The Fight After the Bite
Exploring the innate immune response to malaria infection

Tired out T cells
Is the exhausted phenotype a functional adaptation?
Innate sensing of malaria parasites

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Abstract | Innate immune receptors have a key role in immune surveillance by sensing microorganisms and initiating protective immune responses. However, the innate immune system is a classic ‘double-edged sword’ that can overreact to pathogens, which can have deleterious effects and lead to clinical manifestations. Recent studies have unveiled the complexity of innate immune receptors that function as sensors of Plasmodium spp. in the vertebrate host. This Review highlights the cellular and molecular mechanisms by which Plasmodium infection is sensed by different families of innate immune receptors. We also discuss how these events mediate both host resistance to infection and the pathogenesis of malaria.

Malaria is a disease of poverty and has a major negative impact on political, social and economic stability, and thereby hampers the development of less prosperous human societies. In 2010, ~210 million people were infected with Plasmodium and 1.2 million people, primarily children, died of this devastating disease1. Although the exact numbers are uncertain, Plasmodium falciparum is responsible for about two-thirds of all malaria infections and the vast majority (90–95%) of the infections that cause mortality in sub-Saharan Africa. The remaining malaria infections are due to Plasmodium vivax infection in individuals living in deprived areas of Latin America and Asia2 where the disease has an enormous economic cost, although mortality is not a substantial problem.

The Plasmodium genus belongs to the Apicomplexa phylum, and the parasite has a complex life cycle (FIG. 1). A female Anopheles mosquito injects Plasmodium into the skin, after which sporozoites enter the bloodstream, travel to the liver and undergo asexual replication. The merozoites derived from hepatocytes rapidly invade red blood cells (RBCs), and repeated cycles of invasion, replication and release from RBCs result in exponential growth of the parasite population. More than a century ago, Camillo Golgi proposed the ‘malaria toxin hypothesis’ on the basis that Plasmodium growth is synchronized and peaks of fever typically coincide with the rupture of infected RBCs during schizogony, which indicates that a parasite ‘toxin’ is responsible for many of the symptoms and signs of disease1. It is now clear that the mechanism underlying the malaria toxin hypothesis involves a deleterious activation of innate immune cells by Plasmodium-derived components (known as pathogen-associated molecular patterns (PAMPs)) and host-derived components (known as damage-associated molecular patterns (DAMPs)).

The discovery of various families of innate immune receptors has enriched our understanding of how the host senses microbial infections and initiates immune responses3–6. Considerable progress has been made in identifying the malaria parasite molecules that elicit inflammation and the cognate host receptors that respond to these signals7. These Plasmodium components might be the long sought-after ‘malaria toxin’ that causes end-organ damage and potentially death. In this Review we briefly summarize malaria-associated syndromes, and then focus on recent studies that uncover the molecular and cellular mechanisms by which Plasmodium infection activates different innate immune receptors and related signalling pathways. In the second part of this Review, we discuss the biological relevance of these innate immune receptors for host resistance to infection and for the pathogenesis of malaria. Finally, we elaborate on how this knowledge could be exploited to treat systemic inflammation, avoid organ damage and prevent the most devastating forms of this disease.

Pathogenesis and malaria-associated syndromes

Malaria is a multifactorial disease and its clinical outcome depends on many aspects, such as parasite and host genetics, previous exposure to infection, age, nutritional status, and geographic and socio-economic factors8,9. In non-immune individuals, the first symptoms of malaria — which include fever, headache, muscle pain, chills, vomiting and lethargy followed by malarial paroxysms — appear between 7–15 days post infection and are associated with high levels of circulating cytokines. The activation of innate immune cells and consequent systemic inflammation lead to the initial signs and symptoms of malaria, and can also influence the development of...
the more severe forms of the disease. If left untreated, the uncomplicated symptomatic malaria caused by *P. falciparum* can rapidly evolve into severe illness and lethality. Children with severe malaria may develop anaemia, jaundice, respiratory distress in relation to metabolic acidosis, and/or cerebral disease. In adults, multi-organ involvement is also frequent, and impairment of kidney function may contribute to the development of metabolic acidosis at later stages of infection. Importantly, individuals who are infected with malaria multiple times develop natural acquired immunity; malaria parasitism is low in hyper-immune individuals and consequently, there is no deleterious activation of innate immune cells and the infection is asymptomatic.

**Figure 1 | Plasmodium life cycle and the pathogenesis of malaria.**

**a** | After a mosquito bite, sporozoites travel to the liver to infect hepatocytes and develop into approximately 30,000 merozoites that are released in the bloodstream. Repeated cycles of red blood cell (RBC) invasion, replication and merozoite release will result in the exponential growth of the parasite population and lead to disease. *Plasmodium vivax* sporozoites also differentiate into dormant hypnozoites that may cause disease relapses. Infected RBCs will circulate containing ring-stage parasites, and a small proportion of merozoites will develop into male and female gametocytes that infect mosquitoes, completing the parasite life cycle.

**b** | The removal of infected RBCs by splenic macrophages or the uptake of free haemoglobin results in the activation of innate immune receptors and cytokine storm. The circulating cytokines will cause paroxysms and induce the expression of adhesion molecules by endothelial cells, which mediate parasite sequestration. The sequestration of infected RBCs disrupts blood flow, promotes blood clots, injures endothelial cells and ruptures vascular walls, leading to the extravasation of vascular content and local tissue inflammation. These mechanisms contribute to acute respiratory distress, cerebral malaria or placental malaria. The sequestration of infected reticulocytes is less intense, and these syndromes are not common in *P. vivax* malaria. Haemolysis of infected and bystander (uninfected) RBCs, uptake of altered RBCs by splenic macrophages and cytokine-induced impairment of erythropoiesis cause anaemia. Free haemoglobin catalyses oxidative damage, hypoxia and lactic acidosis, promoting metabolic acidosis, which is aggravated by the altered renal function that is observed in patients with malaria.
The three main pathophysiological events that occur during malaria infection are: the release of pro-inflammatory cytokines; adhesion of *Plasmodium*-infected RBCs to capillaries and venules; and the rupture and removal of parasitized and altered RBCs by splenic macrophages (FIG. 1). These three events are connected and are responsible for the main syndromes that are associated with malaria, which include systemic inflammation, anaemia, metabolic acidosis, as well as cerebral and placental malaria\(^{1,10,11}\) (TABLE 1).

