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Malaria-induced bacteremia as a consequence of multiple parasite survival strategies

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ABSTRACT

Globally, malaria continues to be an enormous public health burden, with concomitant parasite-induced damage to the gastrointestinal (GI) barrier resulting in bacteremia-associated morbidity and mortality in both adults and children. Infected red blood cells sequester in and can occlude the GI microvasculature, ultimately leading to disruption of the tight and adherens junctions that would normally serve as a physical barrier to translocating enteric bacteria. Mast cell (MC) activation and translocation to the GI during malaria intensifies damage to the physical barrier and weakens the immunological barrier through the release of enzymes and factors that alter the host response to escaped enteric bacteria. In this context, activated MCs release Th2 cytokines, promoting a balanced Th1/Th2 response that increases local and systemic allergic inflammation while protecting the host from overwhelming Th1-mediated immunopathology. Beyond the mammalian host, recent studies in both the lab and field have revealed an association between a Th2-skewed host response and success of parasite transmission to mosquitoes, biology that is evocative of parasite manipulation of the mammalian host. Collectively, these observations suggest that malaria-induced bacteremia may be, in part, an unintended consequence of a Th2-shifted host response that promotes parasite survival and transmission. Future directions of this work include defining the factors and mechanisms that precede the development of bacteremia, which will enable the development of biomarkers to simplify diagnostics, the identification of therapeutic targets to improve patient outcomes and better understanding of the consequences of clinical interventions to transmission blocking strategies.

1. Introduction

Malaria remains an enormous health burden throughout much of the world. The World Health Organization (WHO) estimated 229 million cases of malaria and 409,000 deaths worldwide in 2019 (WHO, 2020). The vast majority of cases occur in sub-Saharan Africa (94%) (WHO, 2020) and are caused by infection with the protozoan parasite *Plasmodium falciparum*. Approximately 6% of African children with severe falciparum malaria (SFM) develop invasive bloodstream infections or bacteremia (reviewed in Church and Maitland, 2014); bacteremia has also been associated with *Plasmodium vivax* malaria (Bhattacharya et al., 2013). Concurrent bacteremia in children with falciparum malaria is associated with worsening anemia (Berkley et al., 1999; Graham et al., 2000; Walsh et al., 2000), respiratory distress (Davenport et al., 2016; Were et al., 2011; Kortz et al., 2019) and a case fatality rate of 24.1% relative to 10.2% in malaria alone (reviewed in Church and Maitland, 2014). In an area in Kenya with 29% parasitemia prevalence, 62% of bacteremia cases were attributable to malaria (Scott et al., 2011). The authors concluded, “Malaria infection strongly predisposes to bacteremia and can account for more than half of all cases of bacteremia in malaria-endemic areas.”

Malaria with concurrent bacteremia in children is diagnostically challenging, as bacteremia shares many clinical symptoms with malaria (fever, vomiting, lethargy) (Berkley et al., 1999; Evans et al., 2004; reviewed in Pai et al., 2015) and blood cultures, the gold standard for diagnosing bacteremia, are time intensive, difficult to perform in resource-limited settings (Berkley et al., 1999) and insensitive for detecting bacterial sepsis with malaria (Marik, 2014; Njim et al., 2018). Hogan et al. (2018) reported a direct correlation between bacteremia and parasite burden in a pediatric population in Ghana, while Davenport et al. (2016) showed an inverse correlation in children in Kenya. Krumkamp et al. (2016) noted that the outcome of a study can be reversed depending on the control group selected and offered this as

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a possible explanation for these seemingly contradictory observations. More troubling still, a high proportion of the bacterial isolates from bacteremic malaria patients are multi-antibiotic resistant (reviewed in Deen et al., 2012; Nadjm et al., 2010; Popoola et al., 2019). Although Kortz et al. (2019) found that elevated circulating levels of the cytokine interleukin (IL)-1β were predictive of sepsis with or without malaria, there is no fast, reliable way to identify bacteremic children clinically or with basic lab tests. Accordingly, the WHO recommends that all children hospitalized with SFM in areas of intermediate and high transmission receive immediate broad-spectrum antibiotics with anti-malarial therapy (WHO, 2014).

Bacteremia is also found in adults with malaria, and its clinical importance is becoming better appreciated. Studies from Myanmar in 2016 and 2018 reported 13-15% incidence of bacteremia in adults presenting with falciparum malaria at tertiary care facilities (Nyein et al., 2016; Aung et al., 2018). Adults with bacteremia and malaria together were sicker than those with malaria alone, having higher respiratory coma acidosis malaria scores and greater incidence of acute kidney injury (Nyein et al., 2016). Aung et al. (2018) noted that two of the four adult patients with malaria and bacteremia died, while only one malaria patient without bacteremia (out of 16) died. In 2020, Phu et al. reported that nine of 845 adult patients diagnosed with SFM at a Vietnamese referral center between 1991-2003 were bacteremic and four of these nine patients (44%) died, while mortality among non-bacteremic adult malaria patients was 13% (108 of 836 patients). Further, among the nine bacteremic patients with SFM, three of four with >20% parasitemia died (75%), while 13 of 72 non-bacteremic malaria patients with >20% parasitemia died (18%). The authors surmised that disease severity in patients with bacteremia and >20% parasitemia resulted from parasite-mediated damage to the intestine and to immune function (Phu et al., 2020). Based on these observations, bacteremia can occur across a range of clinical malaria presentations and ages, and is a significant contributor to morbidity and mortality. This review will focus on the factors that predispose individuals with malaria to intestinal barrier damage, increased intestinal permeability, and bacterial translocation across the intestinal barrier during the course of parasite infection.

