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Review

Mouse Models for Unravelling Immunology of Blood Stage Malaria

Adesola C. Olatunde, Douglas H. Cornwall, Marshall Roedel and Tracey J. Lamb*

Department of Pathology, University of Utah, Salt Lake City, UT, USA.
* Correspondence: tracey.lamb@path.utah.edu

Abstract: Malaria comprises a spectrum of disease syndromes and the immune system is a major participant in malarial disease. This is particularly true in relation to the immune responses elicited against blood stages of *Plasmodium*-parasites that are responsible for the pathogenesis of infection. Mouse models of malaria are commonly used to dissect the immune mechanisms underlying disease. While no one mouse model of *Plasmodium* infection completely recapitulates all the features of malaria in humans, collectively the existing models are invaluable for defining the events that lead to the immunopathogenesis of malaria. Here we review the different mouse models of *Plasmodium* infection that are available, and highlight some of the main contributions these models have made with regards to identifying immune mechanisms of parasite control and the immunopathogenesis of malaria.

Keywords: Mouse models; *Plasmodium*; Adaptive Immunity; Innate Immunity; T cells; B cells; Macrophages; Neutrophils; Antibodies; Cytokines

1. The immune response to *Plasmodium* asexual blood stages dictates malarial disease

Malaria is still a significant problem in the world with over 400,000 deaths resulting from 228 million cases in 2019, 85% of them concentrated in 20 countries on the African subcontinent [1]. The RTS,S Mosquirix™ vaccine in children has limited efficacy [2, 3] but current efforts in improving this vaccine appear to be moving towards vaccine-mediated protection that is more durable [4]. Nonetheless, any further improvements in the development of efficacious therapeutics and vaccines requires a better understanding of what constitutes an effective anti-malarial immune response.

Malaria is caused by infection with parasites of the species *Plasmodium*, deposited into the dermis of the skin by female *Anopheles* mosquitos during probing for a blood meal. The sporozoites travel through the blood circulation, invading the liver to undergo several rounds of division in hepatocytes before releasing merozoites into the blood stream where parasites infect red blood cells (iRBCs) and replicate exponentially. Clinical symptoms of malaria are exclusively caused by the erythrocytic lifecycle of *Plasmodium*.

The clinical manifestations of malaria are wide-ranging and include symptoms such as hypoglycemia, acidosis and anemia. Accumulation and sequestration of iRBCs on vascular endothelial cells is associated with vascular activation which is known to underlie organ-specific pathologies such as cerebral malaria, acute lung injury, hepatomegaly and liver fibrosis [5] (**Table 1**). While sterile immunity to malaria generally does not occur, years of repeated exposure to the parasite in endemic regions facilitates the development of clinical immunity that can be characterized by reduced parasite load (anti-parasite immunity) and controlled inflammatory responses to iRBCs (clinical immunity). Malarial disease encompasses a spectrum of virulence which is influenced by a number of factors including genetic variation of both the host and parasite [6-8], the make-up of the intestinal microbiome of the host [9] and environmental influences such transmission intensity or the presence of co-infections [10-12].

Mouse models are commonly used to study the immunology of erythrocytic malaria. Given the well-characterized range of different rodent *Plasmodium* species and strains, as

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well as the plethora of mouse lines currently available to investigators, this article will outline some of the parasite-mouse combinations that are commonly used to study the different facets of blood stage malaria immunology. In addition, we will discuss novel models of rodent malaria that have not yet been fully harnessed to determine the environmental and genetic contributions to generating immune responses to *Plasmodium* iRBCs.

2. Utility of rodent *Plasmodium* species in the investigation of blood stage immunology

Human parasites cannot infect mice unless they are humanized [13, 14]. Whilst humanized mouse models have some utility in the investigation of immune responses to *P. falciparum* in a controlled environment, several species of Plasmodium species exist that naturally infect rodents (**Table 2**). Isolated and cloned from *Thamnomys* thicket rats in the central African Region in the 1960s [15] they have been instrumental to the study of the immununobiology of the erythrocytic stages of *Plasmodium* infection [16]. Although apparently asymptomatic in their original hosts, infection of mice gives rise to a number of different phenotypes of infection, many of which mimic various states of disease found in human *Plasmodium* infection. Rodent *Plasmodium* parasites cannot infect humans making them tractable and non-hazardous models of malaria. However rodent *Plasmodium* parasites have some differences to human *Plasmodium* parasites (e.g differences in variant antigen gene families such as the absence of *Pf*EMP1) (summarized in **Table 2**). It is important to note that no one rodent *Plasmodium* species is able to replicate all features of human *Plasmodium* infection. Therefore, specificity in study focus in combination with the correct choice of model is a key aspect of research into blood stage malaria immunology using rodent models of malaria.

Mice have been instrumental in elucidating the workings of the human immune system [17]. Nonetheless, there are fundamental differences between the physiology of mice and humans such as differences in splenic architecture between human (sinusoidal) and mouse (non-sinusoidal) that would alter the direction of blood flow and possibly the timing or mechanisms by which iRBCs induce splenic immune responses [18, 19]. There is also a different balance of leukocyte subsets [20]. Despite these differences, the main features of the immune response to *Plasmodium* iRBCs (**Figure 1**) are largely replicated with a strong type 1 inflammatory response characterized by interferon-γ (IFN-γ) producing CD4 T cells and the production of anti-parasite antibodies. Mouse models of *Plasmodium* infection provide a tractable and highly informative model to define how the immune system operates in human *Plasmodium* infection, in turn providing critical evidence of immune mechanisms in malaria that simply cannot be obtained in humans. Advancements in both rodent genetic engineering technology [21, 22] and the ability to create transgenic rodent *Plasmodium* parasites [23, 24] **(Table 3)** has facilitated dissection of immune responses to *Plasmodium* infection with unprecedented precision. As such, mouse models of blood stage *Plasmodium* infection are a key tool in understanding the immune responses driving *Plasmodium* parasite control and pathogenesis of malaria.

Selection of a mouse host and parasite species to study immune responses to blood stage *Plasmodium* infection is dependent on the question being asked (**Table 4**). Some mouse- parasite combinations are lethal from around 7 days post-infection whereas others resolve to become a sub-patent infection that can only be detected by molecular methods and, in some cases, can be completely cleared. When selecting which combination to use it is important to determine whether the major goal of any study is to decipher anti-parasite immune responses, clinical immunity, or a combination of both. Other considerations may involve the existence of comparative literature or the existence of databases from "big data" sets available online (**Table 5**) that can be mined *a priori* to identify candidate molecules of importance.