Splenic macrophages and monocytes are main contributors to the cytokine storm that is observed during acute malaria episodes. As the microcirculatory beds filter out altered RBCs, innate immune cells in the spleen clear *Plasmodium*-infected RBCs\(^{12,13}\). Splenic macrophages have a central role in sensing and phagocytosing altered RBCs, and they are exposed to a high number of parasites. As a consequence, at least in mice, these cells respond by producing large amounts of pro-inflammatory mediators\(^14–16\). However, the rupture and removal of infected RBCs by splenic macrophages is not sufficient to explain the pronounced decrease in the number of RBCs\(^{13,14,17}\). Instead, the suppressive effect of pro-inflammatory cytokines on erythropoiesis is thought to contribute to the severe anaemia that is observed in the advanced stages of malaria\(^{13,17}\).

As parasite growth may be synchronized, the release of pyrogentic cytokines — such as interleukin-1β (IL-1β) and tumour necrosis factor (TNF) — is cyclic\(^{17,20,21}\), and paroxysms occur every 48 hours in *P. vivax* and *P. falciparum* infections. Fever can aid host defence by delaying the growth of pathogens that have strict temperature preferences. Indeed, deliberate infection with *P. vivax* was used to induce high fever to eliminate *Treponema pallidum* infection in patients with neurosyphilis\(^{22}\). However, fever is also associated with signs of malaria illness, such as chills, rigours, low blood pressure, headache, excessive perspiration and hyperpyrexia\(^{11,17,23,24}\).

Another key event in malaria pathophysiology is the sequestration of parasitized RBCs into different organs including the lungs, brain, liver, kidneys and placenta\(^{25}\). Exposure to circulating cytokines — in particular TNF and interferon-γ (IFNγ) — or components released from *Plasmodium*-infected RBCs leads to enhanced expression of adhesion molecules by endothelial cells\(^{13,17}\). Also, members of the diverse family of molecules related to *P. falciparum* erythrocyte membrane protein 1 ( PfEMP1)\(^{18}\) are expressed on the surface of infected RBCs and bind to adhesion molecules that are distributed among different host organs and tissues, such as CD36, intercellular adhesion molecule 1 (ICAM1),

### Table 1 | Malaria-associated syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Clinical features</th>
<th>Mechanism</th>
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| **Anaemia**      | • Low haemoglobin levels and RBC counts
                  |                                                                 | • Rupture of infected RBCs                                                 |
|                  | • Pallor                                               |                                                                 | • Removal of infected and altered RBCs by splenic macrophages             |
|                  | • Lethargy with jaundice                               |                                                                 | • Inhibition of erythropoiesis by cytokines                                |
| **Systemic**     | • Alterations in body temperature                       | Parasite activation of splenic macrophages leads to a systemic inflammatory |
| **inflammation** | • Tachycardia                                          | response (cytokine storm) that is associated with dysfunction of cardiovascular, |
|                  | • Rapid breathing, often with impaired gas exchange     | respiratory, renal, neurological, hepatic, and/or coagulation systems      |
|                  | • Arterial hypotension                                 | • Sepsis-like syndrome leads to acute respiratory distress syndrome       |
|                  | • High levels of lactate in the blood                  | Parasitized RBC sequestration causes a disruption of the alveolar–capillary |
|                  | • Altered mental status                                | interface, resulting in leukocyte infiltration, and oedema in the interstitium |
|                  |                                                          | and alveoli, culminating in severe hypoxaemia                            |
| **Metabolic**    | • Hyperventilation                                     | Metabolic acidosis is due to increased glycolysis and the accumulation of |
| **acidosis**     | • Hypoxia                                             | lactic acid, in particular during hypoxia caused by anaemia and/or blood   |
|                  | • Headache                                            | vessel obstruction by sequestering parasites                              |
|                  | • Altered mental status                                | Renal dysfunction and insufficient clearance of lactic acid. The lower blood pH |
|                  | • Nausea                                              | stimulates the brainstem to increase the respiratory rate to expel more carbon |
|                  | • Vomiting                                            | dioxide, resulting in hypoxia, which causes vasoconstriction and cerebral  |
|                  | • Abdominal pain                                       | hypoxia, thus exacerbating cerebral disease                              |
| **Cerebral**     | • Lethargy                                            | Activation of endothelial cells by circulating pro-inflammatory mediators or by |
| **malaria**      | • Unbalanced movements                                 | parasite components                                                       |
|                  | • Seizures                                            | Enhanced expression of adhesion molecules in endothelial cells, parasite   |
|                  | • Impaired consciousness                               | sequestration, obstruction of blood flow, intravascular coagulation, disruption |
|                  | • Coma                                                | of the endothelial barrier integrity, and local tissue inflammation       |
|                  | • Neurological sequelae                                |                                                                          |
| **Placental**    | • Placental insufficiency                               | Parasite sequestration and deposition of haemoglobin in the intervillous space of the placenta results in the activation of placental macrophages, production of chemokines, recruitment of monocytes, intravascular macrophage differentiation, and production of pro-inflammatory cytokines that are deleterious to the fetus |

RBC, red blood cell.
platelet endothelial cell adhesion molecule 1 (PECAM1), complement receptor 1, heparan sulphate and chondroitin sulphate A. Hence, the expression of specific PAMPs and adhesion molecules by host cells is the main determinant of parasite tissue tropism and pathogenicity.\(^7\) For instance, CD36 and ICAM1 are important for parasite sequestration in the brain\(^3,28,29\), and heparan sulphate and chondroitin sulphate A are the main ligands for infected RBCs in the placenta.\(^9\) Non-adherent parasitized RBCs are rapidly cleared in the spleen, whereas parasitized RBCs that are adhered to endothelial cells are protected.\(^2,13\) However, adherence of infected RBCs triggers coagulation by activating thrombin — which catalyses fibrin deposition in blood vessels and amplifies inflammation — and thereby disrupts endothelial barrier integrity and favours local tissue inflammation.\(^1,12\) The obstruction of capillaries and venules, and local inflammation contribute to the development of acute respiratory distress syndrome and metabolic acidosis, as well as cerebral and placental malaria. Of note, high levels of nitric oxide protect against vascular dysfunction and severe forms of malaria are associated with low availability of nitric oxide.\(^11,34\)

In conclusion, systemic inflammation is a central event in the malaria-associated syndromes. Hence, defining the mechanism by which parasite components activate innate immune cells is crucial to understanding the pathophysiology of Plasmodium infection.