2. Damage to the physical barrier of the intestine during malaria

Nausea, vomiting, diarrhea and abdominal pain are common in children presenting with acute falciparum malaria (Sowunmi et al., 2000; Goldman-Yassen et al., 2016; Lo Vecchio et al., 2020; reviewed in Sey et al., 2020) and, in countries no longer endemic for malaria such as the United States, presentation of malaria with gastrointestinal (GI) symptoms increases the risk of misdiagnosis by clinicians (Goldman-Yassen et al., 2016). Malaria can result in gross structural changes to the intestine (reviewed in Coban et al., 2018), perhaps not surprisingly given its large blood flow (~20-25% of total cardiac output) (Hasibeder, 2010) and the potential impact of infected red blood cells (iRBCs) on the GI tract. Studies in humans have noted edema and cellular infiltration of the lamina propria, shortening and widening of the villi, and disruption of blood flow in the jejunum and duodenum (Olsson and Johnston, 1969, reviewed in Phillips and Warrell, 1986). Similar findings have been reported in mice. Shimada et al. (2019) reported that *Plasmodium berghei* ANKA cerebral malaria was associated with shortening of the intestine, while Taniguchi et al. (2015) reported detachment of intestinal epithelial cells, shortening of the villi, and thickening of mucus for the same infection. In the *Plasmodium yoelii nigeriensis* model, Mooney et al. (2015) described infection-association mononuclear infiltrates, edema, loss of goblet cells and proliferation of undifferentiated enterocytes in the mouse large intestine.

Malaria parasite infection can cause tissue damage and dysfunction in a variety of ways. Parasite replication and autoantibody-mediated lysis destroy RBCs and hepatocytes. Widespread destruction of RBCs increases heme release, which contributes to oxidative damage (reviewed in Coban et al., 2018). Parasite accumulation in bone marrow resulting in bone loss, and accumulation of products in perivascular spaces in the brain also occur (reviewed in Coban et al., 2018). Furthermore, iRBCs become “sticky” or cytoadherent, which can result in aggregation with non-infected RBCs (rosetting), autoagglutination of iRBCs through platelet bridges and adherence to host endothelial cells (reviewed in Lee et al., 2019; **Fig. 1**). While all species of malaria parasites can cause rosetting (Lowe et al., 1998), cytoadherence or sequestration of iRBCs to the endothelium of capillaries and venules during human infection is known primarily from falciparum malaria (David et al., 1983, reviewed in Lee et al., 2019), though this has also been observed in mice infected with *P. y. nigeriensis* (Mooney et al., 2015). It has been suggested that cytoadherence protects parasites from splenic clearance (reviewed in Lee et al., 2019), resulting in occlusion of microvessels, tissue hypoxia and cellular damage. Cytoadherence requires a parasite-derived ligand, *P. falciparum* erythrocyte membrane protein 1 (PfEMP1), to be displayed on the surface of the iRBCs and interaction of this ligand with host adhesion molecules ICAM-1, CD36 and CSA (reviewed in Smith et al., 2001). Cytoadherence benefits parasite survival by minimizing clearance through the spleen (reviewed in Lee et al., 2019), but the host eventually mounts an effective antibody response to this highly antigenic protein (Ghumra et al., 2011; Kanoi et al., 2018).

Sequestration of iRBCs has been associated with intestinal capillary blockage (Seydel et al., 2006) in both acute and chronic falciparum malaria (Molyneux et al. 1989; Wilairatana et al., 1997; Sowunmi et al., 2000). Notably, levels of parasite-derived lactate dehydrogenase (pLDH) were higher in the intestines of patients who died from cerebral malaria than in patients with cerebral malaria who died from a non-malaria cause (Seydel et al., 2006). Pediatric patients who died of cerebral malaria also exhibited greater parasite sequestration in the stomach, jejunum, ileum and colon compared to patients who died of severe malarial anemia (SMA) or cerebral malaria (CM) without evidence of parasite sequestration in the brain (Milner et al., 2015). A likely secondary effect of intense parasite sequestration in the GI in SFM is poor enteral absorption of L-glutamine. The intestine accounts for the majority of L-glutamine conversion to L-citrulline (van de Poll et al., 2007), which is subsequently transported to the kidneys for conversion to L-arginine. Although major outcomes of low plasma L-glutamine are hypoargininemia and low nitric oxide (NO) bioavailability, which underlie damage to the microvasculature in SFM (Rubach et al., 2019), low L-glutamine levels in SFM (Planche et al., 2002, Cowan et al., 1999) is also likely associated with intestinal barrier dysfunction (Rubach et al., 2019). Specifically, L-glutamine is necessary for enterocyte development and proliferation, synthesis of intestinal epithelial cell antioxidants and immune proteins and is positively associated with the synthesis and distribution of proteins that form the tight junctions (TJs) and adherens junctions (AJs) of the intestinal epithelium (reviewed in Wang et al., 2015).

