



Published in final edited form as:

Curr Opin Microbiol. 2020 December ; 58: 56–61. doi:10.1016/j.mib.2020.08.006.

The gut microbiome, immunity and *Plasmodium* severity

Morgan L. Waide^{1,2}, Nathan W. Schmidt²

¹Department of Microbiology and Immunology, University of Louisville, Louisville, Kentucky, USA.

²Ryan White Center for Pediatric Infectious Diseases and Global Health, Herman B. Wells Center for Pediatric Research, and Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN, USA

Keywords

Malaria; Gut microbiome; Immunity; Liver stage; Blood stage; B cell; T cell; Disease severity

Introduction

Malaria led to approximately 228 million cases and 405,000 deaths worldwide in 2018 [1]. Caused by the transmission of *Plasmodium* parasites by the female anopheles mosquito, malaria poses a risk for almost half of the world's population, with higher risk of severe disease and mortality in children under the age of five and pregnant women [1]. In addition to the health risk posed by malaria, the disease has a large global economic burden, including the cost of research, distribution of mosquito nets and antimalarials, government spending for in and out patient care, malaria clinics, and lost work due to illness [2–4]. Worldwide efforts to eradicate malaria have led to a decrease in the numbers of mortalities since the early 2000s [5]. However, due to growing resistance to available antimalarials and the lack of an effective, long-lasting vaccine, these numbers have begun to plateau, highlighting the continued need for new, innovative, and affordable methods of treatment [1, 6–9]. Understanding the role of gut microbiota in human health and disease has expanded widely over the last decade, with improved understanding of the ability of gut microbes to alter the immune response to chronic inflammatory and infectious diseases both locally and systemically [10]. Together, the need for novel malaria treatments and the growing knowledge of the role of the gut microbiota in health and disease point to the potential for gut microbiota modulation as a treatment for severe malaria.

Corresponding Author: Nathan W. Schmidt⁰, Address: 1044 W. Walnut St., Indianapolis, IN 46202, Phone: 317-278-5701, nwschmid@iu.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of Interest:

The authors declare no conflict of interest.

Role of gut microbiota in *Plasmodium* infection

While there is still much to understand before gut microbiota modulation becomes a viable and optimal treatment to prevent severe malaria, recent evidence in both rodent models and human studies have pointed to gut microbiota composition as a factor in disease progression [11, 12]. Villarino *et. al.* has shown that, when C57BL/6 mice ordered from different vendors are infected with *Plasmodium yoelii* 17XNL—a nonlethal, rodent-specific strain of *Plasmodium*—mice exhibited profound differences in infection severity, morbidity, and mortality based on vendor, and that these differences in susceptibility are gut microbiota dependent [13**]. The role of the gut microbiota in *Plasmodium* severity was further illustrated in research by Morffy Smith *et. al.* that showed disruption of the gut microbiota in outbred Swiss Webster mice through antibiotic treatment and fecal microbiota transplant resulted in differing susceptibility to and pregnancy outcomes during infection with *Plasmodium chabaudi chabaudi*—a rodent model for chronic malaria [14].

Additionally, research using mouse models have shown that *Plasmodium* infections can lead to changes in gut microbiota and gastrointestinal health. Taniguchi *et. al.* showed that, when C57BL/6 mice were infected with *Plasmodium berghei* ANKA—a lethal, rodent-specific *Plasmodium* strain that, in C57BL/6 mice, leads to experimental cerebral malaria (ECM)—changes in intestinal pathology and gut microbiota composition were seen, and these changes correlated with the development of ECM [15]. It has also been shown by Denny *et. al.* that, in C57BL/6 mice with differing susceptibility to *Plasmodium yoelii* 17XNL, there is an increase of proinflammatory cells in the lamina propria, prolonged liver damage, and changes in cecal metabolites in mice that exhibit severe malaria upon infection [16]. This report demonstrated shifts in gut bacteria composition in mice regardless of infection severity, yet those changes in gut bacteria composition did not alter susceptibility to future *Plasmodium* infections. *P. yoelii nigeriensis* infection also induced changes in gut microbiota, which increased susceptibility to non-typhoid *Salmonella* infections [17]. Contrary to these rodent models, a paper by Mandal *et. al.* looking at gut bacteria composition in Kenyan infants found minimal shifts in gut bacteria following a malaria episode and treatment with artemether+lumefantrine [18], illustrating that gut bacterial composition shifts may vary based on host, infection severity, and *Plasmodium* species.

