PARASITOLOGY

Hidden treasure uncovered?

Although apicomplexan parasites, such as the human pathogens *Plasmodium falciparum*, *Toxoplasma gondii* and *Cryptosporidium parvum*, undergo many morphological changes during their life cycles, recognizable transcription factors are conspicuously absent from their genomes. However, the remarkable sequential expression of genes during the *P. falciparum* intraerythrocytic cycle indicates that a well-timed transcriptional programme is present. A report in the *Proceedings of the National Academy of Sciences USA* now shows that apicomplexans do contain proteins that bind DNA in a sequence-specific manner, providing the first evidence for apicomplexan transcription factors.

De Silva and colleagues investigated the DNA-binding properties of two *P. falciparum* proteins that belong to the apicomplexan AP2 (ApiAp2) family, which share low similarity with the plant DNA-binding proteins AP2/ERF. By screening a protein-binding microarray that contained ~44,000 60-mer features and covered all possible 10-mer sequence variations with recombinant forms of the AP2 domain of the two ApiAP2 proteins, De Silva and colleagues established that these proteins bind to distinct and specific DNA-sequence motifs, which they confirmed biochemically using electrophoretic mobility-shift assays.

Both motifs had a G+C content that was greater than the average for intergenic regions of *P. falciparum* (>90% A+T). This presumably increases specificity, as regulatory motifs are rare in low G+C regions. Using the binding motifs and the *P. falciparum* genome sequence as a guide, De Silva *et al.* went on to determine the possible regulons for the two proteins. The first regulon was enriched in genes that are involved in protein modification, phosphorylation, proteolysis and apical organelle function (which play a part in host invasion), whereas the second regulon contained genes that are involved in binding to the microvasculature. The average timing of expression of the genes in the first regulon lagged behind the expression of its ApiAP2 protein by ~1 hour, which provides further evidence that the ApiAP2 protein regulates these genes. Furthermore, the promoter of the gene that encodes this ApiAP2 protein contains binding motifs for both ApiAP2 proteins examined, suggesting both autoregulation and a cascade of regulation by ApiAP2 proteins. Such a regulatory network could facilitate the remarkable transcriptional pattern that is observed in *P. falciparum*. Testing of a *C. parvum* orthologue revealed cross-species conservation of DNA-binding specificity, but a lack of similarity in predicted target regulon genes indicates a divergence in function.

The discovery of possible transcription factors in apicomplexans might enable a better understanding of the timing of transcription in *Plasmodium* spp. and other apicomplexans, provide insight into the external factors that regulate transcription and, given the lack of similarity to human proteins, provide another much needed drug target.

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ORIGINAL RESEARCH PAPERORIGINAL
De Silva, E. K. *et al.* Specific DNA-binding by Apicomplexan AP2 transcription factors. *Proc. Natl Acad. Sci. USA* **105**, 8393–8398 (2008)