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DATABASES

Entrez Genome Project: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genomeprj
Haemophilus influenzae | *Plasmodium falciparum* | S. Typhi | *Vibrio cholerae*

FURTHER INFORMATION

African Health Research Forum: http://www.afhrf.org/
Artemis: http://www.sanger.ac.uk/Software/Artemis/
Genomes OnLine Database: http://www.genomesonline.org/gold.cgi
Grand Challenges for Global Health: http://www.gcgh.org/Pages/default.aspx
Journal of Infection in Developing Countries: http://www.jidic.org
Mangosteen: http://mangosee.com/mangosteen/index.htm
Medical Research Council Unit in The Gambia: http://www.mrc.ac.uk/AboutUs/UnitsandCentres/UnitCentreDetails/MRC002099
Scientists Without Borders: http://scientistswithoutborders.nyas.org/Splash.aspx?ReturnURL=/default.aspx
The *Salmonella* Network: http://www.oloep.org/salmnet.asp
TWAS: http://www.twas.org/
Wellcome Trust Advanced Courses: http://www.wellcome.ac.uk/Professional-resources/Courses-and-conferences/Advanced-Courses/index.htm
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OPINION

What really happens to dendritic cells during malaria?

Michelle N. Wykes and Michael F. Good

Abstract | As dendritic cells (DCs) initiate all adaptive and some innate immune responses, it is not surprising that DC function during malaria is the subject of intensive investigations. However, the results of these investigations have so far been controversial. Here, we discuss various aspects of these studies, including the influence of the species and strain of *Plasmodium* on DC function, the effects of *Plasmodium* infection on the activation of $CD8^+$ T cells by DCs, the effects of haemozoin and the effects of *Plasmodium* infections on DC Toll-like-receptor signalling.

Malaria affects 300–500 million people and causes more than 1 million deaths per year, mostly in children younger than five. The disease is caused by parasites of the genus *Plasmodium*, which are transmitted by the bite of an infected anopheline mosquito. Four species infect humans: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae*. The parasite first develops in the gut of the mosquito and is passed on in the saliva of an infected insect each time it takes a new blood meal. This asexual stage of the parasite life cycle, which is known as the sporozoite, is then carried in the blood or lymph to the host's liver, where it invades hepatocytes and multiplies. After approximately 1 week, sporozoites develop into merozoites, leave the liver and invade red blood cells (RBCs), where they again multiply, progressively destroying infected RBCs. This results in bouts of fever and progressive anaemia in infected individuals. By adhering to the endothelia of diverse host organs, infected RBCs can be sequestered from the peripheral circulation, which is an important pathogenic mechanism. The obstruction of blood

vessels in the brain, together with aberrant immunological responses, can cause cerebral malaria. Other vital organs can also be damaged, which often leads to the death of the patient.

A malaria diagnosis is based on clinical symptoms, including fever, joint pain and headache, and microscopic examination of the blood. Although drugs are available to treat malaria, increasing resistance to anti-malarial drugs is problematic. In areas where transmission is high, people are continuously infected and only gradually develop immunity to the disease. Until they have acquired such immunity, children remain highly vulnerable. Pregnant women are also highly susceptible, as parasites that express novel surface molecules are selected during pregnancy[1–3] and natural defence mechanisms are reduced.

The immunology of malaria

Clinical studies of malaria in the field, and laboratory studies using rodent models, have provided insights into the mechanisms by which *Plasmodium* spp. induce disease, as well as the host immune responses that protect against disease. However, a vaccine for malaria is not yet available[4–6], which suggests that there are substantial gaps in our knowledge that must be filled before an efficacious vaccine can be designed.

The factors that regulate anti-*Plasmodium* immunity (those processes that kill *Plasmodium* spp. and reduce their biomass in the body) are incompletely understood. People living in endemic areas build up partial immunity to malaria only after recurrent infections over several years[7–9]. Many studies indicate that protection against malaria is dependent on both cell-mediated and humoral mechanisms. Agglutination studies have shown that children mount a humoral response to immunodominant variant epitopes on the surface of infected RBCs, leading to strain-specific, incomplete immunity[10], and that older children and adults respond to several variant antigens, resulting in protective immunity to multiple strains[11]. As variant antigens are specific for each parasite strain, protection is increased with each new infection.