Several studies have also begun to identify the role of gut microbiota in *Plasmodium* infection risk and immune response in humans. In a paper by Yooseph *et. al.*, it was shown that there is an association between the composition of stool bacteria composition at the onset of the ensuing malaria transmission season and susceptibility to *Plasmodium falciparum* infection [19**]. While the gut microbiota was not a good predictor of who would develop a febrile (or symptomatic) infection, it was a good predictor of the likelihood of a *P. falciparum* infection being established as measured by PCR [19**]. Likewise, Mandal *et. al.* found variation in the gut microbiota of Kenyan children who had an increased number of malaria episodes rather than a single episode throughout a malaria season [18]. Furthermore, Yilmaz *et. al.* illustrated that colonization of α -gal producing human gut bacteria *E. coli* O86:B7 leads to α -gal specific antibodies, and these antibodies are cross-protective against *Plasmodium* sporozoite infection of hepatocytes in both a mouse model and human populations [20**]. Together, though these human and mouse studies evaluate

the role of gut microbiota on the host response to *Plasmodium* from different viewpoints, they each illustrate the complex relationship between gut microbiota composition and *Plasmodium* infection.

Immune responses leading to *Plasmodium* clearance and acquired immunity

Though the immune response necessary to clear *Plasmodium* and eventually develop acquired immunity is complex due to factors such as large antigenic variation and a complex life cycle [21, 22], it is well established that the production of *Plasmodium*-specific antibodies are necessary in order to provide at least partial protection from *Plasmodium* infection [23] (Figure 1). However, protection of *Plasmodium*-specific antibodies through immune memory only reaches a protective threshold to clinical malaria after years of *Plasmodium* exposure and can be lost if an individual leaves a malaria endemic region only to return several years later [24, 25]. Studies have shown that it is both a combination of the antibody levels in circulation as well as the number of antigens these antibodies target that can predict protection from clinical malaria [26, 27]. The underlying factors dictating the speed at which an individual gains a protective antibody threshold and develops clinically asymptomatic malaria following *Plasmodium* infection remain unknown.

In the context of *Plasmodium* infections, a range of cell types including T follicular helper (Tfh) and germinal center (GC) B cells have been shown to be critical in developing high-affinity, long-lived antibodies in both rodent and human *Plasmodium* species [28, 29]. It has been shown that disruption of IL-21 signaling produced by Tfh cells leads to sustained high parasitemia in mice infected with *P. yoelii* and lack of immunity to subsequent infections, and the disruption of Tfh cells in particular leads to an inability of mice to clear the typically self-resolving chronic *P. chabaudi* infection [29, 30]. Furthermore, impaired Tfh differentiation and thus inefficient GC responses has been shown in severe malaria infection, and these GC responses were restored upon the blockade of inflammatory cytokines [31]. Additional cytokines affecting the humoral immune response to *Plasmodium* include the presence of IFN γ , which can lead to atypical memory B cells that have reduced effector functions—and B cell intrinsic IL-10—which has been shown to be necessary for GC B cell reaction, efficient antibody responses, and ultimate parasite control and host survival in a murine model [32, 33].

Gut microbiota influence on adaptive immune response

The gut microbiota has a well-established role in the development of a range of immune responses [34]. While a specific mechanism between gut microbiota composition and *Plasmodium* susceptibility was not identified by Villarino *et al.*, it was shown that mice resistant to hyperparasitemia following *P. yoelii* 17XNL infection showed increased numbers of splenic humoral immune cells such as Tfh cells and GC B cells, as well as an increase in *Plasmodium*-specific antibody titers compared to hyperparasitemia susceptible mice [13**]. Additionally, Yooseph *et al.* noted gut microbiota shifts in the age range that children typically develop acquired immunity to *Plasmodium* [19**], suggesting that age-associated gut microbiota changes may play a previously unidentified role in the ability of an individual

to reach a *P. falciparum*-specific antibody threshold that prevents the development of severe disease. This data leads to the exciting prospect that gut microbiota composition is contributing to the adaptive immune response, thus leading to increased resistance to severe disease and the development of a protective antibody threshold to severe malaria.