Sensors of Plasmodium PAMPs

PAMPs are microbial structures that are detected by pattern recognition receptors (PRRs).\(^1,35\) Three Plasmodium PAMPs have been studied in detail — namely, glycosylphosphatidylinositol anchors (GPI anchors), haemozoin and immunostimulatory nucleic acid motifs (TABLE 2). The Toll-like receptors (TLRs)\(^3\) (FIG. 2) detect PAMPs at the membrane of endosomes or at the cell surface, whereas RIG-I-like receptors (RLRs)\(^4\) and NOD-like receptors (NLRs)\(^5\) are cytosolic. Activated PRRs trigger distinct transcripational programmes and induce multiple downstream pathways that are involved in pathogen clearance. However, excessive activation is deleterious as it can cause systemic inflammation and disease. The molecular structures of both PRRs and PAMPs are highly conserved among vertebrate hosts and certain categories of pathogens, respectively. In this section, we discuss experiments — carried out in mouse models or in vitro systems using human cells — that were instrumental in identifying the host PRRs that are activated by Plasmodium PAMPs.

GPI anchors. GPI anchors link most surface proteins to the protozoan plasma membrane and are therefore essential for parasite viability.\(^46\) Importantly, protozoan GPI anchors are potent stimulators of cytokine synthesis by macrophages.\(^4\) This activity is determined by their fine structure, which includes the number and variation of carbohydrate units; the lipid inositol portion (glycerol versus ceramide); and the number, length and degree of saturation of the hydrocarbon chains.\(^36\)

GPI anchors from Plasmodium merozoites have either two or three fatty acyl chains and trigger the phosphorylation of mitogen-activated protein kinases and inhibitor of nuclear factor-κB (NF-κB) family members through the activation of TLR2–TLR6 or TLR1–TLR2 heterodimers and, to a lesser extent, TLR4 homodimers.\(^37,38\) (FIG. 2, TABLE 2). In mouse macrophages, the activation of TLRs induces the production of nitric oxide and the synthesis of pro-inflammatory cytokines, such as TNF and IL-1β.\(^39,40\) In human umbilical vascular endothelial cells, TLR activation by GPI anchors induces the expression of ICAM1, vascular cell adhesion molecule 1 (VCAM1) and E-selectin, as well as the production of nitric oxide.\(^41\)

Haemozoin. During the intraerythrocytic stage, parasites digest haemoglobin as a source of amino acids, which in turn leads to the generation of potentially toxic protoporphyrin metabolites.\(^42,43\) To survive, the parasite uses a detoxification enzyme that polymerizes haem and results in the formation of haemozoin crystals in the food vacuole of the parasite.\(^2\) The parasitized RBCs are phagocytosed by macrophages, neutrophils and dendritic cells (DCs) in various organs such as the spleen, liver and brain. The quantity of haemozoin that is deposited within phagocytes reflects the parasite burden, and coincides with periodic fever and high circulating levels of IL-1β and TNF; therefore, haemozoin may be used as a biomarker of malaria severity.\(^43\) Importantly, in vitro and in vivo studies have demonstrated that haemozoin activates both mouse and human monocytes and macrophages to produce pro-inflammatory cytokines such as TNF and IL-1β, and certain chemokines.\(^44\) By contrast, mouse but not human macrophages produce nitric oxide when stimulated with IFNγ and haemozoin.\(^40\)

Although some studies indicate that β-haematin (synthetic haemozoin) crystals are pro-inflammatory, this matter becomes more complex when the strong adsorptive nature of haemozoin is taken into consideration. Natural haemozoin produced in P. falciparum cultures is normally bound to proteins, lipids and nucleic acids that may be of parasite or host origin.\(^45,51,52\) The DNA binding seems to require certain proteins.\(^45\) The identity of the crucial components of native haemozoin aggregates that trigger inflammation is still a matter of intense debate. It has been shown that synthetic haemozoin binds to, induces conformational changes in and activates TLR9 on mouse DCs and macrophages, and also on human B lymphocytes.\(^46,54,55\) In addition, purified synthetic haemozoin can induce NOD-2, LRR- and pyrin domain-containing 3 (NLRP3)-dependent secretion of IL-1β by lipopolysaccharide (LPS)-primed mouse macrophages and the human THP1 monocytic cell line.\(^46,47,56\) In our view, however, haemozoin bound to P. falciparum nucleic acids traffics into phagolysosomes and the cytosol of host cells, where parasite DNA activates endosomal TLR9, inflammasomes and other cytosolic sensors. (FIG. 2). The activation of inflammasomes requires two signals: first, a priming signal — which can result from TLR9 activation — leads to the transcription of the gene encoding pro-IL-1β, as well as those encoding inflammasome components; second, a signal — which can be provided by, for example, the
crystalline structure of haemozoin — that destabilizes the lysosomal membranes and causes the release of their contents into the cytosol. Shio et al. also found that haemozoin-induced, NLRP3-dependent IL-1β production by mouse macrophages and the THP1 cell line is mediated by the tyrosine kinases SYK and Lyn, as well as cathepsin B. Furthermore, this production is blocked by inhibiting phagocytosis, K+ efflux or the generation of reactive oxygen species. Importantly, haemozoin that is carrying DNA can activate the DNA sensor absent in melanoma 2 (AIM2) to form inflammasome specks, and specks of NLRP3, AIM2 and NLRP12 inflammasomes are also found in circulating monocytes during malaria in humans. Thus, haemozoin has emerged as a key component of innate immune activation by malaria parasites.

