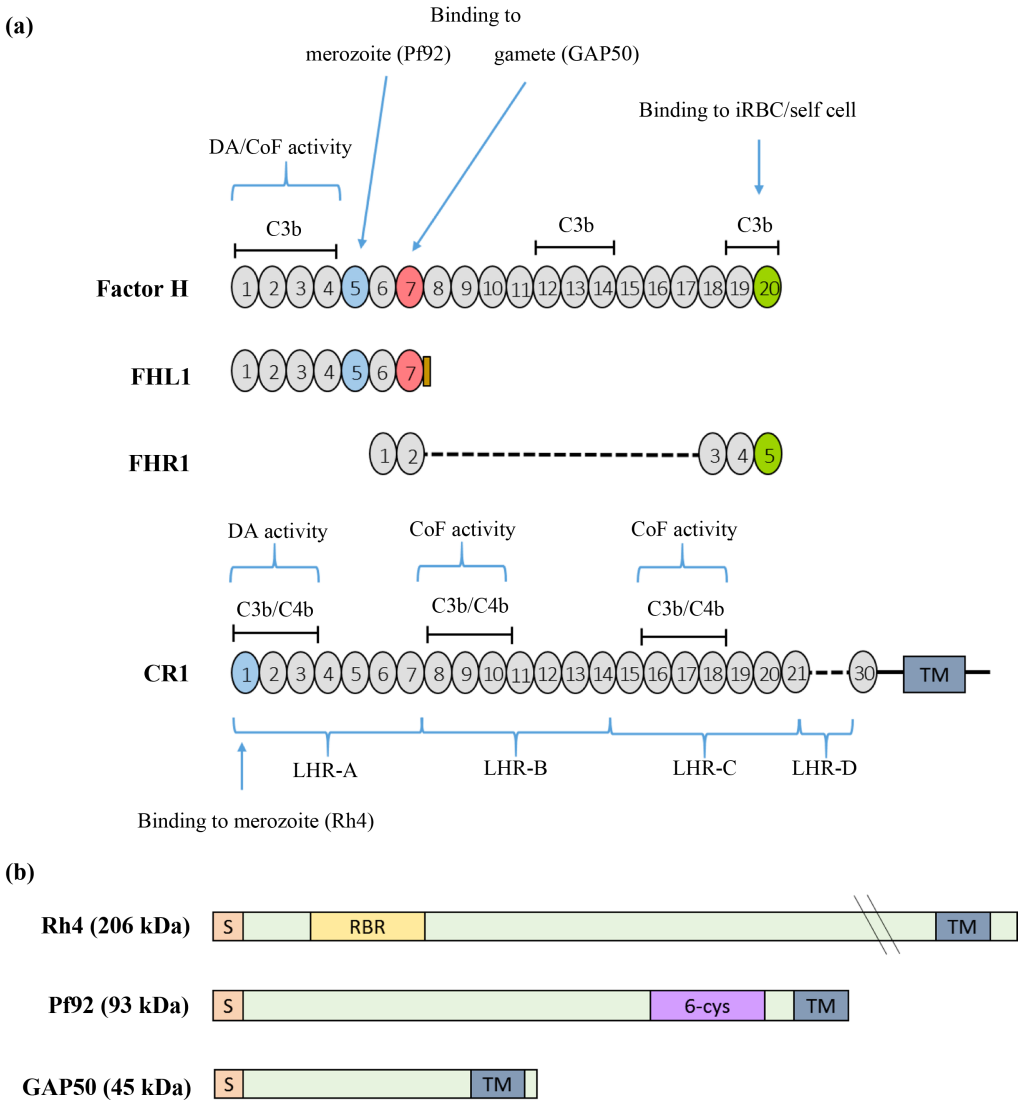

Figure 2. Factor H family proteins and plasmodial complement receptors. (a) Domain structure of FH, FHL1, FHR1, and CR1. The binding sites for C3b, C4b and the plasmodial receptors of merozoites (blue), schizont-iRBCs (green) and gametes (red) are indicated. (b) Domain structures of the identified plasmodial complement receptors. Abbreviations: CoF, co-factor; CR1, complement receptor 1; DA, decay-acceleration; FH, factor H, FHL1, FH-like protein 1; FHR1, FH-related protein 1; LHR, long homogenous region; RBR, receptor-binding domain; S, signal peptide; TM, transmembrane domain.