3. Genetic control of the immune responses to *Plasmodium* infection

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Population-wide genetic diversity and its effect on *Plasmodium* infection is evident in human populations. This can be clearly seen with hemoglobinopathy gene polymorphisms such as sickle cell, thalassemia or glucose-6-phosphate dehydrogenase (G6PD) [25-29] which offer resistance to infection of RBCs by *Plasmodium* and reduced clinical severity when infection does occur. Associations have been found with MHC haplotype [30, 31] with varying results [32], and polymorphisms in immune genes and the promoters controlling their expression have been associated with malarial disease severity. For example allele variants [33] and promoter polymorphisms [34, 35] controlling the expression of the inflammatory cytokine tumor necrosis factor-α (TNF-α) have been associated with the propensity to develop cerebral malaria [34, 35] and anemia [34, 36].

There is now an increasing number of publications using genome wide associate studies (GWAS) for malaria [37-40]. These studies have found associations of polymorphisms encoding erythrocyte calcium pump (ATP2B4) and an endothelial junction protein (MARVELD3) with severe malaria [39], and linkages to genes on chromosome 6q21.3 and possibly 19p13.12 to the development of uncomplicated (mild) malaria [41]. Linkages to asymptomatic malaria have been found on chromosome 5q31[41]. Collectively this data suggests that the development of immune responses during *Plasmodium* infection is, in part, genetically controlled. In support of this notion, the Fulani tribe of western Africa who are generally more resistant to the clinical effects of *Plasmodium* infection have allelic variants of FcγRIIα [42], interleukin (IL)-10 [43] and IL-4 [44] not present in the more susceptible sympatric Dogon tribe [45, 46]. It is thought that these variants allow the Fulani to mount a robust and protective immune response to *Plasmodium* that is characterized by early production of pro-inflammatory cytokines like IFN-γ [47].

In mice *Plasmodium* infections are also genetically controlled [48-51]. Between-strain genetic diversity can explain the variation in disease severity in *Mus musculus* infected with any of the rodent *Plasmodium* lines. For example, it is widely accepted that C57BL/6 mice are susceptible to *P. berghei* ANKA (*Pb*A) infection succumbing to neurological manifestations of infection that resemble cerebral malaria, whereas BALB/c or DBA/2J are more resistant and survive significantly longer dying much later from hyperparasitemia [50]. Linkage studies of *P. chabaudi*-AS-infected crossed lines of inbred, recombinant inbred and congenic inbred lines of mice has led to the identification of several gene regions termed Char (Chabaudi resistance) regions (reviewed in [52] and [53]) which include immune-associated genes such as tumor necrosis factor (TNF) and lymphotoxin-α (LT-α) amongst others demonstrating the importance of immunogenetics in the outcome of *P. chabaudi* infection in mice.

The majority of studies elucidating immune responses to the erythrocytic stage of *Plasmodium* infection are undertaken in genetically uniform inbred mouse strains, many using mice with C57BL/6 and BALB/c backgrounds **(Table 2)**. Whilst beneficial by virtue of uniform background genetics and MHC haplotype, such mice will not inform on the immunogenetic basis of disease severity. Although necessary with respect to studies incorporating genetically modified mouse lines, collectively such studies may bias our understanding of infection immunology due to their highly selected life histories in laboratory settings [54]. Many of these inbred strains have skewed immune responses, such as the Th1 skew in the C57BL/6 mice or Th2 skewed response in the BALB/c mice [55], which have been exploited to understand genetic influences on the differential immune responses mounted to *Plasmodium* parasites and the severity of infection [49]. As such, it is important to be cognizant of this limitation of mouse models when interpreting data that has been collected.

Several studies have endeavored to use outbred mouse lines, with Swiss Webster mice commonly used. Nonetheless, such mice have inbreeding coefficients of ~0.48[56] which is rather removed from humans which are ~0.01-0.08[57, 58]. New endeavors to generate mouse resources which are more aligned with human diversity include wild-derived specific pathogen free (SPF) mice [59], or the Collaborative Cross (CC) mice [60-

 doi:10.20944/preprints202207.0242.v1

63] and Diversity Outbred (DO) mice [61, 64, 65]. These colonies allow assessments of the variation of immune responses to *Plasmodium* infections that may be more akin to humans. Given that all of these under-utilized mouse colonies are SPF, they have the advantage of assessing genetic diversity on anti-*Plasmodium* immune responses in the absence of contributing environmental factors.

4. Modelling the influence of environmental factors on immune responses to *Plasmodium* infection

Genetic diversity in immune responsiveness has been studied in wild-captured mice. However responses in such mice are confounded by environmental factors [66] which includes differences in microbiota [67], a community of microorganisms including bacteria, fungi, viruses and protozoans that colonize a number of external facing environments of humans such as the respiratory tract, gastrointestinal tract and skin. Studies in humans and mice have shown that gut microbiota is associated with the level of malarial disease in those living in malaria-endemic areas [68-70]. This has also been shown in mice [9, 71], specifically with respect to modulating germinal center reactions [71], even within the spleen [72]. This is relevant in the selection of mouse vendor given clear evidence that the severity of erythrocytic *Plasmodium* infection in genetically similar mice obtained from different vendors was significantly altered in response owing to the differences in gut microbiome [9].

Inbred mice that are removed from an SPF environment and have been exposed to natural environments ("re-wilded mice") are found to have a different immune landscape specifically modulated by the microbiota [67, 73]. Recent work has studied the role of genetic diversity in *Plasmodium* immune responses in the context of environmental exposures through co-housing specific pathogen free (SPF) mice with mice obtained from pet shops that were not SPF (so-called "dirty mice") [74]. Influencing the environmental exposure of mice in this way induced a less susceptible phenotype to *P. berghei* ANKA infections but did not alter immune responses sufficiently to fully protect all mice [74]. However, it should be noted that mice obtained from pet shops are highly inbred and do not recapitulate the genetic diversity conferred by wild-derived, CC or DO mice described above.

In addition to the microbiota, there are other environmental factors that collectively can influence the immune responses to *Plasmodium* iRBCs that are hard to consistently replicate in laboratory mice. These include the alteration of the immune landscape of humans by prior and current co-infections including the influence of immune responses to existing liver stage *Plasmodium* parasites [75]. However there has been some success in modelling co-infection scenarios in mice and measuring how immune responses to *Plasmodium* are influenced when co-infections are present (for examples see [76, 77]). In addition, there are likely effects of the human biting rate (HBR) which would alter amounts of mosquito saliva exposure[78-80] which can influence *Plasmodium* infection in mice [81] and possibly influence the entomological inoculation rate (EIR) which may be associated with an varying number and/or multiplicity of *Plasmodium* infection in an individual [82]. Without use of mouse models of blood stage infection where each aspect can be dissected individually, it would be virtually impossible to determine the relative influence each of these environmental factors has on immune responses mounted to blood stage *Plasmodium* infection.

5. Mechanisms of anti-parasite immunity: what have we learnt about control of iRBCs from mouse models of *Plasmodium* infection?

