Plasmodium sporozoites homing to the liver: exploring the interplay between parasite and host factors

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Hematogenous dissemination followed by tissue tropism is a characteristic of the infectious process of many pathogens. Once in the blood of the mammalian host, *Plasmodium* sporozoites specifically arrest in the hepatic sinusoids before infecting the liver. Two adhesive proteins present on the surface of sporozoites – circumsporozoite protein (CSP) and thrombospondin-related anonymous protein (TRAP) – have been proposed to specifically interact with highly sulphated heparan-sulphate proteoglycans expressed by hepatic cells, but evidence of their importance for the selectivity of the interactions between sporozoites and the hepatic sinusoids is lacking. Noteworthy, the model explaining the homing of sporozoites to the liver is based on indirect experiments interpreting the binding of recombinant proteins to liver cells or the outcome of a liver infection by sporozoites. To investigate the role of TRAP and its critical role for the sporozoite gliding motility in the homing to the liver, we combined live imaging techniques in mice and reverse genetics. We found that *trap* knockout (*trap*-) sporozoites are defective in homing to the liver and the deletion of the cytosolic domain that links host ligands that bind to the ectodomain of TRAP to the actomyosin motor (TRAP_CTD-) also failed to home to the liver. The deletion of this domain renders sporozoites incapable of gliding but does not alter the surface localization of the protein. As these mutant parasite lines do not invade the salivary glands of the mosquito and accumulate in the hemolymph, two additional mutants where changes in the adhesive I domain of TRAP previously reported to do not prevent sporozoites from entering the salivary glands, but impact gliding motility were also investigated. These include a mutant in which TRAP I domain was: i) replaced by the I-domain of MIC2 from *Toxoplasma gondii* (TRAP_MIC2), and ii) specifically mutated to shift the charge around the metal ion-dependent adhesion site (MIDAS) motif (TRAP_RevCh). Homing experiments demonstrate that TRAP_RevCh (and to a less extent TRAP_MIC2) sporozoites have a defect in homing to the liver, contrarily to control

sporozoites, indicating that the gliding motility might contribute to the retention of sporozoites in the liver sinusoids. Further experiments are now being conducted to consolidate the contribution of sporozoite motility in this process.

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