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Malaria's Deadly Weapon: A Morphing Molecule that Keeps the Parasite a Step Ahead

A molecule that constantly reinvents itself is one of the many ingenious mechanisms that *P. falciparum* - the mosquito-borne blood parasite that causes the deadliest form of human malaria -- has evolved to protect itself against the human immune system. A new understanding of how this morphing molecule helps the parasite survive inside red blood cells could help scientists develop new treatments for the disease.

A research team led by Louis Schofield - a Howard Hughes Medical Institute international research scholar at the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia - has discovered how a molecule called PfEMP-1 (*Plasmodium falciparum* erythrocyte membrane protein-1) helps the pathogen evade the human immune system.

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- D. Louis Schofield

In research findings published in the August 15, 2007, issue of the journal *Cell Host & Microbe*, Schofield shows that PfEMP-1 prevents immune cells from producing interferon-gamma, which signals other immune cells to attack and destroy infected red blood cells. Although PfEMP-1 strongly suppresses IFN-gamma, Schofield said it appears to have no effect on other cytokines or immune system cells.

The researchers found that PfEMP-1 also causes infected red blood cells to stick to the endothelial cells that line blood vessels. By sticking to blood vessel walls, infected erythrocytes avoid passing through the spleen where

they would be filtered out and destroyed.

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What's intriguing, Schofield says, is that every *P. falciparum* parasite contains 50 to 60 slightly different variants, or alleles, of the gene that encodes PfEMP-1. “The parasite has a repertoire of alleles, but it only expresses one at a time,” he explained. “While one gene is being expressed, it silences the expression of the others.”

PfEMP-1's ability to morph into different variants makes it possible for *P. falciparum* to stay one step ahead of detection and destruction by the human immune system. This gives the parasite time to multiply inside infected red blood cells and spread the infection to other cells.

The research team compared the immune response of human erythrocytes infected with *P. falciparum* to that of erythrocytes infected with parasite cell lines that lacked PfEMP-1 on their surfaces. These knock-down parasites were created by Alan Cowman, a co-author on the study and a Howard Hughes Medical Institute international research scholar also at the Walter and Eliza Hall Institute of Medical Research.

Schofield says his research findings indicate that interferon-gamma does more than signal the immune system to attack the invading parasite. It also appears to control how people react to infection.

“Interferon-gamma is a major regulator of the host-parasite relationship, but it plays a dual role,” Schofield said. “Sometimes it's pathogenic and sometimes it's protective.”

In children or adults infected with the malaria parasite for the first time, that resulting production of large amounts of interferon-gamma can be extremely pathogenic. Every 48 to 72 hours, when a new batch of mature parasites “hatches” from red blood cells, the release of toxins triggers a strong inflammatory response, causing high fever, chills, and flu-like symptoms. According to Schofield, much of *P. falciparum*'s high morbidity and mortality may be caused by interferon-gamma hyperactivating the immune system.

In recurrent infections, the risk of mortality goes down, the symptoms are not as severe, and the infection is easier to control. In these cases, Schofield says interferon-gamma protects the human host by modulating the immune system's response to the parasite.

While others have considered PfEMP-1 as a potential target of malarial vaccines, Schofield said his findings suggest this approach could backfire.

“You might want to be careful about vaccinating against a molecule involved in the regulation of immune responses,” he said. “Especially in young children, vaccinating against PfEMP-1 could be harmful, because it could hyperactivate the immune system.”