Successful control of intraerythrocytic *Plasmodium* parasites requires a robust cellular and humoral immune response that generates broadly-reactive antibodies. Rodent malaria models of *Plasmodium* erythrocytic infection have been instrumental in revealing some of the mechanisms governing the cellular immune responses to *Plasmodium* blood

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stage parasites, as well as spatial information related to immune responses generated in different organs where *Plasmodium* iRBCs sequester. It is challenging to obtain this level of information from human infections where the main available source for immune analysis is the peripheral blood. Here we discuss some of the main findings from use of rodent models of *Plasmodium* blood stage infection.

5.1. Invasion blocking is a key mechanism of anti-parasite antibodies for the control of iRBCs

The importance of humoral immunity in host defense against *Plasmodium* infection was first demonstrated in rhesus monkeys [83] and later in *P. falciparum*-infected children [84, 85] when passive transfer of immune sera limited parasite growth and symptoms associated with the disease. These observations formed the basis of the hypothesis that there is a requirement for sustained antibody production in the control of *Plasmodium* blood stage of infection where the clinical manifestations of the disease occur.

The possible effector functions of these antibodies have been elucidated with careful *in vitro* culture studies. These range from recognition and uptake of iRBCs by phagocytes [86-88], blocking of parasite adhesion and invasion [89], to inhibition of parasite growth [90]. The targets of these antibodies are numerous and involve proteins expressed on the surface of merozoite required for RBC invasion such as merozoite surface protein 1 (MSP-1) or apical membrane antigen 1 (AMA) [91, 92] as well as variant surface antigens such as *Plasmodium falciparum* erythrocyte membrane protein 1 (PfEMP-1) [93]. Positive correlations between the breadth, as well as magnitude, of the antibody response and successful control of iRBCs [91, 92, 94] provide further evidence of the importance of the humoral response in controlling *Plasmodium* iRBCs.

The relative contributions of these mechanisms to parasite control are hard to assign in humans; mouse models of infection have been instrumental in identifying the importance of invasion blocking as a key mechanism of iRBC control *in vivo*. Studies using FcγR-/- mice which are deficient in the FcγR used by phagocytes to detect IgG-opsonized iRBCs demonstrate that IgG-dependent phagocytosis is not a key mechanism of control of iRBCs, at least in the avirulent *P. yoelii* XNL model [95]. This conclusion is supported by a recent study whereby *in vivo* tracking of a single generation of labeled iRBCs of either *P. chabaudi* or *P. yoelii* adoptively transferred into mice demonstrated that parasite-specific IgG does not affect the rate at which iRBC are cleared, but rather it limits the progression of the iRBC to a new RBC by blocking invasion [89]. This is not a surprising finding when most IgG was reactive to merozoites found within schizonts, the terminal stage of iRBCs prior to release of merozoites that will infect new RBCs. The observation that infection of mice with *P. yoelii* XNL line becomes lethal in a B cell deficient host [12, 96] does not differentiate a role of IgG from other isotypes. There is a growing appreciation for the role of IgM in control of iRBCs and IgM may play a role in antibody dependent phagocytosis through the Fcμ receptor, although this receptor is expressed only on B cells in mice [97]. It is also possible that complement-mediated lysis of opsonized iRBCs could role a role in parasite control as shown in *P. falciparum* infections [98, 99] although the effects of complement depletion has been shown to be minimal in the *P. chabaudi* AS mouse model [100].

It is important to note that antibodies do not appear to be an absolute requirement to control all species of *Plasmodium* infection in mice. It has been shown that, unlike in *P. yoelii* XNL infections, B cell deficient mice infected with *P. chabaudi* are able to control acute infection in via antibody-independent mechanisms [96, 101]. Depletion of γδ T cells in B cell deficient mice following *P. chabaudi* AS infection led to exacerbated parasitemia, indicating a more critical role for γδ T cells in cell mediated immune response against *P. chabaudi* [102]. Thus, mouse models of *Plasmodium* infection indicate that some immune mechanisms of iRBC control may be differentially important for different species or clones of *Plasmodium*.

5.2. Memory B cells to Plasmodium blood stage infection can develop and control secondary infection

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Humoral immune responses against malaria develop slowly, inefficiently and wane over time in the absence of reinfection [103-105]. Antibodies are derived from antibody-secreting cells (ASCs) (also called plasma cells) that are generated from a specialized compartment called the germinal center (GC) in secondary lymphoid tissue [106]. Memory B cells and long-lived plasma cells (LLPC) offering protection against re-challenge infections are also thought to develop in the GC after infection. Given that secondary lymphoid tissue is not readily accessible for study in *Plasmodium*-infected humans, mouse *Plasmodium* infections have allowed dissection of cellular responses in malaria. The investigation of B cell responses to blood stage *Plasmodium* have typically utilized both *P. chabaudi* AS and *P. yoelii* XNL. Despite differences in the importance of antibodies for iRBC control between these species, the cellular mechanisms underlying B cell responses to *Plasmodium* blood stage parasites appear similar regardless of which species was used to initiate infection [107-109].

The cellular basis underpinning the lack of efficacious long-lived humoral responses to *Plasmodium* in those living in endemic areas is still incompletely understood. Following infection with *P. chabaudi*, memory B cells and plasma cells specific for MSP1 were still detectable over eight months post-primary infection [110, 111]. Upon secondary infection with homologous parasite, a more rapid production of IgG2c, IgG2b and IgG1 isotypes were observed [110] indicating recall responses were active and functional. In addition to IgG+ memory B cells, individuals in malaria endemic areas have IgM+ memory B cells with somatically hypermutated B cell receptors suggestive of affinity maturation[112]. IgM antibodies from these cells had high invasion blocking capability against *P. falciparum in vitro* suggesting that they may play a key role in controlling iRBCs. Indeed, the significance of these findings can be seen in the *P. chabaudi* mouse model of malaria where IgM+ B cells were the dominant MBCs expanding on challenge infections leading to the early protection against re-infections[111]. One of the key mechanisms underpinning an impaired memory B cell response may be related to apoptosis induced by blood stage infections. Infection of MSP-1 vaccinated BALB/c mice infected with the lethal *P. yoelii* YM strain led to ablation of memory B cells and LLPCs, including those that developed to prior vaccination with MSP-1 or unrelated antigens [113]. Therefore, it could be concluded that, although memory B cells and LLPCs can develop to blood stage infection, more lethal *Plasmodium* infections may have a deleterious effect on these cell subsets via induction of apoptosis, albeit by an unknown mechanism. Much remains to be investigated regarding the longevity of memory B cell and LLPC response to *Plasmodium* blood stage infection.

