Review Article

Interferons and Interferon Regulatory Factors in Malaria

Sin Yee Gun,^{1,2} Carla Claser,¹ Kevin Shyong Wei Tan,² and Laurent Rénia^{1,2}

¹ Singapore Immunology Network, Agency for Science, Technology and Research (A* STAR), Singapore 138648

² Department of Microbiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 119228

Correspondence should be addressed to Laurent Rénia; renia.laurent@immunol.a-star.edu.sg

Received 19 April 2014; Accepted 18 June 2014; Published 15 July 2014

Academic Editor: José C. Rosa Neto

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Malaria is one of the most serious infectious diseases in humans and responsible for approximately 500 million clinical cases and 500 thousand deaths annually. Acquired adaptive immune responses control parasite replication and infection-induced pathologies. Most infections are clinically silent which reflects on the ability of adaptive immune mechanisms to prevent the disease. However, a minority of these can become severe and life-threatening, manifesting a range of overlapping syndromes of complex origins which could be induced by uncontrolled immune responses. Major players of the innate and adaptive responses are interferons. Here, we review their roles and the signaling pathways involved in their production and protection against infection and induced immunopathologies.

1. Introduction

Malaria, a mosquito-borne infectious disease transmitted by *Anopheles* mosquito, remains as one of the leading causes of morbidity and mortality worldwide, particularly in Africa, South-East Asia, and parts of South America [1]. When infected mosquito feeds on a human, the infective form of the *Plasmodium* parasite, sporozoites, is inoculated into the dermis of the host. Most of the motile sporozoites then leave the skin, travel through the blood circulation, and settle in the hepatocytes. During this liver phase, sporozoites undergo several asexual multiplications to form merozoites. Vesicles containing mature merozoites, merozoites, are released into the peripheral blood circulation and ruptured in the lungs to release thousands of merozoites into the blood circulation. These parasites infect red blood cells and initiate the erythrocytic phase [2]. Due to the exponential growth of the parasite, followed by massive destruction of erythrocytes, this stage is responsible for the common clinical manifestations of malaria such as fever, headaches, chills, and diaphoresis [3]. Usually the host immune response can control and eliminate the parasite, yet in some circumstance, patient's conditions deteriorate and develop severe systemic or organ-related pathological conditions such as anemia [4], hypoglycemia, febrile illness, respiratory distress [5], or cerebral malaria (CM) [6].

2. Innate Immunity to Pathogens

For the past decades, it was shown that the host immune response plays an important role in controlling the progression of malaria infection. The adaptive immunity, developed through repetitive infections during childhood, is pivotal in the elimination of *Plasmodium* parasite [7–10]. Yet, studies suggest that the host's ability to control the growth of parasites also relies on the innate immunity [11, 12]. Recent analysis of clinical records from neurosyphilis patients who underwent malaria therapy showed a controlled parasite density, irrespective of parasite strain, during the first and the second parasite inoculation which suggested the presence of a stable innate response [13]. In addition, peripheral blood mononuclear cells (PBMCs) from patients who had no prior exposure to malaria were able to produce proinflammatory cytokines, such as TNF- α , IL-12, and IFN- γ , within 10 hours of exposure to infected red blood cells (iRBCs) [14] demonstrating the activation of innate immune response against malaria parasite. However, proinflammatory cytokines are a double-edged sword. Under normal circumstances, they are essential for the control of parasite growth and sustained protection against the disease pathology, yet excessive and dysregulated production can lead to several immunopathologies [15, 16].

Human genetic diversity, parasite variability, and immune status of host generate various disease profiles of malaria

infections. Fortunately, only a fraction of malaria infection in human leads to pathologies [17]. This diversity in phenotypes is always associated with differences in measured biological and immune parameters. In addition, due to obvious ethnical reasons, analyses of these parameters are largely confined to peripheral blood (serum, plasma, and circulating cells). In most studies, only association but not causal mechanisms can be determined. Thus, malaria research mainly relies on mouse models to investigate the host immune response during malaria infection. Although these models cannot reflect all aspects of human infections, they allow the study of controlled experimental infections. There are 4 rodent malaria species, *P. berghei*, *P. chabaudi*, *P. vinckei*, and *P. yoelii*, 13 subspecies, and various strains and cloned lines [18]. These parasites were isolated from African thicket rats in Central and West Africa more than 50 years ago [19]. Depending on the host and parasite combinations, different disease profiles can be induced and host immune response will determine the outcome of infection (Table 1). These models, when used together with genetically deficient mice, allow in-depth study on protection against infection or immunopathogenesis. For example, the study of CM is hampered by the limited access to tissue samples and difficulty to perform *in vivo* experiments. Susceptible mice infected with *P. berghei* ANKA (PbA) manifest neurological abnormalities similar to human CM. In this model, termed experimental cerebral malaria (ECM), high production of proinflammatory cytokines, sequestration of parasite [20–23] and leukocytes, in particular CD8⁺ T cells [24–26], and presentation of parasite antigen by brain microvessels [27] lead to the damage of the blood-brain barrier (BBB) and death. However, the role of innate immune responses in this pathology still remains to be determined.

When pathogens breach the skin or mucosal barriers, innate immune cells such as macrophages, mast cells, dendritic cells, and fibroblast, as well as circulating leukocytes, including monocytes and neutrophils, sense foreign agent using pattern recognition receptors (PRRs) that identify conserved pathogen-associated molecular patterns (PAMPs) on pathogens [28–30]. PRRs are either membrane-bound, such as toll-like receptors (TLRs) [28, 31–33] and C-type lectin receptors (CLRs) [28, 34–36], or free in the cytosol, such as NOD-like receptors (NLRs) [37–39] and RIG-I-like receptors (RLRs) [32, 40]. These PRRs are distinctly expressed on different cell populations which in turn influence the immunological repertoire elicited by a particular antigen. Professional antigen presenting cells, such as macrophage, B cells [41, 42], and dendritic cells [41, 43, 44], are well equipped with a wide spectrum of PRRs which enables this surveillance team to recognize a great variety of PAMPs and induce specific responses against each class of pathogens. For instance, in human, myeloid dendritic cells (mDCs) express all TLR1–10, but not TLR7, whereas plasmacytoid dendritic cells (pDCs) exclusively express TLR7 and TLR9 [41, 43, 44]. When activated, mDCs preferentially induces IL-12 while pDCs mainly produces IFN- α [44]. Other PRRs, such as dendritic cell-specific intracellular molecule-3-grabbing nonintegrin (DC-SIGN) [45] and DNGR-1 (Clec9A) [46], members of CLRs, expressed on immature DC were implicated in tolerogenic responses in some studies [47–49].

Besides professional antigen presenting cells, some epithelial cells are also furnished with PRRs. TLR2, TLR4, and TLR5 are widely found on pulmonary [50–53] and intestinal [54–56] epithelial cells. Since these surfaces are in continuous exposure to microbial challenges, strategic expression of these TLRs on these surfaces enables prompt recognition and response against bacterial infection. Vascular endothelial cells that line the entire circulatory system express also TLR4 [57, 58], RIG-I [59], and NOD-1 [60].

Upon positive PAMPs recognition, PRRs trigger a cascade of downstream signaling pathways that leads to nuclear translocation of transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), activating protein-1 (AP-1), and interferon regulatory factors (IRFs) into the nucleus. These transcription factors modulate the production of inflammatory cytokines, chemokines, type I interferon (IFN-I), and some interferon-stimulated genes (ISGs) [127, 128], which in turn mobilize immune cells to target pathogens and eliminate infections. Most of these mechanisms have been identified for viral or bacterial infections [129, 130]. However, the precise mechanism by which the innate immune receptors and their signaling trigger the systemic inflammation and immune cells trafficking during malaria infection has yet to be fully uncovered. Here, we review the knowledge of the role of TLR-dependent and TLR-independent pathways and the modulation of IRFs in the activation of interferons (IFN) during malaria infection.

