

Indiana U scientists uncover potential key to better drugs to fight toxoplasmosis parasite

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Discoveries by Indiana University School of Medicine scientists have opened a promising door to new drugs for toxoplasmosis and other parasites that now can evade treatments by turning dormant in the body.

Their findings help explain how the parasite that causes toxoplasmosis transforms into a cyst form that resists drugs and the body's immune system, yet can emerge from its dormant state to strike when a patient's immune system is weakened.

Led by William J. Sullivan Jr., Ph.D., assistant professor of pharmacology and toxicology, and Ronald C. Wek, Ph.D., professor of biochemistry and molecular biology, the research team found a cellular signaling system that takes hold when the parasite is stressed, enabling it to transform into the cyst surrounded by a protective barrier.

The signaling system identified by the IU team could serve as a target to block the transformation into the cyst form or to attack the parasite while in the cyst form. Their report was published in the June 13 issue of the *Journal of Biological Chemistry*.

The *Toxoplasma gondii* parasite converts from an active state to the inactive cyst state when it is stressed, for example, by heat from fever. Stress response mechanisms have been well studied in yeast and other organisms, but the pathways used by the toxoplasmosis parasite had not been determined.

"We found a cellular signal that appears to put the parasite to sleep, which in turn tells us something new about how opportunistic pathogens such as *Toxoplasma* awaken to cause disease during immunosuppression," said Dr. Sullivan.

An estimated 60 million people in the United States are infected with the toxoplasmosis parasite, but for most infection produces flu-like symptoms or no symptoms at all. However, for people with immune system problems – such as those undergoing chemotherapy or people with AIDS – the disease can cause serious effects including lung problems, blurred vision and seizures. Also, infants born to mothers who are infected during or shortly before pregnancy are at risk for severe complications, miscarriages or stillbirths.

Medications to treat *Toxoplasma gondii* are effective but too toxic for extended use, and they don't affect the cyst form, said Dr. Sullivan.

"A healthy immune system can keep this parasite in the cyst state. Without a healthy immune system, this organism can run rampant," said Dr. Sullivan. "This can be a very serious problem for people with AIDS."

The discovery linking this stress-response mechanism to cyst formation and maintenance not only offers a possible target for new drugs, but it could also lead to a preventative vaccine – for animals.

The *Toxoplasma gondii* parasite can infect most animals and birds, but it reproduces in cats, which can shed the parasite in their feces. Humans can be infected through contact with the infected feces or litter. People can also become infected by consuming undercooked meat.

A vaccine to prevent infection in cats and livestock could prevent a significant proportion of human infections, Dr. Sullivan said.

Source: Indiana University

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