5.3. Development of functional anti-Plasmodium blood stage GC responses in the face of IFN-γ

While there is evidence of GCs formation in human malaria, there are some indications that GC reactions might not be optimal during human *Plasmodium* infection [114]. Mouse models have been instrumental in demonstrating that fully functional GCs can develop in a primary blood stage *Plasmodium* infection leading to protective B cell responses. In GCs follicular helper T (Tfh) cells, interact with B cells and help push differentiation of B cells into plasma cells (short-lived and long-lived) and memory B cells [106]. The *P. yoelii* mouse model of infection has been used to show that B cells are the primary cell type expanding Tfh[115]. However upon expansion, IL-21, one of the major Tfh-derived cytokines, has been shown to be important in the development of robust and durable class-switched B cell responses following blood stage infection with *P. chabaudi* AS and *P. yoelii* XNL [107]. Disruption of IL-21-derived signals on B cells led to a diminished level of *Plasmodium*-specific antibodies and increased parasitemia which was correlated with a deficiency in the development of plasma cells and memory B cells [107]. Furthermore, Tfh-deficient $CD4^{Cre}xBcl6^{fl}$ animals or SAP-/- deficient animals were unable to clear chronic infection with *P. chabaudi* AS [116] demonstrating that, although the establishment of chronic infection appears to be antibody-independent, antibodies are critical for control of chronic infection.

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During *Plasmodium* infection GCs form in the context of innate-derived inflammatory responses as well as during responses to existing *Plasmodium* infections, particularly in higher transmission areas where simultaneous multiclonal infection is common[10, 11]. Mouse models of *Plasmodium* infection have demonstrated that B cell priming of Tfh cells in the spleen after blood-stage *Plasmodium* infection is dampened by type 1 interferon via down regulation of T-cell expressed ICOS and interruption of ICOS-ICOSR signaling between GC Tfh and GC B cells, respectively [117]. The interaction between ICOS-ICOSR is critical for Tfh development against blood stage *Plasmodium* infection in mice [118] and negatively regulated by PD-L1 and LAG-3 [119]. IL-6 also plays a role in Tfh differentiation in blood stage *Plasmodium* infection, albeit IL-6R signaling appears to be more important for plasma cell development [120].

A key feature of the immune response in *Plasmodium*-infected individuals is the induction of a strong production of pro-inflammatory cytokines, with IFN-γ a defining cytokine. *P. falciparum*-induced IFN-γ in human infection has been shown to drive the expansion of exhausted, atypical memory B cells [121] which appear to have reduced functionality. Atypical B cells have been shown to develop in the *P. chabaudi* AS model of *Plasmodium* infection [122]. Specifically, these appear to correlate with development of LLPCs [123] suggesting a potential protective role in chronic infection.

Although there is evidence that IFN-γ both supports [124, 125] or impairs GC B cell responses [126-128] in mouse models of *Plasmodium* infection, the effects are likely contextual. T-bet intrinsic expression on B cells, induced by signaling from the IFN-γR is needed for IgG2c isotype class switching during *Plasmodium* blood stage infection and also enhances affinity maturation [125]. This IFN-γ likely comes from IL-21 / IFN-γ expressing Tfh (Tfh1) [129]. Although first described in the periphery of *P. falciparum*-infected individuals [130], rodent models of malaria have been instrumental in demonstrating the lineage and function of Tfh1 [129] with interferon-mediated signaling via interferon regulatory factor 3 (IRF3) supporting a developmental shift away from Tfh to Th1 [131]. More recent studies have comprehensively dissected the intracellular signals governing plasticity of the Tfh/Th1 phenotype in CD4+T cells responding to blood stage *Plasmodium* infection [132]. As such, molecules that down-regulate T-bet mediated IFN-γ secretion in B cells, such as IL-10, [133] promote humoral responses to blood stage *Plasmodium* infection [126]. However, this function appears to be more important for extrafollicular plasmablasts [134] rather than plasma cells developing in the GC. Given that extrafollicular plasmablasts act as a nutrient sink impairing the follicular GC reactions[135] the effects for IFN-γ may occur indirectly via effects on extrafollicular plasmablast activation.

There is still much to be learned regarding the factors that regulate the development of B cell responses to blood stage *Plasmodium*. The discovery of a novel population of NK1.1 T cells supporting antibody production from short lived extrafollicular plasma blasts [136] demonstrates the complexity in the development and control of humoral responses to blood stage *Plasmodium* infections. The main rodent models utilized in investigating humoral responses to malaria involve the species *P. chabaudi* and *P. yoelii* due to their non-lethal phenotype in many backgrounds of mice, including C57BL/6. However, modelling the role of antibodies in severe malaria has been accomplished using *P. berghei* ANKA infections normally employed for immunopathogenesis studies. As such, a study observed that the pro-inflammatory mediators that enhance the onset of pathology associated with severe malaria also affect the development of efficacious humoral immune responses through inhibition of Tfh cell differentiation and consequently compromised GC reactions [137].

5.4. The importance of innate immune cells in iRBC control

Antibody-mediated control of parasites via blocking of invasion is not the only immune mechanism of iRBC control. Much data has been gathered on human *Plasmodium* infections clearly demonstrate functional activity of innate cells against iRBCs. The contribution of innate immune responses to *P. falciparum* in the Fulani tribe in Sub-Saharan

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Africa has been attributed to their greater resistance to infection compared with more susceptible sympatric ethnic groups [138] and innate responses to *P. falciparum* in CHMI studies has been associated with subsequent control of both iRBCs and clinical symptoms [139]. In *P. falciparum* blood stage infection, innate cells of the myeloid lineage [140-142], neutrophils[143, 144], natural killer (NK) [145-149] and γδ-T cells [150] have all been shown to neutralize iRBCs. Correlations of innate cell function with parasitemia or clinical symptoms has suggested the importance of these cells in control of iRBCs. However, mouse models have played a key role in deciphering how innate cells modulate adaptive responses and exert protection against the blood stages of *Plasmodium* in the context of the global response.

One example of this is dissecting the relative roles of cells from the myeloid lineage. Circulating monocytes are able to phagocytose *P. falciparum* [151, 152] and *P. vivax* [153] iRBCs in both an opsonic and non-opsonic [154] manner. The *P. chabaudi* AS model has been used to demonstrate a significant contribution of monocytes[155] over neutrophils[156, 157] in control of iRBCs. Although for neutrophils, this data appears to repeat in the *P. yoelii* XNL model of malaria[158], iRBCs are less controlled in *P. berghei* ANKA infected mice when neutrophils cannot make neutrophil extracellular traps (NETs)[159]. Thus, it seems that differences in the function of myeloid cells may exist amongst rodent parasite species that may be related to parasite life cycle preferences such as infection of reticulocytes (*P. yoelii* XNL) over normocytes (*P. chabaudi* AS) or differences in inflammatory potential from iRBCs of different species.