**Plasmoidal DNA.** As is the case for other protozoa, DNA is an important activator of innate immune responses by Plasmodium parasites in both mice and humans. Of particular interest, the *P. falciparum* genome contains the highest AT content (82%) described in nature. In *silico* analyses indicate that the *P. falciparum* genome contains approximately 300 CpG (cytosine and guanine separated by one phosphate) and 6,000 AT-rich immunostimulatory motifs. Despite the lower AT content (56%), the *P. vivax* genome has a similar number of AT-rich stimulatory motifs (~5,500) and has approximately 2,000 CpG motifs. The higher CpG content may explain the lower pyrogenic threshold of *P. vivax* infection.

When they are in the phagolysosomes, the immunostimulatory CpG motifs of *Plasmodium* DNA activate TLR9 (Fig. 2; Table 2). Phagocytosis of intact infected RBCs results in TLR9 engagement, presumably as a result of parasite degradation and the presence of parasite DNA in the phagolysosome. In addition, parasite DNA can be carried to the inner cellular compartments by haemozoin or protein aggregates. If released in the host cell cytosol, in addition to activating AIM2 inflammasomes, DNA from schizonts also induces type I IFN release in

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**Table 2 | Malaria PAMPs and their role in pathogenesis**

<table>
<thead>
<tr>
<th>Parasite component</th>
<th>Properties</th>
<th>Receptor activation</th>
<th>Pathways</th>
<th>Role in pathogenesis</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPI anchors and GIPLs</td>
<td>• GPIs serve as a bridge between surface proteins and the protozoan plasma membrane&lt;br&gt;• The free forms of GPI anchors (GIPLs) are present in the protozoan surface membranes</td>
<td>• TLR1–TLR2 heterodimer (activated by GPI anchors containing three fatty acid chains)&lt;br&gt;• TLR4 homodimer&lt;br&gt;• TLR2–TLR6 heterodimer (activated by GPI anchors containing two fatty acid chains)</td>
<td>MYD88–NF-κB&lt;br&gt;• Induces macrophage release of pro-inflammatory mediators (for example, TNF and nitric oxide)&lt;br&gt;• Induces the expression of adhesion molecules on endothelial cells</td>
<td>37–41</td>
<td></td>
</tr>
<tr>
<td>Haemozoin</td>
<td>A detoxification crystal formed by haem released from haemoglobin, which is a main nutrient for the parasite during the erythrocytic stage</td>
<td>• TLR9 (induced by haemozoin bound to parasite DNA)&lt;br&gt;• NLRP3, AIM2 and other cytosolic sensors (owing to haemozoin-induced liberation of phagosome contents including DNA)</td>
<td>• MYD88–NF-κB&lt;br&gt;• Assembly of NLRP3 and AIM2 inflammasomes&lt;br&gt;• STING–IRF3</td>
<td>• Mediates induction of pro-inflammatory cytokine production by DCs and macrophages&lt;br&gt;• Promotes caspase 1 activation and cleavage of pro-IL-1β&lt;br&gt;• Mediates induction of type I IFN production</td>
<td>44–55</td>
</tr>
<tr>
<td>DNA</td>
<td><strong>Immunostimulatory CpG motifs</strong>&lt;br&gt;• The <em>P. falciparum</em> genome contains ~300 CpG motifs&lt;br&gt;• The <em>P. vivax</em> genome contains ~2,500 CpG motifs</td>
<td>TLR9&lt;br&gt;MYD88–NF-κB</td>
<td>Induces the release of pro-inflammatory cytokines by DCs and macrophages</td>
<td>45,62,63</td>
<td></td>
</tr>
<tr>
<td><strong>AT-rich motif</strong>&lt;br&gt;• <em>P. falciparum</em> DNA contains ~6,000 AT-rich motifs&lt;br&gt;• <em>P. vivax</em> DNA contains ~5,000 AT-rich motifs</td>
<td>Undefined&lt;br&gt;STING–IRF3</td>
<td>Induces type I IFN production</td>
<td>64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown motif</td>
<td>DNA from different <em>Plasmodium</em> species</td>
<td>AIM2&lt;br&gt;Assembly of AIM2 inflammasomes</td>
<td>Promotes caspase 1 activation and cleavage of pro-IL-1β</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>RNA</td>
<td><strong>Unknown motif</strong>&lt;br&gt;Single-stranded RNA from different <em>Plasmodium</em> species</td>
<td>TLR7&lt;br&gt;MYD88–NF-κB</td>
<td>Undefined</td>
<td>66,68</td>
<td></td>
</tr>
<tr>
<td><strong>Unknown motif</strong>&lt;br&gt;RNA from different <em>Plasmodium</em> species</td>
<td>MDA5–MAVS&lt;br&gt;Type I IFN</td>
<td>• Early activation of innate immune responses&lt;br&gt;• Induces type I IFN production in hepatocytes</td>
<td>66,67,69</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AIM2, absent in melanoma 2; CGP, a cytosine and a guanine separated by one phosphate; DC, dendritic cell; GIPL, glycoinositol phospholipids; GPI, glycosylphosphatidylinositol; IFN, interferon; IL, interleukin; IRF3, IFN-regulatory factor 3; MAVS, mitochondrial antiviral signalling protein; MDA5, melanoma differentiation-associated protein 5; MYD88, myeloid differentiation primary response protein 88; NF-κB, nuclear factor-κB; NLRP3, NOD-, LRR- and pyrin domain-containing 3; P. falciparum, *Plasmodium falciparum*; P. vivax, *Plasmodium vivax*; STING, stimulator of IFN genes protein; TLR, Toll-like receptor; TNF, tumour necrosis factor.
Figure 2 | Innate sensors of Plasmodium PAMPs and malaria DAMPs. RNA derived from merozoites translocates from the parasitophorous vacuole into the cytoplasm of hepatocytes (left panel) and activates melanoma differentiation-associated protein 5 (MDA5), which signals through mitochondrial antiviral signalling protein (MAVS) to induce the production of type I interferons (IFNs). Haemozoin traffics Plasmodium nucleic acids into the phagolysosomes (right panel). Toll-like receptor 7 (TLR7) and TLR9 are activated by parasite RNA and dsDNA, respectively, whereas parasite glycosylphosphatidylinositol (GPI) anchors activate TLR1–TLR2 heterodimers. Haem and host cell-derived microvesicles activate TLR4. TLRs signal through myeloid differentiation primary response protein 88 (MYD88), which eventually leads to the activation of nuclear factor-κB (NF-κB) and the induction of pro-inflammatory cytokines. Haemozoin crystals destabilize phagolysosomes, which leads to the release of their contents into the host cell cytoplasm and the activation of NOD-, LRR- and pyrin domain-containing 3 (NLRP3) and NLRP12 that assemble into inflammasomes. The IFN-inducible protein absent in melanoma 2 (AIM2), which is activated by parasite dsDNA, also forms inflammasomes. Inflammasomes recruit pro-caspase 1 either directly (NLRP12) or indirectly (NLRP3 and AIM2) via the adaptor molecule ASC. This leads to the activation of caspase 1, and the consequent cleavage and secretion of interleukin-1β (IL-1β). Cyclic GMP–AMP synthase (cGAS) generates the second messenger cyclic GMP–AMP (cGAMP), which binds and activates stimulator of IFN genes protein (STING) that in turn activates serine/threonine-protein kinase TBK1. TBK1-mediated phosphorylation of IFN-regulatory factor 3 (IRF3) leads to the expression of IFNβ. In addition, Plasmodium AT-rich motifs activate an unknown receptor that also converges on the STING–TBK1–IRF3 pathway. Question marks indicate that some components of these pathways remain to be characterized. DC, dendritic cell; ER, endoplasmic reticulum; iκB, inhibitor of NF-κB; IKK, iκB kinase; IRAK, IL-1 receptor-associated kinase; MAL, MYD88 adaptor-like protein; TRAF, TNF receptor-associated factor; TRAM, TRIF-related adaptor molecule; TRIF, TIR domain-containing adaptor protein inducing IFNβ.
a TLR-independent manner in both human and mouse phagocytes\(^{42,48}\) (FIG. 2; TABLE 2). A potentially novel cytosolic DNA sensor seems to detect *Plasmodium* DNA as TLR9, DNA-dependent activator of IFN-regulatory factors (DAI; also known as ZBP1), RNA polymerase III, IFNγ-inducible protein 16 (IFI16), retinoic acid-inducible gene I (RIG-I) and mitochondrial antiviral signalling protein (MAVS) could not recognize the *P. falciparum* AT-rich hairpin motifs\(^{41}\). Nevertheless, it was shown that the unidentified receptor for plasmodial AT-rich DNA signals through stimulator of IFN genes protein (STING; also known as TMEM173), serine/threonine-protein kinase TBK1 and IFN-regulatory factor 3 (IRF3), which leads to type I IFN production. The role of cyclic GMP–AMP synthase (cGAS) in this pathway remains to be determined.

