TRANSLATIONAL REGULATION OF *VAR2CSA*, A GENE IMPLICATED IN PLACENTAL SEQUESTRATION OF MALARIA PARASITES.

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Pregnancy-associated malaria is a significant cause of morbidity and mortality inflicted yearly by this disease. Erythrocytes infected with *Plasmodium falciparum* adhere directly to chondroitin sulphate A on the syntitiotrophoblast of the placenta. This interaction is mediated by a particular PfEMP-1 variant, a parasite receptor which is expressed on the erythrocyte surface and encoded by the *var2csa* gene, an unusual member of the *var* multigene family. *var2csa* has a unique 5' noncoding region that harbors a conserved upstream open reading frame (uORF). Reporter constructs with an intact uORF in the 5' upstream region were inactive in transient and stable transfection assays, whereas mutation of the uORF restored expression to levels typical of *var* reporter constructs. Repression was shown to occur at the translational, rather than transcriptional level, revealing a novel form of regulation of a *var* gene. The uORF supports initiation of translation but the sequence of the encoded peptide does not need to be maintained for repression to occur, arguing against a peptide-mediated repression mechanism. Clones of a laboratory line of *Plasmodium falciparum* were identified where *var2csa* is transcribed to high levels but no protein can be detected at the plasma membrane, indicating that translational repression occurs *in vivo*. This novel regulatory mechanism has important implications for design of drugs and vaccines targeting pregnancy-associated malaria.