A second important contribution of mouse models of malaria in the understanding the contributions of NK cells and γδ-T cells. NK cells induce target cell death through natural cytotoxicity, antibody-dependent cellular cytotoxicity (ADCC), engagement of Fas Ligand (FasL) or tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) [148]. PLZF^{-}FcRγ^{-} NK cells have been shown to confer protection in *P. falciparum* infection via cytokine production and ADCC that subsequently inhibits *P. falciparum* growth in RBCs [147, 148]. Although able to directly recognize iRBCs to produce IFN-γ [160, 161], NK activation has been shown to depend on accessory cells of the myeloid lineage [162] as well as T cells [163]. In acute malaria infection, an increase in the γδ-T cell numbers correlate with protection from high parasitemia [150, 164]. Mechanistically, γδ-T cells produce IFN-γ, and granzyme B that inhibits parasite growth in contact-dependent manner [165]. Repeated exposure to malaria has been shown to lead to a decrease in circulating Vδ2^{+} γδ T cell numbers as well as a decrease in pro-inflammatory cytokine production concomitantly with upregulation in immunomodulatory molecules [150, 166, 167] and the expression of Fc receptor CD16 [168]. γδ-T cells displaying CD16^{+} Vδ2^{+} TCRs were able to respond to opsonized *P. falciparum* iRBCs through engagement of CD16 receptors [168]. CD16^{+} Vδ2^{+} T are shown to exhibit some of the features of NK cells and are thought to be more cytolytic than their CD16^{-} Vδ2^{+} T counterparts. Thus, it is hypothesized that this facilitates Vδ2^{+} T cell effector function with respect to ADCC cytotoxicity in the face of chronic and repeated exposure to malaria [168].

Despite overwhelming evidence of the ability of NK cells and γδ-T cells to kill iRBCs in *P. falciparum* infections, mouse models of malaria suggest a greater importance for γδ-T cells compared with NK cells in this respect. γδ-T cells produce IL-21 and IFN-γ that may enhance humoral immune response against blood stage infection [169] and can also express M-CSF that protect against *P. chabaudi* recurrence at the later stage of the infection [164]. Infection of humanized mice with *P. falciparum* confirmed *in vitro* observations of contact dependent NK cell in elimination of iRBCs [145]. Furthermore, using the non-lethal *P. yoelii* XNL mouse model of *Plasmodium* infection it has been shown in an *in vivo* setting that iRBCs induce activation of NK cells via synergistic effects of IL-18 and IL-12 to induce the expression of CD25 and IFN-γ production [170]. However, depletion studies in *P. chabaudi adami* 556KA-infected mice found a more prominent role for γδ T cells compared to NK cells in the control of iRBCs [171], a finding supported by a second study in *P. yoelii*-infected mice which found no significant role for NK cells in parasite control [172].

 doi:10.20944/preprints202207.0242.v1

Collectively, these findings may be due to differences in NK cells between mice and humans [173], or fundamental differences in the relative importance of immune effector mechanisms in iRBC control. However, this illustrates the power of undertaking *in vivo* experiments in a naïve setting where the contribution of different immune cells can be parsed out in a way that is not easy to undertake in culture studies or human infection studies, an exception being controlled human malaria infections[174, 175].

6. Immunopathogenesis of malaria and clinical immunity

While sterile immunity preventing *Plasmodium* infection does not commonly occur, people living in malaria endemic regions ultimately develop clinical immunity that protects against symptoms associated with *Plasmodium* blood-stage infection. Clinical immunity to malaria is characterized by reduced parasitemia and attenuated inflammatory responses [176, 177]. As such, people who develop clinical immunity to malaria often carry *Plasmodium* iRBCs asymptomatically with a low-grade pro-inflammatory immune response that limits blood stage parasite replication.

Based on human studies, clinical immunity has long been thought to center on the acquisition of strong immunomodulatory mechanisms that fine tune the inflammatory response necessary for control of the parasite burden while controlling the inflammation-induced pathology. Clinical symptoms of malaria are driven by type 1 inflammation characterized by IFN-γ, a cytokine known to be important in the development of immune effector mechanisms including high affinity class switched anti-parasite antibody [178, 179] and activation of phagocytes [180]. The main, but not only, sources of IFN-γ found in *P. falciparum* infection include Th1 cells, cytolytic T cells, NK cells and γδ T cells [181], in particular $V\delta2^{+}\gamma\delta$ T cells [150] where high production of pro-inflammatory cytokines by $V\delta2^{+}$-γδ had been shown to protect from infection by *P. falciparum* in children living in a high transmission setting. Analysis of T cell responses after controlled human malaria infection (CHMI) with *P. falciparum* demonstrated that higher blood stage parasitemia was associated with an expansion of T regulatory cells that express CD25 and FoxP3 after schizogony from the liver [175], suggesting down regulation of the inflammatory response supports parasite replication in the blood stage.

At the same time, systemic inflammation appears to correlate with the pathogenesis of malaria. Higher IFN-γ production from γδ T cells diminishes clinical immunity in response to subsequent infections with *P. falciparum* [150], presumably due to inflammation-induced pathogenesis. As such, decreased $V\delta2^{+}$ T cell numbers, and an upregulation of immunoregulatory makers such as Tim-3 and CD57 on γδ T cells is associated with clinical immunity to malaria [150, 166]. Along the same lines, the identification of CD4 T cells producing both IFN-γ and IL-10, termed Tr1 ($Foxp3^{-}$ regulatory T cells) cells, have been identified in *P. falciparum* infected individuals [182] and associated with uncomplicated disease in children. Indeed a longitudinal analysis of children from endemic region indicate a recent exposure to *Plasmodium* infection changes cytokines profile with upregulation in IL-10 only in children with persistent asymptomatic infection [176] suggestion a protection from clinical symptoms of malaria via this immunomodulatory cytokine. Furthermore, there are multiple studies suggesting a protective correlative role for transforming growth factor- β (TGF-β) against clinical symptoms of malaria [183-185]. Collectively this data supports a role for inflammation-suppressing cytokines in protecting against the pathogenesis of malaria.

Mouse models of non-lethal malaria have been used to confirm the importance of immunomodulatory cytokines such as TGF-β [186] and IL-10 [187, 188] against malaria pathogenesis. Nonetheless, IL-10 and TGF- β are both pleiotropic cytokines with several possible sources. Thus, the main contribution of studies in mouse models of *Plasmodium* infection has been the ability to dissect the roles of these pleiotropic cytokines throughout the course of the infection, as well as identify the most potent sources of these cytokines mediating clinical immunity to the blood stages of *Plasmodium* infection. For example, comparison of the lethal (*P. yoelii* 17XL) and non-lethal (*P. yoelii* 17XNL) strains of *P. yoelii* revealed that early production of TGF-β (within 24 hours) is associated with delayed IFN-

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γ and TNF-α production, leading to uncontrolled parasite growth and 100% fatality [189]. This was in contrast with a later (day 5 post-infection) production of TGF-β in the same study which was associated with reduced parasitemia and resolution of the infection. In a similar vein, the timing of IL-10 during the progression of the malarial diseases seems to be crucial in control of severe immunopathology [189, 190].

