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MINIREVIEW

Potential Immune Mechanisms Associated with Anemia in *Plasmodium vivax* Malaria: a Puzzling Question

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The pathogenesis of malaria is complex, generating a broad spectrum of clinical manifestations. One of the major complications and concerns in malaria is anemia, which is responsible for considerable morbidity in the developing world, especially in children and pregnant women. Despite its enormous health importance, the immunological mechanisms involved in malaria-induced anemia remain incompletely understood. *Plasmodium vivax*, one of the causative agents of human malaria, is known to induce a strong inflammatory response with a robust production of immune effectors, including cytokines and antibodies. Therefore, it is possible that the extent of the immune response not only may facilitate the parasite killing but also may provoke severe illness, including anemia. In this review, we consider potential immune effectors and their possible involvement in generating this clinical outcome during *P. vivax* infections.

Malaria remains one of the most important public health problems in the world, with about 3 billion people at risk of contracting the disease and 781,000 deaths estimated annually (1). The global burden of human malaria is caused almost exclusively by two species of parasites: *Plasmodium falciparum* and *Plasmodium vivax*. Existing research efforts have largely focused on *P. falciparum* because of the higher mortality it causes, especially in Africa (2, 3). However, *P. vivax* remains more widely distributed than *P. falciparum* and is a major public health threat affecting populous regions in Asia, the horn of Africa, and Central and South America (4). The spectrum of vivax malaria ranges from presentation as a relatively benign disease to severe and sometimes fatal illness, mainly in children (5, 6) and pregnant women (7). The mortality rates among patients presenting *P. vivax* malaria are comparable to those attributable to *P. falciparum* malaria, as evidenced by hospital-based studies (6, 8, 9). It has been demonstrated that chloroquine resistance parallels severe disease (especially severe anemia) in some areas (10). In addition to the concerns imposed by increasingly drug-resistant parasites, it should not be forgotten that transmission of *P. vivax* is harder to control and eliminate than *P. falciparum* transmission because the former species may cause a relapse after resolution of the primary infection and also due to its early gametocytogenesis. In areas of endemicity, relapse of vivax malaria is an important source of parasite transmission to susceptible vectors and a major cause of malaria in young children (11).

BURDEN OF ANEMIA RELATED TO VIVAX MALARIA

In times of renewed efforts to eradicate malaria, the attention on *P. vivax* increases in consideration of the fact that infections related to this species are also able to cause severe disease, including anemia as one of the major complications (5, 12, 13). Despite the striking statistics, there are few studies focusing on anemia triggered by *P. vivax* (5, 6, 14) and most of what is known about that refers to evidence obtained from studies conducted with *P. falciparum*, leading to the use of proxy pathophysiological processes to explain vivax anemia.

Estimates of rates of severe anemia in vivax malaria range from 1.4% to 32% (15–18). In terms of frequency and severity, the literature points particularly to a greater burden of anemia in young children (9, 15, 19–24) and during pregnancy (7, 25). Cross-sectional studies carried out in the Brazilian Amazon, where *P. vivax* predominates, showed frequencies of anemia of as high as 80% in children and adolescents (15, 16, 18, 19). *P. vivax* disease affects only 25% of children from newborns to those 14 years old. Moreover, severe anemia was reported in hospitalized children and adults in need of red blood cell (RBC) transfusions (26).

Severe anemia in pregnancy is an obstetric emergency in regions of falciparum and vivax malaria endemicity (26–28). In areas of concomitant circulation of the two species, the relative frequency of vivax malaria in pregnant women ranges from 30% in Southeast Asia (18, 25, 29) to nearly 80% in Latin America (30–32), pointing to an increasing risk of anemia in the latter region. Severe neonatal anemia was also reported in a study conducted in Colombia (33). Indeed, an extensive evaluation of data from hospitalized newborns in the Indonesian Papua revealed that severe anemia has an important clinical impact on young infants with congenital malaria (18).

