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Researchers use new finding to clear bloodstream malaria infection in mice

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University of Iowa researchers and colleagues have discovered how malaria manipulates the immune system to allow the parasite to persist in the bloodstream. By rescuing this immune system pathway, the research team was able to cure mice of bloodstream malaria infections.

The findings, which were published Dec. 11 in the Advance Online Publication of the journal Nature Immunology, could point the way to a new approach for treating malaria that does not rely on vaccination and is not susceptible to the parasite's notorious ability to develop drug resistance.

"Malaria is chronic, prolonged infection and the host immune defense has a tough time clearing it and sometimes it never clears it," says Noah Butler, Ph.D., UI postdoctoral research scholar and lead study author. "We've determined that this prolonged infection actually drives dysfunction of the immune cells that are supposed to be fighting the infection, which in essence allows further persistence of the parasite infection."

More specifically, the study showed that the malaria parasite stimulate these key immune cells (known as CD4+ T cells) so that they continuously express molecules called inhibitory receptors. Under normal circumstances, these molecules help to "apply the brakes" to the immune response and prevent over-activation that can be harmful. However, by keeping the mechanism turned on, the malaria parasite damps down the immune response significantly, reducing the T cells'

ability to fight the parasite and allowing it to persist.

Importantly, the team also showed that blocking the action of the inhibitory receptor molecules resulted in immediate and complete clearance of the malaria parasite.

"When we blocked the function of these molecules, we took the brakes off the host's immune response and everything got better -- the overall immune response was dramatically improved and there was immediate control and accelerated clearance of the parasite," says John Harty, Ph.D., professor of microbiology and pathology at the UI Carver College of Medicine and senior study author. "These findings suggest an alternative approach for the treatment of existing malaria infection."

200 million malaria cases

More than half the world's population is at risk of malaria, a mosquito-borne parasite that causes anemia and high fever and which can persist for weeks or months. There are more than 200 million cases of malaria each year and an estimated 800,000 children die from malaria annually.

Harty notes that the current study was done in mice and it is not yet know if the same approach will work in humans. However, two factors suggest the strategy may have potential. First, drugs that block inhibitory receptor molecules are available and currently being tested as cancer therapies. And second, the UI team found that malaria infection in humans does lead to increased expression of inhibitory receptors on CD4+ T cells suggesting that these molecules could represent a viable target for human therapies.

The human findings were the product of an important collaboration between the UI team and malaria researchers working in the sub-Saharan country of Mali. The Mali team based at the University of Bamako

works in a sophisticated lab set up by the National Institutes of Health. In Mali's dry season there are no mosquitoes, so there's no malaria; in the wet season, the mosquitoes come out and malaria appears.

"Workers in the NIH lab obtained blood samples from malaria-free children at the end of the dry season, and then when some of the children returned to the clinic with malaria at the beginning of the next wet season they were treated immediately and the workers also took a second blood sample," Harty explains. "This allowed us to analyze the blood for expression of this inhibitory molecule before and after infection and we found that the molecule went up after infection."

Malaria further compromises immune system

A second collaboration, born closer to home, allowed Harty's team to prove that it is the CD4+ T cells that are disrupted by the malaria infection.

Using a new technique that was developed in the lab of UI microbiologist Steve Varga, Ph.D., the researchers were able to track the behavior of the responding T cells during malaria infection. They found that chronic malaria infection led to sustained expression of the inhibitory receptor molecules on the surfaces of this type of T cell and also showed that the T cells' ability to fight the parasite was significantly reduced.

The study also found that as the parasite persists the inhibitory receptor molecules remain upregulated and the immune system became more and more compromised.

"The T-cells are so over-stimulated that they eventually lose their function or even die -- this is known as T-cell exhaustion," Butler explains.

The concept that prolonged persistence of an "insult" to the immune system, such as cancer or chronic viral infections like HIV, disrupts and exhausts the immune response is well established. However, this study is the first time it has been shown for malaria. The study finding suggests that rescuing CD4+ T cells from exhaustion could be an effective strategy to control and clear bloodstream malaria infections.

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