mosquito midgut stages, which develop in the human blood meal. The influence of host complement factors on the mosquito midgut stages was originally investigated in the chicken malaria model *P. gallinaceum*. It was shown that zygotes were able to evade APC lysis by binding to an (unidentified) component of the blood meal, however, the parasites lost their protection 6 - 8 hours later [90] [91]. The results were subsequently confirmed using the rodent malaria parasite *P. berghei*. Whereas rat ACP factors were present in the mosquito midgut for several hours after the blood meal, the sexual-stage parasites were protected from complement-induced lysis for approximately 3 hours [92]. Later, it was shown that the human ACP is active in the mosquito midgut for approximately 1 hour, during which it represents a severe threat for the emerging gametes of *P. falciparum*, once they have egressed from the enveloping erythrocyte [77]. The protecting factor was identified as FH, which is rapidly bound by the extracellular gametes from the blood meal. Binding of FH to the parasite surface then promotes the inactivation of surface-bound C3b via factor I.

In *P. falciparum* gametes, the FH-binding receptor was identified as the plasmodial transmembrane protein, glideosome-associated protein 50 (GAP50; **Figure 2(b)**). GAP50 was originally assigned to the parasite inner

membrane complex (IMC), an alveolar double-membrane structure underneath the gametocyte plasmalemma, where N-terminal portion of GAP50 protrudes into the IMC lumen [93]-[95]. However, at onset of gametogenesis the IMC disintegrates and GAP50 relocates to the plasmalemma, where it then binds the FH module CCP7 via its N-terminal portion and thus protects the extracellular gametes from attack by the human complement [77] [96].

Abs directed against GAP50 are able to reduce FH-binding to the gamete surface, leading to impaired gametogenesis and blocked transmission of the malaria parasites to the mosquito, making GAP50 a promising new candidate for transmission blocking vaccines [77]. In accordance with these data, known transmission-blocking Abs directed against prominent sexual stage surface proteins like Pfs230 or Pfs25 require active human complement to kill the mosquito midgut stages via the classical complement pathway [97]-[102].

5. Evasion of the Mosquito Immune System?

Mosquitoes possess an innate immune system to defend microbial offenders. In this context it was previously demonstrated that *Anopheles gambiae* mosquitoes have the capacity to mount an immune response against plasmodia. Among others, midgut epithelial cells activate nitration reactions against *Plasmodium* infection, leading to reduced parasite survival by promoting lysis via thioester-containing protein 1 (TEP 1) [103]-[105]. TEP1 is an important component of the mosquito complement-like system. A recent study showed that some parasite lines from areas also endemic to *A. gambiae* are able to evade the mosquito immune system. However co-infection experiments revealed that parasite survival is determined by genetic differences in the various *P. falciparum* strains [106]. Consequently, genetic mapping, linkage group selection and functional genomics showed that *P. falciparum* parasites require the female gamete-specific six-cysteine protein Pfs47 to evade *A. gambiae* mosquito immune responses mediated by TEP1. The activity of Pfs47 may be to prevent TEP1-mediated lysis by suppressing midgut epithelial nitration responses [107].

6. Conclusion

Intracellular pathogens avoid direct exposure to the immune system by infecting host cells and notably, *P. falciparum* is not an exception to this immune evasive strategy. By infecting RBCs and liver cells, malaria parasites eschew destruction by the host immune system, in consequence enhancing their survival and thus maintaining continuous transmission. Sequestration as an immune evasion mechanism is used by both, the asexual and sexual stages of malaria parasites. The blood stages in addition to employing VSAs and polymorphic molecules to escape immune attack also acquire FH to their surface to protect themselves from complement-mediated lysis. Gametes on the other hand have so far been shown only to exhibit complement evasion mechanisms by co-opting FH for protection. There is no published data as at yet demonstrating antigenic variation by gametocytes and/or gamete antigens, but this remains a possibility. As FH polymorphisms have already been described, investigations focusing on the potential implications of these variations on complement evasion and how the occurrence of polymorphic variants influences the incidence of malaria in the endemic setting are current pressing tasks. The findings would be of great benefit for the design of a malaria intervention with a unique opportunity to target both the asexual blood and the sexual stages, thereby preventing disease progression and transmission.

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