Malaria remains a devastating global health problem, resulting in many annual deaths due to the complications of severe malaria. However, in endemic regions, individuals can acquire ‘clinical immunity’ to malaria, characterized by a decrease in severe malaria episodes and an increase of asymptomatic *Plasmodium falciparum* infections. Recently, it has been reported that tolerance to ‘clinical malaria’ and reduced disease severity correlates with a decrease in the numbers of circulating Vγ9Vδ2 T cells, the major subset of γδ T cells in the human peripheral blood. This is particularly interesting as this population typically undergoes dramatic expansions during acute *Plasmodium* infections and was previously shown to play antiparasitic functions. Thus, regulated γδ T-cell responses may be critical to balance immune protection with severe pathology, particularly as both seem to rely on the same pro-inflammatory cytokines, most notably TNF and IFN-γ. This has been clearly demonstrated in mouse models of experimental cerebral malaria (ECM) based on *Plasmodium berghei* ANKA infection. Furthermore, our recent studies suggest that the natural course of *Plasmodium* infection, mimicked in mice through mosquito bite or sporozoite inoculation, includes a major pathogenic component in ECM that depends on γδ T cells and IFN-γ production in the asymptomatic liver stage, where parasite virulence is seemingly set and determines pathology in the subsequent blood stage. Here, we discuss these and other recent advances in our understanding of the complex—protective versus pathogenic—functions of γδ T cells in malaria.

Introduction

Malaria remains a devastating global health problem, responsible for more than 228 million cases per year worldwide, leading to more than 405 000 annual deaths due to severe malaria, such as cerebral malaria (CM), mostly caused by *Plasmodium (P.) falciparum* [1]. The most vulnerable groups affected by malaria are children under 5 years old, which accounted for 67% of all malaria deaths worldwide, and pregnant women [1].

In endemic regions, adults and children older than 5 years acquire considerably rapid ‘clinical immunity’ to malaria, characterized by a decrease in severe malaria episodes and an increase of asymptomatic *P. falciparum* infections [2]. Our understanding of ‘clinical immunity’ is made difficult by the complex life cycle of *Plasmodium* in the host, comprising two stages in two different tissues, liver and blood, together with other factors, such as high genetic variation of the parasite, age of the host and frequency of infection [3].

Abbreviations

CM, cerebral malaria; ECM, experimental cerebral malaria; IFN-γ, interferon-γ; IL-, interleukin; MIP, macrophage inflammatory protein; MSP1, merozoite surface protein 1; *P., Plasmodium*; pRBCs, parasitized red blood cells; RAMA, Rhooptry-associated membrane antigen; Spz, sporozoites; TCR, T-cell receptor; TNF, tumor necrosis factor; WT, wild-type.
In natural infections, malaria is transmitted through the bite of infected Anopheles mosquitoes, in which Plasmodium sporozoites (Spz) are delivered into the skin and from there find their way to the liver [4]. After invading a hepatocyte, the Spz develops and replicates producing a schizont containing thousands of merozoites. Merozoites then egress from hepatocytes and are released into the bloodstream where they invade red blood cells and initiate the blood-stage infection. The clinically ‘silent’ liver stage is thus an essential step in the Plasmodium life cycle that always precedes the cyclic intraerythrocytic infection where the clinical symptoms of malaria, such as CM, appear [4].

Due to this complexity, stemming from both the malaria parasite and the human immune system, interactions between the parasite and the host during infection result in outcomes ranging from protective immunity to ‘clinical immunity’ or to highly deleterious immune responses, particularly in severe malaria [5,6]. One of the immune populations gathering increasing interest in this context are γδ T cells. In this viewpoint, we discuss and integrate recent advances from human and mouse studies toward a better understanding of the multifaceted functions of γδ T during malaria infection, with a particular focus on CM.

γδ T-cell responses to Plasmodium infection

γδ T cells are one of the immune populations that respond most dramatically to Plasmodium infection, given that it induces very marked γδ T-cell expansions both in mice [7–9] and in humans [10–13].