With regards to IL-10, the absence of which turns a non-lethal *P. chabaudi* AS infection into a lethal one [187], mouse models have been used to determine that this cytokine is essential in the control of pathogenic TNF-α production [187, 188]. Mouse models have challenged the notion that these immunoregulatory cytokines were produced by classical CD4+ CD25+ FoxP3+ T regulatory (T reg) cells. Early studies comparing lethal *P. yoelii* 17XL and nonlethal *P. yoelii* 17NL infections demonstrated a similar expansion and activation of Treg following infection with these two strains, indicating that the early activation of Treg does not contribute to the virulence [191]. Indeed, studies of TGF-β induction by *P. yoelii* indicated that the main producers of TGF-β were in fact $CD8^+$ $CD25^+$ T regulatory cells. On the other hand, the main source of IL-10 has been found in both the *P. chabaudi* [192] and *P. yoelii* [191] models to come not from classical T regulatory cells, but rather FoxP3- negative T cells that have been shown to simultaneously-produce IFN-γ [192]. The presence of IL-10/IFN-γ Tr1 cells has been shown in human infection [193] but it is in mouse models that the production of IL-10 and IFN-γ in Tr1 cells has been shown to be dependent on IL-27 signaling [192, 194]. IL-10 production by Tr1 cells ($CD4^+CD25^-$ $Foxp3^-CD127^-$) was able to down-regulate pro-inflammatory responses which would otherwise been able to control low infection with lethal *P. yoelii* 17XL infection [191]. It has been subsequently shown that the immune regulatory role of IL-10-producing Tr1 differs between primary or secondary infection in blood stage *Plasmodium* infection. The use of double IFN-γ-YFP^+ and IL-10-GFP^+ reporter mice have indicated that following resolution of primary infection, the stability and potential of $CD4^+IFNγ^+IL\text{-}10^+$ T cells to become memory is limited [195], in part because they exhibit exhaustion phenotype and are generally unresponsive at the early stage of secondary infection.

Systemic inflammation is correlated with malaria pathogenesis. This is because systemic inflammatory cytokines are indicative of vascular inflammation which mediates organ-specific pathologies malaria. Caused by sequestration of iRBCs via vascular adhesion [196] and trapping of iRBCs in the capillaries due to reduced deformability [197-199], organ dysfunction can result in severe cases. With the advent of luciferase expressing constructs, the rodent *Plasmodium* parasites have been shown to sequester in different organs in mice [200-203]. Given the relative inaccessibility of human organs from patients experiencing severe malaria syndromes, the rodent models of *Plasmodium* infections have been instrumental in dissecting immunopathological mechanisms associated with localized inflammation from sequestered and accumulated iRBCs [203-205]. Models of particular malaria-associated syndromes can be achieved using different combinations of rodent parasite species and mouse backgrounds (**Table 3**). Here, we focus on how mouse models of blood stage malaria have contributed to our understanding of the immunological underpinnings of three of the most well-studied sequelae of malaria: severe malarial anemia (SMA), cerebral malaria (CM) and acute respiratory distress syndrome (ARDS).

6.1. Mechanisms of inflammation-induced SMA

SMA in children is defined as a hemoglobin value <5 g/dL and detectable parasitemia in the blood stream [206]. Although *Plasmodium* replication in RBCs results in physical destruction of the RBC, SMA is more likely caused by mechanisms that result in hemolysis [207] and clearance of both uninfected and iRBCs via erythrophagocytosis [208] in combination with disrupted erythropoiesis in the bone marrow [209]. The relative contributions and mechanisms underlying these different contributors to a reduction in circulating RBCs is difficult to assess in humans without splenic or bone marrow biopsies. Sequestration / accumulation of iRBCs in the inflamed bone marrow has been shown [210]. How-

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ever, mouse models of SMA, principally the non-lethal *P. chabaudi* model, have been instrumental in demonstrating the underlying mechanisms of anemia and in dissecting the relative contributions of each.

Early work in using *P. chabaudi* as a model for SMA established that dyserythropoiesis in malaria may result from stalling of late erythroid progenitor cells [211] and be related to bone marrow inflammation, in particular the pro-inflammatory cytokines IL-12 [212] and macrophage migration inhibitory factor (MIF) [213]. A role for type 2 cytokines, specifically IL-4, has also been shown to suppress late erythroid progenitor cells [214]. Inflammation is likely derived from iRBCs that accumulate in the bone marrow, but early studies suggested that "malaria toxins", free GPI anchors that are released during iRBC schizogeny [215], can directly lead to dyserythropoiesis [216, 217]. Hemozoin has also been shown to induce anemia [218], demonstrating a contribution from parasite products in the suppression of erythrocyte production. Nonetheless, the density of circulating iRBCs is not necessarily related to level of anemia in the *P. chabaudi* model [219] suggesting that direct parasite destruction of RBCs during replication and release of inflammatory products during schizogony plays a more minor role in the severity of malarial anemia. However, given the insoluble and persistent nature of hemozoin, the contribution of hemozoin may be cumulative over time during chronic infection.

Whilst existing data using rodent models of *Plasmodium* infection point to a direct suppression in the development of late erythroid progenitor cells via inflammatory cytokine induction, there may be an indirect effect via cytokine modulation of erythropoietin produced by the kidney [220]. Other studies have investigated whether defects in iron handling also contributes to suppression of erythropoiesis [221] and how this may be reversed [222]. Other than production of new RBCs during the process of erythropoiesis, removal of both infected and uninfected circulating RBC has been shown to occur in the liver via erythrophagocytosis in rodent infections [223]. Moving forward, mouse models of blood stage *Plasmodium* infection will be instrumental in determining how iRBCs interact in the bone marrow niche [224], and the mechanisms by which extramedullary erythropoiesis are established in an attempt to remedy diminished circulating RBCs, particularly in the red pulp of the spleen [225, 226].

6.2. T cell-mediated breakdown of the blood brain barrier in cerebral malaria

Pediatric cerebral malaria (CM) is almost always fatal when not treated with antimalarials, and still has mortality rates between 15% and 20% with treatment [227]. The initiation of CM is thought to occur as a result of sequestration and adherence of iRBCs to the brain vasculature leading to disruption of the blood brain barrier (BBB), a complex of cells and extracellular structures that regulates the exchange of molecules between the blood and the central nervous system. BBB disruption occurs upon activation of brain microvascular endothelial cells. Although markers of vascular activation can be measured in the bloodstream of individuals with CM [228], the mechanism by which the BBB breaks down is poorly understood, in part due to the paucity of brain tissue availability from victims of CM and other control groups for comparison. As such rodent models of CM are essential to enable cellular mechanisms of BBB breakdown in CM to be elucidated and rationally targeted therapeutically.

