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Dream Home: Malaria Parasite Renovates to Suit Its Tastes

The malaria parasite survives in its host by remodeling the red blood cells in which it dwells. Once ensconced in its newly refurbished home, the parasite evades detection by the host's immune system. Alan F. Cowman, a Howard Hughes Medical Institute (HHMI) international research scholar at the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia, and colleagues report on studies that reveal this clever survival strategy, in the December 10, 2004 issue of the journal *Science*. Their findings provide a novel target for new anti-malaria drugs.

Cowman and his research team have identified the mechanism that enables the malaria parasite *Plasmodium falciparum* to export proteins across a cell membrane to establish infection in the erythrocytes, or red blood cells, of the host. The researchers also have identified a subset of proteins--from about 400 surveyed--that appear vital to the parasite's survival in the host.

Cowman is one of 132 HHMI international research scholars in 29 countries. Through its international research program, HHMI is building a global network of outstanding scientists whose work outside the United States is contributing to our understanding of basic biological processes or disease mechanisms. There are 11 international research scholars in Australia.

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- Alan F. Cowman

P. falciparum, which infects several hundred million people each year and kills one to two million, causes the most severe form of malaria in humans. Once in the blood, the parasite's continuous asexual multiplication inside the red blood cells is responsible for the clinical symptoms of malaria and the

associated incidence of disease and death.

To infect the host, the parasite exports proteins through three membranes: the parasite membrane, the parasitophorous vacuole and the erythrocyte membrane.

"It has been an enigma in biology how the parasite transfers proteins across the second membrane, the parasitophorous vacuole, and establishes infection in the erythrocyte," said Cowman. "Once past the parasitophorous vacuole it can renovate the erythrocyte, obtain nutrients and avoid destruction by the body's immune system."

According to Cowman, the sequence in the proteins is the key that enables the parasite to traverse all three membranes. For example, the researchers found that during the asexual stage, the parasite, which is present in the parasitophorous vacuole, remodels the erythrocyte by forming an elaborate membranous network in the cytoplasm of the red blood cell. The invading parasite forms structures important for protein trafficking and for locating the nutrients it needs for survival.

The parasite also remodels the surface of the infected red blood cell membrane with dense elevations called knobs. A protein called PfEMP1 enables the parasite to adhere to the erythrocyte, which is essential if the parasite is to survive in the host. The parasite disguises these alterations, which are made to the surface of the cells, enabling it to complete its 48-hour life cycle, multiply, and cause severe infection without detection by the immune system.

"Adhesion of parasite-infected erythrocytes to host cells is a major factor in the pathology of malaria," Cowman explained. "If the parasite didn't stick to the host erythrocyte, it would be dislodged in the blood stream and eliminated rapidly by organs such as the spleen."

Previous studies have identified five or six *P. falciparum* proteins involved in the infection of host's red blood cells. But Cowman's team--thanks to the completion of the malaria genome sequence--have identified approximately 400 *P. falciparum* proteins that the parasite exports into the erythrocyte. By analysing the fully sequenced parasite genome, they have identified all the genes and proteins involved in malarial infection and deciphered the signaling code, which is critical for the protein export mechanism.

"We have tried removing certain proteins from the parasite--gene knockouts, for example--and the parasite survived well in most cases. So those proteins were not useful drug targets. But some of the exported proteins are unique to *Plasmodium* species, and identifying them has been a major step forward in establishing which are the important ones," Cowman said.

The exported proteins present in all *Plasmodium* species are critical for the malaria parasite's survival. This subset of proteins can cross the parasitophorous vacuole and remodel the erythrocyte, enabling the parasite to grow and infection to succeed. Now, instead of testing all 400 proteins for the development of antimalarial drugs, the researchers can concentrate on the key 10 to 15 proteins implicated in host infection.

Cowman is excited about the implications of the research. The identification of an export mechanism unique to *Plasmodium* species, he said, "raises the possibility of developing completely novel strategies to interfere with multiple aspects of parasite development through a single target."