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## Malaria Parasites Develop in Lymph Nodes

In the first quantitative, real-time imaging study of the travels of the malaria parasite *Plasmodium* through mammalian tissue, researchers at the Pasteur Institute in Paris found the parasites developing in an unexpected place: the lymph nodes.

The parasites' presence in the lymph nodes almost certainly has implications for the mammalian immune response, said Robert Ménard, a Howard Hughes Medical Institute (HHMI) international research scholar who led the study.

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"Parasite development in lymph nodes could be one reason there is so much tolerance to these parasites."

— Robert Ménard

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Ménard and colleagues report their findings in the February 2006 issue of the journal *Nature Medicine*, published online on January 22, 2006.

When a mosquito infected with *Plasmodium* bites a mammal, the immature parasites travel to the animal's liver, which, until now, scientists thought was the only place they could develop, Ménard said. Once they have fully developed, the parasites burst out of the liver cells and infect red blood cells, beginning the onset of malaria.

Although researchers understand this life cycle, no one has measured directly how many parasites a mosquito bite transmits or where else in a mammal's body they travel, said Ménard. To find out, he and his colleagues infected mosquitoes with fluorescently tagged *Plasmodium* parasites, and then allowed the mosquitoes to bite a mouse. From each mosquito bite, they found an average of 20 fluorescent parasites embedded in the animal's skin. Ménard found that the parasites moved through the skin in a random, circuitous path at a speed that is amongst the fastest recorded for any migrating cell.

After leaving the skin, the parasites frequently invaded blood vessels. That was no surprise to Ménard, since they need to travel through blood vessels to get to the liver. However, many of the parasites also invaded lymphatic

vessels. About 25 percent of the parasites injected by the mosquito bites were drained by lymphatic vessels and ended up in lymph nodes close to the site of the bite. Their journey seemed to stop there, as the malaria parasites almost never appeared in lymph nodes farther away.

Within about four hours of the mosquito bite, many of the lymph-node parasites appeared degraded. They were also seen interacting with key mammalian immune cells, suggesting that the immune cells were destroying them.

A small number of the parasites in the lymph nodes, however, escaped degradation and began to develop into forms usually found only in the liver. Up to now, researchers believed that, although both blood and lymphatic vessels take up *Plasmodium* parasites, they all end up in the liver, Ménard said. "Nobody had proposed that they actually might stop" in the lymph nodes and develop there, he observed.

By 52 hours after the mosquito bites, no parasites remained in the lymph nodes, which suggests that they can't develop completely there, Ménard said. Only fully developed parasites can infect red blood cells and cause malaria, so the lymph-node parasites probably don't contribute to the appearance of malaria symptoms, he added. But even partially developed or destroyed parasites could significantly affect how the immune system responds to infection, he noted.

Another unexpected finding adds even more complexity to the mammalian immune response to the malaria parasite. An hour after a mouse was bitten, nearly half of the parasites remained in the animal's skin, and some were detected there even after seven hours. That's really surprising," Ménard said.

Although he cautions that those numbers may be specific to mice and the species of *Plasmodium* the scientists used, it's likely that at least some parasites remain in the skin of any mammal bitten by a malarial mosquito until immune cells come along to sweep them out, Ménard said. This second influx of parasites could prompt a somewhat different immune response in the host, and those parasites might have different fates. Parasites developing in the lymph nodes could have two opposite effects on the body's immune response, he explained. They might alert the body that an invader is present and activate a protective immune response. On the other hand, their presence in the lymph nodes might desensitize the body to the parasites, blunting the immune system's response to liver and blood-cell infection.

"We have to integrate all these new data into something that makes sense from the immune standpoint," the researcher observed. Understanding the intricacies of the mammalian immune response to *Plasmodium* infection might help scientists create better vaccines, including vaccines that target parasites before they develop in the liver, Ménard said. Parasite development in lymph nodes could even be one reason there is so much tolerance to these parasites, he suggested.