Review

Naturally Acquired Antibodies against *Plasmodium falciparum*: Friend or Foe?

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Abstract: Antibodies are central to acquired immunity against malaria. *Plasmodium falciparum* elicits antibody responses against many of its protein components, but there is also formation of antibodies against different parts of the red blood cells, in which the parasites spend most of their time. In the absence of a decisive intervention such as a vaccine, people living in malaria endemic regions largely depend on naturally acquired antibodies for protection. However, these antibodies do not confer sterile immunity and the mechanisms of action are still unclear. Most studies have focused on the inhibitory effect of antibodies, but here, we review both the beneficial as well as the potentially harmful roles of naturally acquired antibodies, as well as autoantibodies formed in malaria. We discuss different studies that have sought to understand acquired antibody responses against *P. falciparum* antigens, and potential problems when different antibodies are combined, such as in naturally acquired immunity.

Keywords: malaria; *Plasmodium falciparum*; immunity; antibodies

1. Introduction

Malaria still inflicts an extreme level of burden on people living in endemic regions [1]. Africa carries the largest share of this burden, which could also be further aggravated in some areas by wars, natural disasters, and epidemics or pandemics of other serious diseases such as Covid-19 [2]. Malaria is caused by different *Plasmodium* species and is transmitted in human populations by bites of infective female Anopheline mosquitoes. The success of *Plasmodium* species as parasitic organisms is based on their ability to evade immune attacks directed against them by the human host, as well as the mosquito vector. During evolution, the genetic background of both humans and mosquitoes has been of importance in forming which parasites can multiply successfully.

Antibodies are considered an efficient product of the immune system and they are generally produced by B cells/plasma cells, but there is an increasing body of evidence to support antibody production by cancerous and normal non-B cells, such as in proximal tubuli cells and epithelial cells [3–6]. Naturally acquired antibodies against infectious agents can exert their effector functions by simple binding (steric hindrance), complement activation, cellular cytotoxicity, and opsonophagocytosis [7]. The attention of the scientific world was called to the importance of antibodies in malaria immunology by exquisitely performed experiments where plasma obtained from adult or cord blood was used to treat parasitological and clinical symptoms of malaria in sick children [8,9]. Later studies have doubted that antibodies should work as a treatment, but the idea of using monoclonal antibodies as part of a treatment protocol is a new possibility [10], even though this kind of treatment might be available mainly for travelers. Despite the fact that the malaria parasite
presents a number of antigens to the immune system, which has the ability to generate a substantial variability in the production of antibodies, most people living in endemic regions are still not able to maintain high levels of effective antibodies for a long period of time. The half-life of antibodies against measles has, for example, been estimated to be around 200 years [11], while antibodies against malaria parasites are only stable for a few months [12–14]. The widespread presence of atypical memory B cells in endemic areas could be one of the reasons for the immune inefficiency [15,16], but there is also evidence that this set of B cells participates in the production of parasite neutralizing antibodies [17].

Here, we review the current knowledge about naturally acquired antibodies elicited against *P. falciparum* and highlight antibody interactions with important antigens expressed as the parasite goes through different stages in the human host as well as the mosquito.

2. Antibody Response in the Dermis and at the Liver Stage

The complex and somewhat treacherous interaction of malaria parasites with the human host begins when a parasite-infected female *Anopheles* mosquito injects about 10–150 sporozoites into human skin [18]. Recent studies using human skin explant revealed that sporozoites move rapidly through the dermis [19,20] in a similar way as was observed in rodent *Plasmodium*, both in vitro and in vivo [21,22]. Moreover, based on rodent *Plasmodium* studies, there is evidence to show that about half of the inoculated sporozoites could remain in the skin where they form extrahepatic exoerythrocytic forms. *P. falciparum* is not known to induce a significant dermal immune response, but a recent study based on a *Plasmodium berghei* animal model showed that anti-sporozoite antibodies targeting mainly the circumsporozoite protein (CSP) have protective functions by inhibiting sporozoite motility through the skin [23]. Although this antibody-mediated protection against sporozoites at the dermal stage has not been demonstrated in naturally infected individuals, it could represent a new level in our understanding of the versatility of antibody responses to *Plasmodium* species.

