



Review

Contribution of allergic inflammatory response to the pathogenesis of malaria disease[☆]

Salaheddine Mecheri^{*}

Biology of Host Parasite Interactions Unit, Institut Pasteur, Paris, France

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ABSTRACT

Plasmodium falciparum, the aetiological agent of human lethal malaria, is responsible for over 2 million deaths per year and malaria episodes may vary considerably in their severity and clinical manifestations. Dysregulated balance of the inflammatory response and a defect in the anti-*Plasmodium* parasite immune response represent the hallmarks of malaria disease. Among the many possible mechanisms, it is now widely recognized that the production of pro-inflammatory mediators and cytokines and upregulation of endothelial cell adhesion molecules play important roles in malaria pathogenesis. We and others provided evidence that some components of allergic inflammatory response to malaria parasites or elicited by by-products of parasite infection may contribute to malaria pathogenesis. This review provides some clue regarding these mechanisms where mast cells and histamine, an inflammatory mediator generated following IgE-independent or IgE-mediated immune response, were found to play a major role in parasite transmission and malaria pathogenesis, respectively. This article is part of a Special Issue entitled: Mast cells in inflammation.

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1. Introduction

Understanding the mechanisms that govern malaria pathogenesis is a major challenge. *Plasmodium falciparum*, the aetiological agent of human lethal malaria, is responsible for over 2 million deaths per year. *P. falciparum* malaria episodes may vary considerably in their severity and clinical manifestations. A characteristic feature of malaria is that the protective immune response is established slowly and only after the individuals have experienced several rounds of infections. Severe malaria is complex and probably cannot be represented by one single pathogenetic scheme, rather a combination of multiple disorders, including destruction of infected and non infected erythrocytes, microvascular obstruction, immunopathological and inflammatory processes which collectively account for the pathogenesis.

The medical implications of improved knowledge of immunological mechanisms associated with resistance or susceptibility to malaria disease are numerous and in particular, permit the design of new therapeutic approaches. The defense mechanisms require cooperation between cellular and antibody (Ab) immune responses [1] and involve for example monocytes and antibody-mediated mechanisms to achieve acquired protective immunity [2]. The biological properties of Abs produced in response to infection are of particular importance, since certain isotypes known as cytophilic Abs can opsonize monocytes and serve for phagocytosis via FcγRI and

FcγRII or participate in both antibody-dependent cellular inhibition (ADCI) as well as antibody-dependent cellular cytotoxicity (ADCC) [3]. In humans, among IgG subclasses, IgG1 and IgG3 are known to be protective while IgG2 and IgG4 are considered to be non-protective. In contrast, the implication of IgE Ab response to parasites in malaria disease is a subject of controversy and is still a matter of debate. The allergic nature of malaria disease has been touched upon intermittently over the last 30 years, but has remained either largely fuzzy (e.g. the beneficial role of anti-histamines) or restricted to single hypothesis-based approaches (e.g. the controversy on the role of IgE). Recently a confluence of increasingly compelling data from human genetic analyses and mouse experimental models suggests for the first time a firm basis upon which one can develop testable hypotheses.

Several lines of evidence support the concept that susceptibility to malaria and atopy may be related to the same immunological defect. In Ethiopia, atopic children had a higher prevalence of malaria attacks [4], while in Tanzania maternal malaria had a protective effect on wheezing in children age of 4 [5]. The role of IgE in clinical and severe malaria is still poorly documented and results are controversial. *P. falciparum*-specific IgE is elevated in malaria patients and has been proposed to play a pathogenic role in severe malaria [6–8], whereas, in asymptomatic individuals, it was associated with protection [9]. Pertinently, explanations for such contradictory results consistently point to the importance of the individual's genetic background and the occurrence of polymorphisms in candidate cytokines such as TNF-α [9,10]. Increased levels of histamine, a major product of allergic responses derived from basophils and MCs, in plasma and tissue,

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^{*} Corresponding author. Tel.: +331 45 68 82 45; fax: +331 44 38 95 21.

E-mail address: smecheri@pasteur.fr.

notably following stimulation by IgE through the high affinity receptor FcεRI, are associated with the severity of disease in humans infected with *P. falciparum* and in animal malaria models [11,12].

The adaptation of the hematophagous arthropods (mosquitoes, sandflies, ticks, etc.) to blood feeding is an essential parameter of host–vector–parasite interactions well exploited by the parasite. Host skin defenses, which ultimate goal is to prevent successful blood meal, and triggered by salivary components consist of blood leakage, haemostasis, pain and itch responses, and immune effector mechanisms. The pharmacological properties of saliva [13] may represent the insect's answer to these mechanisms. They include anti-coagulant, anti-platelet, vasodilatory and anti-inflammatory/immunosuppressive activities [13,14] which contribute to overcome the host defense mechanisms. There is now compelling evidence that vectors are not only syringes injecting parasites, and that co-injected blood-feeding insect saliva has profound effects on parasite transmission [15,16]. Indeed, *Plasmodium berghei* sporozoites delivered into mice through mosquito bites are more infectious than salivary gland extracted sporozoites injected intravenously, suggesting a facilitating role of saliva in parasite transmission [17]. To evaluate the effect of mosquito feeding on the pathogenesis and immune response in malaria, washed *Plasmodium berghei* sporozoites were injected intradermally in the presence or absence of mosquito feeding. We recently observed that mice exposed to mosquito feeding in tandem with the inoculation of sporozoites had higher parasitemias and an elevated progression to cerebral malaria. This was associated with, in particular, elevated levels of interleukin-4 and interleukin-10, suppression of overall transcription in response to infection, and decreased extravasation of dendritic cells and monocytes [18]. Host tissue reactions to salivary components following the insect probing and blood feeding vary from small papules to large pruritic swellings depending on mosquito species and are reminiscent of allergic responses. These observations led us to hypothesize that mosquito saliva might exert immunomodulatory effects within a host exposed to mosquito bites through induction of mast cell degranulation which in turn affects dendritic cell migration and function. Such a mechanism could be of importance for malaria transmission when sporozoites are present in the inoculum.

Given the multiple pharmacologic effects of the mosquito saliva, assessing the immune response to both mosquito saliva and to mosquito-transmitted *Plasmodium* infection is of paramount importance, particularly at the site of inoculation and draining lymph nodes. Accordingly, this review aims at examining how mosquito saliva modulates early innate and subsequent antigen-specific immune responses. We also discuss the implication of components of allergic response-associated inflammatory response in the pathogenesis of severe malaria in murine models of cerebral malaria (CM).

2. *Anopheles* mosquito saliva affects both innate and antigen-specific responses under the control of mast cells

Transmission of malaria via infectious bites consists of probing the skin for blood meal during which sporozoites are inoculated along with saliva. Saliva which serves not only as a vehicle for sporozoites is reported to have profound effects by altering the skin homeostasis. In this respect, it is essential to dissect initial inflammatory events that may determine the outcome of infection and disease pathogenesis.