As noted above, *Plasmodium* spp. have two main life-cycle stages in the mammalian host: the pre-erythrocytic liver stage and the blood stage. Sporozoites travelling from the site of inoculation to the liver can be cleared by antibody. At the liver stage, parasites are known to be cleared by cytotoxic $CD8^+$ T cells and possibly $CD4^+$ T cells. Therefore, vaccines that target this stage are generally aimed at initiating cellular immunity and there has been less emphasis on protection mediated by antibody. By contrast, immunity to the blood stage is less well understood. In non-lethal mouse models of *Plasmodium chabaudi* and *Plasmodium yoelii* str. 17XNL infection, the parasitaemia increases during the first 10 days of a blood-stage infection, peaks around the second week and is cleared by the third to fourth week. After the fourth week, *P. chabaudi* infections can become 'recrudescent', meaning that the parasitaemia reappears after becoming sub-patent (undetectable in blood smears). The initial growth phase (increasing parasitaemia) of a non-lethal *P. yoelii* infection is known to be controlled by macrophages, as parasitaemia levels increase when macrophages are depleted by treating mice with clodronate liposomes[12]. As shown by our group and others, using depletion techniques or gene-targeted mice, the parasitaemia peaks after 10–14 days and is then cleared by $CD4^+$ T cells that produce interferon-γ (IFN-γ)[13–16] (FIG. 1). The final clearance of the residual parasitaemia requires humoral immunity[17–20]. Numerous studies have also shown that interleukin (IL)-12 is an important cytokine in malaria immunity[21–26].

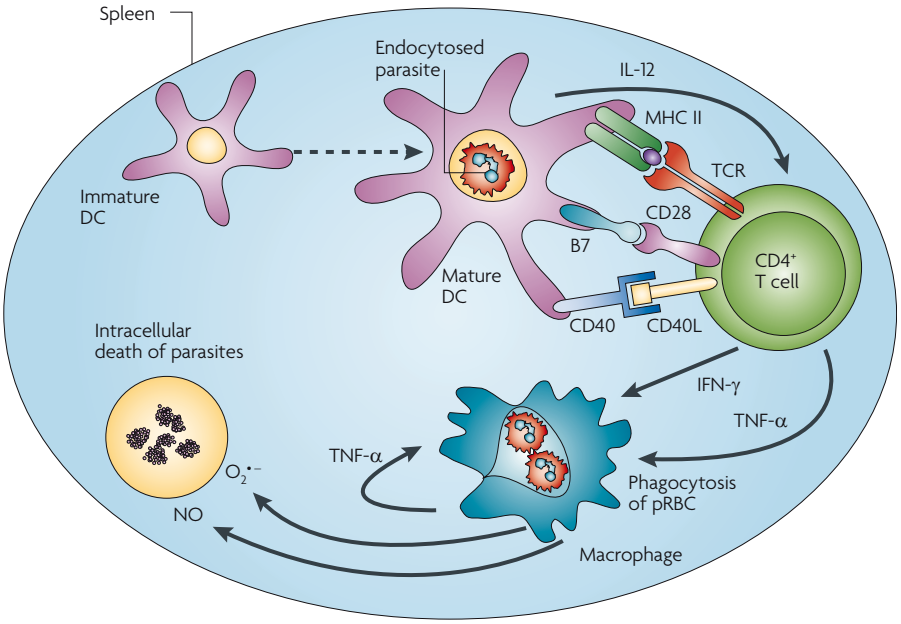

Figure 1 | **A schematic representation of the possible mechanism by which cell-mediated immunity clears *Plasmodium* spp.** Dendritic cells (DCs) endocytose the parasite, which leads to their activation and the presentation of antigens to $CD4^+$ T cells. This activation of T cells leads to macrophage activation, the phagocytosis of parasitized red blood cells (pRBCs) and the elaboration of cytokines and small inflammatory molecules (such as NO and O_2 radicals). T-cell immunity is thought to occur predominantly in the spleen. IFN-γ, interferon-γ; IL-12, interleukin-12; MHC II, major histocompatibility complex class II; TCR, T-cell receptor; TNF-α, tumour necrosis factor-α.