The few sporozoites that are able to make it to the bloodstream quickly invade the hepatocytes and are exposed to the immune system for a relatively short period of time. However, naturally acquired antibodies against whole *P. falciparum* sporozoites have been demonstrated in endemic areas [24,25]. Circumsporozoite protein (CSP) is the dominant antigen on sporozoites and contains an amino acid central repeat region that is composed of different numbers of asparagine–alanine–asparagine–proline (NANP) repeats. Strong antibody responses have been found to be produced against NANP repeats [26–30] and against the other regions of CSP [31]. Naturally acquired antibodies against whole sporozoites are more widespread and could even be higher in children [30] than antibodies against the dominant repeat region (NANP) of CSP. This indicates that antibodies are also elicited against other sporozoite antigens than the immunodominant CSP. Functional activities of anti-sporozoite antibodies have not been well characterized, but recent evidence has shown that naturally acquired IgG antibodies directed against CSP can fix the complement to prevent hepatocyte invasion and kill parasites in vitro [32].

3. Antibodies against Merozoites

The asexual stage of *P. falciparum* is responsible for all known symptoms of malaria; thus, functional antibodies against parasite antigens at this stage should be able to reduce or prevent clinical symptoms of malaria. Merozoite-filled vesicles, merozomes, from parasite-infected hepatocytes release merozoites into the blood stream where they invade erythrocytes to begin a 48-h life cycle that will lead to an exponential increase in production of merozoites. Merozoites in the bloodstream are more exposed to the immune system and studies have identified naturally produced antibodies against a majority of the known merozoite surface proteins as well as against merozoite organelles such as rhoptries and micronemes [33].

Merozoite surface protein 1 (MSP1) is the most abundant protein on the merozoites and plays an important role in erythrocyte binding and invasion [34]. Some studies have
found correlations between anti-MSP1 antibodies and protection against clinical symptoms, while others have not [33,35]. Anti-MSP1 antibodies have been shown to inhibit erythrocyte invasion, enhance monocyte-mediated phagocytosis of parasites, and aid in complement fixation [36–38]. Vaccination of humans with full-length MSP1 leads to the production of antibodies with several of these effector mechanisms [39]. MSP1 is produced as a 196-kDa precursor that undergoes a two-step proteolytic processing essential for both egress [40] and invasion. There is evidence for the existence of naturally acquired antibodies that block this important proteolytic processing of MSP1 [41], called processing inhibitory antibodies, but it is interesting to note that the same study also found antibodies that could interrupt the binding of the processing inhibitory antibodies. Thus, any protective advantage that may be associated with interrupting the MSP1 proteolytic process could also be abrogated by these blocking antibodies, because they target the same epitope. This is one of the few studies that have elegantly shown that antibodies can be beneficial not only for the human, but also for the parasite. Binding of blocking antibodies to the epitope in the presence of processing inhibitory antibodies would ensure the parasite full proteolytic processing of MSP1 and thus a proper invasion of RBCs. Most studies in the field of malaria have focused on finding the antibodies that inhibit the parasites, since these antigens could be potential vaccine targets, but we should probably put more emphasis on showing those results that could also be beneficial for the parasites. Having antibodies that can be both good and bad could be one of the explanations for why no malaria vaccine has yet proven to be fully successful. We have ourselves, for example, shown that inhibitory results can be severely affected depending on which parasite line of *P. falciparum* is used for the experiments [42]. When purified plasma samples (containing mostly antibodies) from endemic areas of Tanzania were used in growth inhibitory assays, parasite-specific antibodies in most samples inhibited the growth of 3D7 and K1 *P. falciparum* lines, but when W2mef was used, the growth was actually enhanced, sometimes as much as 25–50%. It is well established that in endemic areas, many different parasites circulate [43,44] and if antibodies are produced naturally that can enhance the growth of parasites, this is an efficient way for parasites to avoid getting cleared by the human immune system and this should be studied more in detail. It is also known that parasites can vary their invasion pathways to evade inhibitory antibodies [45] and there is evidence that an increase in the growth of parasites can be obtained when naturally acquired antibodies from some individuals are added to *P. falciparum* parasites in vitro [46]. For other pathogens such as the parasite *Leishmania* or viruses like Zika and Dengue, it has been shown that antibody-mediated responses involving the complement or FcR pathways do not always lead to protection or reduced infection, but can sometimes be exploited by these pathogens for enhanced invasion of host cells [47]. This phenomenon is known as antibody-dependent enhancement (ADE) and it is not clear whether *P. falciparum* could also use this mechanism to enhance hepatocyte or erythrocyte invasion. A study suggested that this could definitely be possible, since a monoclonal antibody obtained from MSP1	extsubscript{42} vaccines enhanced parasite invasion and polyclonal IgG enhanced invasion in a complement-dependent manner [48].