Intestinal epithelial TJs and AJs provide a physical defense against bacterial translocation. TJs are comprised of a variety of claudins, zonula occludens (ZO)-1 and occludin (reviewed in Yu et al., 2012), while AJs are comprised of E-cadherin, α-catenin and β-catenin which interact with hemidesmosomes and extracellular matrix/basement membrane proteins (reviewed in Blikslager et al., 2007) and Bischoff et al., 2014). Collectively, TJs and AJs regulate selective paracellular permeability and transcellular transport functions of the intestinal epithelial barrier (Tsukita et al., 2009), with defects in the architecture of these protein complexes associated with nutrient malabsorption and leakiness to ions, macromolecules and enteric microbes (reviewed in Günzel and Yu, 2013, Balzan et al., 2007, and Nagpal and Yadav, 2017). Intestinal barrier dysfunction was first reported in a study of falciparum malaria (< 0.1% parasitemia) that excluded moderately and severely ill patients (Olsson and Johnston, 1969); it was subsequently noted in patients with acute symptoms (<5% parasitemia) (Karney and Tong, 1972), and later described using the lactulose:mannitol (LM) assay in patients with both uncomplicated and SFM (>5% parasitemia or serum bilirubin >50μM), with the highest LM ratios (greatest permeability) associated with SFM (Wilairatana et al., 1997). Although studies