2.1. *Anopheles* mosquito bites activate cutaneous mast cells leading to a local inflammatory response and lymph node hyperplasia

Parasite transmission consists of a delivery in the dermis of sporozoites together with *Anopheles* saliva. Generally bites of many insects elicit sensation of pain and itch, but the bite of mosquitoes causes mainly itch [19,20]. Mosquito bites cause immediate and delayed local cutaneous reactions and occasionally systemic reac-

tions [19–22]. Other studies showed the presence of histamine-mediated and histamine-independent mechanisms in cutaneous itching following mosquito bites [23]. In a first set of experiments, we examined to what extent saliva elicits allergic-type inflammatory responses. We reported that *Anopheles stephensi* mosquito bites result in a local IgE-independent degranulation of skin mast cells as assessed by a rapid dermal inflammation and the hyperplasia of the draining lymph nodes [24]. This provides a mechanism whereby mosquito bites may shape the immune response to microorganisms present in their saliva and inoculated during the blood meal. The sites of mosquito bites are characterized by fluid extravasation and rapid infiltration with polynuclear neutrophils. This local skin reaction results from mast cell activation in that: 1) histological analysis of bitten skin sites shows that mast cells are degranulated and, 2) leukocyte infiltration is not observed in the skin of mast cell-deficient animals unless they are reconstituted with mast cells. Mast cells are known to induce such local reaction by rapidly releasing several mediators including granule-associated histamine, tryptase, TNF-α, MIP-2 as well as eicosanoids, including leukotrienes. A parallel can be made with a previous work showing that increased plasma extravasation was induced by mosquito bites in repeatedly immunized mice with *Aedes albopictus* salivary gland extracts [25]. However, this effect was ascribed to IgE and IgG1-mediated specific immune response. In an earlier report, the intradermal injections with *Anopheles albopictus* salivary gland extracts in humans showed that a high molecular weight fraction elicited an immediate and a delayed response similar to a bite reaction [26]. In our system, the mast cell-dependent inflammatory response at skin sites exposed to *Anopheles stephensi* mosquito bites occurs in naive mice. This indicates that some components in *Anopheles* saliva have the capacity to directly trigger mast cell activation in the absence of saliva-induced specific antibodies. This does not preclude the possibility that repeated exposures to *Anopheles* mosquito bites may induce sensitizing specific IgE antibodies which may then exacerbate the inflammatory response. The mosquito bite also induced cellular infiltrate and hyperplasia of the draining lymph nodes. These alterations consist of an increase of the number of various leukocyte lineages including T lymphocytes, B lymphocytes, dendritic cells, and monocytes/macrophages. The presence of mast cells at the skin site of the mosquito bite therefore not only controls the local granulocyte influx but also promotes leukocyte influx in lymph nodes. Accordingly, it has been reported that peripheral mast cells play a critical role, through TNF-α they produce, in regulating the hypertrophy of draining lymph nodes during infection or following activation by the mast cell secretagogue 48/80 [27]. Our data support these findings in that saliva-induced activation of dermal mast cells similarly induces lymph node swelling via the recruitment of T and B lymphocytes, dendritic cells, and monocytes/macrophages. It must be emphasized that, similar to the observation made by McLachlan et al. [27], in situ activation of skin mast cells upon mosquito bites led to the accumulation of TNF-α within draining lymph nodes. However, in contrast to the findings reported by McLachlan et al., using neutralizing TNF-α antibodies we failed to inhibit lymph node hypertrophy elicited by mosquito bites, suggesting that other factors may be involved in this process [24]. Our observation that mosquito bites cause neutrophil infiltration only in mast cell-sufficient mice, clearly demonstrates that neutrophils are attracted at the site of the mosquito bite by mast cell products, and could contribute to the host defense against the parasites delivered by the mosquito. A high molecular weight glycoprotein from *Anopheles stephensi* saliva endowed with a direct neutrophil chemotactic activity has been observed in vitro [28]. Possibly due to differences in terms of dose and freshness of saliva mediators, our work *in vivo* did not support these observations as mosquito bites failed to induce neutrophil infiltration in mast cell-deficient mice and rather emphasizes a critical role of mast cells in the accumulation of neutrophils at the site of mosquito bite. As the number of mast cells at the site of the

bite seemed not to be different from that of the skin of naïve mice, one can argue that saliva does not act as a chemoattractant for mast cells.

Mast cells can serve as a source of TNF- α and the CXC chemokine macrophage inflammatory protein 2 (MIP-2), mediators which have been implicated in neutrophil recruitment in models of bacterial host defense and T cell-mediated DTH [29,30]. In a model of contact hypersensitivity reaction (CHS), MIP-2 protein was found to be abundant during this inflammatory response in and around mast cells of wild-type mice but absent in mast cell-deficient mice [29]. MIP-2 was also shown to be involved in migration of dendritic cells in contact hypersensitivity (CHS) reaction [31]. The difference in the requirement of TNF- α in our system and in the system described by McLachlan et al. [27] may certainly be due to the presence of particular components within mosquito saliva.

Among further questions that needed to be addressed, it was important to investigate how mosquito bite-induced mast cell activation affects antigen-specific immune responses. Immunosuppressive effect mediated by mast cells has been previously reported in a CHS model in which UVB light induced mast cell degranulation [32,33]. Do mosquito bites alter the immune response in a similar way?

2.2. Mast cell-dependent down-regulation of antigen-specific immune responses by mosquito bites

During inflammatory responses, lymph nodes become the meeting point between entrapped circulating lymphocytes and antigen presenting dendritic cells that have sampled the antigen in the periphery. The adaptive immune response results from this encounter, and therefore benefits in terms of rapidity and intensity from the role played by mast cells in cell migration. It was interesting to examine whether mast cells also influence the nature of the immune response. In individuals sensitized against mosquito saliva and in malaria patients who develop parasite-specific IgE [34], these antibodies may increase innate mast cell responsiveness to mosquito saliva and potentiate their role as sentinels. Our goal was to understand how saliva facilitates *Plasmodium* transmission and to better define the contribution of skin mast cells in *Plasmodium* transmission.

We made the hypothesis that mosquito bites may exert their immunosuppressive activity through mast cell degranulation elicited by salivary components. As reported earlier, mosquito bites induce local mast cell degranulation in the skin [24] with MIP-2 production [35] which was shown to be a key inflammatory cytokine primarily produced by activated mast cells as demonstrated in a CHS reaction model [29]. Our results support these findings in that mosquito bites induce MIP-2 which production was dependent on the presence of mast cells [35]. The early induction of MIP-2 in the skin was followed by a unique production of IL-10 in the draining lymph nodes. The pro-inflammatory activity of MIP-2 in one hand and the immunosuppressive function of IL-10 on the other hand led us to examine the possibility that these cytokines may affect the final outcome of an antigen-specific immune response when this antigen was administered along with mosquito bites. OVA-specific DTH response, used as a prototype of T-cell-mediated immune response, was found to be drastically inhibited in mice exposed to mosquito bites. This decreased DTH response was reflected both by a reduced footpad swelling as well as by diminished leukocyte recruitment in draining lymph nodes. Further analysis of cytokine response of OVA-challenged lymph node cells in vitro demonstrated a significantly reduced IFN- γ (a major cytokine associated with DTH) and elevated IL-10 productions by mosquito bites [35]. These data are compatible with an immunosuppressive activity of *Anopheles* saliva on antigen-specific immune response. This was emphasized by reduced IFN- γ expression by antigen-specific T cells recruited to the skin site of OVA-challenged footpad of mice exposed to mosquito bites. IL-10 was reported to be an important regulator of DTH response in that treatment of

sensitized mice with neutralizing anti-IL-10 antibody prolonged the duration of the hypersensitivity reaction beyond the natural course of the response [36]. Consistent with these observations, our findings show that administration of anti-IL-10 dramatically enhanced IFN- γ expression (20-fold increase) during DTH response in mice not exposed to mosquito bites. Similar treatment of mice exposed to mosquito bites only increased IFN- γ response by approximately 8-fold, suggesting that mosquito bites exert a stronger inhibitory control of DTH response by an IL-10-dependent mechanism. These data provide strong evidence linking IL-10-mediated down-regulation of DTH response to mosquito bites. Although it was suspected that IL-10 could be of mast cell origin, this was not firmly established in this work. In a previous report, Grimaldeston et al. reported evidence that mast cell production of the anti-inflammatory cytokine IL-10 can limit the inflammation and tissue damage associated with chronic low-dose UVB irradiation of mouse skin [37]. More recently, the same group firmly established that IL-10 production by cutaneous mast cells can contribute to the mast cell's ability to suppress inflammation and skin pathology at sites of chronic UVB irradiation in a 1 α ,25-dihydroxyvitamin D3/vitamin D receptor-dependent manner [38].