As dendritic cells (DCs) initiate all adaptive and some innate immune responses (BOX 1), it is not surprising that several groups have started to investigate the role of DCs in natural immunity to malaria. One of the earliest studies suggested that antigen presentation was compromised during malaria, as adherent spleen cells from infected mice, which were thought to be macrophages, were unable to take up equine RBCs[27]. More recently, DC function has been extensively studied during *Plasmodium* spp. infections.

DCs have been shown to induce immunity to malaria[28]. *In vivo* studies of DC trafficking in mice found that splenic DCs are actively engaged in the earliest phase of malarial infection *in vivo* and are likely to be crucial in shaping the subsequent immune response[29]. However, there are contradictory data on the status of DC function during malaria. In this Opinion article, we discuss the effects of *Plasmodium* spp. on the activation of human and murine DCs, the effects of *Plasmodium* spp. infection on the activation of $CD8^+$ T cells by DCs, the effects of haemozoin (a by-product of *Plasmodium* spp. infection of RBCs) on DC function and the effects of *Plasmodium* spp. infec-

Box 1 | **Dendritic cell functions**

T-cell activation
Immature dendritic cells (DCs) are 'sentinels' that capture and process pathogens and self antigens in their immediate environment for presentation to both $CD4^+$ and $CD8^+$ T cells together with activation signals to initiate immune responses.

B-cell activation
DCs can take up and retain proteins in their native form for presentation to, and activation of, B cells.

Immune tolerance
T cells that respond to DCs which carry self peptides are destroyed in the thymus by negative selection. DCs can downregulate immune responses by producing interleukin-10, a cytokine that stimulates T cells and induces T regulatory cells. DCs might also contribute to tolerance by inducing anergy in responder T cells.

Natural-killer-cell activation
It has been suggested that DCs can activate natural killer cells.

Macrophage activation
DCs can secrete interferon-γ and tumour necrosis factor-α, or activate T cells that can secrete these cytokines, which in turn activate macrophages.

See REF. 78 for a more detailed understanding of DC subpopulations and related functions.

tions on DC Toll-like receptor (TLR) signalling.

DC modulation during malaria

Is DC activation compromised during malaria? Urban and colleagues[30] were the first to publish data which suggested that DC function was compromised during blood-stage malaria. Their study found that intact *P. falciparum*-infected RBCs adhere to human monocyte-derived DCs, inhibit DC maturation and subsequently reduce the capacity of DCs to stimulate T cells. The parasitized RBCs bind human DCs and modulate their function by a direct interaction between *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) and CD36, the scavenger receptor[31]. They also found that the uptake and internalization of infected RBCs is not essential for the inhibition of DC function. However, a more recent study now suggests that this inhibition of DC maturation by *P. falciparum* does not require PfEMP1 and is dose dependent[32]. Moreover, another recent study showed that DCs pulsed with *P. vivax* sporozoites elicited specific killing of the *P. vivax* exo-erythrocytic stages within infected hepatocytes[33]. Only three studies have examined the direct effect of *Plasmodium* spp. on the activation and function of human DCs. Two of these studies produced conflicting data and the other used a different species of parasite at a different stage of infection. It is therefore not possible to reach a definite conclusion on the direct effect of the parasite on DC function under experimentally controlled conditions.

However, in an analysis of the frequency of peripheral-blood DCs in children from Kenya, both during acute malaria and convalescence, the frequency of lineage-marker-negative and human leukocyte antigen (HLA)-DR^+, $CD83^+$ (REF. 34) or $CD1c^+$ DCs[35] in children with acute malaria was similar to those from the healthy control group. By contrast, the frequency of $BDCA3^+$ myeloid DCs was significantly increased during acute disease[35]. These studies indicate that DCs are affected during malaria in the field.

