PARASITE CONTROL

γδ T cells burst malaria's bubble

New research demonstrates that γδ T cells recognize *Plasmodium*-infected erythrocytes via interaction of the T cell antigen receptor with the phosphoantigen sensor BTN3A1 and subsequently destroy infected cells through either cytotoxic molecule secretion or antibody-dependent phagocytosis.

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Plasmodium, the parasite that causes the devastating disease known as malaria, wreaks havoc on the human body when it infects red blood cells, known as erythrocytes, preventing them from functioning normally and causing anemia, fever, and — all too often — death[1]. In response to *Plasmodium* infection, the human immune system goes to war against malaria during the condition's 'blood-stage' by destroying infected erythrocytes[2]. Specialized proteins called antibodies bind to malaria parasites and infected erythrocytes, thus enabling various types of white blood cells to kill and remove the infected erythrocytes[3]. This process plays a critical role in enabling most people to survive malaria infection. The fact that it fails to prevent hundreds of thousands of deaths annually[4], however, inspires researchers to work toward understanding how humans might enhance the immune system's ability to fight blood-stage malaria infections. Recent findings from the Judy Lieberman lab at Harvard Medical School[5] provide new insights into what was a vaguely understood role for 'gamma delta (γδ) T cells,' a specialized white blood cell subset, in clearing blood-stage malaria infections. (Fig. 1)

γδ T cells live in human blood and various organs and respond to bacterial and parasitic infection by expanding in number and secreting cell-killing (cytotoxic) proteins[6]. These specialized T cells recognize other cells that are labeled with an immune system–activating danger signal following detection of bacterial or parasitic infection–associated phosphoantigen metabolites[6]. In this issue of *Nature Immunology*, Junqueira et al.[5] focus on a subset of Vγ9Vδ2 (γδ2) T cells that use their T cell antigen receptor (TCR) to recognize BTN3A1, a danger signal presented on the surface of infected cells in the presence of phosphoantigens. Phenotypic characteristics of expanded γδ2 T cell populations found in the blood of individuals experiencing multiple blood-stage malaria infections suggest that those T cells might have changed in response to repeated encounters with *Plasmodium*[7]. Changes in the phenotype of γδ2 T cells in malaria-experienced individuals, together with the fact that patients with higher γδ2 T cell numbers are more likely to respond favorably to antimalarial vaccination[8,9], suggest that γδ2 T cells may play an important role in controlling blood-stage malaria infection. Previous research suggested that γδ2 T cells prevented erythrocyte infection via secretion of cytotoxic proteins[10–12]. It was, however, unclear how these specialized T cell–secreted molecules interfered with malaria parasite propagation and whether or not γδ2 T cells use other mechanisms to combat blood-stage malaria infection.

Interested in describing the way in which γδ2 T cells may counteract blood-stage malaria infection processes, Junqueira et al. studied cells extracted from the blood of patients with malaria and healthy uninfected individuals from Brazil and the United States. In order to study how γδ2 T cells respond to the presence of parasite-infected erythrocytes, they purified and cultured γδ2 T cells in vitro with malaria-infected erythrocytes. In accordance with prior research, the presence of infected erythrocytes triggered the activation of γδ2 T cells and the production of various cytotoxic proteins, including granulysin and granzyme[10–12]. These proteins mediated the destruction of infected erythrocytes and the parasites within. Critically, and resolving the previous conundrum of how γδ2 T cells recognized infected erythrocytes, they found that afflicted erythrocytes expressed BTN3A1, the danger-associated phosphoantigen 'label' described above, which engages the γδ2 TCR to form a physical T cell–erythrocyte synapse. This cell-to-cell contact triggered γδ2 T cell secretion of the cytotoxic proteins granulysin and granzyme. These proteins, in turn, combined to rupture erythrocytes and kill the parasites within, thus bursting the malaria bubble. Importantly, specificity was demonstrated by using antibodies to block the γδ2 TCR or the BTN3A1-presenting molecule and prevent lysis of infected erythrocytes. As is so often the case in a biological world rife with compromise, the malaria parasite derives sustenance in part by scavenging cholesterol from the erythrocyte membrane, but this process renders the infected cell more susceptible to granulysin cytotoxicity. These findings confirm that infected erythrocytes express the danger signal BTN3A1 and that γδ2 T cells recognize it with their TCR and, in response, bind to infected erythrocytes and mediate their destruction via granulysin and granzyme secretion.