3. Recognition of Malarial Ligand by Host Receptors

Malaria parasite travels undetected in the circulation as it is encapsulated in the red blood cells. However, rupture of the matured forms of infected red blood cells exposes the parasite and releases malarial products which trigger host immune response [131–133]. This is evident by the paroxysms of fever and chills which coincide with the time of schizonts rupture [134]. The asexual erythrocytic stage of *Plasmodium* life cycle begins when merozoites are released from infected hepatocytes into the circulation. These merozoites infect red blood cells for source of nutrients and possibly also as a form of sanctuary from peripheral immune cells. Invasion is initiated by the initial contact of the parasite with red blood cells. Weak interactions of some glycosylphosphatidylinositol membrane anchors (GPIs) on the surface of merozoites [135] with receptors on red blood cells [136] trigger mechanisms that further commit the parasite to invasion [137, 138]. During invasion, most GPIs are shed from coat to facilitate entry into the target cells [139, 140]. As the parasite multiplies and feeds on erythrocyte hemoglobin, it detoxifies hemoglobin heme by-product into Hemozoin (Hz) which is kept in the digestive vacuole (DV) [141–143]. Eventually, this DV, together with leftover host hemoglobin, is discharged into the circulation during egress of infective merozoites at the late schizonts stage in an explosive manner [138, 144]. Throughout this process of invasion and egress, the *Plasmodium* parasite continually scatters malarial products which could trigger the immune system.

TABLE 1: Combinations of different mouse backgrounds and parasite strains combinations allow the study of many disease profiles.

Mouse strain	Infection	Infection/pathology/protection	Ref.
C57BL/6 C57BL/6J C57BL/6N C57BL/6AnNCr 129/Ola x C57BL/6 129P2Sv/Ev 129 Sv/Ev x C57BL/6	<i>P. berghei</i> ANKA		[61–76]
	<i>P. berghei</i> ANKA-luc (231c11)		[21, 77]
	<i>P. berghei</i> ANKA-GFP		[78, 79]
	<i>P. berghei</i> ANKA clone 15cy1	ECM	[80, 81]
	<i>P. berghei</i> ANKA-GFP clone 15cy1		[82]
	<i>P. berghei</i> ANKA clone BdS		[26, 83]
	<i>P. berghei</i> ANKA sporozoite		[73]
	<i>P. berghei</i> ANKA clone 15cy1 sporozoite		[80, 84]
C57BL/6	<i>P. berghei</i> K173	Protection from ECM	[67]
	<i>P. yoelii nigeriensis</i> N67C	Lethal hyperparasitemia and severe anemia	[85]
	<i>P. yoelii</i> 17XNL		[86]
	<i>P. yoelii yoelii</i> 265 BY uncloned line	Protection from lethal hyperparasitemia and severe anemia	[87]
	<i>P. yoelii nigeriensis</i> N67		[85]
	<i>P. berghei</i> NK65	Liver injury	[88]
		Malaria-associated acute respiratory distress syndrome	[76]
	<i>P. berghei</i> NK65-GFP	Placental malaria	[89]
	<i>P. chabaudi chabaudi</i> AS	Protection in uncomplicated malaria	[77, 90]
	<i>P. chabaudi</i> AS		[76, 91]
	<i>P. berghei</i> ANKA-luc sporozoite		
C57BL/6.C-H2 ^d /bBy	<i>P. berghei</i> NK65 sporozoite	Liver-stage malaria	[92]
	<i>P. yoelii</i> 17XNL sporozoite		
CBA/J	<i>P. berghei</i> ANKA-GFP sporozoite	Liver-stage malaria	[93]
	<i>P. berghei</i> ANKA	ECM	[75]
	<i>P. yoelii</i> 17X	Protection from lethal hyperparasitemia and severe anemia	[94]
CBA/T6	<i>P. yoelii</i> 17XNL		
	<i>P. berghei</i> ANKA	ECM	[95]
CBA/CaH	<i>P. berghei</i> K173	Protection from ECM	
	<i>P. chabaudi adami</i> 556 KA	Protection against blood-stage malaria	[96]
DBA/2	<i>P. berghei</i> ANKA	Protection from ECM	
		Acute lung injury	[84]
129 Sv/Ev	<i>P. berghei</i> ANKA clone 1.4	ECM	[97]
	<i>P. chabaudi chabaudi</i> AS	Protection against blood-stage malaria	[98]
BALB/c	<i>P. berghei</i> ANKA		[65, 70, 74, 75, 84]
	<i>P. berghei</i> ANKA clone BdS	Protection from ECM	[26]
	<i>P. berghei</i> ANKA-GFP		[79]
BALB/cByJ SW	<i>P. yoelii</i> 17XL	Lethal hyperparasitemia and severe anemia	
	<i>P. yoelii</i> 17XNL	Protection from lethal hyperparasitemia and severe anemia	[94]

Extensive research has identified a few host receptors agonists from *Plasmodium* parasite which promote proinflammatory responses [61, 85, 99, 100, 102–106, 111, 112]. For the liver stage of the infection, *Plasmodium* RNA is the only malarial ligand discovered so far [92]. In the blood stage, several ligands have been identified, such as GPI

[62, 99–103], Hz [63, 104, 145], CpG DNA bound on Hz [105], host fibrinogen [106], heme [107, 108], microparticles [109], AT-rich motifs in malarial genome [61], *Plasmodium* DNA/RNA [85], *P. falciparum* tyrosyl-tRNA synthetase (PfTyrRS) [111], and *P. falciparum* high mobility group box protein (PfHMG) [112]. All the different malarial ligands

TABLE 2: List of malarial ligands that stimulate different signaling molecules to trigger diverse immune responses and affect disease outcome in various experimental models.