Murine γδ T cells consist of various subsets with diverse properties regarding thymic ontogeny, homing to anatomical locations and functional potential [14]. The T-cell receptor (TCR) Vγ chain usage can vary substantially across tissues, and for example, in the liver, γδ T cells can express Vγ1°, Vγ4°, or Vγ6+ TCRs [14]. Like in mice, γδ T cells are also a minor population (1–5% of leukocytes) in the human peripheral blood, but are more abundant in tissues, in particular epithelial layers, such as intestine and skin [15]. Human γδ cells are typically characterized according to the variable regions of TCRδ (instead of TCRγ) chain [16]. While Vδ1° T cells are the major γδ T-cell population at epithelial sites, Vδ2+ T cells, which most often contain a Vγ9 chain, are the main subset in peripheral blood [17]. Vγ9Vδ2 T cells are able to recognize low molecular weight non-peptidic phosphoantigens, enabling them to respond to a diverse range of pathogens, including P. falciparum [18]. In fact, this subset can reach more that 40% of blood leukocytes after primary Plasmodium infections, while producing key pro-inflammatory cytokines, especially type 1 effector cytokines like interferon γ (IFN-γ) and tumor necrosis factor (TNF), in response to parasite antigen stimulation [12,13,19,20].

A considerable number of studies with humans and murine γδ T cells suggest they may paradoxically contribute for both protection and pathology during Plasmodium infection. Some studies have shown that Vγ9Vδ2 T cells are able to control/inhibit parasite replication by targeting and killing extracellular merozoites though a granulysin-mediated process [21–23], as well as killing intracellular late-stage parasites during the intraerythrocytic stage, also through granulysin-mediated release of cytotoxic granzymes [24] (Fig. 1), and act as antigen-presenting cells for αβ T cells in response to intraerythrocytic stage parasites [25]. However, other reports suggested that Vγ9Vδ2 T cells may be linked to pathological outcomes, since a decrease in their numbers (in the blood) is associated with tolerance to ‘clinical malaria’ and reduced disease severity [5,26].

In mice, most studies have been performed with parasitized red blood cells (pRBCs), which bypass the liver stage to directly induce blood-stage infection. A recent study using a Plasmodium chabaudi infection model revealed a macrophage colony-stimulating factor (M-CSF)-producing γδ T-cell subset that provided protection at late stage of infection [27]. In this model, two different types of γδ T-cell responses were observed: During the acute stage, these cells produced mainly IFN-γ, while during the postacute stage, M-CSF was the main cytokine produced and was essential to prevent parasite recrudescence [27]. Other studies have suggested that γδ T cells may exert an immunoregulatory role by controlling alpha-beta (αβ) T-cell function in Plasmodium yoelii 17X nonlethal (17XNL) and P. chabaudi infections [28,29], whereas in Plasmodium berghei XAT (a nonlethal strain) infection model, γδ T cells expressing CD40L promoted dendritic cell activation and induced clearance of the parasite [30].

In the context of Spz immunization studies, several reports have shown that γδ T cells play an important protective role in malaria infection in humans and in P. yoelii 17XNL and P. berghei infection mouse models [31–33]. However, it is still not clear how γδ T cells exert their protective role in the context of immunization studies, namely if they function as effector cells independently of αβ T cells, in particular CD8+ T cells, or instead act as accessory cells, alongside CD8α+ dendritic cells (DC), to induce protective CD8+ T-cell responses [31–33]. In any case, all studies have
suggested an important protective role of γδ T cells during Spz vaccination studies.

**Cerebral malaria**

Severe malaria is a general term that includes various and overlapping lethal syndromes, such as CM and respiratory distress, that may coexist during the malaria infection [34]. The development of severe malaria, and ultimately death, may depend on several factors, such as the species of the parasite, the innate and acquired immunity of the host, as well as the efficacy of antimalarial treatment [34].

Cerebral malaria is one of the most common forms of severe malaria, responsible for the majority of child mortality, presenting between 15% and 25% fatality rate, and for which there is no effective therapy [35]. Although the nature of the cellular and molecular mechanisms leading to CM remains poorly understood two nonexclusive hypotheses, the mechanical (sequestration) obstruction and the immune-driven inflammation, try to explain the complex interactions between the malaria parasite and the host that lead to this pathology [36,37]. However, these two phenomena may not fully explain the genesis of CM [38]. More recently, a new hypothesis has been proposed stating that the involvement of acute liver failure, together with blood–brain barrier breakdown, may be sufficient and necessary for CM development [38]. This hypothesis is further supported by two phenomena that occur during experimental CM (ECM): liver damage due to parasite sequestration/accumulation [39], and
activation of CD8\(^+\) T cells, a process that requires a metabolic shift from oxidative processes to aerobic glycolysis and glutaminolysis, thus requiring high levels of glutamine [40]. Indeed, several reports have linked high glutamine levels, and consequently high ammonia levels, to encephalopathy associated with acute fulminating liver failure [41]. More recently, a study showed the therapeutic potential of blocking glutamine metabolism to rescue mice from ECM development [42]. Overall these studies strengthen the importance of the liver in ECM pathogenesis.