**Plasmodial RNA.** Recent studies indicate that RNA derived from either mouse parasites (such as *Plasmodium berghei* and *Plasmodium yoelii*) or human parasites (such as *P. falciparum*) activate PRRs\(^{49-51}\) (FIG. 2; TABLE 2). A pronounced signature of IFN-inducible genes is observed in hepatocytes soon after mice are infected with sporozoites\(^{52,53}\). The invasion of hepatocytes by sporozoites activates a type I IFN response via melanoma differentiation-associated protein 5 (MDA5; also known as IFIH1) through MAVS and the transcription factors IRF3 and IRF7 (REF. 67). In addition, the erythrocytic stage of *P. yoelii* induces the production of type I IFN in vivo, which is dependent on RNA polymerase III, MDA5 and MAVS, but not RIG-I\(^{68}\). In addition, the RNA sensor TLR7 has a role in the initial activation of innate immunity in a mouse model of malaria\(^{45}\). In all of these studies, the cytosolic sensors and the type I IFN response had a modest but significant role in controlling parasite growth and parasitaemia\(^{66,67,68}\).

**Malaria DAMPs**

DAMPs are endogenous components released from stressed, damaged or dying cells that activate PRRs and inflammasomes, regardless of whether the cells are infected\(^{51}\). Uric acid, microvesicles and haem have been recognized as important malaria DAMPs\(^{71-73}\) (TABLE 3). In addition to the association with severe disease, malaria DAMPs possess intrinsic pro-inflammatory activity, which is in part mediated by the activation of PRRs\(^{71-73}\).

**Nucleic acids and urate crystals.** Circulating human DNA is found in physiological conditions and is thought to be derived from both active release from living cells and from the breakdown of dying cells\(^{35}\). However, DNA is found at elevated levels in both infectious and sterile inflammatory diseases\(^{31}\). In autoimmune diseases, such as systemic lupus erythematosus and psoriasis, high levels of circulating RNA and DNA activate nucleic acid sensors and induce inflammation\(^{31}\). Increased levels of circulating human DNA are also associated with symptomatic *P. vivax* infection in humans\(^{34}\). However, the relevance of this finding to the inflammatory response observed during malaria remains to be determined.

Nucleic acids are also pro-inflammatory owing to their degradation products. Uric acid — a byproduct of purine metabolism — is released in large quantities from dying cells and forms monosodium urate crystals when present at saturating concentrations in body fluids. Importantly, high levels of uric acid and the purine derivative hypoxanthine accumulate in infected RBCs during severe forms of human and mouse malaria, and they are released into the circulation when infected RBCs are ruptured\(^{52,77,78}\). Hypoxanthine is then converted into uric acid and urate crystals, and is internalized by phagocytes, thereby contributing to NLRP3 activation and the inflammatory response during malaria\(^{58}\) (FIG. 2; TABLE 3).

**Microvesicles.** Host cell-derived microvesicles function as a communication system between host cells and they have immune-modulatory effects\(^{73}\). Pathogen-derived microvesicles contribute to inflammation by delivering components, such as antigens and TLR agonists, to antigen-presenting cells. Indeed, microvesicles derived from *Plasmodium*-infected human or mouse RBCs are internalized by macrophages and trigger a cytokine response via TLR4 activation\(^{59,64}\). However, the immunostimulatory components of these microvesicles have not been identified\(^{64}\). Importantly, microvesicles derived from platelets, endothelial cells and leukocytes are also present at elevated levels during *P. vivax* and *P. falciparum* malaria, and their frequency correlates with the severity of disease\(^{65,66}\). Whether the circulating microvesicles are a cause or a consequence of systemic inflammation in human disease remains to be determined. Nevertheless, studies carried out both in cell lines and in mice suggest that these host-derived microvesicles contribute to the overall inflammatory response and the pathogenesis of malaria\(^{79,82}\).