Ligand	Signalling molecules involved	Cell types/mice	Immune responses/functions	Ref.
GPI	TLR1-TLR2 heterodimer	BMDM, PBMC		[99]
	TLR2/TLR1, TLR4, MyD88, ERK1/2, p38, JNK1/2, NF- κ B, AP-1 (c-Jun, ATF-2)	BMDM, PBMC, HEK, MPM	Stimulates production of TNF- α , IL-12, IL-6, and NO	[62, 100, 101]
	MAPK2	BMDM	Stimulates production of TNF- α Controls production of IL-12	[102]
	I κ B- ζ	BMDM	Involved in IL-12 expression	[103]
Hz (<i>Pf</i> 3D7)/ synthetic Hz	TLR9, MyD88	Murine splenocytes, BMDDC Knockout C57BL/6 or 129/Ola x C57BL/6	Stimulates production of TNF- α , IL-12p40, MCP-1, and IL-6 Increases serum level of MCP-1 and IL-6	[104]
	TLR2, TLR9, MyD88	Knockout C57BL/6	Involved in ECM development Promotes parasite and leukocyte sequestration in brain sections Stimulates production of IFN- γ , TNF- α , and IL-12p40	[63]
Malarial CpG DNA (<i>Pf</i> 3D7)	TLR9, MyD88	BMDDC	Stimulates production of IL-12p40 and Rantes	[105]
Host fibrinogen	TLR4, CD11b/CD18-integrin	PBMC	Stimulates release of ROS, TNF, and MCP-1	[106]
Heme	TLR4, CD14, MyD88, I κ B- α , ERK1/2, NF- κ B	MPM, BMDDC, human monocyte-derived macrophages, PBMC	Stimulates production of TNF- α and KC Controls release of PGE ₂	[107, 108]
MPs from infected mouse	TLR4, MyD88	BMDM	Upregulate expression of CD40 Stimulate production of TNF	[109]
Malarial AT-rich motif	STING, TBK1, IRF-3, IRF-7	BMDM, HEK293, knockout C57BL/6	Involved in ECM development Stimulates production of IFN-I, TNF- α , IL-6, and IL-15	[61]
<i>Plasmodium</i> DNA/RNA	MDA5, MAVS, RIG-1, CD14/IL-1R, p38	Knockout C57BL/6, RAW264.7	Stimulates production of IFN-I Controls parasitemia Prevents parasite sequestration in the brain capillaries and apoptosis in the spleen Promotes phagocytosis activity of macrophages	[85]
Unknown in PbA infection	TLR2/4, MyD88	Knockout C57BL/6	Involved in ECM development initiated with sporozoites Partially involved in ECM development initiated with iRBCs Regulates production of IFN- γ , MCP-1, TNF- α , and IL-10	[80]
Unknown ligand in <i>Py</i> 17XNL infection	TLR9, MyD88	Knockout C57BL/6	Controls parasitemia and promotes survival Essential Th1 development and cell-mediated immunity Stimulates production of TNF- α and IL-12 by DC Controls production of IL-10 and IL-4 by DC Induces cytotoxic activity in NK and CD8 ⁺ T cells	[86]

TABLE 2: Continued.

Ligand	Signalling molecules involved	Cell types/mice	Immune responses/functions	Ref.
Unknown	TLR7, TLR9	NK cells, $\gamma\delta$ T cells, CD4 ⁺ T cells	TLR7 mediates IFN- γ production by NK cells 24 h after infection TLR7 stimulates production of IFN-I, IFN- γ , IL-10, and IL-12 TLR9 mediates IFN- γ production by CD4 ⁺ cells and stimulates production of TNF 6 days after infection	[110]
<i>Plasmodium</i> RNA	MDA5, MAVS, IRF-3, IRF-7	Knockout C57BL/6J, BMDDC, MPH	Stimulates production of IFN-I Controls leukocyte recruitment which limits parasite growth in the liver and induction of erythrocytic stage infection	[92]
<i>Pf</i> TyrRs	Unknown	Mouse splenocytes, PBMC, RAW 264.7, THP-1	Stimulates production of TNF- α , IL-6, IL-1 α , and IL-1 β which upregulate expression of ICAM-1 and VCAM-1 receptors	[111]
<i>Pf</i> HMGB	Unknown	Mouse splenocytes, RAW 264.7	Stimulates production of TNF- α , IL-6, IL-8, and IL-1 β and upregulates mRNA expression of iNOS	[112]

BMDM: mouse bone marrow-derived macrophages (C57BL/6 unless otherwise stated); BMDDC: mouse bone marrow-derived dendritic cells; PBMC: human peripheral blood mononuclear cells; HEK: human embryonic kidney epithelial cells; Hz: Hemozoin; iNOS: inducible nitric oxide synthetase; KC: keratinocyte chemokine; MCP-1: monocyte chemoattractant protein-1; MP: microparticles; MPH: mouse primary hepatocytes; MPM: murine peritoneal macrophages; PGE₂: prostaglandin E2; *Pf*TyrRS: *P. falciparum* tyrosyl-tRNA synthetase; *Pf*HMGB: *P. falciparum* high mobility group box protein; RAW264.7: murine macrophage-like cell line; ROS: reactive oxide species; THP-1: human monocytic leukemia cell line.

and their respective signaling molecules involved to induce an immune response are listed in Table 2. However, the exact roles of each of these factors remain to be established.

3.1. TLR-Dependent Signaling. TLRs are central in the sensing and responding to pathogens during innate immunity. Members of TLRs were originally identified in embryo of *Drosophila melanogaster* more than 20 years ago [146]. Later, Medzhitov et al. reported the first human homolog of the *Drosophila* toll protein that is involved in the activation of adaptive immunity [147]. To date, ten TLRs have been identified in human and twelve in mice [148]. In both human and mouse, TLRs 1, 2, 4, 5, and 6 are expressed on cell surface whereas TLRs 3, 7, 8, and 9 are found within the endosomal compartments. TLR10 is uniquely expressed in human [149] and localized on the surface of plasma membrane. TLRs 11, 12, and 13 are only functionally expressed in mice and expressed on the membrane of endosomes [150]. These TLRs recognize PAMPs ranging from DNA and RNA to bacterial products [151]. Subcellular localization of TLR ensures that different pathogenic antigens are promptly recognized by the correct receptor in order to induce proper immune responses and, at the same time, minimize accidental trigger of an autoimmune response. Upon ligand-receptor interactions, TLR signal transduction is initiated leading to production of interferons and induction of proinflammatory cytokines [31, 148, 151, 152].

3.1.1. TLR Polymorphism and Malaria. Studies on genetic epidemiology revealed that TLR polymorphism is associated

with outcome of malaria infection (Table 3). A population study in the Amazonian region of Brazil demonstrated that single nucleotide polymorphisms in TLR1 and TLR6 are associated with incidence of mild malaria [114]. Genetic variations in TLR1 are also capable of influencing susceptibility to placental malaria in Ghanaian mothers [113]. Case control studies demonstrated that common polymorphism in TLR2 and TLR4 can affect CM development [115, 119]. Variants in TLR2 amongst uncomplicated malaria children in Uganda were associated with altered proinflammatory responses [115] and a particular single nucleotide polymorphism in TLR4 amongst African children is correlated with an altered responsiveness to the malarial ligand, GPI, which in turn determine risk to severe malaria [119]. On the other hand, another TLR4 variant assessed in Iran (Baluchi) [116], Burundi [117], Brazil [114], and Ghana [118] was not found to be involved in malaria infection or disease severity.

Effects of TLR9 polymorphism in malaria infection have been most extensively studied amongst all the TLRs. Human genetic studies in endemic regions found a strong correlation in most of TLR9 variants with parasite load in the peripheral circulation [114, 120]. However, association of TLR9 alleles with susceptibility to malaria infection and disease severity varies according to the single nucleotide polymorphism and the regions studied [114, 116–121]. For example, TLR9 T1237C rs5743836 was associated with susceptibility to malaria infection amongst people in Burundi but not in Ghana or Iran. And amongst Ghanaians, susceptibility to mild malaria was correlated with TLR9 T1486C rs187084, but not with TLR9 G2848A rs352140.

TABLE 3: Association of TLRs and adaptor molecules gene polymorphisms with susceptibility to malaria or pathology in human.