Both the sequestration and immunopathology hypotheses have been widely tested in the mouse model for CM, P. berghei ANKA-induced ECM in C57BL/6 mice [43–45]. The ECM model recapitulates many of the features of CM observed in children [46,47], such as the accumulation of pRBCs and CD8\(^+\) T cells in the brain vasculature [45,46,48], and blood–brain barrier (BBB) dysfunction and edema [46]. On the other hand, ECM is also an immune-mediated disease where CD8\(^+\) T cells and the pro-inflammatory cytokine IFN-γ play central pathogenic roles [6,49,50]. Recently, a study showed definitively the presence of CD8\(^+\) T cells in close contact with the microvascularity in brains of children that died with CM, as well as the presence of pRBC along the cerebrovasculature, which may promote endothelial antigen acquisition and cross-presentation to CD8\(^+\) T cells [47]. These findings corroborate the results obtained with the ECM model and reinforce the relevance of this experimental system to elucidate CM associated-pathogenic processes in humans and to assess new therapeutic targets for CM adjunctive therapy.

The vast majority of the studies using the ECM model have challenged the mice with P. berghei-pRBC, a route of infection that bypasses the liver stage of Plasmodium infection, thus neglecting the potential impact of the liver stage in the subsequent (erythrocytic and symptomatic phase) of Plasmodium infection and in CM pathogenesis. In fact, very few studies have shown that pre-erythrocytic or early immune responses may modulate downstream immune responses and thereby impact ECM development or clinical symptoms, respectively, in mice and in humans [26,51–56]. Some of these studies used chemical or genetically modified P. berghei ANKA parasites that after Spz infection showed impaired development during liver and intraerythrocytic stages, thus impacting on subsequent systemic immune responses and, ultimately, on ECM development [53,54]. By contrast, another study with a transgenic P. berghei ANKA parasite that moderately overexpress profilin, an immunomodulatory protein, and that after Spz infection did not show evident developmental impairments, induced an early production of the regulatory cytokine interleukin (IL)-10 and pro-inflammatory cytokines, such as IL-12p70, IL-6, and TNF [56]. This early immune response seemed to dampen the subsequent pro-inflammatory responses during blood stage and prevented the development of ECM [56]. Notably, this transgenic parasite induced lower sterile immunity in the context of immunization studies when compared with wild-type (WT) parasites, suggesting reduced hepatic immune responses [56]. It would be interesting to assess the functional interaction of γδ T cells with this transgenic parasite in the context of whole-Spz vaccination strategies.

**Human γδ T cells in severe malaria**

Several studies have suggested different roles for the two main human γδ T-cell subsets, expressing either Vδ1 or Vδ2 TCRs, in response to P. falciparum in distinct experimental or clinical settings [3,57]. In fact, the response of γδ T-cell subsets seems to depend on several factors such as the age of the host (children or adults), ethnicity, that is, Caucasians or Africans, and malaria endemicity, that is, high or low endemic areas. Although Vγ9Vδ2 T cells seem to be the main γδ T-cell subset in healthy Caucasians, this is not observed in healthy individuals living in malaria-endemic areas [58]. Notably, it has been reported that both Vγ9\(^+\) and Vδ1\(^+\) subsets seem to increase proportionally following P. falciparum infection in patients from malaria-endemic areas [58,59]. Thus, the sustained Vγ9Vδ2 T cell-dominated responses in studies using γδ T cells from peripheral blood of nonexposed individuals have not been corroborated by some African studies [60,61]. Actually, it has been reported that in the context of endemic malaria, where populations are exposed to consecutive malaria infections and/or chronic infection, Vδ1\(^+\) T cells seem to be the main subset in circulation [58]. While there is no clear explanation for this observation, it has been suggested that the retention of active Vγ9Vδ2 T cells in the spleen and/or the reemergence of tissue-resident Vδ1\(^+\) T cells, such as hepatic Vδ1\(^+\) T cells, into the circulation after antimalarial chemotherapy, may change the proportions of both subsets in the peripheral blood [60].