OVERVIEW OF THE MAJOR DETERMINANTS OF VIVAX ANEMIA

Malaria is an intravascular infection that results essentially from the presence of blood-stage parasites inside RBCs during its intraerythrocytic cycle. Hematological disturbances, therefore, may be caused by the destruction of RBCs, by the release of parasites and RBC debris into the circulation, and finally, by a host reaction to these events (34). Although several mechanisms are likely to participate in the generation of anemia in individuals infected with

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malarial parasites, they may be grouped into two main categories: (i) destruction of RBCs in the peripheral circulation, spleen, and bone marrow and (ii) dyserythropoiesis (Fig. 1).

Since *P. vivax* merozoites prefer reticulocytes as host cells (35), as opposed to *P. falciparum*, which targets all types of RBCs, the density of peripheral parasitemia in vivax malaria is often lower than that detected in falciparum infections (36). Despite this, studies on antimalarial therapy have demonstrated that *P. vivax* is responsible for a comparable decrease in the RBC mass because *P. vivax* infection results in a 4-fold-higher removal of noninfected RBCs compared to *P. falciparum* (37, 38) and, in part, because the invasion of reticulocytes interferes with the supply of mature RBCs (37, 39–41). In *P. falciparum* infection, 8.5 uninfected RBCs are destroyed per infected RBC (38, 42), while in *P. vivax* infection, the number of uninfected RBCs that are destroyed is estimated to be around 34 (37). A *P. vivax*-infected reticulocyte is up to two times larger than a noninfected RBC, and Schüffner's dots associated with caveola-vesicle complexes are seen along the infected RBC plasmalemma (43, 44). In contrast to *P. falciparum* deformability, RBC deformability seems to be increased in *P. vivax* infection (45, 46). As a consequence, *P. vivax*-infected RBCs decrease their clearance during their passage through the spleen sinusoids, making sequestration and obstruction to blood flow unlikely in vivax malaria (47).

Another important contributor to anemia is the reduced deformability of nonparasitized RBCs, as experimentally demonstrated in falciparum malaria. At high shear stresses, erythrocytes increased their rigidity and were removed in the spleen (48). In relation to vivax malaria, it has been demonstrated that after passage under microfluidic conditions simulating splenic filter and fine capillary beds, about 15% of nonparasitized RBCs were lost (46). This observation suggests another possible mechanism for RBC destruction, although how it occurs is still unknown.

Other features of *P. vivax* parasites that could be associated with the pathogenesis of severe anemia are rosetting (49, 50) and cytoadherence, a phenomenon that has been recently described in vivax malaria (51–54). *In vitro* studies showed that *P. vivax*-infected RBCs are able to cytoadhere to endothelial cells from the human lung (54) and also to human placental microvasculature (51, 53). It has also been suggested that in the human spleen, *P. vivax* attaches to barrier cells to avoid its clearance from circulation, allowing the release of merozoites in a reticulocyte-rich environment (55, 56). Nevertheless, how cytoadherence influences anemia associated with vivax malaria remains to be investigated. In relation to rosetting, this phenomenon was verified *in vitro* for cells containing parasites with visible malaria pigment (49), and it has been considered a potential contributor to the hypothesized but uncharacterized microvascular obstruction and end-organ pathology described in vivax malaria (57). Recently, another route of normal RBC removal was proposed in a study conducted with Kenyan children presenting with natural *P. falciparum* infection. According to this work, 4-hydroxynonenal, a biomembrane lipid peroxidation product, is prone to diffuse from *P. falciparum*-parasitized RBCs to the nonparasitized ones, leading to their clearance by macrophages (58). Notwithstanding, it is unknown whether this process also occurs in *P. vivax* infection.

It is noteworthy that the overall inflammatory response seems to be stronger in vivax than in falciparum malaria (59, 60), and it is possible that the modifications in the surface of noninfected RBCs may be a direct consequence of cytokine imbalance (61) and oxidative damage (62).

P. vivax infection is accompanied by changes in the host antioxidant defense system which reverse after chloroquine treatment (63). The increase in the level of reactive oxygen species (ROSs) may deplete RBC defense mechanisms, comprising in particular intracellular enzymes, e.g., superoxide dismutase, catalase, and the glutathione system (64, 65). In this manner, alterations in the redox status would play an important role in the pathogenesis of disease, including anemia, as has been proposed for *P. falciparum* (66).

