

Linking microbiota composition with antimalarial antibody response

Ottavia Romoli, Liliana Mancio-Silva, Mathilde Gendrin

► To cite this version:

Ottavia Romoli, Liliana Mancio-Silva, Mathilde Gendrin. Linking microbiota composition with antimalarial antibody response. Trends in Parasitology, 2021, 37 (10), pp.853-855. 10.1016/j.pt.2021.07.007. pasteur-03672692

HAL Id: pasteur-03672692 https://pasteur.hal.science/pasteur-03672692

Submitted on 16 Oct 2023 $\,$

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Version of Record: https://www.sciencedirect.com/science/article/pii/S1471492221001720 Manuscript_70069d61791d3f8b93b6e7709bbed9ae

1	Linking microbiota	composition v	with antimalarial	antibody response
---	--------------------	---------------	-------------------	-------------------

- 2
- 3 Ottavia Romoli¹, Liliana Mancio-Silva^{2, 3, 4}, Mathilde Gendrin^{1,4,*}
- 4
- ¹ Microbiota of insect vectors group, Institut Pasteur de la Guyane, Cayenne, French Guiana,
- 6 France.
- ² Institut national de la santé et de la recherche médicale, Unité 1201, Paris, France.
- 8 ³ Biology of host-parasite interactions unit, Institut Pasteur, Paris, France.
- ⁴ Parasites and insect vectors department, Institut Pasteur, Paris, France.
- 10 * Correspondence: mathilde.gendrin@pasteur.fr (M. Gendrin)
- 11 ORCID IDs:
- 12 OR: 0000-0002-7608-2650
- 13 LMS: 0000-0002-5585-018X
- 14 MG: 0000-0001-6405-6458
- 15
- 16 Keywords: microbiota, malaria, severity, *Plasmodium*
- 17
- 18 Abstract

19 Microbiota composition recently arose as a factor correlating with malaria infection. Mandal *et al.*

20 showed via cecal transplant and antibacterial treatment that the mouse microbiota modulates

21 parasitemia by affecting spleen germinal centers where B-cells are matured. They further

22 identified correlations between microbiota composition and malaria severity in Ugandan children.

24 In mammals, the gut microbiota shapes both mucosal and systemic immunity, impacting the outcome of infections, even those that take place distally from the gut. Malaria infections 25 26 represent an interesting working model on this regard, as the causing *Plasmodium* parasites 27 primarily infect the liver and blood of the mammalian host, without colonizing the gastrointestinal 28 lumen. Plasmodium parasites are transmitted by Anopheles mosquitoes. After being introduced 29 into the skin during a bite, parasites travel to the liver where they multiply inside hepatocytes. The 30 new progeny released in the bloodstream will then cyclically infect and proliferate in red blood 31 cells. Antibodies against *Plasmodium* parasites, which are produced by germinal centers in the 32 spleen, are critical to control infection.

33 Plasmodium infection has recently been found to correlate with microbiota composition in 34 mice [1,2]. These correlations were linked to the presence of specific bacteria [1] or to a gut microbiota-dependent production of *Plasmodium*-specific antibodies in germinal center immune 35 36 cells [3]. To further investigate these associations, Mandal and collaborators took advantage of a 37 mouse model (strain C57BL/6) purchased from two different vendors (Tac, for Taconic Biosciences, 38 and CR, for Charles River Laboratories; [4]). These mice represent a unique system to study associations between gut microbiota composition and malaria infection, as they are characterized 39 40 by a distinct response to *Plasmodium yoelii* 17XNL, with Tac mice efficiently restricting parasitemia 41 and CR being more permissive [2]. Using cecal transplants, Mandal et al. showed that the CR enterotype (i.e. microbiota composition) "dominates" over the Tac one: after cecal transplants 42 43 from CR to Tac, mice shift from a Tac to a CR enterotype, but after a transplant from Tac to CR, 44 mice keep a CR-enterotype. Accordingly, Tac mice receiving CR caecum content exhibit higher 45 parasitemia, but not vice versa (Figure 1A).

