Publication

The 3-phosphoinositide-dependent protein kinase 1 is an essential upstream activator of protein kinase A in malaria parasites

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Cyclic adenosine monophosphate (cAMP)-dependent protein kinase A (PKA) signalling is essential for the proliferation of Plasmodium falciparum malaria blood stage parasites. The mechanisms regulating the activity of the catalytic subunit PfPKAc, however, are only partially understood, and PfPKAc function has not been investigated in gametocytes, the sexual blood stage forms that are essential for malaria transmission. By studying a conditional PfPKAc knockdown (cKD) mutant, we confirm the essential role for PfPKAc in erythrocyte invasion by merozoites and show that PfPKAc is involved in regulating gametocyte deformability. We furthermore demonstrate that overexpression of PfPKAc is lethal and kills parasites at the early phase of schizogony. Strikingly, whole genome sequencing (WGS) of parasite mutants selected to tolerate increased PfPKAc expression levels identified missense mutations exclusively in the gene encoding the parasite orthologue of 3-phosphoinositide-dependent protein kinase-1 (PfPDK1). Using targeted mutagenesis, we demonstrate that PfPDK1 is required to activate PfPKAc and that T189 in the PfPKAc activation loop is the crucial target residue in this process. In summary, our results corroborate the importance of tight regulation of PfPKA signalling for parasite survival and imply that PfPDK1 acts as a crucial upstream regulator in this pathway and potential new drug target.

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