As host genetic factors may exert some influence on malaria susceptibility, these parameters should be considered important determinants of the anemia onset. However, few studies have focused on investigations of human genetic variants that confer some degree of protection against or resistance to *P. vivax* and anemia, limiting our understanding of the associations between these polymorphisms and infection (67). It is well established that *P. vivax* endemicity and estimates of populations at risk are strongly influenced by the proportion of Duffy antigen-negative individuals relatively refractory to the *P. vivax* infection (4, 68). FY*B/FY*X and FY*A/FY*X genotypes are associated with low parasite density, which may favorably impact hemoglobin levels (69). Observational studies have shown protection against *P. vivax* infections conferred by a RBC enzyme (glucose-6-phosphate dehydrogenase) deficiency (70–72) and an erythrocyte membrane disorder (Southeast Asian ovalocytosis) by a mechanism that is independent of the Duffy antigen (73). On the other hand, thalassemias, which are disorders of globin synthesis, appear to increase the susceptibility to vivax malaria in carrier populations from different geographic regions (74–77). The reasons why individuals with thalassemias may be more prone to malaria are related to their ineffective erythropoiesis as well as to the shortened survival of their RBCs, which leads to a high cell turnover, increasing their reticulocyte counts and favoring the infection of these cells by *P. vivax* (76–78). Interestingly, a different association, in which thalassemia would decrease the susceptibility to *P. falciparum*, conferring protection against severe diseases such as anemia, was observed in falciparum malaria (79). This protection appears to be related to the higher levels of antibodies (Abs) that bind to parasitized erythrocytes (80), allowing their phagocytosis by blood monocytes (81).

DYSERYTHROPOIESIS AND IMMUNE-MEDIATED ANEMIA

During a plasmodial infection, the normal erythropoiesis is disturbed in patients with malaria, reflecting erythropoietic suppression and subsequent dyserythropoiesis. In the acute phase of malaria, the ineffectiveness of erythropoiesis may be evidenced by the presence of normal or reduced cellularity associated with a reduced percentage of erythroblasts. On the other hand, in the chronic phase, it may be deduced by an increase in marrow cellularity and also in erythroblast percentages (82).

A series of studies performed with both *P. falciparum* and *P. vivax* infections have shown that a common feature in anemic patients with malaria is the presence of defective erythroblasts exhibiting various abnormalities such as cytoplasmatic vacuolation, nuclei with irregular shape or multinuclearity, intercytoplasmatic bridges, and loss or myelination of parts of nuclear membrane, among others (82–85). These studies have also demonstrated the presence of erythroblasts in different stages of deg-