Though the specific role of gut microbiota on the systemic immune response to *Plasmodium* is still being explored, previous data has shown a role of gut microbiota in the development of adaptive immune-mediated protection from extra-GI infections such as influenza and LCMV (Figure 2) [35, 36]. Of note, these studies demonstrated that mice largely devoid of gut microbiota, as a consequence of broad-spectrum antibiotic treatment, have impaired adaptive immune responses. Therefore, it remains less clear how unique compositions of gut microbiota impact adaptive immune responses. To this end, Teng et. al. provided evidence that specific bacteria among the consortium of other gut microbiota can have an effect on the gut-distal immune system [37*]. In the context of an autoimmune arthritis model, they illustrated that gut commensal segmented filamentous bacteria (SFB) led to differentiation of Tfh cells in Peyer's patches, which then egress and traveled to gut-distal lymphoid tissues where they contributed to GC B cell responses and the production of auto-antibodies (Figure 2) [37*]. In addition to a direct role of gut microbiota on the development of T cells and antibody production, gut microbial products have been shown to have an effect on cytokines such as IL-21 [38, 39], which, as noted above, is essential to the systemic adaptive immune response to *Plasmodium*.

Yilmaz et. al. illustrated that bacteria present in the gut microbiota can have an influence on antibody production through cross reactivity, and it is known that a larger breadth of *Plasmodium* antigens to which an individual produces antibodies leads to fewer cases of clinical malaria [20**, 26, 27]. Together, this data suggests that altering gut microbiota composition could benefit the development of a more efficient adaptive immune response to *Plasmodium* and lead to increases in *Plasmodium* antigens that are targeted by the immune response. Though additional research needs to be performed to identify the mechanism by which gut microbiota may be shaping adaptive immunity to *Plasmodium*, altering gut microbiota composition to modulate adaptive immunity and thus decrease severe or symptomatic malaria remains a potential novel treatment for *Plasmodium*.

Problems and potential of treating malaria through modulating gut microbiota

Gut microbiota modulation as treatment for diseases, including malaria, has a number of benefits including its low cost. Mathematical modeling used to evaluate the cost-effectiveness of probiotic distribution in sub-Saharan Africa found that probiotic intervention leading to a 2- to 14-fold decrease in incidence of severe malaria would be extremely cost effective for the majority of the region [40]. In addition to being a very low cost therapeutic, probiotic bacteria can be freeze-dried and delivered orally, removing the need for refrigeration or trained medical professionals to provide hands on delivery. Furthermore, gut microbiota supplementation has the potential to prime the host immune system to respond better to *Plasmodium* rather than targeting the parasite, thus removing the

possibility of loss of effectiveness due to *Plasmodium* resistance. The potential to target gut microbiota as a preventative treatment was illustrated in a study that showed oral symbiotic treatment to target gut microbiota in rural Indian infants provided significant reduction in sepsis-related deaths and unexpectedly a reduction in lower respiratory tract infections [41*].

Though a better understanding of gut microbiota and utilizing the knowledge as a treatment for a range of diseases is an area of research that is important to a variety of fields, there remain important challenges that must be considered as this field moves forward. One of these challenges is identifying the optimal window of treatment for gut microbiota modulation. Villarino *et al.* showed that, while there was a significant decrease in malaria susceptibility in mice following *Lactobacillus* and *Bifidobacterium* treatment, this only occurred after several weeks of treatment with a broad-spectrum antibiotic cocktail [13**]. Treating otherwise healthy individuals with antibiotics prior to probiotic administration would not only be expensive and encourage the emergence of antibiotic-resistant bacterial strains, but has been shown to negatively affect gut microbiota recovery following probiotic treatment, potentially leading to negative health effects [42]. Still, because gut microbiota of young children—the age most at risk for severe malaria infection and mortality—is very dynamic [43], there likely exists a period where gut microbiota modulation would be most effective.

Finally, even if altering gut microbiota is not sufficient on its own to prevent severe malaria, better understanding how gut microbiota influences the host antibody response to *Plasmodium* could open the door for gut microbiota modulation in combination with vaccination to improve the efficacy and longevity of a malaria vaccine. Evidence shows that gut microbiota influences antibody responses to a range of vaccinations including the influenza vaccine, meningococcal vaccine, and Infanrix®-hexa combination vaccine [44–46]. Future research targeting gut microbiota modulation in combination with *Plasmodium* vaccination holds the potential to not only aid in the host immune response to vaccination, but also to expand the breadth of the immune response to vaccinated antigens and provide longer lasting host memory.