**Haem.** Haemolysis and the release of haemoglobin is an important aspect of malaria pathophysiology. The oxidation of free haemoglobin leads to the release of the haem moiety that catalyses the formation of reactive oxygen species, which results in oxidative stress and, consequently, microvascular damage\(^{83}\). Haem also promotes inflammation by activating endothelial cells, which leads to the expression of adhesion molecules, increased vascular permeability and finally, tissue infiltration of leukocytes\(^{83}\). Although haem activates TLR4 in mice\(^{85}\), it is probably the excess of free haem that leads to inflammation, primarily by inducing oxidative damage, cell death and tissue injury\(^{84}\). This toxic effect is prevented by haem oxygenase 1, which degrades haem and thereby attenuates the signs of severe malaria in mice\(^{86}\). However, a recent study suggests that carboxyhaemoglobin — a haem oxygenase 1 byproduct — may exacerbate organ dysfunction in severe human disease\(^{86}\). Nevertheless, in both mice and humans, increased circulating levels of ferritin — which stores iron — seem to protect the host from malaria\(^{82}\).

**Immunity to Plasmodium infection**

After multiple malaria infections, most individuals living in hyperendemic areas develop natural acquired immunity and the main surrogate marker of protection is the high level of circulating merozoite-specific...
antibodies\(^3,10,88\). When infected, hyper-immune individuals will develop low parasitaemia and asymptomatic infection. The merozoite-specific antibodies are thought to mediate host resistance to infection by blocking parasite invasion of RBCs, or by opsonizing infected RBCs and promoting phagocytosis and parasite elimination by macrophages\(^88,89\). In addition, studies carried out in mice and humans indicate that both sporozoite-specific neutralizing antibodies and cytotoxic CD8:\' T cells are important components of immune-mediated resistance to the hepatic stage of the *Plasmodium* life cycle\(^88,89\). However, it is not clear whether sporozoite-specific immune responses contribute to natural acquired immunity or whether they are only relevant to vaccine-induced protection\(^88\). Different studies have disclosed mechanisms by which innate immunity influences the development of acquired immunity, but the role of innate immune receptors in this process is still elusive\(^89\). The studies discussed above have unveiled the complexity of innate immune receptors that function as sensors of malaria parasites and we are beginning to understand how they mediate host resistance to *Plasmodium* infection. In this section, we discuss the known mechanisms of host defence that are triggered by the activation of PRRs.

**Innate immunity.** Sporozoites stimulate the expression of type I IFN-inducible genes in hepatocytes during *Plasmodium* replication inside a parasitophorous vacuole\(^67,68\) (Fig. 3). Type I IFN-induced proteins mediate the recruitment of natural killer (NK) cells and NKT cells, which are important sources of IFN\(\gamma\), and trigger the expression proteins that mediate control of parasite replication, such as those that are involved in the production of nitric oxide and other toxic components that interfere with parasite schizogony in the liver\(^67,69\). However, a single sporozoite will generate thousands of merozoites and type I IFN-mediated parasite control is inefficient\(^67,69\). The parasites that survive immunological control in hepatocytes are released into the bloodstream where they initiate the erythrocytic cycle and cause full-blown malaria in non-immune individuals.

TLRs, NF-\(\kappa B\)-inducible pro-inflammatory cytokines and IFN\(\gamma\)-inducible genes are upregulated during the erythrocytic cycle in both human and mouse malaria\(^5,6,4,9,91\). IFN\(\gamma\) also has an important role in priming innate immune cells and promoting pro-inflammatory responses, and in activating the effector functions of macrophages that mediate resistance to infection\(^92–95,165\). Of note, treatment with IL-12 during either the hepatic or erythrocytic stages of malaria protects mice in a manner dependent on IFN\(\gamma\), TNF and nitric oxide\(^96,97\). However, both antibody-mediated and T cell-mediated immunity are ultimately required for effective control of parasite burden and malaria\(^98,99\).

**Bringing innate and acquired immunity.** DCs have a central role as a bridge between innate and acquired immunity\(^99\). As mentioned above, parasite DNA activates DCs via TLR9 and cytosolic sensors to produce cytokines that mediate host resistance to infection\(^64,62,68,100–104\). An important mechanism of resistance to *Plasmodium* infection in mice is the myeloid differentiation primary response protein 88 (MYD88)-dependent production of IL-12 by DCs, and the subsequent release of IFN\(\gamma\) by NK cells\(^100–104\). This process results in the polarization of CD4:\' T helper 1 (Th1) lymphocytes that produce IFN\(\gamma\)\(^98,97\), which activates
effectector functions, maintains the pool of effector memory T cells and promotes long-term resistance to Plasmodium infection. The T<sub>h</sub>1 lymphocytes also direct the IgG2c isotype switch and the secretion of protective merozoite-specific antibodies. However, the lack of a functional gene encoding MYD88 or IL-12 only partially affects the development of T<sub>h</sub>1 cell-mediated immune responses, which indicates that other PRRs and cytokines (such as IL-18) are also involved in the induction of IFN<sub>γ</sub> production by NK cells and T cells, and in promoting host resistance to mouse malaria.

DCs are also sources of type I IFNs, but the role of these cytokines in host resistance to Plasmodium infection is less well understood. On the one hand, IFNα mediates resistance to Plasmodium chabaudi infection in mice by generating new DCs in a manner that depends on uric acid and FMS-related tyrosine kinase 3 ligand (FLT3L). On the other hand, type I IFNs modulate DC function and impair the development of protective T lymphocytes during mouse malaria. These contrasting effects may be dependent on parasite strain. Importantly, in mice, virulent malaria...
Plasmodium strains subvert the function of DCs, and thereby impair the production of IL-12 and the development of T cell-mediated immunity. Consistent with this, the function of human DCs is impaired when they are exposed to infected RBCs or haemoglobin. Furthermore, patients with symptomatic P. falciparum or P. vivax malaria have decreased levels of circulating DCs. Hence, modulation of DC function is an important mechanism of parasite escape from host immune responses.

