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PARASITE PHYSIOLOGY

RNase silences *Plasmodium* antigens

Immune evasion by *Plasmodium falciparum* involves differential expression of *var* genes, which encode members of the *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) family that are expressed on the surface of infected erythrocytes; however, the mechanistic basis of antigenic variation is poorly understood. Now, Scherf and colleagues identify a novel exoribonuclease that silences the expression of *var* gene transcripts, which are involved in the pathogenesis of severe malaria.

P. falciparum usually expresses only one *var* gene variant at a time (known as monoallelic expression), and the *upsA* subgroup in particular is associated with severe malaria. Apart from histone modifications, other potential post-transcriptional mechanisms that control antigenic variation are understudied, which led the authors to examine whether RNA-based regulation might occur. Bioinformatic analysis of the *P. falciparum* genome identified a non-canonical exoribonuclease that contains a putative RNase II domain (termed PfRNase II), and immunoelectron microscopy, in combination with RNA degradation experiments, showed that it localizes to the nucleus and degrades single-stranded RNA. Collectively, these data suggest that PfRNase II has a potential role in mediating the decay of mRNAs.

But does PfRNase II target *var* gene transcripts? RNA sequencing analysis of total RNA revealed that, compared with wild-type parasites, *upsA* genes were strongly upregulated in parasites that expressed a defective PfRNase II. Furthermore, real-time quantitative PCR (qPCR) showed that different combinations of up to three distinct *upsA* genes, together with a *upsC* gene, were upregulated simultaneously in single parasite clones, which indicates that loss of PfRNase II activity abolishes monoallelic *var* gene expression and induces the switching of *upsA* genes. Chromatin immunoprecipitation (ChIP)–qPCR confirmed that PfRNase II is enriched at the promoters and introns of silenced *upsA* transcripts, and transcription analysis revealed that the nascent transcripts are only short-lived, cryptic mRNAs. Finally, the authors demonstrated that PfRNase II activity is clinically relevant, as parasites from patients with severe malaria showed an inverse correlation between the levels of *PfRNase II* and *upsA* mRNAs.

This study identifies a novel exoribonuclease that promotes monoallelic *var* gene expression in malaria parasites. It will be interesting to see whether this mechanism is a widespread phenomenon for the control of antigenic variation in *Plasmodium* spp.

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> “a novel exonuclease that promotes monoallelic *var* gene expression in malaria parasites”

ORIGINAL RESEARCH PAPER Zhang, Q. *et al.* Exonuclease-mediated degradation of nascent RNA silences genes linked to severe malaria. *Nature* http://dx.doi.org/10.1038/nature13468 (2014)