Conclusion

Recent research has shown that gut microbiota plays an important role in the severity and outcome of *Plasmodium* infections in both humans and mice. The specific bacteria driving these differences, the interplay between bacteria and host response, and the mechanism by which severe malaria is being prevented, however, remain to be fully understood. Though more research would need to be done before clinical trials can be pursued, treating young children—the population most at risk of severe malaria and malaria-associated mortality—with probiotics to modulate their microbiome remains an encouraging prospect, and better understanding the interplay between gut microbiota and the host response to *Plasmodium* will open the door to a range of novel treatment options for malaria.

Acknowledgements

We apologize to the authors who have made important contributions to the subject areas discussed in this article that we were not able to reference owing to space constraints. This work was supported in part by a grant from the National Institute of Allergy and Infectious Disease of the National Institutes of Health (1R01AI123486) to N.W.S. Support provided by the Herman B. Wells Center to N.W.S. was in part from the Riley Children's Foundation. The project described was supported by the Indiana University Health - Indiana University School of Medicine Strategic Research Initiative. *S.D.G.*

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest

- of outstanding interest

1. WHO. World Malaria Report 2019.
2. Haakenstad A, et al., Tracking spending on malaria by source in 106 countries, 2000–16: an economic modelling study. *Lancet Infect Dis*, 2019 19(7): p. 703–716. [PubMed: 31036511]
3. Gallup JL and Sachs JD, The economic burden of malaria. *Am J Trop Med Hyg*, 2001 64(1–2 Suppl): p. 85–96. [PubMed: 11425181]
4. Alonso S, et al., The economic burden of malaria on households and the health system in a high transmission district of Mozambique. *Malar J*, 2019 18(1): p. 360. [PubMed: 31711489]
5. Roser M and Ritchie H. Malaria. 2020; Retrieved from: '<https://ourworldindata.org/malaria>' [Online Resource]].
6. Ashley EA, et al., Spread of artemisinin resistance in *Plasmodium falciparum* malaria. *N Engl J Med*, 2014 371(5): p. 411–23. [PubMed: 25075834]
7. Hamilton WL, et al., Evolution and expansion of multidrug-resistant malaria in southeast Asia: a genomic epidemiology study. *Lancet Infect Dis*, 2019 19(9): p. 943–951. [PubMed: 31345709]
8. Menard D and Dondorp A, Antimalarial Drug Resistance: A Threat to Malaria Elimination. *Cold Spring Harb Perspect Med*, 2017 7(7).
9. Phyto AP, et al., Declining Efficacy of Artemisinin Combination Therapy Against *P. Falciparum* Malaria on the Thai-Myanmar Border (2003–2013): The Role of Parasite Genetic Factors. *Clin Infect Dis*, 2016 63(6): p. 784–791. [PubMed: 27313266]
10. Durack J and Lynch SV, The gut microbiome: Relationships with disease and opportunities for therapy. *J Exp Med*, 2019 216(1): p. 20–40. [PubMed: 30322864]
11. Mukherjee D, Chora AF, and Mota MM, Microbiota, a Third Player in the Host-*Plasmodium* Affair. *Trends Parasitol*, 2020 36(1): p. 11–18. [PubMed: 31787522]
12. Ippolito MM, et al., Malaria and the Microbiome: A Systematic Review. *Clin Infect Dis*, 2018 67(12): p. 1831–1839. [PubMed: 29701835]
13. Villarino NF, et al., Composition of the gut microbiota modulates the severity of malaria. *Proc Natl Acad Sci U S A*, 2016 113(8): p. 2235–40. [PubMed: 26858424] **Genetically identical mice ordered from different vendors have profound differences in *Plasmodium yoelii* infection severity, and that these differences are driven by the gut microbiota.
14. Morffy Smith CD, et al., Composition of the gut microbiota transcends genetic determinants of malaria infection severity and influences pregnancy outcome. *EBioMedicine*, 2019 44: p. 639–655. [PubMed: 31160271]
15. Taniguchi T, et al., *Plasmodium berghei* ANKA causes intestinal malaria associated with dysbiosis. *Sci Rep*, 2015 5: p. 15699. [PubMed: 26503461]
16. Denny JE, et al., Differential Sensitivity to *Plasmodium yoelii* Infection in C57BL/6 Mice Impacts Gut-Liver Axis Homeostasis. *Sci Rep*, 2019 9(1): p. 3472. [PubMed: 30837607]
17. Mooney JP, et al., Inflammation-associated alterations to the intestinal microbiota reduce colonization resistance against non-typhoidal *Salmonella* during concurrent malaria parasite infection. *Sci Rep*, 2015 5: p. 14603. [PubMed: 26434367]