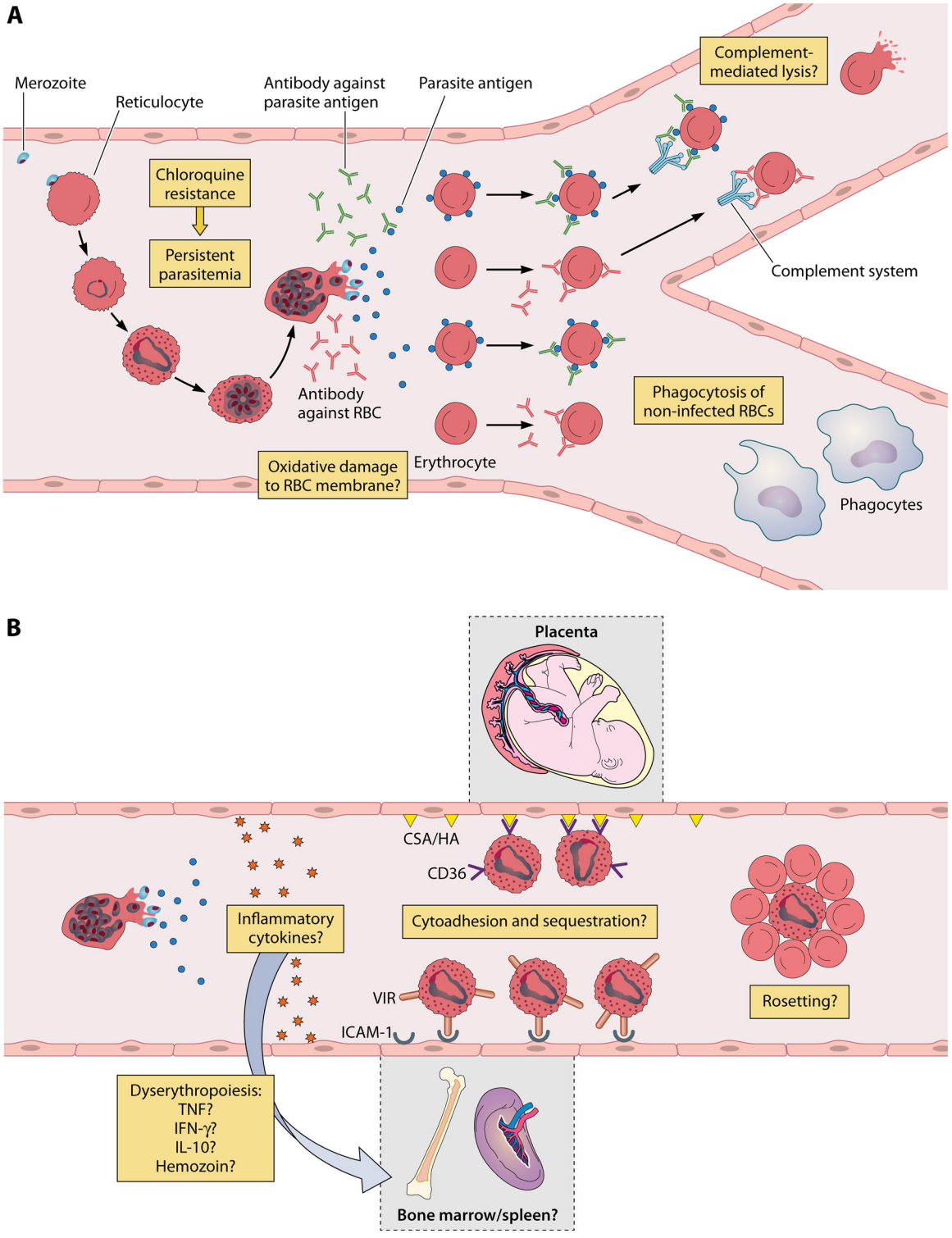

FIG 1 Anemia in *Plasmodium vivax* malaria and possible immune mechanisms associated with destruction of infected and noninfected red cells. (A) During its intraerythrocytic cycle, *P. vivax* promotes extensive changes in the host reticulocyte, leading to its rupture. Parasites, antigens, and debris are released into the circulation. In response to these molecules, the host induces a strong immune response which may damage red blood cell (RBC) membranes or still lead to hemolysis or phagocytosis of both noninfected and infected erythrocytes. *P. vivax* has developed resistance to chloroquine, which may delay parasite clearance, therefore contributing to anemia. (B) Immune mediators may also act in the bone marrow and spleen, causing a toxic effect on erythroid lineages and leading to dyserythropoiesis. Moreover, *P. vivax*-infected RBCs seem to be able to cytoadhere to endothelial cells from these organs and also to the placental microvasculature. Another possible route of RBC loss is via rosetting. It has been suggested that these RBC aggregates may interfere negatively in erythropoiesis or that the noninfected RBCs attached to the infected one are destroyed in some way. However, the mechanisms that link cytoadherence/rosetting to anemia remain unknown. CSA, chondroitin sulfate A; HA, hyaluronic acid.

radation inside the cytoplasm of macrophages from bone marrow, suggesting that erythrophagocytosis was an important mechanism involved in the degradation of injured erythroblasts (86).