It is well established that mast cells contribute to the development of DTH reactions [29,39]. In our system, however, we found that mosquito bites inhibit in a mast cell-dependent manner the induction of DTH response to an immunogenic antigen injected immediately after and at the same site as the mosquito bite. A similar immunosuppressive effect mediated by mast cells has been previously reported in a CHS reaction model in which UVB light induced mast cell degranulation [32,33]. During the sensitization phase of DTH response, dendritic cells capture the antigen, migrate to draining lymph nodes and undergo a maturation process required for the activation of naïve T cells. We speculate that mosquito saliva induces the release of a particular set of inflammatory mediators by activated mast cells that may affect the maturation of adjacent dendritic cells which fail to ultimately elicit fully activated effector T cells. It is known that the ability of dendritic cells to direct the development of naïve T cells into Th1, Th2 or regulatory T cells is largely dependent upon the signals that they receive in the peripheral tissues at the time of antigen capture. Histamine, which mast cells are the major storage site, is an attractive candidate as a dendritic cell modulator especially during early phases of the immune response. Histamine was reported to have immunosuppressive effects, such as inhibition of polymorphonuclear chemotaxis [40] and monocyte IL-12 secretion [41], as well as induction of IL-10 production [41]. Interestingly, analysis of cytokine production by cultured lymph node cells after completion of DTH response indicates that increased production of IL-10 by mosquito bites was correlated with the presence of mast cells. Hence, it was tempting to explore if histamine had any role in malaria pathogenesis.

3. Role of histamine-mediated signaling in the pathogenesis of severe malaria in mice

The above mentioned results led us to hypothesize that allergic response-associated inflammatory reaction influences the course of infection with *Plasmodium* parasites. Earlier reports indicate that specific components of the innate immune system, including eosinophils [42], basophils [43], and mast cells [44], could play important roles in the pathogenesis of malaria. Increased levels of histamine in plasma and tissue, derived from basophils and mast cells, are associated with the severity of disease in humans infected with *P. falciparum* and in several animal models of infections with *Plasmodium* [11,12,45]. In addition, higher levels of IgE, which binds to basophils and mast cells and can trigger histamine release, are associated with the severity of infection with *P. falciparum* [7]. The effects of histamine are exerted through three classical G protein-coupled histamine receptor subtypes, designated H1R, H2R, and H3R,

which are thoroughly described pharmacologically [46], and a recently identified fourth member of the histamine receptor family, H4R [47]. Histamine also modulates several biological functions of vascular endothelial cells. During an acute inflammatory response, the histamine-induced increase of P-selectin (CD62P) expression on endothelial cells mediates the initial recruitment of inflammatory cells, including neutrophils, from the blood [48]. In vascular endothelial cells, H1R stimulation leads to several cellular responses including the release of nitric oxide [49] and enhances vascular permeability, particularly in postcapillary venules as a result of endothelial cell contraction [50,51]. Several of these effects of histamine might be exploited by *Plasmodium* parasite to survive in its mammalian host. The increase in vascular permeability appears to be a component of malaria pathogenesis and could be advantageous for the parasites, as sporozoites or blood-stage parasites, since it facilitates their entry and exit from blood vessels. The vasodilatory effects of histamine might promote spread of the parasite through the vasculature. In a follow up study, we assessed the relevance of histamine in malaria pathogenesis and its association with disease severity.

3.1. H1R- and H2R-mediated signaling play a role in the pathogenesis of infection with *Plasmodium berghei* (Pb)

We evaluated the hypothesis that the histamine signaling during infection with *Plasmodium* results in an inflammatory process that exacerbates disease by inducing immunopathology or by facilitating the dissemination, adherence and sequestration of parasites in tissues. The implication of histamine was examined by using a murine model of cerebral malaria (CM). This disease model consists of the infection of a susceptible C57BL/6 mouse strain with the *Pb* ANKA parasite strain. Neurological signs followed by death occur between 6 and 11 days post-infection. Using this model, and based on divergent approaches using H1R^{-/-} and H2R^{-/-} mice, anti-histamine drugs, and histamine-deficient mice, we demonstrated that histamine signaling was associated with the severity of disease [52].

The mechanisms by which histamine contributes to disease severity and at which stage of the parasite life cycle they operate is unclear. Mice genetically deficient in H1R and H2R as well as mice treated with H1 and H2 anti-histamines have delayed mortality as compared to similarly infected wild-type mice untreated with the anti-histamines, suggesting that production and binding of histamine to these two receptors are deleterious to the host [52].

3.2. Susceptibility to infection with *Pb* ANKA is associated with the HDC gene

To unequivocally determine the effect of histamine on the course of infection with *Plasmodium*, histidine decarboxylase-knock out (HDC^{-/-}) mice were used. HDC^{-/-} mice infected via mosquito bites with *Anopheles stephensi* female mosquitoes harboring the *Pb* ANKA parasite, a strain which causes CM in the susceptible C57BL/6 mouse strain, although they eventually succumbed from the infection, they died at much later times than similarly infected control C57BL/6 mice and did not exhibit any signs of CM [52]. These data implicate histamine in progression to CM, and suggest that histamine signaling could lead to enhanced immunopathological responses. Importantly, results showing comparable parasitemia between groups infected with parasites from the *Pb* ANKA strain do not support the possibility that the inability of histamine-free mice to develop CM resulted from reduced parasite burden.

In an attempt to better determine at which stage of parasite development histamine mediates its adverse effects, HDC^{-/-} mice were also infected with *Pb* ANKA-parasitized red blood cells thus bypassing the pre-erythrocytic phase. Identical to what was observed following infectious mosquito bites, histamine-free mice did not

develop CM and survived significantly longer than similarly infected control C57BL/6 mice [52]. These data indicate that although histamine is produced during all stages of infection with *Plasmodium* parasites (i.e. by histamine-producing mast cells in the skin and in the liver during the pre-erythrocytic stage of parasites development, and by histamine-producing basophils in the blood where infected red cells circulate), the pathogenic effects of histamine are likely prevailing in the latter stages of infection. However, the possibility that histamine also plays a role in the skin and/or the liver during the initial phases of the infection cannot be excluded. Indeed, during the initial phases of the infection, specifically the pre-erythrocytic stages of parasite development, histamine release may be triggered in the dermis when sporozoites are inoculated via mosquito bites. In this context, *Anopheles* saliva induces MC degranulation [24]. During later phases of infection, particularly during the blood stage of parasite development, histamine production can be elicited from circulating basophils either via cross-linking of parasite-specific IgE antibodies or by the translationally controlled tumor protein (TCTP), a parasite-derived homolog of the histamine releasing factor (HRF). TCTP has been found in the plasma of patients infected with *P. falciparum* and was shown to trigger histamine release from basophils and IL-8 secretion from eosinophils [53]. The existence of a *Plasmodium* protein that stimulates histamine release lends support to the hypothesis that histamine signaling is advantageous to the pathogen, and thus harmful to the host. These findings could provide a rational basis for higher levels of histamine in blood and in tissues during malaria as a result of the activity of vector- or parasite-derived constituents. Amplifying the host inflammatory response, via histamine signaling, may be a strategy developed by the parasites to create conditions advantageous for their own survival and persistence. Our results in HDC^{-/-} mice showed that in the absence of histamine, the disease severity was significantly attenuated. The adverse effect of histamine was highlighted by the delayed non-CM death from *Pb* ANKA resulting from the interruption of histamine signaling. The reason that infection with *Pb* ANKA remains lethal in histamine-free HDC^{-/-} mice remains unclear. It seems plausible that, although inhibiting histamine signaling may abrogate immunopathology, it cannot stop the adverse effects of hyperparasitemia. In addition to its distinctive efficiency in producing CM in mice, the possibility exists that *Pb* ANKA also elicits inflammatory mediators other than histamine that promote progression of infection even in HDC^{-/-} mice.

