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Infection of mammalian liver by the malaria parasites relies of a network of parasite kinases

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There are 240 million cases of malaria leading to nearly 400,000 deaths each year. It is caused by five species of the protozoan parasite, *Plasmodium*, transmitted to humans by mosquitoes, in the form of 'sporozoites'. Sporozoites invade hepatocytes where they develop intracellularly into 'liver stages'. Liver stages exit the hepatocytes in membrane-bound vesicles, termed 'merosomes', that disintegrate in the blood-stream. There, liver stages infect erythrocytes and initiate the symptomatic step of malaria. Blocking *Plasmodium's* liver cycle could prevent disease and a better understanding of the key pathways at this step can identify drug targets for malaria chemoprophylaxis. We report that sporozoite entry into hepatocytes requires the parasite's cGMP-dependent protein kinase (PKG) and Calcium-Dependent Protein Kinases 1, 4 and 5 (CDPK1, CDPK4 and CDPK5). PKG and CDPK5 are also required for the parasite's egress from the hepatocyte. Chemical inhibition of *Plasmodium* PKG abolishes sporozoite motility by preventing secretion of proteins that enable adhesion of sporozoites to the extracellular matrix. Depletion of CDPK1, 4 and 5 also decreases sporozoite motility, but without significantly affecting their adhesion to the substrate. Since motility is required for sporozoites to a) disseminate from the site of deposition in the dermis, migrate through cell- and tissue-layers to enter the blood stream and c) enter a hepatocyte, its inhibition significantly decreases sporozoite infectivity. Chemical inhibition or knockdown of PKG and CDPK5 has a second effect – inhibiting either the formation or release of merosomes. Mice treated with a PKG inhibitor are significantly less susceptible to infection by sporozoites, providing preliminary evidence that chemical inhibition of parasite PKG can block infection in animals. By revealing the requirement for PKG, CDPK1, 4 and 5 in *Plasmodium* invasion of and egress from hepatocytes, our work provides biological and chemical validation for targeting these *Plasmodium* kinases for chemoprotection against malaria.

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