TLRs/ adaptors	SNPs	Association	Region	Ref.
TLR1	S248N rs4833095	Placental malaria and anemia	Ghana	[113]
	I602S	Susceptibility to malaria infection	Amazon	[114]
TLR2	$\Delta 22$	No association with serum cytokines (TNF, IFN- γ , IL-1 β , IL-6, IL-10) levels	Uganda	[115]
		Susceptibility to cerebral malaria		
	GT _n	No association with serum cytokines (TNF, IFN- γ , IL-1 β , IL-6, IL-10) levels No association with cerebral malaria		
TLR4	D299G rs4986790	No association with susceptibility to malaria infection	Burundi, Amazon, Ghana, Iran	[114, 116–118]
		No association with risk of placental malaria	Ghana	[118]
		Maternal anemia		
	T399I	Severe malaria		[119]
		No association with mild malaria	Iran	[116]
TLR6	S249P	Severe malaria	Ghana	[119]
		Susceptibility to mild malaria	Amazon	[114]
TLR9	G1174A rs352139	No association with susceptibility to malaria infection	Burundi	[117]
		Susceptibility to mild malaria	Ghana	[120]
		Level of parasitemia		
		No association with serum TNF α level	Uganda	[121]
		No association with serum IFN- γ level in mild malaria children		
		Level of serum IFN- γ level in CM children		
		No association with susceptibility to malaria infection		
	T1237C rs5743836	No association with disease severity	Ghana, Iran	[116, 118, 120]
		No association with placental malaria	Ghana	[119]
		Susceptibility to malaria infection		[118]
		Level of parasitemia	Burundi	[117]
		No association with serum TNF α level	Amazon, Ghana	[114, 120]
		No association with serum IFN- γ level in mild malaria children	Uganda	[121]
		Level of serum IFN- γ level in CM children		
	T1486C rs187084	No association with susceptibility to malaria infection	Burundi, Ghana, Iran	[116–118, 120]
		No association with disease severity		[119]
		No association with placental malaria	Ghana	[118]
		No association with level of parasitemia		[120]
	G2848A rs352140	Level of parasitemia	Amazon	[114]
		No association with level of parasitemia	Ghana	[120]
		Susceptibility to mild malaria infection		
TIRAP	S180L rs8177374	No association with susceptibility to malaria or severity of infection	Burundi, Amazon	[114, 117]
		Mild malaria and severe malaria	Gambia, Vietnam, Kenya	[122]
		Mild malaria	Iran	[116]

CM: cerebral malaria; $\Delta 22$: 22 base pair deletion in the first untranslated exon; GT_n: GT dinucleotide repeat in the second intron; mild malaria: patients suffer fever with temperature greater than or equal to 38°C, malaise, muscular pain, headache, and parasite load greater than or equal to 5000 parasite/ul of blood; severe malaria: patients who suffer anaemia, prostration, respiratory distress, convulsions, and/or impaired consciousness; cerebral malaria (CM): patients who experience coma with *P. falciparum* on blood smear and have no other cause for coma.

Besides TLR, effects of single nucleotide polymorphism of coadaptor molecule, TIR domain-containing adaptor protein, TIRAP, on malaria infection were also investigated. A particular TIRAP variant was correlated with mild malaria amongst people living in Iran [116], Gambia, Vietnam, and Kenya [122]. However, when the same TIRAP alleles were sampled in Burundi and Amazon, no association with susceptibility to malaria or disease severity was observed [114, 117]. These findings suggest that variants in TLR are capable of altering disease outcome during malaria infection but polymorphism in the strains of *Plasmodium* in different regions could also account for the different association.

3.1.2. TLR in Malaria Infection. Purified GPI from *P. falciparum* iRBCs [153] was preferentially recognized by TLR2/TLR1 or TLR2/TLR6 heterodimer and, to a lesser extent, TLR4 *in vitro* [99, 101]. TLRs-GPI interactions trigger the recruitment of MyD88, which phosphorylates a series of mitogen-activated protein kinases (MAPKs) including extracellular-signal-regulated kinases 1/2 (ERK1/2), p38 MAPK, and c-Jun N-terminal kinases 1/2 (JNK1/2) [62, 100, 101]. Following that, nuclear translocations of transcription factor such as NF- κ B and AP-1, comprising the activation of transcription factor-2/c-Jun (ATF-2/c-Jun) [100, 102], stimulate production of proinflammatory cytokines such as TNF- α , IL-6, IL-12, and nitric oxide (NO) [100, 102, 154]. Interaction of nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor, zeta (I κ B- ζ) with NF- κ B, promotes IL-12 production [103]. However, the concentration of GPI on the surface of merozoites is too low to account for this potent stimulatory effect observed [155].

A study by Pichyangkul et al. described an unknown, heat labile, malarial product in the schizont-soluble fraction that is able to upregulate expression of CD86 and stimulate IFN- α production by human plasmacytoid dendritic cells. When mouse bone marrow-derived dendritic cells (BMDDC) were stimulated with the same schizont fraction, upregulated expressions of CD40, CD86, and IL-12 production were observed [156]. Later, this ligand was proposed to be a metabolic by-product, Hemozoin (Hz), that is present in *P. falciparum* schizont lysate [157]. It is recognized by TLR9 to induce production of proinflammatory cytokines such as TNF- α , IL-12p40, MCP-1, and IL-6 [104]. However, this discovery was refuted by Parroche et al. who suggested that Hz only serves as a vehicle to deliver the malarial DNA, a TLR9 ligand, to the endosome for TLR9 sensing [105]. Similarly, Barrera et al. also supported the claim that Hz is only a vehicle for other malarial ligands, such as host fibrinogen. In this case, instead of TLR9, TLR4 and CD11b/CD18-integrin on monocytes were shown to recognize these malarial ligands [106]. In response to these, Coban et al. have recently demonstrated that both DNase-treated natural Hz and synthetic Hz are recognized by TLR9 and able to elicit an immune response via MyD88 [145]. These highly discordant results are likely due to different methodologies adopted by each group to purify the malarial Hz. Parroche et al. and Sharma et al. purified free Hz biocrystals using a magnetic separator [61, 105], whereas both Barrera et al.

and Coban et al. utilized different protocols that largely consist of various chemical and mechanical procedures to obtain the natural Hz [104]. Despite disagreement on the ligand that stimulates the immune response, *in vitro* studies by both Parroche et al. and Coban et al. agreed upon the importance of TLR9 in *P. falciparum* infection. During *P. falciparum* infection, activation of TLR9 mediates production of IL-12 and IFN- γ . These proinflammatory cytokines in turn enhance expression of TLR and prime the signaling pathway to be more sensitive to TLR agonist [158].

Heme is released into the circulation when cell-free hemoglobin, from ruptured schizonts, is oxidized by reactive oxygen species (ROS) or other free radicals present in the plasma. The prosthetic group is recognized by TLR4, along with coreceptor CD14 [107, 108]. This interaction triggers MyD88 recruitment, I κ B α degradation, ERK1/2 phosphorylation, and eventually NF- κ B activation. Endotoxin contamination was abolished through the use of polymyxin B, anti-TLR4/MD2, and lipid A antagonist which inhibit effect of lipopolysaccharide (LPS) [108]. A study on a population of *P. vivax*-infected Brazilians discovered a correlation between high concentrations of heme in the plasma with disease severity. This is mediated through the activation of antioxidant enzyme Cu/Zn superoxide dismutase (SOD-1) which impairs production of anti-inflammatory mediators, such as Prostaglandin E2 (PGE₂) and TGF- β , by PBMCs [107]. In the same study, plasma level of proinflammatory cytokine, TNF- α , was found to be positively correlated with total heme and SOD-1 [107]. Heme can be detrimental in other ways such as its toxic effects on endothelial cells [159–161] and hepatocytes [162]. At the same time, it promotes survival [163], activation [164], and migration [165] of polymorph nuclear cells. Taken together, it seems to suggest that free heme in the plasma could engage in multiple signaling pathways to promote a proinflammatory immune response, which possibly exacerbates the malaria infection.