Analogous to these data that reveal the adverse effects of histamine for the host during infection with *Plasmodium*, a human study demonstrated that the concentration of histamine in plasma was increased by almost 5-fold in children suffering from malaria [54]. Additionally, in this study higher levels of histamine were observed in the brains of children with severe malaria as compared to lesser disease presentations. Among the histamine-associated biological activities relevant to features predictive of severe CM in humans are increased intracerebral blood flow [55], increased vascular and blood-brain barrier permeability [56] and oedema [57]. Strikingly, the resistance of histamine-deficient mice to CM was clearly identified by a preserved blood-brain barrier integrity in contrast to the greatly increased permeability of the brain vasculature with large clusters of infected erythrocytes observed in infected C57BL/6 mice.

3.3. Histamine production is associated with overall increase of inflammatory response genes during malaria disease

The possibility exists that the resistance of HDC^{-/-} mice to CM resulted from an impaired or improved capacity of these mice to produce some immune mediators in response to infection with *Pb* ANKA. Therefore, the levels of expression of various relevant molecules at the mRNA and protein levels were compared between HDC^{-/-} and C57BL/6 mice infected with *Pb* ANKA. Indeed, analysis of

a number of inflammatory proteins, and other immune response-associated molecules including IFN- γ , IL-6, IL-10, KC, MCP-1, MIP-1 α , CTLA-4, and ICOS, indicates that an inflammatory response, although attenuated, was induced in HDC $^{-/-}$ mice [52]. Several reports indicate that the CM pathologies seen in mice following infection with *Pb* ANKA result from the induced pro-inflammatory immune response. In agreement, IFN- γ which was shown to be implicated in the pathogenesis of experimental CM [58], reached significantly higher levels in the brain tissue and plasma of CM-sensitive C57BL/6 mice than in HDC $^{-/-}$ mice [52]. Similarly, our results showing higher levels of IL-6 in the plasma and increased expression of IL-6 transcripts in the brain of CM-sensitive C57BL/6 mice than in HDC $^{-/-}$ mice were also in agreement with reports showing higher production of IL-6 in response to TNF- α by endothelial cells of brain capillaries of mice genetically sensitive to CM development [59]. Our results showing a lower cerebral expression of IL-10 by HDC $^{-/-}$ mice, which diverge from murine CM experiments that suggest a protective effect for IL-10 in CM [60], yet are in accordance with observations in humans that showed an increase in IL-10 with CM as compared to mild malaria patients [61]. IL-4 expression corresponded with CM in our model, in agreement with previous studies, which demonstrated that deficiency in IL-4 or IL-4 receptor alpha led to higher resistance to *Pb* ANKA [62].

In the absence of histamine signaling, profound alterations of the immune response may also occur. A characteristic feature of CM is the sequestration of CD8 $^{+}$ and CD4 $^{+}$ T cells in the brain capillaries [63–65]. This was confirmed by results in our study showing a reduced sequestration of CD8 $^{+}$ and CD4 $^{+}$ T cells in the brain of infected HDC $^{-/-}$ mice [52]. These data suggest that the histamine produced following infection with *Pb* ANKA triggers inflammation that leads to the sequestration of T cells in brain capillaries, a prominent component of CM pathogenesis.

Several studies reported a crucial role of ICAM-1 in malaria pathogenesis and, notably, ICAM-1-deficient mice are protected from CM [66]. In this model, ICAM-1 $^{-/-}$ mice survived more than 15 days despite a similar level of parasitaemia in wild-type and knockout mice, a phenotype that is comparable to HDC $^{-/-}$ mice. Results from our studies confirmed the correlation between ICAM-1 expression,

both at the protein and transcript levels, and susceptibility to CM. The low levels of ICAM-1 expression in brain microvascular endothelial cells in histamine-deficient HDC $^{-/-}$ mice could represent a mechanism leading to the lack of T cell sequestration in the brain capillaries of these mice. Indeed, histamine has been shown to stimulate endothelial cells to express ICAM-1 and VCAM-1 [67] and Cetirizine, an H1-receptor antagonist, has been shown to have anti-inflammatory properties through the inhibition of leukocyte recruitment and activation, and by the reduction of ICAM-1 expression on keratinocytes [68] and on conjunctival and nasal epithelial cells [69]. In concordance with our observation of a predominant role for ICAM-1 as compared to VCAM-1 in malaria pathogenesis, infusion of anti-ICAM-1 but not anti-VCAM-1 mAb prevents cytoadherence of infected erythrocytes in a *P. yoelii* model of CM [70].

4. Conclusions and perspectives

In this review, we provided some clue on how components of the allergic response may contribute to *Plasmodium* parasite transmission and disease pathogenesis. With regard to the implication of histamine as a key inflammatory product in malaria pathogenesis, a schematic representation is provided in Fig. 1. Although malaria vaccine development remains a central and ultimate goal, alternative chemotherapy-based approaches such as histamine receptor antagonists have the potential to be highly valuable. Such treatment could be part of an integrated control strategy, and also be a useful candidate in intermittent preventive treatment strategies that target specific high-risk groups such as children and pregnant women. A therapeutic value in the treatment of malaria infection is supported by the fact that antihistaminic drugs such as chlorpheniramine potentiate the anti-*Plasmodium* effect of mefloquine, quinine or pyronaridine [71]. Furthermore, given the availability of anti-histamines, such treatment could be implemented rapidly to alleviate the burden of malaria in endemic areas.