More extensive studies of DC–*Plasmodium* interactions have been carried out in mouse models of malaria. *P. chabaudi* infections of mice have been studied by several groups. Early studies on the *in vitro* activation of granulocyte–macrophage colony-stimulating factor (GM-CSF)-stimulated mouse bone-marrow-derived DCs found that these cells secreted tumour necrosis factor-α (TNF-α), IL-6, and IL-12p40 and IL-12p70 following exposure to non-lethal *P. chabaudi* schizonts[36]. DCs were also found to be fully functional *in vivo*, 6 days after infection with *P. chabaudi*[37]. DCs respond to rodent *P. chabaudi* infections in mice by upregulating expression of the co-stimulatory molecules CD40, CD54 (also known as ICAM-1) and CD86, which are required for successful T-cell activation, and subsequently migrating from the marginal zone of the spleen into T-cell areas within 5 days of infection[29]. However, another *P. chabaudi* study suggests that although DCs can present antigens to T cells their clustering is still impaired[38], which might also account for the reduced proliferation of T cells in these mice[39,40].

More detailed studies of the direct role of infected RBCs during murine malaria have found that splenic $CD11c^+$ DCs exhibit higher levels of uptake of *P. chabaudi*-parasitized RBCs than of non-infected RBCs[16]. *In vivo*, infected RBCs induce the maturation of DCs, IL-12 and IFN-γ production and stimulate $CD4^+$ T-cell proliferation[16]. Moreover, following a *P. chabaudi* infection, both $CD8^+$ and $CD8^-$ DCs can present malaria peptides, but only $CD8^-$ DCs that are isolated at the acute phase of infection stimulate antigen-specific T-cell responses[41].

Although studies have shown that DCs from infected mice can initiate T-cell responses[15,16,41], the functional capacity of splenic $CD11c^+$ DC populations changes over the course of an infection. IFN-γ production by $CD4^+$ T cells and IL-12-associated protection has been observed early after infection (6 days)[37,41]. As the infection progresses, there is an increase in the ability of DCs to produce IL-10, but they still retain their capacity to activate naive T cells[42]. Approximately 7–10 days after a non-lethal *P. yoelii* str. 17XNL or lethal *P. berghei* or *P. yoelii* str. YM infection, $CD11c^{low}CD45RB^{high}$ DCs become prevalent in the spleen, overtaking the conventional $CD11c^+$ DCs[43]. Similarly, our studies showed a predominance of $CD11c^+CD45RB^+$ DCs 7 days after infection[40], and these DCs induced IL-10-expressing $CD4^+$ T cells[43]. Other studies have shown that when mice are infected with *P. chabaudi* and transfused with ovalbumin-specific $CD4^+$ T cells after 12 days, the antigen-specific T cells undergo a similar initial activation as those in uninfected mice. This was indicated by the upregulation of CD69 and increased size and blastogenesis (an indicator of activation)[39]. However, the transferred T cells did not have the same number of replication cycles in infected mice as in uninfected mice[39]. This is not surprising, as $CD11c^+CD45R^+$ DCs, which are generally considered to be markers for plasmacytoid DCs, become prevalent during non-lethal *P. chabaudi* and *P. yoelii* str. 17XNL infections[40,43] and are known to be less efficient at priming T cells[44,45], possibly because of their high IL-10 and negligible IL-12 expression[43].

Finally, during the later stages (17 days) of a non-lethal *P. yoelii* infection, DCs become refractory to TLR-mediated IL-12 and TNF-α production[42]. This stage of infection is characterized by antibody- and IL-4-associated, IFN-γ-independent protection[46]. As the disease progresses, IL-4 and IL-10 production also prevails, which coincides with a switch from T helper 1 (T_H1) to T_H2 cells. The timing of these distinct DC responses has been reported to coincide with increased levels of apoptosis in the $CD8^+$ DC population and an increase in the number of $CD8^-$ DCs in the spleen[41].

