A var gene upstream element controls protein synthesis at the level of translation initiation in Plasmodium falciparum

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Clonally variant protein expression in the malaria parasite Plasmodium falciparum generates phenotypic variability and allows isogenic populations to adapt to environmental changes encountered during blood stage infection. The underlying regulatory mechanisms are best studied for the major virulence factor P. falciparum erythrocyte membrane protein 1 (PfEMP1). PfEMP1 is encoded by the multicopy var gene family and only a single variant is expressed in individual parasites, a concept known as mutual exclusion or singular gene choice. var gene activation occurs in situ and is achieved through the escape of one locus from epigenetic silencing. Singular gene choice is controlled at the level of transcription initiation and var 5' upstream (ups) sequences harbour regulatory information essential for mutually exclusive transcription as well as for the trans-generational inheritance of the var activity profile. An additional level of control has recently been identified for the var2csa gene, where an mRNA element in the 5' untranslated region (5' UTR) is involved in the reversible inhibition of translation of var2csa transcripts. Here, we extend the knowledge on post-transcriptional var gene regulation to the common upsC type. We identified a 5' UTR sequence that inhibits translation of upsC-derived mRNAs. Importantly, this 5' UTR element efficiently inhibits translation even in the context of a heterologous upstream region. Further, we found var 5' UTRs to be significantly enriched in uAUGs which are known to impair the efficiency of protein translation in other eukaryotes. Our findings suggest that regulation at the post-transcriptional level is a common feature in the control of PfEMP1 expression in P. falciparum.
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