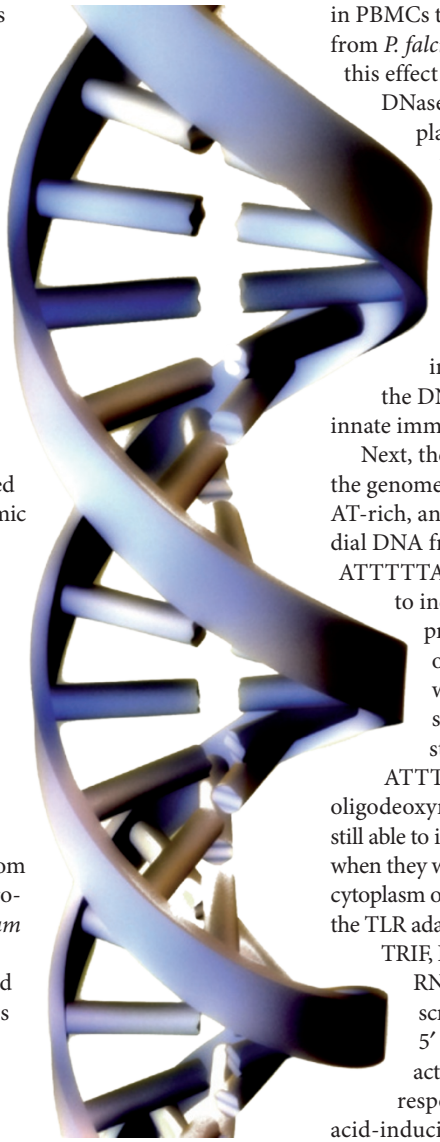
INNATE IMMUNITY

AT-rich DNA trapped in the cytoplasm

Pathogen-derived DNA triggers the production of type I interferons (IFNs) and other pro-inflammatory cytokines. DNA sensors identified to date include Toll-like receptor 9 (TLR9) in endosomes, and DNA-dependent activator of IFN-regulatory factors (DAI; also known as ZBP1), RNA polymerase III, absent in melanoma 2 (AIM2) and IFNγ-inducible protein 16 (IFI16) in the cytoplasm. Now, a study published in *Immunity* reports that parasite-derived AT-rich DNA is detected by an as yet unknown cytoplasmic DNA sensor and induces type I IFNs.



Analysis of peripheral blood mononuclear cells (PBMCs) from patients with malaria indicated a high level of expression of type I IFNs, and the authors investigated what initiates this response to *Plasmodium falciparum* infection. Haemozoin is an insoluble crystal — formed from haemoglobin following erythrocyte infection with *P. falciparum* — that binds to plasmodial DNA. Imaging studies revealed that, following its phagocytosis by PBMCs, haemozoin localizes in lysosomes and later in the cytoplasm. Interestingly, IFNβ expression was induced in PBMCs treated with haemozoin from *P. falciparum* cultures, and this effect was blocked following DNase treatment. Moreover, plasmodial DNA delivered to the cytoplasm also induced type I IFNs. These results suggest that haemozoin binds to plasmodial DNA and delivers it to the cytoplasm of innate immune cells, where the DNA can then trigger an innate immune response.

Next, the authors observed that the genome of *Plasmodium* spp. is AT-rich, and cytoplasmic plasmodial DNA fragments containing the ATTTTTAC motif were sufficient to induce type I IFNs. The pro-inflammatory activity of these DNA fragments was dependent on their stem–loop secondary structure. Strikingly, ATTTTTAC motif-containing oligodeoxynucleotides (ODNs) were still able to induce IFNβ expression when they were delivered to the cytoplasm of cells deficient for TLR9, the TLR adaptor proteins MYD88 and TRIF, IFI16 or DAI. Although RNA polymerase III transcribes AT-rich DNA into 5′ triphosphate RNA, which activates the type I IFN response through retinoic acid-inducible gene I (RIG-I), components of this pathway were also not required for the induction of type I IFNs by plasmodial DNA. Thus, the authors suggest that AT-rich plasmodial DNA induces type I IFNs through an as yet unknown cytoplasmic DNA sensor.

Moreover, they demonstrated that stimulator of interferon genes (STING) and TANK-binding kinase 1 (TBK1) — which are both downstream effectors of the DNA-induced type I IFN response — are essential for innate immune activation by plasmodial DNA, and cytoplasmic ATTTTTAC motif-containing ODNs formed a complex with STING and TBK1. Further studies showed that IFNβ expression in response to AT-rich cytoplasmic DNA is induced via interferon-regulatory factor 3 (IRF3) and IRF7.

Finally, in a model of cerebral malaria, mice deficient for the type I IFN receptor were almost completely protected from death, and mice deficient for IRF3 and IRF7 exhibited less severe symptoms than wild-type controls. So, the characterization of the type I IFN-inducing cytoplasmic AT-rich DNA sensor may provide a new target for the treatment of malaria pathogenesis.

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ORIGINAL RESEARCH PAPER Sharma, S. *et al.* Innate immune recognition of an AT-rich stem-loop DNA motif in the *Plasmodium falciparum* genome. *Immunity* 4 Aug 2011 (doi:10.1016/j.immuni.2011.05.016)

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