On further investigation, Junqueira et al. unexpectedly observed γδ2 T cells engulfing or phagocytosing infected erythrocytes and destroying their contents, a process previously thought to be restricted to specialized myeloid cells of the immune system. As previously mentioned, infected erythrocytes are coated with antibodies during blood-stage malaria. γδ2 T cells were able to phagocytose infected erythrocytes when the erythrocyte surfaces were bound by antibodies because antibody subunits interacted with γδ2 T cell–expressed CD16. Importantly, phagocytosis of infected erythrocytes should strengthen the overall immune response against blood-stage malaria because it enables γδ2 T cells to augment the antiparasitic functionality of other white blood cells. Therapeutic or vaccination strategies that include this process in their design may benefit from increased efficacy.

Together, these findings expand our understanding of how γδ2 T cells may work to combat blood-stage malaria in humans and inspire new hypotheses about how these cells may respond to other infectious or autoimmune disease processes. This new evidence reveals that parasite-infected erythrocytes upregulate the signals required for their recognition by specialized γδ2 T cells, leading to lysis of the infected erythrocyte and destruction of the internal parasite using the granzyme–granulysin pathway of cellular cytotoxicity. This decreases infection of healthy erythrocytes, demonstrating how killing of infected erythrocytes by γδ2 T cells may facilitate