Apical membrane antigen 1 (AMA1) is a micronemal protein that is transferred to the merozoite surface just prior to merozoite egress [49]. Like MSP1, AMA1 undergoes proteolytic processing [50] to be functional in erythrocyte invasion. The ability of AMA1-specific invasion inhibitory antibodies raised in rabbits to inhibit proteolytic processing [51] may suggest that naturally acquired AMA1-specific antibodies in humans could also function through inhibiting proteolytic processing. Indeed, protective antibodies directed against AMA1 have been reported in children and adults living in some endemic areas [52,53], but these antibodies could be strain-specific due to high polymorphisms seen in AMA1 [54]. Erythrocyte binding antigens (EBAs), especially EBA175, EBA140, and EBA 180, have repeatedly been shown to elicit antibodies, which may possess invasion inhibitory activities in endemic populations [14,45] and they have also been associated with protection. The reticulocyte-binding homologue family of proteins is localized in the rhoptries and is also the target of blood-stage antibody response. Prominent among this protein fam-
ily are PfRH1, PfRH2, PfRH3, PfRH4, and PfRH5; they coordinate with EBA members to make erythrocyte invasion successful. A study in a Kenyan population showed that antibodies produced against PfRH2a/b and PfRH4 were acquired in an age-dependent manner [45]. A prospective study conducted in Papua New Guinea showed that IgG subclass responses to PfRH2 were predominantly IgG1 and IgG3 and strongly associated with a reduced risk for symptomatic malaria [55]. This study was important because the entire PfRh2a/b was expressed in eight fragments and all of them elicited an antibody response that showed a significant association with reduced risk for malaria. Another study in a low malaria transmission region of Peru also found that the IgG1 response against PfRh2a/b was significantly higher in asymptomatic individuals, and that the elevated total IgG antibody response against the proteins was positively associated with decreased parasitemia [56]. PfRh5 is a potential vaccine, because it is a highly conserved protein and also plays essential roles in invasion [57]. A recent study reported a low seroprevalence of antibodies against PfRh5 in a complex with Pf113 and CyRPA (cysteine-rich protective antigen) in a Ghanaian population [58], and an earlier study [59] also found a low seroprevalence of PfRh5-specific antibodies in Mali, but these antibodies were found to have parasite inhibitory activities. It is intriguing that naturally acquired IgG antibodies produced against highly polymorphic parasite antigens, such as MSP1 and AMA1, are more prevalent and also have approximately two orders of magnitude higher IgG reactivity than PfRh5-specific antibodies. However, it is known from before that not only the level, but also the function of antibodies could be of importance in the development of natural immunity against malaria [60]; thus, even if the concentration of PfRh5 antibodies might not be high, the antibodies could still be of major significance. The majority of the parasite antigens enumerated above, and those not mentioned such as MSP2, MSP2, MSP3, MSP7, MSP9, MSP10, and GAMA, elicit complement fixing antibodies and they can all contribute to the immune system armament against the asexual stage of *P. falciparum* [61]. Protection from an antibody response to a single antigen is not likely to be sufficient for sustained protection against malaria in endemic regions. This was demonstrated in a Kenyan population where high levels of antibodies as well as responses to multiple antigens were found to be predictive of protection against malaria [62].

