Research exposes new target for malaria drugs

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The malaria parasite has waged a successful guerrilla war against the human immune system for eons, but a study in this week's Journal of Biological Chemistry has exposed one of the tricks malaria uses to hide from the immune proteins, which may aid in future drug development.

Malaria parasites (plasmodia) are transmitted to people via infected mosquitoes. Once inside their human hosts the parasites first set up shop in liver cells, then move into red blood cells (RBCs) to replicate and wait for the next mosquito to help continue the cycle.

After plasmodia infect a blood cell, they send out clusters of sticky proteins to the cell surface, enabling them to attach to blood vessels and escape destruction by the host's spleen while they replicate. This tactic can be especially problematic during pregnancy as malaria-infected RBCs congregate in the vessel-rich placenta (the source of food and oxygen for the growing fetus), creating health problems such as anemia, low birth-weight, fever and more.

Targeting these sticky proteins with drugs is difficult, however, as plasmodia contain many different varieties, which they use to evade the human immune system. However, certain parts of the protein have to remain constant for proper function, and in this study, Matthew Higgins generated high-resolution 3-D structures of a malarial sticky protein that binds to placenta, PfEMP1, to detail how plasmodia protect these conserved areas.

Higgins found that a variable region of PfEMP1 covers a section that is important for docking up with the placental wall. When the infected RBC gets close to chondroitin sulphate, a structural molecule on blood vessels, the variable region moves aside and ever so briefly exposes the binding region, just enough to allow anchoring to take place. Higgins notes that women in regions where malaria is endemic do gain some immunity to the build-up of RBCs at the placenta after multiple pregnancies by developing an immune response for PfEMP1. Targeting this conserved binding domain of the protein with pharmaceuticals that mimic chondroitin sulphate and expose this region might be an approach to hasten this immunity.

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