Genetic organization and expression profiling of the Plasmodium falciparum var gene repertoire

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ABSTRACT

The *var* gene encoded *P. falciparum* membrane protein-1 (PfEMP1) expressed at the infected red blood cell surface is an important target for the development of protective anti-malaria immunity and is implicated in the pathology of malaria through its ability to adhere to host endothelial receptors. Each parasite genome contains approximately 60 *var* gene copies and the parasite is thought to evade immune responses by presenting antigenically diverse PfEMP1 variants. It has been shown that a common and conserved subset of PfEMP1 is associated with severe malaria and thus expression of this subset may confer a selective advantage to the parasite in non-immune individuals, perhaps by allowing particularly efficacious endothelial sequestration and consequently high effective growth rates. This study aimed to define PfEMP1 subtypes and their functional differences.

The first fully sequenced *P. falciparum* genome (the 3D7 genome) enabled a comprehensive analysis of a single parasite's full *var* gene repertoire. The analysis showed that *var* genes can be divided into three major groups, A-C as well as at least three single copy intergenomic conserved *var* genes *var1-3* and allowed the design of both 3D7 *var*/PfEMP1 specific as well as universal *var* group specific real time PCR primers.

3D7 gene specific primers were used in real time PCR on 3D7 parasites isolated from experimentally infected malaria naïve volunteers. The study revealed that all *var* genes are transcribed at liver release but that *var* genes of type A were among the lowest transcribed and an increased expression of a subset of A and B *var* genes in parasites exhibiting with high multiplication rates. The 3D7 *var* gene specific primers were also applied to investigate the *var* gene transcription in the sexual stages of the parasite life cycle. The study showed that transcription in gametocytes is unlinked to *var* transcription in their asexual progenitors and suggested a programmed *var* transcription in favour of *var* group C genes.

Finally, the genetic organization of *var* genes was exploited to design *var* gene group specific primers for the investigation of *var* transcription in parasites collected from malaria infected Tanzanian children. Transcription of *var* group A and B genes were found to be higher in parasites from individuals suffering from severe malaria compared to parasites from individuals with uncomplicated malaria, whereas genes belonging to group C were transcribed at similar levels in both patient groups.

In conclusion, the present dissertation suggests that *var* subtypes can be defined based on primary sequence similarities, and that these represent a functional diversification of the PfEMP1 family that has relevance for the disease outcome. Further elucidation of *var* subfamilies and their function are important for the development of a PfEMP1 based anti-malaria vaccine.