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Researchers locate protein that could 'turn off' deadly disease carrier

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Researchers from Boston College have discovered a protein that plays a pivotal role in the progression of the deadly diseases toxoplasmosis and malaria and shown that its function could be genetically blocked in order to halt the progress of the parasite-borne illnesses, the team reports in the current edition of the journal *Science*.

The protein, identified as DOC2.1, plays a similar role in the secretion of microneme organelles that are crucial to the mobility of the parasitic protozoa *Toxoplasma gondii*, which causes toxoplasmosis, and Plasmodium falciparum, which causes malaria, report Marc-Jan Gubbels and Gabor Marth, both professors of biology at Boston College.

The researchers say the discovery could lead to the development of drugs that target the protein in order to block the mechanism that advances the two diseases.

"The mechanism of microneme secretion, which is required for host cell invasion, is a valid drug target," said Gubbels. "Since neither microneme secretion nor invasion itself are currently targeted by any anti-malaria drugs, a potentially new class of anti-malaria reagents can be developed. The high incidence of drug resistance against malaria is a big problem, so new drugs are urgently needed."

Gubbels said researchers in his lab obtained a temperature-sensitive mutant of *Toxoplasma gondii*, which displayed a mobility defect preventing it from host cell invasion. Marth, a computational biologist,

sequenced the parasite's genome and identified 33 possible sites in the genome responsible for the defect. Lab work isolated a single mutation in the DOC2.1 gene that was associated with a microneme secretion defect responsible for the mobility defect.

Co-author Manoj T. Duraisingh, of the Harvard School of Public Health, generated a Plasmodium mutant wherein DOC2.1 expression could be shut off and demonstrated the protein was also crucial to microneme secretion in the parasite that causes malaria.

Gubbels said the findings reinforce the dramatic advances made possible by complete genome sequencing and computational biology, which are Marth's areas of expertise. These approaches bypass the need for the difficult and time-consuming task of mapping causative mutations by genetic crosses as used in model organisms.

"The re-sequencing method will permit the study of eukaryotic pathogens by forward genetics, which has shown its power in studies of model organisms, such as yeast and fruit flies," said Gubbels. "To date, many of these pathogens have limited experimental and genetic accessibility, but this roadblock can now be lifted."

Added Marth, "We are now working with a number of research teams to gain insight into other critical pathogenic pathways, and already see promising initial results."

Researchers from Children's Hospital Boston and University of Oxford (U.K.) also contributed to the research.

Provided by Boston College

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