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## Research Identifies Malaria Proteins that Remodel Red Blood Cells

After a malaria parasite invades a red blood cell, it sends a crew of proteins inside to do some major remodeling.

But this rehab job isn't meant to refinish the floors. The proteins gut the red blood cell, transforming it from a vital oxygen delivery system into a nest for new parasites. These renovations are what make malaria so dangerous: they cause infected red blood cells to harden and stick inside blood vessels. When this happens in the brain or in the placenta of a pregnant woman, the results are deadly.

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That's why HHMI international scholar Alan Cowman and his colleagues set out to understand the proteins that oversee this destructive remodeling. Cowman, from the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia, and his colleagues present the first systematic examination of remodeling proteins from the most deadly species of the malaria parasite, *Plasmodium falciparum*, in a paper published online July 11, 2008, in the journal *Cell*. Brendan Crabb, another HHMI international scholar at the institute, is a co-author of the paper.

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The researchers have figured out the roles of 56 proteins involved in this remodeling. This includes eight proteins that act like painters, putting down a sticky layer on the cell's surface, and two more that act like carpenters, building knobs on the surface of the cells. They also identified several carpenter-like proteins that change the cell structure so it's rigid.

Perhaps more important, they have found an additional 30 proteins that are essential to the parasite's survival inside red blood cell. If the research team can understand what these proteins do, they may eventually be able to design a drug that could stop the parasite or make it less likely to kill.

Malaria parasites go through a series of steps on their way to causing human disease. They travel from a mosquito bite on the skin to the liver, where they hunker down and multiply. They then fan out into the bloodstream, where they invade red blood cells both in an attempt to evade the immune system and to remodel them for their own use. This is key to the parasite's survival in the host and the key to its pathogenesis, Cowman said.

To identify the role of each protein involved in red blood cell remodeling, the research team had to create a parasite without the gene that creates it. This modified parasite is called a knockout. While red blood cell rehabilitation requires a work crew of as many as 400 proteins, Cowman's team started their analysis with 200 of these, focusing on those that seemed unique or that had been linked to important roles before. This *Cell* paper describes the first 83 genes, many found only in *P. falciparum*.

The research has taken five years because identifying the function of genes in *P. falciparum* isn't easy, Cowman explained. They have to knock out the genes one by one, then run a number of tests to find out what has changed about the parasite and the red blood cell it attacked. It's very difficult, and no one has every attempted anything on this scale before, he said.

What they found was worth the effort. The team has identified two proteins responsible for building porcupine-like protrusions on the walls of red blood cells; without these knobs, infected cells don't stick to vessel walls. Several other proteins were responsible for turning a flexible red blood cell into a rigid sphere that clogs up small blood vessels. The most interesting of the newly-identified proteins may be those responsible for placing a glue-like adhesive called PfEMP1 on the outer walls of the red blood cell. This adhesive, called a virulence protein, is the primary factor that sticks these rehabbed red blood cells to blood vessel walls. Cowman expects they will find more proteins involved in creating PfEMP1.

But the biggest part of the researchers' job is just beginning. They want to understand the role of the 30 proteins that the parasite can't live without. These essential proteins will require a new set of approaches, because they have found that a traditional gene knockout kills the parasite. While this proves the proteins are essential, it doesn't explain what they do inside the parasite. Cowman suspects that many may be involved in the parasite's uptake of nutrients.

Eventually, the team hopes to identify targets for new treatments against malaria. Targeting these essential proteins might kill the parasite, which is a good solution. But even better might be targeting proteins that would weaken the malaria parasite rather than killing it. This would leave enough of the parasite to stimulate the immune system to respond, but prevent most of the major illness caused by the parasite. In some ways, it would be better than

actually killing it, Cowman said.

This study is the first step toward figuring out what proteins to target in a vaccine. The blood stage causes all of the infection and the disease. That is the reason we are trying to understand how it interacts with the host, he said.

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