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PARASITE BIOLOGY

The antisense antigen switch

Antigenic variation, which is an important strategy used by the malaria parasite *Plasmodium falciparum* to evade the human immune system, results from switches in the expression of members of the multicopy *var* gene family. The *var* genes encode erythrocyte membrane protein 1 (PfEMP1), which is expressed on the surface of infected erythrocytes, with only a single PfEMP1 variant being expressed at any given time. The regulatory mechanisms controlling *var* gene expression are not fully understood, but Dzikowski and colleagues now show that antisense long noncoding RNAs (lncRNAs) contribute to the mutually exclusive activation pattern of these genes.

var loci exhibit a distinctive genetic architecture, in which an upstream promoter controls mRNA transcription and an internal promoter directs bidirectional transcription of two lncRNAs. The sense lncRNA is postulated to have a role in regulating epigenetic memory by imprinting *var* genes for silencing, but little is known about the antisense lncRNA, other than that its sequence is complementary to the variable region of its cognate *var* gene, which led the authors to reason that it might have a role in *var* gene activation.

Using reverse transcription quantitiative PCR on parasite cell lines, the authors demonstrated that the cognate antisense lncRNA of the active *var* gene was expressed, whereas no antisense transcripts from silenced *var* gene loci were detectable. Furthermore, lncRNAs were found to be produced from late ring-stage parasites during the intraerythrocytic cycle when the upstream promoter of their corresponding *var* gene was active, which shows that the antisense lncRNA is associated exclusively with the active *var* gene. Moreover, chromatin immunoprecipitation experiments showed that the antisense lncRNAs are incorporated into chromatin, providing additional evidence for a potential role in gene regulation.

Next, the authors tested whether delivery of an antisense lncRNA could activate expression of its cognate *var* gene. Indeed, transfection of the antisense transcript into cells in which the corresponding *var* gene was silent resulted in *var* gene activation in a sequence- and dose-dependent manner. By contrast, knockdown of the antisense lncRNA using peptide nucleic acids silenced the active *var* gene and induced antigen switching.

Together, these data provide compelling evidence that antisense lncRNAs contribute to *var* gene activation and antigenic variation in *P. falciparum*. Although the precise mechanistic details of *var* gene activation remain elusive, Dzikowski and colleagues suggest that antisense lncRNAs may regulate gene expression through the recruitment of chromatin-remodelling enzymes or transcription factors, or by preventing the binding of gene-silencing insulator proteins.

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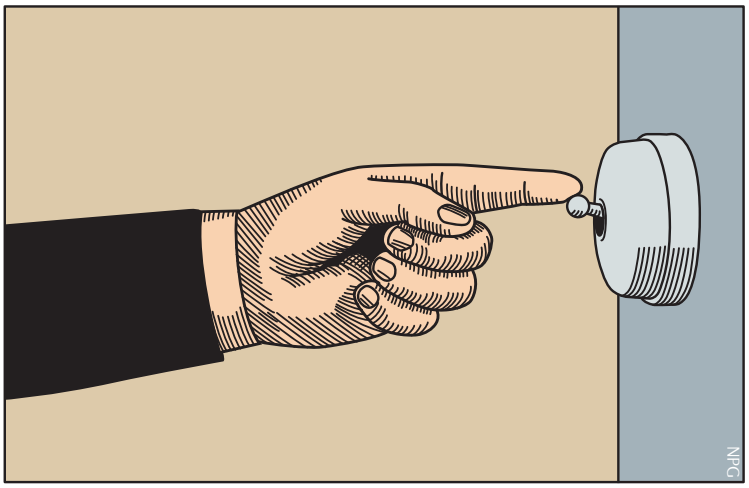

> “lncRNAs contribute to *var* gene activation and antigenic variation in *P. falciparum*”

ORIGINAL RESEARCH PAPER
Amit-Avraham, I. *et al.* Antisense long noncoding RNAs regulate *var* gene activation in the malaria parasite *Plasmodium falciparum*. *Proc. Natl Acad. Sci. USA* http://dx.doi.org/10.1073/pnas.1420855112 (2015)