Microparticles (MPs) are submicron vesicles produced through membrane budding during immune-activation or cell death. Extensive studies revealed that MPs are capable of influencing biological functions such as expression of adhesion molecules by endothelial cells [166] and leukocyte recruitment [167]. In addition, these minute vesicles also play a part in pathology, for instance, by inducing nitric oxide synthesis [168, 169] and delivering mRNA into other cells [170, 171]. During malaria infection, MP derived from iRBCs affects disease progression by strongly inducing bone marrow-derived macrophages (BMDM) to produce TNF [109, 172]. *In vitro* study revealed that MP, and not LPS contamination, engages in a TLR4-MyD88 signaling pathway to induce this immune response. Since MP could contain other parasite proteins, like GPI and Hz, in the vesicles, it was not surprising that both TLR2 and TLR9 were also found to be involved in the induction of this MP-mediated signaling pathway. In fact, synergic engagement of all these TLRs with MP and other parasite ligands stimulated a proinflammatory response stronger than that induced by iRBCs [109].

The TLR signaling pathway is also involved in the development of placental malaria [89]. Study of *P. berghei* NK65-induced placental malaria in mice showed that MyD88 is

essential in the production of proinflammatory cytokines such as IL-6, IFN- γ , and TNF- α . In addition, the MyD88 pathway also affects the survival rates of pups from malaria-infected mothers [89]. Unfortunately, no specific TLR or malarial ligands were identified to account for the activation of this MyD88 signaling pathway.

3.1.3. TLR in ECM. Optimal production of proinflammatory cytokines can control parasite growth but overwhelming secretion of these soluble mediators can lead to immunopathologies such as cerebral malaria. Human population studies have demonstrated that single nucleotide polymorphism in TLRs can affect susceptibility to cerebral malaria [113–121]. However, no exact mechanism can be derived from such studies. Using the murine model of ECM, specific immune responses upon TLR-ligand interactions can be studied.

TLR2/TLR4, which recognizes malarial GPI, despite playing no role in the early stage of *P. chabaudi* infection (IFN-I secretion in this model is mediated by TLR7) [110], is important in ECM. The absence of these receptors leads to an attenuated proinflammatory response and protection from ECM lethality [63, 80]. However, different model seems to display varying degrees of reliance on this signaling pathway to induce ECM. Using wild-type (WT) and TLR2-knockout (KO) or MyD88-KO in C57BL/6 background mice infected with 10^6 fresh PbA iRBCs intraperitoneally, Coban et al. [63] showed that ECM pathogenesis totally relies on TLR2-MyD88 signaling pathway. Activation of this pathway led to sequestration of parasites and infiltration of pathogenic T cells into the brain, two important factors responsible for damaging the brain endothelial cells. On the contrary, in this model, TLR4 was shown not to be involved in ECM development. Conversely, Kordes et al. showed that WT and TLR2/4 double knockout (DKO) in C57BL/6 background mice, infected with 10^4 fresh PbA(clone 15cyl) iRBCs intravenously, trigger a proinflammatory response that is partially dependent on TLR2/4-MyD88 signaling pathway to cause ECM [80]. Unlike blood-stage infection, intravenous inoculation of PbA (clone 15cyl) sporozoites has absolute dependence on MyD88-dependent TLR2/4 pathway to develop ECM [80]. Inconsistency in the involvement of TLR2/4 in these models could be attributed to different infection regimens or the parasite strain/clones used. In a separate study, it was revealed that heme engages with TLR4-MyD88 signaling pathway to secrete TNF- α in mouse peritoneal macrophages and BMDDC. In fact, heme can also engage in a TLR4-independent pathway to induce production of ROS, expression of heme oxygenase-1 (HO-1), and recruitment of neutrophils [108]. Besides TLR2/4, TLR9 is also shown to play a role in ECM [63]. Coban et al. demonstrated that ECM pathogenesis relied on TLR9-MyD88 signaling to induce systemic proinflammatory responses and sequestration of parasite, Hz, and leukocytes in the brain [63].

In addition, TLR9 was discovered to work in synergy with TLR7 to induce IFN-I and IFN- γ production in mice infected with many other strains of *Plasmodium*, like *P. chabaudi*, *P. berghei* NK65, *P. berghei* K173, *P. yoelii* YM (PyYM), *P.*

yoelii 17X (Py17X), and *P. vinckei petteri* infection [90, 110]. C57BL/6 mice infected with Py17XNL were shown to rely on TLR9-MyD88 signaling pathway to induce production of proinflammatory cytokine and increase commitment to Th1 and cytolytic activity by NK and T cells [86].

Despite all these findings that supported the involvement of TLR2/TLR4/TLR9 in ECM development, Lepenies et al. held a different opinion. Using triple TLR2/4/9 KO mice on C57BL/6 mice, intraperitoneally inoculated with PbA iRBCs that was maintained through alternate cyclic passage in *Anopheles stephensi* mosquito and BALB/c mice, they demonstrated that ECM induction is independent of TLR2/4/9 [64]. Such disparity in research findings could be due to the unique maintenance of parasite strain/clones used. Similarly, in spite of all these studies that demonstrated the importance of TLR, the study by Togbe et al. [78] casts some doubt on the importance of TLR cascade in the development of ECM. In his study, C57BL/6 mice were infected with a cloned line of PbA tagged with GFP. Results showed that deficiency in TLR did not prevent development in ECM, lungs, or liver pathology. Once again, these conflicting results emphasized the diversity of the immune response to malaria infection in different animal models [65].

3.2. TLR-Independent Signaling. In the erythrocytic stage, AT-rich motifs in the *P. falciparum* genome can also induce secretion of IFN-I, TNF- α , IL-6, and IL-15 via a TLR-independent pathway. This ligand engages in a distinct signaling pathway that involves cytoplasmic nucleic sensor STING, downstream kinase TBK1, and interferon regulatory factor (IRF) 3/7 [61]. Besides, *Pf*TyrRS [111] and *Pf*HMGB [112] are two other malarial ligands that were shown to induce proinflammatory activity. However, more studies are needed to identify the specific receptors that recognize these two ligands. Other cytoplasmic signaling molecules, such as the member of RLR family and its adaptor molecule, melanoma differentiation-associated protein 5/mitochondrial antiviral signaling protein (MDA5/MAVS), were also associated with IFN-I signaling during acute phase of nonlethal *P. yoelii nigeriensis* N67 (PyN N67) infection in C57BL/6 mice [85]. On the contrary, STING and MAVS were found to be redundant in early *P. chabaudi* infection [110] and *P. yoelii* liver-stage infection [126].

Host innate immune response does not only exist in the erythrocytic stage of the parasite life cycle. In fact, control of parasitic growth starts as early as in the asymptomatic liver stage [173, 174]. Liver resident cells of C57BL/6 and BALB/c mice were shown to induce IFN-I production upon infection with PbA or Py17XNL sporozoite, independent of TLR-MyD88 pathway [92]. The *Plasmodium* RNA was found to be identified by MDA5, which typically recognizes double stranded DNA. This triggers the assembly of MAVS, which mediates downstream production of IFN-I. Liver-stage specific IFN-I mobilizes leukocytes into the vicinity of infected hepatocytes to limit parasite load in the liver and consequently influences the induction of erythrocytic stage infection. Besides MDA5, there are other unknown malarial

ligands that signal through Mavs as evident by the differential IFN-I response in MDA5^{-/-} and MAVS^{-/-} mice [92].