The classical pathway by which histamine is released from its natural stores, mast cells and basophils, involves IgE/Fc ϵ R1 complexes. We can argue that *Plasmodium* parasite-specific IgE antibodies sensitize mast cells and basophils and probably other Fc ϵ R1 cells

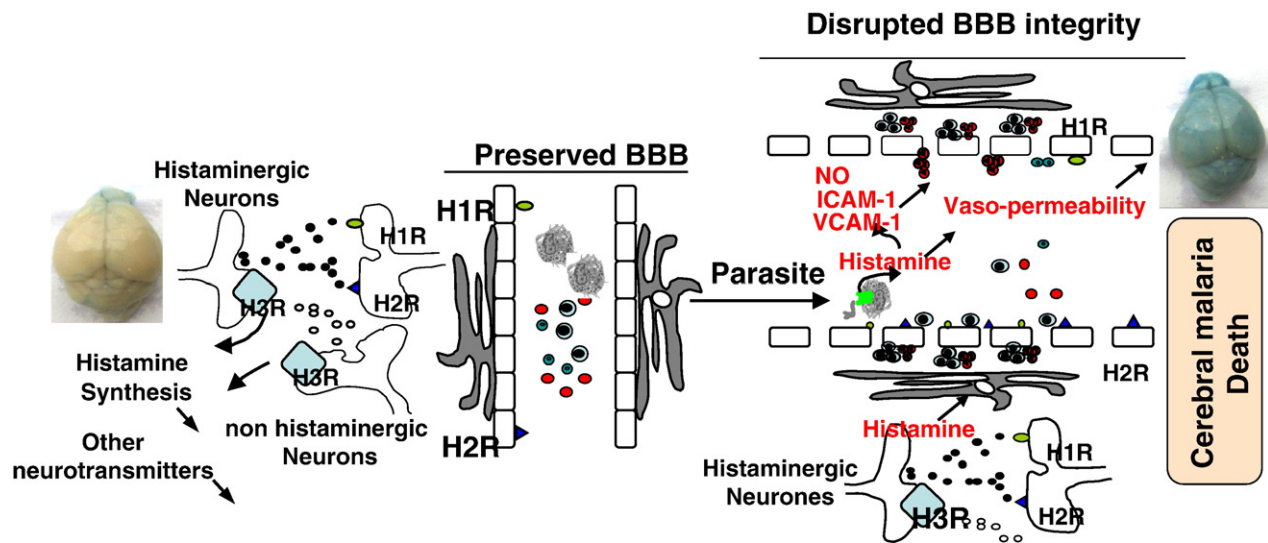


Fig. 1. Schematic representation of the pathogenetic events occurring in the brain of *Pb* ANKA-infected C57BL/6 mice. Histamine levels were found to be elevated in the plasma of infected mice and were correlated to parasitemia levels. Using multiple approaches, including HR blockers, H1R or H2R-KO mice and HDC-KO mice, it was demonstrated that histamine is directly involved in the increase of blood capillary permeability and disruption of the blood–brain barrier (BBB). Intact BBB integrity is represented on the right hand side of the figure with endothelial cells reinforced by a layer of astrocytes. Molecular (qRt-PCR) and histological analyses in the brain taken at day 6 post-infection with *Pb* ANKA parasites demonstrates that histamine is responsible for the increased synthesis of NO, the over-expression of adhesion molecules ICAM-1 and VCAM-1 and increased capillary permeability as shown by the Evans blue dye extravasation (right hand side of Fig. 1). This leads to the sequestration in the capillary endothelium of CD4 and CD8 T cells and the formation of hemorrhagic lesions containing infected red blood cells. The synthesis and release of histamine, which is also a neurotransmitter, is negatively controlled by the H3R receptor [71]. We recently found that this receptor has a protective effect against CM since H3R $^{-/-}$ mice were less resistant to CM as compared to wild-type mice [71].

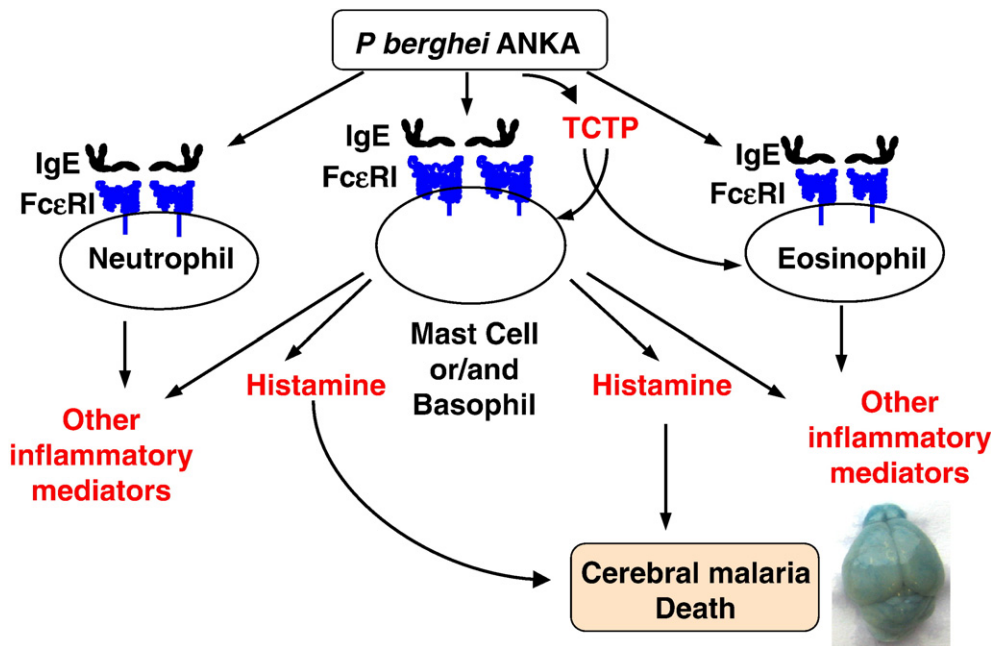


Fig. 2. Upstream events leading to the initiation of histamine-mediated inflammatory events. Our hypothesis is that the bridging of IgE Abs bound to FcεRI expressed on mast cells, basophils and possibly other inflammatory cells such as neutrophils and eosinophils can initiate or amplify this process. Alternatively or concomitantly, the translationally controlled tumor protein (TCTP) known as a histamine releasing factor (HRF) secreted by *Pb* ANKA and by many other *Plasmodium* parasite strains including *P. falciparum* is able to directly trigger inflammatory responses following activation of basophils.

which, once activated by parasite antigens, release histamine and other inflammatory mediators (Fig. 2). In addition, histamine releasing factor (TCTP) produced by *Plasmodium* parasites represents an alternative mean by which histamine release may occur (Fig. 2).

This review addresses the possibility that IgE-mediated allergic response or atopy may represent risk factors for developing severe forms of the disease. Genetic studies have established a linkage of chromosome 5q31 region to the density of blood *P. falciparum* parasites [72,73]. This finding was borne-out in a murine mouse model using *P. chabaudi* as infecting parasite where one quantitative trait locus for resistance to malaria has been mapped to a region homologous to the human 5q31-q33 [74]. The 5q31 locus that is known to contain immune response gene cluster, including the genes encoding the IL-4, IL-5, and IL-13 cytokines, was shown to be associated with inflammatory diseases including asthma [75,76]. In addition to this locus, three new regions located on chromosome 5p15-p13 and 13q13-q22 were associated with *P. falciparum* clinical malaria attacks and chromosome 12q21-q23 was associated with the maximum parasite density during asymptomatic carriage were recently identified [77]. It is interesting to note that these new three regions have all been previously found to be linked to asthma/atopy [78–80]. Further immuno-epidemiological as well as experimental studies are needed to firmly establish the nature of the relationship between allergy/atopy and malaria disease.

