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Novel DNA-sensing pathway in immune response to malaria

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Until very recently, it was unclear why infection with malaria causes fever and, under severe circumstances, an infectious death. Although the parasite has an abundance of potentially toxic molecules, no one knew which ones were responsible for the inflammatory syndrome associated with disease. Now, a new study identifies a novel DNA-sensing mechanism that plays a role in the innate immune response to the parasite that causes malaria. The findings, published online August 4th by Cell Press in the journal *Immunity,* provide new insight into how the immune system detects malaria and may have broad implications for treatment of multiple infectious diseases.

Malaria, the world's most common infectious disease, is caused by the parasite Plasmodium falciparum. Previous studies have implicated a role for Toll-like receptor (TLR) proteins in the host's ability to sense microbial pathogens like *P. falciparum*. TLRs are thought to detect regions of pathogen DNA that contain repeats of cytosine and guanine bases and regulate production of the immune chemical type I interferon. However, *P. falciparum* DNA is made predominantly of adenine (A) and thymine (T) bases and, thus far, a role for nucleic acid sensors in malaria has not been fully explored.

"Although TLR9 has been implicated in regulating type I interferon production during malaria in humans and mice, the unusually high A and T content in the DNA of *P. falciparum* prompted us to examine the possibility that malarial DNA triggers TLR9-independent DNA sensing pathways," says one of the study's senior authors, Dr. Douglas T.

Golenbock from the University of Massachusetts Medical School. Dr. Golenbock and colleagues showed that the AT-rich regions of the *P. falciparum* genome potently induced production of type I interferons via a novel TLR9-independent pathway. The researchers went on to show that the AT-rich DNA sensing involved an unknown receptor that coupled to molecules previously linked with DNA-mediated type I interferon production.

Taken together, the results suggest that this novel AT-rich DNA sensing pathway is important in the immune response to Plasmodial infection and may play a role in other infections as well. "As all organisms are defined by their DNA, it should not be surprising that it constitutes one of the most potent and specific immune activators," concludes study coauthor Dr. Kate Fitzgerald. "The importance of DNA recognition and type I interferon production is only now beginning to be appreciated in a large spectrum of infectious illnesses. In view of our results, as well as the emerging literature on DNA sensing, we predict that immune recognition of DNA will be an increasingly common theme in pathogenesis."

Provided by Cell Press