Our group recently compared the function of DCs during infection with five strains of murine parasites, and found a dichotomy in the phenotype and function of DCs between lethal and non-lethal strains[40,47] (FIG. 2). In these studies, we also found that DCs from infections with non-lethal *P. yoelii*

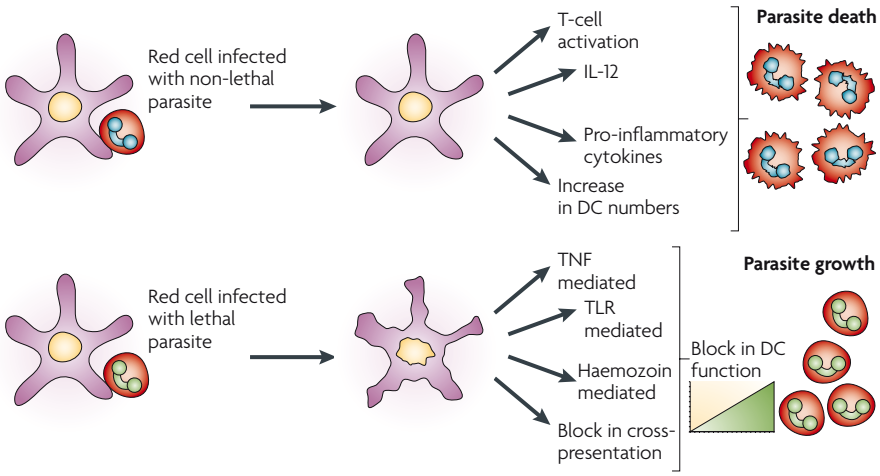

Figure 2 | **A comparison of how non-lethal and lethal *Plasmodium* spp. affect dendritic cell function.** Dendritic cells (DCs) that interact with non-lethal *Plasmodium* spp. are activated and are therefore able to stimulate T-cell proliferation, secrete interleukin (IL)-12 and initiate the production of pro-inflammatory cytokines. These responses lead to parasite clearance. By contrast, DCs that interact with lethal parasites are non-functional, which can be mediated by tumour necrosis factor (TNF)-α, haemozoin and resistance to Toll-like receptor (TLR) signalling. The infection subsequently grows, leading to host death.

str. 17XNL and *P. chabaudi* were fully functional, as described above, and secreted a high level of IL-12 (REFS 40,47). When DCs from non-lethal *P. yoelii* str. 17XNL-infected mice were transferred to naive mice, the recipient mice survived challenge with a lethal infection, and this effect was mediated by IL-12 (REF. 40). By contrast, DCs from mice infected with three lethal parasite strains, *P. yoelii* str. YM, *Plasmodium vinckei* and *P. berghei*, lacked functionality, as they were unable to prime T cells or secrete IL-12 (REFS 40,47). For *P. vinckei* and *P. berghei*, the loss of DC function was partially mediated by TNF-α[47]. Moreover, during a lethal *P. berghei* str. ANKA infection, conventional DCs, but not plasmacytoid DCs, were required for the induction of malaria parasite-specific $CD4^+$ T-cell responses, which led to pathology that was associated with experimental cerebral malaria[48]. These studies show important strain-specific influences on the ability of DCs to initiate immune responses to *Plasmodium* spp., highlight the need to consider the species and strain of the parasite when assessing the function of DCs and the need for additional studies on human DC function and pathogenesis.

