Malaria parasite zeroes in on molecule to enhance its survival

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A team of researchers from Princeton University and the Drexel University College of Medicine has found that the parasite that causes malaria breaks down an important amino acid in its quest to adapt and thrive within the human body. By depleting this substance called arginine, the parasite may trigger a more critical and deadlier phase of the disease.

The scientists believe that shedding light on this poorly understood aspect of malaria metabolism has given them new insights on the interactions between the parasite and its human hosts. The work also may point the way to better treatments.

"The more we know about the parasite's metabolic network, the more intelligent we can be about targeting therapies that will cure malaria," said Kellen Olszewski, a graduate student at Princeton University and first author of the Feb. 18 *Cell Host & Microbe* paper describing the work. The project was led by Manuel Llinás, an assistant professor of molecular biology and the Lewis-Sigler Institute for Integrative Genomics at Princeton.

As a central part of the research, the scientists created a "metabolomic" profile of the parasite, *Plasmodium falciparum*. Metabolomics is a new field that aims to analyze metabolic processes by simultaneously measuring the levels of all of the more than 500 core metabolites that make up an organism's "metabolic network." A metabolite is a chemical involved in metabolism, the process by which an organism takes up

nutrients from the environment and converts them to energy and the molecular building blocks that cells use to grow. Amino acids, sugars, nucleotides and vitamins are all metabolites.

To conduct the study, the team used a mass spectrometry-based method developed in the neighboring laboratory of Joshua Rabinowitz, an assistant professor of chemistry at Princeton and another author on the paper. Mass spectrometry is a highly sensitive technique that identifies chemicals based on their size and electrical charge.

The researchers were interested in seeing how the concentrations of metabolites in parasite-infected human red blood cells change over a single 48-hour "generation" of parasite growth. Scanning the data, the scientists noted that arginine levels dramatically dipped by the end of one 48-hour cycle.

"The parasite destroys this amino acid specifically and preferentially over all other amino acids," Olszewski said.

Follow-up experiments showed that the parasite doesn't break down arginine in order to grow, suggesting that this process serves some secondary function that helps *P. falciparum* proliferate within the human body. Arginine is an essential fuel for the human body's immune system, which uses it to produce a molecule called nitric oxide that is highly toxic to foreign organisms. The parasite-led attack on arginine may be an attempt by the parasite to "switch off" a human immune function that might threaten its survival, the researchers said.

Scientists are interested in studying the metabolism of *P. falciparum* to understand how organisms adapt to a parasitic lifestyle. Understanding this is important because many of the drugs used to treat malaria successfully in the past have targeted some aspect of the parasite's metabolism.

"Designing the next generation of anti-malarial drugs will likely require a detailed knowledge of the 'weak points' in the parasite's metabolic network," Llinás said.

According to the World Health Organization, some 350 to 500 million people are infected with malaria every year by mosquitos carrying one of the four human malaria parasites, *P. falciparum*, *P. vivax*, *P. malariae* or *P. ovale*. The *P. falciparum* infections are by far the most deadly, killing more than 1 million people each year, mainly young children and pregnant women. The disease, which can incapacitate a victim for several weeks, also imposes a massive social and economic burden. People living in endemic areas can be infected up to several times a year. About 60 percent of the cases of malaria worldwide and more than 80 percent of malaria deaths occur in sub-Saharan Africa.

Source: Princeton University