

 PARASITE PHYSIOLOGY

Linking virulence and transmission in malaria

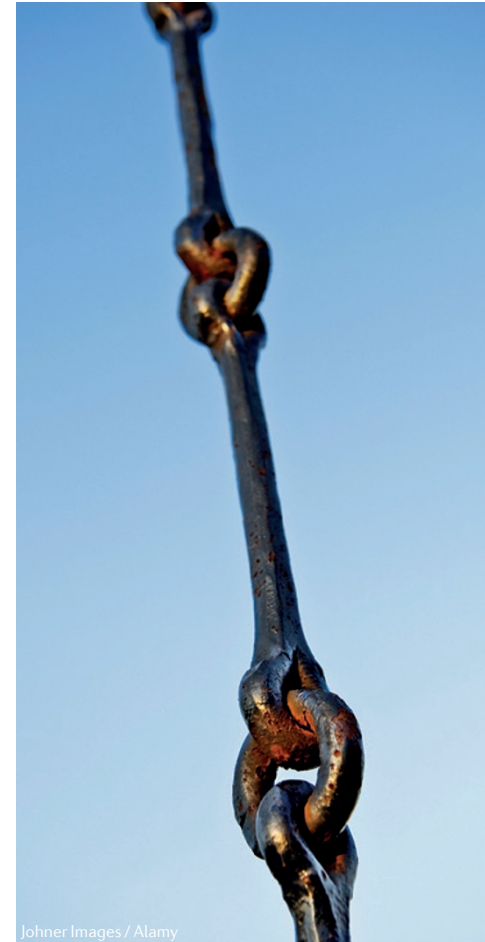
To ensure transmission to the next human host, the malaria parasite *Plasmodium falciparum* must differentiate from asexually replicating parasites, which proliferate in human erythrocytes, to sexual gametocytes, which are taken up by mosquitoes during a blood meal. Furthermore, asexual parasites evade host immune responses by regularly switching the expression of antigens on the surface of infected erythrocytes. Although epigenetic modifications are suggested to be involved in regulating both sexual differentiation and antigenic variation, the mechanistic basis of this is not fully understood. Two studies now identify the *P. falciparum* proteins heterochromatin protein 1 (PfHP1) and histone deacetylase 2 (PfHda2) as key regulators of both processes, which provides a mechanistic link between parasite virulence and transmission.

Antigenic variation in *P. falciparum* is primarily mediated by switching the expression of the *var* genes, which encode the *P. falciparum* erythrocyte membrane protein 1 (PfEMP1). Each parasite expresses only one *var* gene at a time but can switch which gene is expressed to evade immunity. As histone modifications are known to contribute to changes in the expression of *var* genes, Brancucci, Bertschi *et al.* and Coleman, Skillman *et al.* investigated how two chromatin-associated proteins — PfHP1 and PfHda2, respectively — contribute to the regulation of antigenic variation. Brancucci, Bertschi *et al.* generated a conditional loss-of-function variant of PfHP1, which binds to the trimethylated lysine 9 residue of histone 3 (H3K9me3) and represses

gene expression, whereas Coleman, Skillman *et al.* conditionally depleted PfHda2, which is a predicted histone deacetylase. Notably, the depletion of both proteins resulted in the derepression of many genes, and the strongest derepression corresponded to the *var* genes. The increased expression of multiple *var* genes was associated with decreased levels of H3K9me3 in both mutants, and PfHP1-depleted parasites were shown to co-express several PfEMP1 variants. Together, these data show that gene repression that is mediated by PfHP1 and PfHda2 regulates antigenic variation.

In addition to the derepression of *var* genes, depletion of PfHP1 and PfHda2 also resulted in increased expression of several genes that are associated with sexual differentiation, particularly *pfap2-g*, which encodes the master regulator of gametocytogenesis — the transcription factor AP2-G. Using an *in vitro* gametocyte conversion assay, PfHda2-depleted parasites were found to produce more gametocytes than wild-type *P. falciparum*. Similarly, immunofluorescence assays showed that a higher proportion of PfHP1-depleted parasites differentiated into gametocytes than wild-type *P. falciparum*. These data show that PfHP1 and PfHda2 control sexual differentiation in *P. falciparum* by regulating the expression of *pfap2-g*.

Collectively, these results demonstrate that PfHP1 and PfHda2 regulate both antigenic variation and gametocytogenesis. This is consistent with a model in which PfHda2-mediated H3 deacetylation increases H3K9me3 levels and



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thereby functions as an upstream regulator that promotes the binding of PfHP1 to chromatin. Given the central role that these two proteins have in regulating the virulence and transmission of *P. falciparum*, it will be interesting to see whether PfHP1 and PfHda2 interact to form a silencing complex and whether such a complex constitutes a promising drug target to prevent the transmission of malaria.

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ORIGINAL RESEARCH PAPERS Brancucci, N. M. B., Bertschi, N. L. *et al.* Heterochromatin protein 1 secures survival and transmission of malaria parasites. *Cell Host Microbe* **16**, 165–176 (2014) | Coleman, B. I., Skillman, K. M. *et al.* A *Plasmodium falciparum* histone deacetylase regulates antigenic variation and gametocyte conversion. *Cell Host Microbe* **16**, 177–186 (2014)

“ PfHP1 and PfHda2 regulate both antigenic variation and gametocytogenesis ”