Infection of C57Bl/6J mice with *P. berghei* ANKA recapitulates many of the features that characterize human CM (HCM) (**Table 4**) and is a commonly used model described as experimental cerebral malaria (ECM) [229]. Whilst other models of ECM exist, the *P. berghei* ANKA model does not rely on extremely high parasitemia to cause disease. Infected mice usually die between 6 and 10 days after infection [230] with accumulation of iRBCs to the brain microvasculature [231] and the activation of brain endothelial cells [232, 233]. Human studies suggest that both host and parasite factors mediate the development of CM in *P. falciparum*-infected children. As such there is some debate on the utility of this rodent model of CM, particularly since there are some differences in the expression of parasite adhesion molecules such as CD36 on human brain microvascular endothelial cells [234, 235] compared with mouse [236]. Furthermore *P. berghei* ANKA lacks *Plasmodium*

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falciparum erythrocyte membrane protein-1 (PfEMP-1), a ligand of both intercellular adhesion molecule-1 (ICAM-1) and endothelial protein C receptor (EPCR) on brain endothelial cells, and this interaction is thought to facilitate sequestration [237]. *P. berghei* ANKA iRBC accumulation in organs relies on the expression of the schizont membrane-associated cytoadherence protein (SMAC) on the surface of *P. berghei* ANKA iRBCs and CD36, a host molecule that is not highly expressed on brain endothelial cells [236]. Nonetheless, there is ample microscopic evidence of sequestered iRBCs on the endothelial lining, particularly using 2-photon techniques [238-240] and experiments with luciferase-expressing *P. berghei* ANKA strain which clearly show focused accumulation in the brain, particularly in the brain stem and olfactory bulb [241-246].

Inflammation related to sequestered iRBCs is thought to be a central facet of the pathogenesis of CM, and is necessary for the pathogenesis of ECM. Neuroinflammation often involves the production of TNF-α but ablation of TNF-α using Etanercept has been shown in pediatric CM did not reduce the mortality rate of CM [247]. Data using the ECM model of CM concurs with these findings whereby infection of TNF-α deficient mice still die from BBB breakdown in ECM in the same time frame as intact animals [248]. Indeed, ECM has been critical in demonstrating that importance of lymphotoxin-α (LT-α), rather than TNF-α in mediating breakdown of the BBB[248, 249].

In addition to TNF-α and LT-α, interferons are a key facet of the neuroinflammatory response to iRBCs. *Plasmodium* parasites are known to induce type 1 IFNs (IFN-I) which, depending on context, have the capacity to both suppress and activate innate and adaptive immune cells, promote pro-inflammatory cytokine production and enhance parasite clearance. All IFN-I subtypes signal through heterodimeric IFN-I receptor (IFNAR) functioning in both an autocrine and paracrine manner. The binding of IFN-I to IFNAR induces a signal cascade that initiates the transcription of interferon stimulated genes (ISGs). Host genetic variation can lead to differences in gene regulatory regions of the IFNAR1 subunit of IFNAR. The development of cerebral malaria in children has previously been associated with a variant of IFNAR1 associated with a higher expression of IFNAR1[250-253]. This suggests that Type 1 interferon signaling to be a pathogenic event [250] and is a finding supported by studies in ECM[254, 255].

Similarly, there have been associations with polymorphisms in the IFN-γ receptor [256] and lower levels of plasma IFN-γ [257] with development of CM suggesting that IFN-γ is protective. This is in agreement with polymorphisms in the IFN-γ gene promoter which are associated with increased transcription of IFN-γ and protection from CM [257]. The ECM model of CM relays a different story: IFN-γ has been shown to be necessary for death to occur in ECM[230, 258], in particular that derived from endothelial cells [259] to induce trafficking of pathogenic T cells to the brain [259, 260] and cross-presentation of merozoite-derived epitopes on major histocompatibility complex (MHC)-I [263] for recognition by infiltrating parasite-reactive CD8 T cells and BBB disruption. In ECM, IFN-γ leads to upregulation of adhesion molecules on brain microvascular endothelial cells enhancing the adhesive properties of *P. berghei* ANKA iRBCs [261]. The reason for the apparent difference in the role of IFN-γ in BBB disruption is unknown, but may be related to the differences exerted on parasite control mechanisms initiated by IFN-γ.

One of the significant breakthroughs in our understanding of the immunological underpinning of CM from the ECM model was the demonstration that CXCR3 [262] and CCR5 [263]-dependent CD8 T cell infiltration into the brain is necessary for disruption of the BBB[264]. In mice IFN-γ, including that secreted by NK cells [262], induces production of CXCR3- and CCR5-responsive chemokines in the neurovascular unit thus facilitating recruitment of pathogenic CD8 T cells and other immune cells to the CNS [261]. Whilst initial studies on human autopsy samples indicated a cellular infiltrate that was largely devoid of CD8 T cells [265, 266], indicating a potential fundamental difference in the etiology of BBB breakdown between human CM and mouse ECM, more in depth studies from pediatric CM victims in Malawi have provided evidence that CD8 T cells do infiltrate the brain [266, 267], and this increase in CD8 T cells is correlated to density of iRBC sequestration [267].

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The mechanisms by which CD8 T cells mediate breakdown of the BBB via effects in the endothelium are still poorly understood but the ECM model has been critical in elucidating some of the parameters by which this occurs. It has been shown in ECM that lytic molecules perforin and granzyme B [268, 269] are essential components in this process. Evidence of apoptosis in brain endothelial cells can be observed in autopsy samples of pediatric CM cases [270, 271] as may be expected via the lytic action of incoming primed CD8 T cell recognition of cross-presenting brain endothelial cells. However, although apoptosis can also be seen in brain sections of *P. berghei* ANKA as well as via 2-photon microscopy [240], it is minimal. Furthermore, infected mice do not have a significantly increased cleaved caspase compared with naïve mice [269]. Whilst other mechanisms of brain microvascular endothelial cells such as necrosis, ferroptosis and pyroptosis have not been extensively investigated, this data does suggest that perforin and granzyme are acting through non-cell death-inducing pathway that disrupts the BBB. In this regard findings in the ECM model are similar to Theiler's murine encephalomyelitis in mice, another model of CD8 T cell dependent disruption of the BBB, where perforin but not FasL is required to mediate vascular leakage and death[272].

