INFECTIOUS DISEASE

Malaria parasites hide in plain sight in the dry season

Plasmodium falciparum parasites survive the dry season by accepting increased clearance rates through the host spleen, which leads to a persistent lower-level infection.

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Malaria parasites are highly adapted to their ecology, which includes a human host and a mosquito vector. Every year mosquito numbers go from boom to bust, which presents a unique challenge to the parasite. This is especially dramatic in the West African Sahel, where rainfall goes from 300 mm per month at its peak down to single digits during the dry season and, as a result, as breeding sites dry up, mosquito numbers plummet. With almost no mosquito biting through the dry season, malaria parasites are stuck in their human hosts for the next 6–9 months before they have a chance of transmission[1]. In this issue of *Nature Medicine*, Andrade et al. report their study of the transcriptional and phenotypic changes in parasites during the dry season, in which they found that during the dry season, parasites undergo transcriptional changes that make them less sticky[2] (Fig. 1).

What do the parasites do when there are no mosquitoes? It is known that *Plasmodium vivax*, a major cause of malaria in the world, adapts to the dry season by developing a prolonged incubation stage in the liver. This hypnozoite stage can remain dormant for 9 months before emerging to multiply rapidly in the blood during the infection stage, waiting for the next mosquito bite to allow transmission to a new host[3]. On the other hand, *Plasmodium falciparum*, the predominant malaria-causing species in Africa, has no hypnozoite stage, so it must hide in plain sight — i.e., in the blood.

Malaria parasites in the blood make non-immune hosts sick. The outcome of this is cure or mortality, and neither is very good for the parasite if it wants to survive and infect someone else. Since early last century, light microscopy has shown the presence of *P. falciparum* parasites in blood smears from asymptomatic people between malaria seasons[1]. More recently, molecular techniques have shown low-level *P. falciparum* infections even in areas of Southeast Asia associated with lower levels of human immunity[4].

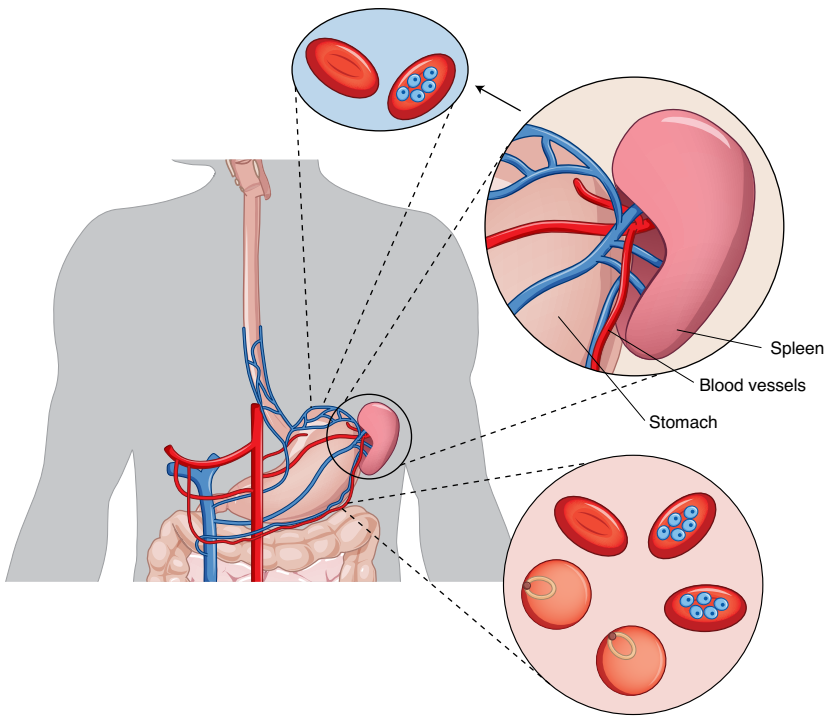

Fig. 1 | *P. falciparum* parasites can be partially cleared from circulation by the spleen. *P. falciparum* circulates in the blood, including circulation through the spleen. Splenic circulation reduces the abundance of parasites in the blood, but the parasite can evade this by sticking to blood vessel walls to evade circulation through the spleen.

Andrade et al. studied in detail the host and *P. falciparum* parasite adaptions among a cohort of 600 Malians in the West African Sahel through the wet and dry seasons[2]. They confirmed the known pattern of low-density asymptomatic infections through the dry season, and also confirmed that the parasites were a genetically similar population through the wet and dry seasons, so whatever adaption had happened was not selective.

P. falciparum parasites alter the surface of red blood cells by pushing variant surface antigens (VSAs) through the cell membrane and out onto the cell surface. This activity is quite costly to the parasite, as it exposes antigens that would otherwise be hidden safely inside the red blood cell, away from host antibodies. The parasite mitigates this by making the antigens highly variable to elude previously raised immune responses. However, the parasite takes the trouble to express VSAs, as the VSAs enable the parasite to stick to the walls of the host blood vessels, which allows it to avoid circulating through the host's spleen. The spleen is very efficient at clearing parasites, which makes it worth the parasite's

investment to avoid going there. The VSAs are expressed in the second 24 hours of the parasite's 48-hour life cycle in the blood, so late-stage parasites are rarely present in blood samples[5].

The transcription patterns that Andrade et al. found among dry-season parasites tended to be at a later stage[2], which implies that the parasites are less stuck to blood-vessel walls than one would normally expect. They were able to show that the parasites were less likely to be sticky in an in vitro simulation of the spleen, and although the authors were not able to show it definitively, there were hints of reduced expression of VSAs in vitro despite the relative older age of parasites.

Persistent low-level infection would still cause substantial symptoms in non-immune hosts, and potentially an immune host with a vigorous immune response that failed to clear the parasite could become even more unwell. However, the immune responses seen by Andrade et al. in people carrying parasites during the dry season were low, and there was no evidence of an inflammatory response[2].

This fits with previous observations showing that human hosts with chronic infection acquire immunoregulatory responses to avoid the sort of cytokine production that would lead to symptoms[6]. Thus, the hosts avoid acute illness (although there are chronic effects on health of so-called 'asymptomatic parasitemia'), and the parasites accept a strategy associated with lower overall numbers, with the trade-off being that they stand a chance of infecting a mosquito and getting to a new human host.

The authors' work here adds to the knowledge of transcriptional strategies that pathogens use to balance rapid growth (usually associated with virulence factors) and persistence and transmission[7]. The transcriptional profiles of parasites vary by intensity of transmission; that is, when mosquito biting is infrequent, the priority is achieving transmission for the few bites available, whereas when biting is more frequent, the priority is overcoming host immunity[8].

So, what is next? Translation to clinical benefit would mean learning more about the mechanisms the parasite uses to make these switches in behavior, so as to manipulate it in favor of the human host. Further assembly of the VSA sequence could reveal the switches made by the parasites, and further insight into how VSA expression is regulated could reveal where pathways could be targeted by therapeutics. VSAs and cytoadherence are substantial mediators of virulence. A parallel puzzle is the mosquito — how it copes with the long dry season, yet achieves rapid emergence and multiplication when the rains come[9]. Vector control is a mainstay of malaria control, and eradicating low numbers of vectors during the dry season may have parallels with the attempts to eradicate parasites during the dry season. It is well known that parasites evolve in response to drug pressure and host immunity. Andrade et al. have shown transcriptional regulation that leads to adaptive strategies in response to ecology, which opens a new avenue of investigation[2]. ❐

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Competing interests

The author declares no competing interests.