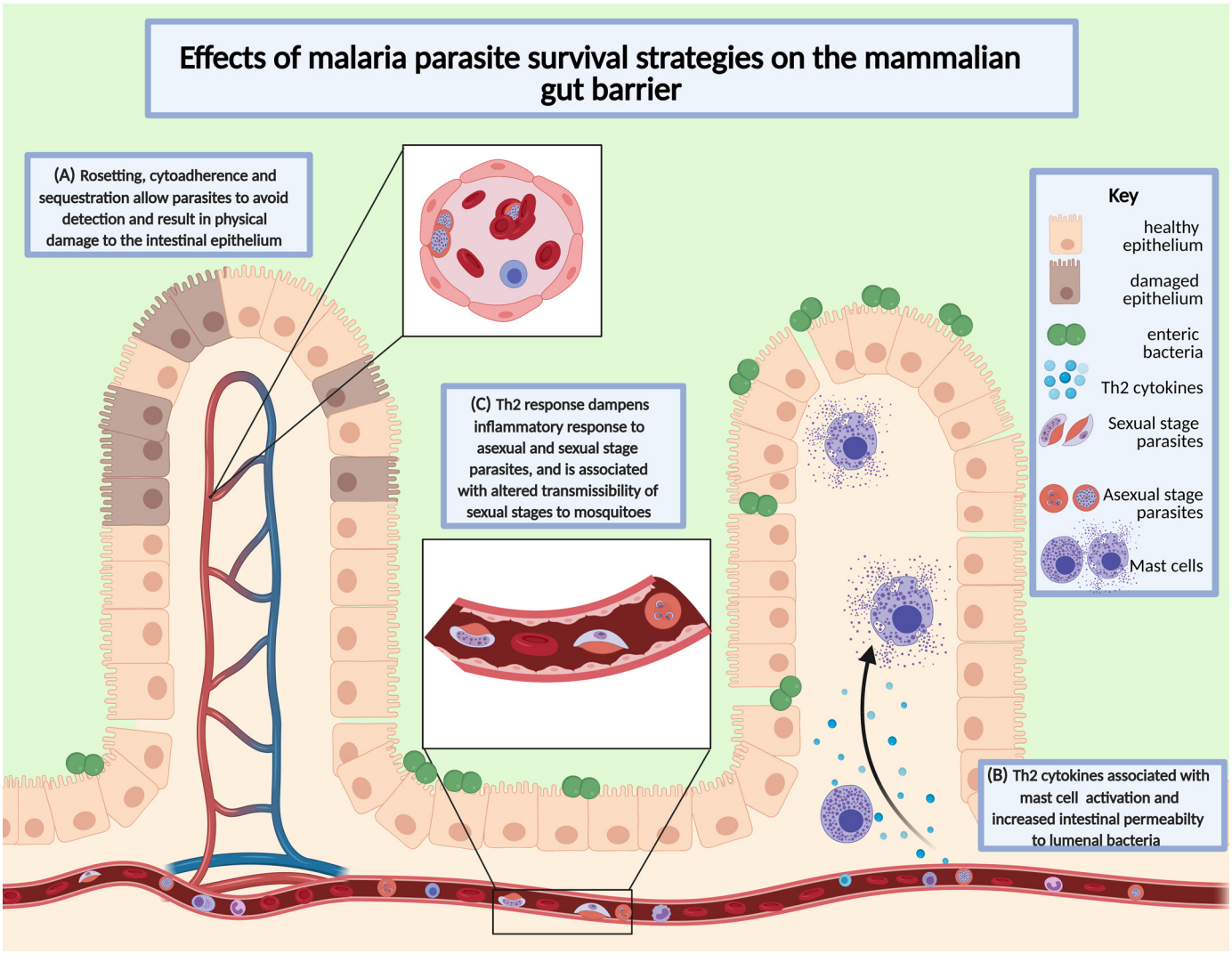

Fig. 1. Changes to the mammalian gastrointestinal (GI) microenvironment during malaria. **(A)** Malaria parasite-infected red blood cells (RBCs) are both stiffened and sticky and can adhere to uninfected RBCs and to the GI vascular endothelium, resulting in micro-occlusions that prevent parasite clearance but also lead to hypoxia and damage to the GI epithelium. This damage is consistent with a weakened physical barrier or "leaky gut" that is associated with the translocation of enteric bacteria into host tissue and blood. **(B)** While both Th1 and Th2 cytokines are produced during malaria, a skewing toward Th2 cytokines, including IL-3,-4,-5,-9 -10 and -13, can promote intestinal mastocytosis and local mast cell activation in the GI. These responses can dampen systemic Th1-associated anti-parasite immunity and associated immunopathology, further degrade the GI physical barrier and weaken the local immunological barrier to translocating enteric bacteria. **(C)** Beyond the mammalian host, elevated synthesis of Th2 cytokines has been associated with altered transmission of sexual stage parasites to mosquitoes, biology that is evocative of parasite manipulation of the mammalian host. Collectively, these observations suggest that malaria-induced bacteremia may be an unintended consequence of a Th2-shifted host response that promotes parasite survival and transmission.

in humans have associated increased intestinal permeability with varying clinical presentations of malaria, insights into *temporal* changes in intestinal permeability over the course of parasite infection have necessarily come from animal models.

Chau et al. (2013) reported that *P. y. nigeriensis* infection was associated with increased LM ratios at 2-4 days post-infection in CBA/J mice that persisted in some animals through 10 days (Chau et al., 2013). Prolonged co-infection with *Plasmodium yoelii yoelii* 17XNL and the enteric pathogen *Salmonella enterica* serotype Typhimurium (non-typhoidal *Salmonella* or NTS) was associated with disruption of ZO-1 and E-cadherin in the ileum as well as increased translocation of NTS in both CBA/J and C57BL/6J mice (Chau et al., 2013; Potts et al., 2016). Infection of C57BL/6J mice with *P. y. yoelii* 17XNL has also been associated with non-specific translocation of enteric bacteria into the blood (detected with eubacterial *16S* qPCR) by 4 days after infection at levels that were significantly higher than control at 6, 8, and 10 days post-infection (Cespedes et al. 2020). Other studies reported observations only at later timepoints of infection. For example, Denny et al. (2019) reported that infection of C57BL/6N mice with *P. y. yoelii* 17XNL was associated with increased intestinal permeability to fluorescein isothiocyanate (FITC)-dextran at 7 and 14 days after infection. Alamer et al. (2019) reported that C57BL/6J mice infected with *Plasmodium chabaudi chabaudi* (AS) exhibited increased intestinal permeability to bacterial lipopolysaccharide binding protein at day 6 post-infection and to FITC-dextran at day 8 post-infection. Taniguchi et al. (2015) reported increased intestinal permeability to FITC-dextran in C57BL/6 mice but not in BALB/c mice at 9 days following *P. berghei* ANKA infection. While patterns of reported intestinal permeability are somewhat dependent on parasite strains, mouse strains and the assays used, these models affirm that malaria-induced barrier dysfunction – as evidenced by translocation of macromolecules and enteric bacteria – is evident from detection of early circulating parasites to peak parasitemia.

