Scientists find ideal target for malaria therapy

February 3 2010

Scientists at Washington University School of Medicine in St. Louis have identified a protein made by the malaria parasite that is essential to its ability to take over human red blood cells.

Malaria, which is spread by mosquito bites, kills between 1 million and 3 million people annually in Third World countries. Death results from damage to red blood cells and clogging of the capillaries that feed the brain and other organs.

"The malaria parasite seizes control of and remodels the red blood cell by secreting hundreds of proteins once it's inside," says Dan Goldberg, M.D., Ph.D., professor of medicine and of molecular microbiology and a Howard Hughes Medical Institute Investigator. "But without this protein, plasmepsin V, those other proteins can't get out of the parasite into the blood cell, and the infectious process stops."

The closest equivalent to plasmepsin V in humans is a protein called beta secretase, but it's only distantly related. The significant differences between the malarial protein and its closest human relative may mean scientists will be able use drugs to disable plasmepsin V with little worry of adverse side effects on human biology, according to Goldberg.

The results are reported in *Nature*.

Goldberg had studied plasmepsin V previously and knew it was a malarial protease, or an enzyme that cuts other proteins. When another

lab showed that proteins important to the infectious process were being clipped in a part of the parasite where Goldberg knew plasmepsin V was active, he and his colleagues wondered whether it was doing the clipping.

The proteins secreted by the malaria parasite have a common segment or tag that plasmepsin V recognizes and acts on, clipping off part of the protein. Goldberg believes that when the tag is removed, the remainder of the protein is bound to another protein that acts as a chaperone, bringing the proteins to a channel in the malaria parasite's outer membrane. The channel allows the protein to leave the parasite and enter the red blood cell.

Goldberg compares the journey to a theater visit.

"There's a ticket-taker who greets you at the start and takes part of your ticket," he says. "That's plasmepsin V. He then hands you to an usher who gets you to your final destination."

In the test tube, parasites in which plasmepsin V had been disabled were unable to secrete the infectious proteins that allow them to commandeer red blood cells.

"This is the key enzyme that determines whether proteins get out to remodel the red blood cell or not, so it's a very attractive target for therapy," Goldberg says. "Another reason it's a good potential drug therapy target is that it doesn't vary much in different strains of malaria."

In a second paper in the same issue of *Nature*, a group in Australia will report similar conclusions.

Goldberg and his colleagues are continuing to explore how plasmepsin V works.

More information: Russo I, Babbitt S, Muralidharan V, Butler T, Oksman A, Goldberg DE. Plasmepsin V licenses Plasmodium proteins for export into the host erythrocyte. *Nature*, February 4, 2010.