Can DCs activate CD8+ T cells during malaria? Rodent $CD8^+$ T cells were originally thought to have a role only in the clearance of the pre-erythrocytic stage of malaria. This was supported by the unparalleled success of immunization with whole, irradiated sporozoites, which demonstrated that protection is mediated by these cells[49,50]. A murine *P. yoelii* model has recently been used to define the early events that lead to the development of protective $CD8^+$ T-cell responses to the circumsporozoite protein[51]. This study found that $CD8^+$ T cells that are protective against the liver stage of malaria can be primed by DCs in cutaneous lymph nodes after an infectious mosquito bite. Activated $CD8^+$ T cells then travel to systemic sites, including the liver, and no longer require antigen-presenting cells for protection. In other studies, the activation of $CD8^+$ T cells by DC subsets has been compared using the murine *P. berghei* model. In a comparison of peptide-pulsed $CD8\alpha^-$ or $CD8\alpha^+$ murine DCs, it was found that both DC subsets have the ability to prime and boost $CD8^+$ T-cell responses to epitope pb9 of the circumsporozoite protein of *P. berghei* and are involved in the activation of memory $CD8^+$ T cells[52]. Moreover, DCs pulsed with untreated and irradiated *P. berghei* sporozoites were similarly capable of priming central memory T-cell responses[53]. It is therefore clear that DC activation of $CD8^+$ T cells is unaffected by the pre-erythrocytic stage of infection.

However, a study of the blood stage of the non-lethal parasite *P. yoelii* str. 17XNL observed that DCs from infected mice have an immature phenotype and are unable to initiate $CD8^+$ T-cell responses to subsequent liver-stage antigens[54]. If this is also true for humans, an individual would be unable to mount an immune response to a subsequent infection following one round of infection (FIG. 3). This study thus highlights the importance of DCs in $CD8^+$ T-cell activation. It has also been suggested that during a rodent *P. berghei* infection, reduced $CD8^+$ T-cell priming can be caused by impaired cross-presentation by activated DCs[55]. This study proposed that systemic inflammatory activation reduced $CD8^+$ T-cell priming but did not otherwise globally inhibit T-cell proliferation[55].

Finally, we recently showed that $CD8^+$ T cells are responsible for the dramatic loss of marginal-zone macrophages that occurs during a blood-stage infection[56]. These studies indicate that the activation of $CD8^+$ T cells, which requires DCs, is not restricted to liver-stage disease and that DCs that are influenced by one stage of infection might affect clearance of the parasite following reinfection. These studies question whether the priming of $CD8^+$ T cells against sporozoites is normal in endemic areas.

Does haemozoin block DC activation? Haemozoin, a by-product of *Plasmodium*-mediated degradation of haemoglobin in RBCs, could have a deleterious effect on DC function. In early reports, it was observed that during a *P. falciparum* infection, large proportions of resident macrophages and circulating monocytes (which can mature into DCs) contain substantial amounts of haemozoin and are severely impaired in their ability to generate oxidative bursts or phagocytose other particles[57]. Haemozoin was originally produced from *P. falciparum* cultures by osmotic shock[57]. This haem was shown to be associated with histidine-rich proteins[58] or glycosylphosphatidylinositol (GPI) anchors of *Plasmodium*, which elicit the production of proinflammatory responses by the innate immune system of mammalian hosts[59–61]. Later studies reported that the maturation of haemozoin-fed monocytes into DCs was severely impaired even when the haemozoin was free of lipids and GPI anchors. This was shown by the reduced expression of major histocompatibility complex class II antigens and the co-stimulatory molecules CD83, CD80, CD54 and CD40, compared with unfed or latex-loaded DCs[62,63]. Finally, an *in vivo* study has reported that haemozoin-containing DCs reside in T-cell areas of the spleen and that T cells that are subsequently activated by these DCs lack effector function, as shown by the failure to migrate into lymphoid-organ follicles[39].

Contrasting results were obtained from studies that investigated the uptake of synthetic or purified haemozoin that was free of genomic DNA, proteins and lipids on DCs, as opposed to haemozoin ingestion from infected RBCs. Purified haemozoin enhanced the maturation of DCs and promoted IgG2a antibody responses to a DNA vaccine plasmid that encoded a *P. falciparum* transmission-blocking antigen[64]. This effect was mediated by TLR9, was sensitive to the anti-malarial drug chloroquine and was dependent on signalling by the TLR adaptor protein MyD88 (REF. 65).

