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Sporozoite Ligand and Hepatocyte Receptors of Malaria Parasites

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Infected mosquitoes inject malaria sporozoites into the vertebrate host during their blood meal. Within minutes, the parasites are found in the liver, initiating the infection. Sporozoites of all malaria species are uniformly covered by the circumsporozoite protein (CS), which contains a conserved COOH-terminal sequence designated region II-plus. This region is the parasite's hepatocyte-binding ligand, which binds to heparan sulfate proteoglycans (HSPGs) on the hepatocyte membrane. Based on the sequence of region II-plus, a multiple antigen peptide was synthesized. It mimics the hepatocyte-binding ligand since it inhibits both CS binding to HepG2 cells *in vitro*, as well as CS clearance in mice. Recently, we have shown, that the CS protein interacts not only with cell surface heparan sulfate, but also with the low density lipoprotein receptor-related protein (LRP). Binding of ^{125}I-CS protein to purified LRP can be inhibited by the receptor-associated protein (RAP). Blockage of LRP by RAP or anti-LRP antibodies on heparan sulfate-deficient CHO cells results in more than 90% inhibition of binding and endocytosis of recombinant CS protein. Heparinase-pretreatment of LRP-deficient flbroblasts of blockage of LRP on heparan sulfate-deficient CHO cells by RAP, lactofemn or anti LRP antibodies reduces *Plasmodium berqhei* invasion by 60-70%. Parasite development in heparinase-pretreated HepG2 cells is inhibited by 65% when RAP is present during sporozoite invasion. We have obtained evidence that CS and remnant lipoproteins compete not only *in vitro* but also *in vivo* for the same liver cell receptors. As predicted by these observations, apoE-enriched β-VLDL inhibits sporozoite invasion of HepG2 cells, and malaria parasites are less infective in LDL-receptor knock-out mice maintained on a high fat diet.

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