3. Damage to the immunological barrier of the intestine during malaria

In addition to the physical barrier of the intestine, the immunological barrier of this tissue provides critical protection against disseminating enteric bacteria and is characterized by synthesis of inflammatory cytokines (some of which can also induce changes in TJ and AJ proteins) (Günzel & Yu, 2013), macrophage activation and neutrophil recruitment (Knoop et al., 2016, reviewed in Marchetti et al., 2013 and Wang et al., 2015). In humans, NTS colonization causes self-limiting gastroenteritis in otherwise healthy individuals, but in immunocompromised individuals NTS can escape the intestine and produce systemic infection. Malaria increases the risk for developing invasive NTS (Church et al., 2016), perhaps as a result of alterations to the immunological barrier of the intestine that modify the resident microbiota as observed in co-infected mice (Mooney et al., 2015). Malaria increases the risk of systemic infection with other bacterial pathogens as well. For example, Harding et al. (2020) showed that *P. y. yoelli* 17XNL infection in mice increased the risk of *Listeria monocytogenes* and *Streptococcus pneumoniae* bacteremia. In the absence of malaria, defenses against bacterial translocation are mediated by IL-23 and IL-6 induction of a T cell-dependent axis of IL-17 that promotes neutrophil recruitment together with tumor necrosis factor (TNF)-α, while induction of interferon (IFN)-γ drives macrophage activation and chemokine synthesis to sustain the synthesis of antimicrobial peptides and influx of neutrophils that eliminate bacteria that breach the epithelial barrier (reviewed in Valeri and Raffatellu, 2016). Malaria parasite infection in both humans and mice can dampen neutrophil recruitment and oxidative burst, however, via upregulation of heme oxygenase (HO)-1 and IL-10 (Ekregbesi et al. 2018; Cunnington et al., 2011, reviewed in Mooney et al., 2019). Both mouse and human blood-stage malaria parasites also suppress innate T cell synthesis of IFN-γ via direct activation of $CD4^+Foxp3^+CD25^+$ regulatory T cells, enabling parasite evasion of host immune detection and destruction (Kurup et al., 2017; Fu et al., 2020). Intriguingly, Lu et al. (2006) reported that in mice, suppression of host immunity by $CD4^+Foxp3^+CD25+$ regulatory T cells was dependent on mast cells (MCs), findings that generated substantial interest in the interactions between MCs and T cells and contributed to the evolving paradigm that MCs are critical participants in tuning host immunity (reviewed in Hershko and Rivera, 2010), including that of the intestinal mucosa (reviewed in Reber et al., 2015).

4. Role of mast cells (MCs) in intestinal permeability

MCs are major regulators of intestinal barrier integrity (reviewed in Bischoff and Krämer, 2007). In both humans and rodents, these c-kit receptor-positive, high affinity IgE receptor (FcεRI)-positive cells are released from the bone marrow and mature in tissues where they can persist for up to 40 days (Enerbäck and Löwhagen, 1979, reviewed in Ribatti, 2018). MCs are also concentrated in the skin and respiratory tract, which like the GI, are sites exposed to the external environment. While their roles in allergic reactions and anaphylaxis are perhaps the most well characterized (reviewed in Amin, 2012), human MCs are also sources of angiogenic vascular endothelial growth factor (VEGF) and IL-8 (Feoktistov et al., 2003), reflecting MC functions in wound healing and tissue remodeling (Trautmann et al., 2000). MCs express Toll-like receptors (TLRs) in both humans and mice (reviewed in Sandig and Bulfone-Paus, 2012) and in mice were found to release antimicrobial cathelicidin in response to certain groups of bacteria (Di Nardo et al., 2008). Studies in mice indicate that MCs generally play a more indirect role in bacterial infections, usually by recruiting other cells to the site of infection (Malaviya et al., 1996, reviewed in Piliponsky and Romani, 2018). IgE-mediated MC activation, however, has been associated with protection against skin infection in mice by *Staphylococcus aureus* (Starkl et al., 2020). Upon activation, MCs release preformed granules loaded with effector molecules, including histamine, serotonin, heparin, MC proteases (MCPTs) and cytokines, the proportions and composition of which are influenced by the nature of the stimulus and tissue context. The speed of effector release and placement at sites of pathogen entry highlight the importance of MCs in innate immune responses. In response to context-specific stimuli, MCs also shape the adaptive immune response with the synthesis and release of cytokines that polarize not only T-helper 2 (Th2)-type responses (IL-4, IL-5, IL-13), but also Th1 (IL-12, IFN-γ), Th17 (IL-6, transforming growth factor-β1), and Th22 responses (IL-6, TNF-α).

The roles of MCs as regulators of Th2 responses and the necessity of MCs for the resolution of GI helminth infections are well-studied in mice (Hepworth et al., 2012; Reitz et al., 2017; Shimokawa et al., 2017; 2019, reviewed in Vukman et al., 2016). Following infection, MCs are recruited to the intestinal villi where they express MCPTs, which function with histamine to increase intestinal permeability that is necessary for GI helminth expulsion and recovery from infection (McDermott et al., 2003). In mice, induced MCPT-1 cleaves the tight junction protein occludin-11 while MCPT-4, the likely functional homolog of human chymase, degrades BP180 of hemidesmosomes and activates matrix metalloprotease (MMP)-9 (Lin et al., 2011), which degrades proteins of the extracellular matrix and basement membrane, essential components of the epithelial barrier (reviewed in Yu et al., 2012 and Blikslager et al., 2007). MCs are also critical in maintaining intestinal barrier function under homeostatic conditions, as both MC-deficient $Kit^{W\text{-}sh/W\text{-}sh}$ [Wsh] and MCPT-4-/- mice were found to have reduced paracellular and transcellular permeability under basal conditions (Groschwitz et al., 2009, reviewed in Piliponsky and Romani, 2018). In this context, MCPT-4 was required for restoration of normal intestinal permeability in MC-deficient mice (Groschwitz et al., 2009, reviewed in Piliponsky and Romani, 2018).