An emerging topic is the role of human γδ T cells in ‘clinical malaria’. Although multiple studies have been performed with malaria-naïve and infected adults [12,20,62,63], considerably fewer have been done in children from endemic countries that develop severe malaria, in particular CM, and are subjected to recurrent Plasmodium infections [5,26,55,61,63–65]. Of note, studies performed in children and adults from African
endemic countries showed that percentage and activation markers of γδ T cells do not seem to discriminate 'clinical malaria' cases from asymptomatic infections [61,62,64]. Indeed, it has been reported that age, level of previous exposure, and antimalarial chemotherapy are crucial determinants of malaria-induced γδ T-cell responses and in the observed proportions of Vγ9Vδ2 T cells and Vδ1+ T cells in peripheral blood [3,64]. A study using convalescent samples from children with severe malaria and living in high endemic areas showed that CD14+ monocytes and γδ T cells were the predominant cellular sources of TNF, macrophage inflammatory protein (MIP)-1β, and MIP-1α after in vitro stimulation with pRBC [26]. Interestingly, recent studies have shown a decrease in Vγ9Vδ2 T-cell numbers associated with tolerance to clinical malaria and reduced disease severity [5]. Thus, in malaria-endemic areas, the loss and dysfunction of Vδ2+ T cells may represent a mechanism of disease tolerance that seems to contribute to the development of 'clinical immunity' in children that are subjected to successive malaria episodes [5,65]. The production of pro-inflammatory cytokines, such as TNF and IFN-γ, by Vδ2+ T cells may have two opposing effects during malaria infection, on the one hand an antiparasitic effect that limits parasite burden, but on the other hand, it can promote the development of clinical symptoms [26]. Therefore, the acquisition of 'clinical immunity' may depend on the ability of the host to down-modulate pro-inflammatory responses by Vδ2+ T cells, which will favor the presence of asymptomatic infections and perpetuate P. falciparum transmission in endemic countries, as suggested by several studies [5,19,66] (Fig. 1). Nonetheless, it is still not very clear how Vγ9Vδ2 T cells contribute to both 'clinical immunity' and susceptibility to severe disease in the course of P. falciparum infection as well as the role of Vδ1+ T cells during infection [57].

**Murine γδ T cells in experimental cerebral malaria**

Effector lymphocytes, especially CD4+ and CD8+ T cells, as well as pro-inflammatory cytokines, like IFN-γ, TNF, and lymphokine alpha, have long been shown to play crucial roles in ECM pathogenesis [6]. In fact, mice (in the C57Bl/6 genetic background) deficient for all T cells, or just γβ T cells, or only CD8+ T cells, all fail to develop ECM upon P. berghei ANKA infection [8]. Although an early pro-inflammatory immune response has been associated with protection against infection, this needs to be followed by a rapid resolution of inflammation in order to prevent immunopathology [67]. It is therefore critical to dissect the early, innate-like immune responses that drive the induction of inflammation and subsequent pathological processes in ECM.

In fact, γδ T cells are endowed with an innate capacity to produce high amounts of IFN-γ and IL-17, which is preprogrammed during thymic development [9,68,69]. However, the pioneering study addressing the role of γδ T cells in ECM development, which used P. berghei ANKA pRBCs, showed that mice deficient for γδ T cells (TCRδ−/−) developed ECM similarly to control mice, while mice depleted of γδ T cells by monoclonal antibody were partially protected from CM [70]. This prompted us to recently readdress the role of γδ T cells in ECM in a setting that is closer to the natural infection, namely by using mosquito bite or Spzs to initiate the infection. Importantly, these routes, unlike pRBCs inoculation, lead to infection of the liver and development of the parasite inside hepatocytes before they egress to the blood. Importantly, until very recently nothing was known about the properties and contributions of γδ T cells during a primary Spz-induced *Plasmodium* infection on the course to ECM development.

**Pathogenic role for γδ T cells in ECM upon liver-stage infection**

The liver is a central organ for several crucial metabolic processes in addition to its nutrient storage and detoxifying capacities [71]. Besides these functions, its critical position between the gastrointestinal system and the systemic circulation system makes this organ crucial for innate and adaptive immunity against pathogens as well as for induction of tolerance to non-pathogens, such as dietary antigens [71,72]. The liver is composed of parenchyma cells, among which hepatocytes comprises 60–80% of the cells, and non-parenchyma cells, with the lymphocyte population comprising ~25% of the total cells [71,72]. In healthy conditions, the liver is an anti-inflammatory or tolerogenic organ but under specific conditions is able to mount robust immune responses against infectious or noninfectious stimuli [72]. In fact, in a *P. berghei* Spzs infection model a robust innate type I IFN response was observed during the liver stage [73]. Despite this, the mechanisms regulating the balance between an efficient immune response and tolerance are essential for liver function, even if they remain poorly understood [71,72].