A study by Parroche and colleagues[66] could clarify this issue. They found that natural haemozoin is contaminated with parasite DNA, which is extremely A+T rich, is highly pro-inflammatory and mediates the release of systemic cytokines[66]. However, to be active, the parasite DNA must be bound to haemozoin, which is proposed to amplify biological responses by targeting parasite DNA to a TLR9-containing intracellular compartment.

What is known about DC TLR function during malaria? TLRs are pattern-recognition molecules that are expressed on or within innate immune cells (such as DCs) and recognize specific conserved components on different microorganisms. In blood-stage malaria infections, when the parasites exit RBCs to re-infect other RBCs, there is a continuous release of products that can activate TLRs and induce the production of pro-inflammatory cytokines. MyD88 is an essential downstream signalling molecule that is associated with most TLRs. A recent study found that the MyD88 that is expressed by DCs has an important role in pro-inflammatory responses, T-cell activation and malaria pathogenesis, but is not crucial for the immunological control of the blood stage of *P. chabaudi* infection[67]. By contrast, TLR2$^{-/-}$, TLR4$^{-/-}$, TLR6$^{-/-}$, TLR9$^{-/-}$ or CD14$^{-/-}$ mice that were infected with *P. chabaudi* showed no change in the course of infection as measured by parasitaemia, body weight or temperature. Similarly, mice that were deficient for TLR1–4, TLR6, TLR7 or TLR9 and their adaptor proteins MyD88, TIRAP and TRIF were as sensitive to the development of fatal cerebral malaria as wild-type control mice[68].

The TLR9–MyD88 signalling pathway has been implicated specifically in the activation of human and mouse plasmacytoid DCs[69]. This study found that schizonts or soluble schizont extracts activated plasmacytoid DCs to upregulate CD86 expression, produce IFN-α and promote the proliferation of γδ T cells and the production of IFN-γ[69]. Finally, an analysis of the expression of TLR2, TLR4 and TLR9 on antigen-presenting cells in patients with mild and severe forms of *P. falciparum* malaria found that all patients showed increased surface expression of TLR2 and TLR4 on CD14^{+} monocytes and myeloid DCs and decreased intracellular expression of TLR9 on plasmacytoid DCs compared with those of healthy controls[70]. Overall, TLR signalling on DCs seems to be associated with the mediation of immune responses, but is not necessary for the direct clearance of parasites.

An exciting observation from the viewpoint of vaccine development was the finding that overstimulation by TLRs renders murine DCs refractory to further activation[42]. When DCs were isolated from a mouse 17 days after a *P. yoelii* infection and cultured with CpG DNA, all DC subsets had a decreased ability to secrete IL-12 and had a substantially increased ability to secrete IL-10 compared with DCs from naive mice. By contrast, DCs from IL-10 knockout mice secreted IL-12, which highlights the role of IL-10 in mediating this block in DC responsiveness. The authors thus reasonably proposed that the changes that happen to DCs during infection represent a mechanism for controlling host inflammation while maintaining effective adaptive immunity. A recent study has found that a regulatory CD11c^{low}CD45R^{high} DC population that is predisposed to the expression of IL-10 becomes prevalent in the spleen 7–10 days after a *P. yoelii* infection[43]. It might be that these DCs prevail until 17 days after infection and are tolerant to TLR signalling to reduce inflammation. In theory, this would suggest that as infection progresses, with an increase in parasite load, DCs would develop TLR tolerance. However, this would also result in subsequent immune dysfunction at later stages of infection. From the perspective of a whole-parasite vaccine[71–73], the dosage of the parasite could therefore be crucial. In fact, we have demonstrated that sub-patent infections (low doses of live parasite) can induce more efficient immunity than patent infections[74,75], perhaps owing to improved immune priming when antigen overload is avoided.