46 Mandal and colleagues then perturbed the microbiota by providing mice with five 47 alternative antibiotic treatments. They observed a strong decrease in parasite burden when

48 treating CR susceptible mice with these antibiotics, which links the bacterial component of the gut microbiota to P. yoelii infection. Using vancomycin, an antibiotic that does not cross the gut 49 50 barrier, at different time points prior to or after *Plasmodium* infection, they linked microbiota 51 perturbation with efficiency of parasite clearance. First, they found that antibiotic treatment 52 several weeks before infection reduced P. yoelii parasitemia in CR mice and protected animals 53 against experimental cerebral malaria upon subsequent *Plasmodium berghei* ANKA infection. Second, treatment 7 days after infection was still able to significantly reduce P. yoelii infection 54 burden, indicating that microbiota perturbation can rapidly influence defense against infection. 55 Finally, to investigate connections between microbiota and immunity, the authors examined 56 57 germinal center reactions in CR mice treated with vancomycin. They found that vancomycin 58 treatment induced the production of CD4+ follicular helper T cells and germinal center B cells. 59 Disruption of germinal center functions mitigated the effect of antibiotic-treatment on immune 60 cells and on parasitemia (Figure 1B).

61 The authors also assessed correlations between malaria infection and microbiota 62 interactions in a small cohort of children in Uganda. They found different bacteria compositions in the asymptomatic Plasmodium falciparum-infected patients, the infected with severe malarial 63 64 anemia and the non-infected children. They did not identify any bacteria that appear protective 65 against severity, but rather found that the frequency of specific bacteria, such as *Flavonifractor* 66 plautii, Escherichia coli and Faecalibacterium prausnitzii positively correlated with severe malaria. This profiling allowed them to build a supervised machine learning model that predicted P. 67 falciparum status with 74% accuracy. 68

This work sheds new light into the interplay between microbiota and immune system. It demonstrates that bacteria, rather than fungal, eukaryotic, or viral components of the microbiota, are responsible for the observed effects on parasitemia in mice, as antibacterial treatment fully

72 recapitulates the impact of cecal transplant. By providing an intriguing example of antibiotic treatment strengthening the immune system, this study may have important implications in 73 74 humans, especially in malaria-endemic regions where antibiotics are often prescribed to treat 75 non-specific febrile symptoms or used as self-medication [5,6]. An association between malaria 76 infection and microbiota composition in humans has been described in few independent studies 77 [1,7]. Such correlations may be explained both by an influence of specific bacteria on host immunity affecting malaria infection [1], as highlighted in Mandal et al.'s study, and by the 78 79 alteration of host physiology by *Plasmodium*, promoting colonization by specific bacteria [8,9].

On an experimental perspective, this work further highlights that besides host and parasite genetics, the host microbiota can strongly influence the outcome of malaria infections in the laboratory. Microbiota, which is directly related to host diet and nutrition, should be monitored as an additional experimental variable to achieve reproducible and solid results across replicates and laboratories [10]. Reproducibility could be improved by using experimental models with a known microbiota composition, using for instance germ-free mice recolonized with specific microbiota communities.

Our understanding of interactions between gut microbiota and malaria severity is still 87 88 preliminary and further studies are needed to understand the mechanisms behind these results, 89 to identify bacterial species responsible for these observations and to assess whether these results 90 could be recapitulated in other mouse models or with other parasites. While we are far from 91 discovering the "magic pill" that will make us resistant to infectious diseases, such advances in the 92 study of microbiota-immune system crosstalk may eventually lead to the development of 93 probiotics as living therapeutics for improving human health, even when dealing with pathogens that never infect the gut. This also opens perspectives to personalized medicine, which considers 94 95 each patient's identity in terms of genome, proteome and metabolism, and which may also

96 include the microbiota composition as an important parameter to monitor and to link to specific

97 medical conditions.