**Vaccine-induced immunity.** After a mosquito bite, only a few sporozoites invade hepatocytes, thus a vaccine that blocks this obligatory step of the Plasmodium life cycle may induce sterile immunity. Indeed, experimental inoculation of irradiated sporozoites or intact sporozoites in healthy individuals receiving chloroquine is very effective as a vaccine against Plasmodium infection in humans. The potential of such a vaccine is currently being investigated further in clinical trials. Does the high level of protection that is observed in response to the administration of attenuated sporozoites reflect efficient activation of the innate immune system? The ability of sporozoite RNA to trigger a type I IFN gene signature in an MD-5-dependent and MAVS-dependent manner may help to answer this question. If this is important for the development of sporozoite-specific immunity, the use of poly I:C (a double-stranded RNA and potent inducer of type I IFN) may be a preferable adjuvant for a vaccine against the hepatocytic stage of malaria. In addition, RTS,S — the most advanced vaccine against malaria — uses the circumsporozoite protein, which is the dominant protein found on the sporozoite surface. Although sterile immunity was not achieved in a Phase III trial of this vaccine, immunized children experienced a ~50% reduction in the incidence of clinical infections. However, in another study with similar first year efficacy (43.6%), the level of protection dropped to 0.4% during the fourth year (with 32.1% overall across the four-year study), which indicates that the RTS,S vaccine needs considerable improvement.

An alternative approach is an anti-malaria vaccine that targets the erythrocytic stage of the Plasmodium life cycle. For instance, vaccination with a synthetic segment of Plasmodium GPI anchor, which is a potent TLR2 activator, was shown to prevent inflammation-induced pathology and mortality in a mouse model of malaria. Although it does not block transmission, natural acquired immunity controls the exponential parasite growth in RBCs, and prevents the excessive activation of innate immune cells, as well as clinical signs of disease. Consistent with this, vaccination with either merozoite surface protein 1 (MSP1) in combination with MSP2 or the apical membrane antigen 1 induces a small, but significant reduction of clinical cases caused by parasite strains carrying the vaccine alleles of the merozoite antigens. The main candidate for a P. vivax-specific vaccine is the Duffy-binding protein, which is expressed by merozoites and is necessary for reticulocyte invasion.

However, antigen variation among different parasite isolates and the induction of protective levels of parasite-specific antibodies are major obstacles to overcome. The latter issue reflects the growing interest in innate immunity in the malaria field and the search of novel vaccine adjuvants that work through PRRs. For instance, the choice of adjuvant formulation substantially affected the efficacy of the RTS,S vaccine in a Phase II clinical trial. In addition, the identification of functionally important malaria PAMPs may lead to the development of new immunological adjuvants. For example, Plasmodium-derived GPI anchors could be used as a vaccine adjuvant. Furthermore, highly pure synthetic haemoglobin is an effective adjuvant in animal models, and is a potential vaccine vehicle owing to its ability to bind proteins, DNA and lipids. Hence, haemoglobin could be used to deliver antigen and adjuvants to lysosomes and the host cell cytoplasm to promote the activation of intracellular PRRs and antigen presentation via the exogenous and endogenous pathways. Furthermore, both CpG motifs and AT-rich motifs that are found in the Plasmodium genome may be developed as adjuvants that induce DCs to express co-stimulatory molecules, such as IL-12 and type I IFN, which would favour the development of protective B cell-mediated and T cell-mediated immune responses.

**Implications for malaria pathogenesis**

A hallmark of the innate immune response during both human and mouse malaria is pro-inflammatory priming; at very early stages of infection, Plasmodium parasites stimulate the production of IFNγ by NK cells and NKT cells. IFNγ pre-activates the innate immune system to respond to minute amounts of microbial products, and this enhanced ability to respond to microorganisms during immunosurveillance protects against infectious insults. However, this pro-inflammatory priming means that the innate immune system can overreact leading to a deleterious response (FIG. 3). In this section, we discuss the importance of different innate immune receptors and the cytokine storm in the pathogenesis of malaria. By reviewing immunogenetic and field studies conducted in patients with malaria, we provide evidence that these mechanisms are relevant to human disease.

**MYD88 and TLRs.** Bacterial superinfections in children with malaria have recently been recognized as important cofactors for severe disease. The risk of developing severe P. falciparum malaria is estimated to increase 8.5-fold in children with bacteraemia, and case-control and longitudinal studies indicate that children undergoing malaria episodes have an increased susceptibility to infection with non-typhoidal Salmonella species and other bacteria. Consistent with this, Plasmodium-infected mice are highly susceptible to infection with non-typhoidal Salmonella species. It has been reported that malaria-induced immune-modulatory haem oxygenase 1 and IL-10 dampen the effector functions of neutrophils and macrophages. Similarly, impaired neutrophil function has been described both in P. falciparum and P. vivax malaria.
**Plasmodium** infection also lowers the threshold for bacteria-induced septic shock. Malaria loads the gun and bacteria pull the trigger—a expression that reflects the mechanism by which *Plasmodium* infection enhances sensitivity to microbial infection. By promoting TLR hyperresponsiveness and the assembly of inflammasomes, IFNγ priming lowers the threshold for septic shock in mice by more than 100-fold14,16. Although IFNγ-deficient mice infected with *P. chabaudi* are highly resistant to LPS challenge, the role of TLR9 and IL-12 in pro-inflammatory priming is partial, which suggests that other PRRs and IFNγ-inducing cytokines also contribute to this response15,16.