5. MCs as mediators of intestinal permeability in malaria

While it is reasonably well accepted that GI helminth infections are regulated by MCs, direct evidence of involvement of these cells in GI pathology due to protozoan infections is more limited. In general, MCs have diverse effects on protozoan infections, with the potential for both protective and detrimental action (reviewed in Lu and Huang, 2017). The observations that follow along with work summarized above suggest that GI pathology in malaria derives, in part, from the activation of MCs.

High histamine levels reported in SFM (Enwonwu et al., 2000; Srichaikul et al., 1976) would be expected to increase endothelial activation (reviewed in Kunder et al., 2011) and synergize IL-3-enhanced cytoadherence of iRBCs (Ringwald et al., 1993) to increase tissue damage, including in the GI where iRBC sequestration in SFM is notable. Histamine can also reduce E-cadherin adhesion to decrease TER (Zabner et al., 2003) and induce actin reorganization to diminish barrier integrity (Trepat et al., 2005) in human cell lines and it can inhibit ZO-1 expression in human and bovine cell lines (Gardner et al., 1996; Takeuchi et al., 2001). In line with these findings, treatment with disodium cromoglycate to prevented degranulation of MCs decreased vascular leakage in mice infected with *P. berghei ANKA,* while treatment with a MC degranulator increased leakage (Huang et al., 2019). As MCs are the major sources of histamine, these observations have suggested that malaria is associated with recruitment of MCs to the intestine and their functional involvement in intestinal barrier disruption. Data from non-human primate and mouse models have supported these inferences. In particular, *Plasmodium fragile* infection of macaques was associated with MC recruitment to the ileal submucosa, crypts and villi at 14 days after infection, whereas stained ileal sections from uninfected macaques showed a complete absence of detectable MCs (Potts et al., 2016). Chau et al. (2013) reported that MCs were similarly recruited to the mouse ileum, in a pattern that reflected rising parasitemia, in *P. y. nigeriensis*-infected CBA/J mice. MC recruitment in this model was associated with rising histamine levels in the mouse ileum and with bacterial translocation that was reduced by L-arginine or L-citrulline supplementation, suggesting that malaria-associated L-arginine deficiency

promoted ileal mastocytosis (Chau et al., 2013). In humans, observations that low NO levels can result in MC activation (reviewed in Coleman, 2002), suggested that L-glutamine and L-arginine deficiencies in malaria could contribute to intestinal barrier dysfunction in multiple ways (Rubach et al., 2019; Planche et al., 2002; Cowan et al., 1999). In particular, *P. y. yoelii* 17XNL-infected MC-deficient WBB6F1/J mice exhibited reduced intestinal permeability and reduced NTS translocation to the blood, liver and spleen relative to co-infected wild type controls (Potts et al., 2016). In the same studies, antihistamine treatment of *P. y. yoelii* 17XNL-infected CBA/J mice protected against E-cadherin degradation and to a lesser extent, enteric bacterial translocation to the spleen, suggesting that histamine was necessary but not sufficient for MC degradation of the intestinal barrier during malaria (Potts et al., 2016). Collectively, these observations suggested that early and sustained malaria-induced mastocytosis contributes to intestinal barrier dysfunction, but the mechanism(s) whereby MCs mediate this damage remain to be elucidated.