The liver is highly enriched in innate immune cells, such as macrophages (Kupffer cells), natural killer (NK), natural killer T (NKT) cells, and also γδ T cells,
in addition to more adaptive lymphocytes, namely γδ T cells and B cells [74]. γδ T cells constitute 15–25% of the total number of hepatic T cells and have been suggested to be important inducers of hepatic inflammation. Hepatic γδ T cells can produce high levels of pro-inflammatory cytokines, such as IL-17, TNF, and IFN-γ [71], and comprise various Vγ TCR chains, that is, Vγ1, Vγ4, and Vγ6 in mice and Vδ1 and Vδ3 in humans [16].

Several studies have shown that hepatic γδ T cells may play different functional roles, that is, pathogenic or protective, depending on the experimental models studied [71]. For example, during *Listeria monocytogenes* infection, Vγ4+ T cells, which are the major IL-17 producing cell type in the liver, are crucial for protective immunity during early infection [75]. In contrast, during *Schistosoma japonicum* infection, IL-17 production by γδ T cells, also the major IL-17-producing cell type in this infection model apparently, plays a pathogenic role since the neutralization of IL-17 reduced liver inflammation and pathology [76]. Moreover, it was recently shown that hepatic γδ T cells predominately producing high levels of IL-17A exhibited a Vγ chain repertoire distinct from γδ T cells of other organs [77].

Besides their potential role in immunization studies [31-33], the function of γδ T cells in primary pre-erythrocytic *Plasmodium* infection remains understudied and is of utmost importance to understand if the innate immune responses that occur in the liver may impact ECM pathogenesis. In addition, the crossstalk between liver and blood stages of *Plasmodium* infection has been poorly studied and remains incompletely understood but is crucial for inducing effective adaptive immune responses against the infection [78,79].

We have addressed the impact of γδ T cells and liver-stage infection on ECM development using a Spz-induced infection model [51]. We showed that TCRδ−/− mice are resistant to ECM when infected with *P. berghei* ANKA Spz, the liver-infective form of the parasite and the natural route of infection, in contrast to the susceptible phenotype when challenged with *P. berghei* ANKA-pRBC [51]. The observed pathogenic role of γδ T cells in ECM development was strictly dependent on the liver stage without affecting the intrahepatic development of the parasite or inhibiting parasite replication during the intraerythrocytic stage of infection [51]. In fact, a decreased pro-inflammatory microenvironment was observed in TCRδ−/− livers, suggesting a mechanism of disease tolerance since the lack of immunopathology did not involve reduced parasite growth rate or load [80-82]. These findings raise some issues in the context of immunization studies and, consequently, in the balance between sterile immunity and inflammation-induced immunopathology.

Interestingly, during Spz-induced liver infection, hepatic γδ T cells were the main IL-17A-producing cells, as seen in other infections [83,84], while IFN-γ+ γδ T cells were only a fraction of the total hepatic IFN-γ+ cells; however, IFN-γ+ γδ T cells seem to be required for optimal IFN-γ production by other hepatic lymphocytes, such as CD4+ and CD8+ T and NK cells (unpublished data). Along these lines, a new specific M-CSF-producing γδ T-cell subset was recently identified in the liver (as well as spleen and lung) of mice infected with *P. chabaudi*, suggesting that these cells might shape the myeloid compartment in postacute stage of the infection [27]. In fact, the crossstalk between γδ T cells and myeloid cells has already been observed in other infections and cancer models [85,86]. Therefore, it would be interesting to assess the role of these M-CSF-producing γδ T cells in the liver, their crossstalk with other immune cells and the potential impact in malaria pathogenesis after *P. berghei* Spz infection.

Importantly, in our study, liver infection impacted on the subsequent intraerythrocytic stage of the parasite by promoting an early IFN-γ response by γδ T cells that conditioned IFN-γ production by splenic CD4+ and CD8+ T cells (Fig. 2) [51]. Indeed, previous studies have shown the importance of innate IFN-γ production by γδ T cells from malaria naïve human donors, as well as the impact of IFN-γ on the differentiation of effector CD4+ Th1 cells that promote CD8+ T-cell accumulation in the brain, leading to ECM development [87,88]. Consistent with these studies, our Spz infection study showed that γδ T cells promoted the accumulation of inflammatory IFN-γ-producing and cytotoxic T cells in the brain, key features of ECM development (Fig. 2) [51]. It would be interesting to address the potential interaction between γδ T cells and CD8+ T cells in/with the cerebrovasculature in the ECM model and in human samples.