References

- [1] H. Bouharoun-Tayoun, C. Ouevray, F. Lunel, P. Druilhe, Mechanisms underlying the monocyte-mediated antibody killing of *Plasmodium falciparum* asexual blood stages, *J. Exp. Med.* 182 (1995) 409–418.
- [2] H. Groux, J. Gysin, Opsonization as an effector mechanism in human protection against asexual blood stages of *Plasmodium falciparum*: functional role of IgG subclasses, *Res. Immunol.* 141 (1990) 529–542.
- [3] H. Bouharoun-Tayoun, P. Druilhe, *Plasmodium falciparum* malaria: evidence for an isotype imbalance which may be responsible for delayed acquisition of protective immunity, *Infect. Immun.* 60 (1992) 1473–1481.
- [4] A. Haileamlak, D. Dagoye, H. Williams, A.J. Venn, R. Hubbard, J. Britton, S.A. Lewis, Early life risk factors for atopic dermatitis in Ethiopian children, *J. Allergy Clin. Immunol.* 115 (2005) 370–376.
- [5] J. Sunyer, C. Mendendez, P.J. Ventura, J.J. Aponte, D. Schellenberg, E. Kahigwa, C. Acosta, J.M. Antó, P.L. Alonso, Prenatal risk factors of wheezing at the age of four years in Tanzania, *Thorax* 56 (2001) 290–295.
- [6] G. Elghazali, H. Perlmann, A.S. Rutta, P. Perlmann, M. Troye-Blomberg, Elevated plasma levels of IgE in *Plasmodium falciparum*-primed individuals reflect an increased ratio of IL-4 to interferon-gamma (IFN-gamma)-producing cells, *Clin. Exp. Immunol.* 109 (1997) 84–89.
- [7] P. Perlmann, H. Perlmann, G. Elghazali, M.T. Blomberg, IgE and tumor necrosis factor in malaria infection, *Immunol. Lett.* 65 (1999) 29–33.
- [8] P. Perlmann, H. Perlmann, B.W. Flyg, M. Hagstedt, G. Elghazali, S. Worku, V. Fernandez, A.S. Rutta, M. Troye-Blomberg, Immunoglobulin E, a pathogenic factor in *Plasmodium falciparum* malaria, *Infect. Immun.* 65 (1997) 116–121.
- [9] S. Berczky, S.M. Montgomery, M. Troye-Blomberg, I. Rooth, M.A. Shaw, A. Farnert, Elevated antimalarial IgE in asymptomatic individuals is associated with reduced risk for subsequent clinical malaria, *Int. J. Parasitol.* 34 (2004) 935–942.
- [10] J. Duarte, P. Deshpande, V. Guiyedi, S. Mécheri, C. Fesel, P.-A. Cazenave, G.C. Mishra, M. Kombila, S. Pied, Total and functional parasite specific IgE responses in *Plasmodium falciparum*-infected patients exhibiting different clinical status, *Malar. J.* 6 (2007) 1–13.
- [11] U. Bhattacharya, S. Roy, P.K. Kar, B. Sarangi, S.C. Lahiri, Histamine & kinin system in experimental malaria, *Indian J. Med. Res.* 88 (1988) 558–563.
- [12] B. Maegraith, A. Fletcher, The pathogenesis of mammalian malaria, *Adv. Parasitol.* 10 (1972) 49–75.
- [13] A.A. James, P.A. Rossignol, Mosquito salivary glands: parasitological and molecular aspects, *Parasitol. Today* 7 (1991) 267.
- [14] R.G. Titus, J.M. Ribeiro, The role of Vector saliva in transmission of arthropod-borne disease, *Parasitol. Today* 6 (1990) 157.
- [15] Y. Belkaid, S. Kamhawi, G. Modi, J. Valenzuela, N. Noben-Trauth, E. Rowton, J. Ribeiro, D.L. Sacks, Development of a natural model of cutaneous leishmaniasis: powerful effects of vector saliva and saliva preexposure on the long-term outcome of *Leishmania major* infection in the mouse ear dermis, *J. Exp. Med.* 188 (1998) 1941.
- [16] J. Ribeiro, Role of saliva in blood-feeding by arthropods, *Annu. Rev. Entomol.* 32 (1987) 463.
- [17] J.A. Vaughan, L.F. Scheller, R.A. Wirtz, A.F. Azad, Infectivity of *Plasmodium berghei* sporozoites delivered by intravenous inoculation versus mosquito bite: implications for sporozoite vaccine trials, *Infect. Immun.* 67 (1999) 4285–4289.
- [18] B.S. Schneider, C. Mathieu, R. Peronet, S. Mecheri, *Anopheles stephensi* Saliva Enhances Progression of Cerebral Malaria in a Murine Model, *Vector-Borne and Zoonotic Dis* 11 (2011) 423–432.
- [19] K. Mellanby, Man's reaction to mosquito bites, *Nature* 19 (1946) 554.
- [20] T. Reunala, P. Lappalainen, H. Brummer-Korvenkontio, P. Coulie, T. Palosuo, Cutaneous reactivity to mosquito bites: effect of cetirizine and development of anti-mosquito antibodies, *Clin. Exp. Allergy* 21 (1991) 617–622.
- [21] D.R. McCormack, K.F. Salata, J.N. Hershey, G.B. Carpenter, R.J. Engler, Mosquito bite anaphylaxis: immunotherapy with whole body extracts, *Ann. Allergy Asthma Immunol.* 74 (1995) 39–44.
- [22] Z. Peng, M. Yang, F.E.R. Simons, Immunologic mechanisms in mosquito allergy: correlation of skin reactions with specific IgE and IgG antibodies and lymphocyte

