A major role for the Plasmodium falciparum ApiAP2 protein PfSIP2 in chromosome end biology

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The heterochromatic environment and physical clustering of chromosome ends at the nuclear periphery provide a functional and structural framework for antigenic variation and evolution of subtelomeric virulence gene families in the malaria parasite Plasmodium falciparum. While recent studies assigned important roles for reversible histone modifications, silent information regulator 2 and heterochromatin protein 1 (PfHP1) in epigenetic control of variegated expression, factors involved in the recruitment and organization of subtelomeric heterochromatin remain unknown. Here, we describe the purification and characterization of PfSIP2, a member of the ApiAP2 family of putative transcription factors, as the unknown nuclear factor interacting specifically with cis-acting SPE2 motif arrays in subtelomeric domains. Interestingly, SPE2 is not bound by the full-length protein but rather by a 60kDa N-terminal domain, PfSIP2-N, which is released during schizogony. Our experimental re-definition of the SPE2/PfSIP2-N interaction highlights the strict requirement of both adjacent AP2 domains and a conserved bipartite SPE2 consensus motif for high-affinity binding. Genome-wide in silico mapping identified 777 putative binding sites, 94% of which cluster in heterochromatic domains upstream of subtelomeric var genes and in telomere-associated repeat elements. Immunofluorescence and chromatin immunoprecipitation (ChIP) assays revealed co-localization of PfSIP2-N with PfHP1 at chromosome ends. Genome-wide ChIP demonstrated the exclusive binding of PfSIP2-N to subtelomeric SPE2 landmarks in vivo but not to single chromosome-internal sites. Consistent with this specialized distribution pattern, PfSIP2-N overexpression has no effect on global gene transcription. Hence, contrary to the previously proposed role for this factor in gene activation, our results provide strong evidence for the first time for the involvement of an ApiAP2 factor in heterochromatin formation and genome integrity. These findings are highly relevant for our understanding of chromosome end biology and variegated expression in P. falciparum and other eukaryotes, and for the future analysis of the role of ApiAP2-DNA interactions in parasite biology.

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