Surprisingly, during liver stage, the relative quantity of parasites developing in the liver and the prepatency period of the infection was not significantly different between TCRδ−/− and WT mice (Fig. 2). Therefore, we hypothesized that parasites derived from the liver of both mouse strains were qualitatively different, resulting in different degrees of virulence [51]. In fact, it has been known for some time that parasite virulence and disease severity increases with serial blood passage of *Plasmodium* through mice, primates, or humans and that mosquito transmission resets *Plasmodium* virulence [89-91]. In addition, recent studies
have corroborated these findings showing differences in gene expression between blood and mosquito passage parasites and their impact in parasite virulence and host immune responses [91–93].

Our transcriptional analyses of parasites derived from TCRδ−/− and WT mice following Spz infection revealed differential expression of various surface and rhoptry glycosylphosphatidyl inositol-anchored merozoite proteins, such as MSP1 and RAMA [51]. Notably, several of these proteins are potential targets for host immune cells during the intraerythrocytic stage, since it was shown that they induce pro-inflammatory responses and contribute to malaria pathogenesis [94–97]. Of note, these parasite proteins have been considered as potential components of a multivalent subunit vaccine against malaria [98–100]. Importantly, the transcriptional changes (relative to WT controls) observed in liver stage-derived parasites from TCRδ−/− mice or from IFN-γ−/− mice were very similar, suggesting a key role for IFN-γ in the γδ T cell-dependent transcriptional modulation of Plasmodium parasites. To functionally demonstrate the impact of this modulation in ECM pathogenesis, we performed adoptive transfer experiments, in which we found pRBCs collected from TCRδ−/− mice to be substantially less pathogenic than those from WT mice (Fig. 2) [51].

Overall, these observations firmly established the role of γδ T cells in promoting an IFN-γ-rich inflammatory microenvironment and impacting the expression of Plasmodium immunogenic proteins, thus increasing parasite virulence and promoting immunopathology in ECM (Fig. 2).

**Concluding remarks**

Several studies have significantly enhanced our knowledge on the diverse roles played by γδ T cells in malaria infection. This notwithstanding, additional mechanistic and functional studies are still required to answer several open questions, such as how to integrate the evidence that on one hand γδ T cells are required, either as effector or accessory cells, while on the other hand, they seem to contribute to severe malaria pathogenesis. In fact, γδ T cells seem to play a dual role in malaria infection, that is, a protective function in whole-Spz sterile immunity and a pathogenic role in severe malaria. How to balance this tradeoff when developing γδ T cell-based therapeutic strategies will be challenging, since on the one hand sterile immunity presupposes the presence of hepatic γδ T cells and on the other hand these cells seem to be drivers of immunopathology under the natural route of infection.

Although mouse models have been an irreplaceable tool to study the function of γδ T cells [101,102], it is essential to translate and apply such findings in human clinical settings. However, this is complicated by distinct developmental programs and tissue locations of γδ T cells between human and mice and because there are no mouse orthologues to the human Vγ9+ and

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**Fig. 2.** γδ T cells and IFN-γ modulate the pathogenicity of liver-derived parasites in ECM development. Graphical summary of adoptive transfer experiments showing that pathogenic role of γδ T cells in ECM is dependent on the liver stage of infection. In the presence of IFN-γ producing γδ T cells, the parasite that egresses the liver is more virulent and induces the inflammatory cascade that leads to ECM development. By contrast, pRBCs collected from TCRδ−/− mice are substantially less pathogenic than those from WT mice.

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Vα1+ subsets. Importantly, it is crucial to understand the complexity of γδ T cells in terms of their different tissue-specific homing, functional plasticity, activation mode, antigen recognition, recall functions, and cross-talk with other immune cells, in order to elucidate their role in malaria infection and, in particular, CM.

Though sterile immunity to Plasmodium may be the ultimate goal of vaccination strategies, therapies inducing clinical tolerance to malaria seem to be a more achievable goal in the short term. Importantly, a more comprehensive knowledge of the interaction between the host immune responses and the virulence mechanisms of the parasite in severe malaria will be fundamental for the development of effective immunological therapies. Furthermore, a better understanding of the basic biology and functions of liver-resident γδ T cells will be most valuable for the development of more efficacious Spz-based vaccines to induce sterile immunity and/or improved γδ T cell-based prophylactic or therapeutic strategies to induce ‘clinical immunity’ and overcome susceptibility to severe disease.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

AP and BSS conceived and wrote the manuscript.

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