Malaria virulence genes: Complex control

Review by Dr Catherine Merrick– Keele University

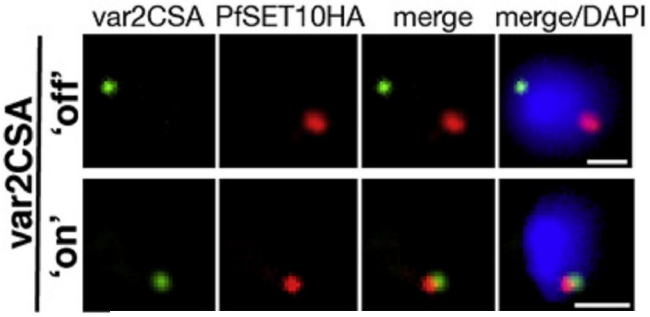

Image taken from Volz *et al.* (2012)

A new paper published in Cell Host and Microbe (Volz *et al.* (2012)) improves our understanding of the chromatin-bound complexes that control a crucial virulence trait in the human malaria parasite.

Plasmodium falciparum causes disease by invading red blood cells. It multiplies inside them and modifies their surfaces with proteins called PfEMP1s that bind to the walls of capillaries. This is crucial for parasite survival but it also contributes to disease, particularly when infected cells accumulate in vessels of the brain and placenta. Understanding the mechanisms that control the expression of these adhesive PfEMP1 proteins is therefore of great interest to malaria biologists.

PfEMP1 is not expressed uniformly: instead, parasites regularly switch between about 60 different variants. This allows them to stay ahead of the immune system and sustain a chronic infection. The parasite has a large family of '*var*' genes encoding different PfEMP1 proteins and their expression is varied by changes in chromatin structure: so-called epigenetic switching. Volz and co-workers have now characterized a new member of the epigenetic toolkit: the histone methyltransferase PfSET10. They present evidence that PfSET10 methylates lysine 4 of histone H3 (H3K4) within the single active *var* gene. This is thought to mark the gene in a 'poised' state, allowing the parasite to maintain its expression over several division cycles and thus avoid premature exhaustion of the PfEMP1 repertoire. This 'epigenetic memory' is central to antigenic variation.

Volz *et al*. show that PfSET10 binds to unmethylated histone H3 and, although an active recombinant enzyme could not be made, an immunoprecipitate enriched in endogenous PfSET10 did methylate recombinant H3. Furthermore, the protein co-localizes in the parasite nucleus with the active euchromatic*var* gene, which occupies a distinct spot from silent heterochromatic *var* genes. A specific influence on the active *var*was further evidenced by RT-PCR in a parasite carrying GFP-tagged PfSET10. Tagging may alter the enzyme's activity, and these parasites showed a specific increase in transcription of the active *var* gene, while general *var* silencing remained intact.

Interestingly, PfSET10 co-precipitated with actin, which has been proposed to help to localize the active *var* gene within the nucleus. It also associated with other DNA- or RNA-binding proteins with which it may form a large chromatin-modifying complex. Further work is now required to find out how all these players are linked in the unified transcriptional control system that underpins the persistence of chronic malaria.

Full text article: *http://www.sciencedirect.com/science/article/pii/S1931312811004033.*
PfSET10, a Plasmodium falciparum Methyltransferase, Maintains the Active var Gene in a PoisedState during Parasite Division. 2012. Volz JC, et al. 2012 Cell Host Microbe; 11(1):7-18.

Catherine Merrick is new to the faculty of Life Sciences at Keele University, having completed her first post-doc at Harvard: she uses molecular genetics to study virulence traits in the malaria parasite.