Interethnic differences in antibody responses to some blood-stage antigens such as ring-infected erythrocyte surface antigen (RESA) and Pf322 have been used as indirect evidence for the existence of an association between naturally acquired immunity and human genetic factors [63]. A genome-wide association that assayed 174950 single nucleotide polymorphisms (SNPs) found 25 SNPs with a possible influence on MSP1 antibody responses [64]. However, an earlier multicenter study in Africa and Asia that assayed 202 SNPs only found moderate evidence for an association of antibody responses to MSP2 and CD36 [65]. Meanwhile, earlier investigations based on classical twin and parent–offspring studies have demonstrated heritability of antibody responses against RESA, MSP1, and MSP2 [66–68]. These genetics studies have shown that host factors could also play important roles, apart from parasite factors, in the pattern of natural antibody response observed in endemic regions. Bigger studies involving many different populations and SNPs are needed to show if and how genes have been selected during our co-evolution with *P. falciparum*.

4. Antibodies against the Surface of the Infected Red Blood Cell

Obstructions of small blood vessels are caused by binding of proteins expressed by *P. falciparum* on the surface of infected red blood cells (iRBC) to human endothelial cells. This process is central for the development of severe forms of malaria mainly in children. One of the main iRBC proteins is *P. falciparum* erythrocyte membrane protein 1 (PfEMP1), and antibodies targeting PfEMP1 have been shown to be associated with a reduced risk of severe malaria in children in endemic areas [69]. A study comparing antibodies against merozoite surface proteins and anti-PfEMP1 antibodies found the latter to be more protective in younger and older children, while the former exerted protective
effects only in older children [70]. VAR2CSA is a member of the PfEMP1 protein family that is responsible for sequestration of *P. falciparum*-iRBC in the placenta by binding to chondroitin sulphate A (CSA) [71]. The sequestration of parasites expressing VAR2CSA is mainly responsible for pregnancy-associated malaria (PAM) and causes significant damage to maternal and neonate health in endemic areas. VAR2CSA is produced as a protein with six Duffy-binding like (DBL) domains and three antigenically important interdomain (ID) regions [72]. Natural antibodies targeting these domains and antibodies that prevent CSA binding have been shown to be acquired in a sex and parity-dependent manner in endemic areas and are considered to be protective against PAM [73–77], but they have also been shown to exist in men and children [78]. The main mechanism of action of these antibodies has been shown to be inhibition of binding to CSA, but more cytophilic antibodies directed against VAR2CSA could also function by opsonic phagocytosis of placenta-specific parasites [79,80]. However, a recent systemic and meta-analysis of 33 studies conducted in endemic areas [81] could not find anti-VAR2CSA to be associated with protection against PAM or birth outcomes, but rather with exposure to infection. This strong correlation of anti-VAR2CSA antibodies with exposure has made these antibodies be considered as a powerful tool for monitoring the levels of malaria burden and transmission in endemic areas, irrespective of whether they are protective or not [82,83].

5. Autoantibodies at the Blood-Stage

Autoantibodies targeting different human cellular components have been associated with *P. falciparum* infections in endemic areas. Autoantibodies can be directed against membrane phospholipids [84–86], erythrocyte membrane proteins [87,88], or DNA [89]. During an acute episode of malaria, it is quite common to become DAT (Direct Antiglobulin Test)-positive, a sign that there are autoantibodies bound to RBC. This can later disappear, even though studies have found around 5% of an apparently healthy adult population in Kenya and Thailand to be DAT-positive [90,91]. Another study has shown a relationship between DAT-positivity and acquired protective immune responses against malaria [92], indicating that these antibodies could have a protective effect.

Not much is known about the mechanisms through which autoantibodies are generated in malaria infection, but it has been suggested that the expression of parasite proteins such as PfEMP1 on erythrocyte membranes could be an initiation step. For instance, a genome-wide study [93] found that PfEMP1 shares a 14-amino acid motif with a human serum protein, vitronectin. This creates a molecular mimicry pathway for autoantibody generation during a normal immune response directed against PfEMP1. Cysteine-rich interdomain region 1 (CIDR1α) of PfEMP1 has also been suggested as a polyclonal activator of B cells that can cause production of non-specific IgM [94], which could be a pathway for autoreactivity. Autoantibodies could also be generated against components such as phosphatidylserine (PS), which is a membrane phospholipid not normally exposed, since it is a resident of the plasma membrane inner leaflet, but it is exposed when the erythrocyte ruptures.