- proliferation response to mosquito antigens, *Ann. Allergy Asthma Immunol.* 77 (1996) 238–244.
- [23] E. Ohtsuka, S. Kawai, T. Ichikawa, H. Nojima, K. Kitagawa, Y. Shirai, K. Kamimura, Y. Kuraishi, Roles of mast cells and histamine in mosquito bite-induced allergic itch-associated responses in mice, *Jpn J. Pharmacol.* 86 (2001) 97–105.
 - [24] C.E. Demeure, K. Brahimi, F. Hacin, F. Marchand, R. Peronet, M. Huerre, P. St-Mezard, J.F. Nicolas, P. Brey, G. Delespesse, S. Mecheri, Anopheles mosquito bites activate cutaneous mast cells leading to a local inflammatory response and lymph node hyperplasia, *J. Immunol.* 174 (2005) 3932–3940.
 - [25] E. Ohtsuka, S. Kawai, T. Ichikawa, H. Nojima, K. Kitagawa, Y. Shirai, K. Kamimura, Y. Kuraishi, Roles of mast cells and histamine in mosquito bite-induced allergic itch-associated responses in mice, *Jpn J. Pharmacol.* 86 (2001) 97.
 - [26] K. Oka, N. Ohtaki, T. Yasuhara, T. Nakajima, A study of mosquito salivary gland components and their effects on man, *J. Dermatol.* 16 (1989) 469.
 - [27] J.B. McLachlan, J.P. Hart, S.V. Pizzo, C.P. Shelburne, H.F. Staats, M.D. Gunn, S.N. Abraham, Mast cell-derived tumor necrosis factor induces hypertrophy of draining lymph nodes during infection, *Nat. Immunol.* 4 (2003) 1199.
 - [28] M. Ohashi, M. Harada, S. Suguri, H. Ohmae, A. Ishii, The role of saliva of *Anopheles stephensi* in inflammatory response: identification of a high molecular weight neutrophil chemotactic factor, *Parasitol. Res.* 87 (2001) 376.
 - [29] T. Biedermann, M. Kneilling, R. Mailhammer, K. Maier, C.A. Sander, G. Kollias, S.L. Kunkel, L. Hultner, M. Rocken, Mast cells control neutrophil recruitment during T cell-mediated delayed-type hypersensitivity reactions through tumor necrosis factor and macrophage inflammatory protein 2, *J. Exp. Med.* 192 (2000) 1441.
 - [30] R. Malaviya, T. Ikeda, E. Ross, S.N. Abraham, Mast cell modulation of neutrophil influx and bacterial clearance at sites of infection through TNF- α , *Nature* 381 (1996) 77.
 - [31] A.H. Enk, V.L. Angeloni, M.C. Udey, S.L. Katz, An essential role for Langerhans cell-derived IL-1 β in the initiation of primary immune responses in skin, *J. Immunol.* 150 (1993) 3698.
 - [32] P. Alard, I. Kurimoto, H. Niizeki, J.M. Doherty, J.W. Streilein, Hapten-specific tolerance induced by acute, low-dose ultraviolet B radiation of skin requires mast cell degranulation, *Eur. J. Immunol.* 31 (2001) 1736.
 - [33] P.H. Hart, M.A. Grimaldeston, G.J. Swift, F.A. Jaksic, P. Noonan, J.J. Finlay-Jones, Dermal mast cells determine susceptibility to ultraviolet B-induced systemic suppression of contact hypersensitivity responses in mice, *J. Exp. Med.* 187 (1998) 2045.
 - [34] R.S. Desowitz, *Plasmodium falciparum* immunoglobulin E in sera from an area of holoendemic malaria, *Trans. R. Soc. Trop. Med. Hyg.* 83 (1989) 478–479.
 - [35] N. Depinay, F. Hacin, W. Beghdadi, R. Peronet, S. Mecheri, Mast cell-dependent down-regulation of antigen-specific immune responses by mosquito bites, *J. Immunol.* 176 (2006) 4141–4146.
 - [36] T.A. Ferguson, P. Dube, T.S. Griffith, Regulation of contact hypersensitivity by interleukin 10, *J. Exp. Med.* 179 (1994) 1597–1604.
 - [37] M.A. Grimaldeston, S. Nakae, J. Kalesnikoff, M. Tsai, S.J. Galli, Mast cell-derived interleukin 10 limits skin pathology in contact dermatitis and chronic irradiation with ultraviolet B, *Nat. Immunol.* 8 (2007) 1095–1104.
 - [38] L. Biggs, C. Yu, B. Fedoric, A.F. Lopez, S.J. Galli, M.A. Grimaldeston, Evidence that vitamin D(3) promotes mast cell-dependent reduction of chronic UVB-induced skin pathology in mice, *J. Exp. Med.* 207 (2010) 455–463.
 - [39] P.W. Askenase, H. Van Loveren, S. Kraeuter Kops, Y. Ron, R. Meade, T.C. Theoharides, J.J. Nordlund, H. Scovern, M.D. Gerhson, W. Ptak, Defective elicitation of delayed-type hypersensitivity in W/W^v and Sl/Sl^d mast cell deficient mice, *J. Immunol.* 131 (1983) 2687–2694.
 - [40] T.B. Bury, J.L. Corhay, M.F. Radermecker, Histamine-induced inhibition of neutrophil chemotaxis and T-lymphocyte proliferation in man, *Allergy* 47 (1992) 624–629.
 - [41] I.J. Elenkov, E. Webster, D.A. Papanicolaou, T.A. Fleisher, G.P. Chrousos, R.L. Wilder, Histamine potently suppresses human IL-12 and stimulates IL-10 production via H2 receptors, *J. Immunol.* 161 (1998) 2586–2593.
 - [42] J.A. Kurtzhals, C.M. Reimert, E. Tette, S.K. Dunyo, K.A. Koram, B.D. Akanmori, F.K. Nkrumah, L. Hviid, Increased eosinophil activity in acute *Plasmodium falciparum* infection—association with cerebral malaria, *Clin. Exp. Immunol.* 112 (1998) 303–307.
 - [43] M.A. Nyakeriga, M. Troye-Blomberg, S. Bereczky, H. Perlmann, P. Perlmann, G. ElGhazali, Immunoglobulin E (IgE) containing complexes induce IL-4 production in human basophils: effect on Th1–Th2 balance in malaria, *Acta Trop.* 86 (2003) 55–62.
 - [44] T. Furuta, T. Kikuchi, Y. Iwakawa, N. Watanabe, Protective roles of mast cells and mast cell-derived TNF in murine malaria, *J. Immunol.* 177 (2006) 3294–3302.
 - [45] T. Srichaikul, N. Archararit, T. Siriasawakul, T. Viriyapanich, Histamine changes in *Plasmodium falciparum* malaria, *Trans. R. Soc. Trop. Med. Hyg.* 70 (1976) 36–38.
 - [46] S.J. Hill, C.R. Ganellin, H. Timmerman, J.C. Schwartz, N.P. Shankley, J.M. Young, W. Schunack, R. Levi, H.L. Haas, International Union of Pharmacology. XIII. Classification of histamine receptors, *Pharmacol. Rev.* 49 (1997) 253–278.
 - [47] C.L. Hofstra, P.J. Desai, R.L. Thurmond, W.P. Fung-Leung, Histamine H4 receptor mediates chemotaxis and calcium mobilization of mast cells, *J. Pharmacol. Exp. Ther.* 305 (2003) 1212–1221.
 - [48] A.R. Burns, R.A. Bowden, Y. Abe, D.C. Walker, S.I. Simon, M.L. Entman, C.W. Smith, P-selectin mediates neutrophil adhesion to endothelial cell borders, *J. Leukoc. Biol.* 65 (1999) 299–306.
 - [49] J. Van De Voorde, I. Leusen, Role of the endothelium in the vasodilator response of rat thoracic aorta to histamine, *Eur. J. Pharmacol.* 87 (1993) 113–120.
 - [50] G. Majno, S.M. Shea, M. Leventhal, Endothelium contraction induced by histamine-type mediators: an electron microscope study, *J. Cell Biol.* 42 (1969) 647–672.
 - [51] E. Svensjö, G.J. Grega, Evidence for endothelial cell-mediated regulation of macromolecular permeability by postcapillary venules, *Fed. Proc.* 45 (1986) 89–95.
 - [52] W. Beghdadi, A. Porcherie, B.S. Schneider, D. Dubayle, R. Peronet, M. Huerre, T. Watanabe, H. Ohtsu, J. Louis, S. Mecheri, Inhibition of histamine-mediated signaling confers significant protection against severe malaria in mouse models of disease, *J. Exp. Med.* 205 (2008) 395–408.
 - [53] S.M. MacDonald, J. Bhisutthibhan, T.A. Shapiro, S.J. Rogerson, T.E. Taylor, M. Tembo, J.M. Langdon, S.R. Meshnick, Immune mimicry in malaria: *Plasmodium falciparum* secretes a functional histamine-releasing factor homolog in vitro and in vivo, *Proc. Natl Acad. Sci. USA* 98 (2001) 10829–10832.
 - [54] C.O. Enwonwu, B.M. Afolabi, L.O. Salako, E.O. Idigbe, N. Bashirelah, Increased plasma levels of histidine and histamine in falciparum malaria: relevance to severity of infection, *J. Neural Transm.* 107 (2000) 1273–1287.
 - [55] L. Edvinsson, B.B. Fredholm, Characterization of adenosine receptors in isolated cerebral arteries of cat, *Br. J. Pharmacol.* 80 (1983) 631–637.
 - [56] M. Wahl, L. Schilling, Regulation of cerebral blood flow—a brief review, *Acta Neurochir. Suppl. (Wien)* 59 (1993) 3–10.
 - [57] C.R. Newton, N. Peshu, B. Kendall, F.J. Kirkham, A. Sowunmi, C. Waruiru, I. Mwangi, S.A. Murphy, K. Marsh, Brain swelling and ischaemia in Kenyans with cerebral malaria, *Arch. Dis. Child.* 70 (1994) 281–287.
 - [58] V. Amani, A.M. Vigario, E. Belnoue, M. Marussig, L. Fonseca, D. Mazier, L. Renia, Involvement of IFN- γ receptor-mediated signaling in pathology and anti-malarial immunity induced by *Plasmodium berghei* infection, *Eur. J. Immunol.* 30 (2000) 1646–1655.
 - [59] J. Lou, Y. Gasche, L. Zheng, B. Critico, C. Monso-Hinard, P. Juillard, P. Morel, W.A. Buurman, G.E. Grau, Differential reactivity of brain microvascular endothelial cells to TNF reflects the genetic susceptibility to cerebral malaria, *Eur. J. Immunol.* 28 (1998) 3989–4000.
 - [60] S. Kossodo, C. Monso, P. Juillard, T. Velu, M. Goldman, G.E. Grau, Interleukin-10 modulates susceptibility in experimental cerebral malaria, *Immunology* 91 (1997) 536–540.
 - [61] J.L. Baptista, G. Vanham, M. Wery, E. Van Marck, Cytokine levels during mild and cerebral falciparum malaria in children living in a mesoendemic area, *Trop. Med. Int. Health* 2 (1997) 673–679.
 - [62] M. Saeftel, A. Krueger, S. Arriens, V. Heussler, P. Racz, B. Fleischer, F. Brombacher, A. Hoerauf, Mice deficient in interleukin-4 (IL-4) or IL-4 receptor α have higher resistance to sporozoite infection with *Plasmodium berghei* (ANKA) than do naive wild-type mice, *Infect. Immun.* 72 (2004) 322–331.
 - [63] E. Belnoue, M. Kayibanda, A.M. Vigario, J.C. Deschemin, N. van Rooijen, M. Viguier, G. Snounou, L. Renia, On the pathogenic role of brain-sequestered α CD8⁺ T cells in experimental cerebral malaria, *J. Immunol.* 169 (2002) 6369–6375.
 - [64] G.E. Grau, D. Morrow, S. Izui, P.H. Lambert, Pathogenesis of the delayed phase of Rauscher virus-induced thrombocytopenia, *J. Immunol.* 136 (1986) 686–691.
 - [65] D.M. Yanez, D.D. Manning, A.J. Cooley, W.P. Weidanz, H.C. van der Heyde, Participation of lymphocyte subpopulations in the pathogenesis of experimental murine cerebral malaria, *J. Immunol.* 157 (1996) 1620–1624.
 - [66] N. Favre, C. Da Laperousaz, B. Ryffel, N.A. Weiss, B.A. Imhof, W. Rudin, P.F. Piguet, Role of ICAM-1 (CD54) in the development of murine cerebral malaria, *Microbes Infect.* 1 (1999) 961–968.
 - [67] S. Kimura, K.Y. Wang, A. Tanimoto, Y. Murata, Y. Nakashima, Y. Sasaguri, Acute inflammatory reactions caused by histamine via monocytes/macrophages chronically participate in the initiation and progression of atherosclerosis, *Pathol. Int.* 54 (2004) 465–474.
 - [68] T. Shimizu, J. Nishihira, H. Watanabe, R. Abe, T. Ishibashi, H. Shimizu, Cetirizine, an H1-receptor antagonist, suppresses the expression of macrophage migration inhibitory factor: its potential anti-inflammatory action, *Clin. Exp. Allergy* 34 (2004) 103–109.
 - [69] G. Ciprandi, M.A. Tosca, C. Cosentino, A.M. Riccio, G. Passalacqua, G.W. Canonica, Effects of fexofenadine and other antihistamines on components of the allergic response: adhesion molecules, *J. Allergy Clin. Immunol.* 112 (2003) S78–S82.
 - [70] D.K. Kaul, X.D. Liu, R.L. Nagel, H.L. Shear, Microvascular hemodynamics and in vivo evidence for the role of intercellular adhesion molecule-1 in the sequestration of infected red blood cells in a mouse model of lethal malaria, *Am. J. Trop. Med. Hyg.* 58 (1998) 240–247.
 - [71] S. Nakornchai, P. Konthiang, Potentiation of antimalarial drug action by chlorpheniramine against multidrug-resistant *Plasmodium falciparum* in vitro, *Parasitol. Int.* 55 (2006) 195–199.
 - [72] L. Flori, B. Kumulungui, C. Aucan, C. Esnault, A.S. Traore, F. Fumoux, P. Rihet, Linkage and association between *Plasmodium falciparum* blood infection levels and chromosome 5q31–q33, *Genes Immun.* 4 (2003) 265–268.
 - [73] A. Garcia, S. Marquet, B. Bucheton, D. Hillaire, M. Cot, N. Fievet, A.J. Dessein, L. Abel, Linkage analysis of blood *Plasmodium falciparum* levels: interest of the 5q31–q33 chromosome region, *Am. J. Trop. Med. Hyg.* 58 (1998) 705–709.
 - [74] M. Hernandez-Valladares, P. Rihet, O.K. ole-MoiYoi, F.A. Iraqi, Mapping of a new quantitative trait locus for resistance to malaria in mice by a comparative mapping approach with human chromosome 5q31–q33, *Immunogenetics* 56 (2004) 115–117.