Data obtained by transmission electron microscopy revealed two cases of vivax malaria in which parasites were detected in erythroblasts, suggesting that the destruction of these cells by *P. vivax* could be an underlying mechanism contributing to *P. vivax*-related anemia (87). Moreover, bone marrow aspirate from a Brazilian Amazon patient with chronic *P. vivax* infection presenting with splenomegaly and thrombocytopenia showed schizonts inside RBCs, without parallel detection of parasites in the peripheral blood (88).

Recently, an *in vitro* study conducted with hematopoietic $CD34^+$ cells derived from umbilical cord blood showed that *P. vivax* could directly inhibit erythroid development. The authors also showed that the presence of the parasite inhibited the growth as well as the differentiation of the erythroid progenitors (41). However, despite the fact that the parasite has perturbed cell division and differentiation, the presence of the parasite did not lead to cell death. Therefore, the importance of erythroblast parasitism in severe *P. vivax* anemia is still unknown and it is unlikely that the situation occurs in *P. falciparum* infection, in which there is obstruction of the bone marrow microvasculature by parasitized red blood cells (86).

Besides the direct effects of parasites, the defective erythropoiesis in malaria may also be linked to parasite-derived molecules that cause a toxic effect in erythroblasts or in other erythroid progenitor cells. A second possible factor that may also exert an influence in erythropoiesis is the production of immune mediators, by host cells, as a response to parasite products; when released, these mediators would damage surrounding haematopoietic cells, altering their morphology and function (82). In this regard, it has been demonstrated that the presence of hemozoin, a metabolic product generated during the digestion of hemoglobin, in plasma, leukocytes, or erytroid precursors, was able to inhibit erythropoiesis (89). Studies conducted with bone marrow sections obtained from children who died as a result of severe malaria showed an association between the amount of hemozoin and the proportion of abnormal erythroid cells (90). The negative effects of hemozoin in the erythroid expansion seem to be related to its ability to stimulate the release of cytokines, chemokines, or lipoperoxidases, molecules that inhibit erythropoiesis by bone marrow macrophages (90). Although hemozoin has been considered an important mediator of apoptosis leading to impairment in RBC production during falciparum anemia (90), it remains unknown whether a similar phenomenon also occurs during *P. vivax* infections.

An imbalance in the production of host immune mediators could be another important factor contributing to anemia, especially in *P. vivax* malaria, in which the inflammatory response seems to be more intense than that observed in *P. falciparum* infections with a similar parasite biomass (59, 60, 91, 92). It has been shown that *P. vivax* patients presenting with moderate to severe anemia exhibited higher concentrations of monocyte chemoattractant protein-1 (MCP-1) (17) It was shown that patients with mild anemia associated with vivax malaria presented higher levels of gamma interferon (IFN-γ) and interleukin-10 (IL-10) (93), as well as tumor necrosis factor (TNF) (61), than the nonanemic ones. IFN-γ, TNF, and IL-10 are some mediators released as a result of T cell activation (82). Elevated levels of TNF alone, or in combination with other cytokines or chemokines, have been associated with the inhibition of the erythroid progenitor cells such as burst-forming unit-erythroid (BFU-E) and CFU-erythroid (CFU-E) cells (94). IFN-γ is another potent inhibitor of erythropoiesis (95). It has been proposed that the negative effects of IFN-γ and TNF in erythropoiesis are related to their ability to induce accelerated apoptosis in the nucleated erythrocyte precursors (96, 97), to their ability to interfere in the expression and regulation of specific transcription factors that control erythroid differentiation (95), and also to their ability to interfere in the production of erythropoietin (98), a hormone which promotes erythropoiesis by stimulating the proliferation, differentiation, and maturation of erythroid progenitors (99). In contrast to IFN-γ and TNF, IL-10 is an anti-inflammatory cytokine that regulates the expression of surface and soluble TNF receptors (100). Since elevated levels of IL-10 seem to limit the TNF effects in neighboring cells, it has been suggested that high IL-10/TNF ratios in plasma from patients with malaria may be associated with protection, while an inverse relation may be indicative of severe anemia (101, 102). Other cytokines that may also be produced during malaria are IL-12, IL-18, and migratory inhibitory factor (MIF). The first two are secreted from macrophages and stimulate natural killer cells as well as B and T cells to produce IFN-γ (34, 103, 104). In B cells, IL-12 also seems to stimulate antibody production. Since it has been believed that IL-12 modulates macrophage activity, which is associated with increased erythrocyte destruction, some studies have demonstrated that higher levels of this cytokine are associated with a better outcome (105–107). MIF is a potent inhibitor of erythroid differentiation, and it may suppress erythropoietin-dependent erythroid colony formation and hemoglobin production (108). The role of MIF in plasma from uncomplicated *P. vivax* malaria patients has been investigated, and its levels have been positively associated with parasite density but not with hematological parameters (109).