18. Mandal RK, et al., Longitudinal Analysis of Infant Stool Bacteria Communities Before and After Acute Febrile Malaria and Artemether-Lumefantrine Treatment. *J Infect Dis*, 2019 220(4): p. 687–698. [PubMed: 30590681]
19. Yooshef S, et al., Stool microbiota composition is associated with the prospective risk of *Plasmodium falciparum* infection. *BMC Genomics*, 2015 16: p. 631. [PubMed: 26296559] **Gut microbiota composition prior to the onset of malaria season is a predictor of the risk of a *Plasmodium falciparum* infection in Malian children.
20. Yilmaz B, et al., Gut microbiota elicits a protective immune response against malaria transmission. *Cell*, 2014 159(6): p. 1277–89. [PubMed: 25480293] **The presence of α -gal antibodies is associated with protection from *Plasmodium falciparum* in humans, and murine gut colonization with α -gal expressing *E. coli* O86:B7 results in cross-reactive antibodies that are protective against *Plasmodium* infection.
21. Belachew EB, Immune Response and Evasion Mechanisms of *Plasmodium falciparum* Parasites. *J Immunol Res*, 2018 2018: p. 6529681. [PubMed: 29765991]
22. Long CA and Zavala F, Immune Responses in Malaria. *Cold Spring Harb Perspect Med*, 2017 7(8).
23. Cohen S, Mc GI, and Carrington S, Gamma-globulin and acquired immunity to human malaria. *Nature*, 1961 192: p. 733–7. [PubMed: 13880318]
24. Crompton PD, et al., A prospective analysis of the Ab response to *Plasmodium falciparum* before and after a malaria season by protein microarray. *Proc Natl Acad Sci U S A*, 2010 107(15): p. 6958–63. [PubMed: 20351286]
25. Weiss GE, et al., The *Plasmodium falciparum*-specific human memory B cell compartment expands gradually with repeated malaria infections. *PLoS Pathog*, 2010 6(5): p. e1000912. [PubMed: 20502681]
26. Osier FH, et al., Breadth and magnitude of antibody responses to multiple *Plasmodium falciparum* merozoite antigens are associated with protection from clinical malaria. *Infect Immun*, 2008 76(5): p. 2240–8. [PubMed: 18316390]
27. Nogaró SI, et al., The breadth, but not the magnitude, of circulating memory B cell responses to *P. falciparum* increases with age/exposure in an area of low transmission. *PLoS One*, 2011 6(10): p. e25582. [PubMed: 21991321]
28. Figueiredo MM, et al., T follicular helper cells regulate the activation of B lymphocytes and antibody production during *Plasmodium vivax* infection. *PLoS Pathog*, 2017 13(7): p. e1006484. [PubMed: 28700710]
29. Perez-Mazliah D, et al., Follicular Helper T Cells are Essential for the Elimination of *Plasmodium* Infection. *EBioMedicine*, 2017 24: p. 216–230. [PubMed: 28888925]
30. Perez-Mazliah D, et al., Disruption of IL-21 signaling affects T cell-B cell interactions and abrogates protective humoral immunity to malaria. *PLoS Pathog*, 2015 11(3): p. e1004715. [PubMed: 25763578]
31. Ryg-Cornejo V, et al., Severe Malaria Infections Impair Germinal Center Responses by Inhibiting T Follicular Helper Cell Differentiation. *Cell Rep*, 2016 14(1): p. 68–81. [PubMed: 26725120]
32. Obeng-Adjei N, et al., Malaria-induced interferon-gamma drives the expansion of Tbethi atypical memory B cells. *PLoS Pathog*, 2017 13(9): p. e1006576. [PubMed: 28953967]
33. Guthmiller JJ, et al., Cutting Edge: IL-10 Is Essential for the Generation of Germinal Center B Cell Responses and Anti-*Plasmodium* Humoral Immunity. *J Immunol*, 2017 198(2): p. 617–622. [PubMed: 27940658]
34. Kamada N and Nunez G, Regulation of the immune system by the resident intestinal bacteria. *Gastroenterology*, 2014 146(6): p. 1477–88. [PubMed: 24503128]
35. Abt MC, et al., Commensal bacteria calibrate the activation threshold of innate antiviral immunity. *Immunity*, 2012 37(1): p. 158–70. [PubMed: 22705104]
36. Ichinohe T, et al., Microbiota regulates immune defense against respiratory tract influenza A virus infection. *Proc Natl Acad Sci U S A*, 2011 108(13): p. 5354–9. [PubMed: 21402903]
37. Teng F, et al., Gut Microbiota Drive Autoimmune Arthritis by Promoting Differentiation and Migration of Peyer's Patch T Follicular Helper Cells. *Immunity*, 2016 44(4): p. 875–88. [PubMed: 27096318] *The presence of segmented filamentous bacteria in the gut microbiota of mice led to