In addition, MYD88-deficient mice infected with *P. chabaudi* are more resistant to systemic manifestations, such as cytokinaemia, changes in body weight, temperature and liver damage14,15,17. Similarly, in the *P. berghei* model of placental malaria, mice lacking functional MYD88 had reduced levels of IL-6 and TNF, and unaltered fetal body weight, contrasting with the lower body weight of fetuses from infected wild-type mice18. Furthermore, inflammatory infiltrates and cytokinaemia are reduced and pathology of experimental cerebral malaria is attenuated in MYD88-deficient mice10,11,19. Although the role of TLR2 and TLR4 in *Plasmodium* infection is controversial46,66,102,106,139,147, the data indicating a role for TLR9 in experimental cerebral malaria are more consistent. Therapy with the TLR antagonist E6446, which binds both DNA and RNA within lysosomes, is highly effective at protecting mice against experimental cerebral malaria12. Since protection against experimental cerebral malaria is only partial in TLR9-deficient mice, it is possible that the E6446 is also blocking the activation of TLR7, and other cytosolic DNA and RNA sensors53,64,68.

Hence, PRRs promote the development of cerebral malaria and sepsis-like syndrome by stimulating the production of extreme levels of the same cytokines that are involved in host resistance to *Plasmodium* infection. For instance, the development of experimental cerebral malaria is attenuated in mice deficient for functional genes encoding IFNγ-inducible adhesion molecules, such as CXC-chemokine ligand 9 (CXCL9) and CXCL10, which are important for the recruitment of CD8+ T cells to the central nervous system11,12. Furthermore, treatment with TNF-specific monoclonal antibodies prevents the development of cerebral malaria in mice14. However, in small clinical trials, treatment with TNF-specific antibodies or the anti-inflammatory drug pentoxifylline was not shown to be effective in preventing human disease caused by *P. falciparum*148,149, and the role of cytokines and inflammation in cerebral malaria is still a matter of debate28,29.

**Inflammasomes and IL-1β.** Despite strong in vitro evidence that haemoglobin triggers the formation of NLRP3 inflammasomes, different studies show that the lack of functional NLRP3, ASC, caspase 1, IL-18 or IL-1 receptor has only a minor impact (or no impact) on the control of parasitaemia and the development of mouse cerebral malaria14,16,140. Thus, the role of inflammasomes, IL-1β and IL-18 in host resistance to *Plasmodium* infection is questionable16,46,140. Nevertheless, in both humans and mice, *Plasmodium* infection results in expression of an inflammasome gene signature, the formation of NLRP3, NLRP12 and AIM2 inflammasomes, and caspase 1 activation16. In addition, NLRP3, ASC and caspase 1 were shown to have an important role in mediating haemozoin-induced local inflammation, and may be involved in organ damage observed during malaria. During mouse malaria, inflammasomes and IL-1β are also key players in enhanced sensitivity to bacteria-induced septic shock16. As a result, hypersensitivity to bacterial superinfection is prevented by treating mice with an IL-1R antagonist18. Furthermore, as IL-1β is highly pyrogenic, inflammasomes are probably important mediators of malaria paroxysms in humans16,11,65.

**Cytosolic sensors and type I IFNs.** The importance of nucleic acid sensors and type 1 IFN release is now being appreciated in the context of various infectious diseases, beyond their traditional roles in antiviral immunity. In a mouse model of cerebral malaria—using the ANKA strain of *P. berghei*—mice deficient for the type 1 IFN receptor, IRF3 or IRF7 exhibited less severe symptoms and delayed mortality compared with infected wild-type mice46,66,102,146,147. Type 1 IFNs dampen the development of Th1 cell responses that control parasitaemia at a very early stage of infection and thereby cause a worsening the disease67,98,109. However, in another study, it was shown that therapy with IFNα protects mice from cerebral malaria, suggesting that the involvement type 1 IFNs in this process is more complex148.

**Genetics and human disease.** Various studies have associated single nucleotide polymorphisms (SNPs) in inflammatory genes with resistance or susceptibility to *P. vivax* or *P. falciparum* malaria. Although most of these studies are inconclusive because they used a small cohort of patients, protection against severe disease has been associated with SNPs in the genes encoding TNFα, IFNAR1 (a subunit of the type I IFN receptor)146,150, IL-12 (REF. 151), IFNγ152,153, IL1β154, CD40 ligand (CD40L; also known as TNFRSF5)155 and inducible nitric oxide synthase (also known as NOS2)156. Several SNPs identified in the genes encoding TLRs, such as TLR4 (REF. 157) and TLR9 (REF. 158), were associated with low birth weight and maternal anaemia. SNPs in TLR9 are also associated with increased levels of IFNγ in children with cerebral malaria109 and increased parasitaemia in patients with *P. vivax* malaria160. Furthermore, hemizygosity for a SNP in the gene encoding the TLR2 and TLR4 MYD88 adaptor-like protein (MAL; also known as TIRAP) may protect against death due to malaria161.

**Concluding remarks.** More than 150 years after the discovery of *Plasmodium* by Laveran in 1861, malaria remains a devastating disease that accounts for ~1 million deaths every year. Although there are tools with which to eliminate the disease, the eradication of malaria will be
extraordinarily expensive in the absence of an effective vaccine. Years of research on malaria pathogenesis have culminated in the consensus that the clinical manifestations are mostly owing to a deleterious activation of innate immune cells. It is now clear that Plasmodium infection activates innate immune cells through signaling pathways downstream of PRRs, but further investigation is required to develop a better understanding of the biological role of specific receptors in malaria. We highlight studies indicating the crucial role of haemozoin in the activation of TLRs, inflammasomes and other cytosolic sensors by Plasmodium DNA. We also emphasize the importance of IFNγ-mediated pro-inflammatory priming and TLR hyperresponsiveness in promoting the cytokine storm and therefore, in each of the malaria-associated syndromes, as well as hypersensitivity to bacterial superinfection. Finally, the search for potent and better-tolerated adjuvants is a major goal for the development of an effective anti-malaria vaccine. Hence, any effort to eradicate malaria from the world requires a better understanding of the innate immune response to Plasmodium infection.
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This study demonstrates the importance of parasite strain on the activation of various innate immune receptors during Plasmodium infection.


This study demonstrates the importance of parasite strain on the activation of various innate immune receptors during Plasmodium infection.


This study demonstrates the ability of sporozoite RNA to induce type I IFN in an MDA5-dependent manner.

This study defines the expression of pro-inflammatory genes during human malaria.


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This study identifies the expression of pro-inflammatory genes during human malaria.


This study reports an enhanced frequency of bacterial infections in children undergoing acute malaria episodes.


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