The role of these cytokines in dyserythropoiesis has been most studied in *P. falciparum* infections, so it is still obscure in vivax malaria and remains to be properly investigated. Recently, a network analysis was attempted to identify the mediators that drive vivax malaria pathogenesis. Levels of a panel composed of different biomarkers of inflammation, tissue damage, and oxidative stress were measured in a large number of individuals, whose data were stratified into different groups according to disease severity and clinical outcome. The results showed that lethality was associated with interactions among markers related to hemolysis-induced damage such as tumor necrosis factor (TNF), hemoxygenase-1 (HO-1), and superoxide dismutase-1 (SOD-1) (110). Since anemia was not included in their analysis, further studies considering this hematological feature will be required to dissect the interactions that lead to RBC loss. Understanding these intricate interactions might be the key that would lead to better and preventive management of *P. vivax*-associated anemia.

THE COMPLEMENT SYSTEM AND MALARIA

It is known that an important component of the innate immunity is the complement system, which consists of more than 30 fluid-phase or membrane-bound proteins that play an important role in the rapid destruction of invading microorganisms and also of damaged or altered self-tissues (111). The involvement of complement in *Plasmodium* infections has been widely reported in malaria literature (10, 112, 113) and extensively reviewed elsewhere (114). Different reports have demonstrated that during ma-

laria, complement activation is increased (115, 116). Thus, it is necessary that the host complement regulatory proteins, molecules that protect normal cells from autologous complement-mediated lysis, are expressed in sufficient levels to control complement activation on the cell surface and thereby maintain physiological homeostasis (117). Along these lines, several works have suggested that the erythrocyte complement regulatory proteins may play an important role in the pathogenesis of anemia, protecting nonparasitized RBCs from destruction. This hypothesis was tested by different researchers, who reported that changes in the expression patterns of some complement regulatory proteins such as complement receptor 1 (CR1) (118), decay-accelerating factor (CD55), and membrane inhibitor of reactive lysis (CD59) may render RBCs more susceptible to lysis, increasing their destruction and resulting in anemia (119–124). Studies conducted in areas of *P. falciparum* endemicity have documented that higher levels of CR1 and CD55 are exhibited in RBCs from children with uncomplicated malaria or who are uninfected than in RBCs from those with severe anemia (119–121). Furthermore, a study conducted on susceptible children in western Kenya demonstrated an association between low levels of complement regulatory proteins on RBC surfaces and increased risk of C3 deposition on their membranes (125). These data suggest that lower expression levels of such biomarkers would contribute to an increased clearance of erythrocytes, leading to anemia in falciparum malaria. It has also been hypothesized that there is age-dependent regulation of the expression pattern of RBC regulatory complement proteins (121). As there is no available information in the literature concerning these aspects of *P. vivax* infection, it would be a breakthrough to understand if these processes involving the complement system also participate in pathophysiological mechanisms related to this species.

ANTIBODIES AND MALARIA: PROTECTIVE OR PATHOGENIC?

In terms of adaptive immune responses, it is important to emphasize that antibodies are the principal effector molecules that participate in the specific host-parasite interactions. Furthermore, these molecules may act in concert with other factors and it has been known that their protective or pathogenic role is related not only to the magnitude at which they are produced but also to their effector functions.