- the production of Tfh cell dependent autoantibodies in the systemic lymphoid tissues in an autoimmune arthritis model.
38. Cho H, et al., Microbiota-dependent IL-21 signaling regulates intestinal immune cell homeostasis and immunopathology to infection *The Journal of Immunology*, 2017 198(1).
 39. Kim M and Kim CH, Regulation of humoral immunity by gut microbial products. *Gut Microbes*, 2017 8(4): p. 392–399. [PubMed: 28332901]
 40. Greenhalgh S and Chandwani V, Advocating an attack against severe malaria: a cost-effectiveness analysis. *BMC Public Health*, 2020 20(1): p. 17. [PubMed: 31910842]
 41. Panigrahi P, et al., A randomized synbiotic trial to prevent sepsis among infants in rural India. *Nature*, 2017 548(7668): p. 407–412. [PubMed: 28813414] *Treatment of Indian infants with *Lactobacillus plantarum* and fructooligosaccharide (a probiotic and prebiotic respectively) led to a significant decrease in sepsis related death compared to placebo treated infants.
 42. Suez J, et al., Post-Antibiotic Gut Mucosal Microbiome Reconstitution Is Impaired by Probiotics and Improved by Autologous FMT. *Cell*, 2018 174(6): p. 1406–1423 e16. [PubMed: 30193113]
 43. Tanaka M and Nakayama J, Development of the gut microbiota in infancy and its impact on health in later life. *Allergol Int*, 2017 66(4): p. 515–522. [PubMed: 28826938]
 44. Oh JZ, et al., TLR5-mediated sensing of gut microbiota is necessary for antibody responses to seasonal influenza vaccination. *Immunity*, 2014 41(3): p. 478–492. [PubMed: 25220212]
 45. Ciabattini A, et al., Role of the Microbiota in the Modulation of Vaccine Immune Responses. *Front Microbiol*, 2019 10: p. 1305. [PubMed: 31333592]
 46. Lynn MA, et al., Early-Life Antibiotic-Driven Dysbiosis Leads to Dysregulated Vaccine Immune Responses in Mice. *Cell Host Microbe*, 2018 23(5): p. 653–660 e5. [PubMed: 29746836]
 47. Barry A, et al., Functional antibodies against *Plasmodium falciparum* sporozoites are associated with a longer time to qPCR-detected infection among schoolchildren in Burkina Faso. *Wellcome Open Res*, 2018 3: p. 159. [PubMed: 30828645]
 48. Flores-Garcia Y, et al., Antibody-Mediated Protection against *Plasmodium* Sporozoites Begins at the Dermal Inoculation Site. *mBio*, 2018 9(6).
 49. Holz LE, Fernandez-Ruiz D, and Heath WR, Protective immunity to liver-stage malaria. *Clin Transl Immunology*, 2016 5(10): p. e105. [PubMed: 27867517]
 50. Sato Y, et al., The Liver-Stage *Plasmodium* Infection Is a Critical Checkpoint for Development of Experimental Cerebral Malaria. *Front Immunol*, 2019 10: p. 2554. [PubMed: 31736970] **10**
 51. White NJ, Malaria parasite clearance. *Malar J*, 2017 16(1): p. 88. [PubMed: 28231817]

Highlights

- Gut microbiota is associated with malaria in rodents and humans.
- Gut microbiota influences systemic adaptive immune responses.
- Probiotic treatment in infants can decrease infection-related mortality.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