In recent studies (Cespedes et al., 2020) affirmed ileal mastocytosis and MC activation in *P. y. yoelii* 17XNL-infected C57BL/6J mice along with associated increases in MC-activating cytokines, including stem cell factor (SCF), granulocyte-macrophage colony stimulating factor (GM-CSF), Regulated on Activation Normal T cell Expressed and Secreted (RANTES), IL-3, -4, -5, -6, -9, -10 and -13. These cytokines have been associated with broad effects on MC function and intestinal permeability (Fig. 1). Both IL-4 and IL-10 promote MC survival, development, and proliferation (reviewed in Paul, 1991, Mosmann et al., 1986; Hamaguchi et al., 1987; Thompson-Snipes et al., 1991; Rennick et al., 1995). MCs can in turn produce Th2 cytokines that function in autocrine and paracrine signaling and can induce the synthesis of Th2 cytokines in other cells, resulting in an expanded network of predicted effects of MCs on intestinal permeability. In particular, MC-dependent upregulation of IL-4, -6, -9, -10, -13 and -15 may mediate the effects of ileal mastocytosis on intestinal permeability during malaria. For example, IL-4 has been shown to increase transcellular resistance and paracellular permeability in human colonic epithelial cells *in vitro* independent of its effects on MC activation and regulation (Ceponis et al., 2000; Wisner et al., 2008). IL-13, which shares the IL-4 receptor α subunit with IL-4, is capable of upregulating claudin-2 in humans and mice (Heller et al., 2008, reviewed in Luettig et al., 2015; Prasad et al., 2005; Suzuki et al., 2011; Amasheh et al., 2002; Furuse et al., 2001; Van Itallie et al., 2003), inducing apoptosis in mice (Heller et al., 2008) and decreasing TER in canine kidney cells (Amasheh et al., 2002). IL-6 and IL-10, in particular, have been shown to have somewhat contradictory effects on intestinal permeability, depending on the animal model and assay used (reviewed in Al-Sadi et al., 2009). Studies in a mouse model of sepsis, for example, suggested that IL-10 and IL-6 interact to alter intestinal permeability (Wang et al., 2001), while IL-10 alone can enhance IgE-dependent MC activation in mouse models of food allergy (Polukort et al., 2016). Although (Polukort et al., 2016) did not measure permeability directly, IL-10 knockout mice did not develop allergic diarrhea nor evidence of MC-induced damage to the gut barrier. In contrast, another study demonstrated IL-10 to be protective against an increase in permeability under homeostatic conditions, with IL-10-deficient mice having higher permeability to mannitol relative to their IL-10 intact counterparts (Madsen et al., 1999). In addition to IL-6 and IL-10, the T cell cytokine IL-9 has been implicated in colitis and food allergy, two pathologies of the intestine that result in increased permeability (Gerlach et al., 2015; Liu et al., 2016; Forbes et al., 2008). Deficiency in IL-9 results in protection against 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis, with knockout mice having elevated levels of TJ proteins claudin-4, claudin-7, occludin and junctional adhesion molecule-A compared to wild type animals (Gerlach et al., 2015). Similarly, IL-9 overexpression in mice induced increased intestinal mastocytosis, increased permeability, decreased TER, and increased levels of MCPT-1 and MCPT-2 (but not MCPT-5) following oral antigen challenge (Forbes et al., 2008).

As enzymatic mediators of MC activity, MCPTs or chymases can directly alter intestinal permeability. While human MC chymase is the product of a single gene, 14 chymase genes have been identified in mice (Gallwitz and Hellman, 2006). MCPT-4, the mouse functional homolog of human MC chymase, is integral to intestinal permeability under homeostatic conditions, as MCPT-4-deficient mice have increased TER, decreased permeability to FITC-dextran and horse radish peroxidase (HRP), decreased epithelial migration and decreased expression of TJ claudin-3 (Groschwitz et al., 2009). Beyond direct effects on intestinal permeability, MCPT-4 has also been reported to be protective in mouse models of sepsis by degrading TNF-α (Piliponsky and Romani, 2018). TNF-α treatment can induce paracellular permeability, decrease TER, and disrupt ZO-1 and occludin protein expression, effects that can be mitigated by treatment with the TNF-α inhibitor adalimumab (Al-Sadi et al., 2013; Xu et al., 2019). Accordingly, MCPT-4 may alter intestinal permeability indirectly as well by changing the local cytokine milieu. In this context, histamine, MCPTs and MC-derived IL-10 would be predicted to inhibit neutrophil chemotaxis (Grimbaldeston et al., 2007; Hirasawa et al., 2002; Bury et al., 1992), while MC-derived IL-10 could reduce proliferation of $CD4^+/CD8^+$ T cells (Leveson-Gower et al., 2013) as well as T cell activation (Lu et al., 2006, reviewed in de Vries and Noelle, 2010). IL-15, produced primarily by MCs and basophils in mice (Colpitts et al., 2013, reviewed in Eberle and Voehringer, 2016) contributes to intraepithelial T lymphocyte development in the intestine (Ma et al., 2009) and can induce protective early innate and later adaptive responses in malaria (Zarling et al., 2013; Ing et al., 2005), but also suppresses MC bactericidal responses and neutrophil recruitment (Orinska et al., 2007). Thus, early and prolonged MC activation in the ileum during malaria, together with increasing levels of IL-10 and IL-15, could reduce T cell-amplified macrophage function and neutrophil recruitment and function, thereby limiting immune defenses against bacteria that translocate across a damaged intestinal epithelial barrier. Although extrapolating findings across models can be challenging, the human intestinal immune response to falciparum malaria has important commonalities with intestinal immune responses in mouse models of malaria. Specifically, while mouse and human MCs exhibit notable differences in their compositions of tryptases and chymases (reviewed in Galli et al., 2015), both human and murine MCs contribute to the regulation of malaria-induced intestinal permeability. Further, *P. yoelii*-infected RBCs have been observed to sequester in the gut microvasculature (Mooney et al., 2015), making this a useful model for addressing mechanistic questions related to falciparum malaria-induced GI pathology.