In malaria, the protective role of antibodies has been well documented by several groups, who demonstrated that the passive transfer of immunoglobulins purified from immune adults to malarial patients can control the infection by reducing parasitemia and protecting individuals against severe disease (126, 127). On the other hand, experiments conducted with *P. falciparum* have shown that the tagging of the surface of noninfected RBCs by parasite proteins, as well as the tagging of the erythroid precursor cells in bone marrow, may elicit a specific antibody response, triggering phagocytosis and complement activation and inducing the clearance of these cells (128–131). These data suggest that specific immune responses induced by some parasite antigens may contribute to malaria pathogenesis, playing a role in the development of malarial anemia. Data from the past show *P. vivax* antigens on the surface of infected human RBCs (132). Regarding *P. vivax* infection, an association between specific antibodies and anemia has also been observed (133). In this scenario, we cannot exclude the possibility of a dual role for specific antibodies against *P. vivax*. They may participate in both immunity and the pathogenesis of malaria. Taking all these observations into account, further studies are necessary to better elucidate the functional activity of *P. vivax*-specific antibodies, a vital concern in vivax malaria studies.

AUTOANTIBODIES: A NEGLECTED BUT PROMISING RESEARCH ISSUE

Another element of the adaptive immunity that may also take part in the destruction of noninfected RBCs that occurs in *Plasmodium* infections is the presence of autoantibodies, molecules induced with regard to autologous components of RBCs. The presence of these circulating immunoglobulins has been well documented both in falciparum and in vivax infection (134–136), and it has been speculated that they are produced in response to cross-reactive antigenicity between parasite and host as well as to normal or altered host proteins. Nevertheless, the relationship between malaria and autoantibodies is still a controversial issue and many hypotheses have been proposed to explain this link. One hypothesis is that infection by *Plasmodium* parasites induces host autoimmune responses that may be, in part, responsible for some malaria clinical manifestations. Along these lines, it has been shown that, in malaria, autoantibodies may be associated with anemia (137–139) and thrombocytopenia (140) as well as kidney pathology (141). Interestingly, sera from patients with vivax malaria seem to present higher levels of antierythrocyte immunoglobulins compared to sera from patients infected with *P. falciparum* (136). It is possible that the recognition of surface proteins from noninfected RBCs by autoantibodies or even cross-reacting antibodies, whose levels are increased during *P. vivax* infection, leads to the opsonization of normal RBCs, facilitating their removal by erythrophagocytosis. The increase in levels of malaria autoantibodies may be associated with molecular mimicry, a mechanism in which a foreign antigen produced by a pathogen shares structural, functional, or immunological similarities with a self-antigen. This strategy may represent an attempt by the parasite to manipulate its host to trigger an immune response directed against autoantigens, facilitating pathogen evasion from the immune system (142). Indeed, it has been demonstrated that two distinct molecules expressed in different *Plasmodium* life stages, Pf25 and MSP-1, possess epidermal growth factor (EGF) motifs (143–145). In addition, it has been recently shown that a 14-amino-acid motif in PfEMP1 exhibits identity with human vitronectin (146). Considering this information, it is possible to speculate that *Plasmodium* parasites may also mimic RBC proteins, a hypothesis that should be further evaluated in *P. vivax* anemia.

RETURNING TO OLD CONCEPTS TO PROPOSE NEW IMMUNE MECHANISMS AGAINST VIVAX ANEMIA

In the challenging task of understanding anemia in vivax malaria, and in order to continue moving forward, an important step that may help the scientific community to better elucidate the mechanisms involved in this hematological feature is to go back to old concepts. This strategy may be a good attempt to answer the following question: how are noninfected RBCs removed from circulation in a *P. vivax*-infected patient?