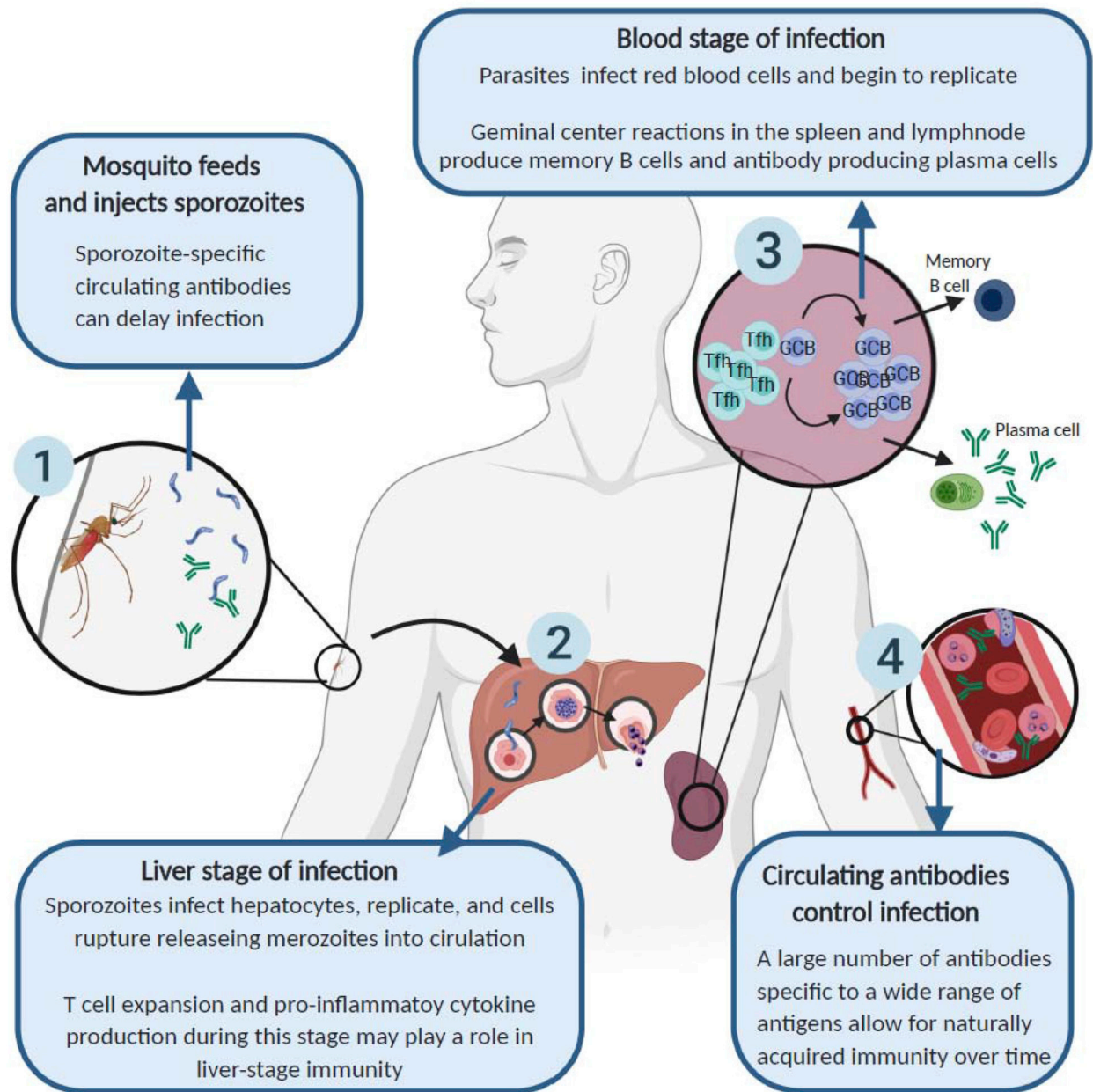


Figure 1. Adaptive immune response to *Plasmodium*. Schematic illustrating the role of the adaptive immune system in controlling a *Plasmodium* infection from initial parasite inoculation (1) through the liver (2) and control of blood stage of infection (3,4). When a mosquito feeds on a human host, sporozoites are injected into the skin where neutralizing antibodies have been found to immobilize invading sporozoites and delay infection [47, 48]. During the “clinically silent” liver stage of the infection, CD8⁺ T cells have been observed migrating to the liver to play a role in liver-stage immunity [49], while immune cell expansion and pro-inflammatory immune responses during liver stage play a role in the development of cerebral malaria [50]. Finally, during the blood stage of infection, parasites undergo replication in red blood cells that allows the immune system to recognize *Plasmodium* antigen and mount an adaptive immune system response, leading to

B cell responses that produce high affinity antibodies that enter into circulation, and lead to the elimination of infected red blood cells [51]. Repeated exposures to *Plasmodium* lead to the development of naturally acquired immunity to clinical malaria over time [25].

