VACCINES

A novel vaccine target for malaria

> immunization with PfGARP may protect against blood-stage *P. falciparum*

Malaria is a leading cause of death in children; however, developing an effective vaccine has been challenging. Raj et al. now show that *Plasmodium falciparum* glutamic-acid-rich protein (PfGARP), an 80 kDa antigen expressed on the surface of erythrocytes infected by *P. falciparum*, is a malaria vaccine candidate for specifically targeting the blood stage of *P. falciparum*.

Drawing on their Tanzanian birth cohort study, in which they monitored parasitaemia in infants, the authors pooled plasma from individuals that were resistant to malaria and separately pooled plasma from individuals that were susceptible to malaria. Differentially biopanning a *P. falciparum* 3D7 blood-stage cDNA library with these pools identified 11 parasite antigens that were recognized specifically by antibodies in sera from malaria-resistant individuals, including PfGARP.

The authors found that PfGARP is specifically expressed in the early trophozoite stage and, importantly, previous analyses indicate that genome variation is low in the immunorelevant portion, referred to as PfGARP-A. Thus, they immunized mice with recombinant PfGARP-A (rPfGARP-A) or with a eukaryotic expression vector encoding PfGARP-A and found that, in growth-inhibition assays (GIAs) of parasite-infected human red blood cells (RBCs), PfGARP-A antiserum from mice immunized with either construct inhibited parasite growth by 94–99% compared with controls. Polyclonal PfGARP-A antibodies purified from adults living at the study site in Tanzania also inhibited parasite growth by 94–99% compared with controls. Furthermore, a monovalent antigen-binding fragment of a monoclonal antibody against rPfGARP-A inhibited parasite growth by 76–87%. Thus, PfGARP antibodies kill parasites in infected RBCs independently of cellular effector functions, the complement system or antigen cross-linking.

Interestingly, mitochondrial membrane potential and the integrity of the food vacuole were lost in parasites treated with PfGARP antibodies. Furthermore, PfGARP antibodies activated caspase-like cysteine proteases, and caused DNA fragmentation, in parasites. These data suggest that PfGARP antibodies trigger programmed cell death in *P. falciparum*.

To assess the clinical relevance of PfGARP antibodies, the authors measured anti-PfGARP immunoglobulin (IgG) levels in plasma obtained at 48 weeks of age from 246 children in their Tanzanian birth cohort; 48.8% of samples contained PfGARP IgG antibodies. Children had been followed for an average of 64 weeks, and models indicated that individuals without PfGARP IgG antibodies were 2.5-fold more likely to develop severe malaria over the follow-up period than individuals with PfGARP IgG antibodies.

Similarly, in a cohort of 135 Kenyan male individuals who were treated for malaria and followed with weekly blood smears for 18 weeks, models indicated that individuals without PfGARP IgG antibodies had an almost twofold higher density of parasites in blood smears than individuals with PfGARP IgG antibodies. Thus, these antibodies appear to reduce the risk of severe malaria and parasitaemia.

Finally, the authors immunized five *Aotus* monkeys with nucleoside-modified mRNA encoding PfGARP-A encapsulated in lipid nanoparticles, or rPfGARP-A emulsified in adjuvant. Three doses were given at 3-weekly intervals, and animals were challenged intravenously on day 63 with RBCs infected with blood-stage *P. falciparum* FVO. Immunized monkeys generated an antibody response, and control monkeys had 4.6-fold higher parasitaemia on day 13 than monkeys immunized with the mRNA vaccine and 3.5-fold higher parasitaemia on day 11 than monkeys immunized with the protein-based vaccine. Thus, both vaccines partially protected monkeys from high parasite burden in blood.

Immunization with PfGARP may protect against blood-stage *P. falciparum*, and PfGARP antibodies could inform antibody-based treatments for malaria. It will be interesting to see if vaccination with PfGARP synergizes with vaccines targeting other parasite stages.

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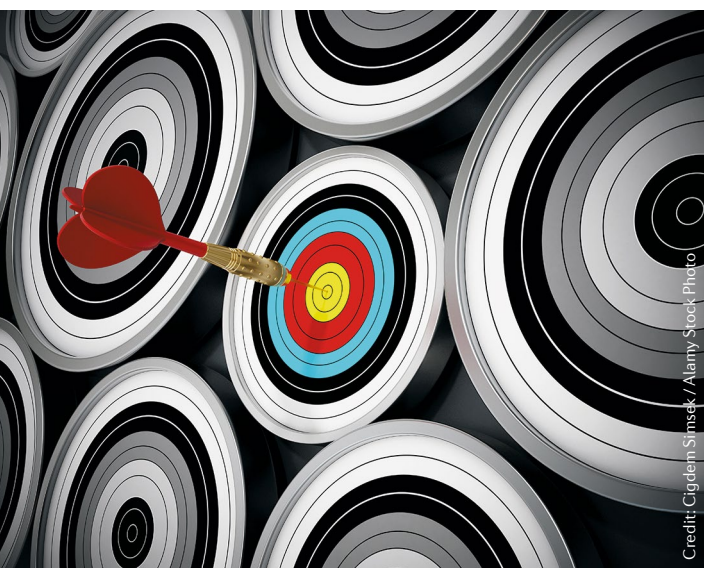
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ORIGINAL ARTICLE Raj, D. K. et al. Anti-PfGARP activates programmed cell death of parasites and reduces severe malaria. *Nature* https://doi.org/10.1038/s41586-020-2220-1 (2020)