98

99 Acknowledgements

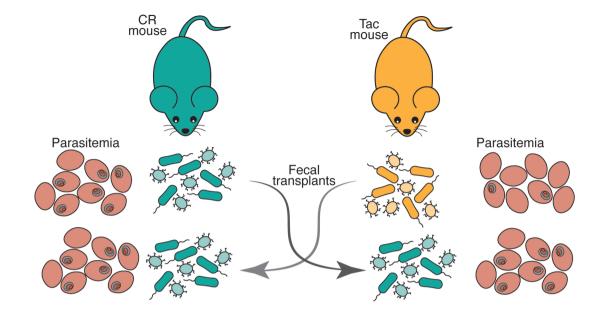
- 100 This work is funded by the French Government's Investissement d'Avenir program, Laboratoire
- 101 d'Excellence "Integrative Biology of Emerging Infectious Diseases" (grant no. ANR-10-LABX-62-
- 102 IBEID) and by ANR JCJC MosMi to MG (grant no. ANR-18-CE15-0007).
- 103

104 Declaration of Interests

- 105 The authors declare no competing interests.
- 106
- 107 References
- 108
- 1 Yilmaz, B. *et al.* (2014) Gut Microbiota Elicits a Protective Immune Response against Malaria
 Transmission. *Cell* 159, 1277–1289
- 2 Villarino, N.F. *et al.* (2016) Composition of the gut microbiota modulates the severity of malaria.
 Proc National Acad Sci 113, 2235–2240
- 3 Waide, M.L. *et al.* (2020) Gut Microbiota Composition Modulates the Magnitude and Quality of
 Germinal Centers during Plasmodium Infections. *Cell Reports* 33, 108503
- 4 Mandal, R.K. *et al.* (2021) Dynamic modulation of spleen germinal center reactions by gut
 bacteria during Plasmodium infection. *Cell Reports* 35, 109094
- 5 Griensven, J. van *et al.* (2020) Point of care biomarkers to guide antibiotic prescription for acute
 febrile illness in sub-Saharan Africa: promises and caveats. *Open Forum Infect Dis* 7, ofaa260-
- 119 6 Yeika, E.V. et al. (2021) Comparative assessment of the prevalence, practices and factors
- associated with self-medication with antibiotics in Africa. *Trop Med Int Health* DOI:
- 121 10.1111/tmi.13600
- 122 7 Yooseph, S. *et al.* (2015) Stool microbiota composition is associated with the prospective risk of
- 123 Plasmodium falciparum infection. *Bmc Genomics* 16, 631

- 8 Walker, G.T. *et al.* (2021) Malaria parasite infection compromises colonization resistance to an
 enteric pathogen by reducing gastric acidity. *Sci Adv* 7, eabd6232
- 9 Mukherjee, D. *et al.* (2020) Microbiota, a Third Player in the Host–Plasmodium Affair. *Trends Parasitol* 36, 11–18
- 128 10 Mandal, R.K. et al. (2020) Temporospatial shifts within commercial laboratory mouse gut
- 129 microbiota impact experimental reproducibility. *Bmc Biol* 18, 83
- 130

Figure 1. The gut bacterial microbiota modulates spleen germinal center reactions during 131 132 *Plasmodium yoelii* infections. (A) Gut microbiota composition differs in mice purchased from two 133 distinct vendors (CR, Charles Rivers Laboratories; Tac, Taconic Biosciences) and correlates with different ability to control parasitemia during P. yoelii infection (CR: susceptible to 134 135 hyperparasitemia; Tac: resistant to hyperparasitemia). Fecal transplants can induce the CR 136 phenotype in Tac mice but not vice versa. (B) An antibacterial treatment reduces parasite burden and induces the production of germinal center B cells and CD4+ follicular helper T cells. Disruption 137 138 of germinal center functions mitigates the effect of antibiotic treatment on immune cells and on 139 parasitemia.



В

Α