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

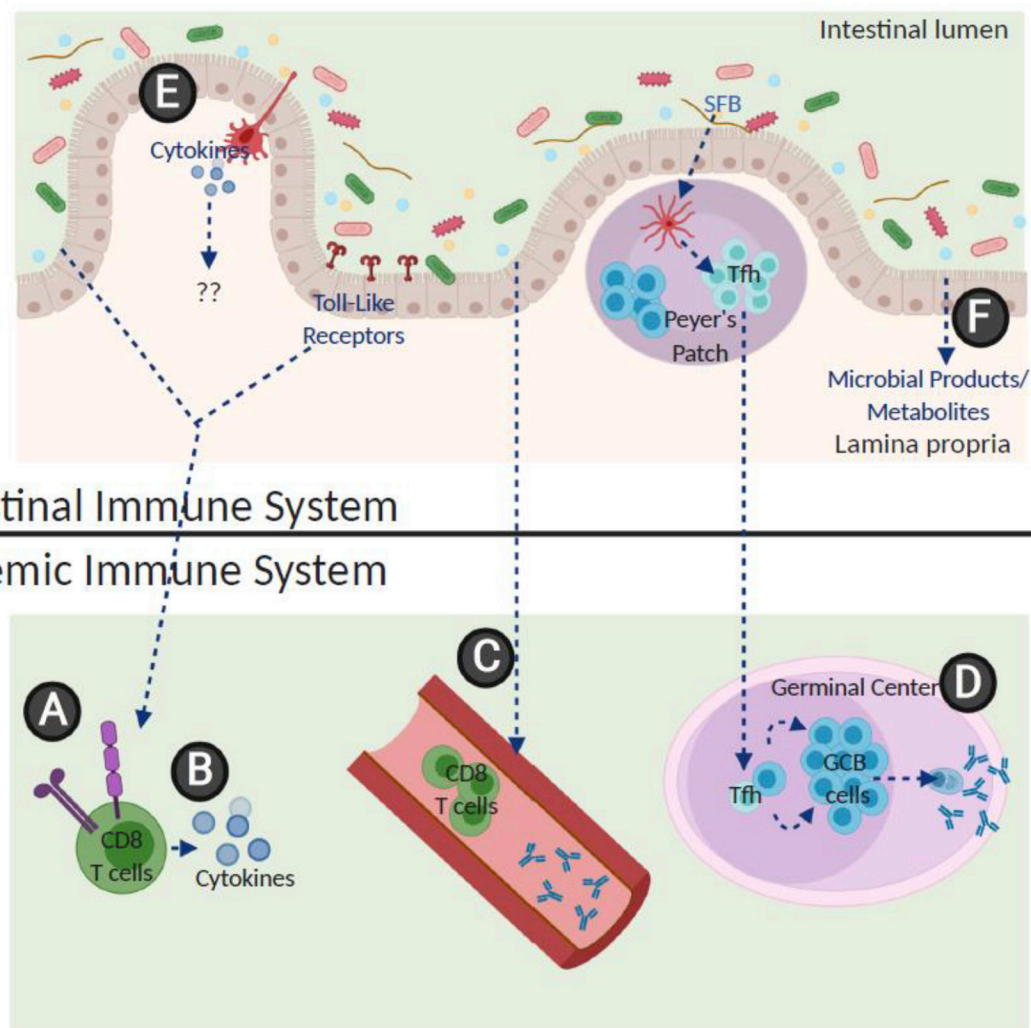


Figure 2. The known effects of the gut microbiota on the systemic immune system. (A) The presence of gut microbes have been found to lead to increased numbers of viral specific CD8⁺ T cells in the spleen and lungs as well as a decrease in surface inhibitory molecules on these cells during a viral infection [35, 36]. (B) CD8⁺ T cells also have increased inflammatory cytokine production when the gut microbiota is present, as well as (C) increased numbers of circulating T cells and viral specific antibodies in the blood [35, 36]. (D) Tfh cells primed by SFB in the Peyer's Patches have been shown to migrate systemically, leading to GC B cell activation and autoantibody production in an autoimmune arthritis model [37*]. (E) While dendritic cells in the lamina propria are known to produce cytokines in response to the gut microbiota and (F) a range of microbial products such as short-chain fatty acids and other metabolites such as PAMPs are known to enter circulation, the exact role these play on the systemic adaptive immune response remain unclear.