6. Effects of host Th2 response on malaria parasite transmission

There is growing evidence to suggest that the host immune response influences malaria parasite transmission (Fig. 1). While high levels of pro-inflammatory cytokines including TNF-α are associated with SMA (Achidi et al., 2013) and CM (reviewed in Leão et al., 2020), lower levels of this cytokine have been observed in patients with *P. falciparum* in high transmission areas compared to patients living in low transmission areas (Ademolue et al., 2017). In the non-lethal model *P. y. yoelii* 17XNL, Cespedes et al. (2020) similarly noted consistent, low levels of circulating TNF-α over the course of infection. TNF-α has gametocytocidal properties (Naotunne et al., 1991; Westwood et al., 2020), and blockade of TNF receptor 1 has been shown to both reduce disease severity and increase parasite transmission from mice infected with *P. c. chabaudi* to mosquitoes (Long et al., 2008). Additionally, in falciparum malaria, IL-10 can inhibit TNF-α production during infection (Ho et al., 1995) and a low IL-10 to TNF-α ratio is predictive of severe disease (Othoro et al., 1999), suggesting that the shift towards Th2 immunity, while protecting the host from an overwhelming inflammatory response, may also be contributing to increased parasite transmission. IL-10 is increased in asymptomatic pregnant women with malaria as compared to healthy controls (Wilson et al., 2010), and IL-10 is known to inhibit

monocyte and macrophage function promoting tolerance versus activation (reviewed in (Niikura et al., 2011; de Waal Malefyt et al., 1991). Interestingly (Cespedes et al., 2020) observed that peak circulating IL-10 levels in mice coincided with a significant decrease in circulating monocytes. Given that phagocytosis by monocytes and macrophages can control parasitemia in general and gametocytemia in particular (reviewed in de Jong et al., 2020), elevated IL-10 could enhance gametocyte survival. The connection between milder disease and increased transmission is further corroborated by the fact that higher gametocytemia has been associated with asymptomatic malaria in humans (reviewed in Lindblade et al., 2013) and by the fact that asymptomatic individuals have been reported to transmit infection to mosquitoes more readily (Gouagna et al., 2004). The broadly distributed cell surface receptor CD36 also appears to be important in increasing the early synthesis of Th1 cytokines, as infected *CD36*$^{-/-}$ mice showed impaired production of Th1 cytokines and an early increase of Th2 cytokines such as IL-4 and IL-10 relative to infected wild type animals (Thylur et al., 2017). Th1 cytokines like INF-γ enhance the phagocytic activity of polymorphonuclear neutrophils and macrophages (Thylur et al., 2017, reviewed in Kurup et al., 2019), and as might be expected, *CD36*$^{-/-}$ mice showed reduced uptake of iRBCs by splenic macrophages and polymorphonuclear neutrophils (PMNs) at 5- and 8-days post-infection with *P. yoelii* 17XNL (Thylur et al., 2017). CD36 is also involved in phagocytosis of gametocytes (Smith et al., 2003), suggesting that a Th2-skewed response protects parasites against clearance by host immune cells.

7. Summary

Like other parasitic infections, malaria can trigger a Th2-type immune response characterized by allergic inflammation, including activation of MCs and the release of histamine (Enwonwu et al., 2000; Beghdadi et al., 2008; Chau et al., 2013; Potts et al., 2016; Wu et al., 2018; Céspedes et al., 2020). In general, a cytotoxic Th1 immune response balanced with an antibody-mediated Th2 immune response is required to clear parasites while preventing immunopathology as a result of an overwhelming Th1 response (Wu et al., 2018; Cespedes et al., 2020). However, a Th2-biased immune response is less effective than a Th1 response for clearing intracellular parasites (Urban et al., 1996) and perhaps owing at least in part to the parasite sequestration in the endothelium of the GI, results in allergic inflammation of the intestine. Allergic inflammation in the intestine is associated with the release of MC mediators and degradation of TJs and AJs, which favors higher permeability to lumenal bacteria. The parasite benefits twice from this arrangement, because in addition to protecting the parasite from the human host response, a Th2-type response may favor parasite transmission, at least in part by reducing gametocyte killing and phagocytosis (Fig. 1). Therefore, malaria-associated intestinal barrier damage within the mammalian host may represent effects of parasite manipulation of the host immune response that ultimately increases both parasite survival and transmission. Unfortunately for the mammalian host, this also results in a greater risk for bacterial dissemination from the gut, which can increase malaria-associated morbidity and mortality. Future research needs include a better understanding the factors and mechanisms that precede the onset of malaria-induced intestinal permeability. Such studies will provide the basis for identification of potential targets for therapeutic intervention and/or biomarkers to predict which patients are likely to develop bacteremia, thus simplifying diagnosis and improving treatment decisions and outcomes.

Declaration of Competing Interest

None.

Author Contributions

Erinn Donnelly: Writing – original draft, Writing – review & editing, Visualization. **Judy Van de Water:** Writing – review & editing. **Shirley Luckhart:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition.

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