These findings may occur via downregulation of tight-junction and adherens-junction proteins which normally enable endothelial cells to dynamically control the passage of solutes and other molecules across the BBB [273]. Disassembly and downregulation of junction proteins on brain microvascular endothelial cells has been observed in both pediatric CM autopsy samples [274] and in ECM [239, 242]. In ECM CD8 T cell-degranulation may induce downregulation of junction proteins via release of perforin [269, 275] which could augment expression of vascular activation-induced molecules such as the tyrosine kinase receptor EphA2 which has been shown to mediate the loss of tight junction on both human and mouse brain microvascular endothelial cells [242]. In the Theiler's murine encephalomyelitis model, leakage and downregulation of tight junction proteins occurs before an increase in apoptosis markers [275]. Thus, the timing of BBB breakdown in ECM and CM relative to initial *Plasmodium* infection may be important in the interpretation of ECM studies as applied to CM.

The rodent model of ECM does not perfectly recapitulate all aspects of pediatric CM but is a crucial tool in unravelling the most important mechanisms that lead to fatal pathogenesis. Endothelial cells are only one player in the neurovascular unit that also includes mural cells (pericytes), astrocytes and microglia[276]. It is hard to discount the potential role of these accessory cells in disassembly of inter-endothelial junction proteins in CM given that astrocytes and microglia are both activated in ECM [277-279] and the known role they play in regulation of BBB integrity. Indeed, molecules secreted from these cells upon activation can be measured in the cerebral spinal fluid of children with CM [280] and pediatric autopsy samples demonstrate activation of microglia and astrocytes in fatal CM [281]. The mechanisms by which these accessory cells become activated, and the mechanisms which control endothelial cell junction protein modulation in CM, remain to be discovered. Given the difficulty in studying these cells, it is likely that the ECM model will be instrumental in disentangling the cellular and molecular basis of endothelial cell junction disassembly. In addition, the ECM model is likely to be important in the identification of possible avenues for therapeutic targeting, such as possible IL33 administration to induce anti-inflammatory cytokine expression and the expansion of anti-inflammatory macrophage and regulatory T cell populations [282] or IL-15 complex treatment to protect BBB leak by expanding a population of IL-10 producing NK cells [283].

6.3. Mechanisms of malaria-associated acute lung injury (MA-ALI) in malaria-associated acute respiratory distress syndrome (MA-ARDS)

Pulmonary complications arising from *Plasmodium* infection can occur with all species but in particular *falciparum*, *vivax* and *knowlsei.* This is a syndrome of severe malaria resulting in up to 40% mortality even with treatment [284]. Though more common in adults infected with *vivax* malaria, in children, MA-ARDS can often present along with

cerebral complications [285]. MA-ARDS is characterized by increased permeability of pulmonary capillary endothelial cells and alveolar epithelial cells, with pulmonary edema (PE), hypoxia [284] and in some cases fibrosis [286-288]. Most data related to the pathogenesis of MA-ARDS and MA-ALI comes from post-mortem studies of lung tissue from adult fatalities of *Plasmodium* infection showing apoptosis of alveolar cells [289]. However, the immunological mechanisms underlying MA-ARDS and MA-ALI in *Plasmodium* patients is relatively understudied and poorly understood.

Pulmonary vascular activation is thought to arise in response to the sequestration of iRBCs resulting in inflammation in the lung microvasculature [289, 290] characterized by expression of TNF-α [285], von Willebrand factor (VWF) and angiopoietin-2 (ANG2) [291]. However, sequestration of iRBCs is likely to occur via a different suite of adhesion molecules upregulated on the pulmonary vasculature compared with the BBB. For example, EPCR expression which is a key molecule mediating adhesion of iRBCs on brain microvascular endothelial cells [292] has been found to be significantly down-regulated on pulmonary vasculature endothelial cells in those who have succumbed to MA-ARDS [285] compared with those dying of other malaria-related syndromes.

Although some studies employ the *P. berghei* ANKA strain used to study ECM by virtue of the fact this strain sequesters in the lung [293, 294] and the ultrastructure of the infected lung looks similar to postmortem samples from victims of MA-ARDS [295], MA-ARDS and MA-ALI are more commonly studied using infections with the NK65 strain of *P. berghei* [204]. The advantages of the *P. berghei* NK65 models are that they do not appear to result in neurological manifestations of infection and have higher ARDS clinical scores, than *P. berghei* ANKA infection [204]. Parasites accumulate in the lung vasculature, with an increase in VWF expression as also found in human *Plasmodium* infections. There are two primary strains of *P. berghei* NK65 used for studies in the pathogenesis of MA-ARDS and MA-ALI: the Edinburgh strain (*P. berghei* NK65E) and the New York strain (*P. berghei* NK65NY). Possibly due to slower growth of iRBCs due to the predilection of *P. berghei* NK65NY to infect reticulocytes, the *P. berghei* NK65NY does not recapitulate MA-ARDS despite sequestering in the lung tissue. However the Edinburgh Strain results in rapid death of C57BL/6 mice from days 6-10 post-infection and recapitulates features of MA-ARDS seen in humans such as extensive neutrophil infiltration, an increase in pulmonary VWF expression[296] and an increase in protein concentration in lungs [204]. *P. berghei*-NK65E has been used to demonstrate the critical role of VWF in alveolar leakage[296].

In mice, MA-ARDS and ALI appear to have similarities regarding the underlying pathogenesis of ECM. Studies on MA-ARDS / ALI using *P. berghei* ANKA infections have demonstrated that IFN-γ, upregulation of chemokines[297] and functioning CD8 T cells are all necessary for lung sequestration of iRBCs and pulmonary edema[298]. In addition, pulmonary vascular leak and BBB breakdown are dependent on the presence of platelets[299]. Unlike the BBB where molecules such as ICAM-1 and EPCR have been shown to play a key role, sequestration in the lung appears to be more dependent on the scavenger receptor CD36[236]. There also appears to be differences in the importance of myeloid cells with infiltration of neutrophils[300] and monocytes[301] to the lung which, at least for monocytes, appear to play a key role in controlling iRBC numbers.

The suite of *P. berghei* strains available to study this syndrome of malaria will be of some help in the interpretation of pulmonary autopsy samples from patients who have died of MA-ARDS and MA-ALI, a necessary endeavor given the lack of other tractable options to study this in *Plasmodium*-infected humans.

7. Conclusion

In summary this review has highlighted the utility of the rodent models of *Plasmodium* infection with regards to understanding the immunology of blood stage malaria. Several models exist although none completely recapitulate all aspects of malaria. However, this reflects the heterogeneity of this disease. Choosing the correct model to investigate specific aspects of this disease is essential in order to be able to extrapolate to human *Plasmodium* infections. There is still a plethora of key outstanding questions that remain

in the field of blood stage immunology of malaria. With the advent of genetically modified rodent *Plasmodium* strains and an ever-increasing catalog of genetically modified mouse strains available, the interpretation of how immune responses shape parasite dynamics and immunopathogenesis of infection will allow discoveries to be made with increasing precision. In turn this will be instrumental in the rational design of novel immunologically-based therapeutic strategies that are badly needed in the fight against this disease.

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