Early studies conducted in the 1970s showed that enhanced expression of neoantigens (antigens that arise from changes in components already present in the cell membrane) occurs under physiological conditions during erythrocyte aging. These neoantigens constitute targets for auto-Abs that, in association with enhanced complement components, culminate in phagocytosis

(147–150). According to several studies, anti-band 3 antibodies mediate this senescent RBC removal (149, 150). Band 3 is the major integral protein of the RBC membrane, comprising 25% to 30% of its total protein. Band 3 is an anion exchanger protein mediator and is responsible for cell flexibility and shape maintenance (151). In old RBCs, clusters of band 3 are formed and constitute an important target for natural occurring antibodies (152–154). In *P. falciparum* areas of endemicity, band 3 immune responses seem to be beneficial since malaria-immune children with higher levels of antibodies induced by two conserved band 3 peptides present a lower mean parasite density than nonimmune children (155). Other studies have evidenced that, during *P. falciparum* infections, synthetic peptides overlapping human band 3 may inhibit not only the RBC invasion but also the cytoadherence/sequestration by antibody-mediated clearance of infected RBCs (156, 157). On the other hand, a different role for anti-band 3 immunoglobulins was proposed (158). According to that work, higher anti-band 3 titers were detected in the high-infection group of children. Interestingly, during the follow-up of these infants, five of them exhibited a significant loss of hemoglobin associated with an increase in anti-band 3 titers (158).

In order to explain the clearance of *P. falciparum*-parasitized erythrocytes, a band 3/complement RBC removal model was proposed (154). According to literature data, approximately 1 million band 3 molecules are dispersedly expressed on RBC surface (154). Nevertheless, during the aging of erythrocytes, these molecules form band 3 clusters with hemichromes (products derived from hemoglobin degradation) originated by oxidative stress. Thereafter, the immune system recognizes and quickly eliminates those clusters. It has been shown that *P. falciparum*-infected erythrocytes, in addition to senescent RBCs, also display these clusters. These data lead to the hypothesis that those band 3 antibodies may be involved in the mediation of RBC removal. Taking all this information into account, a question remains: could this model be used to explain the destruction of uninfected RBCs in vivax malaria via extravascular hemolysis?

Recently, it has been proposed that decay-accelerating factor (DAF; a complement receptor that accelerates the decay of C3 and C5 convertases) exerts a crucial role in the RBC recognition by macrophages (159). According to this model, DAF forms a complex on the surface of the RBC membrane through its association with C3b, glycophorin A, and band 3 (DAF-C3b-GPA-Band 3). This complex is thought to alter the viscoelastic properties of the erythrocyte membrane. As a result, RBCs containing such a complex in their membrane become less deformable than normal ones and are cleared from circulation by macrophages in the liver or spleen. By this model, it may be noted that global changes in RBC membrane organization are directly linked to complement activation. We believe that it is important to clarify whether this mechanism is also involved in the destruction of uninfected RBCs during vivax malaria. Further studies are necessary to resolve this issue.

GAPS OF KNOWLEDGE AND FUTURE STUDIES

Considering that some attention was given only recently to the major complications of *P. vivax* infection, such as severe anemia, data on the pathogenesis of *P. vivax*-triggered anemia almost do not exist. Therefore, any future study on this issue will be relevant, as seen with *P. falciparum*. The anemia induced by *P. vivax* infections is still crudely understood, and the mechanisms that lead to the loss of uninfected RBCs remain unclear. The lack of an appropriate culture method and the difficulties involved in performing *in vivo* assays limit the tools available to study this parasite. However, the possible involvement of the host immune system in generating anemia may be evaluated using blood samples from different patients living in areas of endemicity. The link between the number of previous malaria episodes and the generation of severe anemia may also provide interesting information. It is still important to investigate what is behind the immune system dysregulation described in the literature and why some individuals residing in areas of endemicity display severe symptoms such as anemia whereas others do not. Furthermore, it is interesting to evaluate whether this difference is due to host polymorphisms and intrinsic divergences between infected patients and their own immunity or also due to polymorphisms between parasite strains that could induce different immune responses. The confirmation of the existence of molecular mimicry by *P. vivax* and its probable involvement in increasing autoantibody levels, including levels of immunoglobulins against RBC membrane proteins, is another exciting and interesting research field in which proteomic and genomic approaches could give us some important clues. Studies in all these directions may lead to the identification of biomarkers that could serve as prognostic indicators as well as guidelines for a more accurate strategy of treatment and better clinical management of infected patients and severe cases.

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