4. Interferons

Recognition of PAMPs by PRRs triggers a cascade of downstream signaling pathways which stimulates production of IFN-I, IFN- γ , and many other proinflammatory mediators. The IFN compartment comprises 3 classes, namely, IFN-I, IFN-II, and IFN-III. IFN are renowned for their antiviral properties and share common secondary structure. Yet each class of IFN binds to distinct multichain receptor complexes. They engage in different JAK-STAT molecules, drive the expression of different interferon stimulated response elements (ISRE) and/or interferon-gamma activated sequences (GAS) elements [175], and induce various interferon stimulated genes (ISGs), which in turn regulate development, host defense, and signaling [176]. In humans and mice, the IFN-I family comprises 13 types of IFN- α and 1 IFN- β [177]. IFN-II consists of solely interferon gamma (IFN- γ), while there are 3 types of IFN-III, namely, IFN λ 1, IFN λ 2, and IFN λ 3 [175].

4.1. Type II Interferon (IFN- γ). IFN- γ is the only form of type II IFN. It regulates several components of the immune system such as antigen presentation [178–181], antimicrobial mechanism [182–184], leukocyte development [185], and immune cells trafficking [186, 187]. It is the most widely studied interferon in malaria infection since it is primarily involved in host defense against intracellular pathogens. Its protective role as an immune mediator emerged as early as in the liver stage [126, 188–193]. *In vitro* study of human recombinant IFN- γ treatment on *P. berghei* sporozoites-infected murine hepatocytes [190] or human hepatoma cells [189] identified an inhibitory effect of IFN- γ on parasite multiplication. Further *in vivo* study validated the importance of IFN- γ in protective immunity as it inhibits intracellular development of parasite within hepatocytes following challenge with *P. berghei* [194], *P. yoelii* [191], or *P. vivax* sporozoites [188] in mice and chimpanzee, respectively. Recently, Miller et al. demonstrated that IFN- γ secreted in primary *P. yoelii* sporozoite infection is the key innate mediator that controls liver-stage parasite growth in a secondary infection [126]. Above all, this inhibitory effect of IFN- γ on parasite development in liver stage extends and influences the initiation of blood stage parasite growth [126].

IFN- γ also plays a crucial protective role during blood-stage infection of various parasite strains. Administration of exogenous recombinant IFN- γ leads to control of parasite growth in *P. chabaudi adami* 556KA-infected CBA/CaH mice. After infection has been resolved, continuous IFN- γ treatment fully protected these mice from subsequent infection [96]. Lower level of parasitemia was also observed in IFN- γ treated SW mice that were infected with lethal strain of *P. yoelii*. In addition, these treated mice also exhibited better survival outcome [94]. *P. chabaudi* AS-infected mice treated with monoclonal antibody against IFN- γ had less control of parasite multiplication [195], once again suggesting that IFN- γ is essential for limiting parasite growth. Similar findings were observed in *P. chabaudi* AS-infected mice that

were deficient in IFN- γ receptor. However, these mice had lower survival rates as compared to the WT controls [91]. This suggests that IFN- γ production at different period during infection could alter survival outcome. In *P. berghei* infection, IFN- γ also plays a protective role by mediating parasite clearance [196]. Population study of children in Papua New Guinea showed that high and early IFN- γ responses seem to protect from symptomatic malaria [197].

However, production of high level of IFN- γ during parasite blood stage development is associated with predisposition to severe malaria, such as CM. Studies in animal model of ECM corroborated findings from human study that IFN- γ is essential for the development of CM [66]. IFN- γ signaling in the brain regulates expression of adhesion molecules which influence parasites and leukocytes sequestration in the brain microvessels [97]. At the same time, there is also evidence that IFN- γ promotes trafficking of leukocytes, including pathogenic CD8⁺ T cells, to the brain [81, 83]. IFN- γ is essential in both protective immunity and pathogenesis of severe diseases [198]. Whether it protects or harms the host depends on when and where it is produced [67].

4.2. Type I Interferon (IFN- α/β). Unlike IFN- γ , IFN-I is only starting to gain more attention with increasing evidence that supports its role in protection [87, 199, 200]. This cytokine regulates various immune mechanisms such as MHC expression [201], antigen presentation [201], and T cell expansion [202, 203]. Furthermore, IFN-I can also modulate production of IFN- γ [204] and prime IFN- γ -mediated immune responses [205]. The earliest report which revealed its significance in malaria demonstrated that exogenous administration of unpurified mouse serum IFN was able to protect CF-1 mice from PbA sporozoite infection [206]. Although the experiment suggested a role for IFN-I, this unpurified mouse serum contains mediators other than IFN-I [207], such as IL-6, which have activity against *Plasmodium* liver stages [208]. Following that, a study of treatment with recombinant human IFN- α , which cross-reacts with mouse cells, did not show any effect on near matured (42 h) liver stage after a challenge with *P. yoelii* sporozoite [87]. However, recent analysis of liver transcriptome obtained from PbA [92] or Py [92, 126] sporozoite-infected C57BL/6 or BALB/c mice revealed an upregulation of genes expressions that are linked to IFN signaling. IFN-I was found to act during the very late phase of the liver stage and this liver specific IFN-I production partially limits parasite growth in the liver and influences initiation of erythrocytic stage infection [92]. In mice, *P. yoelii* and *P. berghei* liver stages last a minimum of 48 h and 51 h, respectively [209], and the effect of IFN-I was only apparent after 48 h but not 42 h after sporozoite infection. Interestingly, the IFN-I effect was indirect and mainly mediates the recruitment of leukocytes around liver-stage parasites. IFN- γ -secreting immune cells, in particular CD1d-restricted NKT cells, are the main players responsible for the innate elimination of liver stage [126]. Leukocyte-mediated inhibition of liver-stage parasite further leads to a reduced development of parasitemia [92]. More importantly,

this innate immune response can facilitate parasite elimination in subsequent liver-stage infection [126, 191]. In fact, early production of IFN-I prior to infection can impair parasite establishment [92].

Compared to liver-stage infection, IFN-I has a more striking role against blood stage parasites. Previous work shows that treatment of C57BL/6 mice with pure recombinant IFN- α inhibits *P. yoelii* or *P. berghei* blood stage development [87]. This effect was indirect and mediated by IFN- γ [210]. During early stage of *P. chabaudi* infection, IFN-I induced by the infection plays a pathogenic role by suppressing IFN- γ producing CD4⁺ T cells that control parasite load in C57BL/6 [77] but not in 129 Sv/Ev mice [98]. These results are not contradictory but suggest different levels of IFN-I and the duration of action is essential for proper immune response to control parasite growth.

In human, polymorphism in the receptor of IFN-I, IFNAR, has been shown to be robustly associated with progression of CM [79, 200]. It was further revealed that peripheral blood mononuclear cells from Malawian children recovering from severe malaria had higher expression of genes involved in interferon pathway [211]. In murine model, recombinant IFN- α [210] or IFN- β [68] treatment protected mice from ECM death. When PbA-infected C57BL/6 mice were administered with recombinant human IFN α , increased level of IFN- γ in treated mice was observed, which was linked to improved control of parasitemia and survival [210]. On the other hand, IFN- β treatment prevented ECM death by suppressing the expression of chemokine receptor CXCR3, the production of IFN- γ , and chemokine ligand CXCL9. Consequently, decreased T cells migrate and sequester in the brain thereby preserving a better vascular integrity of blood brain barrier as compared to nontreated WT controls [68]. However, IFN-I induced endogenously during *Plasmodium* infection plays a pathogenic role in ECM development. Absence of IFN-I signaling, in mice deficient in IFNAR, either delayed [82] or fully protected [77, 79] the mice from ECM. Haque et al. [77] attributed this protection to a restrained parasite growth in the absence of IFN-I pathway whereas Ball et al. [79] and Palomo et al. [82] concluded that deficiency in IFN-I signaling reduced sequestration of pathogenic T cells in the brain. All these conflicting data suggest that effects of IFN-I might rely on precise level and timing of expression of systemic IFN-I.