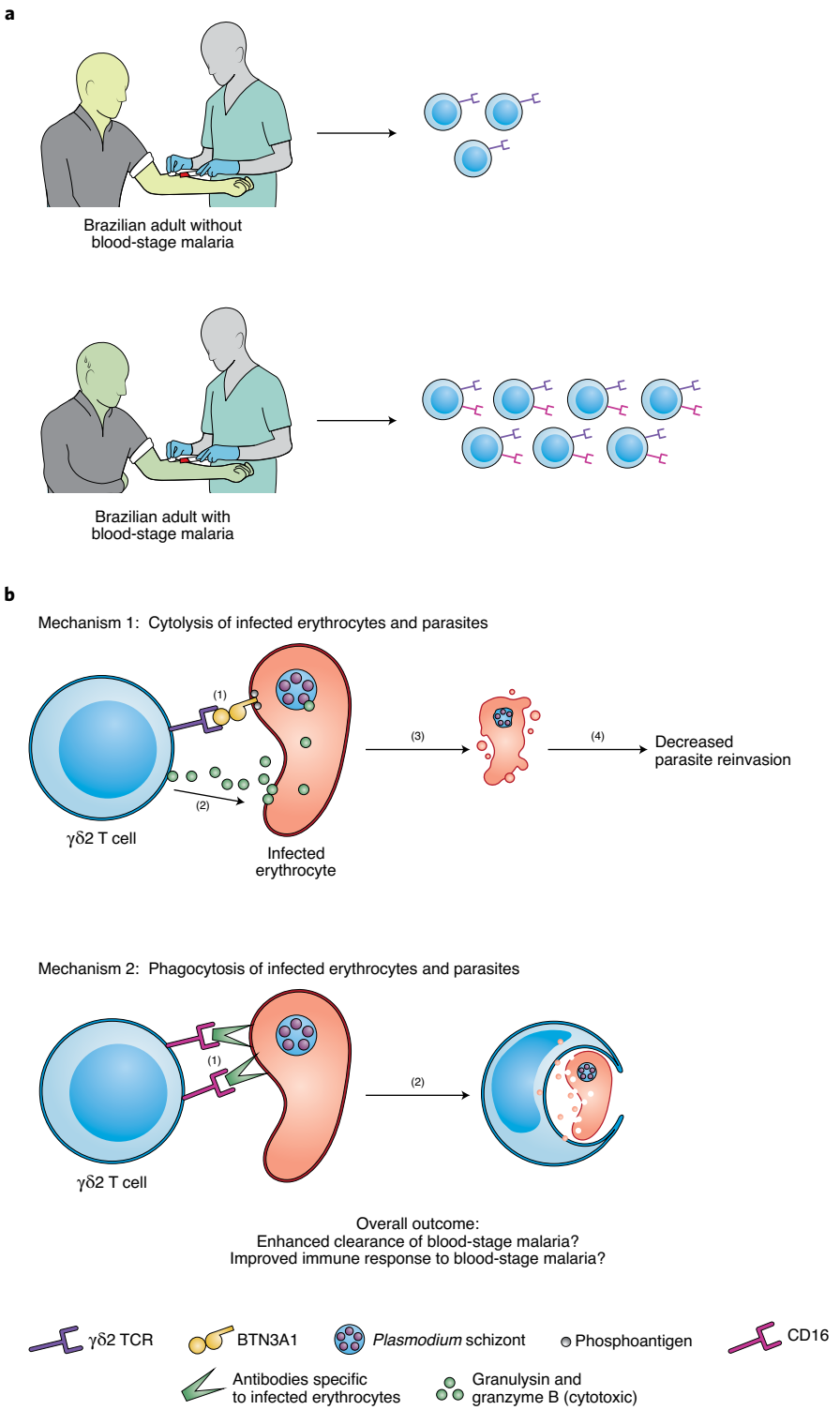

Fig. 1 | γδ2 T cells target *Plasmodium*-infected erythrocytes for destruction. a, Adults with blood-stage malaria infection have increased numbers of γδ2 T cells in the blood. These cells exhibit changes suggestive of activation and/or exhaustion. **b**, γδ2 T cells target infected erythrocytes in vitro for destruction by either secreting cytotoxic molecules or phagocytosing erythrocytes.

decreased parasitemia and disease reduction in malaria-infected humans. Additionally, and importantly, Junqueira et al. describe how γδ2 T cell parasite control could occur via antibody-mediated phagocytosis of infected erythrocytes, a finding that may lead to new discoveries regarding the control of blood-stage malaria by human intervention or that may even help to identify and limit malaria-associated pathology. The suggestion that γδ2 T cell antibody-mediated phagocytosis may contribute to the control of other infectious diseases or to the pathogenesis of autoimmune hemolytic anemias may inspire researchers to design experiments that rigorously evaluate this possibility.

These findings raise intriguing questions, and they provide direction for future studies. To what degree do the two newly characterized processes, namely γδ2 T cell destruction of infected erythrocytes and phagocytosis of infected erythrocytes, contribute, in either primary or recurrent infection, to the control of human blood-stage malaria? As the researchers note, these processes may influence subsequent immunological activity. It may be that γδ2 T cell–mediated lysis of infected erythrocytes causes the release of soluble danger- and pathogen-associated molecules that may further activate the immune system and contribute to host morbidity. It may also be true that γδ2 T cell phagocytosis of infected erythrocytes facilitates γδ2 T cell–mediated conditioning of other immune cells, thus augmenting the protective blood-stage malaria response. Additionally, since interactions between γδ2 T cells and infected erythrocytes may shape the local inflammatory milieu and thus disease pathogenesis, it will be of interest to study whether such interactions primarily occur in capillary beds found in organs such as the brain or in vascularized tissues such as the spleen or liver.

Perhaps future research will describe methods by which γδ2 T cell clearance of infected erythrocytes can be enhanced to promote the prevention and treatment of malaria infection. Researchers would benefit from gaining insight into how repeated malaria infections or vaccinations sculpt human γδ2 T cell quantity and functionality. It is important to note that furthering these ideas will require the use of either non-human primate tissue or human blood, as rodents commonly used in research lack granulysin and the type of γδ2 T cell referred to above. Scientists may then find means to manipulate, control or modify γδ2 T cell functionality to enhance host immunity to the parasite. ❐

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References

1. Crutcher, J. M. & Hoffman, S. L. in *Medical Microbiology* 4th edn (ed. Baron, S.) Ch. 83 (The University of Texas Medical Branch at Galveston, 1996).
2. Crompton, P. D. et al. *Annu. Rev. Immunol.* **32**, 157–187 (2014).
3. Long, C. A. & Zavala, F. *Cold Spring Harb. Perspect. Med.* **7**, a025577 (2017).
4. World Health Organization. *World Malaria Report 2018* (World Health Organization, 2018).
5. Junqueira, C. et al. *Nat. Immunol.* https://doi.org/10.1038/s41590-020-00847-4 (2021).
6. Lawand, M., Déchanet-Merville, J. & Dieu-Nosjean, M.-C. *Front. Immunol.* **8**, 761 (2017).
7. Farrington, L. A. et al. *J. Infect. Dis.* **213**, 1483–1490 (2016).
8. Zaidi, I. et al. *J. Immunol.* **199**, 3781–3788 (2017).
9. Ishizuka, A. S. et al. *Nat. Med.* **22**, 614–623 (2016).
10. Costa, G. et al. *Blood* **118**, 6952–6962 (2011).
11. Guenot, M. et al. *Infect. Immun.* **83**, 3816–3824 (2015).
12. Hernández-Castañeda, M. A. et al. *J. Immunol.* **204**, 1798–1809 (2020).