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Malaria Parasites Power Through Cells on Their Way to Infection

Malaria-causing parasites evade the immune system by ducking in and out of cells in a high-speed chase with the body's emergency responders.

New research by Howard Hughes Medical Institute international research scholar Robert Ménard and his colleagues shows that this pursuit may start much earlier than previously thought, right after the first itchy mosquito bite.

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— Robert Ménard

The parasites begin to evade their immune system pursuers as soon as they move out of the mosquito and into the skin. They charge through and kill any cell that gets in the way en route to the bloodstream, their speedway to the liver.

Researchers had previously thought that the parasites just made this dash through cells, a process called cell traversal, once they got to the liver. Instead, they may just be slowing down once they get to the liver.

It is a total shift in thinking, said Ménard, of the Institut Pasteur in Paris. The role of this traversal activity is not in the liver but to reach the liver. The research was published February 14, 2008 in the journal *Cell Host & Microbe*.

Malaria-carrying mosquitoes deposit the parasite *Plasmodium falciparum* in the skin of their victims. The parasite then makes its way to its first important stop in the liver. That's where the parasite settles in for several days of growing and dividing before sending off thousands of offspring into the bloodstream, which is what causes a person to get sick.

Until recently, the skin phase did not exist—not in the textbooks, but also not in the research, Ménard said.

But his new work shows that cell traversal is crucial for the trip from the skin to the liver. Those parasites that can't flee the body's innate immune system—the leukocytes that hunt down invaders—can't make it to the liver at all.

Studying *Plasmodium berghei*, a form of the malaria parasite that infects rodents, Ménard and his colleagues watched parasites as they entered the mice after they were bitten by the mosquitoes. They compared healthy parasites to two mutant parasites that could not traverse cells because they carried different genetic mutations.

The studies showed that the mutant parasites had no problem reproducing in the liver when placed there, a finding that contradicts previous studies. But the mutations still caused a serious setback for the parasites - they could not get to the liver. Instead, they got stuck near their entry point on the skin, where they were easy targets for leukocytes.

These mutants are immediately blocked, he explained.

By contrast, the healthy parasites had two defenses against the immune system. The first is speed. Malaria parasites are almost 10 times faster than leukocytes chasing them. But because they move in a random way, the parasites still can get caught.

The second is evasion. The parasites dive into cells, then jump out the other side. The cell almost always dies as a result of this invasion.

The number of cells traversed by parasites between the skin and the bloodstream is not known. But the parasites only have two hours to get from the bite site to the liver before their ability to move fades away.

Ménard and his colleagues now want to examine how the parasites manage to move through the cells.

This entire skin step has been totally overlooked. It was just unknown, he said. We are now realizing how important it is.