New molecular target identified for treating cerebral malaria

January 30 2015

Credit: CDC

A drug already approved for treating other diseases may be useful as a treatment for cerebral malaria, according to researchers at Harvard T. H. Chan School of Public Health. They discovered a novel link between food intake during the early stages of infection and the outcome of the disease, identifying two molecular pathways that could serve as new targets for treatment.

"We have known for a long time that nutrition can affect the course of infectious disease, but we were surprised at how rapidly a mild reduction in food intake could improve outcome in a mouse malaria model," said senior author James Mitchell, associate professor of genetics and complex diseases. "However, the real importance of this work is the identification of unexpected molecular pathways underlying cerebral malaria that we can now target with existing drugs."

The study appears online January 30, 2015 in *Nature Communications*.

Cerebral malaria—a severe form of the disease—is the most serious consequence of infection by the parasite *Plasmodium falciparum*, resulting in seizures, coma, and death. Currently there is a lack of safe treatment options for cerebral malaria, particularly for use in children, who represent the majority of cases. Even patients who receive early treatment with standard antimalarial chemotherapeutic agents run a high risk of dying, despite clearance of the parasite. Moreover, around 25% of survivors develop neurological complications and cognitive impairment.

Lead authors Pedro Mejia and J. Humberto Treviño-Villarreal, both researchers at Harvard T.H. Chan School of Public Health, found that leptin—a hormone secreted from fat tissue with roles in suppressing appetite, but also in activating adaptive immune and inflammatory responses—is increased upon infection in a mouse model of cerebral malaria, and turns out to be a major bad actor in promoting neurological symptoms and death. Remarkably, Mejia, Treviño-Villarreal and colleagues showed that reducing leptin using a variety of means, either genetically, pharmacologically, or nutritionally by reducing food intake during the first two days of infection, protected against cerebral malaria.

The researchers also found that leptin acted primarily on cytotoxic T cells by turning on the well-studied mTOR protein, for which

pharmacologic inhibitors are readily available. In their animal model, treating mice with the mTOR inhibitor rapamycin protected them against the neurological complications of cerebral malaria. Protection was due in part to a preservation of the blood brain barrier, which prevented the entry of blood cells carrying the parasites into the brain. As rapamycin is already FDA-approved for use in humans, trials in humans for cerebral malaria treatment with this drug may be possible, according to the researchers.

More information: "Dietary restriction protects against experimental cerebral malaria via leptin modulation and T-cell mTORC1 suppression," Pedro Mejia, J. Humberto Treviño -Villarreal, Christopher Hine, Eylul Harputlugil, Samantha Lang, Ediz Calay, Rick Rogers, Dyann Wirth, Manoj Duraisingh, and James R. Mitchell, *Nature Communications*, online January 30, 2015, 6:6050, DOI: 10.1038/ncomms7050 (2014).

Provided by Harvard School of Public Health