Scientists find genetic basis for key parasite function in malaria

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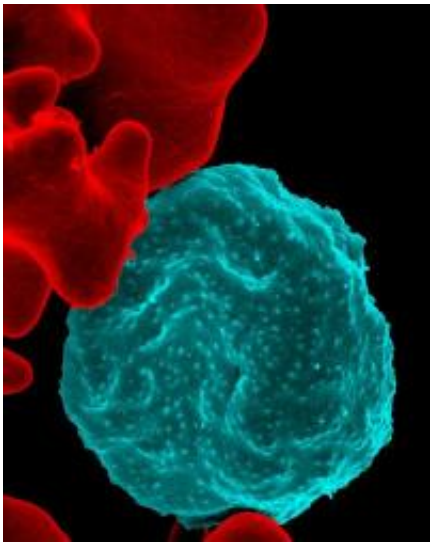

This is a colorized electron micrograph of red blood cell infected with malaria parasites (blue). The small bumps on the infected cell show how the parasite remodels its host cell. Uninfected cells (red) have smoother surfaces. Credit: NIAID/RML

Snug inside a human red blood cell, the malaria parasite hides from the immune system and fuels its growth by digesting hemoglobin, the cell's main protein. The parasite, however, must obtain additional nutrients from the bloodstream via tiny pores in the cell membrane. Now, investigators from the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, have found the genes that malaria parasites use to create these feeding pores.

The research was led by Sanjay A. Desai, M.D., Ph.D., of NIAID's Laboratory of Malaria and Vector Research. In 2000, Dr. Desai co-discovered the primary type of feeding pore on parasite-infected blood cells, an ion channel known as the plasmodial surface anion channel (PSAC). Ion channels are pore-forming proteins that allow the movement of calcium, sodium and other particles into or out of the cell. A report of the team's new findings, which build on this original discovery, is now online in *Cell*.

"Despite recent progress in controlling malaria worldwide, the disease continues to kill more than 700,000 people, primarily young children, every year," said NIAID Director Anthony S. Fauci, M.D. "Dr. Desai and his colleagues have discovered the genetic basis of a fundamental aspect of malaria parasite biology, and in doing so, they have opened up potential new approaches to developing antimalarial drugs."

Scientists have known for decades that malaria-infected red blood cells have greater nutrient uptake than non-infected cells, presumably to support parasite survival and growth, noted Dr. Desai. But, he added, "It was debated whether the parasite co-opts existing human channels or uses its own proteins to remodel the red blood cell membrane."

To answer this question, the NIAID team screened nearly 50,000 chemicals for their ability to block nutrient uptake by cells infected with either of two genetically distinct lines of Plasmodium falciparum malaria parasites, HB3 and Dd2. Most chemicals were equally active against the two lines, but one, ISPA-28, stood out because it was 800 times more active against the nutrient channels of Dd2-infected red blood cells than against those of HB3-infected cells.

If the PSAC protein is made by the parasite, the scientists reasoned, the strikingly different effects of ISPA-28 on the two lines may reflect genetic differences. To explore this possibility, the investigators

measured how well ISPA-28 inhibited PSAC activity in daughter parasites resulting from a genetic cross between the HB3 and Dd2 lines. They found that most daughter parasites made channels that were identical to those of one or the other parent, indicating that parasite genes play an important role. The inheritance pattern of ISPA-28 action on channels led the researchers to chromosome 3, where they found two parasite genes, clag3.1 and clag3.2, that appear to encode the PSAC protein.

This genetic evidence was bolstered when they showed that individual parasites express either the clag3.1 gene or the clag3.2 gene, but not both simultaneously. They found that switching between the two genes produced changes in PSAC behavior that could be predicted. Malaria parasites use gene switching as a way to protect essential proteins from attack by the immune system, Dr. Desai explained.

"We were surprised to discover a role for clag genes in PSAC activity," said Dr. Desai. This family of genes, which do not look like other ion channel genes, was previously thought to be involved in helping infected cells adhere to the inner lining of blood vessels. Clag genes are found in all species of malaria parasites, noted Dr. Desai, and this fact, along with the discovery that the parasites can choose between one of two channel genes to ensure nutrient uptake, strongly suggest that PSAC is required for parasite survival within red blood cells.

The discovery of parasite genes required for PSAC activity opens up several new research directions, said Dr. Desai. For example, development of antimalarial drugs that target these channels could be accelerated. The NIAID team has already found PSAC inhibitors that kill malaria parasites. Dr. Desai's team also is exploring how the PSAC protein is transported from the parasite to the red blood cell membrane, as preventing this transport may be another way to kill malaria parasites.

More information:

-- W Nguitragool et al. Malaria parasite clag genes determine nutrient uptake channel activity on infected red blood cells. *Cell* DOI:10.1016/j.cell.2011.05.002 (2011).

-- SA Desai et al. A voltage-dependent channel involved in nutrient uptake by red blood cells infected with the malaria parasite. *Nature* 406:1001-05 (2000).

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