Autoantibodies targeting DNA and other cytoplasmic components could be a form of homeostatic response to mop up cellular fragments, or debris produced during erythrocyte rupture that accompany blood-stage infection, or are generated by oxidative damage associated with antimalarial drug use [95]. If this is the case, then these antibodies will not have any protective effect against future *P. falciparum* infections. On the contrary, they could instead do more harm than good. Autoantibodies have been shown to aggravate malaria pathology by inducing cell lysis, microthrombosis, and inflammation [96]. A recent study demonstrated a clear correlation between kidney injury and autoantibodies against DNA and PS in Ugandan children with severe *P. falciparum* malaria [89]. Anemia, a major symptom of malaria, has also been shown to be associated with anti-PS antibodies [85,89,97]. However, there are also autoantibodies that could be associated with protection against malaria, as found in a Liberian population where antibodies targeting Band 3 neoanti-
gens were found [98], and sera obtained from autoimmune patients could have similar effects [99]. Anti-Band 3 (neoantigen) antibodies correlated with lower parasite density and higher hematocrit [98,100], suggesting a possible role in protection against malaria, even though the correlation could also just be a result of exposure, since the neoantigens are not naturally exposed when there is no malaria. However, it is interesting to note that during the recent years, it has been speculated that having malaria is protective against certain autoimmune diseases such as systemic lupus erythematosus (SLE), and sera of patients with SLE has been shown to inhibit in vitro the growth of \textit{P. falciparum} [101].

6. Antibodies at the Human–Mosquito Junction

Gametocytes are specialized and permanently differentiated forms of \textit{Plasmodium} that are responsible for parasite transmission from the human host to the Anopheles mosquito. Mosquitoes pick up gametocytes when they take blood meals from infected humans. In response to the environment in the mosquito lumen, gametocytes transform and after fertilization, they form a zygote. Pfs230 and Pfs48/45 belong to the 6-cystein protein family that is expressed on the surface of gametocytes and play important roles in fertilization [102]. Studies have found naturally produced antibodies against these antigens in most endemic areas, even in individuals with limited exposure to malaria [103]. A more recent study found non-febrile school children living in a high transmission area to produce more anti-Pfs230 antibodies compared with a similar group of children in a low transmission area [104]. Mosquitoes also ingest these antibodies as they take blood meals and the antibodies can exert their transmission blocking activities by blocking fertilization, which is an important step in malaria transmission. Pfs47 is also a member of the 6-cysteine family of proteins [105]. The immune system of Anopheles mosquitoes can limit \textit{Plasmodium} infection, but Pfs47 can be used by the parasite to subvert the complement-like immune mechanism of the mosquito in order to establish an infection [106]. The interaction of Pfs47 with its receptor on midgut cells disrupts an apoptosis pathway mediated by the JNK/caspase complex, a step necessary for killing the invading parasite by membrane lysis [107]. The midgut cell receptor of Pfs47 was recently shown to be P47Rec, a highly conserved protein [108]. This efficient evasion of the cellular and humoral components of the mosquito immune system is the first significant barrier cleared by \textit{P. falciparum} parasites in their transmission cycle. It could be challenging to produce effective antibodies against Pfs47 as the majority of monoclonal antibodies produced against full-length recombinant Pfs47 lacked transmission blocking activities, and some antibodies even seemed to increase the transmission [109].

7. Conclusions

There is no lack of antibody attacks against \textit{P. falciparum} in the human host as antibodies accompany the parasites through all the stages of development, and human anti-parasite antibodies are even carried on into the mosquitoes. Although the functional roles of autoantibodies are still enigmatic, their contribution to malaria pathogenesis cannot be disregarded. The ability of malaria parasites to complete their life cycle despite the abundance of antibody attacks is probably a high level of evolutionary success with a win–win situation between the human host and the parasites. Antibody responses are able to protect the host enough for the host to survive, but not enough to kill the parasites; thus, parasites can survive in low numbers and be transmitted to a new host. The field of malaria research where combinations of antibodies with different specificities are used together needs more focus in future studies to elucidate what happens in real life in a human being during the development of natural immunity against malaria.

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