5. Interferon Regulatory Factors

Both IFN-I and IFN- γ are essential in the immune response against malaria infection. Production of IFNs is triggered upon recognition of malaria antigen by receptors as discussed above. Although an array of receptors and downstream signaling molecules have been implicated, all signaling pathways ultimately converge to a few downstream transcription factors, such as IRFs, which regulate gene expression of IFNs. The family of IRFs comprised 9 members, namely, IRF1-9. Each IRF binds to a unique set of ISRE to stimulate transcription of diverse genes that are translated into functional

proteins [212, 213]. The diverse roles of a few IRFs in malaria infection have been uncovered recently (Table 4).

5.1. Interferon Regulatory Factor 1. The first member of the IRF family identified that binds to the promoter region of IFN- β gene is IRF-1. This transcription factor is expressed in many cells types. It mediates signaling of both IFN-I and particularly IFN- γ , a strong inducer of IRF-1 expression. IRF-1 regulates antigen presentation, monocyte/macrophage differentiation, T cell development, and B cell growth [214] and promotes Th1 response [215]. In humans, the IRF-1 gene is located in chromosome 5q31-33 region and variation in 5q31-33 region was associated with variations in parasite density during *P. falciparum* erythrocytic infection [216]. A subsequent study in West African ethnic groups identified that polymorphisms in IRF-1 gene could lead to differential abilities to control *P. falciparum* infection [123]. Despite the fact that Mangano et al. discovered a correlation between IRF-1 and control of *P. falciparum* infection [123], they found no association of this transcription factor in the development of severe malaria pathology amongst African children [124]. Using mice deficient in IRF-1, Tan et al. showed that IRF-1 is essential in limiting parasite growth and survival outcome of PbA infection [125]. Further animal studies also demonstrated that IRF-1 regulates antigen presentation [214] and is indispensable in the pathogenesis of ECM. When infected with PbA, mice deficient in IRF1 were partially protected from ECM with a lesser control in parasite growth in the circulation [69]. Microarray analysis of brains from ECM-susceptible C57BL/6 mice as compared to ECM-resistant BALB/c mice revealed an increase of IRF-1 gene expression [70]. Similarly, IRF-1 gene expression was higher in brain from CBA/T6 mice infected with ECM-causing PbA parasite than with non-ECM causing *P. berghei* K173 parasite [95]. With this evidence, there is a need to further investigate the exact implication of IRF-1 in these different immune mechanisms which are essential for ECM pathogenesis [27].

Recently, Wu et al. also demonstrated that higher expression of IRF-1 gene and production of IFN-I enabled better control of parasitemia in nonlethal *P. yoelii* N67-infected mice than in lethal *P. yoelii* N67C-infected mice [85]. However, the role of IRF-1 in IFN- β signaling remains controversial as stimulation of splenocytes from IRF-1 deficient mice with malarial genome-alike AT-rich oligonucleotides did not abrogate IFN- β production [61]. This discrepancy could be due to the use of different malaria ligand to induce IFN-I production comforting previous speculation of multiple signaling pathway to produce IFN-I [217].

5.2. Interferon Regulatory Factor 3/7. Among the 9 IRFs, IRF-3 and IRF-7 are the master regulators of IFN-I. They are responsible for driving the initial transcription of IFN-I during early stage of infection. Induction of IFN-I is generated through a biphasic mechanism which warrants transcriptional efficiency and diversity of targeted genes. IRF-3 is constitutively expressed in the cytoplasm of all cells and resides as an inactive form. Upon phosphorylation, activated IRF-3 translocates into the nucleus and forms enhanceosome

TABLE 4: Diverse roles of different IRFs in malaria infection.

	Host /model	Infection	Functions	Ref.
IRF-1	Human	<i>P. falciparum</i>	Controls parasitemia	[123]
			Not involved in development of severe malaria	[124]
		<i>Py nigeriensis</i> N67 iRBCs	Plays a role in IFN-I signaling	[85]
	Mice	PbA iRBCs	Involved in ECM development Controls parasitemia	[69]
			Involved in ECM development Promotes parasitemia	[125]
			Regulates production of IFN- γ and IL12p4 Controls CD8 ⁺ T cells numbers	[72]
	<i>Ex vivo</i>	AT-rich oligonucleotides	Plays a role in ECM development No effect on IFN- β production by splenocytes	[70, 95] [61]
IRF-3	Mice	<i>P. yoelii</i> sporozoite	Mediates IFN-I-induced innate response during liver-stage infection	[126]
		<i>P. chabaudi</i> iRBCs	Mediates splenic IFN- α , but not IFN- β , transcription in red pulp macrophages	[90]
			Not involved in IFN-I production	[110]
IRF-5	<i>Ex vivo</i>	AT-rich oligonucleotides	Not involved in IFN- β production by splenocytes	[61]
IRF-7	Mice	<i>Py nigeriensis</i> N67 iRBCs	Plays a role in IFN-I signaling	[85]
		PbA iRBCs	Plays a role in ECM development	[70, 71]
		<i>P. chabaudi</i> iRBCs	Mediates splenic IFN-I transcription in red pulp macrophages	[90]
			Involved in IFN-I production	[110]
IRF-3 and IRF-7	Mice	PbA sporozoite	Mediate IFN-I response in liver-stage infection	[92]
		PbA iRBCs	Control parasite load in the liver	
	<i>Ex vivo</i>	AT-rich oligonucleotides	Involved in ECM development	[61]
		<i>Pf</i> iRBCs	Mediate IFN- β production by splenocytes Mediate IFN- β production by macrophages	
IRF-8	Mice	PbA iRBCs	Plays a role in ECM development	[95]
			Regulates production of proinflammatory cytokines	[72]
			Mediates IFN-I production Controls antigen processing and presentation and chemotaxis	
IRF-9	Mice	<i>Py nigeriensis</i> N67 iRBCs	Plays a role in IFN-I signaling	[85]
		PbA iRBCs	Plays a role in ECM development	[72]

with other transcription factors, namely, NF- κ B and AP-1 [218], which will lead to IFN- β transcription [219–221]. On the other hand, IRF-7 is expressed at very low levels in the cytoplasm of most cells. Positive feedback of IFN- β increases IRF-7 expression. Like IRF-3, it undergoes nuclear translocation and forms heterodimer with IRF-3 to bind with ISRE. Unlike IRF3, IRF-7 induces maximal transcription of both IFN- α and IFN- β [222]. The role of IRF-3 and IRF-7 in malaria infection remains poorly defined.

When mice deficient in either IRF-3 or IRF-7 were infected with PbA sporozoite, significant impairment in IFN-I response was observed. Consequently, these deficient mice had higher parasite load in the liver and peripheral circulation as compared to their WT counterparts. Initiation of blood-stage infection was also found to be 1-day

earlier in the KO as compared to WT mice [92]. On the other hand, only mice deficient in IRF-3 displayed marked impairment in the control of parasite burden in the liver upon secondary *P. yoelii* sporozoite infection [126]. Such disparity could be attributed to the strain of parasite or the time point measured in each study. Since IRF-3 stimulates IFN- β production [219–221] and IRF-7 induces both IFN- α and IFN- β production [222], the significance of IRFs in each infection model could possibly hint on the importance of IFN- α and/or IFN- β at different window of the liver-stage infection. When stimulated with infected red blood cells or AT-rich motif derived from genome of *P. falciparum*, splenocytes obtained from mice deficient in both IRF-3 and IRF-7 had attenuated IFN- β production, demonstrating a role for one or both of these factors in IFN- β production [61].