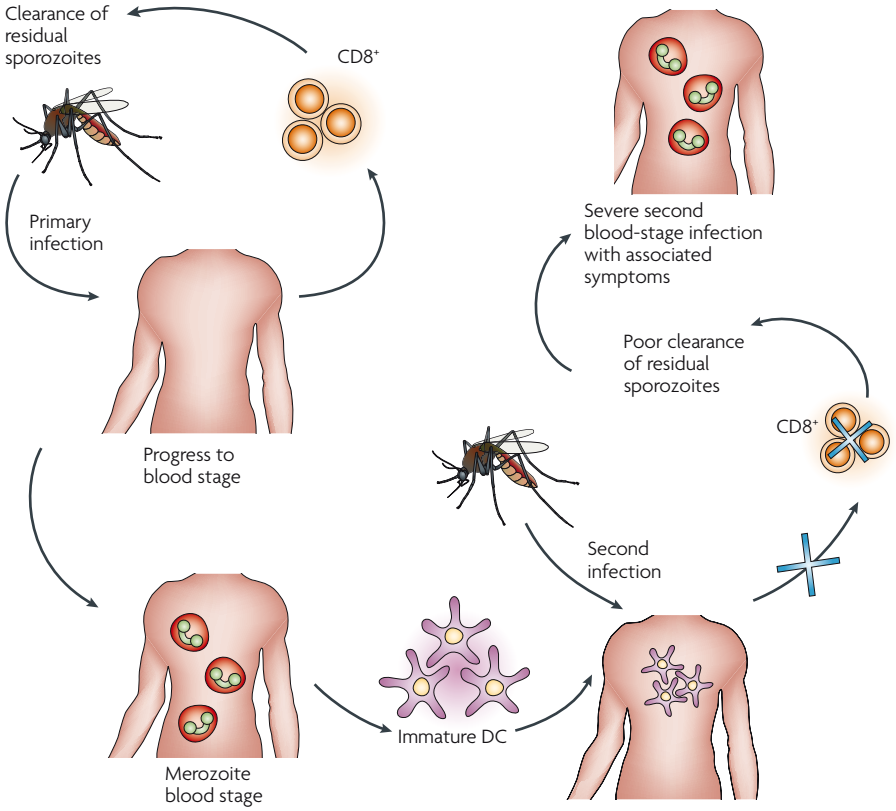

Figure 3 | **A schematic representation of how a blood-stage infection might influence reinfection.** A primary infection with the sporozoite stage of *Plasmodium* spp. is cleared by CD8^{+} T cells and only a few of these sporozoites progress to a blood-stage infection, resulting in mild symptoms. The immature dendritic cells (DCs) that ensue from this stage of the infection are unable to initiate CD8^{+} T-cell responses to subsequent liver-stage antigens, which renders the host susceptible to more serious disease during the second infection.

Conclusions

DCs play a crucial part in the initiation of all immune responses, including the response against malaria infection[76]. As such, it would be in the interests of a successful parasite to inhibit DC function. In the 8 years since *P. falciparum* was first shown to affect DC function, there have been conflicting reports on the effects of malaria on DC function, both in humans and in many mouse models. This controversy has not been due to a lack of reproducibility, but is related to the use of human or mouse models and different species and strains of parasites at pre-erythrocytic or blood stages of infection[77]. Recent studies in murine models indicate that only infections with virulent, lethal parasites inhibit DC function and that DC function is actually enhanced by non-lethal infections[40,47] (FIG. 2). This would partly explain the conflicting observations. Future human and mouse studies will thus be required to address this issue when undertaking and interpreting experiments with DCs. It is essential that we understand the effect of the parasite on DC function in the initiation of immune responses, as this impacts on vaccination in endemic areas. In particular, if DC function is compromised during malaria or if DCs are refractory to stimulation later in the infection, then individuals would need to be drug cured before vaccination to generate optimal immune responses.

The most relevant questions for future research in this field include: do the effects of the parasite on DC function that have been observed in the mouse model also apply to human parasites; will the effect of the infection on DC activation or function affect immunization with malaria or other vaccines; and can we cure malaria by modulating DC function?

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DATABASES

Entrez Genome Project: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genomeprj
Plasmodium chabaudi | *Plasmodium falciparum* | *Plasmodium vivax* | *Plasmodium yoelii*

FURTHER INFORMATION

Michael F. Good's homepage: http://www.qimr.edu.au/research/labs/michaelg/index.html

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