Malaria

Thermoregulation in a parasite's life cycle

The life cycle of the malaria parasite *Plasmodium falciparum* goes through three developmental stages (schizogony, gametogony and sporogony), each of which presents different environmental constraints that must be met by an adaptive response in the parasite. Here we show that thermoregulation, in which the transcription of select RNAs is upregulated at cooler temperatures, is crucial to the developmental transition that occurs during the transmission of *P. falciparum* from human to mosquito. Our findings offer new insight into how the malaria parasite senses and reacts to its environment.

Switching between two sequence types of ribosomal RNA (designated A and S) occurs during the developmental cycle of *Plasmodium*[1–5]. Although the resulting ribosomes still translate messenger RNA into protein, there are functional variations between the two types[6]. Polymorphisms in the sequences preceding two mature A-type rRNAs (A1, A2; GenBank accession numbers, AF503871 and AF5033868) and two mature S-type rRNAs (S1, S2; GenBank accession numbers, AF 503869 and AF503870) enabled us to follow the regulation of transcription of each precursor independently[7] by real-time polymerase chain reaction. We found that precursors A1 and A2 are the predominant forms during schizogony, whereas S1 predominates during gametogony and S2 during sporogony.

We investigated the effect of temperature as a differential regulator of transcription. A single asexual parasite culture was split and the portions were incubated for 3 h at four different temperatures (Fig. 1a). The transcription of *A1* and *A2* remained relatively constant, but the rate of *S*-gene transcription was sensitive to temperature: at 42 °C, neither *S* gene was transcribed; *S2* transcription increased 4.4-fold at 31 °C and 15-fold at 26 °C (monitored for comparison with *S2* transcription at 37 °C). The *S1* gene was affected by decreasing the temperature, but not as markedly.

We used nuclear run-on analysis[8] to confirm this pattern of temperature regulation (Fig. 1b). We also measured the rates of transcription of three mRNAs, namely those encoding the *P. falciparum* proteins HRPIII, MSP-1 and CSP (Fig. 1a). Our findings are consistent with the rRNA results in that the levels of the mRNAs associated with schizogony, HRPIII and MSP-1, tend to fall off at reduced temperature, whereas CSP mRNA, which is associated with sporogony, increases. If the duration of culture is extended to 7 h, the difference in *S2* transcription at 26 °C and at 37 °C is more than 20-fold (Fig. 1c).

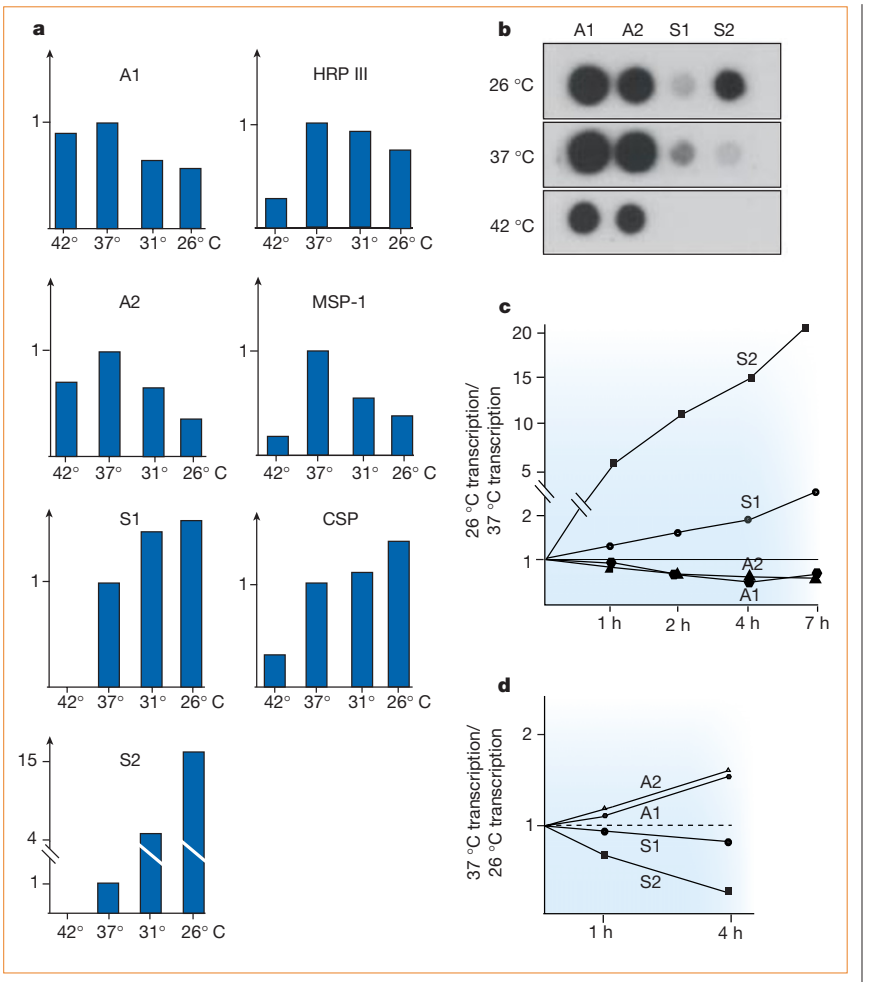

Figure 1 Effect of temperature on the transcription of selected genes in the malaria parasite. **a,** Transcription of individual genes (see text) at different temperatures likely to be encountered by *Plasmodium falciparum*. Results in asexual blood-stage parasites were determined by real-time polymerase chain reaction; the amount of transcription at 37 °C was taken as unity. **b,** Nuclear run-on analysis of the variation in transcription from ribosomal RNA genes with temperature. **c,** Changes over time in the relative levels of transcription at 26 °C and 37 °C of the different rRNA genes during the asexual blood stage. **d,** Changes over time in the relative levels of transcription at 37 °C and 26 °C of rRNA genes in mosquito-stage parasites.

This transcriptional control is evident by simply altering the temperature of the mosquito itself: we find that transcription of the *S2* gene, but not of the other rRNA genes, is inhibited by warming (Fig. 1d).

A strong, cold-stimulated promoter might be responsible for this selective control of transcription. When we transfected *P. falciparum* with a chimaeric plasmid containing an *S2* promoter region aligned with a fragment of the luciferase gene, we found that promoter control was fully operative over the range of temperatures at which *P. falciparum* is viable in culture (results not shown).

Temperature control is important with regard to malaria, given that vacillating ambient temperatures affect the rate of development of *P. falciparum* in the mosquito[9]. Our results provide a framework for understanding how the malaria parasite responds to its environment, as well as indicating how this process might be investigated further.

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CORRECTIONS & AMENDMENTS

CORRIGENDUM

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Corrigendum: Malaria: Thermoregulation in a parasite's life cycle

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In the first paragraph of this Brief Communications, accession numbers are provided for four rRNAs. The database that they refer to is incorrect (it should be the European Nucleotide Archive (ENA) rather than GenBank), the order in which the accessions are indicated is also incorrect, and there is an extra '3' in one the of accession numbers. The text should say: "…two mature A-type rRNAs (A1, A2; ENA accession numbers, AF503871 and AF503870) and two mature S-type rRNAs (S1, S2; ENA accession numbers, AF503869 and AF503868)…".