Fatal attraction

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The malaria parasite *Plasmodium falciparum* can cause both severe and fatal disease. This stems, in part, from the adherence and sequestration of parasitized erythrocytes at blood microvasculature sites throughout the body. A recent study that analyzed tissues recovered from patients that had succumbed to malarial infection now suggests that the expression of a small number of parasite-encoded *var* genes contributes to organ-specific sequestration, and subsequent disease.

The *var* genes encode *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) proteins, a set of highly diverse surface-expressed protein variants that mediate the adhesion of erythrocytes infected with asexual blood-stage parasites to the host endothelium. By adherence and sequestration within the microcirculation of tissues, parasitized erythrocytes are able to escape spleen-mediated clearance, and severe malaria can develop if the local interactions are extensive. Furthermore, switching of the expressed PfEMP1 protein during the course of a blood-stage infection is an important part of antigenic variation, which is used by the parasite to escape the human host defences. To investigate the role of *var* gene expression in severe and fatal malaria infections, Montgomery and colleagues focused on a unique resource of tissue samples taken from patients with fatal paediatric malaria. Reporting in *Molecular Microbiology*, the authors analyzed *var* gene transcription by *P. falciparum* parasites that were extracted from the brain, lung, heart and spleen of a small group of these patients.

The expression of *var* genes in human hosts is highly complex. Despite detecting parasite expression of up to 102 different *var* genes in a single host, the authors found that only one or two of these genes were expressed at high levels within the brain and heart tissue of these patients. This was particularly evident in brain tissue, where dominant *var* types constituted 30–50% of all clones detected, despite being present at only low levels in other organs. Indeed, the pattern of dominant *var* gene expression by the parasite varied between organs. These findings strongly suggest that the PfEMP1 proteins encoded by a small number of *var* genes are responsible for the adherence and sequestration of parasitized erythrocyte within the brain microvasculature. The authors also investigated whether there were any similarities in *var*

gene expression patterns between patients. Their analysis revealed that there was significant overlap in the *var* types expressed by parasites that infected different patients. In addition, the organ-specific localization of *var* gene expression was conserved between patients. For example, identical *var* types were expressed in the brains of multiple patients from a single malaria season.

Together, these findings provide convincing evidence that specific variants of the PfEMP1 protein mediate the preferential sequestration of *P. falciparum*-infected erythrocytes within the microvasculature of specific organs in the human host. These data also suggest that the number of *var* types that mediate parasite adherence is limited, a finding that could be exploited in the development of new agents designed to block or reverse this pathogenic process.

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ORIGINAL RESEARCH PAPER

Montgomery, J. et al. Differential *var* gene expression in the organs of patients dying of *falciparum* malaria. *Mol. Microbiol.* 6 July 2007 (doi:10.1111/j.1365-2958.2007.05837.x).

A haematoxylin- and eosin-stained section of brain taken from a patient with paediatric cerebral malaria. The image shows a collection of parasitized red blood cells within the lumen of a larger blood vessel, at $\times 1,000$ oil magnification. Image kindly provided by Dan Milner, Harvard School of Public Health, Boston, USA.