

Researchers identify biomarker to predict if someone infected with malaria will get sick

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Credit: CDC

Immunological signatures can predict whether malaria-infected children will develop fever or other symptoms, suggests a study publishing September 3 in the journal *Immunity*. Surprisingly, activation of the well-known tumor-suppressor protein p53 is associated with enhanced protection against malaria fever—and increasing p53 in human immune cells and in mice results in a decrease in malaria-induced inflammation. The authors say the findings could lead to new strategies for dampening the harmful inflammatory responses associated with some infections and identifying individuals who might be at risk for such responses.

"Malaria is caused by the *Plasmodium falciparum* parasite and remains a major killer of children in Africa," says senior study author Peter Crompton of the National Institute of Allergy and Infectious Diseases. "Our limited understanding of how the human immune system controls malaria-induced inflammation and parasite growth impedes the development of vaccines and adjunctive therapies for this devastating disease."

Malaria is caused by parasites that are transmitted to people through the bites of infected mosquitoes. In 2017, there were approximately 219 million malaria cases worldwide and 435,000 malaria deaths. *P. falciparum* is the most prevalent malaria parasite in Africa and is responsible for most malaria deaths globally. In areas of intense transmission, children who survive the first five years of life have typically acquired immunity to severe malaria. But in non-immune individuals, *P. falciparum* malaria can cause fever and rapidly progress to severe illness and death if not treated early.

The development of a safe and effective vaccine could play a critical role in malaria elimination efforts. Although progress is being made, a malaria vaccine that reliably induces long-term protection remains elusive. The complexity of the *Plasmodium* parasite and the incomplete understanding of critical processes, such as host immune protection and disease pathogenesis, have hampered efforts to develop a vaccine.

Antimalarial drugs, in combination with mosquito control programs, have played a key role in controlling malaria in endemic areas, resulting in significant reduction of the geographic range of malarial disease worldwide. But the emergence and spread of drug-resistant parasites and insecticide-resistant mosquitos have contributed to a re-emergence of malaria, turning back the clock on control efforts. The need for new strategies to prevent malaria infection and disease has become a critical priority on the global malaria research agenda.

To gain insights into host factors that might protect against malaria disease, Crompton and first author Tuan Tran of Indiana University School of Medicine applied a systems biology approach to study children who differed in their ability to control parasite growth and fever following *P. falciparum* infection. They collected and analyzed [blood](#)

[samples](#) from healthy, uninfected Malian children at enrollment before the malaria season, during bi-weekly scheduled visits, and at their first malaria episode of the ensuing season. Specifically, the researchers integrated whole-blood transcriptomics with flow-cytometric analysis of blood cells and cytokine and antibody profiles. They focused on children aged 6-11 years, the age during which malaria immunity begins to be acquired in this region.

During the first malaria season, the researchers identified three distinct outcomes of *P. falciparum* infection. Twenty children were immune and showed no symptoms, 26 children showed early fever at the time of infection, and 34 children experienced delayed fever two days to two weeks later. Protection from malaria symptoms was associated with a pre-infection signature of B cell enrichment, platelet and monocyte activity, T helper cell responses, including interferon-driven pro-inflammatory responses, and p53 activation. In addition, control of parasite growth was associated with increased immunoglobulin G and Fc receptor activation prior to infection.

After this analysis, the researchers next set out to specifically investigate the role of p53 in malaria. Using multiple approaches in the laboratory, they found that increased p53 attenuates malaria-induced inflammation in human monocytes and in a mouse model of malaria, providing evidence that p53 activation contributes to the control of malaria fever. However, this study does not prove that p53 is directly involved in controlling the inflammatory response to malaria in humans.

"There has been extensive research on p53 in the context of cancer, but much less is known about its role in the immune response to infections, particularly in humans," Crompton says. "It may be that low expression of p53 in blood could serve as a marker for individuals or populations at greater risk of harmful inflammation when infected by malaria or other pathogens. Or perhaps increasing p53 pathways relevant to controlling inflammation could potentially reduce the severity of late-stage [malaria](#)."

Crompton notes that it will also be important to

investigate whether the findings are generalizable to other human populations and other [infectious diseases](#), and potentially to autoimmune diseases. "It will also be interesting to investigate the nexus between pathogen-induced modulation of p53 expression, particularly in the context of chronic or repeated infections, and cancer risk," he says.

More information: *Immunity*, Tran et al.: "A molecular signature in blood reveals a role for p53 in regulating malaria-induced inflammation"

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