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Cholesterol and Malaria May Use Same Doorway to Liver Cells

All current anti-malaria drugs target the parasite that causes the disease, but those are becoming less effective due to increasing drug resistance. Now, Howard Hughes Medical Institute researchers report that they may be able to fight malaria by targeting human liver cells instead of parasites.

HHMI international research scholar Maria M. Mota and her colleagues have identified a receptor on human liver cells that appears to help the malaria parasite sneak inside to fully develop. The SR-BI receptor is normally an entry point for HDL cholesterol and other lipids from the bloodstream into liver cells, which break them down. But new experiments show that the malaria parasite may also be using this doorway. When scientists disabled the SR-BI receptor, they saw a dramatic reduction in the number of infections from two species of malaria in mouse and human cells. The experiments are presented in the September 2008 issue of *Cell Host & Microbe*.

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This study establishes the first clear molecular link between malaria infection and cholesterol uptake pathways, thus describing a new intervention strategy in the fight against malaria, says Mota, a faculty member at the Instituto de Medicina Molecular at the University of Lisbon in Portugal.

Malaria parasites enter the human bloodstream via mosquito bites and travel to the liver, where they burrow into liver cells, multiply, and return to the bloodstream to wreak havoc on the body.

Previous research had linked the lipoprotein clearance rate by the liver to increased malaria infection, so Mota thought the parasite might enter liver cells by hijacking the liver's own cellular machinery. The group focused its attention on the part of liver cells that filter fatty molecules like cholesterol

and other lipids out of the bloodstream.

Mota's team used RNA interference (RNAi) to examine the receptors that filter lipoproteins. The RNAi technique permitted the researchers to create cell lines with specific genes inactivated. They then tested each cell line to see how it responded to the malaria parasite. We looked through 53 lipoprotein receptors and found one that really stood out from the rest, Mota says. That receptor was SR-BI (class B, type I scavenger receptors). Removing SR-BI cut down infections in these cells more than any other receptor they tested.

To confirm their suspicions about SR-BI's key role in malaria, the team conducted a series of experiments that examined mouse cells, human cells, and living mice. First, they induced mouse cells to produce much more of the protein than usual. When they exposed those cells to the parasite that causes malaria in mice, they found the cells were infected more readily than cells with a normal amount of the receptor. The team then tested the receptor's role in a line of human cells with a human-specific malaria parasite, and got similar results.

Cells in living animals often respond differently than cultured cells, so Mota's team explored SR-BI's role in live mice. First they suppressed the gene for SR-BI in these mice, and later injected them with a malaria-causing parasite. Forty hours after exposure, the researchers examined whether the parasite infected the animals' liver cells. They found that the mice with reduced SR-BI had liver infection levels 50-70 percent lower than the normal mice.

Mota's team also infected another set of mice, which had been genetically engineered to lack natural SR-BI. These mice were no better off than the control group, however. Since these mice live their whole lives without SR-BI, they may have developed a compensatory mechanism for delivering lipids to their liver cells, she says. The malaria parasites might be hitching a ride on that alternative path.

The results don't rule out other pathways of infection, but they do strongly suggest that SR-BI helps parasites enter liver cells, she says. It could be that malaria parasites use SR-BI as a bridge into liver cells, or that SR-BI primes liver cell membranes for the parasites somehow, she explains. Importantly, the lack of SR-BI also leads to a reduction in parasite development and replication inside the liver cells. What we see is that the number of parasites gets much smaller if we block SR-BI.

Mota says the malaria parasite may have originally chosen SR-BI for an evolutionary reason. One hypothesis is that SR-BI plays a direct or indirect role in providing cholesterol for the parasites to construct their cell membranes. Her team intends to test that theory by finding a way to block cholesterol delivery to liver cells to determine whether cholesterol shortage limits a parasite's growth. If so, the team may have found a way to fight malaria that will be hard for the parasite to out-evolve—stealing the biological bricks and mortar the parasite needs to build its cellular home.

The team is currently working with the company Cenix BioScience to develop and test new molecules that will work on this pathway, Mota says, but they are aware that interfering with cholesterol metabolism in people is not straightforward. Still, she explains, a single treatment with one such molecule *in vivo* gives an infection reduction of 80 percent which is an encouraging result.

Hepatitis C virus and protozoan infections may use a similar mechanism to enter liver cells, Mota says, so if the team can decipher how malaria infects the liver, there may be other benefits, too.