- [75] J.W. Holloway, C. Lonjou, B. Beghe, Q. Peng, T.R. Gaunt, I. Gomes, I.P. Hall, J.C. Dewar, J. Wilkinson, N.S. Thomas, S.T. Holgate, N.E. Morton, Linkage analysis of the 5q31–33 candidate region for asthma in 240 UK families, *Genes Immun.* 2 (2001) 20–24.
- [76] J. Xu, D.A. Meyers, C. Ober, M.N. Blumenthal, B. Mellen, K.C. Barnes, R.A. King, L.A. Lester, T.D. Howard, J. Solway, C.D. Langefeld, T.H. Beaty, S.S. Rich, E.R. Bleeker, N.J. Cox, Genomewide screen and identification of gene-gene interactions for asthma-susceptibility loci in three U.S. populations: Collaborative Study on the Genetics of Asthma, *Am. J. Hum. Genet.* 68 (2001) 1437–1446.
- [77] A. Sakuntabhai, R. Ndiaye, I. Casadémont, C. Peerapittayamongkol, C. Rogier, P. Tortevoe, A. Tall, R. Paul, C. Turbpaiboon, W. Phimpraphi, J.F. Trape, A. Spiegel, S. Heath, O. Mercereau-Puijalon, A. Dieye, C. Julier, Genetic determination and linkage mapping of *Plasmodium falciparum* malaria related traits in Senegal, *PLoS ONE* 3 (2008).
- [78] S.K. Iyengar, K.B. Jacobs, L.J. Palmer, Improved evidence for linkage on 6p and 5p with retrospective pooling of data from three asthma genome screens, *Genet. Epidemiol.* 21 (Suppl 1) (2001) S130–S135.
- [79] N. Jang, G. Stewart, G. Jones, Polymorphisms within the PHF11 gene at chromosome 13q14 are associated with childhood atopic dermatitis, *Genes Immun.* 6 (2005) 262–264.
- [80] T. Kurz, S. Hoffjan, M.G. Hayes, D. Schneider, R. Nicolae, A. Heinzmann, S.P. Jerkic, R. Parry, N.J. Cox, K.A. Deichmann, C. Ober, Fine mapping and positional candidate studies on chromosome 5p13 identify multiple asthma susceptibility loci, *J. Allergy Clin. Immunol.* 118 (2006) 396–402.