FIGURE 1: (a) Signaling pathway induced by malarial ligand during liver-stage infection. *Plasmodium* RNA is recognized by MDA5 (melanoma differentiation-association protein 5) present in the cytoplasm. Ligand-receptor interaction triggers assembly of MAVS (mitochondrial antiviral signaling protein) that aggregate on the surface of mitochondria. This eventually leads to the activation of both IRF-3 and IRF-7 which regulate transcription of IFN-I. Besides MDA5, activation of other receptors can also trigger aggregation of MAVS. However, this specific receptor and its corresponding malarial ligand have yet to be identified. (b) Signaling pathway induced by malarial ligand during erythrocytic-stage infection. Surface TLR4 recognizes a number of malarial ligands such as GPI (glycosylphosphatidylinositol membrane anchor) and MP (microparticles). Together with CD14 or CD11b/CD18 integrin, it can recognize heme and host fibrinogen, respectively. Both TLR heterodimer TLR1/TLR2 and TLR2/TLR6 recognize GPI. Within the endosomal compartment, Hz (Hemozoin) and CpG DNA are recognized by TLR9. In addition, TLR7/TLR9 heterodimer has been proposed to recognize an unknown malarial ligand. These ligand-receptor interactions trigger 3 proposed pathways. (1) TLR-dependent pathway involves the recruitment of MyD88 (myeloid differentiation primary gene 88) to TLR, which phosphorylates downstream MAPKs (mitogen-activating protein kinases), such as ERK1/2 (extracellular-signal-regulated kinases 1/2), p38 MAPK, and JNK1/2 (c-Jun N-terminal kinases 1/2). Subsequently, NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and AP-1 (activating protein-1) translocate into the nucleus and stimulate production of proinflammatory cytokines. At the same time, phosphorylated MAPKs or MyD88 can induce activation of IRF-3 and IRF-7 to transcribe IFN-I and ISGs (interferon stimulated genes). (2) Activation of TLR-independent pathway triggered by AT-rich motif present in the *plasmodial* genome engages STING, TBK1, IRF-3, and IRF-7. (3) Another TLR-independent pathway involves MDA5 and MAVS. *PfTyrRS* (*P. falciparum* tyrosyl-tRNA synthetase) and *PfHMGB* (*P. falciparum* high mobility group box protein) were shown to induce proinflammatory responses but the exact signaling pathways have yet to be identified.

In mice infected with *P. chabaudi*, early IFN-α production by red pulp macrophages is dependent on both IRF-3 and IRF-7. Intriguingly, contrary to what is observed with viruses [223–226], IFN-β production was independent of IRF-3 [90, 110], suggesting an alternate pathway of activation for malaria parasite. Microarray analysis of brain from ECM-susceptible mice showed a higher transcriptional activity of IRF-7 than ECM-resistant [70] and uninfected control mice [71]. Double IRF-3/IRF-7 deficient mice infected with PbA were resistant to ECM upon infection [61] confirming a role for IFN-I in ECM. However, the precise functions of IRF-3 and IRF-7 in CM remained to be determined.

5.3. Interferon Regulatory Factor 8. IRF-8 is one of the unique IRFs that is only expressed in immune cells [227]. Unlike

IRF-3 and IRF-7, expression of IRF-8 is induced by IFN-γ instead of IFN-I. This transcription factor coordinates growth and differentiation of myeloid cells, such as macrophages and dendritic cells, and production of proinflammatory cytokines, such as IFN-I and IL-12p40 [227]. Together with IRF-1 [228], IRF-8 directs transcription programs in immune cells towards a Th1-dominated response [229]. Since ECM is a Th1-mediated pathology [230–232], it is not surprising that amplification in IRF-8 gene expression was observed in the brains of ECM-susceptible PbA-infected CBA/T6 mice [95]. Mice with dysfunctional IRF-8 are protected from ECM due to downregulated transcriptional activity of many IRF-8-dependent genes which are essential in various aspects of the immune response during PbA infection. These modulated genes are involved in antigen processing and presentation,

chemotaxis, maturation of phagosomes, and production of proinflammatory cytokines [72]. Though both reports concurred that IRF-8 is involved in ECM development, further research is mandatory to ascertain its role in human CM.

5.4. Other Interferon Regulatory Factors. Apart from IRF-1, IRF-3, IRF-7, and IRF-8, some studies have also briefly explored the role of IRF-5 and IRF-9 in malaria infection. IRF-5 is expressed in B cells and dendritic cells. Like IRF-7, it is mainly regulated by IFN-I. This transcription factor interacts with IRF-1, IRF-3, and IRF-7 to induce expression of proinflammatory cytokines [233, 234]. The only report on IRF-5 in malaria infection revealed that it is dispensable in the production of IFN- β by splenocytes in response to stimulation by AT-rich oligonucleotides that resemble those in the malarial genome [61]. Another member, IRF-9, is expressed constitutively in many cell types and unlike the rest of the IRFs, it functions only when it dimerizes with STAT1 and STAT2 to form an active trimeric complex, known as ISGF3. This complex binds to ISRE and activates ISGs [235, 236]. During nonlethal PyNN67 infection, IRF-9 participates in the production of IFN-I to control parasite growth [85]. A robust IRF-8-dependent amplification of IRF-9 was detected in brain of mice infected with PbA [72]. These separate studies seem to hint on the possibility of more IRFs involvement in the immune response during malaria infection.

6. Future Perspectives

In Figure 1, we illustrate the different malarial ligands and the various signaling pathways triggered to produce IFN-I and proinflammatory cytokines in the liver and erythrocytic stages. Though controversial, these studies demonstrated that IFN-I [77] and IFN- γ [94] produced during infection may modulate the course of disease progression. However, the same immune response that initially protects the host could inevitably contribute to the pathogenesis of severe malaria [66, 82, 94].

Thus far, the most effective malaria treatment is administration of antimalarial drugs, Chloroquine (CQ) or Artemisinin (ART) and its derivatives, which solely targets the parasite. But the emergence of CQ/ART-resistance parasite species rendered these treatments increasingly ineffective [237, 238]. In the recent years, increased knowledge of the host immune response uncovers a potential to employ host-directed therapy in malaria infection. In fact, immunotherapy has emerged as a hot topic for both research and treatment against a diverse array of disease over the last few centuries [239–241]. Specifically, interferon therapy has been widely reported to treat cancer [242–246] and viral infections [247–249]. Recently, a synthetic innate defense regulator-1018 (IDR-1018) adjunctive treatment, in combination with antimalarial drug, demonstrated efficacy against ECM [250]. Taken together, these data offer the possibility of interferon treatment as an immunotherapy for malaria infection. Thus, dissecting the innate signaling pathways and their corresponding cytokine responses would

provide further insights into the induction of adaptive immune response and offer some directions on vaccine or drug developments.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Sin Yee Gun, Carla Claser, Kevin Shyong Wei Tan, and Laurent Rénia contributed equally to the paper.

Acknowledgments

This work was supported by an intramural grant from Singapore's Agency for Science, Technology and Research (A*STAR). Sin Yee Gun is supported by a postgraduate scholarship from the Yong Loo Lin School of Medicine, National University of Singapore, Singapore.

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